www.jpeds.com • THE JOURNAL OF PEDIATRICS

Management of Asymptomatic Wolff-Parkinson-White Pattern by Pediatric Electrophysiologists

Henry Chubb, MBBS, PhD[1], Robert M. Campbell, MD[2], Kara S. Motonaga, MD[1], Scott R. Ceresnak, MD[1], and Anne M. Dubin, MD[1]

Objective To determine the present-day approach of pediatric cardiac electrophysiologists to asymptomatic Wolff-Parkinson-White (WPW) pattern and to contrast to both published consensus statements and a similar survey.

Study design A questionnaire was sent to 266 Pediatric and Congenital Electrophysiology Society physician members in 25 countries; 21 questions from the 2003 survey were repeated, with new questions added regarding risk stratification and decision making.

Results We received 113 responses from 13 countries, with responders having extensive electrophysiology experience (median 15 years [IQR 8.5-25 years]). Only 12 (11%) believed that intermittent pre-excitation and 37 (33%) that sudden loss of pre-excitation on exercise test were sufficient evidence of accessory pathway safety to avoid an invasive electrophysiology study. Optimal weight for electrophysiology study was 20 kg (IQR 18-22.5 kg), and 61% and 58% would then ablate all right-sided or left-sided accessory pathways, respectively, regardless of electrophysiological properties, whereas only 23% would ablate all septal accessory pathways ($P < .001$). Compared with 2003, respondents were more likely to consider inducible arrhythmia (77% vs 26%, $P < .001$) as sufficient indication alone for ablation.

Conclusions In the context of recent literature regarding the reliability of risk-stratification tools, most operators are now performing electrophysiology study for asymptomatic Wolff-Parkinson-White regardless of noninvasive findings. Many will then proceed to default ablation of all accessory pathways distant from critical conduction structures. *(J Pediatr 2019;213:88-95)*.

It is estimated that there are >30 000 children with asymptomatic Wolff-Parkinson-White (WPW) pattern in the US today.[1-3] Many are identified by general pediatricians in the course of routine investigations for unrelated illnesses, or through routine screening for activities such as competitive sports. However, asymptomatic WPW has a small but significant risk of sudden cardiac death (SCD), thought generally to be due to rapid antegrade conduction of atrial fibrillation (AF) across the accessory pathway leading to ventricular fibrillation.[4] Multiple studies have suggested noninvasive and invasive risk stratification techniques to help determine likelihood of a lethal accessory pathway,[5-7] and the majority of patients with asymptomatic WPW will undergo initial risk assessment using ambulatory electrocardiogram (ECG) monitoring or exercise stress test.

In 2003, we performed a survey of the pediatric electrophysiology community,[8] finding that the majority were relying upon invasive risk stratification, performing electrophysiology studies and then using those electrophysiology study-derived indices to guide risk stratification for ablation. Around that time, reviews and editorials suggested a conservative approach when risk-stratifying asymptomatic children discovered to have WPW on ECG.[9,10]

Dedicated guidelines for the management of asymptomatic WPW in children were ultimately published in 2012.[4] These guidelines, endorsed by the Pediatric and Congenital Electrophysiology Society (PACES) and Heart Rhythm Society (HRS), proposed noninvasive risk stratification (in the form of ambulatory ECG or exercise stress test) and possible electrophysiology study in children age over 5-8 years with asymptomatic WPW. Ablation of asymptomatic WPW was considered a class IIa indication for those with designated invasive markers of higher risk (shortest pre-excited R-R interval (SPERRI) in AF (SPERRI-AF) or SPERRI on atrial pacing (SPERRI-Ap) ≤250 ms) (**Figure 1**), and a class IIb indication for those without. Subsequently,

AF	Atrial fibrillation	LTE	Life-threatening event
Ap	Atrial pacing	PACES	Pediatric and Congenital Electrophysiology Society
APERP	Accessory pathway effective refractory period	RAP	Right-sided accessory pathway
CrSAP	Critical septal accessory pathway	RF	Radiofrequency
ECG	Electrocardiogram	SCD	Sudden cardiac death
HRS	Heart Rhythm Society	SPERRI	Shortest pre-excited R-R interval
LAP	Left-sided accessory pathway	WPW	Wolff-Parkinson-White

From the [1]Division of Pediatric Cardiology, Department of Pediatrics, Stanford University, Stanford, CA; and [2]Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA

The authors declare no conflicts of interest.

