Intracardiac ablation for atrioventricular nodal reentry tachycardia using a 6 mm distal electrode cryoablation catheter: Prospective, multicenter, North American study (ICY-AVNRT STUDY)

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Abstract

Introduction: Radiofrequency (RF) ablation is effective for slow pathway ablation, but carries a risk of inadvertent AV block requiring permanent pacing. By comparison, cryoablation with a 4-mm distal electrode catheter has not been reported to cause permanent AV block but has been shown to be less effective than RF ablation. We sought to define the safety and efficacy of a 6-mm distal electrode cryoablation catheter for slow pathway ablation in patients with atrioventricular nodal reentry tachycardia (AVNRT).

Methods and results: Twenty-six U.S. and eight Canadian centers participated in the study. Patients with supraventricular tachycardia (SVT) thought likely to be AVNRT were enrolled. If AVNRT was inducible and confirmed to be the clinical SVT, then the slow pathway was targeted with a cryoablation catheter using a standardized protocol of best practices. Acute success was defined as inducibility of no more than one echo beat after cryoablation. Primary efficacy was defined as acute success and the absence of documented recurrent AVNRT over 6 months of follow-up. Primary safety was a composite of serious procedure-related adverse events and/or device-related complications. Note that 397 subjects met enrollment criteria after the EP study and received cryoablation. Mean ablation procedure duration (including a waiting period) was 89 ± 40 minutes, and mean fluoroscopy time was 4.8 ± 5.9 minutes. Isoproterenol was...
administered before cryoablation in 53% and after the last lesion in 85% of cases. Acute procedural success was realized in 95% (378 of 397) of subjects. No subject received a permanent pacemaker due to AV block. The slow pathway could not be ablated in 19 subjects, including: 12 due to inefficacy, 2 due to transient AV block, and 5 due to both inefficacy and transient AV block. RF ablation was used in the same procedure in 11 of 19 failed subjects, and was ineffective in 3 subjects. Among the group with acute success, 10 subjects (2.7%) had documented recurrent AVNRT over the 6-month follow-up period, and all occurred within 3 months of the index cryoablation. Serious procedure-related adverse events occurred in 4 subjects (1.0%), including one each: tamponade, pulmonary embolism, femoral vein hemorrhage, and diagnostic EP catheter knotting. None of these serious adverse events were related to use of the cryoablation catheter. Overall, 93% of subjects had successful slow pathway ablation at 6 months with the study cryoablation catheter.

Conclusions: Cryoablation for AVNRT using a focal 6-mm catheter was safe and effective. It resulted in a low risk of recurrence over 6 months of follow-up with no incidence of AV block requiring permanent pacing.

KEYWORDS
arrhythmias, atrioventricular block, atrioventricular reentrant tachycardia, catheter ablation, cryoablation, radiofrequency ablation

1 INTRODUCTION

There are 89,000 new cases of supraventricular tachycardia (SVT) annually in the United States,1 and atrioventricular nodal reentrant tachycardia (AVNRT) is the most common mechanism.2 When treatment by catheter ablation is necessary, radiofrequency (RF) ablation is effective for slow pathway ablation but carries a risk of complete heart block necessitating permanent pacing.3 Cryothermal ablation offers the ability to test the efficacy and safety at a site before permanent lesion creation. Furthermore, it allows a stable catheter position due to adherence of the tip at the site of interest after a critically low temperature has been reached (cryoadherence).

The first cryocatheter approved by the FDA for slow pathway ablation with a 4-mm distal electrode was safe but not as effective when compared with RF ablation.4 A cryocatheter with a 6-mm distal electrode was developed with the goal of making larger lesions,5 and it was found to be more effective than the original.6,7 When these larger catheters were compared with RF ablation, acute efficacy was similar but recurrence rates were still higher8–12; however, the usage of a best practices methodology was not mandated in these studies. The ICY-AVNRT study (NCT01426425) was undertaken to test the hypothesis that incorporating best practices would result in safety and efficacy similar to that reported with RF ablation.

