Original Research

Cryoablation of Atrioventricular Nodal Reentrant Tachycardia in Children and Adolescents: Improved Long-Term Outcomes with Increasing Experience

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Background: Cryoablation is increasingly used for the treatment of atrioventricular nodal reentrant tachycardia (AVNRT). There are limited data regarding its efficacy and late outcomes in the pediatric population.

Methods: We reviewed the clinical records of 70 consecutive pediatric and adolescent patients (mean age: 12.2 ± 3, range: 5-19 years) with AVNRT, with or without additional structural heart disease, who underwent catheter ablation with the intention to use cryoablation as the primary modality between September 2004 and July 2011.

Results: The acute success rate was 97.14%. No long-term complications occurred. Patients were followed up for an average time of 46 ± 22.5 months (range 5-90). The recurrence rate was 16%, decreasing from 28% in the first 25 cases to 8.9% in the last 45 cases ($p<0.05$). Wenckebach point prolongation during cryo-applications was associated with a lower recurrence rate ($p<0.05$). No other risk factors for recurrence were identified, including persistence of slow pathway conduction. Patients with congenital heart disease had a similar success rate to patients with a structurally normal heart.

Conclusions: When applied to pediatric patients, cryoablation has an excellent success and safety profile, which can improve with increasing experience. Transient Wenckebach point prolongation during cryo-applications may be associated with improved late outcomes.

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Atrioventricular nodal reentrant tachycardia (AVNRT) is the second most common form of paroxysmal recurrent tachycardia in children. Radiofrequency ablation has long been the first-line therapy for this type of tachycardia, with a high success rate documented in several studies.[1,2] However, a small but definite risk of damage to the AV node, with a 1-2% incidence of permanent AV block, has been reported.[3] Because of this risk, and the undesirable effects of long-term pacing, cryoablation has emerged as a new modality with the potential to replace radiofrequency ablation, based on its promising safety profile. However, data regarding the long-term outcome of cryoablation in children are limited. Moreover, the criteria for effective cryoablation lesions, equivalent to those for radiofrequency ablation, have not been defined. Our study sought to demonstrate the long-term results from the clinical application of this technique and to identify predictors of tachycardia recurrence in this population.

Methods

Patients

This was a retrospective study of pediatric and adolescent patients with AVNRT, who underwent cryoablation in the period from September 2004 to February 2010. The demographic and clinical data of the patients enrolled are presented in Table 1. A total of 70 consecutive patients (37 females) were enrolled, who were referred for an electrophysiology (EP) study and ablation because of diagnosed or suspected AVNRT, according to the standard criteria. The mean age was 12.2 ± 3 years (range 5-19). Five patients (7%) demonstrated additional structural cardiac anomalies. These included one child with hypertrophic cardiomyopathy, one with a small patent arterial duct, two with a ventricular septal defect (one after surgical repair), and one with a partial atrioventricular septal defect after surgical repair. In 25 patients, oral antiarrhythmic drugs had been administered. However, in 16 of them the arrhythmia had been only partially or poorly controlled.

In order to detect late recurrences, only patients with a follow-up period longer than 4 months were included.

The research protocol was approved by the hospital's ethics committee. Informed consent was obtained from the patients' parents.

Electrophysiology study

The EP study and ablation were performed under general anesthesia in 61 patients, whereas local anesthesia and conscious sedation were used in 9. Diagnostic quadripolar catheters were introduced from the femoral veins and placed in the high right atrium, His bundle, coronary sinus, and right ventricular apex. The EP study protocol included measurement of baseline intervals, followed by incremental atrial and ventricular pacing, and single atrial and ventricular extrastimuli for the induction of tachycardia. If tachycardia was not inducible, isoproterenol infusion was initiated, with the infusion rate adjusted according to patient's heart rate response (aiming at an increase of 25-30% from baseline) and the protocol was repeated. Double or triple atrial extrastimuli and atropine (0.04 mg/kg bolus infusion) were used additionally, if necessary, for the induction of tachycardia.

Table 1. Demographic and clinical data of the patients enrolled in the study.

Age (years, mean ± SD)	12.2 ± 2.9
Weight (kg, mean ± SD)	55 ± 15
Female, n (%)	37 (53)
Additional heart disease, n (%)	5 (7)
Additional arrhythmia substrate, n (%)	9 (12.8)
Previous AAD administration, n (%)	25 (35.7)
Failure of AAD treatment, n (%)	16 (64)
Typical AVNRT, n (%)	56 (93.3)
Both forms of AVNRT, n (%)	4 (6.7)

AAD – antiarrhythmic drugs; AVNRT – atrioventricular nodal reentrant tachycardia.

