Comparison of Electrophysiologic Profiles in Pediatric Patients with Incidentally Identified Pre-Excitation Compared with Wolff-Parkinson-White Syndrome

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The rising utilization of screening electrocardiograms has resulted in increased incidental identification of ventricular pre-excitation in pediatric patients. We compared accessory pathways of incidentally identified pre-excitation to Wolff-Parkinson-White Syndrome (WPW) with the aim to identify factors important in preprocedural counseling and planning. This single-center, retrospective study of patients ≤18 years without congenital heart disease identified 227 patients diagnosed with pre-excitation and referred for invasive electrophysiology study between 2008 and 2017. WPW Syndrome was diagnosed in 178 patients, while 49 patients had incidental identification of pre-excitation. Anterograde conduction of incidentally identified accessory pathways was not clinically different between the two cohorts at baseline or upon isoproterenol infusion. However, the proportion of accessory pathways meeting high-risk criteria was significantly lower than in patients diagnosed with WPW, 12% versus 28% ($p < 0.05$). Retrograde conduction at baseline of incidentally diagnosed accessory pathways was slower with a median block cycle length 365 milliseconds (IQR 260 to 450) versus 290 milliseconds (IQR 260 to 330, $p < 0.01$). In the incidentally identified cohort, right-sided, paraHisian, and fascicular pathways were more common with fewer attempted ablations (71% vs 94%, $p < 0.001$) and lower success rate (91% vs 97%, $p < 0.001$). A binomial logistic regression analysis further indicated patients incidentally identified with pre-excitation were associated with having lower rates of inducible supraventricular tachycardia, atrial fibrillation, and ablations performed, in addition, to having right-sided pathways. In conclusion, as patients with incidentally identified pre-excitation present more frequently for consideration of invasive electrophysiology study, these results impact procedural approaches, technical considerations, patient counseling, and outcome expectations.
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Incidental identification of pre-excitation is occurring more often in the current era due in part to the increased utilization of electrocardiograms (ECGs). In the 2015 National Hospital Ambulatory Medical Care Survey there were a reported 136 million emergency department visits in the United States, with nearly 1 in 5 patients < 15 years old. An ECG is performed in 19.4% of all emergency room encounters, which is a 13% increase since 2006.[1] Furthermore, current hand-held devices and smart phone applications allow for ECG recordings that are acquired with greater ease, speed, and efficiency.[2] Additionally, despite a lack of endorsement by the American Heart Association, cardiac screening prior to athletic participation has gained popularity in the United States.[3] Also, providers often order an ECG prior to prescribing certain medications, such as stimulants for the treatment of Attention Deficit Hyperactivity Disorder, regardless of current recommendations and evidence.[4,5] Although patients incidentally identified with pre-excitation are asymptomatic, this is not necessarily a benign condition since patients may still have a high-risk accessory pathway (AP) that is capable of supporting a life-threatening arrhythmia.[6−9] Sudden cardiac arrest due to pre-excitation is an infrequent event, however, the potential for a fatal outcome, coupled with the limitations of noninvasive risk stratification, often leads health care providers to recommend an invasive electrophysiologic (EP) study along with therapeutic catheter ablation in patients with incidentally diagnosed pre-excitation.[10−13] While previous studies have evaluated the risk of asymptomatic pre-excitation, our aim was to identify specific accessory pathway characteristics that are unique to the population of incidentally identified pre-excitation compared with patients diagnosed with Wolff-Parkinson-White Syndrome (WPW) syndrome.

Methods

This is a retrospective study at a single tertiary-care center of pediatric patients who underwent invasive EP study between January 1, 2008 and December 31, 2017. Patients were identified by review of a clinical database. Patients

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≤18 years of age with pre-excitation on a surface ECG were included. Patients with more than trivial congenital heart disease were excluded. Patients were categorized as having incidentally identified pre-excitation or WPW. Patients diagnosed with WPW reported cardiac symptoms, including palpitations, chest pain, dyspnea, presyncope, or syncope, had documented supraventricular tachycardia (SVT), or experienced sudden cardiac arrest prior to the invasive EP study. The local institutional review board approved this study.

