Loss of ventricular preexcitation during noninvasive testing does not exclude high-risk accessory pathways: A multicenter study of WPW in children

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BACKGROUND Abrupt loss of ventricular preexcitation on noninvasive evaluation, or nonpersistent preexcitation, in Wolff-Parkinson-White syndrome (WPW) is thought to indicate a low risk of life-threatening events.

OBJECTIVE The purpose of this study was to compare accessory pathway (AP) characteristics and occurrences of sudden cardiac arrest (SCA) and rapidly conducted preexcited atrial fibrillation (RC-AF) in patients with nonpersistent and persistent preexcitation.

METHODS Patients 21 years or younger with WPW and invasive electrophysiology study (EPS) data, SCA, or RC-AF were identified from multicenter databases. *Nonpersistent preexcitation* was defined as absence/sudden loss of preexcitation on electrocardiogram, Holter monitoring, or exercise stress test. *RC-AF* was defined as clinical preexcited atrial fibrillation with shortest preexcited R-R interval (SPERRI) $\leq$ 250 ms. AP effective refractory period (APERP), SPERRI at EPS , and shortest preexcited paced cycle length (SPPCL) were collected. *High-risk APs* were defined as APERP, SPERRI, or SPPCL $\leq$ 250 ms.

RESULTS Of 1589 patients, 244 (15%) had nonpersistent preexcitation and 1345 (85%) had persistent preexcitation. There were no differences in sex (58% vs 60% male; $P=.49$) or age (13.3$\pm$3.6 years vs 13.1$\pm$3.9 years; $P=.43$) between groups. Although APERP (344$\pm$76 ms vs 312$\pm$61 ms; $P<.001$) and SPPCL (394$\pm$123 ms vs 317$\pm$82 ms; $P<.001$) were longer in nonpersistent vs persistent preexcitation, there was no difference in SPERRI at EPS (331$\pm$71 ms vs 316$\pm$73 ms; $P=.15$). Nonpersistent preexcitation was associated with fewer high-risk APs (13% vs 23%; $P<.001$) than persistent preexcitation. Of 61 patients with SCA or RC-AF, 6 (10%) had nonpersistent preexcitation (3 SCA, 3 RC-AF).

CONCLUSION Nonpersistent preexcitation was associated with fewer high-risk APs, though it did not exclude the risk of SCA or RC-AF in children with WPW.

KEYWORDS Children; Exercise testing; Life-threatening event; Noninvasive evaluation; Pediatric; Pediatric and Congenital Electrophysiology Society (PACES); Wolff-Parkinson-White syndrome

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Introduction

Wolff-Parkinson-White syndrome (WPW) is associated with a real, but unknown, risk of sudden cardiac death in children and young adults due to atrial fibrillation (AF) with rapid antegrade conduction via the accessory pathway (AP) and resultant ventricular fibrillation (VF).[1–5] Abrupt loss of ventricular preexcitation on noninvasive testing, or nonpersistent preexcitation, has historically been thought to indicate a long AP refractory period and lower risk of life-threatening events.[6,7] The current expert consensus on asymptomatic ventricular preexcitation in children suggests that routine invasive risk stratification is not required if there is abrupt loss of ventricular preexcitation on noninvasive testing (electrocardiogram, Holter monitoring, or exercise stress test [EST]).[8]

In single-center studies of children with nonpersistent preexcitation, high-risk APs at invasive electrophysiology study (EPS) were seen in 6%–12% at baseline and 11%–21% with isoproterenol.[6,9,10] These data challenge the notion that nonpersistent preexcitation indicates low-risk AP conduction characteristics. Our objective was to compare clinical features and AP conduction characteristics between patients with nonpersistent and persistent preexcitation in a large cohort of children with WPW to further define the occurrence and relationship of high-risk APs and development of sudden cardiac arrest (SCA) or rapidly conducted preexcited atrial fibrillation (RC-AF) in these patients.

Methods

A retrospective, multicenter, international study was performed by analyzing data from 26 centers. De-identified patient data were gathered from 2 large multicenter retrospective pediatric WPW databases (Online Supplemental Figure 1). The first database was from a retrospective case-control study comparing children with WPW and a history of SCA or RC-AF to children with WPW who underwent EPS and did not have SCA or RC-AF.[2] The second database was a multicenter retrospective cohort study of children with WPW who had undergone EPS.[11] Although the majority of patients in this study have been included in other studies of pediatric WPW, only a small minority (12 patients) had information on features of persistent and nonpersistent preexcitation published[9] (Online Supplemental Figure 1). All centers received local investigational review board approval.

