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Sudden Cardiac Death as the First Clinical Manifestation in 2 Infants with Asymptomatic Ventricular Preexcitation

Short running title: Asymptomatic Wolff-Parkinson-White in infants

Authors:

Moises Rodriguez-Gonzalez, MD[*1], Miguel A. Matamala-Morillo, MD[1], Ana Castellano-Martinez, MD[1]

[1, *1]Pediatric Cardiology Department of Puerta del Mar Universitary Hospital. Cadiz, Spain.

Correspondence to: Moises Rodriguez-Gonzalez, MD

Postal address: Department of Pediatric Cardiology, Hospital Universitario Puerta del Mar, 21st of Ana de Viya Avenue, Cadiz, Spain, 11009

Tel & Fax: +34 956002700
Email: moirogo@gmail.com
ORCID ID: 0000-0002-5587-435X

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Abstract

Introduction: The real risk of sudden cardiac death (SCD) in asymptomatic Wolff-Parkinson-White syndrome (AWPWS) is still not well known, and controversial literature is found about the best management strategy. Most worrisome is that SCD has been reported as the first event in asymptomatic or undiagnosed AWPWS infants. So adequate risk stratification to prevent the occurrence of life-threatening arrhythmias is warranted in these patients, but none of the available tests for this is a good option.

Case report: We report 2 cases of AWPW infants that experienced SCD as the first clinical manifestation.

Conclusion: AWPWS in infants is a non-rare and challenging condition that implies a very low but real risk of SCD, which is very difficult to determine accurately with diagnostic methods currently available. In this article we review the literature about the subject andand discuss about the adequate management of these patients.

Keywords: Wolff Parkinson White syndrome; Sudden Cardiac Death; Infant

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1. Introduction

Wolff–Parkinson–White syndrome (WPWS) is a type of ventricular preexcitation (VPE) caused by the existence of atrioventricular accessory pathways (AP). Epidemiological data indicates that the it is observed in 0.1%-0.3% of routine ECG performed in the general population, and 0.55% among the first-degree relatives of an index case[1-4]. Although it is the most common cause of supraventricular tachycardia (SVT) in children, usually as orthodromic atrioventricular re-entrant tachycardia (AVRT), the majority of children are asymptomatic. Also, up to 60% of asymptomatic patients with VPE are estimated to be children and adolescents[2-4].

Asymptomatic WPWS (AWPWS) constitutes a common and sometimes conflicting clinical scenario in pediatrics. Natural history in these patients is usually benign with a rate of spontaneous arrhythmia observed during the follow-up ranging from 8% to 21%[2-4]. Moreover, there is the possibility that pre-excitation may spontaneously disappear; anterograde conduction through the AP disappears in 40 % of patients in the first year of life, and in a similar percentage of cases, SVT becomes non-inducible, suggesting the loss of retrograde conduction. In children and adolescents, the probability of losing pre-excitation varies from 0 to 26 %[5,6].

Remarkably, sudden cardiac death (SCD) may occur and may be the initial symptom in these patients[5-8]. The assumed mechanism is ventricular fibrillation (VF) secondary to rapid stimulation of the ventricles due to atrial fibrillation (AF) rapidly conducted through the AP. Of note, a prospective study of 184 asymptomatic children with WPW followed for 5 years with 2 Holter monitor per year, showed that 12% had AF, an incidence significantly higher than seen in asymptomatic adults with WPW[9]. SCD can occur when the AP has a short anterograde effective refractory period (AERP), allowing many atrial impulses during AF to be conducted to the ventricle[10]. However, the existing evidence about the real risk of SCD is weak, and advice on whether or not to invasively stratify the risk of SCD and ablate the AP through electrophysiological study (EPS) is not clarified.

In the present article we present 2 cases of sudden cardiac death in infants with AWPW S pattern, and review the literature and discuss about the best risk-stratification strategy in infants with asymptomatic WPW.

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2. Cases Presentation

Case 1:

A two-month-old previously healthy male was evaluated in our Pediatric Cardiology clinic for a heart murmur. Familiar and personal history was unremarkable. He was asymptomatic. Physical exam was normal. ECG revealed a VPE pattern (Figure 1A). Echocardiography showed no anomalies. 24 hour-Holter monitoring revealed sinus rhythm with loss of preexcitation at higher heart rates (Figure 1B). No episodes of tachyarrhythmia were detected. He was diagnosed with AWPWS. No treatment was initiated, and a close clinical and ECG follow-up was scheduled. He did well until six months of age. Parents reported that he was crying vigorously at home and suddenly stopped breathing and became unresponsive. They started basic cardiopulmonary resucitation (CPR) while waiting for the emergency services that found him collapsed and continued with advanced CPR. Unfortunately, the CPR was unsuccessful, and he died on the way to the hospital. No ECG was recorded, but we believe that the most probable cause of death was VF.

