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Recurrent single echo beats after cryoablation of atrioventricular nodal reentrant tachycardia: The pediatric population

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A B S T R A C T

Background: Cryoablation for atrioventricular nodal reentrant tachycardia (AVNRT) is effective and safe with a reported limitation of lower success and higher recurrence rates. We have observed cases in which slow pathway conduction was eliminated as demonstrated by atrial extra-stimulus testing within 1 min of cryo-energy delivery but returned following tissue rewarming. Frequently, slow pathway conduction persisted despite multiple acutely successful lesions over a broad anatomic region. We aimed to determine if return of slow pathway conduction after elimination during cryoablation represents a risk for recurrent AVNRT with the same intermediate term results as slow pathway ablation. We hypothesize that remnant single echo beats in the absence of sustained slow pathway conduction and inducible AVNRT is an acceptable end point after clear slow pathway elimination during cryoablation.
Methods: Retrospective chart review of patients undergoing attempted slow pathway ablation for AVNRT using solely cryoablation between January 2015–January 2018.
Results: Forty-four patients met inclusion criteria with at-least 2 features of dual AVN physiology. 19 patients had return of slow pathway conduction shortly after clear elimination during cryoablation (Group A) while 25 did not (Group B). All in Group A had recurrent single echo beats but none had sustained slow pathway conduction at the end of the procedure nor AVNRT recurrence at 1 year.
Conclusion: Recurrent single echo beats with absent sustained slow pathway conduction and non-inducible AVNRT may be an acceptable endpoint for slow pathway ablation of AVNRT using cryoablation when there is elimination of slow pathway demonstrated during energy delivery.

1. Introduction

Atrioventricular nodal re-entry tachycardia (AVNRT) is the most common supraventricular tachycardia in the adolescent and adult population [1]. The underlying substrate for the arrhythmia was first proven by Denes et al. as being the presence of dual (AV) nodal pathways [2]. Although present in about 20–30% of the general population, dual AVN physiology only gives rise to symptomatic tachycardia in an estimated 3% of cases [3]. Radiofrequency ablation for AVNRT was first introduced in 1982 by Gallagher et al. [4] and targeted the fast pathway [5]. This approach soon proved to have a high rate of complete atrioventricular block (10–20%) [6] and so the target for ablation was moved to the slow pathway. Cryoablation has been used as an alternative to radiofrequency ablation since it has been theorized to have a lower incidence of atrioventricular block. A meta-analysis comparing cryoablation and radiofrequency ablation showed that cryoablation is a safe and effective treatment for AVNRT though late-recurrence may be more common with cryoablation [7]. The decreased risk of permanent AV block makes it a particularly attractive option in pediatric patients [8].

Prior reports have stated that slow pathway modification using cryotherapy may not be as successful as with radiofrequency energy and in order to minimize potential recurrences [9], slow pathway ablation should be the endpoint used for cryoablation. We have observed multiple cases at our center in which we documented slow pathway ablation (noted by atrial extra-stimulation pacing early during cryo lesion placement) with return of slow pathway conduction after rewarming. In most of these cases, this was documented despite multiple lesions over a broad anatomic

Abbreviations: AVNRT, Atrioventricular nodal re-entry tachycardia; AV, atrioventricular; ERP, Effective refractory period.

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region in the posterior triangle of Koch. We aimed to determine if the return of slow pathway conduction after clear slow pathway elimination during cryoablation represents a risk for recurrent AVNRT. We hypothesized that remnant slow pathway conduction (slow pathway modification) with single echo beats in the absence of sustained slow pathway conduction and non-inducible AVNRT is an acceptable end point of success after clear slow pathway elimination was demonstrated during cryo lesion placement.

2. Methods

We performed a retrospective chart review of all pediatric patients (age 0–21 years) undergoing primary catheter ablation for AVNRT with cryo-thermal energy as the only ablation energy source during the period of January 2015–January 2018 in the electrophysiology laboratory at Children's Healthcare of Atlanta. Patients with a prior electrophysiology study, attempt at ablation with radiofrequency ablation and those with evidence of an accessory pathway were excluded. The St. Jude Velocity Mapping system was used for the procedure in each of the cases. The institutional review board at Children's Healthcare of Atlanta approved this study.

