Pre-excitation on the electrocardiogram: what next?

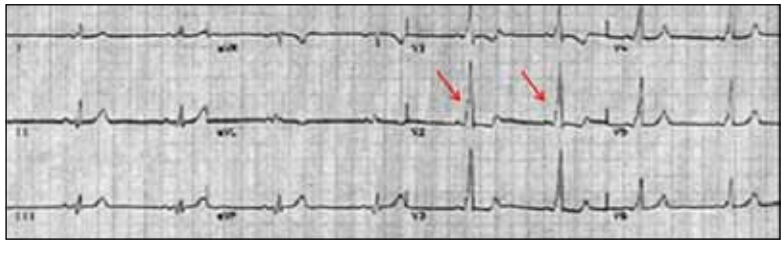
Ventricular pre-excitation, or a delta wave, on the electrocardiogram in an asymptomatic individual is frequently encountered in clinical practice. Management remains challenging and practice currently varies. This article reviews the evidence and suggests an approach to such patients.

Ventricular pre-excitation is a frequently encountered electrocardiogram abnormality (*Figure 1*), and is estimated to occur in 0.1–0.2% of the population (Triedman, 2009). Many of these individuals will have no symptoms of palpitations or documented arrhythmias. This pattern is caused by the eccentric activation of the ventricular myocardium via an atrio-ventricular accessory pathway. The increased risk of sudden cardiac death is thought to be the result of the rapid conduction of atrial arrhythmias to the ventricle, via the accessory pathway, which degenerates into ventricular fibrillation (Dreifus et al, 1971). Sudden cardiac death associated with the asymptomatic ventricular pre-excitation is estimated to be between 0.05% and 0.5% a year (Triedman, 2009), and is greatest in the young because of the tendency of the accessory pathway to conduct more slowly as we age (Klein et al, 2009).

Over the years, there has been a swing in practice from invasive investigation and prophylactic ablation to the current watchful waiting approach. Uncertainty over the absolute risk of sudden cardiac death (Blomström-Lundqvist et al, 2003; Cohen et al, 2012), the poor positive predictive value of an invasive electrophysiological study and complications associated with catheter ablation have made the management of this group of patients challenging. The 2003 joint guidance from the American Heart Association/American College of Cardiology/European Society of Cardiology recommended that use of electrophysiological studies should be restricted to individuals exhibiting ventricular pre-excitation with high risk occupations, e.g. athletes, pilots and those in the military (class IIA indication) (Blomström-Lundqvist et al, 2003; Cohen et al, 2012). The North American Society of Pacing and Electrophysiology went further, giving catheter ablation of an accessory pathway in the asymptomatic individual a class III indication (Scheinman et al, 2003). Unsurprisingly, current practice varies widely across European centres (Svendsen et al, 2013).

In light of guidance for young patients (aged 8–21 years) by Heart Rhythm Society and the Pediatric and Congenital Electrophysiology Society (Cohen et al, 2012) (*Table 1*), this article reviews risk stratification through non-invasive and invasive testing strategies, and discusses other considerations in the management of asymptomatic individuals with pre-excitation on electrocardiogram.

Figure 1. Electrocardiogram of delta waves (indicated by red arrows) and short PR interval.



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Risk stratification

Non-invasive testing

The electrocardiogram or holter monitor allows one to establish if ventricular pre-excitation is persistent or intermittent. The finding of intermittent pre-excitation indicates a long antegrade refractory period of the accessory pathway, and therefore a low risk of sudden cardiac death (Cohen et al, 2012), although, very rarely rapid accessory pathway conduction has been seen in such patients (Pietersen et al, 1992; Medeiros et al, 2001; Aleong et al, 2009). Intermittent pre-excitation does not exclude patients from developing atrioventricular re-entry tachycardia. A long follow-up study of military aviators, lasting 22 years, found 8.3% with intermittent pre-excitation could develop atrioventricular re-entry tachycardia, but in contrast to 23% who had persistent pre-excitation (Fitzsimmons et al, 2001).

The electrocardiogram can also allow an assessment of the antegrade characteristics of the accessory pathway during atrial fibrillation with pre-excitation. The shortest pre-excited RR interval reflects the functional refractory period of the accessory pathway. A shortest pre-excited RR interval of <250 msec (equivalent to >240 bpm) is more commonly seen in patients with

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Wolff–Parkinson–White syndrome (ventricular pre-excitation with symptoms) who have experienced cardiac arrest (Cohen et al, 2012).

