Catheter Cryoablation of Cardiac Arrhythmias

For many cardiac arrhythmias, catheter cryoablation is now a safe and effective alternative to RF ablation. Freezor®, a 7F cryocatheter, has been in clinical use in Europe, Canada and the US for several years. In that time, it has established a record of safety and effectiveness in the treatment of arrhythmias, particularly in peri-nodal procedures. With its demonstrated safety profile – especially important when working around the atrioventricular (AV) node – Freezor® represents a new paradigm in treatment alternatives for electrophysiologists.

The Biology of Cryotherapy

Cryotherapy is the use of cooling and freezing in living tissue to affect cellular function and activity. To produce cryotherapeutic temperatures, heat energy is removed from the tissue, rather than ‘injecting’ cold energy into the tissue. Multiple factors influence the effectiveness of catheter-based cryotherapy. Chief among these are tip contact (to remove heat from the tissue, the catheter tip must be in contact with the tissue); tip temperature (the catheter tip temperature applied determines if the cells are subjected to hypothermia or killed); and freeze duration (longer freeze times will cause more tissue damage).

During cryoablation, the removal of heat from the tissue creates a temperature gradient that extends from the catheter tip to the edge of the ‘cryotherapy zone’. At the tip/tissue interface of the catheter, the cryotherapy temperature can be either -30°C and -75°C, depending on the type of intervention (cryomapping or cryoablation). The temperature in the cryotherapy zone ranges from the sub-zero cryogenic temperature at the tip/tissue interface to body temperature at sites distant from the catheter tip. This zone is ‘dynamic’ as it expands during freezing and shrinks upon re-warming. In living tissue, vascularity always provides a heat source and will, as a result, cause local variations in temperature (see Figure 1).

Cryomapping and Cryoablation Mechanisms

Catheter-based cryotherapy includes two complementary procedures – cryomapping, which allows for the confirmation of target sites, and cryoablation, which destroys the cells responsible for the arrhythmia. When cells are cooled below body temperature, a series of events occurs. Beginning at a tissue temperature around 32°C, the cell membranes lose transport capability, and ion pump activity decreases. These changes result in a decrease in the rate of spontaneous depolarization, loss of resting membrane potential, a decrease in action potential amplitude, and an increase in action potential duration, along with a corresponding increase in refractory period.

Conduction velocity slows and local conduction block in the region being cooled may occur. As long as cell temperatures do not fall below freezing, these changes are reversible – cells recover normal function when they are warmed. In the electrophysiology laboratory, these temporary changes in excitability and conduction can be easily detected as local increases in refractory period and/or transient local conduction block. For example, in a patient with Wolff-Parkinson-White syndrome, cryomapping near the site of the accessory pathway can cause temporary disappearance of the delta wave during sinus rhythm. Another example would be cryomapping in the region of the slow AV nodal pathway in a patient with AV nodal re-entrant supraventricular tachycardia (SVT), which can cause temporary block in the slow pathway and render the SVT non-inducible. This type of cryomapping, termed ‘efficacy cryomapping’, can help to identify appropriate sites where cryoablation is likely to be successful in permanently abolishing the target arrhythmia. Another type of mapping, termed ‘safety cryomapping’, can actually be performed either in cryomapping or cryoablation mode. With this approach, the effects of cryoapplication at a given site are closely monitored for the appearance of unintended consequences, like the production of AV block. When undesirable effects occur during cryomapping or cryoablation, the tissue is allowed to rewarm and the catheter is then moved to another mapping site. The utility of this approach is based on the observation that effects seen during cryomapping are typically reversible, as long as catheter tip temperatures are maintained at or above -30°C and the time of application is limited to less than 80 seconds. In a recent multicenter study, the electrophysiologic effects of cryomapping performed in this manner were completely reversible within seconds more than 80% of the time. Similarly, adverse effects that
occur during cryoablation are also usually reversible if cryoapplication is halted promptly.

**Ice Formation**

When cell temperatures are lowered below the freezing point, ice formation occurs inside and outside the cell, resulting in permanent tissue damage. At fast cooling rates – that is, at, or very close to, the tip-tissue interface – water cannot leave the cell fast enough, therefore, ice forms within the cell. Intracellular ice destroys internal cellular structure, resulting in cell death. At slower cooling rates – affecting cells farther away from the tip-tissue interface – ice crystals form in the extracellular space, creating an osmotic imbalance that causes the cell to dehydrate and shrink. As intracellular ice crystals form, they cause a rupture of the cell membrane, resulting in cell death.

**Thawing**

Significant tissue destruction also occurs during thawing. As the temperature rises from -75°C to 37°C, small ice crystals thaw and reform into larger crystals and large crystals reform as small ones – throughout the thawing process, the overall volume of crystallization diminishes as the temperature rises. This reorganization of crystal size and shape causes cell membrane disruption that results in cell death.

**Post-thaw**

Cells are also killed after being exposed to the freeze/thaw cycle. This cell destruction occurs via two mechanisms – necrosis and apoptosis. The first of these, necrosis (or cell rupture), is delayed death whose occurrence peaks after six hours following thawing. Necrosis occurs in tissue that has been frozen or subjected to sub-zero temperatures. It is an event that completes the cryoablation process by filling in the periphery of the lesion. It does not cause new cell damage and does not increase the size of the lesion.

The second post-thaw cell death mechanism is apoptosis (or cell suicide). The freeze affects genetic architecture, causing the cell to self-destruct. The occurrence of cell suicide peaks 12 hours after thawing in cells that were partially frozen or severely stressed without experiencing ice formation. It is an event that completes the cryoablation process by filling in the periphery of the lesion. Apoptosis does not cause new cell damage and does not increase the size of lesion.