Definitions

Nonpersistent preexcitation was defined as intermittent absence of ventricular preexcitation on ECG or Holter

monitoring or sudden loss on EST. *RC-AF* was defined as clinical preexcited AF with shortest preexcited R-R interval (SPERRI) $\leq$ 250 ms or clinical preexcited AF associated with hemodynamic compromise, syncope, or seizure, regardless of clinical SPERRI.[2] A *high-risk AP* was defined as antegrade AP effective refractory period (APERP), shortest preexcited paced cycle length (SPPCL) during atrial pacing, or SPERRI during AF (EPS-SPERRI) $\leq$ 250 ms at invasive EPS *in the absence of isoproterenol*, given the lack of established risk stratification guidelines using isoproterenol.[2] SCA occurs when absent or ineffective cardiac mechanical activity causes a cessation of circulation, which can lead to sudden cardiac death (SCD) if left untreated. For this study, we included SCD or resuscitated SCA requiring cardiopulmonary resuscitation and/or documentation of VF under the category of SCA.

Patient selection

Inclusion criteria were a diagnosis of asymptomatic or symptomatic WPW, age $\leq$21 years, and classification as either nonpersistent or persistent preexcitation. Patients were excluded for the presence of a lone fasciculoventricular pathway. Three centers entered data into both original databases. Duplicate patients were identified by matching all of center location, sex, age at EPS, AP location, and EPS risk stratification values, and duplicate entries were removed.

Data collected

Data collected included patient demographic characteristics, clinical history, invasive EPS findings, and follow-up. Clinical data included age at EPS, presence of hemodynamically significant structural heart disease, symptom status, and presence of either SCA or RC-AF. Noninvasive risk stratification data included the performance of Holter monitoring and/or EST, documentation of loss of ventricular preexcitation on noninvasive evaluation, and heart rate at which ventricular preexcitation was lost on EST. EPS data collected included AP location(s), presence of >1 AP, AP conduction properties, and induction of tachycardia. AP conduction characteristics assessed at EPS included APERP, SPPCL, and/or EPS-SPERRI. If the atrial effective refractory period was reached before APERP, the atrial effective refractory period was used in place of APERP.

Statistical analysis

Frequency tables were generated for all categorical variables. χ^2 or Fisher exact tests were used to detect differences in proportions between patients with nonpersistent and persistent preexcitation. Continuous variables were summarized using mean $\pm$ SD if data were normally distributed or median and interquartile range if data were not normally distributed. Univariate analysis of variance or the Mann-Whitney *U* test was used to compare means for continuous variables between groups. The sensitivity and specificity of nonpersistent preexcitation were calculated to predict the absence of a high-risk AP. Binomial logistic regression analysis was used to assess for independent predictors of the presence of a high-risk AP in patients with nonpersistent preexcitation by using variables of clinical relevance and/or those significantly different between groups ($P \leq .1$) in univariate analysis as independent variables. Variables included in the model are listed in the associated table. Statistical significance was defined as $P \leq .05$. Statistical analysis was performed with SPSS version 20.0 (IBM Corp., Armonk, NY), and graphs were generated using GraphPad Prism version 8.2.1 for Windows (GraphPad Software, San Diego, CA).

Results

Study cohort

The 2 databases contained 1754 patients with WPW. Eight patients were excluded for age >21 years, 51 for duplicate entries, 2 for having only fasciculoventricular pathways, and 104 for absence of classification as nonpersistent or persistent preexcitation (Online Supplemental Appendix 1). Thus, 1589 patients met inclusion criteria for this study. The mean patient age was 13.1$\pm$3.9 years, and 950 (60%) were male (Table 1).

Noninvasive evaluation

Data on completion of Holter monitoring and EST before EPS were available in 1281 patients (81%), with Holter monitoring performed in 36% (456 of 1250) and EST in 30% (383 of 1272). Nonpersistent preexcitation was documented in 244 patients (15%), while 1345 patients (85%) had persistent preexcitation. The distribution of noninvasive testing is presented in Online Supplemental Figure 2. Patients with nonpersistent preexcitation had more extensive noninvasive evaluation than did those with persistent preexcitation (Table 1). In patients with nonpersistent preexcitation, ventricular preexcitation was lost in 135 (55%) on ECG/Holter monitoring only, 50 (20%) on EST only, and 25 (10%) on EST and ECG/Holter monitoring and the testing where preexcitation was lost was undefined in 34 (14%).

Comparison of patient characteristics

Comparisons of patient characteristics between nonpersistent and persistent preexcitation groups are presented in Table 1. There was no difference in sex, age, or ethnicity. Patients with nonpersistent preexcitation were more frequently symptomatic and more frequently had documented supraventricular tachycardia than persistent preexcitation patients.

