DOI: 10.1111/jce.13987

EDITORIAL–INVITED

WILEY

# "A Song of Ice and Fire"—another verse from the world of ablation

J. Philip Saul MD[1] | Martin J. LaPage MD, MS[2]

[1]Department of Pediatrics, West Virginia University School of Medicine, Morgantown, West Virginia

[2]Division of Pediatric Cardiology, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan

**Correspondence**
J. Philip Saul, MD, Department of Pediatrics, West Virginia University School of Medicine, PO Box 9214, Morgantown, WV 26506-9214.
Email: sauljp9@gmail.com

**Disclosures:** None

**Funding information**
National Institutes of Health, Grant/Award Number: 1UG1HD090899-01

**Abstract**

The debate between the use of radiofrequency (RF) or cryoenergy for ablation near the atrioventricular (AV) conducting system or small coronaries has been fueled by the relative efficacies and risks of the two technologies, particularly in smaller hearts. The manuscript by Schneider et al adds another chapter to that ongoing debate.

In this issue of the Journal, Schneider et al[1] continue to enhance our knowledge of the effects of catheter ablation on various cardiac structures both immediately and longitudinally. Adding to an over 20-year history of excellent and similarly focused research from Dr. Paul's laboratory, the current study examines the late effects of "freeze-thaw-freeze" cryoablation applications on the adjacent coronary arteries. Prior studies from the same group have evaluated both acute and late effects of radiofrequency (RF) and cryoablation on the coronaries. This latest study incorporates the widely utilized technique of repetitive cryoablation applications at a target site to maximize efficacy.

Schneider et al[2] find in their porcine model that there were no identifiable coronary effects by angiography or intracardiac ultrasound (ICUS), either acutely or at 6 month follow-up. However, pathological examination at 6 months did demonstrate very mild effects on the coronaries in two of 29 lesions, including mild medial and adventitial thickening, minimal intimal proliferation, and a small intraluminal thrombus at one site of intimal proliferation. Though potentially relevant clinically, these findings are far less concerning than the clearly concerning coronary issues found in this group's and others past studies using RF energy in both animals and humans.[3]

An Invited Editorial on: Schneider H. et al "Double cryoenergy application (freeze-thaw-refreeze) at growing myocardium"

The lack of more than minimal effects in the current study add to the growing list of evidence that cryoablation is a considerably safer technique than RF ablation. Minimal late effects on the coronaries (even with a freeze-thaw-freeze technique), can be added to lesion reversibility, catheter adherence during freeze, decreased thrombus formation, and extremely low risk of inadvertent permanent damage to the conduction system as benefits of cryoablation vs RF. In fact, during an audience survey after a May 2019 debate sponsored by the Pediatric and Congenital Electrophysiology Society (PACES) with 180 electrophysiology health care providers present, not one provider reported more than a 2-week period of complete AV block after cryoablation, supporting the absence in the literature of any patient requiring permanent pacing for a cryo application delivered to treat atrioventricular nodal reentry tachycardia (AVNRT) or an accessory pathway (AP).

Even with a higher safety profile, cryoablation has faced an uphill battle to be accepted as the preferred ablation modality for ablation near vital structures like the AV conduction system or small coronaries. The most prominent barrier has been the early clinical studies on transcatheter cryoablation, which showed decreased efficacy and higher recurrence rates vs RF ablation for typical substrates such as AVNRT or an AP. However, the two techniques were in different stages of development, and since these initial studies, the technique of cryoablation application has evolved with

 © 2019 Wiley Periodicals, Inc. 

larger catheter tips, varying application durations and strategies, and the addition of the freeze-thaw-freeze technique to name just a few, all enhancing the learning curve. Consequently, these early studies are essentially irrelevant in light of modern practice. In fact, a current review of the literature shows that with more contemporary approaches to cryoablation of AVNRT, including the use of a freeze-thaw-freeze cycle, the combined acute and late failure risk for pediatric patients has gone from around 16% to 4%, similar to RF. Despite this evolution, proponents of RF over cryoablation and even guidelines statements, continue to reference these early studies in their assessment of efficacy, which is often prioritized over safety.