All EP studies were performed under general anesthesia with standard placement of diagnostic electrode catheters utilizing the Ensite NavX electroanatomical navigation system for all cases. Patients diagnosed with WPW prescribed an antiarrhythmic discontinued the medication at a minimum of 5 half-lives prior to EP evaluation. AP risk stratification utilized the anterograde AP block cycle length (BCL), the AP effective refractory period (ERP), and shortest pre-excited R−R interval (SPERRI) during atrial fibrillation. A high-risk AP was defined when any one of these parameters were ≤250 milliseconds during baseline testing or ≤220 milliseconds during isoproterenol infusion.[14] Induction of supraventricular arrhythmias, including atrial fibrillation, was attempted during the course of a standard provocative stimulation protocol, which generally included the use of an isoproterenol infusion, with a goal heart rate increase of at least 20%. Arrhythmias were considered sustained with a duration >30 seconds. Catheter ablation was performed with either radiofrequency or cryothermal energy.

In regard to statistical analysis, within the entire pre-excitation cohort, 8 patients were found to have fascicular pathways (nodofascicular, nodoventricular, fasciculoventricular), 6 within the incidentally diagnosed cohort and 2 within the WPW cohort. These patients were included in EP study outcome analysis, however, were excluded from AP characteristic analysis since an atrioventricular pathway was not present. Normality of the dataset was assessed using the Shapiro-Wilk test with $p < 0.05$ indicating a non-Gaussian distribution. A nonparametric Mann-Whitney U test was utilized for comparison of continuous variables between the two study groups, reporting median and interquartile ranges. Fisher's exact analysis was used to determine differences in proportions between categorical variables. A Kruskall-Wallis one-way analysis of variance with post-hoc Dunn's comparison was performed between 4 non-Gaussian distributed groups. A binomial logistic regression analysis was performed to identify factors associated with a single dichotomous-dependent variable. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed with STATA, version 13.1 (Stata Corp., College Station, Texas), and GraphPad Prism, version 5.0b (GraphPad Software, La Jolla, California).

Results

A total of 227 patients with pre-excitation were referred for EP study, of which 178 (78%) were diagnosed with WPW and 49 (22%) with incidentally identified pre-excitation. There were no clinically significant demographic differences between the two cohorts. The ECG indications in the incidentally identified patients included: general medical evaluation, preathletic and premedication screening, precordial murmur, or family history. Of the patients diagnosed with WPW, a history of palpitations was the primary indication for the ECG. Other reasons for the ECG in the WPW group were syncope/presyncope, chest pain, dyspnea, and cardiac arrest (Table 1). Several patients reported more than one cardiac symptom. Noninvasive risk assessment, which included exercise stress test and/or ambulatory cardiac monitor, was performed in 115 (51%) patients prior to EP study. When compared with invasive EP study data, the effectiveness of noninvasive testing identifying pathways meeting high-risk criteria yielded a sensitivity, specificity, negative predictive value, and a positive predictive value of, 0.80 (95% CI 0.56 to 0.94), 0.27 (95% CI 0.18 to 0.37), 0.87 (95% CI 0.70 to 0.90), 0.18 (95% CI 0.11 to 0.29), respectively (Supplemental Table 1).

During invasive EP study, anterograde AP characteristics were evaluated. The APERP was only modestly prolonged in the incidentally diagnosed cohort 340 milliseconds (IQR 310 to 370) versus 320 milliseconds (IQR 290 to 350), $p = 0.01$. However, the APBCL was not significantly different between the two groups, 340 milliseconds (IQR 310 to 420) versus 320 milliseconds (IQR 280 to 390), $p = 0.07$ (Figure 1). In baseline conditions, SPERRI was also not prolonged in the incidental group, 312 milliseconds (IQR 301 to 414) versus 325 milliseconds (IQR 270 to 362), $p = 0.66$. An isoproterenol infusion was administered in 219 (96%) patients. During isoproterenol infusion, the APBCL and the APERP shortened

Table 1
Study cohort characteristics.

