INTRODUCTION

Ventricular pre-excitation is an electrocardiographic finding characterised by a delta wave and short PR interval. It is estimated that 1 in 1000 people will exhibit this pattern on the ECG; however, the true prevalence is likely under-represented because at least half of known patients with pre-excitation do not develop symptoms.¹

This ECG pattern indicates the presence of an accessory atrioventricular pathway (AP), an alternate electrical connection between atria and ventricles bypassing the normal His-Purkinje system. APs can conduct in antegrade direction, retrograde direction or both. Approximately 60%–75% of these pathways are considered ‘manifest’, meaning they are capable of antegrade conduction, and can inscribe the classic pre-excitation pattern on the ECG, and the rest are ‘concealed’, meaning they are only capable of retrograde conduction, cannot produce pre-excitation, but can still participate in atrioventricular (AV) re-entry tachycardias.

The initial description of the syndrome by Wolff, Parkinson and White included 11 patients with pre-excitation and the associated tachycardia, which was collectively termed as Wolff-Parkinson-White (WPW) syndrome. However, many patients with pre-excitation never develop tachyarrhythmias and remain asymptomatic their entire lives. In one cohort study, one-third of asymptomatic individuals with pre-excitation younger than 40 eventually developed symptoms, compared with zero patients over 40 years old at diagnosis.¹ The most common arrhythmia (80%) is atrioventricular re-entrant tachycardia (AVRT), which directly uses the AP in the tachycardia circuit. However, atrial fibrillation (AF) is strikingly common (20%–30%) in patients with WPW, which suggests the AP itself may be involved in genesis of AF,² ³ perhaps as a result of haemodynamic and metabolic consequences of AVRT.

AF is particularly worrisome because most manifest APs lack the decremental properties of the AV node, a ‘safety regulator’ that limits conduction to the ventricles. Rapid antegrade conduction to the ventricles over the AP during AF can increase the likelihood of ventricular fibrillation (VF) and sudden cardiac death (SCD), which is the most feared complication of WPW syndrome. Like most cardiac tissues, each AP has a unique effective refractory period (ERP)—longest interval of input that fails to conduct—which theoretically limits the maximum rate of conduction through the AP. An electrophysiological study (EPS) can allow direct measurement of ERP but also determine the shortest pre-excited R-R interval (SPRRI) during AF. Both metrics directly measure the ability of the AP to conduct rapidly; higher-risk pathways exhibit short ERPs and SPRRI. VF is found to be very unlikely if SPRRI of the AP is >250 ms.⁴ Invasive EP evaluation has been the gold standard for interrogating AP conduction properties and risk stratification. However, clinical and non-invasive evaluation can provide important clues; they are discussed here and are summarised in table 1.

There are some rare ‘atypical’ APs that insert into the cardiac conduction system; these include atriofascicular (Mahaim fibre), nodoventricular, nodofascicular and fasciculoventricular pathways.² These rare pathways lack large-scale data but are generally considered not to be dangerous. The atriofascicular AP is a small fibre that connects the lateral right atrium to the right bundle branch, typically conducts with AV nodal-like decremental property, to produce a wide complex tachycardia with a left bundle branch block like pattern that is often mistaken for ventricular tachycardia. The decremental property prevents rapid conduction during AF. The nodoventricular and fasciculoventricular APs are downstream of the AV node, which protects them from rapid antegrade conduction during AF.

The overall incidence of SCD in asymptomatic individuals with pre-excitation is quite low. A meta-analysis of 20 studies, including 1869 asymptomatic adults with pre-excitation, estimated the risk of 0.13%/year⁶ and may be higher in children in the first two decades of life.⁷ Clinicians should keep in mind that this risk is small and is only slightly higher than the background risk of premature death in an average US adult, just below 0.1%/year.⁸ However, SCD in a patient with pre-excitation is a significant event that cannot be ignored. Since ablation of most APs is curative and carries a low risk of complications, a question remains whether APs should be...
Table 1  Clinical and electrophysiological features associated with increased risk of sudden cardiac death

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<thead>
<tr>
<th>Factors associated with a high-risk accessory pathway</th>
<th>Factors associated with a low-risk accessory pathway</th>
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<tr>
<td>Inducible AVRT during EPS.</td>
<td>Abrupt and complete normalisation of PR interval</td>
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<td>Multiple accessory pathways.</td>
<td>and loss of delta on rhythm monitoring.*</td>
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<td>Shortest pre-excited RR interval during AF ≤250 ms.</td>
<td>Asymptomatic pre-excitation.</td>
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<td>Short antegrade refractory period of AP ≤250 ms.</td>
<td>Low risk on evaluation during EP study (see left</td>
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<td>column).</td>
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*We do not routinely perform exercise or catecholamine infusion studies on patients with pre-excitation. AF, atrial fibrillation; AP, atrioventricular pathway; AVRT, atrioventricular re-entrant tachycardia; EPS, electrophysiological study.

