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Assessing the utility of atrial fibrillation induction to risk stratify children with Wolff–Parkinson–White syndrome

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Original Article

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WPW – Wolff-Parkinson-White; SCD – sudden cardiac death; AP – accessory pathway; SPERRI – shortest-pre-excited-RR-interval; SPPCL – shortest-pre-excited-paced-cycle-length

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Abstract

Background: Wolff–Parkinson–White syndrome is associated with sudden cardiac death from rapid conduction through the accessory pathway in atrial fibrillation. Adult patients are at higher risk for sudden cardiac death if the shortest-pre-excited-RR-interval in atrial fibrillation (SPERRI) is ≤250 milliseconds (msec) during electrophysiologic study. Exclusive conduction through the atrioventricular node in atrial fibrillation is presumed to convey lower risk. The shortest-pre-excited-paced-cycle-length with atrial pacing has also served as a marker for risk stratification. *Objective:* To determine accessory pathway characteristic of patients undergoing induction of atrial fibrillation during electrophysiologic study. *Methods:* We reviewed 321 pediatric patients that underwent electrophysiologic study between 2010 and 2019. Induction of atrial fibrillation was attempted on patients while on isoproterenol and SPERRI was measured if atrial fibrillation was induced. Shortest-pre-excited-paced-cycle-length (SPPCL) was determined while on isoproterenol. *Results:* Atrial fibrillation was induced in 233 (73%) patients. Of those, 104 (45%) patients conducted exclusively through the atrioventricular node during atrial fibrillation (Group A). The remaining 129 (55%) patients had some conduction through the accessory pathway (Group B). In Group A, SPPCL was 260 msec with 48 (46%) conducting through the accessory pathway at ≤250 msec. In Group B, SPPCL was 240 msec with 92 patients (71%) conducting at ≤250 msec ($p < 0.05$). In Group B, SPERRI was 250 msec and had a positive correlation with SPPCL ($p < 0.001$, $R^2 = 0.28$). Almost half (46%) of those with exclusive conduction through the atrioventricular node in atrial fibrillation had rapid accessory pathway conduction with atrial pacing. *Conclusion:* Conduction in atrial fibrillation during electrophysiologic study on isoproterenol via the atrioventricular node may not exclude high-risk accessory pathways in pediatric patients.

The characteristic electrocardiogram pattern found in Wolff–Parkinson–White syndrome was first reported in the early 20th century.[1] Shortly afterwards, the condition was described in individuals who were experiencing paroxysmal supraventricular tachycardia and atrial fibrillation.[2] This was a consequence of an accessory pathway between the atria and the ventricles which did not share the rate-slowing properties of the atrioventricular node.[3] Atrial fibrillation with rapid anterograde conduction through this atrial fibrillation led to ventricular fibrillation and in some instances sudden cardiac death.[4,5,6] Invasive testing involving programmed electrical stimulation with rapid atrial pacing in a cardiac electrophysiology study is typically recommended to stratify risk for sudden cardiac death.[7] In children, an isoproterenol infusion is often used to shorten the accessory pathway anterograde refractory period and increase ventricular rates, increasing the sensitivity of the electrophysiology study to detect malignant forms of Wolff–Parkinson–White.[8] Risk for ventricular fibrillation is estimated by measuring anterograde conduction through the accessory pathway with the shortest pre-excited R-R interval during atrial fibrillation (SPERRI), the accessory pathway effective refractory period (APERP), and shortest paced pre-excited cycle length during atrial pacing (SPPCL). Faster anterograde conduction through the accessory pathway during atrial fibrillation is considered a risk factor for sudden cardiac death. In the adult population, a SPERRI ≤250 msec indicates higher risk for developing malignant arrhythmias, and many recommend this cut-off as the criteria for ablation in an asymptomatic patient.[9,10,11] Conversely, exclusive conduction through the atrioventricular node during atrial fibrillation connotes a loss of pre-excitation and is considered a sign of lower risk. In this study, we present data from our electrophysiology laboratory to determine the accessory pathway characteristics of those children who underwent induction of atrial fibrillation during electrophysiology study.