Occurrences of SCA or RC-AF

Sixty-one patients (4%) experienced SCA or RC-AF (Table 1), with SCA in 29 (2%) and RC-AF in 32 (2%). In patients with SCA, 25 (86%) were successfully resuscitated and 4 (14%) experienced sudden death. Of the 32 patients with RC-AF, 29 (91%) presented with clinical SPERRI $\leq$ 250 ms. For the 3 patients with RC-AF and clinical SPERRI > 250 ms or unknown clinical SPERRI (9%), 1 had syncope while running (clinical SPERRI 320 ms), 1 had seizures

Table 1 Patient characteristics

Clinical characteristic	Persistent preexcitation (n=1345)	Nonpersistent preexcitation (n=244)	*P*
Male sex	809 (60)	141 (58)	.49
Age at EPS (y)	13.1 ± 3.9	13.3 ± 3.6	.43
Race			
White	933/1139 (82)	165/206 (80)	.54
Black	116/1139 (10)	16/206 (8)	.28
Asian	38/1139 (3)	9/206 (4)	.46
Hawaiian/Pacific Islander	15/1139 (1)	0/206 (0)	.15
Native American, Alaskan Native, First Nations	5/1139 (0.4)	0/206 (0)	>.99
>1 ethnic group	32/1139 (3)	16/206 (8)	<.001
Hispanic ethnicity	290/1145 (25)	50/209 (24)	.67
Structural heart disease	75 (6)	16 (7)	.55
Symptoms	1072 (80)	217 (89)	.001
Syncope	132 (10)	15 (6)	.07
Documented supraventricular tachycardia	539 (41)	124 (51)	.002
Noninvasive evaluation			
Holter monitoring performed	313/1044 (30)	143/206 (69)	<.001
Exercise stress test performed	280/1065 (26)	103/207 (50)	<.001
SPERRI during clinical preexcited AF (ms)	200 (170–240) (n=29)	250 (205–295) (n=8)	.04
EPS performed	1340 (99.6)	244 (100)	>.99
Clinical rapidly conducted preexcited AF	29 (2)	3 (1)	.46
Resuscitated sudden cardiac arrest	22 (2)	3 (1)	.79
Sudden cardiac death	4 (0.3)	0 (0)	>.99

Values are presented mean ± SD, median (interquartile range), n (%), or n/total n (%).
AF = atrial fibrillation; EPS = electrophysiology study; SPERRI = shortest preexcited R-R interval in atrial fibrillation.

(unknown clinical SPERRI), and 1 had poor perfusion and hypotension (unknown clinical SPERRI). SCA or RC-AF occurred in 6 patients with nonpersistent preexcitation (3 SCA, 3 RC-AF). An additional 9 patients with persistent preexcitation and 5 patients with nonpersistent preexcitation had clinical preexcited AF that did not meet the RC-AF definition. Clinical SPERRI for any episode of preexcited AF was longer in patients with nonpersistent than persistent preexcitation (Table 1).

Clinical information for patients with nonpersistent preexcitation and SCA or RC-AF is summarized in Table 2. All patients with nonpersistent preexcitation and SCA or RC-AF were previously symptomatic. One patient with nonpersistent preexcitation and RC-AF had Ebstein malformation of the tricuspid valve, and the rest had a structurally normal heart. The ECGs demonstrating nonpersistent preexcitation for patients 4 and 5 (Table 2) are shown in Figure 1.

EPS and invasive risk stratification

EPS was performed in 1584 patients (99.7%). No EPS was performed in 3 patients because of sudden death and in 2 patients because of withdrawal of care after SCA with resultant devastating neurological injury. General anesthesia (GA) was used in the majority (Table 3). Ablation was attempted in 1453 patients (92%). Complications of EPS were seen in 40 patients (3%) (Online Supplemental Table 1).

AP characteristics between patients with nonpersistent and persistent preexcitation are compared in Table 3. The nonpersistent preexcitation group had longer mean APERP and SPPCL, with no difference in mean EPS-SPERRI. There was a substantial overlap in APERP, EPS-SPERRI, and SPPCL values between groups (Figure 2). Patients with persistent preexcitation had a higher proportion of APs with SPPCL $\leq$ 250 ms than did patients with nonpersistent preexcitation, with no difference in the proportion of patients with APERP $\leq$ 250 ms, EPS-SPERRI $\leq$ 250 ms, or multiple APs. A high-risk AP was identified more frequently in patients with persistent preexcitation than in those with nonpersistent preexcitation (23% vs 13%; $P < .001$). The proportion of high-risk AP features between groups is demonstrated in Figure 3.