2 METHODS

The ICY-AVNRT study was a prospective, multicenter single-arm study conducted using the 6 mm distal electrode cryoablation catheter (Freezor Xtra; Medtronic, Minneapolis, MN, USA). Participating sites included 26 centers in the United States and eight centers in Canada. The study was designed in cooperation with the FDA and approved by the institutional review board of each center. Safety and efficacy events were adjudicated by an independent physician committee. The study design is depicted in Figure 1. Patients met the inclusion criteria for study enrollment if they had documented SVT thought to be AVNRT (documented by ECG, trans-telephonic, Holter, or event monitors). Patients were excluded if they had any of the following: (1) history of a sustained ventricular tachyarrhythmia, (2) presence of another supraventricular arrhythmia that could be confused with AVNRT during the follow-up period, (3) a reversible cause of SVT, (4) a previous ablation for AVNRT, (5) amiodarone therapy within the preceding 90 days, (6) unstable angina/myocardial infarction/open heart surgery in the preceding 60 days, (7) New York Heart Association (NYHA) class III or IV heart failure within the preceding 90 days, (8) the presence of a permanent implantable cardiac rhythm device (including loop recorders), (9) history of AV conduction disturbances including first/second/third degree AV block or left bundle branch block, (10) stroke or transient ischemic attack in the last 6 months, (11) life expectancy less than 12 months, (12) pregnant state, (13) unwilling/unable to provide informed consent, (14) unwilling/unable to comply with follow-up visits, (15) age less than 18 years, (16) active infection, (17) history of cryoglobulinemia, (18) contraindications to intracardiac catheter manipulation, or (19) participation in another investigational trial that could confound the results.

2.1 Screening electrophysiology study

Patients meeting the study criteria and giving informed consent were assigned to an invasive electrophysiological evaluation. A complete baseline electrophysiology study was performed, including decremental atrial and ventricular pacing as well as single and double atrial and ventricular extrastimuli. If sustained SVT was not induced, then alternate site pacing was performed. Alternatively, the level of sedation was diminished or medications administered (usually isoproterenol) followed by repeat stimulation. When sustained SVT was induced,
it was evaluated to prove that the mechanism was indeed AV node reentry, thereby satisfying the secondary inclusion criteria. Secondary exclusion criteria resulted in the patient exiting the study and receiving therapy outside of the study at the discretion of the investigator, including: (1) the induction of other supraventricular tachyarrhythmias that might be confused with AVNRT during follow-up and/or require treatment during the study period, (2) the presence of an accessory pathway, (3) the induction of a sustained ventricular tachyarrhythmia, (4) abnormalities of AV conduction, or (5) any indication for implantation of a permanent pacemaker or defibrillator. Subjects meeting the secondary inclusion criteria but none of the secondary exclusion criteria were assigned to undergo ablation of the slow AV nodal pathway using the study catheter. The type of anesthesia, usage of heparin, long sheaths, and/or 3-D mapping were all at the discretion of the investigator.

2.2 Cryoablation procedural best practices

All patients had both coronary sinus and His bundle catheters placed to fluoroscopically define Koch’s triangle. The usual anatomic area of the slow pathway was explored. Sites chosen for ablation were at the discretion of the investigators. Some targeted sites were those typically selected during RF ablation: low frequency and low amplitude atrial electrogram between the coronary sinus ostium and the septal leaflet of the tricuspid valve as previously published.13,14 Other targeted sites included those typically thought to be closer to the compact AV node: higher up the septum and with larger atrial electrograms, as previously published.15 Cryomapping using the temperature plateau feature was not allowed in this study, and the target temperature was \(-75^\circ C\) for every cryothermal delivery. Energy was delivered during AVNRT or during sinus rhythm with programmed stimulation. Acceptable “time-to-effect” was defined as either termination of AVNRT in the slow pathway within 60 seconds or by evidence from programmed electrical stimulation within 60 seconds that the slow pathway was gone or would no longer support AVNRT. If after 60 seconds, the slow pathway function was adjudicated to still be adequate for AVNRT, then power was discontinued, and the catheter was moved to a different location. If during freezing, the slow pathway would no longer support AVNRT, then freezing was continued for 240 seconds unless AV block was observed. The anatomical location by fluoroscopy and electrogram atrial-to-ventricular ratio of this presumed successful site were documented. After thawing to body temperature, another 240 seconds of cryoenergy was delivered at the identical site (using fluoroscopic location, 3-D mapping, and/or electrogram characteristics) while again observing for AV block.

The second cryothermal delivery was delivered to the presumed effective site unless AV block had occurred during the first delivery. All episodes of AV block were classified by type and duration. Additional closely adjacent lesions (to enlarge the area of ablation) were made at the discretion of the investigator. Repeat programmed stimulation was then performed. Mapping and ablation continued until no more than a single echo beat remained, unless the operator felt that the slow pathway could not be ablated without AV block. Repeat stimulation after a 30-minute waiting period was required, and the use of isoproterenol was encouraged after the last cryoablation lesion before the procedure was deemed complete. If acute success could not be safely achieved, the operator was free to pursue alternative treatments. Subjects left with more than a single echo beat as well as those receiving alternative ablation with a non-study catheter were considered acute treatment failures.