0022-3476/$ - see front matter.
https://doi.org/10.1016/j.jpeds.2019.05.058

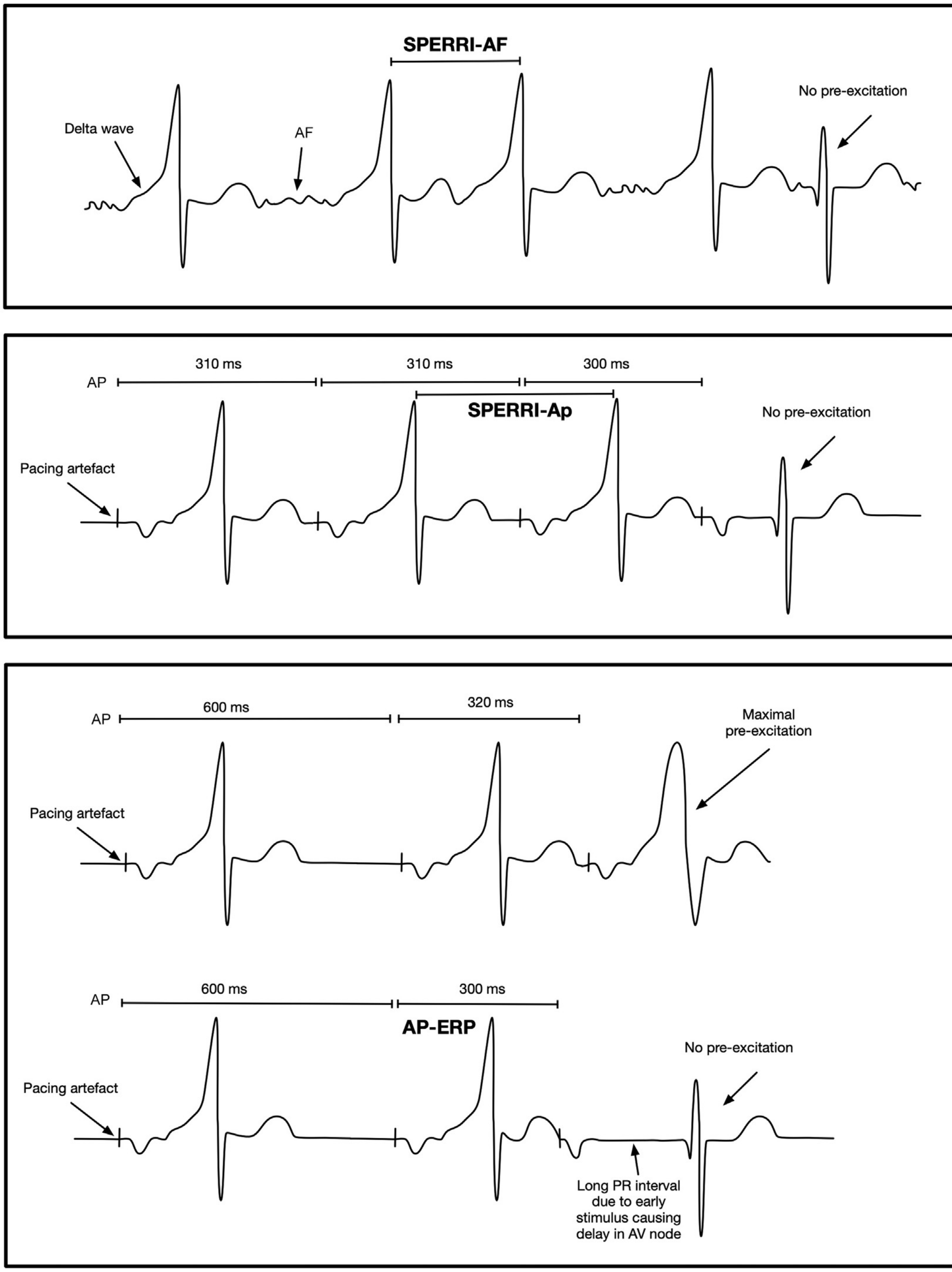

Figure 1. Illustration of the concepts of (*top*) SPERRI-AF, (*middle*) SPERRI-Ap, and (*bottom*) the accessory pathway effective refractory period (AP-ERP), which is the longest interval between stimuli that are not conducted via the accessory pathway (note loss of delta in the lower tracing of the bottom panel). SPERRI-Ap and AP-ERP may only be measured on invasive electrophysiological study, whereas SPERRI-AF may also be measured noninvasively if a patient episode of AF is recorded.

the 2013 European Heart Rhythm Association pediatric arrhythmia guidelines and 2016 PACES/HRS pediatric ablation guidelines issued broadly similar guidance on ablation for children with asymptomatic WPW.[11,12]

Children are at greater risk of sudden death in asymptomatic WPW compared with adults, with a meta-analysis revealing a numerically increased SCD event rate of 1.93 (95% CI 0.57-4.1) compared with an adult SCD event rate of 0.86 (95% CI 0.28-1.75), $P = .07$.[9] Pappone et al investigated both asymptomatic young adults (median age of 36 years) and children and found a striking difference in the rates of life threatening events; 19 of 184 children vs 1 of 293 adults.[13]

At the same time, there is increasing evidence that noninvasive and invasive risk stratification methods may not be as sensitive or reliable as previously thought.[14,15] Mah et al found no difference in the incidence of high-risk invasive markers in patients with intermittent pre-excitation compared with those with permanent pre-excitation. Etheridge found in a multicenter study that patients with life-threatening events may have no high-risk markers on invasive electrophysiology studies.[14]

With these new data emerging, we reassessed the current practice of pediatric electrophysiologists concerning risk stratification and ablation in children. We hypothesized that the threshold for invasive evaluation and ablation of asymptomatic WPW would be lower than it was 15 years earlier, and that the practice of the community would differ significantly from the guidelines.