Factors associated with high-risk APs in patients with nonpersistent preexcitation

Of 213 patients with nonpersistent preexcitation who underwent risk stratification at EPS (87%), 27 (13%) met high-risk criteria. A comparison between nonpersistent preexcitation patients with high- and low-risk APs at EPS is provided in Online Supplemental Table 2. There was no difference in the frequency of loss of preexcitation on ECG/Holter monitoring or on EST on the basis of AP risk. Of the 27 patients with nonpersistent preexcitation and high-risk APs, 3 (11%) were asymptomatic. Using multivariate logistic regression analysis, only GA was independently associated with a lower likelihood of high-risk classification in patients

Table 2 Clinical and EPS findings in patients with nonpersistent preexcitation and SCA or RC-AF

Patient no.	Age at event (y)	Testing defining nonpersistent preexcitation	Event type	Clinical SPERRI (ms)	Symptoms before the event	CHD	AP location	Anesthesia at EPS	EPS data (ms)
1	12.9	Holter monitoring	RC-AF	230	SVT	No	Left anterolateral	Sedation	APERP 225 SPERRI 200
2	13.9	Unknown	RC-AF	200	Palpitations	No	Left lateral	GA	APERP 310 SPPCL 260
3	16.9	EST (loss at HR 140 beats/min)	RC-AF	200	Syncope, SVT	Ebstein anomaly	Right posteroseptal	GA	None tested
4	9.4	ECG/Holter monitoring	R-SCA		SVT	No	Right posterior	GA	No preexcitation during atrial fibrillation
5	16.3	ECG/Holter monitoring	R-SCA		SVT	No	Left posterolateral	GA	APERP 280
6	18.7	ECG/Holter monitoring	R-SCA		SVT	No	Right anteroseptal	GA	APERP 350 SPERRI 370

AP = accessory pathway; APERP = accessory pathway effective refractory period; CHD = congenital heart disease; ECG = electrocardiogram; EPS = electrophysiology study; EST = exercise stress test; GA = general anesthesia; HR = heart rate; RC-AF = rapidly conducted preexcited atrial fibrillation; R-SCA = resuscitated sudden cardiac arrest; SPERRI = shortest preexcited R-R interval in atrial fibrillation at electrophysiology study; SPPCL = shortest preexcited paced cycle length; SVT = supraventricular tachycardia.

with nonpersistent preexcitation (odds ratio 0.23; 95% confidence interval 0.08–0.63; $P<.01$) (Table 4).

Utility of noninvasive testing in predicting the presence of a low-risk AP

Nonpersistent preexcitation was present in 27 of 320 patients with a high-risk AP at EPS. The specificity and positive predictive value of excluding a high-risk AP in the presence of nonpersistent preexcitation were 92% and 87%, respectively, while the sensitivity (16%) and negative predictive value (23%) were low.

There was no statistical difference in median heart rate at which preexcitation was lost on EST in the low-risk vs high-risk AP groups (163 [interquartile range 125–180; range 86–210] beats/min vs 184 [interquartile range 172–197; range 170–200] beats/min; $P=.06$). When looking solely at the predictive value of EST, the specificity and positive predictive value of excluding a high-risk AP in the presence of sudden loss of ventricular preexcitation were 93% and 93%, respectively, with low sensitivity (22%) and negative predictive value (23%).

Subgroup analyses

When patients with nonpersistent preexcitation were subdivided into those with loss of preexcitation on ECG/Holter monitoring (commonly referred to as "intermittent preexcitation") and those with loss of preexcitation on EST alone, the only significant difference was an increased frequency of left free wall APs in patients with intermittent preexcitation (Online Supplemental Table 3). In light of the possibility that incomplete noninvasive testing may have misclassified cases as persistent preexcitation, we performed a subanalysis of patients with Holter monitoring completed, with no differences found compared to our primary analysis (Online Supplemental Table 4). To assess differences between patients who underwent dissimilar testing, we compared subgroups of patients with and without noninvasive testing (Holter monitoring or EST) and with and without invasive risk stratification at EPS (Online Supplemental Table 5). As expected, symptomatic patients were less likely to undergo noninvasive testing.

Discussion

This study represents the largest analysis of EPS findings, risk assessment, and serious arrhythmic events in children with WPW and nonpersistent preexcitation. While nonpersistent preexcitation was associated with a lower likelihood of high-risk conduction properties at EPS, 13% of these patients met high-risk criteria at EPS. Of greatest concern was that subjects with nonpersistent preexcitation experienced RC-AF and SCA. These data challenge the notion that nonpersistent preexcitation confers freedom from risk of cardiac events.

