A CASE FOR EDUCATION

A proposed approach to the asymptomatic pediatric patient with Wolff-Parkinson-White pattern

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Introduction

Children with asymptomatic Wolff-Parkinson-White (WPW) pattern are increasingly being identified as part of routine screening or the investigation of unrelated illnesses. The risk of sudden cardiac death (SCD) in these subjects is significantly increased compared to children without WPW, but the absolute risk is poorly defined and remains very rare. This small risk of SCD must be balanced against the potential complications of a low-risk but invasive investigative and potentially curative procedure such as electrophysiological study (EPS) and catheter ablation. This article reviews the pediatric-specific data regarding these competing risks and should be of benefit to those making decisions regarding the management of pediatric asymptomatic WPW subjects.

Case report

A 12-year-old boy was referred for electrophysiology opinion following the finding of ventricular preexcitation on routine electrocardiogram (ECG). The ECG was performed prior to the initiation of pharmacologic therapy for attention-deficit/hyperactivity disorder, with no prior cardiac symptoms or significant medical history and no family history of note. Investigations included a resting ECG suggestive of a left-sided accessory pathway (AP), normal echocardiogram, persistent preexcitation on 24-hour ambulatory ECG, and no loss of preexcitation on exercise stress test. Following discussion with the patient and family, he underwent endovascular EPS (Figure 1). Highly variable measurements in the antegrade conduction properties of the AP warranted a review of the guidelines and literature in order to determine the optimal treatment strategy for this patient.

Discussion

Epidemiology and pathophysiology

WPW syndrome was originally described in 1930 in 11 patients[1] and was defined as a combination of "bundle-branch block," abnormally short PR interval, and paroxysms of tachycardia. The definition of WPW syndrome has evolved with the advent of a more detailed electrophysiological understanding of preexcitation (it is not a bundle branch block); patients that are asymptomatic may be termed "WPW pattern."

Estimations of the prevalence of asymptomatic WPW pattern are largely based upon prospective adult-only ECG screening studies, most of which date back to screening of military personnel in the 1960s and suggest a prevalence of around 0.1%–0.3%.[2] In children, it might be anticipated that the prevalence is higher. WPW pattern is secondary to defects in the development of the electrically inert annular fibrosis separating atrial and ventricular tissues, and the incidence of these defects is higher in early infancy.[3] However, resolution of manifest preexcitation occurs in ~35% of children aged <3 months (and a further 6% aged 3–6 months),[4] and this is reflected in a more recent study of 43,576 children, which suggested a similar prevalence in children to adults, at 0.08%.[5]

Risks associated with asymptomatic WPW

SCD and life-threatening events

The overriding concern for patients with asymptomatic WPW is the risk of SCD, but the risk is particularly challenging to estimate in children, as the denominator (the number of children with asymptomatic WPW) cannot be clearly defined in the absence of extensive unselective pediatric screening programs. Population-based risk assessments could also underestimate the numerator (the number of children with WPW who have SCD), as postmortem examinations cannot reliably identify APs and a small percentage of pediatric sudden death victims could also have had asymptomatic WPW. The largest retrospective multicenter studies provide a vital insight into risk factors for SCD, but they are less useful for estimating the absolute risk.[6,7] As a best