2.1. Definitions

1. A-H Jump: Atrial extra-stimulus testing was performed during the electrophysiology study. An increase in the local A to local H interval by > 50 ms with a 10 ms decrement in the coupling interval was defined as an A-H jump thus leading to a discontinuous conduction curve [10].
2. Sustained slow pathway conduction: Incremental atrial pacing was performed during the electrophysiology study. During this maneuver, the finding of the PR interval exceeding the RR interval with stable 1:1 atrial to ventricular conduction was indicative of sustained slow pathway conduction
3. Echo beats: During atrial extra-stimulus testing, a retrograde atrial electrogram immediately following the ventricular electrogram was indicative of an echo beat (after confirmation that the antegrade conduction was over the slow pathway)
4. Slow pathway: Presence of slow pathway and thus dual AV node physiology was ascertained if 2 of the above 3 criteria were met; i.e. presence of a discontinuous conduction curve, sustained slow pathway conduction or presence of echo beats
5. AVNRT: A narrow complex tachycardia which met the following criteria [10,11]:
   i) Initiation and termination by atrial or ventricular extra-stimuli or atrial incremental pacing
   ii) Presence of dual AV node physiology ascertained during baseline testing with earliest retrograde activation at the His bundle catheter
   iii) Initiation dependent on critical A-H interval during slow pathway conduction
   iv) Retrograde atrial activation with variable activation of the triangle of Koch (V-A time < 70 ms during tachycardia). There were no patients with atypical AVNRT in our cohort
   v) Evidence that the atrium, His bundle and ventricle are not required for sustaining the tachycardia

Eligible patients were sub-divided into two groups:

Slow pathway modification group (Group A): Patients who had evidence of residual slow pathway conduction at the completion of the procedure as evidenced by an A-H jump and single echo beats despite early testing (between 30 and 60 s into energy delivery and persisting throughout the ablation lesion) showing elimination of slow pathway conduction.

Slow pathway ablation group (Group B): Patients who did not have return of slow pathway conduction after clear slow pathway elimination during cryoablation. Clear slow pathway elimination during cryoablation was defined as loss of all evidence of dual AV node physiology such as A-H jump, echo beats or sustained slow pathway conduction.

The end points for the electrophysiology study were defined as i) elimination of tachycardia if AVNRT was inducible along with loss of evidence of dual AV node physiology, ii) elimination of any evidence of dual AV node physiology if AVNRT was non-inducible or iii) presence of single echo beats in the presence of a persistent A-H jump but absence of sustained slow pathway conduction and non-inducible AVNRT. All patients underwent testing atleast 30 min after end points for the electrophysiology study were met and were monitored in the hospital for atleast 4 h. Patients in Group A specifically were tested 60 min after the end points of the study were met to ensure there was no return of sustained slow pathway conduction or inducible tachycardia. Testing and methods for re-induction included atrial extra-stimulus testing, incremental atrial pacing down to atrioventricular node wenckebach and the use of isoproterenol. All patients in Group A were tested after starting an infusion of isoproterenol, however, the dose, time of testing on isoproterenol and during the washout phase was operator dependent and not standardized.

2.2. Additional data

We collected patient demographic variables for all eligible patients including age, weight and gender as well as electrophysiology study data. Electrophysiology data included the size of the cryoablation catheter used, the presence or absence of inducible tachycardia with and without the use of isoproterenol, baseline AV node effective refractory period (ERP) and the fast pathway effective refractory period, total duration of cryo lesion application along with the duration of the longest lesion and the electrophysiology study data at the end of the case in both the groups.

2.3. Follow up

All patients underwent follow up with their primary cardiologist at 4 weeks and at 12 months following the electrophysiology study unless there were any clinical concerns. An EKG and rhythm strip was performed at every visit; Holter monitoring was performed at the discretion of the primary cardiologist. At every visit, patients were specifically asked about symptoms which may have indicated a recurrence or a new onset arrhythmia. Follow up was limited to 1 year since the last patient enrolled in the study had their ablation 1 year prior to data collection.

2.4. Statistical analysis

Normality of continuous variables was assessed using histograms, normal probability plots and the Anderson-Darling test for normality. Descriptive statistics are presented as counts and percentages for categorical variables and median with interquartile range (IQR) for continuous data with skewed distribution. Comparisons between groups for categorical variables were made using Chi-square tests or Fisher's exact test when expected cell counts were <5 and for continuous variables using Wilcoxon rank-sum tests. Statistical analysis was performed using SAS version 9.4 (Cary, NC) and statistical significance was assessed at 0.05 level.