Prior studies have suggested that loss of AP conduction with noninvasive testing can identify patients at a low risk of a cardiac event.[6,7,12] Sharma et al[12] suggested that

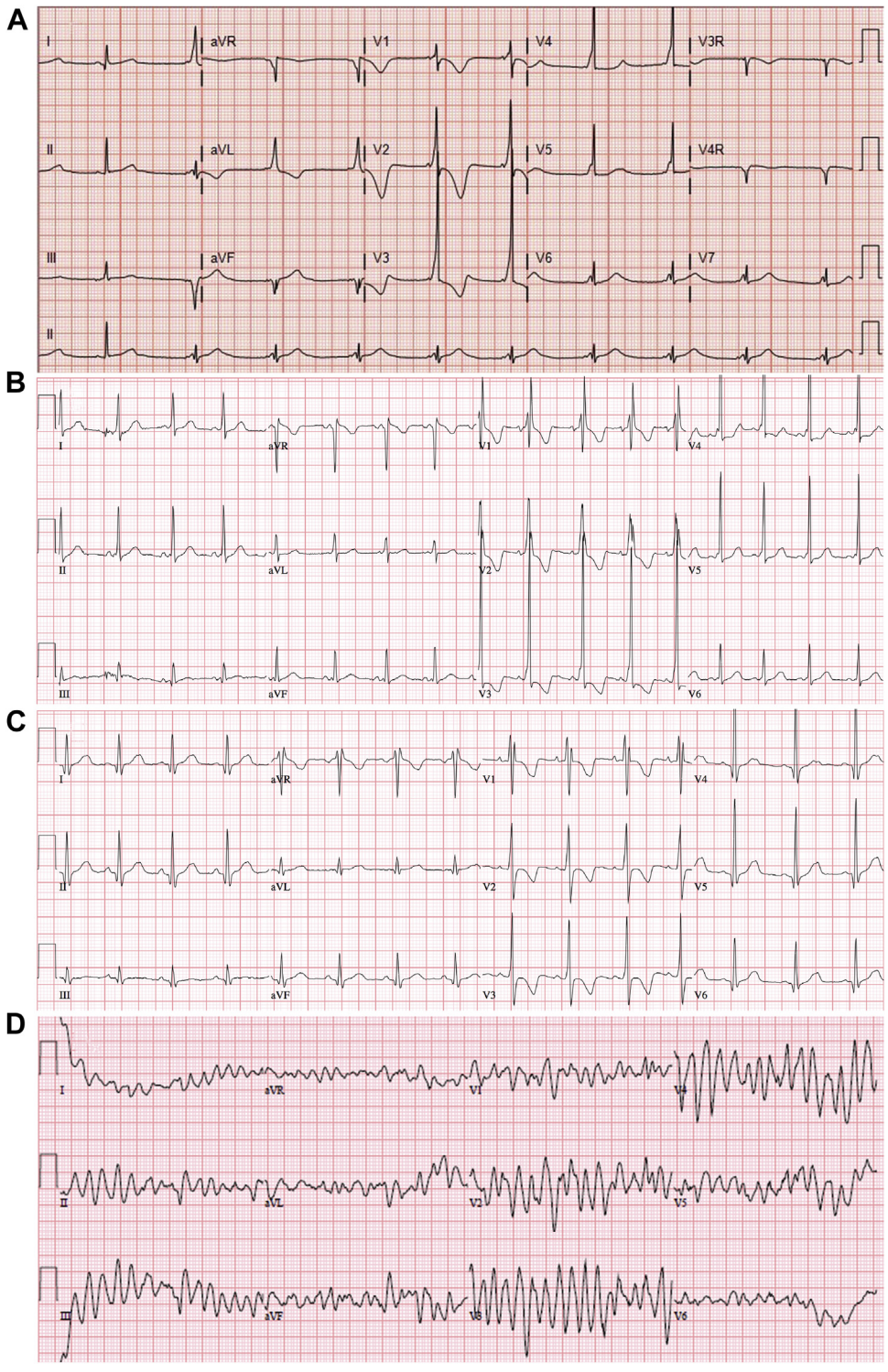

Figure 1 Electrocardiograms (ECGs) for patients 4 and 5 with nonpersistent preexcitation and sudden cardiac arrest (SCA). ECG demonstrating nonpersistent preexcitation (**A**) in patient 4 who later had a resuscitated SCA with an automated external defibrillator documenting ventricular fibrillation. ECGs demonstrating patient 5's ventricular preexcitation (**B**), spontaneous loss of preexcitation (**C**), and ventricular fibrillation during the SCA (**D**). Patient 5 was known to have Wolff-Parkinson-White syndrome and nonpersistent preexcitation. The patient presented to the emergency department after a syncopal episode and developed ventricular fibrillation during the ECG recording.

persistent preexcitation with exercise had a sensitivity of 80%, a specificity of 28.6%, and a predictive accuracy of 11.8% for detecting patients with sudden death. A small study of 24 pediatric patients concluded that the specificity and positive predictive value of loss of preexcitation on EST were 100%.[6] However, recent single-center pediatric studies have demonstrated that patients with nonpersistent preexcitation may still meet high-risk criteria at EPS.[6,9,10,13] Our