Ablated in asymptomatic individuals to eliminate the small risk of SCD.

**APPROACH**

Clinical assessment of a patient with pre-excitation involves evaluating the AP conduction properties and determining the need for ablation. Patients with clinical features of a more dangerous pathway should have a lower threshold for EP study and ablation, whereas invasive management is optional for those with low-risk features.

Practice guidelines agree that patients with inducible or spontaneous documented arrhythmias such as supraventricular tachycardia (SVT) or pre-excited AF should undergo EPS±ablation. Outside of these features, asymptomatic patients with pre-excitation leave a management conundrum; these are individuals with a very small yet measurable risk of life-threatening arrhythmias and SCD.

European Society of Cardiology 2019 guideline recommends invasive evaluation (EPS±ablation) for patients with a high-risk occupation and competitive athletes (class I). All others may still undergo EPS±ablation (class IIa), but a non-invasive evaluation is a reasonable alternative (class IIb) at the discretion of the clinician. The 2015 American Heart Association (AHA) guideline similarly recommends an EPS±ablation for all asymptomatic patients with pre-excitation (class IIa), including those with high-risk occupation (class IIa), but also presents clinicians with an alternative option for observation (class IIa).

In patients with asymptomatic pre-excitation, both guideline committees leave the decision for invasive testing/ablation with the clinician and suggest invasive management for those with a high-risk occupation. If non-invasive assessment is selected, a Holter monitor and an exercise stress test are reasonable to provide additional information, but clinicians should be mindful of potential shortcomings of these tests.

**NON-INVASIVE EVALUATION**

Ambulatory monitoring and exercise/pharmacological stress tests are readily available non-invasive risk stratification tools. Abrupt and complete loss of pre-excitation (intermittent pre-excitation) in sinus rhythm on a Holter monitor, exercise stress test or pharmacological stress test suggests the AP has a long ERP and renders the AP extremely unlikely to conduct quickly during AF (SPRRI in AF of <250 ms) (figure 1A,B, are examples).

Physiologically, intermittent pre-excitation represents periodic complete block in AP conduction, suggesting that the antegrade AP conduction is too fragile to support rapid conduction during AF. To diagnose intermittent pre-excitation, care must be taken to ensure the delta wave is abruptly and completely lost (figure 1A,B). Gradual loss of the delta wave with each successive beat does not qualify as intermittent pre-excitation (example in figure 2). This is because it may reflect progressively less contribution of ventricular activation through the accessory pathway and a larger contribution of conduction through the AV node to ventricular activation. This does not reflect the ability AP to conduct during AF and should not be considered as intermittent pre-excitation. A small retrospective study suggested that gradual loss of pre-excitation is prognostically equivalent to no loss of pre-excitation. Catecholamine excess during exercise recruits the AV node to conduct faster, which often results in ventricular activation via the AV node, leading to less apparent pre-excitation. During exercise and catecholamine testing, the delta wave becomes less obvious and can be obscured by improved AV nodal conduction, making it unclear whether it is truly abruptly lost. For this reason, if exercise and catecholamine testing are to be used, the ECG tracing must be examined very carefully with the aforementioned caveat in mind.

Several studies have questioned the predictive value of intermittent pre-excitation, but in these investigations, isoproterenol and exercise stress testing were used, which may have caused false-positive results. In addition, there remains uncertainty as to whether true intermittent pre-excitation was documented in those studies. Many of the APs cited in these studies are left-sided, which present with a very small amount of pre-excitation due to the activation front reaching the AV node well before the AP; diagnosing intermittent pre-excitation where pre-excitation is subtle often leads to false-positive results. Overall, to date, no deaths have been reported in patients with true intermittent pre-excitation, and we still consider it to be a robust predictor of a low-risk pathway. The AHA guideline places a class I recommendation on using intermittent loss of pre-excitation to classify a low-risk AP. Certainly, seeing abrupt loss of pre-excitation should be reassuring to the patient and clinician that a conservative (non-invasive) approach is safe. Figure 3 illustrates our approach.