Methods

The methods and results are reported conforming to the Checklist for Reporting Results of Internet E-Surveys.[16] Our original 21-question survey[8] was incorporated into a new questionnaire that was extended to assess the approach to individual subgroups of patients with asymptomatic WPW. Physicians were queried as to how they approach risk assessment, electrophysiology study, and decision for ablation (Questionnaires provided in the **Appendix** [available at www.jpeds.com]). The questionnaire was compiled using Qualtrics (Provo, Utah) and circulated to 266 physician members of PACES, working in 25 countries worldwide. In common with the original 2003 questionnaire, individual physicians rather than institutions were surveyed. Accessory pathway locations were divided into 3 groups: right-sided accessory pathway (RAP) distant from critical conduction structures, such as the atrioventricular node or His-Purkinje fibers, left-sided accessory pathway (LAP) distant from conduction structures, and accessory pathway close to conduction structures, such as an anteroseptal or midseptal accessory pathway (critical septal accessory pathway [CrSAP]).

The questionnaire was anonymized without incentive for completion, and consent was obtained for each respondent. Local Institutional Review Board approval was granted prior to circulation.

Questionnaires that were <90% completed were rejected from analysis. Responses to quoted risks and estimated experience were collected as free text. For the purposes of quantitative analysis, experience numbers of ">x" were rounded up by 10%, and for risks "<x" were rounded as follows: <1 to 0.5, <<1 to 0.1, <0.5 to 0.25, and <2 to 1.5. Ranges (eg 5%-10%) were approximated to the mid-point. Normally distributed continuous variables are presented as mean ± SD, and median (with 25th-75th percentile) for non-normal distribution or noncontinuous ordinal data. T test and Mann-Whitney U test were used for comparison of groups respectively. Ordinary 1-way ANOVA was used for multiple comparisons. *P* values of less than .05 were considered significant, and statistical analysis was performed using SPSS v 25 (IBM, Armonk, New York).

Results

From the group of 266 physicians, a total of 128 responses were received (48%), of which 113 were >90% completed and, therefore, accepted for analysis. Eighty-four respondents were from the US, with the remaining 29 from other countries (8 Canada, 4 Germany, 4 Australia, 3 United Kingdom, 2 Italy, 2 Colombia, and 1 each from Argentina, India, Israel, Saudi Arabia, South Africa, and Venezuela).

The median electrophysiology experience for respondents was 15 years (IQR 8.5-25 years, dedicated electrophysiology fellow level or above), over which time respondents had performed a median of 1000 (IQR 400-1500) ablation procedures. Compared with 2003, the cohort in this study had accrued more procedural experience (85% with >200 procedures vs 70% in 2003 [$P = .03$]) over a similar number of years of electrophysiology (86% >5 years vs 86% [$P = .95$]) (**Figure 2**; available at www.jpeds.com). Pediatric electrophysiology procedures in 2018 were performed less frequently with 2 attending electrophysiologists (2018: 13% "always," 65% "sometimes," 23% "never"; 2003: 30% "always," 47% "sometimes," 24% "never"; $P = .03$).

The use of noninvasive investigations (exercise stress test and ambulatory ECG to assess for intermittent or loss of pre-excitation) was not reported in 2003 but in this study varied considerably among respondents. Of note, although 71 (63%) routinely performed ambulatory ECG and 78 (69%) routinely performed an exercise stress test, far fewer believed that the tests could be used as evidence of sufficient accessory pathway safety to advise against invasive electrophysiology study. Only 12 (11%) used an intermittently pre-excited ECG as evidence of a "safe" pathway. A slightly higher proportion (37 [33%]) used loss of pre-excitation on exercise stress test as sufficient evidence of safety. Fourteen respondents (12%) did not routinely perform noninvasive assessments, and they were generally more experienced (2000 vs 1000 lifetime ablations [$P = .02$] and 22 years electrophysiology experience vs 15 years [$P = .01$]).

Intracardiac, rather than transesophageal, electrophysiology study was the preferred invasive method for 109 (96%) respondents in 2018, compared with 55% in 2003 ($P < .001$). In deciding when to perform an electrophysiology study, most electrophysiologists (85 [75%]) were influenced by both age and weight (16% age alone, 8% weight alone). Optimal and minimum values for invasive investigation are summarized in **Table I**, and there was a trend to performing electrophysiology study earlier than in 2003. Operators were also less influenced by nonelectrophysiological factors such as career plans incompatible with WPW (eg, military) or competitive athletics. A much smaller proportion were influenced by attention deficit disorder as a comorbidity, or the need for psychotropic medications.

Table I. Factors affecting decision for invasive investigation (electrophysiological study) of children with asymptomatic WPW

Indications	2018 Survey: Optimal	2018 Survey: Minimum	2003 Survey: Optimal	P value: 2003 vs 2018
Age for electrophysiology study (y)	8 (IQR 6-8) Range 4-10	5 (IQR 4-7) Range 3-10	10 Range 1-13	*
Weight for electrophysiology study (kg)	20 (IQR 18-22.5) Range 15-25	16 (IQR 15-20) Range 5-25	Not assessed	NA

Nonelectrophysiological factors	Strongly influence decision for electrophysiology study	Strongly Influence decision to ablate	No influence	2003 Survey: Strongly influence decision for electrophysiology study	P value: 2003 vs 2018
Career plans incompatible with asymptomatic WPW (eg, military service)	72% (81)	88% (99)	2% (2)	88% (38)	**.03**
Competitive athlete	70% (79)	80% (71)	11% (12)	86% (37)	**.04**
Congenital heart disease	73% (82)	74% (83)	10% (11)	81% (35)	.25
ADHD	33% (37)	28% (32)	59% (67)	44% (19)	.18
Need for psychotropic medications	38% (43)	35% (40)	51% (58)	39% (17)	.86
Reactive airways disease	27% (31)	32% (36)	58% (66)	49% (21)	**.01**
Parental or patient preference in favour of procedure	73% (83)	73% (83)	5% (6)	Not assessed	NA

ADHD, attention-deficit/hyperactivity disorder.
Values are quoted as percentage (total number of respondents).
Bold indicates $P<.05$.
*Insufficient data available from 2003 study to enable statistical analysis.