Table 3 EPS data

Characteristic	Persistent preexcitation (n=1340)	Nonpersistent preexcitation (n=244)	*P*
Anesthesia used			.28
General anesthesia	1220 (92)	217 (89)	
Sedation	92 (7)	24 (10)	
Local anesthesia only	18 (1)	3 (1)	
Risk stratification performed	1256 (94)	214 (88)	<.01
APERP (ms)	312 ± 61	344 ± 76	<.001
EPS-SPERRI (ms)	316 ± 73	331 ± 71	.15
SPPCL (ms)	317 ± 82	394 ± 123	<.001
APERP ≤ 250 ms	120/1144 (11)	14/186 (8)	.21
EPS-SPERRI ≤ 250 ms	65/374 (17)	9/54 (17)	.90
SPPCL ≤ 250 ms	205/1101 (19)	11/179 (6)	<.001
APERP, EPS-SPERRI, or SPPCL ≤ 250 ms	293 (23)	27 (13)	<.001
Supraventricular tachycardia induced			
ORT	805 (60)	170 (70)	<.01
ART	21 (2)	3 (1)	1.0
Atrial fibrillation	456 (34)	81 (33)	.77
Atrial flutter	13 (1)	1 (0.4)	.71
>1 Accessory pathway	83 (6)	15 (6)	.96
Accessory pathway regions			
Right free wall	269 (21)	46 (20)	.60
Left free wall	493 (39)	121 (51)	<.001
Septal	564 (44)	79 (34)	<.01
Ablation performed	1231 (92)	222 (91)	.65
Complications	33 (3)	7 (3)	.70

Values are presented mean ± SD, n (%), or n/total n (%).

APERP = accessory pathway effective refractory period; ART = antidromic reciprocating tachycardia; EPS = electrophysiology study; EPS-SPERRI = shortest preexcited R-R interval in atrial fibrillation at electrophysiology study; ORT = orthodromic reciprocating tachycardia; SPPCL = shortest preexcited paced cycle length.

multicenter cohort study corroborates these studies by demonstrating a relatively high specificity and predictive value for predicting a low-risk AP with noninvasive testing, but also demonstrates that noninvasive testing can miss patients with nonpersistent preexcitation that will meet high-risk criteria at EPS. The loss of ventricular preexcitation on noninvasive testing, therefore, may not completely exclude an AP capable of rapid antegrade conduction.

Although the risk of EPS and ablation are low, the short-term procedural risk must be balanced against the life-time risk of a life-threatening event. Our multicenter data reinforce that nonpersistent preexcitation does not confer an absence of the risk of SCA or RC-AF. All patients in our cohort with nonpersistent preexcitation and SCA or RC-AF were symptomatic before the presentation, which is supportive of performing an EPS in symptomatic patients. However, 11% of patients with nonpersistent preexcitation and a high-risk AP at EPS were asymptomatic. In other words, it is possible for an asymptomatic patient with WPW and nonpersistent preexcitation to have an AP capable of rapid antegrade conduction. Considering the large number of centers and patients included in this study and the low number of SCA and RC-AF episodes in patients with nonpersistent preexcitation, it is likely that SCA or RC-AF in a patient with nonpersistent preexcitation is a rare event, although the risk to an individual patient is unknown. Given the above, in asymptomatic patients with nonpersistent preexcitation, a discussion with the patient and family regarding the risk-benefit ratio of undergoing EPS and possible ablation vs the small but likely nonzero risk of SCA or RC-AF is important.

The only factor that was independently associated with lower-risk AP characteristics in nonpersistent preexcitation was the use of GA at EPS. This raises the question of how testing under GA affects AP characteristics and the predictive ability of EPS risk assessment in children. Since most EPS in children are performed using GA, the implications of these potential limitations on risk assessment are significant.[2] Notably, among subjects with nonpersistent preexcitation who suffered either SCA or RC-AF, the 5 with electrophysiology testing under GA did not meet high-risk criteria while the 1 who had undergone EPS under sedation met high-risk criteria. In particular, patient 4 (Table 2) had documented VF after a syncopal episode while sitting at school, but had no preexcitation during AF at EPS under GA. It is unknown whether the patient's VF was due to initial RC-AF, with GA or other factors masking the ability of rapid AP conduction at EPS, or whether there were other factors that could have contributed to the development of VF.

