Radiofrequency and Cryoablation Therapies for Supraventricular Arrhythmias in the Young: Five-Year Review of Efficacies

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Background: *Cryoablation (Cryo) has augmented radiofrequency (RF) as the ablation energy choice for most supraventricular tachycardias (SVT). Although initial acute results and more recent, but limited, 3–36-month follow-up studies have been reported, more longer follow-up information is required to determine actual efficacy.*

Methods: *Data from patients with structurally normal hearts who underwent reentrant forms of SVT ablation at our institution from January 2005 to December 2009 were reviewed. These included demographics, clinical and electrophysiologic findings, and ablative energies used. Following apparent acute success, all patients were then reevaluated for any potential recurrences of SVT or preexcitation up to 5 years later.*

Results: *A total of 155 patients (83 male) were reviewed (mean age 13.4 ± 3.7 years). Ablations were predominantly right-sided (75%). Atrioventricular reciprocating tachycardia was seen in 74% and atrioventricular node reciprocating tachycardia (AVNRT) in 17% of patients. For concerns of atrioventricular node integrity, Cryo ± RF was user-preferred for anteroseptal accessory fiber locations and AVNRT. Acute success rate was 98% and chronic 83.2% over the next 5 years. Among patients with accessory pathways, recurrence was pathway number and location dependent: significantly higher ($P < 0.05$) if they were right anterior-anteroseptal, multiple, or with a broad-distribution pattern. There were no significant differences in recurrence rates with use of RF or its combination with Cryo.*

Conclusion: *Radiofrequency ablation and Cryo are both effective therapies for pediatric patients. Although use of Cryo with RF in combination may enhance safety while affording comparable success, risk of recurrence still persists in the current era among patients depending on accessory pathways connection location and characteristics. (PACE 2012; 35:711–717)*

supraventricular tachycardia, ablation, radiofrequency, cryotherapy, recurrence

Introduction

Radiofrequency catheter ablation (RFA) has revolutionized the treatment of diverse supraventricular tachycardias (SVT) in children.[1] Although developed in the 1980s and widely applied in the 1990s, formalized guidelines for its use in clinical practice were not developed until recently.[2] Based on data from the Pediatric Radiofrequency Catheter Ablation Registry, acute failure rates fell from 9.6% in the early 1990s to 4.3% at the end of the decade.[3]

RFA, however, can cause complications including thromboembolic events resulting in neurological damage, coronary artery injury, atrioventricular (AV) node injury, conduction block,[4] and even death.[5–7] Cryoablation (Cryo) is a newer energy modality of catheter ablation which has proven to be safe in many studies.[8,9] Previous studies have reported acute success rates of only 69–92% which is less than that reported for RFA[10,11] and higher arrhythmia recurrence compared to RFA.[8]

Most of the initial RFA and Cryo studies reported only acute success results. More recent but limited combined RFA/Cryo studies have reported from 9 to 35% recurrence rates.[12–14] But, there is a paucity of studies comparing early and late ablative success rates using RFA or Cryo or combinations of both in pediatric patients with structurally normal hearts. We sought to identify potential risk factors for SVT recurrence after initial successful ablation in the current era.

Conflict of interest: None.

Disclosures: None.

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Methodology

This was a retrospective study conducted at The Children's Hospital of Michigan, Division of Cardiology. The study was approved by the institutional review committee at Wayne State University School of Medicine, Detroit Medical Center. The inclusion criteria were patients with reentrant forms of SVT with documented evidence by electrocardiogram (EKG), Holter, or event monitor referred for an initial catheter ablation. Patients with repeat procedures were excluded. To allow for a degree of consistency in comparison of energy sources, *per se*, patients with structural congenital heart defects or previous ablations were excluded. As such, only patients with atrioventricular node reciprocating tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), sinus reentry, as well as His bundle reentrant forms of SVT were included in this study. Also, since the purpose was to evaluate energy delivery efficacy in discrete select regions in deference to performance of a more extensive linear "maze," patients with primary atrial muscle tachycardias such as flutter/fibrillation also were not included. Ectopic atrial tachycardia was not included as it was considered to be an automatic tachycardia.