Ablation

Following the EP study and confirmation of the diagnosis, a 6 mm tip cryoablation catheter (Medtronic CryoCath Technologies, Montreal, Quebec, Canada) was introduced. Limited geometry of the right atrium and tricuspid annulus was created with the application of a NavX system (EnSite NavX™ Navigation & Visualization Technology, St Jude Medical, Sylmar California). The segment of tricuspid annulus between the coronary sinus orifice and the His bundle was divided into 3 areas (P, M and A), each subsequently subdivided into 2 sites (P1, P2, M1, M2, A1 and A2). Cryo-lesions were initially applied at the posterior sites (P1, P2), where we usually proceeded to cryoablation directly. When application was needed at sites closer to the AV node, cryo-mapping (temperature of -30°C) was initially performed, followed by cryoablation (temperature of -70°C to -80°C) if there was no evidence of AV conduction impairment during cryo-mapping (i.e. any prolongation of the AV interval or loss of AV conduction). The AH and AV intervals were continuously monitored during delivery of cryo-energy, and the application was immediately interrupted if any significant prolongation of these intervals occurred. After each application, the presence of dual AV nodal physiology was reevaluated by evidence of sustained slow pathway conduction during incremental atrial pacing and/or the presence of AH jump. AVNRT non-inducibility (both at baseline and during isoproterenol infusion) was the primary "acute" endpoint of the procedure, whereas elimination of any indication of slow pathway conduction, as described above, was the secondary endpoint.

In cases in which AVNRT was not inducible during the EP study – despite aggressive programmed stimulation as described above – but tachycardia had been clinically documented, we aimed for complete elimination of slow pathway conduction. Sites of ab-

lation, time of cryo-mapping and cryoablation, total number of lesions, complications, fluoroscopy and total procedure duration were recorded for all patients. Procedure time was the time from patient's entry to patient's exit from the EP lab.

In 36 patients, incremental atrial pacing was routinely performed prior to and during application of cryo-energy; the Wenckebach cycle length was commonly seen to lengthen transiently, compared to baseline, returning to pre-cryoablation values or even lower after the termination of the application. This transient prolongation has also been described in previous studies.[4] In the majority of the cases this prolongation was less than 20%, not accompanied by concurrent PR prolongation during sinus rhythm, and it was always reversible. When greater prolongation of the Wenckebach cycle length (more than 20% of baseline) was observed during cryoablation, the application was stopped. However, even in these cases, neither was concurrent PR prolongation under sinus rhythm during cryo-application observed, nor could this Wenckebach cycle length prolongation be demonstrated after the end of the application.

Following successful cryoablation and a 30-minute waiting period, a repeat EP study was performed both at baseline and during isoproterenol infusion. If the above mentioned endpoints were confirmed, the procedure was terminated and catheters were removed. Patients were observed for 24 hours with continuous ECG monitoring. Two-dimensional echocardiography was performed in case of an excessive number of applications or any other indication related to the procedure. Patients were discharged the following day on no medication, except when a large number of applications had been administered, in which case aspirin (5 mg/kg/day) was prescribed for one month. Routine follow up was scheduled at 2, 6 and 12 months after the procedure in the outpatient clinic and as necessary thereafter. Procedure time, fluoroscopy time, the number of lesions, complications, acute result rate and recurrence rate were evaluated for the first 25 patients, and compared with the values derived from the subsequent 45 patients, so that the effect of the learning curve could be accounted for.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± SD, whereas those without normal distribution are expressed as median and range. Student's t-test and the Mann–Whitney test were used for the between-group comparisons of continuous variables with normal and non-normal distribution, respectively. The chi-square (χ^2) test was performed for comparisons between groups of categorical variables. A binary logistic regression model was used for multivariate analysis of dichotomous dependent variables. Statistical analysis was performed using the SPSS version 17.0 statistical package. All reported p-values are based on two sided tests and the level of significance was set at <0.05.

