RISK-STRATIFICATION STRATEGY FOR SUDDEN CARDIAC DEATH IN THE VERY YOUNG CHILDREN WITH ASYMPTOMATIC VENTRICULAR PREEXCITATION

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Abstract: Asymptomatic VPE refers to the presence of this abnormal ECG pattern in the absence of any symptoms. The natural history in these patients is usually benign, and most children (60%) with VPE are usually asymptomatic. However, Sudden Cardiac Death (SCD) has been reported to be the initial symptom in many patients too. The increased risk of 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). The best method to identify high-risk patients with asymptomatic VPE for SCD is the characterization of the electrophysiological properties of the AP through an Electrophysiological Study (EPS). Also, catheter ablation of the AP with radiofrequency as definitive treatment to avoid SCD can be performed by the same procedure with high rates of success. However, the uncertainty over the absolute risk of SCD, the poor positive predictive value of an invasive EPS, and complications associated with catheter ablation have made the management of asymptomatic VPE challenging, even more in those children younger than 8-year-old, where there are no clear recommendations. This review provides an overview of the different methods to make the risk stratification for SCD in asymptomatic children with, as well as our viewpoint on the adequate approach to those young children not included in current guidelines.

Keywords: Wolff-parkinson-white syndrome, sudden cardiac death, ventricular preexcitation, infant, atrioventricular accessory pathways, ventricular fibrillation.

1. INTRODUCTION

Atrioventricular Re-entrant Tachycardia (AVRT) is the most common cause of Supraventricular Tachycardia (SVT) in young children. It occurs because of the existence of atrioventricular Accessory Pathways (AP) located along the atrioventricular groove, connecting the atrium to the ventricle as a part of the re-entrant circuit that involves the AV node too. In some of these cases, there is anterograde conduction through the AP, resulting in manifesting Ventricular Preexcitation (VPE) on baseline ECG (short PR interval and Delta wave; Fig. 1) that is commonly referred to as Wolff-Parkinson-White syndrome (WPW).

Asymptomatic VPE refers to the presence of this abnormal ECG pattern in the absence of any symptoms. VPE prevalence on baseline ECG is reported to be up to 0.3% in the general population, and 0.55% among the first-degree relatives of an index case [1-4]. In recent years, the use of ECG for screening prior to sports participation, medical or surgical procedures, and initiation of medications has identified increasing numbers of asymptomatic VPE cases in children [1-4]. The natural history in these patients is usually
absolute risk of SCD, the poor positive predictive value of an invasive EPS, and complications associated with catheter ablation have made the management of asymptomatic VPE challenging, even more in those children younger than 8-year-old, where there are no clear recommendations [16, 17].

This review provides an overview of the different methods to make the risk stratification for SCD in asymptomatic children, as well as our viewpoint on the adequate approach to those young children not included in current guidelines.

2. RISK STRATIFICATION FOR SCD IN ASYMPTOMATIC VPE

Some clinical variables, such as male sex, younger age (< 30 year-old), familiar history of WPW, structural heart disease and septal localisation of AP, have been associated with a higher risk of SCD in patients with asymptomatic VPE [1-6]. However, all of them have a modest power to identify these patients, and the SCD risk stratification has focused on the characterization of the electrophysiological properties of the AP [12-17] (Table 1). Both, non-invasive and invasive tests are used for this purpose, but none alone is the best option for all infants and young children.

Non-Invasive Methods: The goal of these tests is to demonstrate that the AP fails to conduct at rapid rates, either in sinus rhythm or during AF. These tests include baseline ECG, Holter monitoring, exercise testing and medication challenge to induce a block in the AP in sinus rhythm.

The main role of baseline ECG and Holter monitoring is that they allow establishing if there is an intermittent VPE (Fig. 2). Also, Holter monitoring helps to identify silent episodes of AVRT or AF, that has been reported to occur in up to 12% of asymptomatic children with VPE [18, 19]. The finding of intermittent preexcitation indicates a long AERP, and therefore a low risk of SCD. Conversely, the appearance of different morphologies of VPE is suggestive of multiple AP, which has been identified as a risk factor for ventricular fibrillation and SCD. Of note, it was recently observed that intermittent preexcitation in children does not connote a lower risk AP by EP criteria [20, 21], and therefore the decision to avoid an invasive EPS based solely on this finding should be taken with caution.

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**Table 1. Summary of 2012 PACES recommendations for management of young patients (8-21 year-old) with asymptomatic VPE.**

| 1. Baseline ECG or Holter monitoring |
|-------------------------------------|
| 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 IEPS. |

| 2. Exercise 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 IEPS. |

| 3. IEPS |
|---------|
| a. If SPERRI in AF is > 250msec and absence of inducible SVT Patient can be followed as in 1a. 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. |
| d. If multiple AP are localized, discuss the risk/benefits of catheter ablation. |

*Abbreviations:* VPE (Ventricular Preexcitation); EP (Electrophysiological); IEPS (Invasive Electrophysiological Study); SPERRI (Shortest Pre-excited R-R Interval); SVT (Supraventricular Tachycardia).
Exercise testing should be performed in all individuals with persistent VPE. Sympathetic stimulation occurring during exercise will shorten the duration of the refractory period of the AP [22]. The best non-invasive indicator of low risk of SCD is the sudden, clear and complete disappearance of pre-excitation during exercise, which indicates a long AERP of AP that is unable to conduct at short RR intervals (< 250 ms) or when in AF [16, 17]. The persistence of VPE during exercise presented a sensitivity of 96% and specificity of 17% in predicting a high risk of SCD in adults [23]. 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. This is especially difficult in children, where the accuracy of this finding is lower than in adults [23]. Also, children must be enough old to perform adequately this test. Therefore, the inability to perform the test or to clearly demonstrate the sudden and absolute loss of manifesting pre-excitation during exercise warrants invasive EPS.