The exercise tolerance test should be the next investigation for all individuals with persistent pre-excitation. Sympathetic stimulation occurring during exercise will shorten the duration of the refractory period of the accessory pathway. If the refractory period of the accessory pathway is reached during exercise, as manifested by the sudden and clear loss of the delta wave, one can be reassured that the accessory pathway is unable to conduct at short RR intervals (≤250 ms), or when in atrial fibrillation. However, one must be careful in ascertaining a true block in the accessory pathway, as delta wave appearance can change during exercise as a result of the relative effects of sympathetic stimulation on atrioventricular nodal conduction and anterograde conduction down the accessory pathway, where loss of the delta wave tends to be gradual. Enhanced atrioventricular nodal conduction with exertion may also obscure the persistent pre-excitation, especially via a left-sided accessory pathway (Cohen et al, 2012). Therefore, several leads should be taken simultaneously and special attention should be given to the sudden occurrence of block in the accessory pathway.

Nevertheless, the exercise tolerance test is a valuable non-invasive tool in identifying individuals at low risk of sudden cardiac death. Persistence of pre-excitation during exercise tolerance test in an adult prospective study showed a sensitivity of 96% and specificity of 17% in predicting a shortest pre-excited RR interval in atrial fibrillation ≤250 ms, factors associated with high risk of sudden cardiac death (Gaita et al, 1989).

To summarize, the presence of intermittent pre-excitation on electrocardiogram or holter monitoring, or the abrupt and clear loss of delta waves on exercise, suggest that the accessory pathway cannot conduct rapidly. These cases can be regarded as low risk, and current Heart Rhythm Society/Pediatric and Congenital Electrophysiology Society guidance recommend only follow up with counselling regarding symptom awareness (Cohen et al, 2012). In cases where there is persistent or uncertain loss of pre-excitation with exercise, or when the patient is unable to perform an exercise tolerance test, an electrophysiological study is then considered.

Invasive testing

Invasive electrophysiological testing either involves a transoesophageal atrial pacing study or an intracardiac electrophysiological study. Either of these techniques is used to determine:

1. Anterograde accessory pathway effective refractory period cycle length, where the accessory pathway fails to conduct anterogradely on rapid atrial pacing
2. Shortest pre-excited RR interval in spontaneous or induced atrial fibrillation. The presence of a short functional refractory period of the accessory pathway in atrial fibrillation is assumed to increase the risk of ventricular fibrillation in these patients
3. Inducibility of an atrioventricular reciprocating tachycardia, with and without isoprenaline (non-selective beta-agonist)
4. Number of accessory connections.

Electrophysiological indices associated with high risk of sudden cardiac death (shortest pre-excited RR interval or anterograde accessory pathway effective refractory period ≤250 ms) were previously derived from work on the Wolff–Parkinson–White population (Dubin et al, 2002; Cohen et al, 2012). In deriving similar markers of high risk in the asymptomatic group, there have been four important studies published (Pappone et al, 2003a, 2004; Santinelli et al, 2009a,b).

The first was a prospective study of 212 asymptomatic adult patients with ventricular pre-excitation of whom 33 became symptomatic over a 5-year period (Pappone et al, 2003a). Those patients had a shorter anterograde accessory pathway effective refractory period at baseline (246 *vs* 283 ms). The combination of a short anterograde accessory pathway effective refractory period and inducibility of supraventricular tachycardia

Table 1. Summary of Heart Rhythm Society/Pediatric and Congenital Electrophysiology Society guidance 2012

Baseline electrocardiogram	1a. If there is intermittent pre-excitation, patient can be followed up by cardiology and should be counselled for symptoms of arrhythmia	
	1b. If there is persistent pre-excitation, patient should undergo stress testing. If unable to perform stress testing, patient should undergo an invasive electrophysiology study	
Exercise stress test	2a. If there is abrupt and clear loss of pre-excitation, patient can be followed up as 1a	
	2b. If there is persistent or unclear loss of pre-excitation, patient should undergo an invasive electrophysiology study	
Diagnostic invasive testing	3a. If SPERRI in atrial fibrillation is >250 msec and absence of inducible supraventricular tachycardia:	Patient can be followed as in 1a
		May consider ablation based on accessory pathway location and/or patient characteristics
	3b. If SPERRI in atrial fibrillation is ≤250 msec, discuss the risk/benefits of catheter ablation	
	3c. If there is inducible supraventricular tachycardia, discuss the risk/benefits of catheter ablation	