Cryolesions are sharply demarcated and heal more rapidly than lesions caused by radiofrequency current, leaving a dense scar that does not affect the electrical activity of surrounding tissue. Preclinical studies have demonstrated minimal endothelial disruption with cryoablation and virtually no overlying thrombus formation. Furthermore, sudden dramatic rises in impedance at the tip/tissue interface do not occur with cryoablation, as sometimes happens with radiofrequency ablation. This translates into a much lower risk of barotrauma and cardiac perforation.

**Cryoadhesion**

As the tissue is cooled below freezing, the tip of the catheter adheres to it. Once the tip has adhered, it does not dislodge. Cryoadhesion provides greater catheter stability, especially important when working around critical structures such as the AV node. In addition, the catheter tip will not dislodge with the termination of the tachycardia or with pacing maneuvers.

**How the Cryotherapy System Works**

The cryoablation catheter is a 7F steerable multipolar catheter similar in appearance and handling characteristics to a standard radiofrequency ablation catheter, though its mode of action is quite different. Pressurized liquid nitrous oxide is delivered to the tip of the catheter from the cryoconsole through an ultra-fine, robust injection tube. Before it is released into the tip expansion chamber, it is further pressurized as it encounters a restriction tube at the distal end of the injection tube. The restriction tube is designed to maximize the temperature drop of the refrigerant prior to entering the expansion chamber. Cooling occurs as a result of the Joule Thompson effect (whereby a decrease in pressure brings about a drop in temperature). As the refrigerant enters the tip expansion chamber (maintained under vacuum) and comes into contact with the tip surface, a liquid-to-gas phase change occurs. The cold liquid refrigerant evaporates as it absorbs heat from the tip that is in contact with the tissue. While tissue and blood flow act as a heat source, the tip of the catheter acts as a heat sink. The warmed vapor is returned to the console through a lumen maintained under vacuum. While there is minimal ice formation around the tip of the catheter, it quickly melts away as soon as the cryo application is terminated; therefore, it poses no threat of breaking off and occluding small vessels.

Multiple features are built into the catheter-console system to ensure safety. The system is always under vacuum – a failsafe that enables it to detect fluid ingress and stop the procedure. Multiple connector checks confirm that everything is properly connected prior to use. A sophisticated algorithm monitors the flow of the refrigerant and return vapor and halts the injection if the flow surpasses normal parameters. A vent system in the console draws back the liquid refrigerant after each injection.
The Clinical Utility of Cryoablation

Of the many hundreds of thousands of catheter ablation procedures performed annually in patients with supraventricular tachycardia, approximately 150,000 involve ablation near the AV node and His bundle. This group is comprised of individuals with AV nodal reentrant supraventricular tachycardia, patients with mid-septal, antero-septal or para-Hissian accessory pathways, and others with focal atrial tachycardia arising near the compact AV node. During radiofrequency catheter ablation in the peri-nodal region, application of RF current usually provokes an accelerated junctional rhythm that impairs one’s ability to monitor anterograde AV conduction during the ablation. Transient AV block, which can be difficult to detect, occurs in 3% to 5% of patients undergoing such procedures. Even if radiofrequency current application is terminated promptly when AV block is first detected, 1% to 2% of patients will be left with persistent complete or high-grade AV block, necessitating implantation of a permanent pacemaker. This is a dreaded complication, particularly in young patients whose target arrhythmia may be troublesome but not life-threatening. In contrast to radiofrequency catheter ablation, cryoablation in the peri-nodal region does not provoke accelerated junctional rhythm, enabling the electrophysiologist to monitor anterograde AV conduction closely throughout the ablation procedure. If AV block appears during cryoablation, it uniformly resolves, usually within a few seconds, as soon as cryoablation is halted. This feature, along with the exceptional catheter stability that stems from cryoadhesion, helps to make cryoablation in the peri-nodal region effective and extremely safe. Worldwide clinical experience with cryoablation of AV nodal re-entrant SVT now probably exceeds several thousand patients and yet not a single case of inadvertent AV block requiring permanent pacemaker implantation has been reported. Similarly, cryoablation has proven safe and effective for patients with midseptal or anterosepal accessory pathways, including patients who have failed a prior attempt at RF ablation or patients in whom RF ablation was not attempted because of concern for damage to the compact AV node and His bundle. For patients undergoing ablation in the peri-nodal region, where one faces a significant risk of inadvertent AV block, catheter cryoablation offers an effective and very safe alternative.

The list of arrhythmias that are suitable targets for catheter cryoablation continues to expand. This approach has proven effective in patients with the permanent form of junctional reciprocating tachycardia in whom a decrementally conducting accessory pathway functions as the retrograde limb of the re-entry circuit. Such accessory pathways frequently prove to be right posteroseptal in location, sometimes arising within the coronary sinus or middle cardiac vein. RF application at such sites may be hampered by high impedance or may damage the right coronary artery which courses through this region. Catheter cryoablation is ideal in such circumstances because of less risk of damage to the coronary arteries and the fact that low blood flow, particularly in the middle cardiac vein, actually augments rather than impedes cryoablation. Catheter cryoablation of common atrial flutter appears to be just as effective acutely and over the long-term as RF ablation, and has the advantage of causing much less patient discomfort when applied to the cavotricuspid isthmus as compared with RF ablation. Isolation of pulmonary veins by cryoablation has been shown to be feasible during ablation of atrial fibrillation (AF) and appears to be associated with a lower long-term risk of pulmonary vein stenosis compared with RF ablation. The safety and efficacy of catheter cryoablation in patients with AF is now being evaluated in a multicenter prospective clinical trial. All of these encouraging results suggest that catheter cryoablation will become an increasingly important arrow in the interventional electrophysiologist’s ablation quiver.

References