All clinical, intracardiac electrophysiological study (EPS) and follow-up data were reviewed. The demographic and clinical data collected included patient's age, gender, ethnicity, height, weight, body surface area, clinical manifestations, as well as presence or absence of preexcitation at rest and on exercise stress testing. EPS data included site and number of locations of accessory pathways (APs), and use of RFA or Cryo or both. Follow-up data at 1–2 weeks and from 3 to 77 months later included recurrence of symptoms; results of treadmill exercise stress testing; and 15-lead EKG, Holter, or telephone event monitor reports and any repeat EPS procedures.

All patients underwent EPS under the same protocol by two established pediatric electrophysiologists. All procedures were performed under standard general anesthesia. Established techniques using multielectrode catheter placement for intracardiac pacing and mapping were performed in all cases. A standard flexible quadripolar roving electrode catheter was used for selective AP site mapping as required. A three-dimensional mapping system (St. Jude Medical, Minnetonka, MN, USA) was used to define anatomical and electrical landmarks to limit fluoroscopic imaging support for all patients post mid-2007.

Among patients with overt preexcitation standard mapping for prograde AP conduction to delineate location was conducted prior to initiation of stimulation protocols. The region of electrical interest was established to include atrial and ventricular activation. For this study, the now standard, albeit somewhat arbitrary, AP site map was used to define general AP locations, with the realization that AP connections are not necessarily discrete and separate as the AV annulus has limited definable boundaries.[3,15] Multiple pathways were defined by established techniques of catheter mapping 1–3 cm apart or change in any preexcited QRS morphology following ablation at different sites or induction of another form of tachycardia with a different QRS morphology or axis.[18] Since fluoroscopic mapping-based identification of presence of multiple APs is inexact, patients in whom mapping of AP connections and ablations were performed across several or adjoining traditional fluoroscopic locations (e.g., anterior-anteroseptal) were said to have broad-distribution fibers, ostensibly with wide atrial and ventricular insertions, in deference to more discrete and, by inference, compact APs.[19]

Standard programmed electrical stimulation (PES) protocols were instituted specifically to only induce tachycardia, not to induce nonclinical atrial flutter/fibrillation (AF). These included single, double, and burst atrial extra stimuli at standard variable drive-paced cycle lengths (all $>$200 ms), both with and without isoproterenol infusion (0.1 mcg/min), as required for arrhythmia induction. Once the SVT mechanism (e.g., AVRT or AVNRT) was identified and any APs located by standard catheter mapping, RFA and/or Cryo ablations were performed. As part of the established EPS protocol at our institution, risk stratification of each patient with evaluation of refractory periods, inducibility of arrhythmias, and concomitantly measured hemodynamics, especially among patients with overt preexcitation and potential for sudden death, was performed. This also permitted a more accurate determination of "success" as the entire EPS stimulation protocol was repeated following ablation. In instances of induced hemodynamic instability, cardioversion was performed.

Each RFA application was performed up to 60 seconds to attain a tissue temperature from 50°C–70°C (Boston Scientific, Natick, MA, USA) and each Cryo was performed using a 4-mm Cryo catheter for up to 4 minutes using the two-tiered approach of initial tissue chilling at –30°C for several seconds followed by cellular disruption achieved at a temperature of −70°C (CryoCath, Medtronic). Once tachycardia occurred, any spontaneous deterioration to AF was recorded. All patients were observed for 60 minutes following apparent successful ablation. This was followed by

a full repeat PES with and without isoproterenol to evaluate inability to reinduce any SVT, as well as administration of adenosine (for AVRT cases) to confirm evidence of any residual accessory orthodromic connections. Recurrence required additional ablation. Success was therefore defined as meeting several criteria following a 60-minute postablation waiting interval: (1) A normal QRS in all patients and no visible preexcitation among those patients with previous preexcitation; (2) Inability to reinduce SVT in spite of repeat PES with and without isoproterenol infusion among all patients; (3) No evidence of residual preexcitation following adenosine administration. Retrograde VA conduction, which can be a common ancillary finding in children, was not uniformly tested in all patients postablation and therefore not included as a success criteria *per se*.

After the procedure, as part of hospital policy, patients were observed overnight and a standard 15-lead EKG to reconfirm a normal QRS and echocardiogram/Doppler to evaluate valve integrity were performed the next day prior to discharge. All patients were then reevaluated from 1 to 2 weeks followed by 1–3 months later and then on a recommended yearly basis for any SVT recurrences. All follow-up clinical evaluations included a standard 15-lead EKG. If patients had any recurrence of clinical symptoms, telephone event and/or Holter monitor recording equipment was provided for confirmation depending on the discretion of the cardiologist. For SVT recurrence, medical management was initiated before repeating the electrophysiology (EP) procedure. For statistical analysis, patients were divided into two groups: Group 1, those with SVT recurrences and Group 2, those without SVT recurrences. Group 1 patients also included those with a return of preablation preexcitation with or without SVT.