In light of the current study, the freeze-thaw-freeze technique is of particular interest. For pediatric electrophysiologist utilizing cryoablation, the technique commonly used seems to be a pattern of (a) cryoapplication for 4 to 6 minutes, (b) brief thawing period (15-60 seconds) and (c) reapplication of cryoablation at the same site, ideally identified by a three-dimensional mapping technique. If the patient is mechanically ventilated, a held expiration before the end of the freeze and continued through the thaw period can help assure the second freeze is in the same location. The use of a triple freeze technique has also been reported.[4] Although Schneider et al[1] credit the application of the freeze-thaw-freeze approach to Drago in 2006,[5] the authors in that paper seemed to be using a "bonus" application added to the site of success 30 minutes after the initial cryoablation application, rather than the freeze-thaw-freeze cycle used by Schneider. From a review of the multiple cryoablation papers published in the surrounding years, no paper before the triple freeze cycle reported in 2013[4] specifically focuses on the double freeze technique, however, between 2005 and 2015, the technique became commonly utilized. Nonetheless, it is still not universally applied by pediatric or adult electrophysiologists.

Somewhat puzzling, is why it took so long to adapt a cryoablation application strategy shown to be advantageous 40 years earlier. One of the earliest publications systematically studying the use of repeated freeze-thaw cycles (for cancer treatment) can be found in the 1968 Nature article by Gill et al,[6] in which they demonstrate clearly that repeated applications create larger lesions than single applications. Likely, as knowledge of the pathobiology of cryoablation grew along with a better understanding of the preclinical literature, the technique changed to the current freeze-thaw-freeze method.

Larger lesions improve efficacy, but simultaneously have the potential to increase the risk of collateral damage to adjacent structures. Hence, the interest of Schneider et al[1] to clarify the potential for coronary artery damage. In clinical practice, it is easy to see the immediate effects of cryoablation delivered too close to the conduction system and terminate the application while the effect remains reversible; however, it is not possible to be forewarned about coronary artery damage during a cryoablation or RF ablation before potentially serious complications occur.

There are many animal studies and numerous clinical reports demonstrating the potential for coronary damage during RF ablation. In fact, using a prospective imaging approach, Schneider and colleagues found a 2% risk of producing coronary artery narrowing in pediatric patients undergoing RF ablation for an accessory pathway.[2] The clinical incidence of coronary artery damage using RF ablation is mostly in case reports; however, it has occurred often enough to lead to at least two separate reviews.[7,8] Alternatively, despite extensive use of cryoablation in the posterior septum, literature evidence for cryoablation catheter damage to the coronaries is essentially limited to that of Schneider and colleagues' laboratory work, and a single case report of transient coronary spasm.[9]

How is it that tissue damage effects are quite different at the coronary artery when comparing the two modalities? In addition to the known shrinkage effects on elastic tissue with heating and RF, which are not present with cooling and cryoablation, we hypothesize that the protection of the coronary arteries also results from a more rapid thawing phase of the cryoablation cycle. The thawing phase of the freeze-thaw cycle has an even more prominent impact on tissue death than the freezing phase; slower thawing is more damaging.[10] Cryoablation lesions in high blood flow areas are shown to be smaller than low flow areas.[11] The blood flow through the coronary likely acts as a continuous rewarming circuit, thereby not allowing for full freeze at the endothelium and rapid thawing once the lesion is complete, attenuating effects at the vessel wall.[12] Of course, it is likely that these same coronary warming effects are also decreasing the efficacy of cryoablation to eliminate APs at adjacent sites.