2.3 Follow-up

A phone interview was performed 8 days after hospital discharge. In-person visits were made at 1, 3, and 6 months. If the subject received outside medical evaluation or treatment, the records were obtained. Any potential adverse side effect was thoroughly investigated and adjudicated by an independent physician committee. The same committee adjudicated any suggestion of an arrhythmia recurrence by reviewing the patient records and/or the results of event monitoring.

2.4 Endpoints

Acute procedural success was defined as no more than a single echo beat after ablation using only the study catheter with or without infusion of isoproterenol. If induction of AVNRT in the baseline state required isoproterenol, its usage after ablation was mandated; otherwise, isoproterenol usage was encouraged. The primary efficacy
The endpoint (chronic success) was a composite of acute success and the lack of documented recurrent AVNRT during the 6-month follow-up period. The primary safety endpoint was defined as a lack of a serious procedure-related or serious device-related adverse event during the study period. Serious adverse events were defined as those events resulting in death, life-threatening illness, injury or permanent damage, impairment of a body structure, or any disorder necessitating invasive therapy or resulting in a prolongation of hospital stay. Adverse events were adjudicated to be procedure-related, device-related, or unrelated.

2.5 | Statistical analysis

A sample size of 353 subjects undergoing the cryoablation procedure and followed for at least 6 months provided 90% power at a type I error level of 0.025 to test the primary efficacy endpoint of the study. The primary endpoints and performance criteria were based on a prior study utilizing a 4 mm electrode cryoablation catheter and published literature for cryoablation and RF treatment of AVNRT. The sample size calculation was estimated using a 6-month efficacy success rate of 89% with performance criteria threshold of >83%. To account for attrition prior to 6 months, the study sample size was estimated at 400 patients. The power (to test the primary safety endpoint) was greater than 90% based on an estimated serious adverse event rate of 3% and a performance criteria threshold of less than 7%. Kaplan–Meier methods were pre-specified and utilized to calculate the 6-month efficacy rate, 6-month safety event rate, and corresponding 95% confidence intervals. The primary analysis population was a modified intent-to-treat cohort (Fig. 2), and it included those subjects who met all inclusion criteria but none of the exclusion criteria (pre- and post-electrophysiology study) and underwent a cryoablation procedure. Baseline and procedure data are summarized using mean and standard deviation values for continuous measures and counts with percentages for categorical responses. The data analyses were generated using SAS/STAT software (2012 SAS Institute version 13.1; Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

The disposition of study subjects is depicted in Figure 2. Total enrollment included 572 patients, of which 550 underwent the screening electrophysiology study. The electrophysiology study excluded 151 patients, and 399 subjects were assigned to treatment with the study catheter. Two patients did not receive treatment at the

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**FIGURE 2**  Patient disposition and outcomes. Total study enrollment was 572 subjects, of which 550 subjects underwent the screening study. In total, 399 subjects were assigned to treatment with the study catheter.
discretion of the investigator, leaving 397 subjects to constitute the treatment group. The baseline characteristics of the group are depicted in Table 1. Females comprised 70% of the group, and the mean age was 53 years old, with Caucasian patients making up 89% of the group. Baseline demographics showed the presence of coronary artery disease in 4.8%, mild valvular heart disease in 8.5%, hypertension in 30%, and previous heart surgery in 6.5% of the cohort. Only one patient had undergone a previous ablation, and it was for atrial fibrillation. Documentation of SVT was by surface ECG in 79%, event monitoring in 12%, and Holter monitoring in 8% of cases. Mean SVT cycle length was $345 \pm 65$ milliseconds, and more than 85% of the patients had experienced arrhythmic symptoms on at least a quarterly frequency per year. Arrhythmia suppression with antiarrhythmic drugs was attempted in 73% of patients. Antiarrhythmic drugs included beta blockers (54%), calcium antagonists (31%), and type I or type III drugs (5%).