Limitations

This study population contains some bias as asymptomatic patients with nonpersistent preexcitation were less likely to undergo EPS. This bias likely explains the increased frequency of symptoms and documented supraventricular tachycardia

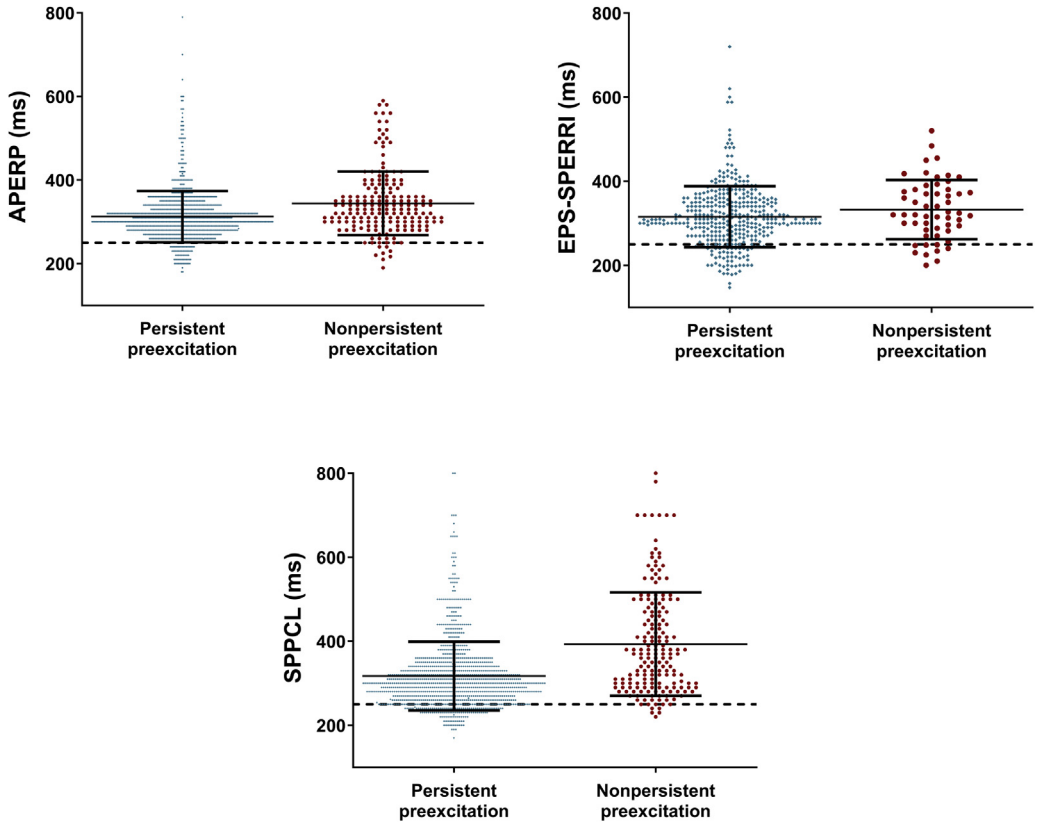

Figure 2 Distribution of risk stratification values at electrophysiology study in patients with nonpersistent and persistent preexcitation. The *dotted line* represents a 250 ms value. APERP = accessory pathway effective refractory period; EPS-SPERRI = shortest preexcited R-R interval in atrial fibrillation at electrophysiology study; SPPCL = shortest preexcited paced cycle length.

in patients with nonpersistent preexcitation in this study and may limit the generalizability of our findings to all patients with nonpersistent preexcitation. It is important not to interpret the 2% rates of SCA and RC-AF as being generalizable to children with WPW, as one of the databases used was enriched with cases of SCA and RC-AF owing to study design.

Patients with nonpersistent preexcitation less frequently had invasive risk stratification, which was likely secondary to their higher rate of cardiac symptoms prompting a lower threshold for ablation regardless of risk stratification data. Not all patients classified as persistent preexcitation underwent noninvasive testing, and it is possible that more complete noninvasive evaluation may have reclassified some patients as having nonpersistent preexcitation.

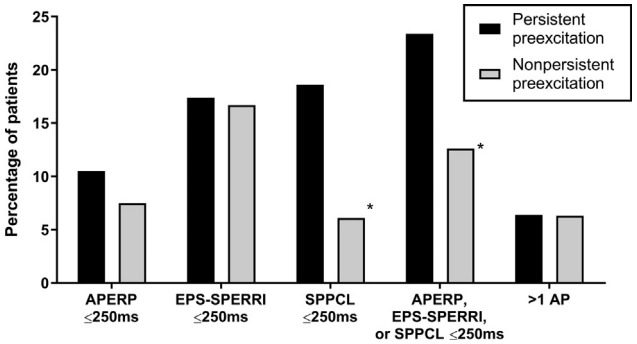

Figure 3 Proportion of high-risk AP features. Comparison of high-risk AP features in patients with nonpersistent and persistent preexcitation. There was no difference in the proportion of patients with SPERRI ≤ 250 ms, APERP ≤ 250 ms, or multiple APs between patients with nonpersistent and persistent preexcitation. AP = accessory pathway; APERP = accessory pathway effective refractory period; EPS-SPERRI = shortest preexcited R-R interval in atrial fibrillation at electrophysiology study; SPPCL = shortest preexcited paced cycle length. *$P \leq .05$.