Results

Electrophysiology study – ablation

During the EP study, AVNRT was inducible in 47 (67.1%) patients at baseline and in 13 (18.6%) patients during isoproterenol infusion, whereas in 10 (14.3%) patients with clinically documented supraventricular tachycardia only dual AV nodal physiology was demonstrated, with no inducible tachycardia. Of those with inducible AVNRT, 56 (93.3%) developed the common type and 4 (6.7%) both the common and the uncommon type of tachycardia (Table 1). There was no patient who exclusively developed the uncommon type of AVNRT. The average tachycardia cycle length was 285 ms.

An additional arrhythmogenic substrate was identified in 9 patients. Sustained atrial flutter was induced in 2 patients. Ventricular pre-excitation was observed in two patients, but the accessory pathway did not participate in the tachycardia circuit and the only tachycardia induced during the EP study was AVNRT. There were also single cases of nodo-ventricular pathway, fasciculo-ventricular pathway, inducible atrial fibrillation, catecholaminergic polymorphic ventricular tachycardia and ventricular tachycardia arising from the Purkinje fibers.

The primary endpoint was reached in all but 2 patients (acute success rate of 97.14%). In these 2 patients the procedure was completed with radiofrequency ablation, as described earlier. It is worth mentioning that in 1 of these cases the location of successful ablation was in the left posteroseptal area (access provided with transseptal puncture), suggesting a left-sided slow pathway location. The median number of cryo-applications was 5 (range 1-21), with a median time of cryo-mapping and cryoablation of 96 (range 17-268) and 1141 (range 220-3732) seconds, respectively. Cryo-applications were performed more fre-

quently in posterior and mid-septal sites, whereas anterior applications were rare. The median fluoroscopy time was 3.6 min (range 0.2–21 min), while the median total procedure time was 180 min (range 100-300 min.). At the end of the procedure, 20 (28.6%) patients demonstrated persistent dual AV physiology. In particular, AH jump was observed in 14 (20%) patients and sustained slow pathway conduction in 6 (8.6%). AV nodal echo beats could be induced at the post-ablation EP study in 10 patients (14.3%).

Complications

Permanent complications were not observed. In 24 procedures, transient impairment of AV conduction occurred during cryo-ablation. Among these, there were 2 cases with 2:1 AV block, 3 cases with mechanical complete AV block and 19 (27.1%) cases with PR-interval prolongation under spontaneous sinus rhythm during application. However, in all cases, the cryo-application was immediately interrupted and AV conduction abnormalities completely resolved before proceeding to the next application.

Follow up

Follow up was completed in all study patients. The mean follow-up time was 45.8 ± 22 months (range 4-90 months). During this period, recurrence of tachycardia was documented in 11 patients (15.7%), 9 of whom underwent a repeat procedure. Additionally, a repeat EP study was performed in 1 patient who reported recurrent palpitations, but neither tachycardia nor dual AV nodal physiology could be detected. Statistical analysis revealed that recurrence was significantly associated with a shorter time of cryo-mapping (p=0.034) and the absence of Wenckebach cycle length prolongation during cryo-application (in 2 out of 5 subjects with recurrence but in none of those without recurrence, from a total of 36 patients in whom Wenckebach cycle length prolongation was measured; p=0.017). However, multivariate analysis failed to demonstrate that any of these parameters was an independent predictor of recurrence. Finally, persistence of slow pathway conduction at the end of the procedure was not statistically associated with an increased rate of recurrence (p=NS).

Learning curve

As described above, the study was divided in two periods, one including 25 patients, who underwent EP study/ablation during the first 30 months of the study, and the other comprising the consecutive 45 patients who underwent EP study/ablation during the last 60 months. Recurrence rate, acute result rate, complications, fluoroscopy time, procedure time, average number of lesions, cryo-mapping and cryoablation times, as well as the complication rate, were evaluated for each period and compared (Table 2). The acute success rate was similar (96% vs. 97.7%, p: NS) and no major complications occurred in either group, although number of lesions increased over consecutive study periods (5 vs. 6.5, p<0.05). The recurrence rate showed a statistically significant decrease, from 28% in the first period to 8.9% in the last, p<0.05). This improvement in long-term results was not associated with any difference in either procedure, fluoroscopy, or cryo-ablation times during the same period of time (Table 2). On the other hand, the cryo-mapping time increased significantly within the same period (64 s vs. 150.5 s, p=0.007).

Discussion

This study reports the long-term outcomes of cryoablation treatment of AVNRT in a pediatric population. Cryoablation exhibited an acute success rate

Table 2. Procedural variables and outcomes of the two groups of patients during the first 30 months (1st period) and last 60 months (2nd period) of the study.