For those performing intracardiac electrophysiology study, all measured at least 1 marker of a high-risk pathway (short accessory pathway effective refractory period [APERP] or SPERRI-AP] inducibility of supraventricular tachycardia, or short pre-excited R-R interval during AF (SPERRI-AF). Isoproterenol was routinely given during electrophysiology study by 51% of operators to attempt to assess pathway characteristics with exercise.

Decision for Ablation

Across all pathway locations, there was no change from 2003 in the percentage of respondents that would ablate all accessory pathways regardless of electrophysiology study findings (25 [22%] in 2018 vs 10 [23%] in 2003, $P = .88$). However, in this study the influence of accessory pathway location upon the decision to ablate was also assessed: location of accessory pathway is related to risk of development of heart block, with ablation of a septal accessory pathway presenting the highest risk. Sixty-six (58%) would always attempt ablation of a LAP, 69 (61%) would always ablate a RAP, but only 26 (23%) a CrSAP ($P < .001$).

For those who would not ablate an accessory pathway regardless of measurements, they were influenced by both electrophysiology study findings and patient factors. All respondents were guided by the measured SPERRI-AF, SPERRI-Ap, and APERP. The median cut-off that respondents believed justified ablation alone on safety grounds for all 3 measures at all locations was 250 ms (**Figure 3**; available at www.jpeds.com). Compared with 2003, the proportion that would consider SPERRI-AF ≤240 ms to be sufficient alone to warrant ablation of a pathway was unchanged: 77% in 2003 vs 86% in 2018 ($P = .10$). However, a much larger proportion in 2018 would consider an APERP <240 ms sufficient alone to warrant ablation (43% in 2003 vs 76% in 2018; $P < .001$, **Figure 2**).

For those who use isoproterenol for at least some of their diagnostic procedures (102 (90%) operators), 61 (60%) do not change their cut-off values. Twenty-one (21%) reduce their cut-offs, but not in a quantitative manner, and 20 (20%) quantify the reduction, shortening critical APERP, SPERRI-Ap, and SPERRI-AF values by an average of 16 ms.

For those pathways that do not achieve the critical conduction threshold for default ablation, respondents were also influenced by other factors (**Figure 4**). Of note, for the majority of operators inducible orthodromic or antidromic atrioventricular re-entry tachycardia was sufficient indication alone for ablation of LAP (36 of 40 [90%]), RAP (33 of 36 [92%]), or CrSAP (58 of 75 [77%]); in 2003 it was sufficient for only 11 of 43 respondents (26%, $P < .001$).

Operator perception of procedural risks and benefits was assessed in the context of the requirement for the procedure outcome to be weighed against leaving an accessory pathway untreated. Most accessory pathway ablations were performed using radiofrequency (RF) energy (87%), compared with 13% using cryoablation, and operators quoted higher acute success rate, lower recurrence rate but higher complication rate for RF compared with cryoablation (**Table II**). Twelve (11%) operators exclusively used RF, and no operators exclusively used cryoablation. Interestingly, in 2003 the quoted rates of acute success were higher, but the quoted rates of complications and recurrence were also higher.

Impact of Experience

Responders from the US were generally more experienced (17 ± 9 years vs 12 ± 8 years; $P = .007$). Following Bonferroni