Methods

This is a single-center retrospective chart review of pediatric patients (age 21 years and below) with Wolff–Parkinson–White who underwent programmed electrical stimulation at the New York-Presbyterian Morgan Stanley Children's Hospital between January 2010 and December 2019. Data were collected from the institutional electrophysiology study database and the patients' electronic medical record. By design, an electrophysiology study was performed on all subjects included in the study. Those with fasciculoventricular accessory pathway were excluded from the study as these pathways have not been shown to be linked to sudden cardiac death.[12] The study was approved by the Columbia University Irving Medical Center Institutional Review Board.

Demographic data and baseline patient characteristics were collected from patient charts, including patient's age, gender, weight, height, baseline intracardiac intervals, effective refractory periods, and presence of congenital heart disease (CHD). None of the patients presented after aborted cardiac death or malignant atrial fibrillation. Almost all patients underwent ablation during electrophysiology study. Ablation was performed based on clinical indications or rapid conduction characteristics in asymptomatic patients.

All except for one electrophysiology study were conducted under general anaesthesia. Baseline intracardiac intervals were recorded in each study. The SPPCL during RAP was reported at baseline and while on isoproterenol if used. APERP values while on ISO were not reported, as once atrial fibrillation was achieved during RAP, the isoproterenol infusion was terminated and the refractory period was no longer measured. The isoproterenol dose administered varied between 0.01 and 0.04 mcg/kg/min to obtain an increase in the sinus rate of at least 25%. Atrial fibrillation episodes that were sustained for a minimum of 30 seconds were reported and included in this study. SPERRI was reported if induction of atrial fibrillation with conduction through the accessory pathway was achieved. If induction through the atrioventricular node was achieved, the ventricular rate was not reported.

The patients were divided into three groups depending on the presence and mode of conduction in atrial fibrillation. Those with induction of atrial fibrillation were separated depending on if anterograde conduction occurred exclusively through the atrioventricular node (Group A) versus through both the atrioventricular node and the accessory pathway or exclusively through the accessory pathway (Group B). Patients in whom atrial fibrillation during electrophysiology study could not be induced were included in Group C. SPERRI was measured in all patients in Group B. All continuous variables were summarised using median and interquartile range. Logistic regression analysis and Pearson's correlation coefficient was used to compare accessory pathway functional characteristics between the groups. The Wilcoxon rank test was used for univariable analysis. Statistical significance was defined as $p < 0.05$.

Results

A total of 355 patients with preexcitation on surface ECG underwent electrophysiologic study during this time. There were 18 patients that had more than one electrophysiology study and only the data from the initial study were included in our analysis. There were 14 patients with a fasciculoventricular accessory pathway that were excluded, and two patients were excluded due to lack of pre-excitation during electrophysiology study.

Of the remaining 321 patients (Table 1), the median age at the time of procedure was 14.3 years (IQR: 11.2–16.9). There were 140 female patients (43%). In 290 of these studies, isoproterenol was used to attempt to induce atrial fibrillation (90%), with atrial fibrillation successfully induced in 233 patients (73%). There were 104 patients out of the 233 (45%) that had exclusive conduction through the atrioventricular node during atrial fibrillation (Group A), and 129 patients (55%) had at least some conduction through the AP (Group B). Atrial fibrillation was unable to be induced in 88 patients (27%) (Group C).

Table 2 shows the characteristics of the accessory pathways. The median SPPCL prior to initiating isoproterenol was longer in Group A than in Group B (340 msec (IQR 295–370) versus 300 msec (IQR 260–320), $p < 0.001$). Similarly, while on isoproterenol, the SPPCL was longer in Group A than in Group B (260 msec (IQR 240–300) vs. 240 msec (IQR 220–250), $p < 0.001$). On isoproterenol, 48 patients (46%) in Group A had conduction through the accessory pathway during atrial pacing (SPCCL) ≤250 msec while 92 (71%) in Group B had SPCCL ≤250 msec ($p < 0.001$). The median APERP was 310 msec (IQR 295–340), with 5 patients (4.8%) conducting at ≤250 msec in Group A versus 300 msec (IQR 270–320), with 18 patients (14%) conducting at ≤250 msec in Group B ($p = 0.03$). SPERRI in Group B was 250 msec (IQR 220–270) and had a positive correlation with SPPCL ($R^2 = 0.28$, $p < .001$) and with APERP ($R^2 = 0.47$, $p < .001$).