	Incidental pre-excitation	WPW syndrome
	n = 49	n = 178
Male	68%	63%
Age @ EPS (years)	12.7 ± 0.6	12.7 ± 0.3
<5yo	0%	1%
5-11yo	43%	35%
>12yo	57%	64%
Family history of arrhythmia	21%	20%
Antiarrhythmic prescribed	–	23%
Weight (kg)	55.5 ± 3.5	51.7 ± 1.5
Race/Ethnicity		
White	48%	48%
Hispanic	17%	25%
Black	6%	4%
Asian	8%	8%
Other/Unknown	21%	15%
ECG Indications		
General medical evaluation	27 (55%)	–
Pre-athletic screen	8 (16%)	–
Pre-medication screen	8 (16%)	–
Precordial murmur	3 (6%)	–
Arryhthmia family history	3 (6%)	–
Palpitations	–	158 (89%)
Syncope/Presyncope	–	56 (21%)
Chest pain	–	15 (8%)
Dyspnea	–	11 (6%)
Cardiac arrest	–	2 (1%)

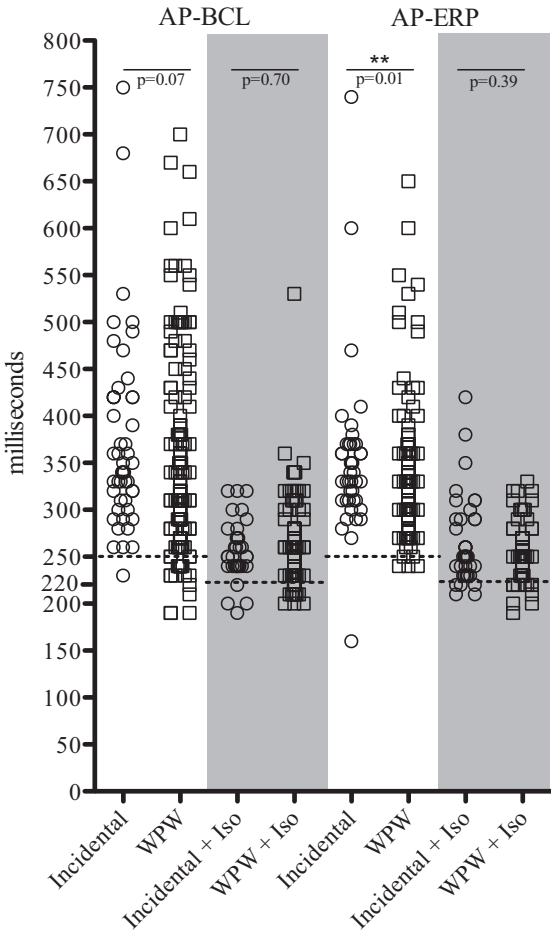

Figure 1. Individual patient distribution of accessory pathway block cycle lengths (APBCL) and effective refractory periods (APERP) at baseline conditions and during isoproterenol infusion. Dashed line at 250msec in baseline condition and 220msec during isoproterenol infusion indicates high-risk thresholds. Circle = Incidental pre-excitation, Square = WPW. Shaded area represents isoproterenol infusion condition. Mean values were compared using Mann-Whitney U test.

prominently in both groups with no significant differences between groups, APBCL 250 milliseconds (IQR 240 to 270) versus 250 milliseconds (IQR 230 to 280) milliseconds, $p = 0.70$; APERP 250 milliseconds (IQR 230 to 290) versus 250 milliseconds (IQR 240 to 270), $p = 0.39$. The SPERRI was not compared during an isoproterenol infusion since it did not occur or was not reported often enough. During the course of standard programmed stimulation in the baseline condition, atrial fibrillation was induced significantly less often in the incidental pre-excitation cohort (12% vs 32%, $p < 0.05$). A binomial logistic regression analysis indicated that patients with inducible atrial fibrillation were more likely to have WPW Syndrome than incidentally diagnosed pre-excitation and have a high-risk AP. The presence of SVT was not an independent predictor of atrial fibrillation induction (Supplemental Table 2).

With respect to retrograde AP conduction, ventriculo-atrial (VA) conduction was present equally in the two cohorts, (94% vs 94%), but the VABCL was prolonged in patients who were incidentally diagnosed, 365 milliseconds (IQR 260 to 450) versus 290 milliseconds (IQR 260 to 330), $p < 0.01$ (Figure 2). Upon isoproterenol infusion, no differences were observed between incidental pre-excitation and WPW syndrome, 255 milliseconds (IQR 245 to 280) versus 250 milliseconds (IQR 250 to 260) $p = 0.42$, respectively. Consequently, orthodromic reciprocating tachycardia could be induced in only 33% of incidentally diagnosed pre-excitation patients, while 79% of WPW patients had inducible orthodromic reciprocating tachycardia during baseline conditions ($p < 0.001$). With isoproterenol administration, an arrhythmia was induced in 58% versus 90%, ($p < 0.001$) (Figure 2). Antidromic reciprocating tachycardia was induced infrequently: 2 patients in the incidentally diagnosed group versus 4 patients in the WPW cohort.