Primum non nocere—first, do no harm—the well-known mantra of the physician should come to mind when weighing the evidence for cryoablation vs RF ablation. For the pediatric patient especially, where adjacent structures are in closer proximity and adverse consequences hold more serious life implications, prioritization of safety over efficacy should be standard. The Schneider study shows that even cryoablation can have minor coronary effects, but quite minimal in comparison with RF. Nonetheless, this added evidence for cryoablation safety may still not sway the minds of those practitioners who have long concluded that it is a less effective modality. Some feel that "in their hands" RF ablation is definitely safe, perhaps even after never evaluating the nearby coronaries. Of course, as stated above, most RF-related coronary injury is silent, and fortunately even with RF, complete AV block is rare.

For those that favor cryoablation for selected substrates to limit procedure risk, this study is just another satisfying reference in a growing body of evidence. For now, the cryoablation vs RF ablation battle will carry on. Unlike the popular television series, this will not be the final season for the Game of Ablations!

## ORCID

*J. Philip Saul* http://orcid.org/0000-0001-7582-677X

## REFERENCES

1. Schneider HP, Stahl M, Schillinger W, et al. Double cryoenergy application (freeze-thaw-freeze) at growing myocardium: lesion

volume and effects on coronary arteries late after energy application. Implications for efficacy and safety in pediatric patients. *J Cardiovasc Electrophysiol*. 2019;30(7):1137-1144.
2. Schneider HE, Kriebel T, Gravenhorst VD, Paul T. Incidence of coronary artery injury immediately after catheter ablation for supraventricular tachycardias in infants and children. *Heart Rhythm*. 2009;6(4):461-467.
3. Paul T, Bökenkamp R, Mahnert B, Trappe HJ. Coronary artery involvement early and late after radiofrequency current application in young pigs. *Am Heart J*. 1997;133(4):436-440.
4. Qureshi MY, Ratnasamy C, Sokoloski M, Young ML. Low recurrence rate in treating atrioventricular nodal reentrant tachycardia with triple freeze-thaw cycles. *Pacing Clin Electrophysiol*. 2013;36(3): 279-85.
5. Drago F, Silvetti MS, DeSantis A, Grutter G, Andrew P. Lengthier cryoablation and a bonus cryoapplication is associated with improved efficacy for cryothermal catheter ablation of supraventricular tachycardias in children. *J Interv Card Electrophysiol*. 2006;16(3):191-198.
6. Gill W, Fraser J, Carter DC. Repeated freeze-thaw cycles in cryosurgery. *Nature*. 1968;219(5152):410-413.
7. Pothineni NV, Kancharla K, Katoor AJ, et al. Coronary artery injury related to catheter ablation of cardiac arrhythmias: a systematic review. *J Cardiovasc Electrophysiol*. 2019;30(1):92-101.
8. Castano A, Crawford T, Yamazaki M, Avula UM, Kalifa J. Coronary artery pathophysiology after radiofrequency catheter ablation: review and perspectives. *Heart Rhythm*. 2011;8(12): 1975-1980.
9. Miyazaki S, Ichihara N, Takagi T, Iesaka Y. Coronary artery spasm during cryothermal cavotricuspid isthmus ablation. *J Cardiovasc Electrophysiol*. 2015;26(9):1019-1020.
10. Iwasawa J, Miyazaki S, Takagi T, et al. Cavotricuspid isthmus ablation using a catheter equipped with mini electrodes on the 8 mm tip: a prospective comparison with an 8 mm dumbbell-shaped tip catheter and 8 mm tip cryothermal catheter. *Europace*. 2016;18(6):868-872.
11. Baust JG, Gage AA. The molecular basis of cryosurgery. *BJU Int*. 2005;95(9):1187-1191.
12. Pilcher TA, Saul JP, Hlavacek AM, Haemmerich D. Contrasting effects of convective flow on catheter ablation lesion size: cryo versus radiofrequency energy. *Pacing Clin Electrophysiol*. 2008; 31(3):300-307.

**How to cite this article:** Saul JP, LaPage MJ. "A Song of Ice and Fire"—another verse from the world of ablation. *J Cardiovasc Electrophysiol*. 2019;30:1135-1137. https://doi.org/10.1111/jce.13987