Discussion

Although uncommon, children with Wolff–Parkinson–White may experience sudden cardiac death as the first manifestation of their disease.[13] Persistent preexcitation during periods of stress such as exercise has high sensitivity for detection of patients at risk.[14] Therefore, assessing accessory pathway conduction properties through electrophysiology study constitutes an appropriate preventive strategy. An expert consensus statement from PACES/HRS regarding Wolff–Parkinson–White risk stratification promoted use of invasive testing in asymptomatic individuals whose non-invasive testing could not clearly demonstrate abrupt loss of preexcitation with exercise.[15]

Historically, complete loss of preexcitation during non-invasive testing was assumed to represent a lower risk accessory pathway and thus a lower risk of sudden cardiac death.[9,16] Recently, this assumption has been called into question as it has been shown that intermittent pre-excitation does not necessarily indicate the absence of a high-risk accessory pathway.[17]

Studies focussed on risk stratification through invasive testing have shown that risk for sudden cardiac death is lower if conduction via the accessory pathway occurs at a slower rate during electrophysiology study, represented by a longer SPERRI during atrial fibrillation. Historically, this has been established as an SPERRI greater than 250 msec.[9,10,11] It follows that evidence of exclusive conduction of atrial fibrillation through the atrioventricular node during invasive testing – a complete loss of preexcitation – can be considered an indicator of a low-risk accessory pathway.

In our study, we identified pediatric patients with exclusive anterograde conduction of atrial fibrillation through the atrioventricular node while on isoproterenol to determine if indeed this is the best discriminator of lower risk in this patient population. We hypothesised that if these children still had other

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Table 1. Demographics and baseline EP properties.

	Group A AF through AVN	Group B AF through AP	Group C Unable to Induce AF	P*	P^
Total Patients	104	129	88	—	—
Age at EPS					
Median (Q1, Q3) (yrs)	14.2 (11.2, 17.1)	14.6 (12.7, 17)	13.3 (9.4, 16.8)	0.24	0.02
Gender					
Female	54 (52%)	43 (33%)	40 (45%)	0.01	0.58
Baseline HV Interval					
Median (Q1, Q3) (msec)	11 (1,23)	12 (1, 23)	11 (4, 25)	0.83	0.59
Baseline AH Interval *Median (Q1, Q3) (msec)*	59 (51, 67)	62 (52, 73)	61 (53, 70)	0.12	0.65
Baseline WCL					
Median (Q1, Q3) (msec)	300 (270, 330)	280 (270, 310)	305 (280, 340)	0.23	0.23
Location of AP (%)					
Right	23 (22)	26 (21)	20 (23)	0.13	0.34
Left	43 (41)	42 (33)	38 (45)		
Septal	33 (32)	59 (46)	27 (32)		
Ablation Performed	92 (88%)	126 (98%)	83 (94%)	0.004	0.80
Successful Ablation	92 (100%)	121 (96%)	81 (96%)	0.053	0.54
CHD	9 (8.6%)	17 (13%)	6 (6.8%)	0.28	0.25

P* compares Groups A versus B, P^ compares Groups A + B to C.

Table 2. Functional characteristics of AP.

	Group A AF through AVN	Group B AF through AP	Group C Unable to Induce AF	P*	P^
Total Patients	104	129	88	—	—
APERP					
Median (Q1, Q3) (msec)	310 (295–340)	300 (270–320)	305 (280–340)	<0.001	0.26
SPPCL					
Median (Q1, Q3) (msec)	340 (295, 370)	300 (260, 320)	205 (270, 370)	<0.001	0.88
APERP ≤250 *(msec)*	5 (4.8%)	18 (14%)	7 (7.9%)	0.03	0.82
ISO used during EPS	103 (99%)	117 (91%)	70 (80%)	0.006	<0.001
SPPCL on ISO					
Median (Q1, Q3) (msec)	260 (240,300)	240 (220, 250)	250 (230, 300)	<0.001	0.16
SPPCL ≤250 ms on ISO	48 (46%)	92 (71%)	38 (43%)	<0.001	0.11
SPERRI during AF *Median (Q1, Q3) (msec)*	—	250 (220, 280)	—	—	—

P* compares Groups A versus B, P^ compares Groups A + B to C [xx].