All incidentally diagnosed patients had a single AP, whereas 8 patients in the WPW cohort had multiple APs. With respect to anatomic location, left-sided APs were significantly less prevalent in the incidentally diagnosed cohort. Conversely, right-sided APs, including paraHisian and fascicular pathways, were more common in the incidentally diagnosed cohort. None of the patients with a fascicular pathway had an inducible arrhythmia. For the entire study cohort, aggregate right-sided APs trended to have slower anterograde conduction characteristics than left-sided, and paraHisian APs had significantly more prolonged anterograde conduction as compared with left-sided pathways (Table 2).

Patients with incidental pre-excitation underwent attempted ablation significantly less often than patients with WPW (71% vs 94%, $p < 0.001$). Additionally, there was a lower rate of successful elimination of AP conduction in patients with incidental pre-excitation (91% vs 97%, $p < 0.001$). All unsuccessful ablations occurred in patients with right-sided APs. Radiofrequency energy was used primarily for catheter ablation in both groups. Of patients with incidentally diagnosed pre-excitation who underwent catheter ablation, 65% had high-risk anterograde AP conduction characteristics and/or inducible sustained SVT. Within the WPW cohort, 94% had similar indications for ablation (Table 3). When APBCL, APERP, and SPERRI data were combined to evaluate a larger data set, univariate analysis indicated that incidentally diagnosed patients had a lower incidence of an AP meeting high-risk criteria than the WPW cohort (12% vs 28%, $p < 0.05$). A binomial logistic regression analysis indicated patients who underwent ablation were more commonly diagnosed with WPW and had inducible SVT more frequently. However, having a high-risk AP was not an independent predictor in this model (Table 4). There were no procedural complications in the cohort of patients with incidental pre-excitation. There were three minor complications in the WPW cohort, including transient first-degree and complete AV block, all of which resolved by the end of the procedure. These three minor complications were associated with right-sided pathways.

To discern relation associated with incidental identification of pre-excitation, regression analysis revealed right-sided APs, a lower frequency of inducible SVT, and atrial fibrillation were all associated within this patient group. Additionally, there were reduced odds of having an ablation