Statistics

This was a retrospective study. All data were reported as mean and standard deviation for continuous variables and frequency for categorical variables. The two groups were compared using independent sample *t*-test, Mann-Whitney U test, Fisher's exact or χ^2 tests depending on the distribution of the data. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 155 patients with structurally normal hearts underwent catheter ablation at our institution for the indicated forms of SVT from January 2005 to December 2009. Of these, 83 were males and 72 were females. Mean age at catheterization was 13.4 ± 3.7 years. Based on listed ethnicity, 99 (64%) were of European-, 34 (22%) African-, five (3%) Mid-Eastern-, and one (1%) Asian-American ancestries.

Of the initial 155 patients, acute success was achieved in 153 (98%). Later, 24 patients (16.8%) developed recurrence of SVT or overt preexcitation at a mean follow-up interval of 38 months (Group 1), whereas 129 had no evidence of either recurrence (Group 2). Median follow-up interval was 41 months (1–77 months) and 21 patients (13.5%) were lost to follow-up. Of the remaining 134 patients not lost to follow-up, clinical information was available on 108 patients (81%) at 2 years, 82 (61%) at 3 years, 52 (39%) at 4 years, and 29 (22%) at 5 years postablation. Although patients in the recurrence group were younger than those in the nonrecurrence group ($P < 0.05$), the other demographic distributions including weight, sex, and race were not significantly different between both groups (Table I). Pre-EPS, overt preexcitation on resting EKG was seen in 82 patients (53%). This included 13 (50%) in Group 1 and 69 (54%) in Group 2. This was not significantly different ($P = 0.8$). Tachycardia types were typical for a pediatric population: 74% atrioventricular reentry (AVRT) with accessory bypass fibers, 17% "slow-fast" AV node (AVNRT), 5% sinus node, and 4% His bundle reentry.

Fifty-five patients (36%) had more than one accessory connection catheter map location including 58% of Group 1 and 31% of Group 2 ($P = 0.01$). Among these patients, multiple accessory connection locations encompassing both right and left valve locations were found

Table I.

Patient Demographics between Groups

	Recurrence (n = 26)	No-recurrence (n = 129)	P- value
Age	11.7 ± 3.6	13.6 ± 3.6	<0.05
Weight	54 ± 21	53 ± 22	0.9
Sex—Male	10 (39%)	73 (57%)	0.1
European ancestry	17 (65%)	82 (64%)	0.9
African ancestry	7 (27%)	27 (21%)	0.6
Mid-Eastern ancestry	1 (4%)	4 (3%)	1.0

No significant difference between the two groups in terms of gender, weight, and ethnicity. Patient age, however, was significant. There was only one patient of Asian ancestry. That patient had no recurrence.
Value expressed as mean ± standard deviation or as number (percentage).

in 10% whereas broad-distribution connections were found in 26%. Of these latter, the most common was an overlap between right anterior and anteroseptal catheter-mapped regions. The average number of mapped AP locations in Group 1 was 1.7 ± 0.7 and 1.4 ± 0.6 in Group 2 ($P < 0.05$).

Ablations were required in variable areas depending on accessory fiber locations or mechanism of SVT. In this review, AVNRT was considered a right-sided tachycardia which contributed to the difference between right and left locations. Therefore, ablations were predominantly performed on the right side: 112 patients (75%) versus left side in 54 patients (25%). Among all patients with right-sided tachycardia foci, anteroseptal locations were seen in 42 patients (20%), anterior in 33 (15%), and midseptal in 30 (14%); AVNRT was seen in 35 (17%), sinus node reentry in 11 (5%), and His bundle in five (4%). AVNRT ablations were performed to either eliminate or modify "slow" AV pathway conduction properties.

Among AVRT mechanisms, SVT recurrence was significantly higher among patients following right anteroseptal fiber ablation with a 33% recurrence rate ($P < 0.01$ between both groups) and an odds ratio of 4.2. Recurrence was not significantly higher in the other fiber locations, including AVNRT (Table II). However, among patients with multiple or broad-distribution AP distributions, 27% had recurrences ($P = 0.01$ between both groups) and an odds ratio of 3.0.