3. Results

Forty-four patients met inclusion criteria during the study time period. All patients had evidence of at least 2 features of dual AVN physiology: discontinuous conduction curve, sustained slow pathway conduction or presence of echo beats. Nineteen patients had return of slow pathway conduction shortly after clear slow pathway elimination during cryoablation (Group A) while 25 patients had no return of slow pathway conduction (Group B). All patients had symptoms suggestive of an arrhythmia or a history of an inappropriately elevated heart rate (palpation by a school nurse); while 16 patients in Group A and 20 patients in Group B had documented supraventricular tachycardia. Only 1 patient in Group A had partial anomalous pulmonary venous drainage s/p surgical repair while the rest of the patients in the study had a structurally and functionally normal heart. The demographic characteristics were not significantly different between the 2 groups (Table 1).

All patients in Group A had evidence of discontinuous conduction curve (A-H jump) and 16/19 patients had echo beats while 23/25 patients in Group B had a discontinuous conduction curve and all had echo beats. All patients in both groups had evidence of sustained slow pathway conduction. A total of 6 patients in each group had non-inducible tachycardia. In Group A, all 6 of these patients had a discontinuous conduction curve and echo beats while in Group B only 1 patient did not have a discontinuous conduction curve. The patient in Group B without a discontinuous conduction curve had a very long AH interval suggestive of a slow pathway despite the absence of a "jump" and in combination with sustained slow pathway conduction suggested the presence of a slow pathway. The baseline electrophysiology study data including size of the cryoablation catheter tip used, the presence or absence of inducible tachycardia with and without the use of isoproterenol, baseline AV nodal effective refractory period and the fast pathway effective refractory period, total duration of cryoablation lesion application along with the duration of the longest lesion was also not significantly different between the 2 groups (Table 1 and Fig. 1). The median lesion number during which there was initial loss of evidence of dual AVN physiology was 6 and 7 in Group A and Group B respectively ($p = 0.11$) with the majority of these lesions being 4 min long (Fig. 1). In Group A, the median time to return of evidence of dual AVN physiology was 5 [2–10] minutes.

At the conclusion of the electrophysiology study the AVNERP for patients in the two groups were not significantly different ($p = 0.502$). All patients in Group A had recurrent single echo beats with an A-H jump. However, no patients in Group A had sustained slow pathway conduction or inducible AVNRT at the end of the procedure. We were able to follow all patients for 1 year after their procedure and none of the patients in Group A had recurrence of AVNRT at 1 year follow up compared to 1 patient in Group B ($p = 1.000$) (Table 2).

The patient in Group B who had recurrence was a 14 year old female, who had a history of palpitations and had an irregular heart rate documented on a well child check with a normal baseline EKG (no ventricular pre-excitation). A Holter monitor demonstrated narrow complex tachycardia at a rate ~260 bpm. During the electrophysiology study, she had evidence of a discontinuous conduction curve, sustained slow pathway conduction and echo beats with a fast pathway ERP of 400 ms and an AVNERP of 320 ms. She had inducible tachycardia with atrial extra-stimulus testing without isoproterenol. Adenosine challenge in sinus rhythm and with ventricular pacing demonstrated atrio-ventricular and ventriculo-atrial dissociation suggesting an absence of an accessory pathway. She had a total of 14 cryoablation lesions placed during the study (total duration 50 min, longest lesion 4 min) with evidence of slow pathway being eliminated on lesion number 11. However, at 6 months post ablation, she complained of recurrent palpitations and a Holter monitor demonstrated a narrow complex tachycardia at 222 bpm. She was taken back to the electrophysiology lab and was found to have AVNRT again which was cryoablated. She has been recurrence free since her second ablation.

4. Discussion

Cryoablation is used for AVNRT ablation in specialized populations with an increased risk of AV block, such as the pediatric population [12]. During application of a cryoablation lesion, liquid nitrogen is pumped into the catheter which changes state to gas in the tip, cooling it down to approximately minus 80° celsius. Before creating an irreversible lesion, cryotherapy offers the possibility of observing the electrophysiological effect of the lesion prior to permanent tissue damage [13]. This 'test-freeze' allows the operator to check if ablation at the desired location will be effective and safe. Safety is guaranteed since creation of any kind of AV block during cryomapping to date has been shown to be fully reversible [14].

Cryo induced permanent lesion formation on the cellular level is characterized by three phases: the freeze/thaw phase, the hemorrhagic and inflammatory phase, and, the replacement of this acute lesion by fibrosis. In contrast, radiofrequency ablation induces thermal lesion formation both through resistive and conductive heating of myocardial tissue. The quality of the thermal injury is dependent upon both time and temperature with tissue temperatures of 50 °C or higher being necessary to create irreversible myocardial injury [15]. While prior studies have reported reduced recurrence rates of AVNRT following radiofrequency ablation as

Table 1
Patient demographics and baseline electrophysiology study characteristics in the two groups.