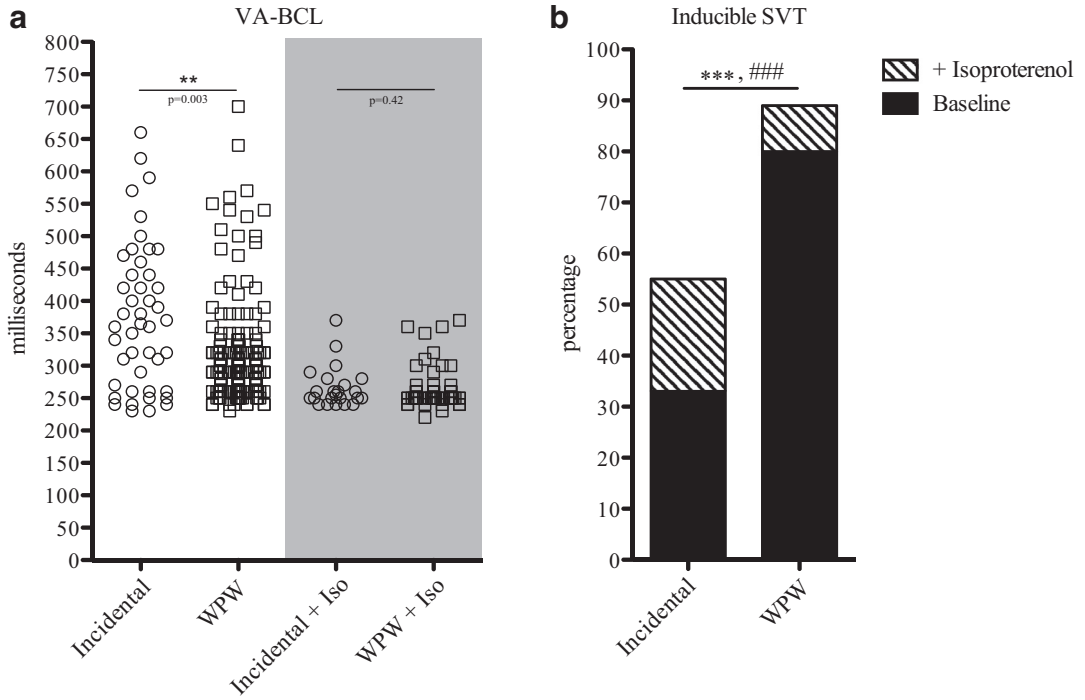

Figure 2. *(a)* Individual patient distribution of ventriculo-atrial block cycle length (VABCL). Circle = Incidental Pre-excitation, Square = WPW. Shaded area represents isoproterenol infusion condition. Mean values were compared using Mann-Whitney U test. *(b)* Percentage of patients with inducible SVT during invasive EP at baseline *(solid)* and during isoproterenol *(striped)*. Proportions compared using Fisher's Exact analysis.

performed. Importantly, in this model and population, the presence of a high-risk AP was just as likely between incidentally identified pre-excitation and WPW patients (Table 5).

Discussion

Incidentally identified pre-excitation continues to be a diagnostic challenge and often leads to difficulties in clinician decision-making and patient communication. During the study time period, 22% of referrals for invasive EP study at this single center were for management of incidentally identified pre-excitation, with a large contribution of ECGs performed for preathletic or premedication screening. The comparison of this population to patients diagnosed with WPW provided an opportunity to identify qualities within patients incidentally identified with pre-excitation that can aid clinical assessment and plan.

Noninvasive techniques, such as ambulatory cardiac monitors and exercise stress tests, are recommended during the initial diagnostic evaluation of pre-excitation for AP risk stratification. The 2012 Pediatric and Congenital Electrophysiology Society/Heart Rhythm Society (PACES/HRS) consensus statement describes intermittent pre-excitation identified on noninvasive testing as potential evidence for a low-risk AP.[15] We found that noninvasive techniques had a sensitivity and negative predictive value of 80% and 87%, respectively. Although screening benefits of noninvasive testing have been shown in the literature, we also observed the previously reported limitations of noninvasive testing that include a low specificity of 27% and low positive predictive value of 18%. Furthermore, the accurate assessment of loss of pre-excitation during noninvasive studies, particularly in pediatric patients, is challenging due to competitive AV nodal conduction that makes pre-excitation difficult to discern, especially at elevated heart rates, which can limit the utility of these tests.[11–17]

Despite the lack of clinical significance in APERP, APBCL, and SPERRI between the two groups, we found

Table 2
Accessory pathway location.

	Incidental pre-excitation	WPW syndrome	p value	AP-BCL	p value
Multiple pathways	0	8 (4.5%)	ns		
Location					
Left	8 (16.3%)	103 (58.2%)	<0.001	343 ± 9	
Right	41 (83.7%)	82 (40.7%)	<0.05	350 ± 10	
Fascicular	*6 (12.2%)*	*2 (1.1%)*	*<0.001*	*394 ± 30*	
ParaHisian	*8 (16.3%)*	*8 (4.5%)*	*<0.01*	*427 ± 34*	*<0.05**

* Kruskall-Wallis reporting means +/− SD with posthoc Dunn's, ParaHisian vs Left

Table 3
Univariate analysis of ablation characteristics.

	Incidental pre-excitation	WPW syndrome	p value
Ablation performed	35 (71%)	168 (94%)	<0.001
Ablation indication			
SVT induction only	17 (49%)	108 (64%)	ns
High-risk pathway only	2(6%)	1(0.6%)	ns
SVT+High-risk	4 (11%)	49 (29%)	0.03
Mode			
Radiofrequency	32 (91%)	150 (89%)	ns
Cryoablation	2 (6%)	5 (3%)	ns
Both	1 (3%)	13 (8%)	ns
Successful	32 (91%)	163 (97%)	<0.001
Complications	0 (0)	3 (2%)*note*	ns