Another non-invasive method to detect high-risk patients is to make a pharmacological challenge with IC class antiarrhythmic agents. The block of the VPE after the administration of these drugs is associated with a longer AERP at EPS [22]. However, the specificity of loss of VPE after administration of IC class antiarrhythmic agents is also poor, and therefore is no longer utilized [23].

To summarise, the presence of intermittent pre-excitation on baseline 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 PACES position statement for risk stratification in the young (aged 8-21 years) asymptomatic VPE patients (Table 2) recommends only follow up with counselling regarding symptom awareness. Conversely, an EPS is recommended as a Class IIA (level of evidence B/C) indication when non-invasive testing is ambiguous or uncertain regarding the risk, when there is a coexistent cardiac abnormality, and when multiple accessory pathways are suspected [16, 17].

**Invasive Methods:** Invasive EPS either involves a Transesophageal Atrial Pacing Study (TAPS) or an Intracardiac EPS Study (IEPS). Either of these techniques are employed to determine EP properties of the AP that are associated to high-risk for SCD (Table 1).

IEPS is the examination that offers the best cost/benefit ratio for risk stratification in asymptomatic VPE. Although the negative predictive value of SPERRI or APERP ≤ 250 msec and AVRT inducibility are near 100% to predict SCD, the positive predictive value remains very low, which is in part due to the very low incidence of SCD in this group [5, 11-17]. According to recent surveys most pediatric electrophysiologists (84%) used IEPS to risk-stratify asymptomatic children with VPE, with high rates of successful of RFA (>90%) [24]. Of note, the ablation of the AP is reported to decrease the incidence of potential future symptomatic
arrhythmias [14]. Also, a randomised clinical trial that evaluated the results of prophylactic catheter ablation in children (aged 5-12 years) with asymptomatic VPE showed that the absence of prohylactic ablation was an independent predictor of arrhythmic events [25]. Despite this evidence, one must bear in mind that the low-risk of SCD of asymptomatic patients and the low predictive positive value of EPS must be weighed against the invasive nature of the procedure, which carries a potential risk of complications (5%-15%), with major ones reported in 0.9%-4.2% (death 0.12%) [12-17, 24]. Furthermore, the prolonged exposure to radiation and high recurrence rates of arrhythmia after successful procedures (7%-17%) are of particular concern [12-17, 24]. Also, catheter ablation is associated with increased risk of injury of coronary arteries and potential enlargement of the scar with growth [12-17, 24]. All the above argue against the systematic referral of every child with asymptomatic VPE for an EPS or RFA, which could result in severe and potentially life-threatening complications, that possibly surpass the number of deaths caused by untreated disease. Thus, catheter ablation is a Class IIA (level of evidence B/C) indication for young patients (aged 8-21 years) with asymptomatic when high-risk electrophysiological properties of the AP at an Electrophysiological Study (EPS) are observed, whatever the risk/benefits of the procedure have been taken into account [16, 17]. However, if high-risk criteria were not fulfilled, deferral of ablation, with follow up and counseling, would be considered reasonable. The IEPS in very young children (< 8 year-old) is not as safe as for older children. An IEPS to stratify risk and RFA procedure should only be considered in those children (overall those < 15 Kg) when the high-risk factors determined non-invasively are present, and whenever the risk of complications (judged mainly by localisation of the AP, the body surface area of the patient, and the medical team experience) is low. Also only centres with large experience should perform IEPS and catheter ablation in this population. As such, NAPSE and PACES have given catheter ablation in a child < 5-8 years of age a class III indication, and IIB for those ≥ 5 years [16, 17].

TAPS is still considered in current guidelines as a suitable option for evaluating asymptomatic VPE [26]. It has been shown that TEPS is useful to determine the EP properties of the AP and to manage the risk stratification in children because of its high correlation with EPS [26, 27]. It can easily be performed in small facilities and small children. Furthermore, it is a less-expensive, semi-invasive and safe technique avoiding potential vascular complications and radiation exposure of EPS. These advantages make TEPS an adequate alternative risk-stratification approach in small infants. However, some limitations must be taken into consideration when using TEPS for risk stratification [26, 27]. Firstly, the accuracy of TEPS to locate the AP and to discern multiple APs is low. Secondly, it could be painful and requires the use of sedation. More importantly, the values of the AERP of and SEPRRI during AF are higher than those determined by EPS, and inducibility of AF is more difficult during TEPS compared to EPS. This is important because some cases could be wrongly classified as a low-risk patient. To avoid this, lower cut-off values (< 280-300 ms) may be selected for risk stratification [26, 27]. Finally, catheter ablation could not be performed in the same procedure.