Variable	Group A (N=19, 43.2%)	Group B (N=25, 58.8%)	p-value
Age, years	15.2 (10.7–16.0)	13.5 (11.4–16.3)	0.74
Weight, kg	51.8 (36.2–64.0)	53.0 (42.5–56.7)	0.72
Gender			0.13
Male	9 (47.4%)	6 (24.0%)	
Female	10 (52.6%)	19 (76.0%)	
Cryo Tip			0.85
6 mm	7	12	
8 mm	12	13	
Inducible tachycardia	13 (68.4%)	19 (76.0%)	0.57
Inducible tachycardia without isoproterenol	6 (46.2%)	9 (47.4%)	0.95
AVNERP (ms)	275 (260–280)	280 (250–300)	0.90
Fast pathway ERP (ms)	320 (280–380)	330 (290–340)	0.79
A-H jump	19 (100.0%)	23 (92.0%)	0.63
Echo beats	16 (84.2%)	25 (100.0%)	1.00
Sustained slow pathway conduction	19 (100.0%)	25 (100.0%)	

ERP: Effective refractory period.

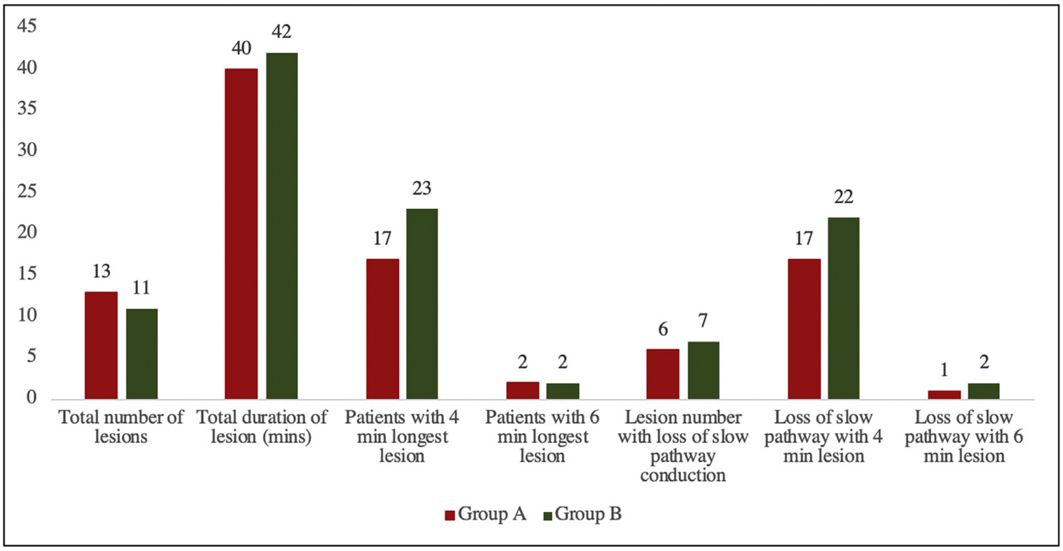

Fig. 1. Characteristics of the electrophysiology study: initial loss of slow pathway conduction.

Table 2
Characteristics of the electrophysiology study: return of slow pathway conduction.

Variable	Group A	Group B	p value
Time to return of evidence of dual AV node physiology (mins)	5 [2–10]	–	
Number of lesions post-return	9 [8–15]	–	
Longest lesion post return			
3	1 (5.3%)	–	
4	17 (89.5%)	–	
6	1 (5.3%)	–	
Inducible tachycardia	0 (0.0%)	0 (0.0%)	
AVNERP (ms)	320 (280–380)	320 (280–340)	0.502
Recurrent Echo beats	19 (100.0%)	–	
A-H jump	19 (100.0%)	–	
Sustained slow	0 (0.0%)	–	
Recurrence at 1 year	0 (0.0%)	1 (4.0%)	1.000

ERP: Effective refractory period.

compared to cryoablation, the risk of AV block especially in pediatrics may outweigh this benefit for some patients.

