Pre-excitation on the ECG – what next?

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Introduction

Ventricular pre-excitation is a frequently encountered electrocardiogram abnormality, and is estimated to occur in 0.1-0.2% of the population\(^1\). Many of these individuals will have no symptoms of palpitations or documented arrhythmias. This pattern is due to the eccentric activation of the ventricular myocardium via an atrioventricular accessory pathway (AP). The increased risk of sudden cardiac death (SCD) is thought to be due to the rapid conduction of atrial arrhythmias to the ventricle, via the AP, which degenerates into ventricular fibrillation (VF)\(^2\). SCD associated with the asymptomatic ventricular pre-excitation is estimated to be between 0.05%-0.5% a year\(^1\), and is greatest in the young due to the tendency of the AP to conduct more slowly as we age\(^3\).

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 SCD\(^4,5\), the poor positive predictive value of an invasive electrophysiologic (EP) study, and complications associated with catheter ablation, have made the management in this group of patients challenging. The 2003 joint guidance from the AHA/ACC/ESC recommended that EPS use should be restricted to individuals exhibiting ventricular pre-excitation with high risk occupations (class IIA)\(^4,5\). NASPE went further giving catheter ablation of an AP in the asymptomatic individual a class III indication\(^6\). Unsurprisingly, current practice varies widely across European centres\(^7\).

In light of recently published guidance for young patients (aged 8-21 years) by HRS and PACES\(^4\), we will review risk stratification through non-invasive and invasive testing strategies, and discuss other considerations in the management of asymptomatic individuals with pre-excitation on ECG.

Risk stratification

Non-invasive testing

The ECG 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 AP, and therefore a low risk of SCD\(^4\). Although, very rarely rapid AP conduction has been seen in such patients\(^9,10\). Intermittent pre-excitation does not exclude patients from developing atrio-ventricular re-entry tachycardia (AVRT). In a long follow up study of military
aviators lasting 22 years, they found 8.3% with intermittent pre-excitation could develop AVRT, but in contrast to 23% who had persistent pre-excitation\textsuperscript{11}.

The ECG can also afford an assessment of the antegrade characteristics of the AP during AF with pre-excitation. The shortest pre-excited RR interval (SPERRI) reflects the functional refractory period of the AP. A SPERRI of <250 msec is more commonly seen in patients with Wolf-Parkinson-White (WPW) syndrome (ventricular pre-excitation with symptoms) who have experienced cardiac arrest\textsuperscript{4}.

The ETT 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 AP. If the refractory period of the AP is reached during exercise, as manifested by the sudden and clear loss of the delta wave, one can be reassured the AP is unable to conduct at short RR intervals (≤250ms, equivalent to ≥ 240bpm) or when in AF. However, one must be careful in ascertaining a true block in the AP, as delta wave appearance can change during exercise due to the relative effects of sympathetic stimulation on AV nodal conduction and anterograde conduction down the AP, where loss of the delta wave tends to be gradual. Enhanced AV nodal conduction with exertion may also obscure the persistent pre-excitation, especially via a left-sided accessory pathway\textsuperscript{4}. Therefore, several leads should be taken simultaneously and special attention should be given to the sudden occurrence of block in the AP.

Nevertheless, ETT is a valuable non-invasive tool in identifying the individuals at low risk of SCD. Persistence of pre-excitation during ETT in an adult prospective study showed a sensitivity of 96% and specificity of 17% in predicting a SPERRI in AF ≤250ms, factors associated with high risk of SCD\textsuperscript{12}.

To summarise, the presence of intermittent pre-excitation on ECG or holter monitoring, or the abrupt and clear loss of delta waves on exercise, suggest the AP cannot conduct rapidly. These cases can be regarded as low risk, and current HRS/PACES guidance recommend only follow up with counselling regarding symptom awareness\textsuperscript{4}. In cases where there is persistent or uncertain loss of pre-excitation with exercise, or when the patient is unable to perform an ETT, an EP study is then considered.

**Invasive testing**

Invasive EP testing either involves a transesophageal atrial pacing study or an intracardiac EP study. Either of these techniques is employed to determine:

1. anterograde accessory pathway effective refractory period (APERP) cycle length, where the AP fails to conduct anterogradely on rapid atrial pacing

2. shortest pre-excited R-R interval (SPERRI) in spontaneous or induced atrial fibrillation. The presence of a short functional refractory period of the AP in AF is assumed to increase the risk of VF in these patients.

3. Inducibility of an AV reciprocating tachycardia, with and without isopreterenol

4. number of accessory connections
EP indices associated with high risk of SCD (SPERRI or APERP ≤250ms) were previously derived from work on the WPW population\textsuperscript{4,13}. In deriving similar markers of high risk in the asymptomatic group, there have been four important studies published recently\textsuperscript{14-17}.

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\textsuperscript{14}. Those patients had a shorter APERP at baseline (246 vs 283ms). The combination of a short APERP and inducibility of SVT had a positive predictive value of 47\% with a negative predictive value of 97\% in regard to subsequent arrhythmic events (most commonly, occurrence of AVRT). There were three initially asymptomatic patients with an APERP <200 ms and a SPERRI <230 ms who subsequently developed VF.