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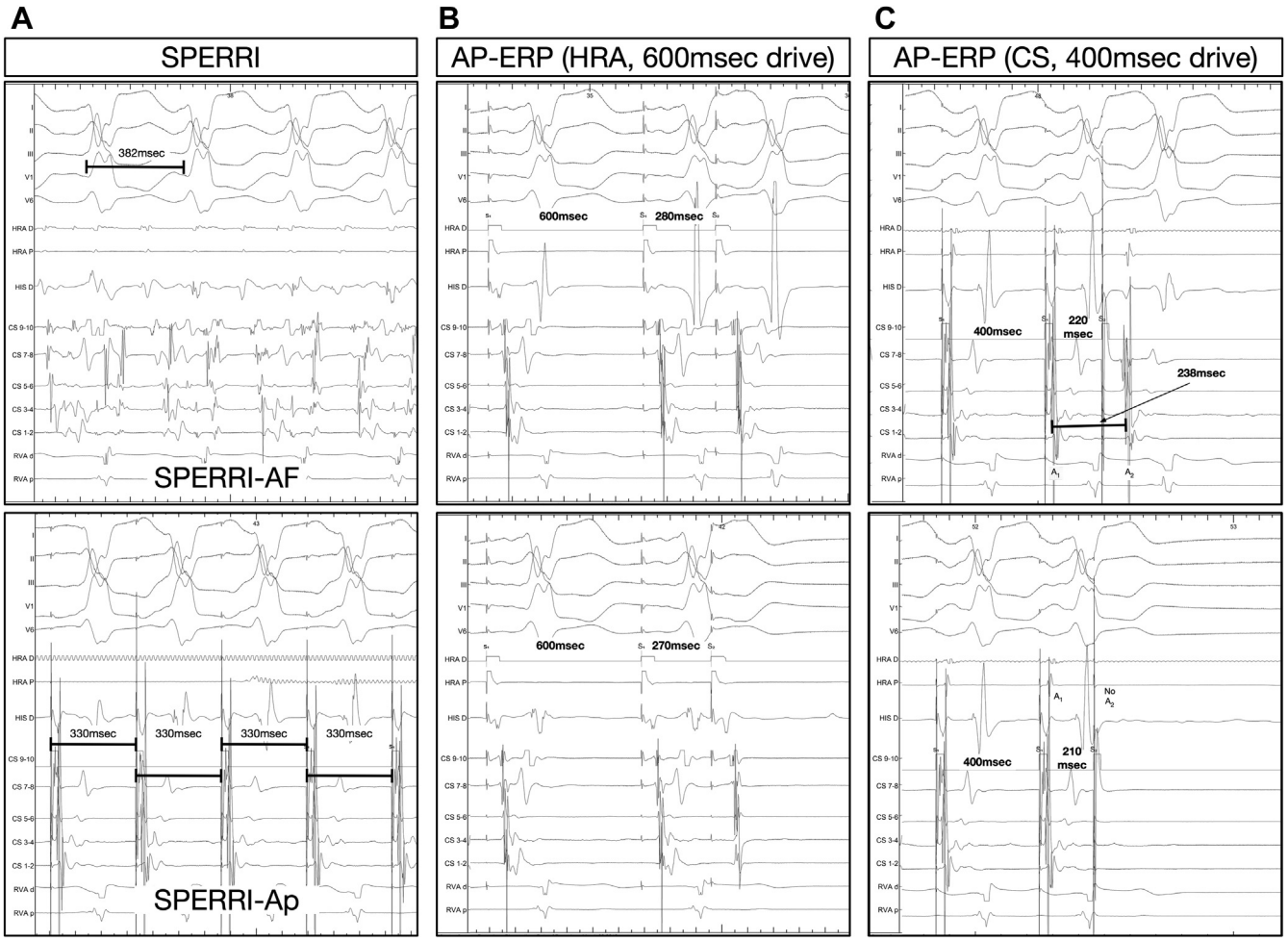

Figure 1 Electrophysiological study in a patient with asymptomatic Wolff-Parkinson-White (left posterior accessory pathway [AP]) demonstrating variation in anterograde conduction properties of the pathway under differing conditions. **A:** (Top) Shortest preexcited R-R interval in atrial fibrillation (SPERRI-AF) 382 ms; (Bottom) shortest preexcited R-R interval on atrial pacing (SPERRI-Ap) 330 ms. **B:** AP effective refractory period (AP-ERP): on pacing from high right atrium (HRA), 600 ms drive train, AP-ERP 270 ms. **C:** AP-ERP on pacing from proximal coronary sinus (CS), 400 ms drive train, AP-ERP <238 ms; note that AP-ERP should be measured based upon local A_1-A_2 interval (upper right, measured at site of earliest ventricular activation at CS 3–4), but atrial effective refractory period was reached prior to AP-ERP (bottom right). There are no established guidelines as to how AP-ERP values should be interpreted.

available estimate, meta-analysis suggests an overall risk of SCD of around 1 per 1000 patient-years in adults and double that in children.[8] However, these risk estimates must then be personalized to each patient based upon both noninvasive and invasive risk stratification measures.

Life-threatening events (LTEs) are typically 10–20 times more common than SCD[7] and are generally defined in this population as aborted SCD or a clinical episode of preexcited atrial fibrillation (AF) with shortest preexcited R-R interval (SPERRI-AF) <250 ms with or without hemodynamic compromise.[6] However, balancing the absolute risk of these sentinel events against the risks and benefits of intervention is more controversial and may push practitioners towards ablation in an effort to avoid these lower-risk (nonfatal) events.