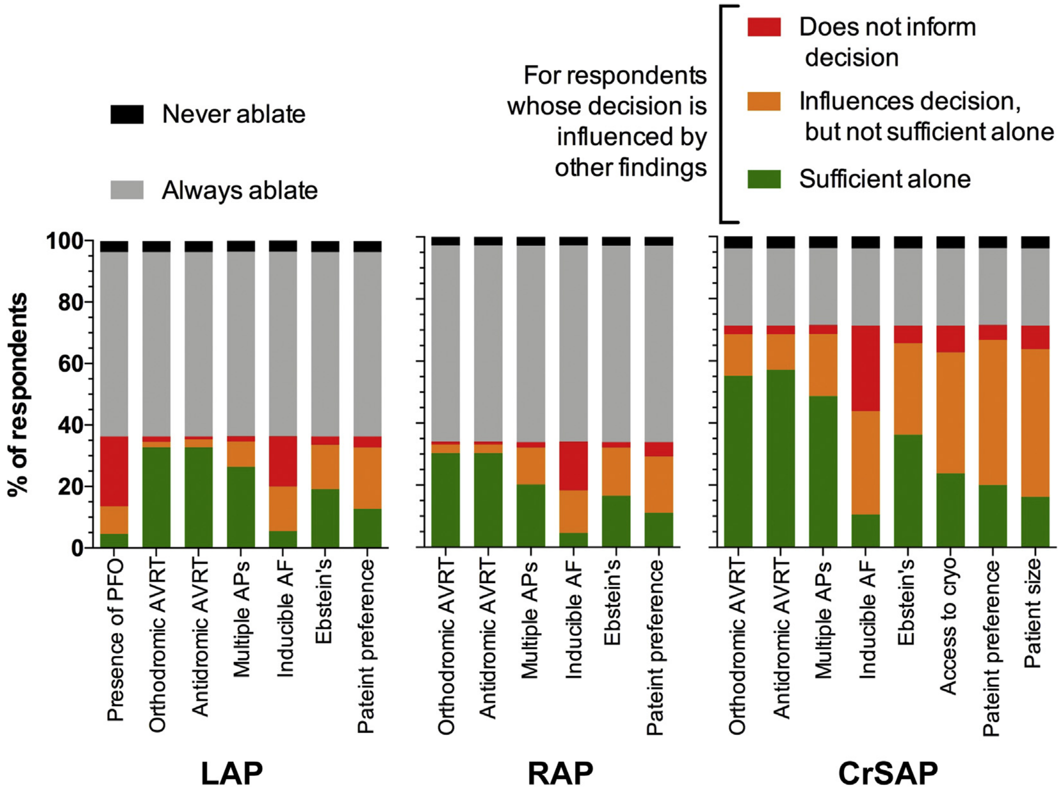

Figure 4. Factors influencing operator decision to ablate at the 3 assessed accessory pathway location categories, when pathway did not fulfill antegrade conduction property thresholds (eg, SPERRI-AF). *AVRT*, atrioventricular re-entrant tachycardia; *cryo*, cryoablation; *PFO*, patent foramen ovale.

correction for multiple analyses, there was no significant correlation between any continuous response variable and the number of years of practice, except for other indices of experience. Those that would ablate a LAP or RAP regardless of electrophysiology findings were of a similar level of experience as those that would not (15 ± 8 years vs 16 ± 9 years; $P = .92$).

Discussion

This study found that most operators do not believe that noninvasive markers of a 'safe' accessory pathway, such as intermittent pre-excitation, are sufficiently sensitive to replace invasive electrophysiology study for children with asymptomatic WPW. When operators went on to perform an electrophysiology study, the decision to ablate the accessory pathway is much more strongly influenced by accessory pathway location than by noninvasive or invasive risk stratification measurements. These findings are in sharp contrast with published guidelines and even with the same survey administered in 2003.

Compared with 15 years ago, operators are now choosing to ablate in the context of some lower-risk invasive risk stratification findings. The implementation of default ablation of asymptomatic WPW likely reflects the improving outcome of ablation procedures,[17] coupled with the increasing recognition that risk-stratification of accessory pathways is imperfect, regardless of the investigation technique.[14,18]

The responses in this study suggest that pediatric electrophysiologists generally interpret that the inherent risk of a life-threatening event (LTE) associated with asymptomatic WPW is greater than the risk of the ablation procedure itself, particularly for those accessory pathways distant from critical conduction structures.

Overall, it may be reasonable to estimate the risk of a potentially LTE (such as pre-excited AF) in an unselected cohort of children with asymptomatic WPW to be around 1%-2% per year,[13] and the risk of a clear LTE (such as ventricular fibrillation or SCD) at approximately 0.1%-0.5% per year.[4,13] However, the prospect of more accurate assessments of the natural history and risk of LTEs in children is unlikely given the growing evidence of potential harm in leaving all children with asymptomatic WPW untreated.

In addition to the risk of LTE, there is also the prospect of more benign, but none-the-less clinically significant, supraventricular tachycardia. Unsurprisingly, asymptomatic WPW is associated with a future risk of development of atrioventricular re-entry tachycardia,[13] but there is also the increased risk of development of AF later in life for those with accessory pathways. Finally, some individuals with pre-excitation demonstrate significant hemodynamic effects

Table II. Quoted rates of success, complications, and recurrences following ablation for asymptomatic WPW.

	2018			2003	
Category	RF ablation	Cryoablation	*P* value RF vs cryoablation	RF ablation	*P* value (RF 2018 vs 2003)
Major complication					
Median (IQR)	1% (0.5-1) Range 0.1%-5%	0.5% (0.5-1) Range 0.1-5%	**.04**	NA	NA
<1%	79%	88%	.07	63% (27)	**.04**
<2%	93%	99%	.06	77% (33)	.007
Acute success					
Median (IQR)	95% (94-97) Range 80%-100%	90% (85-95) Range 70%-99.9%	**<.001**	NA	NA
>90%	87%	46%	**<.001**	98%	**.04**
>95%	31%	8%	**<.001**	74%	**<.001**
Recurrence rate (%)					
Median (IQR)	5% (3%-7.5%) Range 1%-18%	10% (7-15%) Range 2-50%	**<.001**	NA	NA
<5%	69%	13%	**<.001**	56%	**.03**
<10%	95%	61%	**<.001**	86%	.06

Bold indicates $P < .05$.

of the dyssynchronous ventricular activation, particularly with septal accessory pathways[19]; this alone may be an indication for ablation[12] and was not directly assessed in this survey.