In the second study, a review of clinical and invasive EP data of 184 asymptomatic children with ventricular pre-excitation was performed over a median follow-up of 5 years\textsuperscript{15}. The study showed significantly different EP characteristics in patients who later became clinically symptomatic (which included 3 VF arrests) when compared to those who remained asymptomatic: APERP ≤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 ECG at high risk for arrhythmias (APERP <250ms, and inducible AF or SVT) were randomized to ablation (20 patients) or observation (27 patients)\textsuperscript{16}. During the 3 years of follow-up, 7 children in the observation group developed symptoms, 5 had SVTs and 2 had AF with rapid ventricular response. Five others in the observation group were observed to have silent AF on ambulatory monitors and 1 died suddenly, though the rhythm was never recorded. In the ablation group, 1 patient had a recurrence of AVRT and no deaths. Within the control group, the authors found multiple accessory pathways conferred an increased risk for developing these arrhythmias. Curiously, no comparison of the characteristics of the AP was made between those with a single and multiple APs.

The fourth trial was a long term prospective follow up study of 293 asymptomatic adult patients with ventricular pre-excitation\textsuperscript{17}. All of whom had a baseline EP study, with the primary end point being the occurrence of an arrhythmic event. During the median follow up of 67 months, 18 adults developed AVRT, 14 developed AF and 1 had a VF arrest, though no deaths occurred. The authors found younger age, APERP ≤250ms and inducibility of AVRT were predictors of total arrhythmic events and potentially life-threatening arrhythmic events, defined as arrhythmias having a SPERRI ≤250ms. Interestingly, whilst multiple APs predicted total arrhythmic events as in the third study, it did not reach statistical significance in predicting the occurrence of arrhythmias that had a SPERRI ≤250ms.

In terms of predicting SCD, the positive predictive value of the SPERRI to predict SCD remains very low\textsuperscript{18}, which is in part due to the very low incidence of SCD in this group. The negative predictive value of the SPERRI >250 milliseconds is well established\textsuperscript{4,18}, and the effective refractory period of the AP may also be used for risk stratification. The inducibility of atrioventricular re-entrant tachycardia predicts subsequent AVRTs, but not SCD, with positive predictive values that vary widely between 0\% and 70\%, and a negative predictive values >95\%\textsuperscript{18}. 
Therefore, if the SPERRI or APERP is \( \leq 250 \text{msec} \) or if AVRT is induced, the risks/benefits for 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 AP in high risk asymptomatic individuals was studied by the Italian group of investigators in a randomised control trial\(^1\). There were no deaths in either the ablation group (n=37) or control group (n=35), but found 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. 15 had SVTs, 4 had AF and one had a VF event in the control group, compared to 2 patients who both had SVTs in the ablation group. No deaths occurred at the end of the follow up period. A similar study was conducted in children, 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 EP study and catheter ablation**

The low risk of SCD 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 heart block (0.9%)\(^4\). These procedures may also result in the induction of VF, even in those who are asymptomatic\(^4\).

**Athletes**

WPW syndrome accounted for approximately 1% of deaths in a long-term registry of sudden death in athletes\(^20\), although it is unknown if these were truly asymptomatic individuals. Many cases of SCD with WPW 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 EP study in asymptomatic athletes with ventricular pre-excitation only engaged in moderate to high level competitive sports (what is considered medium to high level of sports is covered in the conference document)\(^21\). Whilst in Europe, the European Society of Cardiology mandates that all athletes with ventricular pre-excitation require an EP study as part of risk stratification\(^20\).

An athlete is considered to be at high risk of SCD if there is a SPERRI <240ms in AF or <220ms during stress or isoproterenol, multiple accessory pathways are present, or if AF is easily inducible\(^4,20\). Ablation is generally recommended in asymptomatic athletes with pre-excitation in both sets of guidelines (class IIA)\(^20,21\).

**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 AVRT becomes non-inducible in a similar percentage\textsuperscript{22}. However, SVTs can recur in 30% of individuals at an average age of 7-8 years\textsuperscript{23}. If a WPW 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\textsuperscript{23}. As such, NAPSE and PACES have given catheter ablation in a child < 5 years of age a class III indication, and IIB for those ≥5 years\textsuperscript{22}.

Children and young adults with structural heart disease are at risk for both atrial tachycardia and AV reciprocating tachycardia, which make them prone to unfavourable haemodynamics. Ablation may therefore be considered regardless of the antegrade characteristics of the accessory pathway\textsuperscript{4}.

Summary of HRS/PACES guidance 2012\textsuperscript{4}

1. Baseline ECG
   a. If there is intermittent pre-excitation, patient can be followed up by Cardiology and should be counselled for symptoms of arrhythmia
   b. If there is persistent pre-excitation, patient should undergo stress testing. If unable to perform stress testing, patient should undergo an invasive EP study

2. Exercise stress test
   a. If there is abrupt and clear loss of pre-excitation, patient can be followed up as 1a.
   b. If there is persistent or unclear loss of pre-excitation, patient should undergo invasive EP study

3. Diagnostic invasive testing
   a. If SPERRI in AF is >250msec and absence of inducible SVT:
      i. Patient can be followed as in 1a
      ii. May consider ablation based on AP location and/or patient characteristics
   b. If SPERRI in AF is ≤250msec, discuss the risk/benefits of catheter ablation
   c. If there is inducible SVT, discuss the risk/benefits of catheter ablation

Conclusion
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 AP during these non-invasive tests, an EP study can determine the length of refractory period of the AP and inducibility of SVT. If the AP has a short refractory period or arrhythmias can be induced, the benefits and risk of an invasive catheter ablation should be based on individual considerations such as age, gender, occupation, and athletic wishes.

Reference:

1. Triedman JK Management of asymptomatic Wolf-Parkinson-White Syndrome. Heart 2009; 95,1628-34