	1st period	2nd period	p
Number of patients	25	45	
Cryo-mapping time (s, median, range)	64 (17-215)	150.5 (58-268)	0.007
Cryoablation time (s, median, range)	1179.5 (240-1947)	1310 (836-3732)	0.4
Number of applications (median, range)	5 (1-11)	6.5 (4-20)	0.017
Fluoroscopy time (min, median, range)	4.1 (1.4-21.2)	4.3 (1.9-7)	0.19
Procedure time (min, median, range)	180 (120-270)	155 (100-240)	0.17
Acute success	24	44	1.0
Recurrence of tachycardia	7	4	0.046

of 97.14% in terms of AVNRT non-inducibility after procedure termination, although elimination of slow pathway conduction could be achieved in only 71.4 % of patients. Apart from occasional transient AV conduction impairment, no major complications developed. The average AVNRT recurrence rate was 16%, but it was markedly reduced over time, from 28% to 8.9%. At the same time, cryoablation, fluoroscopy, and procedure times did not change significantly between these two periods of the study. These results suggest that cryoablation is a technique characterized by an efficacy comparable to that of radiofrequency ablation and exceptional safety, both of which can improve as experience and familiarization with the technique develop.

There are few existing studies reporting the clinical application of cryoablation in the setting of AVNRT treatment in pediatric population.[5-9] In the majority of them, follow-up periods were relatively short (average follow-up periods less than 13 months, ranging between 0.8 and 30 months), which is an important limitation, as recurrences can appear late after the procedure.[10] However, all of these studies report similarly high rates of acute success, exceeding 95%.

To our knowledge, there have been only three studies[10-12] with a relatively long follow-up period (two of them with mean follow-up periods of 29.5 and 36 months and one with a maximum follow-up period of 32 months). The acute success rates reported in these studies were 97-100%, whereas late recurrence rates ranged from 6.5% to 15%, values similar to those observed in our study. In one of these studies, an improvement in long-term success was reported, with a recurrence rate decline from 15% during the first half of the study to 8% during the last period of the study;[12] this is in agreement with our observations. A related literature review shows that the contemporary success rate of cryo-ablation (both acute and long-term) is remarkably high, even though relatively lower than that of radiofrequency ablation.[2,4,8] Nevertheless, the exceptional safety profile and the anticipated potential for improvement in outcomes, as experience with cryoablation evolves, have rendered this technique a preferred option for AVNRT treatment in the pediatric population,[13] which presents special anatomic issues as a result of the small size of the triangle of Koch and the potentially abnormal location of the AV node in the context of congenital heart disease.

A number of studies attempted to identify predictors of successful cryo-ablation and tachycardia recurrence.[11] In one study, by Chanani et al, only a longer fluoroscopy time was significantly associated with recurrence, but multivariate analysis failed to further support this observation.[7] In another study, Bastani et al reported that the presence of residual AV dual physiology after the completion of the procedure was a significant predictor of tachycardia recurrences.[5] However, in our study, persistent dual AV nodal physiology was not found to be a predictor of recurrence. Nevertheless, on the basis of the experience of other authors, we continue to aim for complete slow pathway elimination within reasonable limits of time, number of cryoablations, and fluoroscopy.

As described above, in our study Wenckebach cycle length prolongation was frequently observed during incremental atrial pacing at the time of cryoablation. We noticed that in 2 out of 5 patients with recurrence of tachycardia, in whom the Wenckebach cycle length during cryoablation had been monitored, such a prolongation had not been induced. In contrast, Wenckebach cycle length prolongation was present in all patients who were free of recurrence during follow up ($p=0.017$). Given the complete reversibility of this phenomenon, we theorize that this transient Wenckebach cycle length prolongation is related to the formation of the ice-ball during cryo-application, exerting mechanical pressure on the compact AV node. However, our study was not designed to define a cut-off value for Wenckebach cycle length prolongation associated with the highest predictive accuracy for slow pathway elimination. Nevertheless, this sign may be considered the equivalent of an accelerated junctional rhythm induced after successful radiofrequency ablation.

