

Cryoablation outcomes for AV nodal reentrant tachycardia comparing 4-mm versus 6-mm electrode-tip catheters

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BACKGROUND Cryoablation is increasingly used to treat atrioventricular nodal reentrant tachycardia (AVNRT). It is unknown whether larger electrode-tip cryocatheters improve outcomes without compromising safety.

OBJECTIVE This study sought to compare acute and long-term success with 4-mm versus 6-mm electrode-tip cryocatheters for AVNRT.

METHODS We conducted a 2-group cohort study on 289 patients, age 45.5 ± 15.9 years (76.8% female), who underwent transcatheter cryoablation as a first-time procedure for AVNRT with 4-mm ($N = 152$) or 6-mm ($N = 137$) electrode-tip catheters.

RESULTS Acute procedural success was achieved in 90.7% (95% confidence interval 86.9% to 93.7%) with no difference between the 2 electrode-tip sizes. A shorter fluoroscopy time (16.1 ± 11.3 versus 20.3 ± 14.9 minutes, $P = .0096$) and trend toward briefer procedural duration (166.6 ± 49.1 versus 173.5 ± 53.0 minutes, $P = \text{NS}$) were noted with 6-mm electrode tips. Transient AV block occurred in 5.2%, with complete recovery in 4.4 ± 2.6 seconds.

Over a median follow-up of 155 days, recurrences were less common with 6-mm electrode tips. Actuarial event-free survival rates at 1, 3, 6, and 12 months with 6-mm versus 4-mm electrode-tip cryocatheters were 96.7%, 93.4%, 91.9%, and 88.5% versus 89.9%, 87.0%, 84.1%, and 77.1%, respectively, with no recurrence thereafter ($P = .0457$). In multivariate analyses adjusting for baseline imbalances and medical therapy postablation, cryoablation with a 4-mm-tip catheter incurred a 2.5-fold increased risk of recurrence (hazard ratio 2.5, 95% confidence interval 1.0 to 6.1, $P = .0420$).

CONCLUSION In patients with AVNRT, cryoablation with 6-mm electrode-tip catheters is safe and is associated with fewer recurrences on long-term follow-up compared with 4-mm electrode-tip cryocatheters.

KEYWORDS Arrhythmia; Catheter ablation; Cryothermal energy; AV nodal reentrant tachycardia

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Introduction

Transcatheter cryothermal slow pathway modification is an effective treatment for AV nodal reentrant tachycardia (AVNRT), with a safety profile superior to that of radiofrequency (RF) ablation.^{1–9} However, valid concerns have been raised regarding potentially lower efficacy when compared with RF ablation. To date, 2 pilot studies have randomized patients with AVNRT to cryoablation with 4-mm electrode-tip catheters versus RF ablation. Whereas 1 reported no difference in acute and long-term outcomes,^{10,11} the second favored RF ablation.⁸ One factor that may contribute to lesser efficacy with 4-mm electrode-tip cryoablation is an average lesion volume less than half that created by 4-mm RF catheters.¹² It may be conjectured, therefore, that cryocatheters with larger distal electrode tips may confer additional benefit. The purpose of this study was to

compare acute and long-term success rates with 4-mm versus 6-mm electrode-tip cryocatheters for AVNRT.

Methods

Study design

A 2-group cohort study was conducted on all patients having undergone a first transcatheter ablation procedure for AVNRT with cryothermal energy at the Montreal Heart Institute between May 1999 and February 2006. The study protocol was approved by our local institutional review board, and all patients provided written informed consent. Patients with prior ablation of a different arrhythmia substrate were included if AVNRT had not been previously targeted. Those presenting with recurrent AVNRT were excluded, regardless of whether the initial procedure utilized RF or cryothermal energy.

Patient records were reviewed to determine clinical variables, procedural outcomes, and arrhythmia-free survival based on routine follow-up, including clinical visits, electrocardiograms, Holter monitors, rhythm strips, and event recordings. Electronically stored data from electrophysiology procedures were reviewed and relevant parameters before and after cryoablation retrieved, including number and

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duration of applications and procedural and fluoroscopy times.