### 3.2 Acute efficacy outcomes

The mean procedure time was $149 \pm 56$ minutes, which included the electrophysiology study, catheter ablation, 30-minute waiting period, and follow-up programmed stimulation. Total fluoroscopy time was $11.5 \pm 9.4$ minutes. The mean ablation procedure time was $89 \pm 40$ minutes with an ablation fluoroscopy time of $4.8 \pm 5.9$ minutes. Note that 3-D mapping systems were employed in 42% of cases, and long sheaths were used with 35% of cryoablation catheters. AVNRT was slow-fast in 95% of cases, and other atrial arrhythmias were induced in 5.8% of cases. Isoproterenol was administered before ablation in 53% of cases and after the last cryoablation in 85% of cases. Therefore, 32% of patients who did not receive isoproterenol before ablation received it after the last cryoablation lesion. Cryoablation was guided by programmed stimulation in 75% of attempts or delivered during AVNRT in 32% of attempts. Median nadir temperature was $-79^\circ C$ (IQR: $-77^\circ C$ to $-80^\circ C$). Repeat lesions at sites thought to be successful were delivered in 90% of the cases. The median number of cryoablation deliveries per patient was seven (IQR: 4 to 11). Of these, 36% were incomplete lesions (<60 seconds), and 64% were classified as lesions (>60 seconds). The 30-minute waiting period was performed in 96% of patients.

Acute procedural success was realized in 95% of cases. In total, 95% of subjects received two lesions at the successful site, and 52% of subjects received one or more lesions at closely adjacent sites. Among subjects with acute procedural success, dual AV nodal physiology was abolished in 72%. Zero echo beats were seen in 72% of those patients, with the remainder having a single echo beat. As depicted in Figure 3, the anatomical location of the successful site was above the level of the roof of the coronary sinus in 60% of subjects. The electrogram AV ratios at the successful sites are depicted in Table 2. In a significant proportion of patients, the successful ablation sites had higher AV ratios than those typically associated with successful RF ablation, and investigators were trained to consider targeting such sites after a previous study suggested this site to be safe and effective.  

**TABLE 1** Subject baseline characteristics

| Characteristic | Treatment Cohort (N = 397) |
|---------------|-----------------------------|
| Age (years)   | $53 \pm 14$ |
| Body mass index (lb/in$^2$) | $29 \pm 7$ |
| Female gender | 70% |
| Caucasian race | 89% |
| Hypertension | 30% |
| Pulmonary valve dysfunction | 1.5% |
| Coronary artery disease | 4.8% |
| Minor valvular heart disease | 8.5% |
| Previous heart surgery | 6.5% |
| Arrhythmic frequency | |
| Daily | 11% |
| Weekly | 27% |
| Monthly | 33% |
| Quarterly | 16% |
| Biannually | 10% |
| Yearly | 3.6% |
| Antiarrhythmic drug exposure | 73% |
| Beta blockers | 54% |
| Calcium antagonists | 31% |
| Type I or III | 4.8% |

*Continuous characteristics reported as mean ± standard deviation, categorical characteristics reported as percentage of patients having the characteristic.*

![Figure 3](image-url) **FIGURE 3** Anatomic location of successful sites. The anatomical location of the majority of successful lesions was above the level of the entrance of the coronary sinus.
### TABLE 2  Electrogram characteristics at successful cryoablation site

| AV ratio | Successful site (N = 378) |
|----------|---------------------------|
| ≥1.0     | 146 39%                   |
| 0.50–0.99| 79 21%                    |
| 0.21–0.49| 99 26%                    |
| ≤0.20    | 52 14%                    |

*aAV ratio not reported for two subjects.

Acute success was not realized in 19 subjects (4.8% of the treatment group). Reasons for failure included failure to ablate the slow pathway in 12 subjects, AV block in 2 subjects, and both in 5 subjects. Of these 19 subjects, 12 went on to alternative therapy, including: antiarrhythmic drugs in 1 subject and immediate RF ablation in 11 subjects. RF ablation catheters included a 4-mm distal tip in 9 subjects, a 5-mm distal tip in 1 subject, and an irrigated-tip in 1 subject. Outcomes of RF ablation included persistent inducibility of AVNRT in 3 subjects, transient complete AV block in 1 subject, and permanent first degree AV block in 1 subject. Therefore, 8 of 11 patients (73%) were deemed to have a satisfactory outcome following RF ablation.