During the EPS, RFA and/or Cryo were used depending on the location of the APs and at the discretion of the electrophysiologist performing the procedure. With concern for AV node integrity, RFA and Cryo were preferably used for AP locations away from and in close proximity to the normal conduction pathway, respectively. For most of the fiber locations close to the conduction pathway, like AVNRT, Cryo was used first for cryomapping and cryoablation. RFA was then used in the same location when it was deemed safe by cryomapping or for placing linear lesions further away from the conduction pathway. Patients were divided into three groups based on type of energy source used for ablation. RFA alone was used in 87 patients (107 fiber locations), Cryo alone in nine patients (11 fiber locations), and both RFA/Cryo were used in 59 patients (97 fiber locations). Cryo with/without RFA was preferably used for AVNRT and right anteroseptal fibers to optimize avoidance of AVN conduction damage. RFA alone was preferred for left-sided fibers. When required due to fiber location, coronary sinus RFA was also performed (Table III). The number of RFA ablations applied was higher in the RFA + Cryo group compared to RFA group, indicating that this group required more ablations to achieve success. The number of Cryo, though higher in RFA + Cryo group compared to Cryo alone, did not reach statistical significance. Electroanatomic 3D mapping was used for all patients post mid-2007. However, comparison on recurrence cannot be made between those patients with and without 3D mapping as the follow-up period was significantly higher for patients without 3D mapping compared to those in whom it was used, resulting in higher recurrences in the pre-2007 group without use of 3D mapping.

There were 34 African-American patients forming 22% of the study group, including 16 males (47%). Of these, 22 (65%) had overt preexcitation. Seventeen (50%) of them exhibited multiple or broad-distribution right-sided AP connections compared to only 31% in the non-African-American races. This difference was significant ($P = 0.04$). A total of 51 AP fiber locations were identified among this ethnic group, including 40 (78%) right-sided and 11 (22%) left-sided fibers. Among the right-sided APs, right anterior were seen in 12 (30%), right anteroseptal in eight (20%), and midseptal in nine (23%). AVNRT was seen in seven (17%), sinus reentry in two (5%), and His reentry in two (5%).

Acute success rates as defined earlier (inability to reinduce any arrhythmia, no preexcitation with adenosine, and a normal QRS morphology) was 98%. Both Cryo with/without RFA Groups had 100% acute success. Of the two patients in the RFA-only Group who had acute failure, one had both right anterior and anteroseptal fibers and the other had left posterolateral fibers. Both patients

Table II.

Accessory Fiber Locations/Ablation Sites between Groups

Fiber Locations	Recurrence (n = 42)	No-recurrence (n = 173)	P-value
Right anteroseptal	14 (33)	28 (16)	<0.01
Right anterior	8 (19)	25 (15)	0.1
Midseptal	4 (10)	26 (15)	0.3
Left posterolateral	6 (14)	48 (28)	0.2
AVNRT	5 (12)	30 (17)	0.8
Sinus reentry	2 (5)	9 (5)	1.0
His bundle	3 (7)	7 (4)	0.2

Recurrence is significantly higher in patients with right anteroseptal fiber locations ($P < 0.01$). No other fiber locations were associated with increased recurrence.
Value expressed in number (percentage).

Table III.

Accessory Fiber Locations between Groups Based on Type of Energy Source Used for Ablation

Fiber Locations	RFA (n = 107)	Cryo (n = 11)	RFA + Cryo (n = 97)	P-value
Number of patients	87	9	59	
Right anteroseptal	13 (12)	3 (27)	26 (27)	< 0.01
Right anterior	16 (15)	0 (0)	17 (18)	0.1
Midseptal	14 (13)	0 (0)	16 (16)	0.8
Left posterolateral	44 (42)	0 (0)	10 (10)	< 0.01
AVNRT	10 (9)	5 (46)	20 (21)	< 0.01
Sinus reentry	8 (7)	1 (9)	2 (2)	0.2
His bundle	2 (2)	2 (18)	6 (6)	0.36
Number of RFA	13 ± 11	–	21 ± 16	0.01
Number of Cryo	–	7 ± 5	11 ± 8	0.5