The main exposure variable was size of the cryocatheter electrode tip, binomially categorized as 4-mm or 6-mm. Primary efficacy end points were acute procedural success and long-term arrhythmia-free survival. Acute procedural success was defined as the inability to induce sustained AVNRT after at least 1 cryogenic application.⁴ Long-term arrhythmia-free survival was defined as the absence of objectively documented supraventricular tachycardia on clinical follow-up or of symptoms suggestive of recurrent AVNRT confirmed by inducibility on repeat electrophysiological testing. Acute procedural effects on slow pathway conduction in patients with acute success were classified as: (1) elimination of dual AV nodal physiology, (2) persistent dual AV nodal physiology with no AV nodal echo beats, or (3) persistent dual AV nodal physiology with AV nodal echo beats but noninducibility of tachycardia with and without an intravenous isoproterenol infusion.¹³ Tachycardia was defined as more than 3 AV nodal echo beats.⁴

Transcatheter cryoablation

Electrophysiology procedures were performed in the fasting state, off all AV nodal blocking agents and antiarrhythmic drugs for >5 half-lives, and under conscious sedation provided by an anesthesiology service (i.e., continuous propofol infusion with boluses of midazolam and fentanyl). A diagnostic electrophysiology study was performed using three 5F quadripolar catheters (Supreme, St. Jude Medical, Minnetonka, MN) with or without a 6F or 7F decapolar catheter (Livewire, St. Jude Medical) introduced through right and left femoral veins and placed in standard high right atrium, His, right ventricular apex, and coronary sinus positions. All patients underwent atrial and ventricular programmed electrical stimulation at 2 drive trains (600 msec and 400 msec) with up to 2 extrastimuli, using an EP-3 computerized stimulator (EP Medsystems Inc., West Berlin, NJ). If AVNRT was not induced, the protocol was repeated on an isoproterenol infusion titrated up to 5 $\mu\text{g}/\text{min}$. All recordings were bipolar with the gain set at 0.5 mV/mm and filtered at 30 to 500 Hz.

After completing the diagnostic study, a 7F cryocatheter was introduced through the femoral vein and an intravenous bolus of 2500 IU of unfractionated heparin was administered. One of two 7F quadripolar steerable cryoablation catheter models was used, with either a 4-mm (Freezor) or 6-mm (Freezor Xtra) distal electrode tip. Catheter selection was not randomized since the 6-mm electrode-tip catheter was not available for commercial use until the latter part of our study period. Consoles and catheters (CryoCath Technologies Inc., Montreal, QC, Canada) have been previously detailed.^{4,5,14,15} In short, the console allows 2 modes of operation, cryomapping and cryoablation. In the cryomapping mode, temperature of the distal tip may be decreased to -30°C for up to 80 seconds to deliver a reversible application. In the cryoablation mode, this temperature may be

further lowered to -80°C for up to 4 minutes, thereby producing a permanent lesion.

After cryocatheter positioning, a cryomapping application was performed to assess safety (i.e., failure of AH prolongation by more than 25% from baseline) and efficacy (i.e., failure to induce tachycardia using a previously successful stimulation protocol). Cryoablation was then performed. Programmed stimulation was pursued during cryoablation, and if tachycardia was reinducible, cryoablation was terminated and the catheter was repositioned. If no tachycardia was inducible, the application was continued for a total of 4 minutes, provided no AH interval prolongation or AV block occurred. Programmed stimulation was repeated after ablation. If acutely successful, observation with programmed stimulation on or off isoproterenol was performed, typically for 30 minutes or more. Patients were discharged the next day barring any complication.

Patient follow-up

Time 0 was defined as time of the transcatheter cryoablation procedure. Outpatient follow-up was scheduled at 3 months with a 12-lead electrocardiogram. Holter monitoring, event recorders, and further clinical follow-up was at the discretion of the treating cardiologist. To maximize completeness of follow-up, referring cardiologists were contacted by telephone. Patient-years were accrued until the most recent clinical visit with a cardiologist.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation or median and interquartile range (25th, 75th percentile) depending on their distribution. Categorical variables are summarized as frequency and percentage. Two-group comparisons of baseline and procedural characteristics were assessed by independent sample *t* tests or nonparametric Mann-Whitney *U* tests where appropriate. Nominal variables were compared with Fisher exact tests. Event-free survival curves were plotted and compared using the Kaplan-Meier method and log-rank statistic. A Cox proportional hazards model was used to determine whether electrode tip size was predictive of recurrent AVNRT while controlling for follow-up duration and potential confounders. Two-tailed *P* values $<.05$ were considered statistically significant. Testing was performed with SAS software version 9.1 (SAS Institute, Cary, NC).