**PHARMACOLOGICAL THERAPY**

Medical therapy is an option for patients with symptomatic arrhythmia involving APs; it can acutely terminate tachycardias involving the AP and can play a role in long-term suppression. Class IA, class IC and class III antiarrhythmic agents are known to lengthen the antegrade and retrograde ERP of
APs, which would reduce the incidence AF as well as the rate of AP conduction during AF, thereby reducing the risk of VF.13–15 Propafenone has been well studied in this space. However, drug effects on the AP ERP appear to at least partially reverse with catecholamines and exercise, and their protective activity may not be sufficient during certain activity levels and autonomic tone.16 17 Overall, antiarhythmic medications are rarely selected in preference to a curative procedure due to lack of data in preventing sudden death, variable effects on AP ERP, inconvenience, cost and significant side-effect profile.

There are some notable medication contraindications in patients with pre-excitation.18 Beta blockers are ineffective in controlling the ventricular rate in pre-excitation, while digoxin and non-dihydropyridine calcium channel blockers have been shown to shorten AP ERP and to accelerate the ventricular rate during pre-excitation AF.18–20 Amiodarone generally increases AP ERP; however, some case reports have suggested that it increases rate in pre-excitation AF, which leads to its contraindication in patients with pre-excitation according to clinical practice guidelines.18 21 These medications are not contraindicated in patients with concealed APs (no antegrade conduction).

**THERAPEUTIC ABLATION: SHOULD ALL PATHWAYS BE ABLATED?**

There is no question that certain APs should undergo ablation. These include APs capable of rapid conduction characterised by a short ERP

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**Figure 1** (A) Holter monitor tracing demonstrating intermittent pre-excitation. The first two QRS complexes are not pre-excited, and pre-excitation abruptly resumes beginning with the third QRS complex. Note that gradual change in the degree of pre-excitation does not. (B) Another heart rhythm tracing showing abrupt loss of pre-excitation. The top and bottom channels are simultaneous. The first four beats are pre-excited, and the next four beats are not pre-excited at all. This patient’s atrioventricular pathway likely has a long effective refractory period and would not be expected to conduct rapidly during atrial fibrillation.

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**Figure 2** Holter monitor tracing demonstrating gradual loss of pre-excitation. The top tracing shows a pre-excited QRS that gradually becomes less pre-excited. Pre-excitation is seemingly lost at the end of the tracing but may be too subtle to see. This does not represent intermittent loss of pre-excitation because it is not clear if the AP abruptly stopped conducting or if the degree of pre-excitation is too small to see on the surface ECG. This is commonly found on exercise stress tests where the AV nodal conduction velocity increases due to catecholaminergic effects, and there is a comparatively greater degree of ventricular activation via the AV node (less fusion with AP); pre-excitation becomes very subtle and often impossible to distinguish from true abrupt loss of pre-excitation. Unlike intermittent loss of pre-excitation, gradual loss of pre-excitation is not diagnostically helpful and has outcomes similar to those of patients with fixed pre-excitation. AP, atrioventricular pathway; AV, atrioventricular.

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**Figure 3** Proposed care pathway for patients with asymptomatic pre-excitation. EP, electrophysiological.

1. **Patient with pre-excitation on ECG**
   - Symptoms / Documented Arrhythmia
   - Asymptomatic Pre-Excitation
   - Intermittent Pre-Excitation
   - No Intermittent Pre-Excitation

2. **EP Study +/- Ablation**
   - Observation & Follow-Up

3. **Careful discussion with patient about small risk of procedure vs. small lifetime risk of arrhythmia**

(≤250 ms) on EP study or short SPRRI (≤ 250 ms) during AF (spontaneous or induced during EP study). In patients with pre-excitation, AVRT seems to precede AF; hence, lack of inducible AVRT on EP study has been considered a good prognostic sign. Finding of multiple APs also increases the risk of life-threatening arrhythmic events by an odd ratio (OR) of 3.1, presumably due to increased ventricular dysynchrony generated by numerous depolarisation wavefronts. Multiple APs are commonly found in patients with Ebstein’s anomaly. Patients without the aforementioned risk factors have been historically considered low risk, leaving pathway ablation optional.

When risk stratifying in the EP laboratory, it is important to mimic conditions during which the aforementioned risk factors were derived. Patients should not be sedated or minimally sedated as general anaesthesia undoubtedly influences AP conduction properties and can lead to false negatives. However, it is unavoidable in some patients especially in the paediatric population. There are currently insufficient data to risk stratify with isoproterenol because the risk cutoffs (ERP and SPRRI) were validated on baseline measurements without pharmacological agents. Induction of AF during the EP study offers the most direct measure of AP conduction during AF (SPRRI); however, it may require deeper sedation and cardioversion. Practically, induction of AF is helpful if it changes management, such as in cases where other risk factors are borderline/low risk and is unnecessary if the decision to ablate the AP is already made.