An invasive electrophysiology study is not without risk (and cost), and those surveyed were clearly divided as to how to implement the findings of noninvasive studies. The most recent 2015 American College of Cardiology / American Heart Association / Heart Rhythm Society adult supraventricular tachycardia guidelines are definitive regarding intermittent pre-excitation, giving a class I recommendation that intermittent pre-excitation on resting ECG, or sudden loss of delta on exercise stress test, are useful to identify patients at low risk of rapid conduction over the accessory pathway,[20] and the 2012 pediatric guidelines are in agreement (class IIa).[4]

However, there is increasing evidence that these noninvasive surrogates of accessory pathway properties are not sensitive for high-risk accessory pathways in the pediatric population. Wackel et al retrospectively reviewed the correlation between invasive and noninvasive predictors for 135 children with WPW: 24 were categorized as low-risk based upon non-invasive criteria alone, but 2 of these (8%) were subsequently found invasively to have high-risk accessory pathways (defined as SPERRI-Ap ≤250 ms).[6,21] The sensitivity of continuous pre-excitation during an exercise test for predicting SCD in a WPW cohort has been found to be only 80%, with a specificity of <30%.[7] Mah et al found no difference in the incidence of high-risk accessory pathways (defined as APERP or SPERRI ≤250 ms) in those with and without intermittent pre-excitation.[15] The majority of surveyed pediatric electrophysiologists do not believe that noninvasive risk stratification is sufficient evidence of accessory pathway safety despite the guidelines suggesting the utility of these tests. This may also partially explain why few respondents are influenced by the presence of reactive airways disease or the need for psychotropic medications,[22] given that most recommend invasive testing regardless of findings.

The use of electrophysiology study for accessory pathway risk stratification has typically focused on the APERP, SPERRI-Ap, and SPERRI-AF. Ideally, there would be cut-offs in these markers to dichotomize the low- from high-risk populations, but clearly this is not universally achieved: any cut-off will be a tradeoff of sensitivity vs specificity. In the context of low procedural risk, there is a willingness to over-treat in the aim of eliminating all high-risk accessory pathways. However, it is becoming increasingly clear for noninvasive and invasive markers that there are no cut-offs with 100% sensitivity: patient with accessory pathways with benign measured conduction properties may still experience LTEs. A recent large multicenter study affirmed this concern, as 37% of children with LTEs in that series did not have high-risk accessory pathway characteristics at electrophysiology study.[14]

When cut-offs were employed, there was a general consensus toward 250 ms for all three invasive markers, a remarkable longevity for a quantitative criterium first proposed by Klein et al nearly 40 years ago.[6] However, isoproterenol was used and interpreted in very different ways. Guidelines do not suggest any specific method of interpretation, but studies have shown that the proportion of subjects achieving nominated cut-off thresholds approximately double following isoproterenol.[4,18,23] The impact of isoproterenol for assessing risk and gauging what should be deemed a "high-risk" accessory pathway remains to be determined.

The 2012 asymptomatic WPW guidelines[4] recommend significantly less intervention than observed in real-world practice. The more recent, but more general, 2016 guidelines on pediatric ablations[12] do not address the noninvasive investigation of asymptomatic WPW, but do suggest ablation more strongly in those >15 kg with a high-risk accessory pathway (SPERRI-AF ≤250 ms or SPERRI-Ap ≤250 ms or multiple accessory pathways) and congenital heart disease, making it a class I recommendation. The inclusion of multiple accessory pathways as a sufficient marker of high-risk is new to the 2016 guidelines, but ablation of a high-risk accessory pathway in those without congenital heart disease remains a class IIa recommendation. In addition, the size for consideration of ablation has (generally) decreased from ≥5-8 years[4] to ≥15 kg.[12]

In practice, this survey reflects that the decision to ablate is not based upon hard and fast rules, and this is particularly the case when balancing risk and benefit for septal accessory pathways. Complications associated with ablation have trended toward a decrease over the last 15 years,[17] and this is reflected in the quoted risks in 2018 vs 2003 and in the proportion of respondents that will routinely ablate lower risk accessory pathways. It is interesting, though, that such a wide range of complication and success rates are quoted, with some clinicians quoting rates up to ×50 higher or lower than others.

A questionnaire is limited by the scope and precision of the questions and responses. Clearly, there are many more factors and nuances that inform the clinicians' decisions, and in particular this questionnaire did not assess the use of the pre-ablation ECG to inform likely pathway location and the subsequent impact of that information, or the impact of proven retrograde conduction without arrhythmia induction. Furthermore, there is inevitably a variation in the individual interpretation of questions, such as the definition of a "major" complication, and there is the potential for respondent selection bias which we are unable to quantify. For comparison with the 2003 study, the individual responses are no longer available and, therefore, statistical analysis was against published results only.

Despite the numerous studies that aim to identify the risk factors that delineate a high-risk accessory pathway, it is clear that there is not currently a single optimal approach to guide definitively the treatment for this patient population. With the incremental improvements observed in accessory pathway ablation outcome and complication rates, this study demonstrates that clinicians have become more reluctant to leave accessory pathways untreated. Many are performing default ablation of all accessory pathways, including, for some, those close to the critical conduction system. ■

We thank the PACES research group for their assistance in the circulation of this survey.