fewer high-risk APs in univariate analysis in the incidentally identified group (12% vs 28%). However, when incorporated into a logistic regression model, patients with incidentally identified pre-excitation did not have reduced odds of having a high-risk AP within our study population. It is important to recognize high-risk APs do occur in incidentally diagnosed patients, albeit with a potentially reduced frequency.[18–20] With regard to retrograde AP conduction, incidentally identified pre-excitation patients had significantly slower VA conduction compared with the WPW cohort associated with a reduced incidence of inducible orthodromic reciprocating tachycardia. Importantly, atrial fibrillation was also induced significantly less often in the incidentally identified pre-excitation cohort. The etiology of atrial fibrillation in the setting of pre-excitation is believed to arise from multiple mechanisms, including anterograde and retrograde conduction qualities of the AP, degeneration of intra-atrial reentrant tachycardia or AV reciprocating tachycardia, and intrinsic molecular properties of atrial myocytes, in part described in familial forms of WPW relating to the PRKAG2 gene.[21–24] Therefore, based on their lower frequency of inducible atrial fibrillation, incidentally diagnosed patients may have a unique electrical substrate impacting their risk profile. These results help to understand the lack of cardiac symptoms, particularly paroxysmal palpitations, in the incidentally identified pre-excitation cohort and highlights potential fundamental differences in atrial and AP physiology between the cohorts. This concept is supported by a recent meta-analysis of asymptomatic pre-excitation patients who underwent long-term follow-up that revealed low rates of spontaneous atrial fibrillation over several years.[25]

In a univariate comparison and in multiple logistic regression analysis of ablation predictors, those with incidental pre-excitation were significantly less likely to undergo catheter ablation therapy compared with symptomatic WPW patients. This discrepancy can partly be attributed to the noted prevalence of fascicular pathways and low-risk paraHisian APs. Furthermore, slow retrograde conduction resulting in a lack of inducible SVT in the incidentally diagnosed pre-excitation cohort also may contribute to reduced ablation rates. This information is important to consider during preprocedure consultation sessions. However, it is important to further consider that AP conduction characteristics may evolve over time when considering if an AP is likely to be high-risk. Thus, it is possible that an incidentally identified patient may have simply been detected prior to the onset of symptoms confounding results, although less likely in this study population as there were no differences in age between the two groups.

Table 4
Predictors of ablation.

	Odds ratio (95% CI)	p value
WPW syndrome	2.95 (1.10-7.92)	0.03
High-risk accessory pathway	0.84 (0.26-2.67)	ns
SVT induction	7.39 (2.38-22.91)	<0.001

Table 5
Factors associated with incidental identification of pre-excitation.

	Odds ratio (95% CI)	p value
Right side pathway	3.64 (1.47-8.99)	<0.01
SVT induced during EPS	0.20 (0.09-0.45)	<0.001
Atrial fibrillation induced during EPS	0.25 (0.08-0.72)	<0.01
High risk accessory pathway identified	1.01 (0.40-2.61)	0.97
Ablation performed	0.33 (0.12-0.97)	0.045

The noted preferential distribution of right-sided APs in incidental pre-excitation and left-sided APs in WPW may suggest a fundamental physiologic difference of the AP for which the basis is not completely understood. Currently, there are inconclusive data regarding risk-stratification of APs according to anatomic location in asymptomatic or WPW patients.[26,27] Therefore, the importance of anatomic location in predicting long-term risk still remains to be determined, and a suspected AP location does not appear to be an adequate indicator of performing ablation. Furthermore, we observed that all unsuccessful ablations and complications were associated with right-sided APs. These findings, in addition to a greater incidence of recurrence after a successful procedure eliminating a right-sided pathway, highlight the apparent challenging nature of treating this location with catheter ablation.[28,29] Finally, it is interesting to note that all 8 patients with multiple APs met criteria for high risk and were in the WPW group. The lack of multiple APs in the incidentally diagnosed cohort may portend a lower risk as reported by Etheridge et al.[30]

According to PACES/HRS Consensus Statement, ablation indications for a variety of populations with pre-excitation are currently class II with level of evidence B/C, leading to the possibility of open interpretation of AP risk criteria and ablation benefit. For example, testing during isoproterenol administration, although not standard, may influence the decision for ablation. In addition, patients could have undergone catheter ablation for “softer” indications such as reluctance of the referring provider to prescribe high-risk medications, even though invasive testing demonstrated an AP that did not meet high-risk criteria. Finally, knowing conduction characteristics may evolve over time or identifying APs near high-risk thresholds are also considerations for ablation in the pediatric patient who often has yet to complete growth and has many active years

ahead in which changing AP characteristics may be important during more vigorous life experiences. These are contributing factors leading to catheter ablation in patients without inducible SVT or high-risk AP conduction characteristics.