Results

Baseline characteristics

A total of 289 patients, age 45.5 ± 15.9 years, had a first ablation procedure for AVNRT with 4-mm ($N = 152$) or 6-mm ($N = 137$) electrode-tip cryocatheters at the Montreal Heart Institute between May 1999 and February 2006. Procedural dates with the 4-mm electrode-tip catheter ranged from May 1999 to January 2007, with 2 interventions after January 2005. The date range with 6-mm electrode-tip cryocatheters was January 2004 to February 2006. All patients had inducible AVNRT, with or without an

Table 1 Baseline characteristics

	4-mm tip N = 152	6-mm tip N = 137	P value
Age, years	42.3 ± 15.2	48.9 ± 16.1	.0004
Female, N (%)	116 (76)	106 (77)	.8077
Medical history			
Diabetes, N (%)	4 (2.6)	10 (7.3)	.0658
Dyslipidemia, N (%)	11 (7.2)	16 (11.7)	.2046
Hypertension, N (%)	12 (7.9)	23 (16.8)	.0240
Coronary artery disease, N (%)	6 (3.9)	9 (6.6)	.3346
Valvular heart disease, N (%)	8 (5.4)	7 (5.1)	.9845
Left ventricular ejection fraction ≤40%, N (%)	3 (0.7)	2 (1.5)	.7179
Prior medical therapy attempted			
Beta-blocker, N (%)	41 (27.0)	40 (29.2)	.4890
Calcium channel blocker, N (%)	37 (24.3)	38 (27.7)	.4587
Digoxin, N (%)	3 (2.0)	4 (2.9)	.5873
Propafenone, N (%)	5 (3.3)	6 (4.4)	.6188
Flecainide, N (%)	6 (3.9)	4 (2.9)	.6415
Sotalol, N (%)	15 (9.9)	12 (8.8)	.7760
Amiodarone, N (%)	0 (0)	1 (0.7)	.2896

isoproterenol infusion. Baseline characteristics are summarized in **Table 1**.

Acute procedural success

Overall acute procedural success was achieved in 90.7% of patients (95% confidence interval [CI] 86.9% to 93.7%), with no statistical difference between 4-mm versus 6-mm electrode-tip sizes (91.4%, 95% CI 86.3% to 95.2%) versus 89.8% (95% CI 84.0% to 94.1%, $P = \text{NS}$). In patients with acutely successful cryoablation with 4-mm or 6-mm electrode-tip catheters, complete elimination of slow pathway conduction was achieved in 52.3% versus 52.0%, absence of AV nodal echoes despite dual AV node physiology in 7.9% versus 8.1%, and persistent AV nodal echoes but noninducibility on and off isoproterenol in 38.8% versus 39.8%, respectively ($P = \text{NS}$). Procedural and postprocedural characteristics are summarized in **Table 2**.

Recurrences on follow-up

Over a median follow-up of 154.5 (110.5 to 228.3) days, 22 of 139 (15.8%) patients with acutely successful cryoablation using 4-mm electrode-tip cryocatheters experienced recurrent AVNRT compared with 10 of 123 (8.1%) patients

with 6-mm electrode-tip catheters ($P = .0252$). The median time to recurrence was 30.0 (10.0 to 72.0) days and was no different between the 2 electrode-tip sizes.