Submitted for publication Mar 14, 2019; last revision received May 20, 2019; accepted May 22, 2019.

Reprint requests: Henry Chubb, MBBS, PhD, Heart Center Research Core, Stanford University, 780 Welch Rd, Palo Alto, CA. E-mail: mhchubb@stanford.edu

References

1. Averill KH, Fosmoe RJ, Lamb LE. Electrocardiographic findings in 67 375 asymptomatic subjects. IV. Wolff-Parkinson-White syndrome. Am J Cardiol 1960;6:108-29.
2. Sears GA, Manning GW. The Wolff-Parkinson-White pattern in routine electrocardiography. Can Med Assoc J 1962;87:1213-7.
3. Munger TM, Packer DL, Hammill SC, Feldman B J, Bailey K R, Ballard DJ, et al. A population study of the natural history of Wolff-Parkinson-White Syndrome in Olmsted Count, Minnesota, 1953-1989. Circulation 1993;87:866-73.
4. Cohen MI, Triedman JK, Cannon BC, Davis AM, Drago F, Janousek J, 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. Heart Rhythm 2012;9:1006-24.
5. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. Circulation 2014;130:811-9.
6. Klein G, Bashore T, Sellers T, Pritchett E, Smith W, Gallagher J. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. N Engl J Med 1979;301:1080-5.
7. Sharma A, Yee R, Guiraudon G, Klein G. Sensitivity and specificity of invasive and noninvasive testing for risk of sudden death in Wolff-Parkinson-White syndrome. J Am Coll Cardiol 1987;10:373-81.
8. Campbell RM, Strieper MJ, Frias PA, Collins KK, Van Hare GF, Dubin AM. Survey of Current Practice of Pediatric Electrophysiologists for Asymptomatic Wolff-Parkinson-White Syndrome. Pediatrics 2003;111:e245.
9. Obeyesekere MN, Leong-Sit P, Massel D, Manlucu J, Modi S, Krahn AD, et al. Risk of arrhythmia and sudden death in patients with asymptomatic pre-excitation: a meta-analysis. Circulation 2012;125:2308-15.
10. Pietro D. Asymptomatic children with the Wolff-Parkinson-White pattern: what to do to stratify the risk of serious arrhythmias? J Cardiovasc Med 2009;10:6-7.
11. Brugada J, Blom N, Sarquella-Brugada G, Blomstrom-Lundqvist C, Deanfield J, Janousek J, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace 2013;15:1337-82.
12. Philip Saul J, Kanter RJ, Abrams D, Asirvatham S, Bar-Cohen Y, Blaufox AD, et al. PACES/HRS expert consensus statement on the use of catheter ablation in children and patients with congenital heart disease. Heart Rhythm 2016;13:e252-89.
13. Santinelli V, Radinovic A, Manguso F, Vicedomini G, Gulletta S, Paglino G, et al. The natural history of asymptomatic ventricular pre-excitation a long-term prospective follow-up study of 184 asymptomatic children. J Am Coll Cardiol 2009;53:275-80.
14. Etheridge SP, Escudero CA, Blaufox AD, Law IH, Dechert-Crooks BE, Stephenson EA, et al. Life-Threatening event risk in children with Wolff-Parkinson-White Syndrome: a multicenter international study. JACC Clin Electrophysiol 2018;4:433-44.
15. Mah DY, Sherwin ED, Alexander ME, Cecchin F, Abrams DJ, Walsh EP, et al. The electrophysiological characteristics of accessory pathways in pediatric patients with intermittent pre-excitation. Pacing Clin Electrophysiol 2013;36:1117-22.
16. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6:e34.
17. Dubin AM, Jorgensen NW, Radbill AE, Bradley DJ, Silva JN, Tsao S, et al. What have we learned in the last 20 years? A comparison of a modern era pediatric and congenital catheter ablation registry to previous pediatric ablation registries. Heart Rhythm 2018;16:57-63.
18. Kubus P, Vit P, Gebauer RA, Materna O, Janousek 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;7:218-23.
19. Tomaske M, Janousek J, Razek V, Gebauer RA, Tomek V, Hindricks G, et al. Adverse effects of Wolff-Parkinson-White syndrome with right septal or posteroseptal accessory pathways on cardiac function. Europace 2008;10:181-9.
20. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical

Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2016;13:e136-221.
21. 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;35:1451-7.
22. Batra AS, Alexander ME, Silka MJ. Attention-deficit/hyperactivity disorder, stimulant therapy, and the patient with congenital heart disease: evidence and reason. Pediatr Cardiol 2012;33:394-401.
23. Dubin AM, Collins KK, Chiesa N, Hanisch D, Van Hare GF. Use of electrophysiologic testing to assess risk in children with Wolff-Parkinson-White syndrome. Cardiol Young 2002;12:248-52.

50 Years Ago in *The Journal of Pediatrics*

Vaccination by the Intranasal Route

Plotkin SA. J Pediatr 1969;75:736-8.

Intranasal mucosal immunization, thought to be a relatively recent idea, was a well-known concept 50 years ago, as illustrated by this editorial in *The Journal.* Plotkin commented on various studies conducted with intranasal vaccines for influenza, poliomyelitis, measles, and rubella and highlighted the importance of locally produced antibodies for the protection of various viral infections. The administration of a locally replicating virus through the nasal route may be better than parenteral administration for providing immunity against infection by the microbe.