Other risks and complications

Between 15% and 25% of asymptomatic patients will go on to develop reentrant supraventricular tachycardias.[4,9] The presence of an AP is also associated with the development of AF in later life (though the elimination of the AP may not reduce the long-term risk of AF). Preexcitation of the ventricle may also, on rare occasions, lead to the development of dilated cardiomyopathy secondary to dyssynchronous ventricular contraction. Case reports are limited, but those with right-sided septal or paraseptal APs are generally felt to be at higher risk.[10] Finally, there are significant potential restrictions for some patients with asymptomatic WPW. For example, for participation in competitive sports in Europe it is recommended that all asymptomatic WPW patients over 12 years of age undergo EPS, and ablation of "high-risk" APs (defined as SPERRI-AF <240 ms, "easily" inducible AF, or multiple APs) should be performed[11]; similar advice applies to pilots.

Risk stratification of asymptomatic WPW

Patient history

The assignation of a patient as "asymptomatic" is frequently not clear-cut, where nonspecific symptoms such as

presyncope or poorly characterized palpitations require clinical correlation to determine whether they are caused by paroxysmal tachyarrhythmias. In younger children this may be particularly difficult to define. The utility of the history for risk stratification is also ill-defined and, with the obvious exception of a history that could be consistent with an LTE, other salient findings are more poorly correlated with risk. A recent large multicenter study has suggested that those who have LTEs are less likely to have prior palpitations than age-matched WPW controls (68% vs 47%), and those with "high-risk" pathways are no more likely to become symptomatic.[6] The absence of palpitations is therefore not necessarily reassuring and may even reflect a slightly higher baseline risk.[7] Male sex has also been associated with increased risk,[7] as has the presence of congenital heart disease.[6]

Patient age is important, and there are data suggesting that pediatric asymptomatic WPW subjects are at higher risk than adults.[7] Within childhood, though, this has been evaluated in less detail, and while some older guidelines consider children <12 years of age to be at negligible risk,[11] there is a suggestion that there may actually be a decrease in risk over childhood, with a higher risk observed in younger children.[7,9]

ECG and pathway location

The preexcited 12-lead ECG provides information as to the likely site of the AP, and several algorithms have been developed and validated for the adult population. In children, the algorithms remain useful, but studies suggest their accuracy may be lower.[12] The identification of a septal AP location is particularly important in patient counseling, as it is associated with a higher risk of ablation procedure–related complications; the accuracy of algorithms for predicting a septal location range from 40% to 78% and are improved with higher degrees of preexcitation.[12] There is no clear evidence that any particular conventional AP location represents a higher risk of SCD.[7] However, there are ECG features that have been identified to be suggestive of a fasciculoventricular pathway, which is associated with no SCD or tachyarrhythmia risk and therefore may be left untreated.[13] The specificity of a delta wave amplitude of <2 mm was found to be 88%–94% specific for a fasciculoventricular pathway, but wider evaluation is required in order to assess the clinical utility of these findings.

Pseudo-preexcitation should also be considered in some patient subgroups, such as those with congenital heart disease or hypertrophic cardiomyopathy.[14] This ECG appearance presents a particular challenge, as these are patient subgroups that have been identified to be at higher risk of SCD, but at the same time an invasive procedure itself also entails a higher risk of complications.[15] It has been suggested that in some cases adenosine may provide important information to help guide further management.[14]

Intermittent preexcitation

Intermittent preexcitation may be observed on resting 12-lead ECG, on ambulatory ECG monitoring, or with heart rate acceleration on exercise stress test (Figure 2). Historically, it has generally been interpreted that clear evidence of intermittent preexcitation is indicative of a "low-risk" AP, and guidelines tend to reflect this.[16,17] For exercise stress test, it is important to observe abrupt rather than gradual loss of manifest preexcitation, with gradual loss potentially reflecting simply swifter AV nodal conduction with increased sympathetic drive, and hence masking of the preexcitation (Figure 2).

More recent evidence, however, has begun to demonstrate that intermittent preexcitation is not 100% specific for identification of a "low-risk" AP. In a 2016 study of 295 children at a single institution, "high-risk" EPS characteristics were identified in 31% of patients with abrupt loss of preexcitation on exercise, 5% with intermittent preexcitation, and 12% with persistent preexcitation (54%, 11%, and 16%, respectively, when testing with the addition of isoproterenol).[18] It is important to note that there are concerns regarding the use of EPS-derived surrogates as the gold standard to identify "high-risk" pathways, but these findings still bring into question how intermittent preexcitation should be interpreted.