SPERRI = shortest pre-excited RR interval. From Cohen et al (2012)

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had a positive predictive value of 47% with a negative predictive value of 97% in regard to subsequent arrhythmic events (most commonly, occurrence of atrioventricular re-entry tachycardia). Three initially asymptomatic patients with an anterograde accessory pathway effective refractory period <200 ms and a shortest pre-excited RR interval <230 ms subsequently developed ventricular fibrillation.

In the second study, a review of clinical and invasive electrophysiological data of 184 asymptomatic children with ventricular pre-excitation was performed over a median follow up of 5 years (Santinelli et al, 2009a). The study showed significantly different electrophysiological characteristics in patients who later became clinically symptomatic (which included three ventricular fibrillation arrests) when compared to those who remained asymptomatic: anterograde accessory pathway effective refractory period ≤240 msec (49% *vs* 17%), multiple accessory pathways (47% *vs* 6%), and intact retrograde conduction up the accessory pathway at baseline (84% *vs* 26%).

In a separate prospective clinical trial, 47 asymptomatic children with ventricular pre-excitation on electrocardiogram at high risk for arrhythmias (anterograde accessory pathway effective refractory period <250 ms, and inducible atrial fibrillation or supraventricular tachycardia) were randomized to ablation (20 patients) or observation (27 patients) (Pappone et al, 2004). During the 3 years of follow up, seven children in the observation group developed symptoms, five had supraventricular tachycardias and two had atrial fibrillation with rapid ventricular response. Five others in the observation group were observed to have silent atrial fibrillation on ambulatory monitors and one died suddenly, although the rhythm was never recorded. In the ablation group, one patient had a recurrence of atrioventricular re-entry tachycardia and there were no deaths. Within the control group, the authors found that multiple accessory pathways conferred an increased risk of developing these arrhythmias. Curiously, no comparison of the characteristics of the accessory pathway was made between those with a single and multiple accessory pathways.

The fourth trial was a long-term prospective follow-up study of 293 asymptomatic adult patients with ventricular pre-excitation (Santinelli et al, 2009b). All of these patients had a baseline electrophysiological study, with the primary end point being the occurrence of an arrhythmic event. During the median follow up of 67 months, 18 adults developed atrioventricular re-entry tachycardia, 14 developed atrial fibrillation and one had a ventricular fibrillation arrest, although no deaths occurred. The authors found younger age, anterograde accessory pathway effective refractory period ≤250 ms and inducibility of atrioventricular re-entry tachycardia were predictors of total arrhythmic events and potentially life-threatening arrhythmic events. Interestingly, while multiple accessory pathways predicted total arrhythmic events as in the third study, this did not reach statistical significance in predicting potentially life-threatening arrhythmias.

In terms of predicting sudden cardiac death, the positive predictive value of the shortest pre-excited RR interval to predict sudden cardiac death remains very low (Obeyesekere et al, 2012), which is in part a result of the very low incidence of sudden cardiac death in this group. The negative predictive value of the shortest pre-excited RR interval >250 ms is well established (Cohen et al, 2012; Obeyesekere et al, 2012), and the effective refractory period of the accessory pathway may also be used for risk stratification. The inducibility of atrioventricular re-entrant tachycardia predicts subsequent atrioventricular re-entry tachycardias, but not sudden cardiac death, with positive predictive values that vary widely between 0% and 70%, and negative predictive values >95% (Obeyesekere et al, 2012).

Therefore, if the shortest pre-excited RR interval or anterograde accessory pathway effective refractory period is ≤250 ms or if atrioventricular re-entry tachycardia is induced, the risks and benefits of catheter ablation should be discussed. If both these criteria were not fulfilled, deferment of ablation, with follow up and counselling, would be considered reasonable.