The nasal route has immense potential for vaccination owing to the organized immune systems of the nasal mucosa. The nasal epithelium encloses follicle-associated lymphoid tissues that are important in inducing mucosal immune response. The immune cells such as nearby B-cells can produce IgA at the mucosal sites where respiratory pathogens invade. Studies have shown that nasally administered vaccines induce serum IgG and mucosal IgA that are important for deliberating enhanced efficacy of vaccine.[1,2] Moreover, intranasal immunization has also been reported to induce cross-reactive antibodies that might be indicative of cross-protection. Data published from a study using the Russian intranasal vaccine showed better herd immunity for intranasal live attenuated influenza vaccine than inactivated vaccine.

Intranasal vaccines have come to be accepted as a standard of care. Licensed intranasal vaccines for humans include the trivalent live attenuated influenza vaccines (FluMist, Fluenz) and the Nasovac (live attenuated influenza nasal spray). In the European Union, an intranasal 4-valent live attenuated vaccine for the prevention of influenza in children and adolescents from 24 months up to 18 years of age was licensed in 2013. FluMist is well-tolerated and has exhibited good efficacy. A mild to moderate runny nose/nasal congestion is the most common adverse event after the administration of FluMist. A unilateral, mostly reversible facial palsy has been reported with the intranasal spray vaccine.

Nasal immunotherapy for the treatment of various cancers and Alzheimer disease is currently generating much interest. Focus is also shifting to the use of intranasal vaccines for the treatment of autoimmune diseases such as type 1 diabetes, atherosclerosis, multiple sclerosis, rheumatoid arthritis, lupus, and Crohn's disease.

Deepak Ugra, MD, FRCPCH
Krati Jain, MBBS
Department of Pediatrics
Lilawati Hospital and Research Centre
Mumbai, India

Piyush Gupta, MD, FAMS
University College of Medical Sciences
Delhi, India

References

1. Yusuf H, Kett V. Current prospects and future challenges for nasal vaccine delivery. Hum Vaccin Immunother 2017;13:34-45.
2. Zaman M, Chandrudu S, Toth I. Strategies for intranasal delivery of vaccines. Drug Deliv Transl Res 2013;3:100-9.

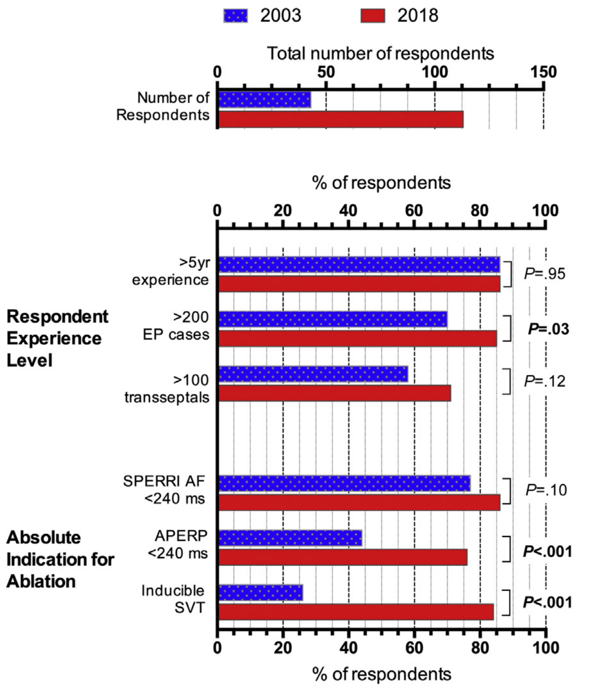

Figure 2. Comparison of responses to surveys performed in 2003 and 2018. "Absolute Indication for Ablation" is proportion of respondents who believed that the parameter cut-off listed was sufficient alone to indicate ablation in an asymptomatic child with WPW. *EP*, Electrophysiology; *SVT*, supraventricular tachycardia.

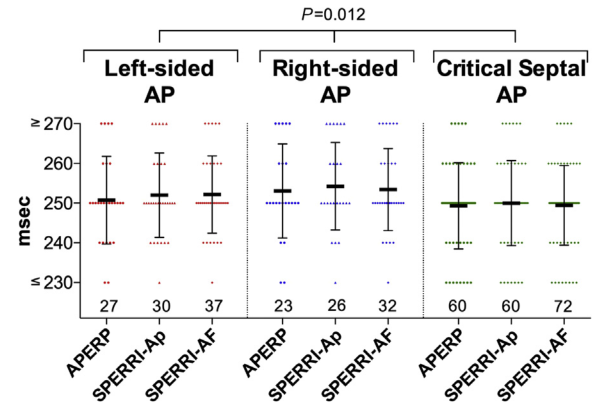

Figure 3. Cut-off values of APERP, SPERRI-Ap, and SPERRI-AF that respondents believed would, by itself, indicate ablation for a pathway at the indicated location. Each point represents the cut-off for a respondent, with total number of respondents who believed that there was a single cut-off for that parameter noted in number above the x-axis. Error bars denote mean ± SD, *P* value for ordinary 1-way ANOVA for cut-off values grouped by pathway location.