### 3.3  Chronic efficacy outcomes

The course of treated subjects is depicted in the Kaplan–Meier analysis (Fig. 4). Among the 378 subjects with acute procedural success, recurrent SVT compatible with AVNRT was documented in 10 subjects (2.7%) over the 6-month follow-up period, with all failure events occurring within 3 months of their index cryoablation procedure. Therefore, overall clinical success was realized in 93% (95% CI: 90–95%) of subjects with the study catheter over the 6-month study period. Ten subjects with recurrent AVNRT during the 6-month follow-up period and 8 who failed the acute procedural success endpoint (and did not acutely cross over to RF ablation) were eligible for retreatment. Among these 18 subjects, 8 subjects had nine ablation procedures. Cryoablation was used in six cases (five cases using the 6-mm Freezor Xtra catheter) and three with RF catheter ablation. Acute procedural success was achieved in all nine procedures.

### 3.4  Safety outcomes

There were 24 total serious adverse events among the 397 subjects. However, only four events were adjudicated to be procedure-related, and none were adjudicated to be related to the use of the study catheter (Table 3). One subject developed tamponade from a diagnostic catheter, but surgical repair was not required. A second subject had bleeding from a femoral venous sheath, which resulted in prolongation of their hospital stay. A third subject had a knotting of a diagnostic catheter that did not require surgical removal. A fourth subject suffered a pulmonary embolus. Among the nonserious procedure-related

### TABLE 3  Procedure-related adverse events

| Adverse Event                  | No. of Events | Serious |
|--------------------------------|---------------|---------|
| All serious adverse events     |               |         |
| Tamponade                      | 1             | Yes     |
| Hemorrhage                     | 1             | Yes     |
| Catheter knotting              | 1             | Yes     |
| Pulmonary embolism             | 1             | Yes     |
| Relevant nonserious adverse events |             |         |
| Arteriovenous fistula          | 1             | No      |
| Nonoccurring adverse events    |               |         |
| Myocardial infarction          | 0             | NA      |
| Stroke or TIA                  | 0             | NA      |
| Permanent pacemaker            | 0             | NA      |
| Death                          | 0             | NA      |

NA = not applicable.
adverse events was one case of arteriovenous fistula. There were no procedure-related cases of myocardial infarction, stroke, transient ischemic attack, or death. Consequently, there were four safety events among 397 subjects, with a safety event rate of 1.0% (95% CI: 0.4% to 2.7%). Serious adverse events unrelated to the procedure or device can be found in the supplement section (Table 15).

3.5 | AV block

Baseline pre-ablation ECG showed right bundle branch block in 9 subjects, but none had first degree (PR interval ≥220 milliseconds) or higher degrees of AV block. During the cryoablation procedure, there were 150 cryoapplications (4.1% of all applications) that resulted in AV block or right bundle branch block that occurred in 101 subjects (25% of all subjects). The characteristics of these episodes are depicted in Table 4. The majority of episodes were first- or second-degree AV block, with 3.5% of subjects experiencing more than one type of block. Among the group with AV block, the highest degree of AV block was first degree in 31%, second degree in 48%, and third degree in 21%. Right bundle branch block without AV block was seen in a single subject in the group. First degree AV block persisted at the procedure end or was seen on the predischarge ECG in five of these 101 subjects. In 2 of the 5 subjects, it had resolved by the 1-month follow-up visit, and in an additional 2 subjects, it had resolved by the 3-month follow-up visit. First-degree AV block persisted beyond the 6-month follow-up visit in 1 subject. No subject was symptomatic, and none required permanent pacing.

3.6 | Best practices

Table 5 lists the best practices that were emphasized in this study and the adherence to those practices. In 75% of the attempts, cryoablation was guided by programmed stimulation, or delivered during AVNRT in 32% of the attempts. Median nadir temperatures during all freeze attempts achieved −79°C, and all freezing attempts targeted a temperature of at least −75°C. A repeat lesion at the site thought to be successful was delivered in 95% of subjects, and additionally, 52% of subjects received one or more additional lesions at a closely adjacent site. A 30-minute waiting period was performed in 96% of the subjects, and isoproterenol was administered after the last cryoablation site. A 30-minute waiting period was performed in 96% of the subjects, and isoproterenol was administered after the last cryoablation site. A repeat lesion at the site thought to be successful was delivered in 95% of subjects, and additionally, 52% of subjects received one or more additional lesions at a closely adjacent site. A 30-minute waiting period was performed in 96% of the subjects, and isoproterenol was administered after the last cryoablation site. A 30-minute waiting period was performed in 96% of the subjects, and isoproterenol was administered after the last cryoablation site.

