

Cryoablation of Accessory Pathways: Incremental Insights on the Way Toward a Therapeutic Panacea?

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Editorial Comment

The heart has reasons that reason does not understand.

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Compared with ablation strategies that result in tissue hyperthermia, cryoablation results in minimal tissue disruption, low risk of thrombosis, excellent demarcation of injured tissue, and preservation of tissue tensile strength. These features should be especially beneficial where arrhythmia substrate is most proximate to vulnerable structures—the specialized atrioventricular (AV) conduction system, the parietal portion of cardiac veins, and the coronary arteries. These concerns are intuitively heightened in smaller hearts. Cryoablation carries additional benefits: Cryoadhesion ensuring catheter stability;¹ and greater potential for reversibility of damage. However, early experience suggests that the price paid for these benefits is lower acute success rates and higher recurrence rates,^{2,3} at least in patients with AV nodal reentry tachycardia and AV reciprocating tachycardia. In this issue of the *Journal*, Kaltman *et al.*⁴ examine their experience with catheter cryoablation of right-sided accessory pathways with special attention to methodological features that may explain some of that “price paid.”

Basic Science of Muscle Cryoablation

When rapidly cooled by contact with a catheter or probe whose temperature is -60° to -70° C, a well-demarcated elliptical hemispheroid of frozen tissue (so-called “ice ball”) develops.⁵ By electron microscopy of skeletal muscle, three histopathological phases are identified. During the “freeze” portion of the “freeze/thaw phase,” intracellular ice crystals (extracellular in border regions) appear, which do not cause membrane disruption. Immediately upon thawing, mitochondria are enlarged and their cristae disrupted. After 10 minutes, distended vesicles appear in the endoplasmic reticulum and transport capacity is lost. By 1 hour, dissolution of myofilaments is evident, and mitochondrial membranes undergo lipid peroxidation with loss of oxidative phosphorylation. By 48 hours, the “hemorrhagic and inflammatory phase” is established, with classic coagulation necrosis. Edema, inflammatory cell infiltration, small areas of hemorrhage, and early capillary ingrowth are present. The “replacement fibrosis phase,” at 2 to 4 weeks, shows dense collagen and fat and a

peripheral rim of small vessels. Even early during this overall sequence, blood flow adjacent to lesions is unperturbed.

Lesion size is determined by catheter temperature, size of the contacting probe (catheter tip), duration of probe contact, and duration and number of freeze/thaw cycles. Larger lesions result from lower temperatures, but lesion size plateaus after about 5 minutes of energy delivery,^{6,7} irrespective of the minimum temperature. Repetitive freeze/thaw cycles may also expand lesion size,^{8,9} probably due to accelerated rate of cooling with successive exposures, possibly related to changes in microcirculation. More recent work using a tissue bath model confirmed the importance of catheter size but also showed the importance of contacting electrode orientation, convective warming, electrode contact pressure,¹⁰ and time to electrode rewarming.¹¹

How Cold? How Long?

In 1977, Harrison *et al.* were the first to apply a cryoprobe to the human AV node in the operating room.¹² They demonstrated reversible AV block after 30 seconds at 0° C, and permanent block with two 90-second applications at -60° C. In patients with intractable supraventricular tachycardia, successful interruption of AV conduction was achieved in 77% to 85% of patients in subsequent reports.^{13,14} More than 20 years passed before a transvenous cryoablation catheter was systematically evaluated in a canine model of AV block. In 1999, Dubuc *et al.* used what at the time was a novel catheter (Cryocath, Montreal, Canada) and Freon[®] (dichlorofluoromethane) as the refrigerant to show that completely reversible AV block would develop at -20° to -30° C, with no acute or chronic pathological changes.¹⁵ Using Genetron AZ-20[®] as a refrigerant to achieve temperatures of -60° C for 5 minutes, permanent AV block could be created, but usually requiring two freeze/thaw cycles.