During AVNRT ablation using cryoablation in our pediatric electrophysiology laboratory, we have observed multiple cases in which slow pathway conduction returned quickly upon rewarming after initial clear elimination of slow pathway conduction during the application of the cryo lesion. Our study did not detect any significant patient variable that would predict return of slow pathway conduction after apparent slow pathway elimination during a cryo lesion. Furthermore, we were unable to identify procedural variables that were associated with recurrence of slow pathway conduction. End-points for cryoablation in the pediatric population for AVNRT where there is some evidence of residual slow pathway conduction is not as well defined compared to radiofrequency ablation. Our practice was to expand the region of ablation once this recurred but often the evidence for slow pathway conduction persisted despite this technique. We were aggressive in expanding the region of ablation in patients with recurrence of slow pathway conduction given the safety of cryoablation, in addition to studies suggesting that complete elimination of slow pathway conduction (no A-H jump or echo beats) results in improved outcomes in patients with AVNRT [16]. This led to an increased number of median lesions in Group A patients. However, the median number of lesions in patients without evidence of recurrence of slow pathway conduction was similar to other studies in the pediatric population [17]. In addition, a study looking at mid-term outcomes (35 months (8–60 months)) following cryoablation of AVNRT in the pediatric population with an 8 mm cryoablation catheter tip, had a median number of lesions of 9 (3–30) per study. This study showed that cryoablation of AVNRT was safe and effective with a low recurrence rate of 1% [18]. This highlights the fact that increased number of cryolesions, even with an 8 mm tip may be safe and improve mid and long term outcomes.

Additionally, we had hypothesized that the return of slow pathway conduction after apparent elimination during a cryo lesion might be related to the size of the cryoablation catheter tip (6 mm vs 8 mm) used during the application of such lesions. However, this study demonstrates that the size of the cryoablation catheter tip was also not related to such recurrences. Based on our data, we did not identify any statistically significant predictors associated with recurrence of slow pathway conduction despite acute success during a cryoablation lesion application. We hypothesize that this finding may be related to the amount of tissue injury created during the cryoablation application, such that we were able to achieve transient success during the lesion. However, as the tissue rewarmed, a portion of the slow pathway was able to recover but not sustain tachycardia or consistent conduction during rapid atrial pacing. In addition, we also sought to compare short/intermediate term success for these patients defined as no recurrence of AVNRT over 1 year of follow up.

The patients in whom slow pathway conduction recurred after initial elimination were labelled as cases undergoing a "slow pathway modification." All of these patients had evidence of recurrent single echo beats and an A-H jump at the end of the case but none had sustained slow pathway conduction (tested on and off isoproterenol). Interestingly, none of these patients had recurrence of symptoms or evidence of supraventricular tachycardia at 1 year follow up while one of the patients who had no evidence of residual slow pathway conduction did recur prior to 1 year. Prior adult studies had suggested that the presence of an A-H jump with a single retrograde echo beat was highly associated with recurrence in patients undergoing cryoablation for AVNRT ($p = 0.0001$). The same study had suggested that the reported relatively high recurrence rates of AVNRT post cryoablation was the failure to eliminate both of these findings [16]. This is in contrast to the commonly accepted end points for radiofrequency ablation of AVNRT, where single echo beats with an A-H jump in the absence of sustained slow pathway conduction or inducible tachycardia is considered an acceptable outcome with a low recurrence risk [19]. Our study suggests that the presence of single echo beats with an A-H jump in the absence of sustained slow pathway conduction along with the absence of inducible tachycardia may be an acceptable endpoint after initial elimination of the slow pathway during cryoablation. The differences in the results between these studies may be secondary to the different demographics of the study population (adults vs pediatrics), the intrinsic differences in the myocardium of the adult and pediatric population [20,21] and the shorter follow up duration of our study.

Our study had limitations including its retrospective nature. Additionally, we did not collect operator variables such as which operator was performing the procedure, years in practice or preference for cryo versus radiofrequency ablation for AVNRT and the dose/time of testing on isoproterenol and during the washout phase was not standardized. Next, this was a single center study which may have skewed the results and limited the generalizability of our findings. Our sample size was small and our data warrants validation by larger prospective studies to improve our statistical power. Finally, our study had a short follow up period of 1 year which may not have captured all of the recurrences.

5. Conclusion

Cryoablation remains an effective and safe method of AVNRT ablation in the pediatric population. Recurrent single echo beats with absence of sustained slow pathway conduction and non-inducible AVNRT appears to be an acceptable endpoint for slow pathway ablation of AVNRT when there is clear elimination of slow pathway demonstrated during energy delivery. However, further larger studies are needed to validate our findings.

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Declaration of competing interest

None of the authors have any conflicts of interest to disclose.

CRediT authorship contribution statement

Soham Dasgupta: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Michael Kelleman:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Robert Whitehill:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - review & editing, Supervision. **Peter Fischbach:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - review & editing, Supervision.

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