As discussed above, evolving experience with this relatively new ablative modality resulted in improvement regarding late outcomes. This is in agreement with previously published results.[12] Fluoroscopy times were also short during this study, but this must be at least partially ascribed to increasing experience with the NavX navigation system, utilized in our department as well as in other centers, with some investigators having reported "zero-fluoroscopy" procedures.[12] The number of lesions increased during the study time, indicative of our practice to administer additional "bonus" cryo-lesions at the successful site.[14] This increase in cryo-applications was not followed by any increase in complications. Similarly, there have not been any major or permanent complications associated with cryoablation in the literature, as opposed to radiofrequency ablation.[15,16]

Conclusions

Cryo-ablation is a relatively new therapeutic modality that is finding increasing use for the treatment of AVNRT. In this study we demonstrated that cryoablation demonstrates an exceptional safety profile when applied for the treatment of AVNRT in a pediatric population, and is also associated with high acute and reasonable long-term success rates, which can improve considerably, as experience and confidence with this technique evolves. An absence of Wenckebach cycle length prolongation during cryoapplication was significantly associated with a recurrence of tachycardia. Studies with a larger number of patients might be necessary to further evaluate these findings and their clinical implications.

References

1. Kugler JD, Danford DA, Houston KA, Felix G. Pediatric radiofrequency catheter ablation registry success, fluoroscopy time, and complication rate for supraventricular tachycardia: comparison of early and recent eras. J Cardiovasc Electrophysiol. 2002; 13: 336-341.
2. Fishberger SB, Whalen R, Zahn EM, Welch EM, Rossi AF. Radiofrequency ablation of pediatric AV nodal reentrant tachycardia during the ice age: a single center experience in the cryoablation era. Pacing Clin Electrophysiol. 2010; 33: 6-10.
3. Fenelon G, Elvas L, D'avila A, et al. Radiofrequency ablation of atrioventricular node reentrant tachycardia: experience in 302 patients. Acta Cardiol. 1995; 50: 397-410.
4. Papagiannis J, Papadopoulou K, Rammos S, Katritsis D. Cryoablation versus radiofrequency ablation for atrioventricular nodal reentrant tachycardia in children: long-term results. Hellenic J Cardiol 2010; 51: 122-126.
5. Bastani H, Schwieler J, Insulander P, et al. Acute and long-term outcome of cryoablation therapy of typical atrioventricular nodal reentrant tachycardia. Europace. 2009; 11: 1077-1082.
6. Miyazaki A, Blaufox AD, Fairbrother DL, Saul JP. Cryo-ablation for septal tachycardia substrates in pediatric patients: mid-term results. J Am Coll Cardiol. 2005; 45: 581-588.
7. Chanani NK, Chiesa NA, Dubin AM, Avasarala K, Van Hare GF, Collins KK. Cryoablation for atrioventricular nodal reentrant tachycardia in young patients: predictors of recurrence. Pacing Clin Electrophysiol. 2008; 31: 1152-1159.
8. Collins KK, Dubin AM, Chiesa NA, Avasarala K, Van Hare GF. Cryoablation versus radiofrequency ablation for treatment of pediatric atrioventricular nodal reentrant tachycardia: initial experience with 4-mm cryocatheter. Heart Rhythm. 2006; 3: 564-570.
9. Skanes AC, Dubuc M, Klein GJ, et al. Cryothermal ablation of the slow pathway for the elimination of atrioventricular nodal reentrant tachycardia. Circulation. 2000; 102: 2856-2860.
10. LaPage MJ, Saul JP, Reed JH. Long-term outcomes for cryoablation of pediatric patients with atrioventricular nodal reentrant tachycardia. Am J Cardiol. 2010; 105: 1118-1121.
11. Drago F, Russo MS, Silvetti MS, De Santis A, Iodice F, Naso Onofrio MT. Cryoablation of typical atrioventricular nodal reentrant tachycardia in children. Pacing Clin Electrophysiol. 2010; 33: 475-481.
12. Gist K, Tigges C, Smith G, Clark J. Learning curve for zero-fluoroscopy catheter ablation of AVNRT: early versus late experience. Pacing Clin Electrophysiol. 2011; 34: 264-268.
13. Collins KK, Schaffer MS. Use of cryoablation for treatment of tachyarrhythmias in 2010: survey of current practices of pediatric electrophysiologists. Pacing Clin Electrophysiol. 2011; 34: 304-308.
14. Drago F, Silvetti MS, De Santis 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: 191-198.
15. 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: 461-467.
16. Vassilikos VP, Efremidis M, Mantziari L, et al. Radiofrequency ablation procedures in Greece: initial experience and results from the national registry 2008-2010. Hellenic J Cardiol. 2012; 53: 108-117.