Other considerations

Efficacy of catheter ablation

The efficacy of prophylactic ablation of the accessory pathway in high risk asymptomatic individuals was studied by the Italian group of investigators in a randomized controlled trial (Pappone et al, 2003b). There were no deaths in either the ablation group (n=37) or control group (n=35), but there was a larger occurrence of arrhythmias in the control group over the ablation group (60% *vs* 5%; P<0.01) at the end of the 5-year follow-up period. Fifteen had supraventricular tachycardias, four had atrial fibrillation and one had a ventricular fibrillation event in the control group, compared to two patients who both had supraventricular tachycardias in the ablation group. No deaths occurred at the end of the follow-up period. A similar study was conducted in children (Pappone et al, 2004), already mentioned earlier, which similarly found that prophylactic ablation reduced the likelihood of further arrhythmic events, and reported no deaths in contrast to the control group which had one.

Complications of invasive electrophysiological study and catheter ablation

The low risk of sudden cardiac death in adults will need to be weighed against an invasive procedure which carries a small, but potentially serious, risk itself. These include venous thrombosis (1%), pulmonary emboli (0.3–0.6%), infection (0.8%), perforation (0.5–0.7%), coronary artery injury (0.8–1.3%) and catheter-induced complete

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heart block (0.9%) (Cohen et al, 2012). These procedures may also result in the induction of ventricular fibrillation, even in those who are asymptomatic (Cohen et al, 2012).

Athletes

Wolff–Parkinson–White syndrome accounted for approximately 1% of deaths in a long-term registry of sudden death in athletes (Corrado et al, 2005), although it is unknown if these were truly asymptomatic individuals. Many cases of sudden cardiac death with Wolff–Parkinson–White have been associated with exercise, and therefore assessment and risk stratification is advisable in all athletes. In the United States, consensus from the 36th Bethesda Conference advocates risk stratification with an electrophysiological study in asymptomatic athletes with ventricular pre-excitation only engaged in moderate to high level competitive sports (what is considered a medium to high level of sports is covered in the conference document) (Pelliccia et al, 2008). In Europe, the European Society of Cardiology mandates that all athletes with ventricular pre-excitation require an electrophysiological study as part of risk stratification (Corrado et al, 2005).

An athlete is considered to be at high risk of sudden cardiac death if the shortest pre-excited RR interval <240 ms in atrial fibrillation or <220 ms during stress or isoproterenol, multiple accessory pathways are present, or if atrial fibrillation is easily inducible (Corrado et al, 2005; Cohen et al, 2012). Ablation is generally recommended in asymptomatic athletes with pre-excitation in both sets of guidelines (class IIA) (Corrado et al, 2005; Pelliccia et al, 2008).

The very young and those with structural heart disease

In the first year of life, the accessory pathway loses its antegrade conduction in as many as 40% of patients, and atrioventricular re-entry tachycardia becomes non-inducible in a similar percentage (Friedman et al, 2002). However, supraventricular tachycardias can recur in 30% of individuals at an average age of 7–8 years (Deal et al, 1985). If a Wolff–Parkinson–White pattern and tachycardia coexist in an individual beyond 5 years of age, they continue to be present more than a decade later in more than 75% of individuals (Deal et al, 1985). As such, North American Society of Pacing and Electrophysiology and Pediatric and Congenital Electrophysiology Society have given catheter ablation in a child <5 years of age a class III indication, and IIB for those ≥5 years (Friedman et al, 2002).

Children and young adults with structural heart disease are at risk for both atrial tachycardia and atrioventricular reciprocating tachycardia, which make them prone to unfavourable haemodynamics. Ablation may therefore be considered regardless of the antegrade characteristics of the accessory pathway (Cohen et al, 2012).

Conclusions

Management of the asymptomatic child or adult currently involves the use of non-invasive studies to identify the low risk patient. In patients not showing block in their accessory pathway during these non-invasive tests, an electrophysiological study can determine the length of refractory period of the accessory pathway and inducibility of supraventricular tachycardia. If the accessory pathway has a short refractory period or arrhythmias can be induced, the benefits and risk of invasive catheter ablation should be based on individual considerations such as age, gender, occupation and athletic wishes. BJHM

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KEY POINTS

- Ventricular pre-excitation is a frequently encountered abnormality on the electrocardiogram.
- These patients should be referred for further risk stratification, which involve non-invasive and invasive tests.
- No clear survival benefit for prophylactic ablation of the accessory pathway in the asymptomatic group.
- The decision for an accessory pathway ablation needs to be based on individual considerations such as age, occupation and athletic demands.

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