Left-sided pathways are more challenging to detect because of subtle preexcitation. Left free wall APs were more common in the nonpersistent preexcitation group, potentially because of misclassification of subtle preexcitation as nonpersistent preexcitation, highlighting a limitation of noninvasive testing, especially in children who often have brisk atrioventricular nodal conduction. Determination of the presence of multiple APs and loss of ventricular preexcitation during noninvasive testing was made by the

Table 4 Multivariable analysis of factors associated with high-risk accessory pathways in nonpersistent preexcitation*

Characteristic	Odds ratio (95% CI)	*P*
Age at EPS	1.01 (0.99–1.02)	.34
General anesthesia	0.23 (0.08–0.63)	<.01
Inducible atrial fibrillation at EPS	1.85 (0.78–4.42)	.16
Left free wall accessory pathway	2.34 (0.94–5.85)	.07

CI = confidence interval; EPS = electrophysiology study.
*Ethnicity not included (unavailable in >20% of patients).

individual centers and was not independently confirmed by the coordinating centers, and it is possible that misclassification of these patients may have occurred.

While many experts have grouped EPS-SPERRI, APERP, and SPPCL data together, and have included APERP $<$ 250 ms in the high-risk group, there are only limited data on the use of APERP and SPPCL as risk assessment tools.[2,14,15] The duration of AF induced at EPS was not documented in the databases, and it is possible that short AF durations (as typically seen in children) may have resulted in a longer EPS-SPERRI than may have been observed with longer AF durations. In addition, the overwhelming majority of the patients in this cohort had testing performed under GA, and the impact of GA on interpretation of EPS data may be problematic.

Conclusion

In this large, multicenter, international study of children with WPW, the overall likelihood of meeting high-risk criteria at invasive EPS was lower in patients with nonpersistent preexcitation, although 13% of these patients had high-risk APs at EPS. In addition, there were patients with nonpersistent preexcitation who experienced SCA or RC-AF, all of whom were previously symptomatic. This study demonstrates that the presence of nonpersistent preexcitation in children with WPW may not guarantee the absence of a high-risk AP or the absence of the risk of SCA or RC-AF.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.05.035.

References

1. Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. N Engl J Med 1979; 301:1080–1085.
2. Etheridge SP, Escudero CA, Blaufox AD, et al. Life-threatening event risk in children with Wolff-Parkinson-White syndrome: a multicenter international study. JACC Clin Electrophysiol 2018;4:433–444.
3. Obeyesekere MN, Leong-Sit P, Massel D, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. Circulation 2012;125:2308–2315.
4. Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic characterization of accessory pathways on management strategies to reduce sudden death among children with Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1996;27:690–695.
5. Di Mambro C, Russo MS, Righi D, et al. Ventricular pre-excitation: symptomatic and asymptomatic children have the same potential risk of sudden cardiac death. Europace 2015;17:617–621.
6. Wackel P, Irving C, Webber S, Beerman L, Arora G. Risk stratification in Wolff-Parkinson-White syndrome: the correlation between noninvasive and invasive testing in pediatric patients. Pacing Clin Electrophysiol 2012; 35:1451–1457.
7. Klein GJ, Gulamhusein SS. Intermittent preexcitation in the Wolff-Parkinson-White syndrome. Am J Cardiol 1983;52:292–296.
8. Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Heart Rhythm 2012; 9:1006–1024.
9. Kiger ME, McCanta AC, Tong S, Schaffer M, Runciman M, Collins KK. Intermittent versus persistent Wolff-Parkinson-White syndrome in children: electrophysiologic properties and clinical outcomes. Pacing Clin Electrophysiol 2016; 39:14–20.
10. Mah DY, Sherwin ED, Alexander ME, et al. The electrophysiological characteristics of accessory pathways in pediatric patients with intermittent preexcitation. Pacing Clin Electrophysiol 2013;36:1117–1122.
11. Ceresnak SR, Dubin AM, Kim JJ, et al. Success rates in pediatric WPW ablation are improved with 3-dimensional mapping systems compared with fluoroscopy alone: a multicenter study. J Cardiovasc Electrophysiol 2015;26:412–416.
12. Sharma AD, Yee R, Guiraudon G, Klein GJ. Sensitivity and specificity of invasive and noninvasive testing for risk of sudden death in Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1987;10:373–381.
13. Dalili M, Vahidshahi K, Aarabi-Moghaddam MY, Rao JY, Brugada P. Exercise testing in children with Wolff-Parkinson-White syndrome: what is its value? Pediatr Cardiol 2014;35:1142–1146.
14. Santinelli V, Radinovic A, Manguso F, et al. Asymptomatic ventricular preexcitation: a long-term prospective follow-up study of 293 adult patients. Circ Arrhythm Electrophysiol 2009;2:102–107.
15. Pappone C, Santinelli V, Rosanio S, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. J Am Coll Cardiol 2003;41:239–244.