Invasive risk stratification

In 1979, Klein and colleagues[19] published a detailed electrophysiological assessment of 25 patients (3 children) with WPW and documented VF and compared them to 73 patients without VF. They noted that the SPERRI-AF was the most useful discriminator, with a cutoff of <250 ms having 100% sensitivity for the VF group, albeit with a specificity of 35%. Since then, multiple groups have attempted to further refine the implementation of EPS findings, which in addition to SPERRI-AF generally also include SPERRI on atrial pacing(SPERRI-Ap) and the effective refractory period of the AP.[9,20] Guidelines generally continue to use SPERRI-AF <250 ms as the optimal discriminator[16] and SPERRI-Ap <250 ms as a surrogate of this in the absence of AF,[21] but it should be noted that the values may differ widely from each other in the same patient at a single study (Figure 1). However, a large multicenter study of children undergoing prospective EPS after LTEs identified that only 65% had SPERRI-AF <250 ms.[6] It appears increasingly likely that there is no invasive EPS measurement with 100% sensitivity in children for "high risk," but it must be acknowledged that all the data suggest that those with longer AP refractory periods are generally at lower risk.

The physiological circumstances at testing are also important to consider. Isoproterenol is frequently used at EPS, but the question as to how to interpret the EPS measurements on isoproterenol remains unresolved in both pediatric and adult populations.[20] Furthermore, the electrophysiological cutoff values were generally derived from EPS performed with conscious sedation, and there is a significant and variable impact of anesthetic agents upon AP conduction properties. The inducibility of arrhythmias may also assist in risk stratification. It is clear that those with antidromic atrioventricular reentrant tachycardia (AVRT) or AF provoked by AVRT are