In multiple regression analysis, patients incidentally identified with pre-excitation were associated with right-sided pathways and reduced rates of inducible SVT and atrial fibrillation, all contributing to lower ablation rates. Preparation for EP study includes a standard conversation with patients and families addressing the intent to treat and the importance of assessing accessory pathway characteristics prior to ablation being performed. This study suggests an increased likelihood that an invasive EP procedure will be diagnostic rather than therapeutic in incidentally identified pre-excitation patients. Additionally, this patient population may require specific resources, including smaller tip catheters, cryothermal energy, and long sheaths that provide better tip stability, especially for substrates in close proximity to the normal conduction system. In conclusion, with the increasing incidental identification of pre-excitation, these results can aid expectations and anticipatory guidance of an invasive EP procedure in this emerging group of patients.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.053.

1. National Center for Health Statistics. *National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables,* pp 1−39. https://www.cdc.govnchsahcdwebtables.htm.
2. Nguyen HH, Van Hare GF, Rudokas M, Bowman T, Silva JNA. SPEAR Trial: Smartphone Pediatric ElectrocARdiogram Trial. Hund T, ed. *PLoS ONE* 2015;10:e0136256.
3. Maron BJ, Friedman RA, Kligfield P, Levine BD, Viskin S, Chaitman BR, Okin PM, Saul JP, Salberg L, Van Hare GF, Soliman EZ, Chen J, Matherne GP, Bolling SF, Mitten MJ, Caplan A, Balady GJ, Thompson PD. Assessment of the 12-Lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12−25 years of age). *Circulation* 2014;130:1303–1334.
4. Leslie LK, Rodday AM, Saunders TS, Cohen JT, Wong JB, Parsons SK. Cardiac screening prior to stimulant treatment of ADHD: a survey of US-Based Pediatricians. *Pediatrics* 2012;129:222–230.
5. Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'Duffy A, Connell FA, Ray WA. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med* 2011;365:1896–1904.
6. Pappone C, Manguso F, Santinelli R, Vicedomini G, Sala S, Paglino G, Mazzone P, Lang CC, Gulletta S, Augello G, Santinelli O, Santinelli V. Radiofrequency ablation in children with asymptomatic Wolff−Parkinson−White syndrome. *N Engl J Med* 2004;351:1197–1205.
7. Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, Gulletta S, Mazzone P, Tortoriello V, Pappone A, Dicandia C, Rosanio S. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff−Parkinson−White syndrome. *N Engl J Med* 2003;349:1803–1811.
8. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, Ciaccio C, Giannelli L, Ionescu B, Petretta A, Vitale R, Cuko A, Calovic Z, Fundaliotis A, Moscatiello M, Tavazzi L, Santinelli V. Wolff-Parkinson-White syndrome in the era of catheter ablation. *Circulation* 2014;130:811–819.
9. Klein GJ, Prystowsky EN, Yee R, Sharma AD, Laupacis A. Asymptomatic Wolff-Parkinson-White. Should we intervene? *Circulation* 1989;80:1902–1905.
10. 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.
11. 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.
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. Novella J, DeBiasi RM, Coplan NL, Suri R, Keller S. Noninvasive risk stratification for sudden death in asymptomatic patients with Wolff-Parkinson-White syndrome. *Rev Cardiovasc Med* 2014;15:283–289.
14. Cohen M, Triedman J. Guidelines for management of asymptomatic ventricular pre-excitation: brave new world or Pandora's box? *Circ Arrhythm Electrophysiol* 2014;7:187–189.
15. Cohen MI, Triedman JK, Cannon BC, Davis AM, Drago F, Janousek J, Klein GJ, Law IH, Morady FJ, Paul T, Perry JC, Sanatani S, Tanel RE. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern. *Heart Rhythm* 2012;9:1006–1024.
16. Czosek RJ, Anderson JB, Marino BS, Mellion K, Knilans TK. Noninvasive risk stratification techniques in pediatric patients with ventricular preexcitation. *Pacing Clin Electrophysiol* 2011;34:555–562.
17. Gaita F, Giustetto C, Riccardi R, Mangiardi L, Brusca A. Stress and pharmacologic tests as methods to identify patients with Wolff-Parkinson-White syndrome at risk of sudden death. *Am J Cardiol* 1989;64:487–490.
18. Di Mambro C, Drago F, Milioni M, Russo MS, Righi D, Placidi S, Remoli R, Palmieri R, Gimigliano F, Santucci LM, Silvetti MS, Prosperi M. Sports eligibility after risk assessment and treatment in children with asymptomatic ventricular pre-excitation. *Sports Med* 2016;46:1183–1190.
19. De Ponti R, Marazzi R, Doni LA, Cremona V, Marazzato J, Salerno-Uriarte JA. Invasive electrophysiological evaluation and ablation in patients with asymptomatic ventricular pre-excitation persistent at exercise stress test. *Europace* 2015;17:946–952.
20. Sarubbi B, D'Alto M, Vergara P, Calvanese R, Mercurio B, Russo MG, Calabrò R. Electrophysiological evaluation of asymptomatic ventricular pre-excitation in children and adolescents. *Int J Cardiol* 2005;98:207–214.
21. Centurión OA, Shimizu A, Isomoto S, Konoe A. Mechanisms for the genesis of paroxysmal atrial fibrillation in the Wolff−Parkinson−White syndrome: intrinsic atrial muscle vulnerability vs. electrophysiological properties of the accessory pathway. *Europace* 2008;10:294–302.
22. Hamada T, Hiraki T, Ikeda H, et al. Mechanisms for atrial fibrillation in patients with Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 2002;13:223–229.
23. Zhang L-P, Hui B, Gao B-R. High risk of sudden death associated with a PRKAG2-related familial Wolff-Parkinson-White syndrome. *J Electrocardiol* 2011;44:483–486.
24. Gollob MH, Green MS, Tang AS-L, Gollob T, Karibe A, Hassan AL-S, Ahmad F, Lozado R, Shah G, Fananapazir L, Bachinski LL, Roberts R. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 2001;344:1823–1831.
25. Obeyesekere MN, Leong-Sit P, Massel D, Manlucu J, Krahn AD, Skanes AC, Yee R, Gula LJ, Klein GJ. Incidence of atrial fibrillation and prevalence of intermittent pre-excitation in asymptomatic Wolff-Parkinson-White patients: a meta-analysis. *Int J Cardiol* 2012;160:75–77.
26. Mah DY, Sherwin ED, Alexander ME, Cecchin F, Abrams DJ, Walsh EP, Triedman JK. The electrophysiological characteristics of accessory pathways in pediatric patients with intermittent preexcitation. *Pacing Clin Electrophysiol* 2013;36:1117–1122.
27. Kubuš P, Vít P, Gebauer RA, Materna O, Janoušek J. Electrophysiologic profile and results of invasive risk stratification in asymptomatic children and adolescents with the Wolff−Parkinson−White electrocardiographic pattern. *Circ Arrhythm Electrophysiol* 2014;7:218–223.