Cryo with or without RFA was preferably used for right anteroseptal fiber locations and AVNRT while RFA alone was preferably used for left-sided fiber locations.
P-value comparing RFA group with RFA + Cryo group.
Value expressed in number (percentage) or mean ± standard deviation.

had persistent preexcitation after the ablation, but no tachycardia could be induced with PES after waiting for an hour and parents deciding against further ablations. Following initial success, 16.8% of patients had SVT/preexcitation recurrences during the follow-up interval. Recurrence risk was not significantly different with use of RFA (14%), Cryo (22%), or both (20%). By survival analysis, no significant difference in recurrence was found between the three groups (Fig. 1). The EPS were performed by two electrophysiologists in our institution and the recurrence risk was not significantly different between them. Using regression analysis, recurrence risk was highest in patients with right anteroseptal fibers.

Rhythm complications of flutter/fibrillation occurred in five patients during PES with rapid ventricular response and hemodynamic deterioration that required cardioversion. There were no AV conduction problems associated with any initial ablation. There was no evidence of coronary sinus or AV valve problems clinically or by ultrasound. There were no complications of stroke, coronary artery injury, and no deaths were encountered.

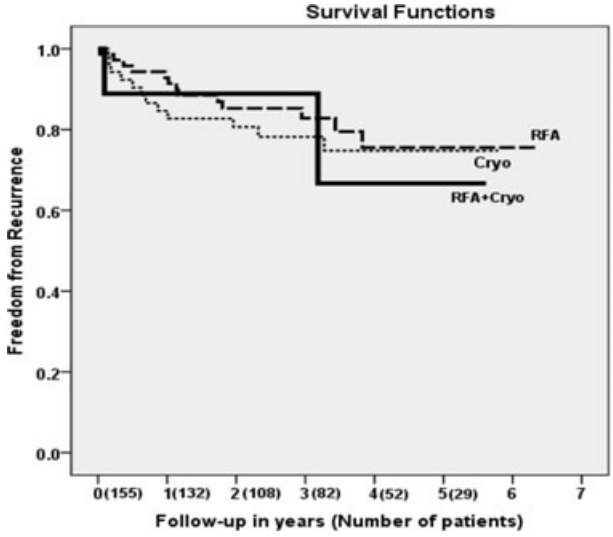

Figure 1. *Kaplan-Meyer curve comparing freedom from recurrence between three groups based on type of energy source used. There is no significant difference in recurrence between the three groups.*

Discussion

SVT is a frequently encountered arrhythmia in pediatric patients. Medical therapy requires patient and family compliance which is often less than optimal and antiarrhythmic drugs can be proarrhythmic. Although surgical ablation was an available alternative previously, catheter-delivered RFA and Cryo have now revolutionalized treatment modalities. The safety and efficacy has been improving over the years with the learning curve phenomenon as applied to use in children.[14,15]

RFA is the widely used older energy source for ablation. The success has been improving over the years. The Pediatric Radiofrequency Catheter Ablation Registry reported an improvement in the initial success rates from 90.4% (1991–1995) to 95.2% (1996–1999) for RFA among all patients.[3] Our report has a better acute procedural success rate for RFA at 98%. Cryotherapy is the newer

modality of treatment. An acute success rate of 87.1% for cryotherapy has been reported, which is less than that for RFA with success rates for AVNRT ablation higher than for AVRT (95.5% vs 62.5%, $P < 0.05$).[10] In our study, with Cryo alone, the acute success rate was 100%, but only a limited number of patients were in this group. For many of our patients, RFA was used together with Cryo and the success rate was also 100%. The reason for such a high acute success rate in our study reflects use of RFA along with Cryo in locations where RFA could be used safely.

Rates of initial success also depended on AP location. In our patient population, among those with AVRT, the fiber locations were predominantly right-sided (66%). This is in contradistinction to the findings of the initial Prospective Assessment after Pediatric Catheter Ablation as well as a more recent study in which right-sided pathways were found in only 17–30% of patients.[4,20] Although the "anatomical maps" do help to standardize ablation catheter locations by fluoroscopy, they are somewhat arbitrary and not based on any direct histological evidence. Previous studies have reported multiple AP fibers in 5–20% of patients based on clinical findings.[20] However, right-sided AP connections are anatomically different from left. The associated folding of the atrium over the ventricle, inherent anatomical variability of the right-sided A-V ring, AP physical characteristics, and orientation relative to atrial and ventricular myocardium may all contribute to an inherent overlap among the sites, especially on the right. Wide AP branching and spatial separation of any two APs, as shown in histologic studies, may present with a clinical picture of multiple or broad-distribution connections, hindering effective catheter mapping and ablation.[16] In the previous era of surgical ablation, an extensive valve annuloplasty was often performed to ensure AP interruption.[17] In this regard, patients with such connections may be expected to have less optimal ablation results than those with more discrete connections.[18,19]