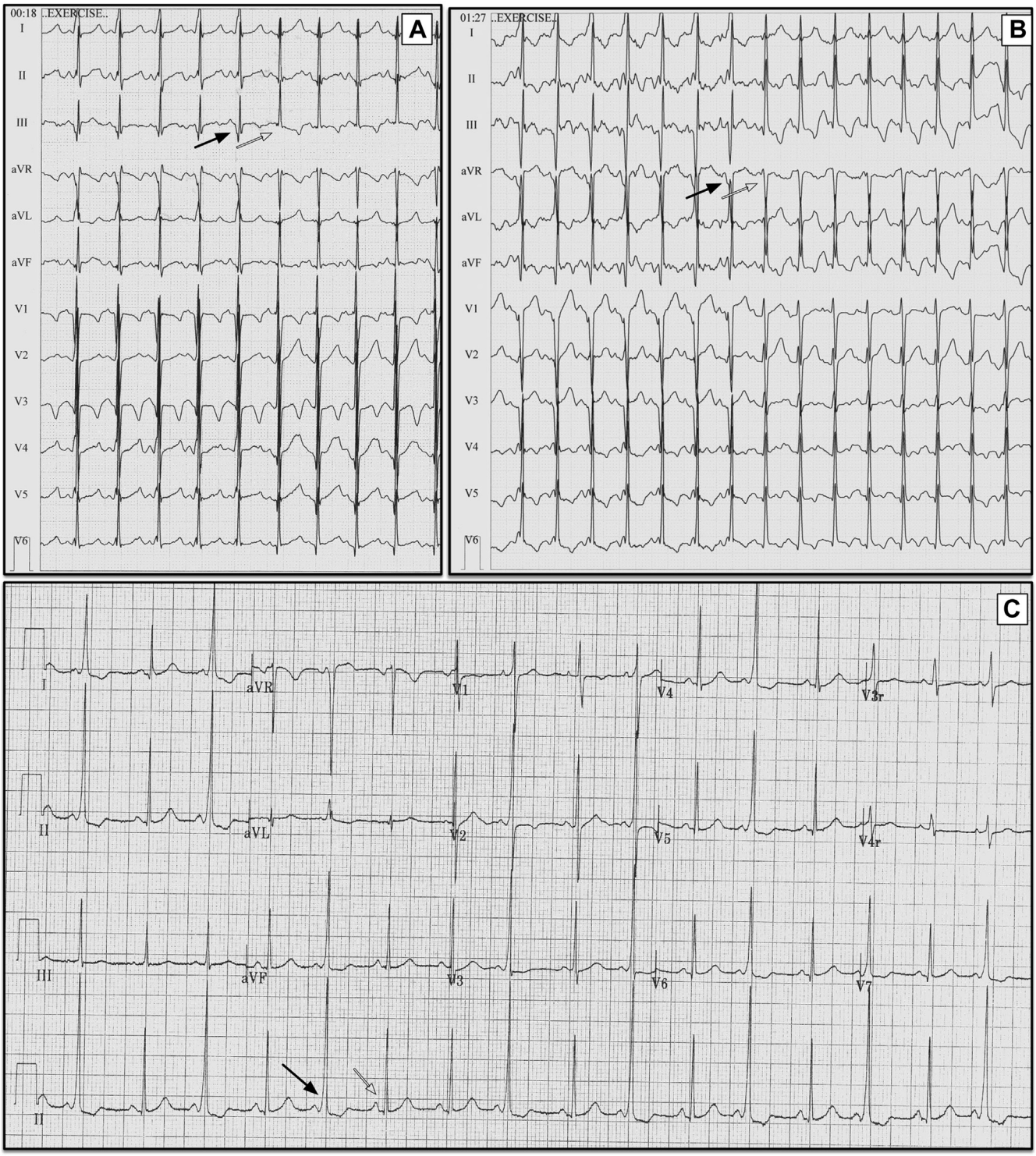

Figure 2 Examples of conventional noninvasive markers of a lower-risk accessory pathway (AP). **A, B:** Abrupt loss of AP conduction on exercise stress test between *black* and *white arrows*. **C:** Intermittent preexcitation on 12-lead electrocardiogram.

at higher risk of LTE, but these findings are rare.[6,7] Much more commonly, orthodromic AVRT may be induced and these subjects appear to be at a slightly *lower* risk than those in whom AVRT is noninducible, but the evidence is limited.[6] Finally, the presence of multiple APs is generally only identifiable on invasive assessment, and the guidelines categorize this as a further risk factor for LTEs,[16,21] with most, but not all, studies demonstrating increased risk with multiple APs.[6,7]

There are also a number of unresolved questions as to the optimal timing and method of EPS for children with asymptomatic WPW. The more comprehensive 2012 asymptomatic WPW guidelines suggest an age of 8 years,[16] while the more recent 2016 catheter ablation guidelines suggest >15 kg.[21]

The use of transesophageal studies has waned, as many operators feel that a transvenous EPS offers an opportunity to treat the pathway at the same procedure if indicated.[22]

Ablation of accessory pathways

There is a single randomized controlled trial of ablation in asymptomatic WPW. This assessed the impact of prophylactic AP ablation in subjects over the age of 13 years who were classified as "high risk," defined as being under the age of 35 years and having inducible arrhythmia.[23] Those that were randomized to ablation had significantly fewer arrhythmia events and there were no significant complications. However, this study was small, with only 35 subjects in each group, and the risks of ablation and LTE/SCD are relatively rare. More recent registry data (MAP-IT) has demonstrated a 98% acute success rate for radiofrequency ablation of WPW (95% at follow-up), with complications in approximately 1%.[15] Additionally, ablation procedures are now performed with minimal fluoroscopy exposure (generally <10 min per case, and frequently <2 min).[15]

These success rates should be balanced against complications, which overall may be as high as 2.5% when including vascular injury such as hematoma at the access site, peripheral nerve injury, permanent injury to the conduction system, and new valve regurgitation.[15] However, the critical cases for the evaluation of risk are those septal pathways close to the conduction system, specifically anteroseptal and midseptal APs. Here, the acute failure rate is higher, as operators take a more cautious approach. For many centers there is a role for cryoablation for septal APs, while alternative approaches such as via the noncoronary cusp should also be considered. For all APs, the risk of injury to the coronary arteries is a concern, particularly in smaller children, and the underlying incidence is unknown, as coronary angiography is not performed routinely postablation. In select cases coronary angiography may be useful to reduce the risk when ablating posteroseptal pathways near or within the coronary venous system.[24]