Observational data have shown that isoproterenol can modify the EP properties of APs and inducibility of supraventricular arrhythmia in patients with VPE [27, 28]. Kubus et al. identified an additional 36.4 % of high-risk patients with isoproterenol when high-risk parameters were absent at baseline EP study in a group of 85 asymptomatic paediatric patients [27]. Thus, the use of intravenous infusion of isoproterenol during EPS or TEPS in children has been advocated as a possible surrogate of adrenergic stimulation.

3. PHARMACOLOGICAL THERAPY

Because the well-known SCD risk in patients with symptomatic VPE and asymptomatic VPE without clear low-risk by non-invasive tests, it makes sense to treat these patients with antiarrhythmic drugs in order to prevent or revert episodes of AVRT or AF until EPS and catheter ablation can be safely performed [29]. Also, pharmacologic management could be necessary in facilities with no easy access to EPS or catheter ablation. There are several and variable approaches to chronic drug therapy of VPE, based on the experience of the pediatric cardiologists. The use of verapamil or digoxin should be avoided in this population due to the increased risk of SCD [29]. Conversely, betablockers or flecainide are good initial options and could be combined if necessary in refractory cases. In our institution, we prefer the use of Flecainide, an IC class antiarrhythmic drug that has proven to be safe and effective in controlling supraventricular arrhythmias in children, even infants, neonates and fetus [30-32]. It is a sodium channel-blocking agent that decreases the velocity of conduction in fast-response cells, with minimal effects on action potential duration and repolarization. Flecainide decreases the conductivity of the AP and has a stabilising effect on the atria, thus preventing and reverting episodes of AVRT and paroxysmal AF [30-32]. As mentioned previously, if VPE disappears after administration of flecainide a short APERP could be assumed, and therefore the patient can be stratified as low-risk. Remarkably, there is an approximated risk of lethal proarrhythmia of 4% when using flecainide in children but always related to the presence of structural heart diseases [32]. So, an echocardiographic study previously to start flecainide is warranted in these patients.

4. OUR VIEWPOINT ABOUT THE ADEQUATE MANAGEMENT OF VERY YOUNG CHILDREN (< 8-YEAR-OLD) WITH ASYMPTOMATIC VPE (FIG. 3)

The actual recommendations for management of asymptomatic VPE are done only for patients between 8-21 years old, an age span routinely cared for by paediatricians and pediatric cardiologists and generally considered old enough to undergo exercise testing and catheter ablation if indicated. Asymptomatic VPE in very young children (< 8-year-old) constitutes a non-rare and challenging condition in paediatrics. Although natural history seems to be good, there is a low but real risk of SCD that can be avoided effectively through catheter ablation in this population. However, an adequate strategy to manage these patients is challenging for various reasons. It is essential to bear in mind that young child and infants might not be able to verbalize and express well their complaints, and therefore, they could be classified as asymptomatic when they are not. Therefore, the absence
of symptoms did not necessarily connote low risk in infants, and risk-stratification in this population is a matter of concern. Of note, even if it is possible to classify an infant as asymptomatic VPE, there are more difficulties in this setting, such as the low accuracy of non-invasive methods, the impossibility to perform exercise test, the risk of complications of EPS, the need of sedation of TEPS and EPS, and the lack of availability of EPS and TEPS in all centres. Besides, it has been reported that the risk of SCD is the same for both symptomatic and asymptomatic children [33]. All the above makes difficult an appropriate risk-stratification.

CONCLUSION

In summary, in this population, there is not a management strategy that is good enough for all patients, and a specific care plan for each particular patient in each particular center (age, body surface area, pediatric cardiologist experience etc.), must be made based on risks and benefits of the strategy chose. In our institution, if it is not possible to clearly classify a patient as asymptomatic or as low-risk for SCD through non-invasive tests (we utilize only exercise test for this purpose, not intermittent preexcitation on Holter
monitoring), or to perform safely an invasive risk-stratification (≥ 30 Kg in our institution), prophylactic treatment with flecainide is started to minimise the risk of malignant arrhythmias at least until the age at which the patient can describe well the presence of symptoms, can comply well with an exercise-test, or an EPS can be performed safely. The choice to observe without treatment in those patients should be preceded by the parents being informed of the small but real risk of life-threatening arrhythmias developing in the absence of treatment. When the EPS is performed, if we classify the patient as high-risk for SCD, a catheter ablation during the same procedure is carried out unless there is high-risk for AV block due to the localization of the AP. In these cases, the catheter ablation is avoided and the patient continues on treatment with flecainide. If parents prefer the catheter ablation, the patient is then referred to a centre with large experience in this setting.

**AUTHORS’ CONTRIBUTION**

Drs. Rodriguez-Gonzalez and Perez-Reviriego conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Castellano-Martinez reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**CONSENT FOR PUBLICATION**

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The authors declare no conflict of interest, financial or otherwise.

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