As depicted in **Figure 1**, actuarial recurrence-free survival rates at 1, 3, 6, and 12 months with 4-mm versus 6-mm electrode-tip catheters were 89.9%, 87.0%, 84.1%, and 77.1% versus 96.7%, 93.4%, 91.9%, 88.5%, respectively, with no recurrence thereafter ($P = .0457$). In multivariate Cox regression analyses adjusting for baseline imbalances (i.e., age, hypertension, and diabetes) and medical therapy post ablation (i.e., beta-blockers and calcium channel blockers), cryoablation with a 4-mm versus 6-mm electrode-tip catheter remained an independent predictor of recurrence (hazard ratio 2.5, 95% CI 1.0 to 6.1, $P = .0420$).

Cryoablation-induced AV block

Transient complete AV block occurred in 15 patients (5.2%) during a cryothermal application: 5 (3.3%) in patients with 4-mm electrode-tip catheters and 10 (7.3%) with 6-mm electrode-tip catheters ($P = \text{NS}$). The mean duration of AV block was 4.4 ± 2.6 seconds, with no significant difference between 4-mm and 6-mm electrode-tip catheters. All completely recovered within 10 seconds. Transient AV block

Table 2 Procedural and postprocedural characteristics in patients with acutely successful cryoablation for AVNRT

	4-mm tip N = 139	6-mm tip N = 123	P value
Procedural characteristics			
Fluoroscopy time, min	20.3 ± 14.9	16.1 ± 11.3	.0096
Total procedural time, min	173.5 ± 53.0	166.6 ± 49.1	.2589
Medical therapy postablation			
Beta-blocker, N (%)	11 (7.2)	14 (10.2)	.2010
Calcium channel blocker, N (%)	4 (2.6)	5 (3.6)	.4394
Digoxin, N (%)	0 (0)	0 (0)	—
Follow-up duration (days)	177.5 (121.8, 218.5)*	138.0 (105.5, 261.0)*	.1524

AVNRT = atrioventricular nodal reentrant tachycardia.

*Nonnormally distributed continuous variables are summarized by median value and interquartile range (25th, 75th percentile).

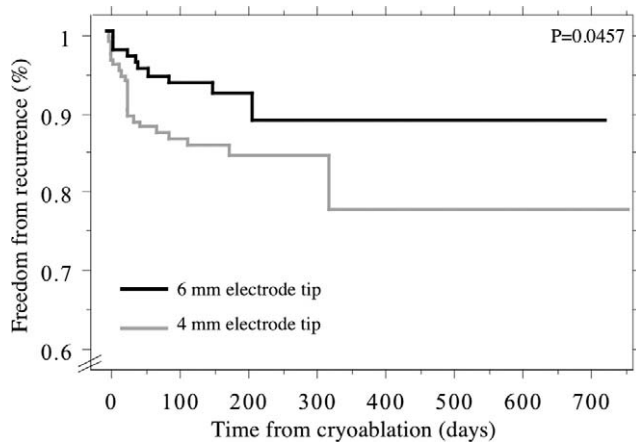


Figure 1 Freedom from recurrence according to type of cryocatheter. Kaplan-Meier recurrence-free survival rates are shown for patients having undergone successful slow pathway modification for AVNRT with 6-mm and 4-mm electrode-tip cryocatheters. AVNRT = atrioventricular nodal reentrant tachycardia.

occurred during cryomapping in 12 patients (4-mm electrode-tip in 4, 6-mm in 8) and cryoablation in 3 patients (4-mm electrode-tip in 1, 6-mm in 2). Additionally, 3 patients experienced transient AV block secondary to mechanical trauma (4-mm electrode-tip in 1; 6-mm in 2). No patient developed permanent AV block during follow-up, and none required a permanent pacemaker. No other complication occurred.

Discussion

In light of the unique safety profile of cryoenergy, some centers have adopted cryoablation as first-line therapy for AVNRT. Proponents of this approach assert that inadvertent permanent high-degree AV block has yet to be reported with cryoablation. This is in contrast to the approximate 1% risk of complete AV block with RF ablation of AVNRT in experienced hands.^{16,17} Advocates of RF ablation as first-line therapy for AVNRT argue that the additional safety advantage is not sufficient justification considering the lesser efficacy of cryoablation. To date, 2 pilot studies comparing RF ablation to cryoablation with 4-mm electrode-tip catheters have yielded disparate results.^{8,10,11} Although concerns over comparative acute efficacy and long-term effectiveness are valid, more definitive studies are required.