TABLE 4 | Right bundle branch or atrioventricular block occurring during cryoablation

| Type of Blocka | Energy Applications Resulting in Block N (%) | Treated Patients Experiencing Block N (%) |
|----------------|---------------------------------------------|------------------------------------------|
| Block          | 150                                         | 101                                      |
| 1st AV         | 68 (45%)                                    | 44 (44%)                                 |
| 2nd AV         | 58 (39%)                                    | 50 (50%)                                 |
| 3rd AV         | 21 (14%)                                    | 21 (21%)                                 |
| RBB            | 1 (0.7%)                                    | 1 (1%)                                   |

aType of block not reported for two energy applications in 2 subjects.

TABLE 5 | List of best practices with references to seminal publications

| Best Practice | Usage | Goal |
|---------------|-------|------|
| Short time-to-effecta | 75% of attempts | Maximize proximity to slow pathway |
| - Guided by programmed stimulation | 32% of attempts | - |
| - Guided by termination of AVNRT | | |
| Rapid cooling and low freezing temperature at ablation siteb | 100% attempts target −7°C | Maximize lesion volume |
| Refreeze at a successful sitec | 95% of subjects | Consolidate the effective lesion |
| Create closely adjacent lesionsd | 52% of subjects | Enlarge volume of ablated tissue |
| 30-minute waiting period | 96% of subjects | Identify/treat early intraprocedural recurrence |
| Isoproterenol after last ablatione | 85% of cases | Identify/treat early intraprocedural recurrence |
| Target higher/more proximal sitesf | 39% of subjects | Maximize acute procedural success |
| Endpoint of zero echo beatg | 72% of successful cases | Minimize late recurrences |

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bWood MA, Parvez B, Ellenbogen AL, et al. Determinants of lesion sizes and tissue temperatures during catheter cryoablation. Pacing Clin Electrophysiol. 2007;30(5):644–654.
cPilcher TA, Saul JP, Hlavacek AM, Haemmerich D. Contrast effects of convective flow on catheter ablation lesion size: Cryo versus radiofrequency energy. Pacing Clin Electrophysiol. 2008;31(3):300–307.
dGill W, Fraser J, Carter DC. Repeated freeze-thaw cycles in cryosurgery. Nature. 1968;219(5152):410–413.
eLustgarten DL, Keane D, Ruskin J. Cryothermal ablation: Mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. Prog Cardiovasc Dis. 1999;41(6):481-498.
fHunt GB, Chard RB, Johnson DC, Ross DL. Comparison of early and late dimensions and arrhythmogenicity of cryolesions in the normothermic canine heart. J Thorac Cardiovasc Surg. 1989;97(2):313–318.
gStern JD, Rolnitzky L, Goldberg JD, et al. Meta-analysis to assess the appropriate endpoint for slow pathway ablation of atrioventricular nodal reentrant tachycardia. Pacing Clin Electrophysiol. 2011;34(3):269–277.

than those typically associated with successful RF ablation (Table 2 and Fig. 3).

4 | DISCUSSION

Using cryoablation best practices, the ICY-AVNRT study demonstrated successful slow pathway ablation in patients with frequent and symptomatic AVNRT over 6 months of follow-up. There were few adverse events, and no AV block requiring permanent pacing. To our knowl-
edge, this study is the largest multicenter study of cryoablation for AVNRT, and it has produced results similar to those described in the literature for RF ablation.8–15

4.1 Usage of best practices

Successful slow pathway ablation requires accomplishing four tasks: (1) identifying the location of the slow pathway, (2) producing a large irreversible lesion encompassing the slow pathway, (3) avoiding damage to the normal AV conduction system, and (4) knowing when no further ablation is required for success. To achieve these goals, best practices have been proposed for cryoablation in this current study. The first factor critical for successful cryoablation is a short time-to-effect. Cryoablation is generally considered to require more precision than RF ablation. Since cryoablation requires more time to produce a lesion, it is imperative to select sites where efficacy can be predicted promptly to avoid wasting time and producing unnecessary lesions. Toward that end, cryoenergy deliveries should be adjudicated by programmed stimulation to be effective within 60 seconds. As with RF ablation, short time-to-effect is considered evidence of ablation at the correct site.

Secondly, rapid cooling is vital to produce lesions of sufficient size to ablate the slow pathway. The first cryothermal ablation system involved utilization of a temperature hold feature at −30°C to assess whether the lesion would be effective. More recently, this feature has fallen out of favor (preferring rapid cooling to at least −75°C). Good contact between the cryoablation electrode and the endocardium is necessary for a rapid and linear decline in temperature to at least −75°C. Lack of such a steep temperature decline should prompt cessation of cryothermal energy and repositioning of the catheter to a more stable site where better contact pressure with the endocardium can be achieved.