As with cryoablation of the AV node, the first experience with cryoablation of accessory AV connections in the human was in the operating room using hand-held probes. In 1977, Gallagher described successful epicardial ablation in two patients having AV connections.¹⁶ Modest hypothermia (0° C) of a concealed septal pathway resulted in transient interruption in conduction. Two applications of temperatures of -60° C were permanently successful. Guiraudon’s remarkable series¹⁷ in which 104 of 105 accessory pathways were successfully ablated confirmed the efficacy of this technique but did little to refine our understanding of temperature and duration thresholds. Indeed, in the surgical era, cryoablation of accessory pathways did not include much effort at titrating energy in order to minimize damage to adjacent structures. Uncertainty regarding the subepicardial depth of the accessory pathway, the existence of the epicardial fat pad, and especially the surgeon’s ability to visualize the coronary arteries mitigated such efforts.

These animal and human experiences have evolved into a strategy of so-called cryomapping (Dubuc used the term “ice mapping”) for a duration and at a temperature thought to be diagnostic for target substrate identification, but at temperatures (about -30°C) not thought to be permanently damaging to that tissue. However, in clinical practice, this method of cryomapping is being applied to a substrate, accessory pathways, for which it was not originally researched. The AV node is immediately endocardial, whereas accessory AV connections are variably epicardial to the annulus fibrosus.^{18,19} It should come as no surprise, then, that temperatures of $\geq 30^{\circ}\text{C}$ interrupted accessory pathway conduction in only 3 of 25 patients in Kaltman’s series.

The subliminal take home message from this series—and from the many reports upon which it was built—is that the time duration required for interruption of accessory pathway conduction may be more important than the absolute temperature at which this event occurs. If this was not the case, then the many published reports in which cryoablation was *not even attempted*, unless the desired end-point was reached by -25°C to -30°C , should have boasted lower recurrence rates than the current series. Such is not the case.

This article is not without its faults. As acknowledged by Kaltman, a major caveat to their main conclusion is that they used 6 mm tip catheters versus 4 mm in most prior series.²⁰⁻²³ *In vitro* studies¹⁰ have shown that a larger cooling electrode promotes lower tissue temperature and larger lesion size, compared with a smaller one. That said, it is difficult to reason how the above conclusions would not also apply to the smaller electrode.

Accessory Pathway Locations

The choice of right-sided pathways in this article is tied to the retrospective nature of this series and the attendant selection bias. There is little anatomic similarity among right free wall, posteroseptal, midseptal, and anteroseptal accessory pathways with respect to their relationships to coronary arteries; and there is little predictability as to their epicardial depth. Moreover, convective warming, as an important predictor of lesion size,¹⁰ potentially makes septal pathways more amenable to cryoablation than do free wall pathways. In that respect, right and left free wall pathways may have more in common than do right free wall and posteroseptal pathways. Similarly, considering the importance of electrode orientation with respect to tissue contact, annular locations that inherently avail themselves to tangential catheter placement (e.g., posterior mitral annulus from a transseptal approach) may also be more prone to successful cryoablation. Generalizing the results of this article, then, to specific accessory pathway locations is probably not reasonable.

The Other Side of the Equation

When considering permanent AV block, the safety record of catheter-based cryoablation is beyond reproach. However, this is based largely upon the cryomapping paradigm. There is less experience with a lower temperature model. Even using a short time to effect model (25 seconds), as employed in Kaltman’s article, one could conjure coincident circumstances that could make the AV node invisibly vulnerable: A markedly preexcited midseptal accessory pathway, necessity

to ablate while in sinus rhythm, and a very brief temperature response time. These very cases promoted interest in cryoenergy over radiofrequency in the first place. From the Pediatric Radiofrequency Registry, we know that early experience with septal pathways resulted in a high incidence of permanent AV block—10% for midseptal pathways.²⁴ As we once retreated from “full energy” radiofrequency application with such hedges as “test burns,” are we not now filling that “risk void” with direct low temperature cryoenergy application in order to improve success rates and lower recurrence rates? Probably not, but this epochal dance we do in clinical medicine is clearly not yet spent.

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