One plausible reason why RF ablation may produce superior results to cryoablation with a 4-mm electrode-tip catheter is the creation of substantially larger lesions. In a randomized preclinical study of 197 ablation lesions in mongrel dogs, we previously found RF lesions to be more than twice as large as cryoablation lesions produced by 4-mm electrode-tip catheters.¹² Differences in surface area rather than lesion depth accounted for these volume effects. One likely contributing factor is adherence of the cryocatheter to underlying tissue. With RF energy, a brushing effect occurs as a result of cardiorespiratory motion during catheter ablation that generates larger lesion dimensions. Al-

though catheter stability is an advantage of cryoenergy, larger lesions may be produced by increasing the size of the distal electrode tip. We hypothesized that cryoablation outcomes for AVNRT may be further improved with 6-mm electrode-tip catheters.

Our study represents the largest cohort of patients with cryoablation for AVNRT and is the first to compare cryocatheters. We report superior outcomes without compromising safety using 6-mm electrode-tip catheters. Our overall acute success rate of 90.7% (95% CI 86.9% to 93.7%) is comparable to prior studies, including a multicenter cohort of 103 patients (91%, 95% CI 84% to 96%)⁴ and a randomized study that included 30 patients with cryoablation for AVNRT (93%, 95% CI 79% to 98%).¹¹ Although in the current study the 6-mm electrode-tip cryocatheter was not associated with a higher acute procedural success rate when compared with the 4-mm electrode-tip cryocatheter, fluoroscopy time was shorter and a trend toward briefer procedural duration was noted.

Despite similar acute success rates with 4-mm and 6-mm electrode-tip cryocatheters, the larger electrode tip was associated with significantly fewer recurrences on long-term follow-up. Recurrence-free survival with the 6-mm electrode-tip catheter was 91.9% at 6 months and 88.5% at 2 years, which approaches reported results with RF ablation.^{16–18} Fortunately, safety was not compromised in achieving superior long-term outcomes with the 6-mm electrode tip. It is unknown whether outcomes may be further safely improved with even larger electrode tips (i.e., 8 mm). Although transient AV block occurred in a sizeable proportion of patients with 6-mm electrode-tip catheters (7.3%), all promptly recovered on cessation of the cryogenic application. Most such events transpired during cryomapping, with a minority during cryoablation. The latter phenomenon has been termed dynamic cryomapping to reflect a changing temperature gradient that spreads radially from the catheter tip–tissue contact. Reversible effects on AV node conduction occur at a temperature of approximately -30°C , which necessarily precedes more intense freezing temperatures of less than -50°C to -60°C that lead to permanent cell death.^{14,15} Moreover, the AV node is thought to be particularly resistant to cryothermal injury.¹⁷

Study limitations

The study was retrospective in nature and subject to the limitations inherent to such designs. Nevertheless, all procedural data were prospectively entered in the Montreal Heart Institute's cryoablation registry, which is systematically upheld. The type of cryocatheter was not randomly allocated, with 6-mm electrode-tip catheters more frequently utilized in the latter half of the study. Because transcatheter cryoablation was first performed in our institution in August 1998, we deliberately initiated the study 9 months later to eliminate a learning-curve effect. All interventions with prior iterations of the 4-mm electrode-tip cryocatheter, including the 9F version and refrigerants other than nitrous oxide, were excluded from the study. More-

over, operator bias favoring the 6-mm electrode-tip cryocatheter is unlikely to be substantial in light of the comparable acute success rates and acute procedural outcomes. Finally, our study did not address whether double freeze-thaw cycles or additional lesions at the site of success could further reduce long-term recurrences.

Conclusions

In patients with AVNRT, slow pathway modification with 6-mm versus 4-mm electrode-tip cryocatheters is associated with fewer recurrences on long-term follow-up. Importantly, safety is not compromised to achieve this incremental benefit. Additional advantages of the larger electrode-tip catheter include shorter fluoroscopy time and possibly briefer procedural duration. In light of these results, it may be argued that the 6-mm electrode tip should replace its 4-mm counterpart as the cryocatheter of choice in adults with AVNRT.

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