28. Van Hare GF, Javitz H, Carmelli D, Saul JP, Tanel RE, Fischbach PS, Kanter RJ, Schaffer M, Dunnigan A, Colan S, Serwer G. Prospective assessment after pediatric cardiac ablation: demographics, medical profiles, and initial outcomes. *J Cardiovasc Electrophysiol* 2004;15:759–770.
29. Van Hare GF, Javitz H, Carmelli D, Saul JP, Tanel RE, Fischbach PS, Kante RJ, Schaffer M, Dunnigan A, Colan S, Serwer G. Prospective assessment after pediatric cardiac ablation: recurrence at 1 year after initially successful ablation of supraventricular tachycardia. *Heart Rhythm* 2004;1:188–196.
30. Etheridge SP, Escudero SA, Blaufox AD, Law IH, Dechert-Crooks BE, Stephenson EA, Dubin AM, Ceresnak SR, Motonaga KS, Skinner JR, Marcondes LD, Perry JC, Collins KK, Seslar SP, Cabrera M, Uzun O, Cannon BC, Aziz PF, Kubuŝ P, Tanel RE, Valdes SO, Sami S, Kertesz NJ, Maldonado J, Erickson C, Moore JP, Asakai H, Mill L, Abcede M, Spector ZZ, Menon S, Shwayder M, Bradley DJ, Cohen MI, Sanatani S. Life-threatening event risk in children with Wolff-Parkinson-White syndrome: a multicenter international study. *JACC Clin Electrophysiol* 2018;4:433–444.