Balancing the risks and benefits

The established guidelines for the management of asymptomatic WPW in children, published in 2012[16] and then updated in 2016 regarding the ablation aspects only,[21] are broadly similar. However, it is clear that pediatric electrophysiologists adopt a wide range of approaches to the management of these patients (Figure 3).[22] Much of the variation is due to the need to balance an ill-defined and very rare but catastrophic outcome (SCD) against a moderately rare, moderately severe, and location-dependent outcome (catheter ablation complication). The delicate equipoise in weighing up these contingency estimations has been demonstrated in a decision tree analysis published in 2013, suggesting it is necessary to treat 112 (adult) asymptomatic WPW patients in order to save 1 life over 10 years. The analysis is highly sensitive to SCD rates and ablation success and complications: the differences observed between the pediatric and adult populations with asymptomatic WPW will alter the contingencies significantly. However, they are currently insufficiently quantified to establish whether the risk ratio should be revised up or down for children.

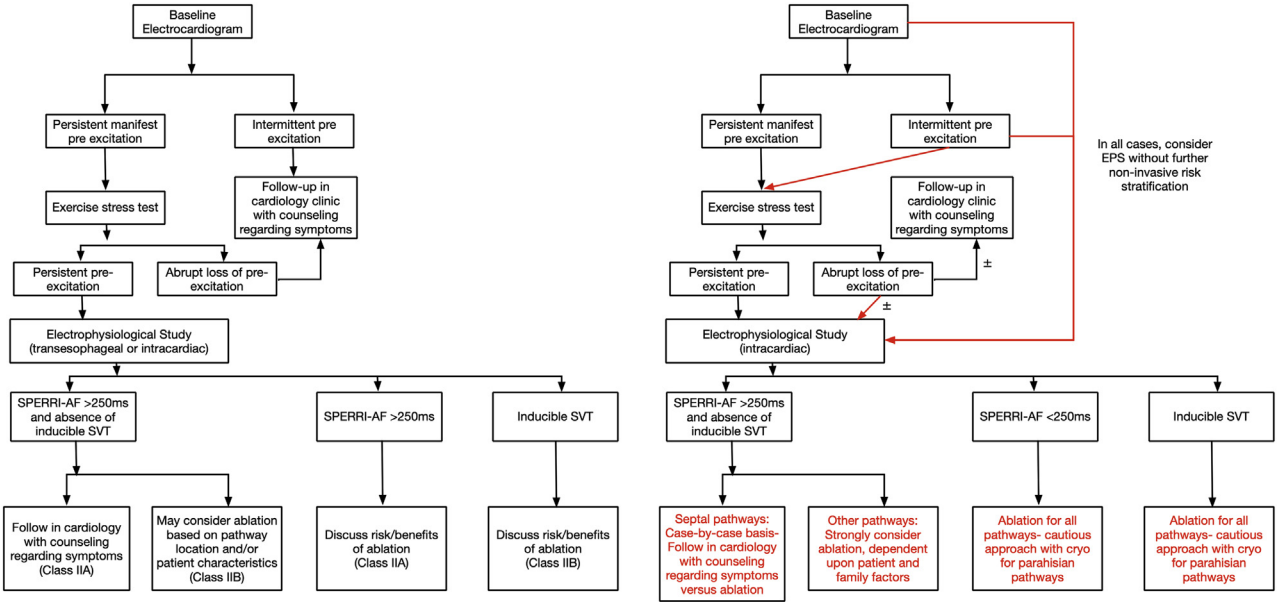

Figure 3 A comparison of the (left) 2012 asymptomatic Wolff-Parkinson-White (WPW) guidelines[16] and (right) our current general approach to asymptomatic WPW children. Based upon more recent publications, we have taken a more proactive approach with a greater likelihood of both performing an invasive electrophysiological (EPS) study and then attempting ablation. For example, based upon recent studies, we would still discuss with the patient and/or family the relative merits of EPS for those with abrupt loss of preexcitation on exercise test. Additionally, we would not use a strict dichotomous shortest preexcited R-R interval in atrial fibrillation (SPERRI-AF) cutoff of 250 ms and are increasingly more likely to attempt an ablation of pathways not meeting strict "high-risk" criteria, but still exhibiting robust antegrade conduction.

Conclusion

For those children with accessory pathways with robust antegrade conduction properties, generally defined as SPERRI-AF <250 ms, ablation is usually deemed necessary based upon our current understanding of the risk of future SCD. However, in every case the estimated risk of leaving an asymptomatic AP untreated must be balanced against the known and unknown risks of ablation. Asymptomatic WPW in children requires careful and informed management on a case-by-case basis.

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