Repeated freezes at the successful site is the third important factor for durable success. Refreezing at the successful site has been shown in animal studies to enlarge and consolidate the lesions histologically.5,16 The first freeze likely interrupts the microcirculation of warm blood such that the second freeze meets less thermal resistance, resulting in an even steeper temperature decline curve and a larger volume of ablated tissue. By contrast, cryoballoon catheter ablation in patients with atrial fibrillation has demonstrated effectiveness of a single-freeze application during pulmonary vein isolation.17,18 However, to our knowledge, there is no pivotal study examining the efficacy of a single-freeze approach in the focal cryoablation of AVNRT. When using a focal cryoablation catheter, refreezing at the successful site and/or closely adjacent site(s) should still be common practice in an attempt to reduce the chance of arrhythmia recurrence.

Other important best practices used in this study included: the usage of a 30-minute waiting period with isoproterenol challenge before the final assessment of acute efficacy, the utilization of ablation sites with high AV amplitude ratios, and the striving for the endpoint of zero echo beats at the termination of the ablation procedure. Previous studies have enacted some of these best practices. The utilization of a 30-minute waiting period before final acute efficacy assessment is common in other clinical studies of AVNRT employing cryofocal catheters.4,6,10–12,15 Similarly, there has been a group of AVNRT studies using isoproterenol testing to assess final efficacy.6–12 However, only two studies have aimed for an endpoint of no echo beats,4,15 with other studies accepting a single echo beat for the acute efficacy endpoint.6–12 A summary of slow pathway ablation studies suggests that leaving a single echo beat likely results in a higher risk of recurrence of AVNRT.19 Lastly, studies of slow pathway cryoablation seldom report AV ratios at the successful site. Two studies did report AV amplitude ratios ranging from 1:4 to 1:2.8,11 In general, physicians experienced in RF ablation are rightly hesitant to ablate higher up the septum and further back in the right atrium, knowing that such sites are close to the compact AV node and are associated with greater risk of AV block. However, with cryoablation (since AV block is always transient), such sites can be safely approached. Our study best practice encouraged ablating at such sites if ablation at more traditional sites was ineffective. In summary, we propose that our study represents the most consistent adherence to all best practices and approximates what can be expected from slow pathway cryoablation of AVNRT.

4.2 Efficacy of cryoablation

Historically, acute procedural success in other studies using the same cryoablation catheter ranges from 93% to 98%.6–9,11 In studies where the slow pathway was targeted with RF energy, acute procedural success ranges from 95% to 100%,8,9,11,15 and these results are comparable to the 95% acute procedural success rate realized in this current study. A large proportion of the successful ablation sites in this study were higher up the septum and had higher AV ratios than those typical for successful RF ablation. The higher than typical AV ratio may be a physician-user selection preference given the transient nature of AV block with cryoablation. Although it is true that the RF catheter is not adhered to the endocardium (but moves relative to the intended ablation target), it would be unusual to target sites (with RF energy) with AV electrogram ratios approaching those associated with successful cryoablation in this study. With cryoablation, there is some catheter movement before cryoadherence is realized, but the electrograms are visible. When adherence occurs and before freezing artifact sets in, the cryothermal energy can be stopped if the electrograms look inconsistent with the intended site of ablation.

With both cryoablation and RF ablation, the limitation of acute success is almost always the fear of producing heart block by ablating too close to the compact AV node/His bundle. The proposed advantage of cryoablation is that such block will resolve without the need for permanent pacing, as was demonstrated in this study. Nevertheless, in this multicenter study with a wide range of cryoablation investigator experience, concern over AV block may have impacted the achievement of acute procedural success. A second lesion at the successful site could not be delivered in 14 cases because of AV block. Furthermore, AV block was reported to be the sole reason for abandoning cryoablation in two subjects and a contributing factor in five subjects where acute procedural success was not realized. Thus, AV block (albeit transient) appeared to be a major factor limiting acute procedural success.

Whether cryoablation at other sites, such as further inside the coronary sinus targeting the so-called left inferior AV nodal extension would have increased the chance of success is unknown,14 but the
lower than expected success in patients who acutely crossed over to RF ablation would suggest that failure in these patients was not necessarily related to the energy source or anatomical location of ablation. Interestingly, in our study, less than 10% of successful sites were at the mouth of the coronary sinus, and none were further inside targeting the left inferior AV node extension.