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characteristics of a high-risk pathway, this may affect how they have been historically risk stratified.

It should be noted that recently it has shown that accessory pathway characteristics measured during electrophysiology study under general anaesthesia – specifically SPERRI – may not necessarily correlate with non-invasive measurements during clinical episodes of atrial fibrillation, calling into question its utility in risk stratification.[18]

Our study specifically analysed accessory pathway functional characteristics in electrophysiology study that used ISO. We hypothesised that this would most accurately represent real-life risk in children since the use of isoproterenol can mimic the beta-adrenergic stimulation that occurs during exercise by shortening the APERP, leading to increased ventricular rates during atrial fibrillation.[19] The use of isoproterenol during electrophysiology study has been shown to shorten pathway functional properties, leading to an increase in the number of children who are classified as exhibiting adverse accessory pathway parameters.[13] Thus, the use of isoproterenol can be particularly beneficial in children undergoing electrophysiology study, as many require sedation and general anaesthesia, which can stifle the beta-adrenergic response seen in exercise.

It must be noted that use of isoproterenol in risk stratification of children with Wolff–Parkinson–White remains controversial. In a recent retrospective review, Escudero et al. showed that despite an increase in sensitivity, there was an associated decrease in specificity in identifying children with prior life-threatening events who had undergone electrophysiology study with ISO.[20]

Baseline rate of conduction through the accessory pathway during pacing was represented by the SPPCL. In a recent multi-centre international study, Etheridge et al. demonstrated that SPERRI, SPPCL, and APERP ≤250 msec were all associated with life-threatening events in children.[13]. Thus, despite limited data on their utility in risk assessment – especially while using isoproterenol – APERP and SPPCL ≤250 msec have been used as a common surrogate marker of a high-risk accessory pathway in electrophysiology study. Our study showed a positive correlation of SPERRI with SPPCL in Group B, showing consistency in the pathway functional characteristics.

We found that those with conduction of atrial fibrillation exclusively through the atrioventricular node (Group A) on average had slower conduction through the accessory pathway than those with conduction of atrial fibrillation through the atrioventricular node and accessory pathway or accessory pathway exclusively (Group B). However, while the average SPPCL in Group A had a longer cycle length than in Group B (median of 260 msec versus 240 msec, $p = 0.03$), a significant number (46%) of patients in Group A had a SPPCL ≤250 msec. Despite having conduction of atrial fibrillation exclusively through the atrioventricular node, rapid conduction through the accessory pathway with rapid atrial pacing persisted in many of these patients. This suggests that measuring the SPERRI during atrial fibrillation may not be ideal for identifying high risk pathways. The fast rates of conduction through the atrioventricular node in children undergoing electrophysiology study on ISO may very well be masking strong transmission via the accessory pathway represented by the short SPPCL.

Furthermore, since SPERRI may not be the optimal measure of risk, patients that do not have *any* inducible atrial fibrillation during electrophysiology study (like those in Group C) can still be considered at high risk. In our study, 43% of patients in Group C had a SPPCL ≤250 msec while on isoproterenol, showing that a significant percentage may still have an accessory pathway capable of rapid conduction to the ventricles during exercise.

There are several limitations to our study. Since we analysed pathway characteristics on ISO, our results may not be readily extrapolated to studies in which ISO was not used. As this was an electrophysiology database review, data on symptomatic presentation are not available; however, none of the patients presented with aborted cardiac death or haemodynamically unstable atrial fibrillation. Finally, this study was conducted at a single institution in New York City, which may constrain generalisability.

In conclusion, children with exclusive conduction through the atrioventricular node in atrial fibrillation during electrophysiology study might still have a potentially high-risk pathway. This suggests that induction of atrial fibrillation may not be the best marker for risk stratification in this population.

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Competing interests. None.

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