Catheter ablation has a very high success rate in eliminating the AP—upwards of 95%. This raises the question: if we can remove the very small risk of sudden death with a potentially curative procedure, why wouldn’t we ablate all APs? Unfortunately, ablation does not come without risk. The most common risk is collateral damage to the AV node leading to AV block, which has been reported in 0.17%–2.7% of ablations. This would require pacemaker implantation, which comes with a lifetime of pacemaker procedures. These implications include generator replacements and complications related to ageing leads, with the highest lifetime procedural burden in paediatric patients. The risk of AV block is higher in patients with paraseptal APs and highest in mid-septal APs due to proximity to the AV node and the bundle of His. Cryoablation can slightly reduce this risk by allowing prediction of acute lesion effect with ice mapping prior to delivering an irreversible lesion—at a cost of a potentially slightly higher risk of AP recovery. Other serious complications include risk of perforation, tamponade and stroke most often resulting from trans-septal access and ablation within the left atrium. Coronary artery damage has also been reported, especially in APs that require ablation in the coronary sinus or middle cardiac vein.

Balancing a very small 0.13% risk of clinically important arrhythmia with a 0.17%–2.7% of serious procedural risk is not an easy decision and is one that should be thoughtfully considered by the patient based on their own values and preferences. In children, the stakes are even higher since they may have a higher lifetime risk of arrhythmias but may also suffer a lifetime of consequences in the case of inadvertent damage to the AV node during ablation. Our approach is to classify APs into four categories based on the risk of ablation and lifetime risk of life-threatening arrhythmias if the AP is left untreated (table 2). Asymptomatic APs that are far from the AV node and those that are deemed higher risk on EP study should generally have a lower threshold to ablate—as long as the patient accepts a small procedural risk to prevent a rare (<1 in 1000 patient years) arrhythmic event. The threshold to ablate should be much higher for right-sided APs and those that are close to the AV node, since they tend to have a higher procedural risk, which in most cases is higher than the small lifetime risk of clinically significant arrhythmia.

**CONCLUSIONS AND SUMMARY**

Patients with pre-excitation and documented arrhythmia should undergo an EPS and ablation. However, patients with asymptomatic pre-excitation

<table>
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<th>Table 2 Classification of asymptomatic accessory pathways based on risk of procedure and risk of life-threatening arrhythmias</th>
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<td><strong>High-risk</strong></td>
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<td><strong>High-risk ablation</strong></td>
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<td><strong>Low-risk ablation</strong></td>
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**AP**, atrioventricular pathway.
Key messages

⇒ In patients with asymptomatic pre-excitation the lifetime risk of sudden death is low.
⇒ Electrophysiological ablation procedure is optional in patients with asymptomatic pre-excitation and should be based on a careful discussion with the patient, which includes potential risks of ablation versus a small lifetime risk of arrhythmia.
⇒ Intermittent pre-excitation suggests an accessory pathway with a long effective refractory period (ERP) and should be reassuring to the patient and clinician.
⇒ Intermittent pre-excitation should be distinguished from gradual pre-excitation on an ECG; the latter is not helpful in risk stratifying patients.
⇒ Medical therapy with class I and III antiarrhythmic drugs is an option in patients with symptomatic arrhythmia since some of these medications increase the ERP of the accessory pathway; however, medical therapy is rarely selected in preference to a curative procedure.
⇒ Ablation of accessory pathways near the AV node carry the highest procedural risk of damaging the AV node (0.17%–2.7%); other potential complications of accessory pathway ablation include cardiac perforation/tamponade, stroke and damage to coronary arteries.

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should be evaluated with a non-invasive risk stratification test. Sudden and complete loss of pre-excitation suggests a low-risk pathway—one that can be safely observed without introducing further risk of invasive procedures. However, absence of intermittent pre-excitation warrants a thoughtful and informed discussion with the patient as to whether they wish to have an EPS and potential ablation if the accessory pathway is deemed of sufficient risk. This decision requires balancing the small attendant procedure risk versus accepting the arguably equally small risk of a conservative approach with further follow-up.

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ORCID iD  Anthony Tang http://orcid.org/0000-0003-3056-3114

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