A comparison between our data and the previous reports mentioned earlier also shows an interesting discrepancy in patient ethnicity. Our database shows that 22% of our patients were of African-American ancestry compared to 3–7%. There were more patients with broad-distribution or multiple fiber locations as noted earlier. Our data, therefore, suggest that ethnicity may be an important component of AP type and location and, by inference, tachycardia recurrence. Since there are regional ethnic population diversities across the United States, any one pediatric EP center may have limited exposure to any one ethnic group. In this regard, we agree with the recent report by Hsu et al. that ethnicity may be an important variable contributing to different reported AP locations, successes, and recurrences among different institutions.[21] However, a larger multi-institutional/multi-ethnic population study will be required to further evaluate this concept.

We purposely used a very broad definition of "recurrence" to include both only recurrent preexcitation as well as bona fide tachycardia. In this regard, the late 5-year recurrence rate in our study was 16.8%. Previous studies have reported recurrence rates varying from 4.7 to 45%, with RFA at 4.7–8.2%[12,13] and Cryo even higher at 13–45%.[14,22] In our current study, no significant differences in recurrence rates were noted for use of RFA or RFA + Cryo (14 and 20% respectively, $P = 0.5$). The Cryo-only group had recurrence rate of 22% which was not significantly different compared to others, but as this group had very limited number of patients, this comparison may not be adequately powered. The use of RFA combined with Cryo could have improved the overall success rates in our study group. The recurrence rate also varied depending on substrate location. Although there has been improvement over the last two decades, the success rate for RFA ablation of right is less than for left-sided pathways, 90% versus 98%.[4] From the international registry, a 75% success rate was reported for right septal fibers.[11] In our study, higher recurrence was noted for right-sided fibers with right anteroseptal fibers (33%), right anterior (24%), left-sided fibers (20%), and AVNRT (14%).

AV block has been reported to occur in 1.2% of patients following ablation, mostly for AVNRT and septal accessory pathways.[4] Unlike RFA, Cryo has been associated with a decreased incidence of reported complications. It has been shown that cooling of the myocardium to $-30^{\circ}C$ results in reversible tissue modification.[23] This adds a theoretical benefit of predetermining any potential adverse problems prior to definitive cellular disruption once the temperature reaches $-70^{\circ}C$. In animal studies, cryoablated sites were more homogeneous and showed viable myocytes with fibrotic tissue changes but no signs of chronic inflammation.[24] Cryo has also been shown to have better catheter adherence and spares the endothelial lining leading to less thrombogenicity compared to RFA.[25,26] Use of Cryo for fiber locations close to AV node and limiting RFA to safer regions could be the cause for the low incidence of complications in our study.

Unlike previous studies, we have reported long-term follow-up in pediatric patients. We have used RF with Cryo which is different compared to previous studies. Compared to previous studies, although our overall success rates seem to be

similar, we had many patients with right-sided APs and we have higher success rates for these fibers. We thus propose that use of RFA with Cryo together would increase success rates compared to either energy source alone for those fiber locations that have traditionally been known to have poor ablation success.

Limitations

This was a single-center retrospective study with a relatively small number of patients in the Cryo-only group. Also, our patient demographics and accessory fiber locations differ from other studies making generalization of the results difficult. Further multicenter prospective studies, including ethnic diversity, will be needed to validate the findings.

Conclusion

RFA and Cryo are safe and efficacious treatment options for pediatric patients with SVT. They are associated with excellent acute procedural success. But since first applied, chronic efficacy of ablation therapies in the young have not yet been well established. Our report demonstrates that in spite of apparent acute success, the risk of late recurrence, either as QRS preexcitation and/or arrhythmias, persists in the current era especially among patients with broad-distribution, multiple and those with anteroseptal accessory fiber locations. Use of Cryo with RF in combination may enhance safety while affording comparable success, especially for fiber locations that have been traditionally known to have higher recurrence rates.

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