4.3 | Safety of cryoablation

There was a low incidence of serious adverse events related to the procedure in this study, and no serious adverse events related to the study cryoablation catheter were reported. There was no malfunction of the cryoablation system that precluded attempting slow pathway ablation. Tamponade was seen in one subject unrelated to the ablation catheter or cryotherapy. Pulmonary embolism has been reported after slow pathway ablation using both RF and cryoenergy, but it is thought to be related to instrumentation within the femoral veins rather than thrombus at the ablation site. Notably, in this study, no patient died or suffered a neurologic event, and no patient developed symptomatic AV block or required permanent pacing.

Avoiding permanent AV block is imperative in younger patients who would face decades of dependency on permanent pacing. A meta-analysis of RF slow pathway ablation studies has reported the incidence of AV block requiring permanent pacing to be about 0.8%.3 Potential efficacy of a RF application on the slow pathway is suggested by the occurrence of accelerated junction rhythm (AJR) with intact VA conduction. Nonetheless, predicting the ultimate effect of an RF lesion on AV conduction is imperfect. Measures to protect the normal AV conduction system include ablating further away from the presumed location of the compact AV node/His bundle, avoiding rapid AJR, monitoring for retrograde block in the fast pathway during AJR, and atrial pacing at rates faster than AJR to ensure integrity of antegrade AV conduction. With cryoablation, the advancing wavefront of tissue freezing is slow and allows for time to discontinue freezing with even a hint of impending AV block. Additionally, the coldest temperatures are at the electrode rather than at a distance. Lastly, although cryoablation has been associated with permanent right bundle branch block and first degree AV block, complete AV block requiring permanent pacing has not been reported.

4.4 | AV block caused by cryoablation

AV block caused by cryoablation is reported in 5% to 23% of patients, but typically resolves before the end of the ablation procedure.6,11,20–23 Because the protocol in this study required two (240 seconds) cryothermal applications at the successful site, and given the high percentage of patients who received additional lesions at closely adjacent sites, more AV block might have been expected than previously reported with cryoablation. The 25% incidence of transient AV block in this study is consistent with this more aggressive cryoablation methodology. Nevertheless, only a single patient was left with a lasting effect on AV conduction (first degree AV block). Importantly, no patients were symptomatic and none required permanent pacing. These data suggest that transient AV block should not preclude persistent attempts at cryoablation of the slow pathway in patients with AVNRT.

5 | LIMITATIONS

The size of this study, the number of centers, the varying level of cryoablation experience among the investigators, and the rigorous adjudication of endpoints provide a reasonable simulation of what can be achieved with cryoablation for AVNRT in the EP community at large. Nevertheless, it is not a randomized controlled trial, and comparisons with RF ablation are inferential as the current study is a single-arm examination of the 6 mm cryoablation catheter. Data references regarding efficacy and safety of RF catheter ablation were provided to give historical perspective to the traditional ablation methodology used in the treatment of patients with AVNRT.

As is typical for large trials, some subjects were lost to follow-up (5.3% for the chronic success endpoint and 6.0% for the safety endpoint), thereby reducing the number available for analysis. The 6-month follow-up period (although typical of studies involved in FDA approval of ablation catheters) is limited. Late AV block has not been reported with cryoablation as it has with RF ablation.24,25 Thus, it seems unlikely that additional safety events will be observed, but recurrence of AVNRT will likely occur in additional patients over time as it does with RF ablation. In this study, 13.6% of patients had an arrhythmia frequency of 1 or 2 events per year, and in some of these subjects, AVNRT may have not recurred simply due to the natural history (frequency) of their arrhythmia.

Lastly, this is a study of a specific cryoablation catheter rather than cryoablation in general and the results apply only to the study catheter. Patients who failed the acute efficacy endpoint were generally crossed over to ablation with an RF catheter but not treated with other cryoablation catheters.

6 | CONCLUSIONS

The ICY-AVNRT study demonstrates that cryoablation in patients with frequent paroxysms of AVNRT using a 6-mm electrode catheter according to recommended best practices is safe and effective with a low risk of recurrence over 6 months of follow-up, with no patients requiring permanent pacing.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Wells P, Dubuc M, Klein GJ, et al. Intracardiac ablation for atrioventricular nodal reentry tachycardia using a 6 mm distal electrode cryoablation catheter: Prospective, multicenter, North American study (ICY-AVNRT STUDY). *J Cardiovasc Electrophysiol.* 2018;29:167–176. [https://doi.org/10.1111/jce.13367](https://doi.org/10.1111/jce.13367)