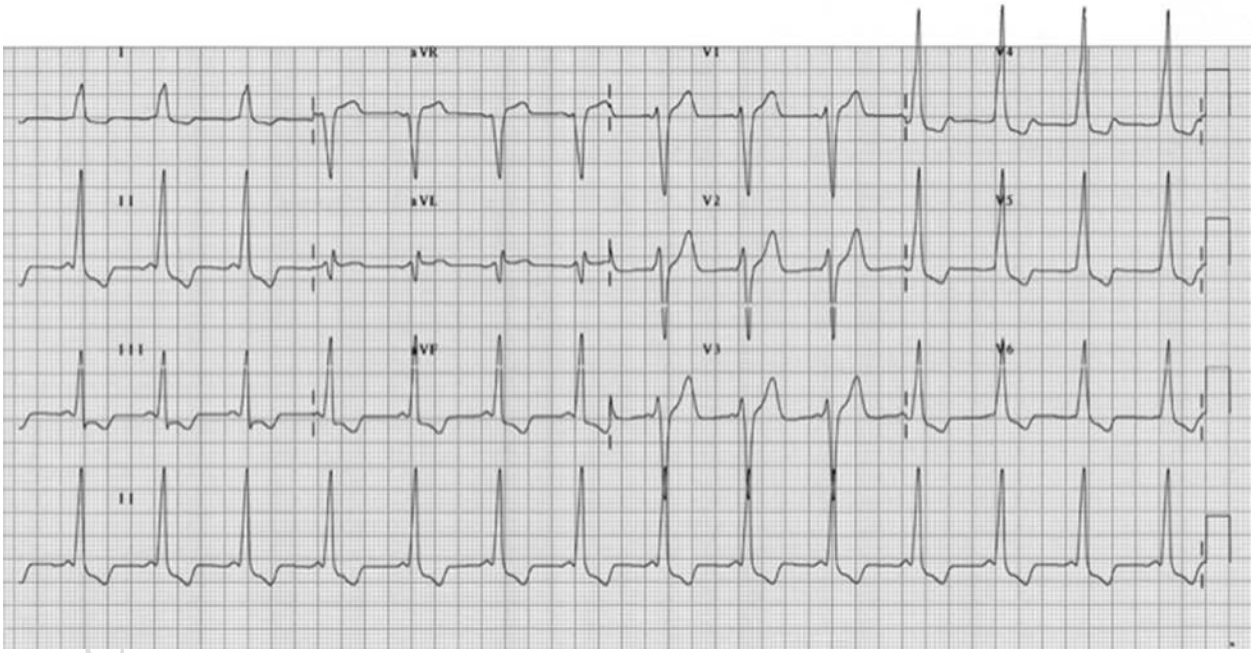

Figure 1A. ECG showing short PR interval with delta wave (Wolff-Parkinson-White syndrome).

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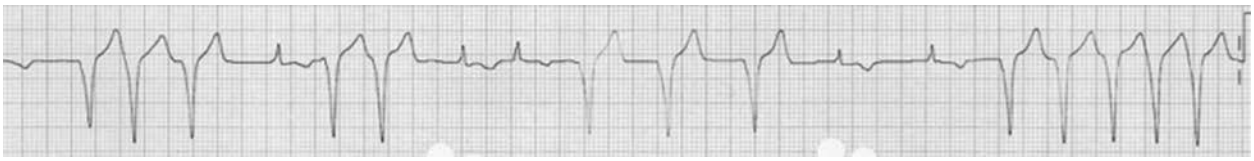

Figure 1B. Holter monitoring record showing intermittent VPE.

Case 2:

8-year-old previously healthy female consulted our Pediatric Cardiology clinic for self-limited episodes of palpitations. Familiar history was negative. Personal history revealed a sudden infant death episode at four months old. Parents described that they heard throaty sounds and went to look at the cradle. They found her daughter blue, stiff and unreactive. The emergency services found her unconscious, not breathing and pulseless at home. After 10 minutes of advanced resuscitation, normal vital signs were recovered, and she was taken to our hospital. All the tests performed (including ECG) were reported as normal, and she was discharged. The current research of palpitations shows baseline electrocardiogram with ventricular preexcitation (Figure 2A) resulting in the diagnosis of WPWS. Echocardiography was normal. 24-hour Holter revealed a continuous WPW pattern with no episodes of tachyarrhythmia. The treadmill test was unremarkable, but preexcitation did not disappear with higher heart rates. We reviewed the ECG traces performed by the emergency medical services after resuscitation at patient´s home and found a striking VPE pattern (Figure 2B). We think that the sudden infant death episode could have been secondary to a VF in the context of an undiagnosed WPWS, although it cannot be demonstrated because of the absence of ECG recording during the resuscitation. She underwent EPS and satisfactory radiofrequency catheter ablation (RFA) of AP without complications. At 1 year follow-up, she remained asymptomatic with normal ECG and echocardiography studies (Figure 2C).

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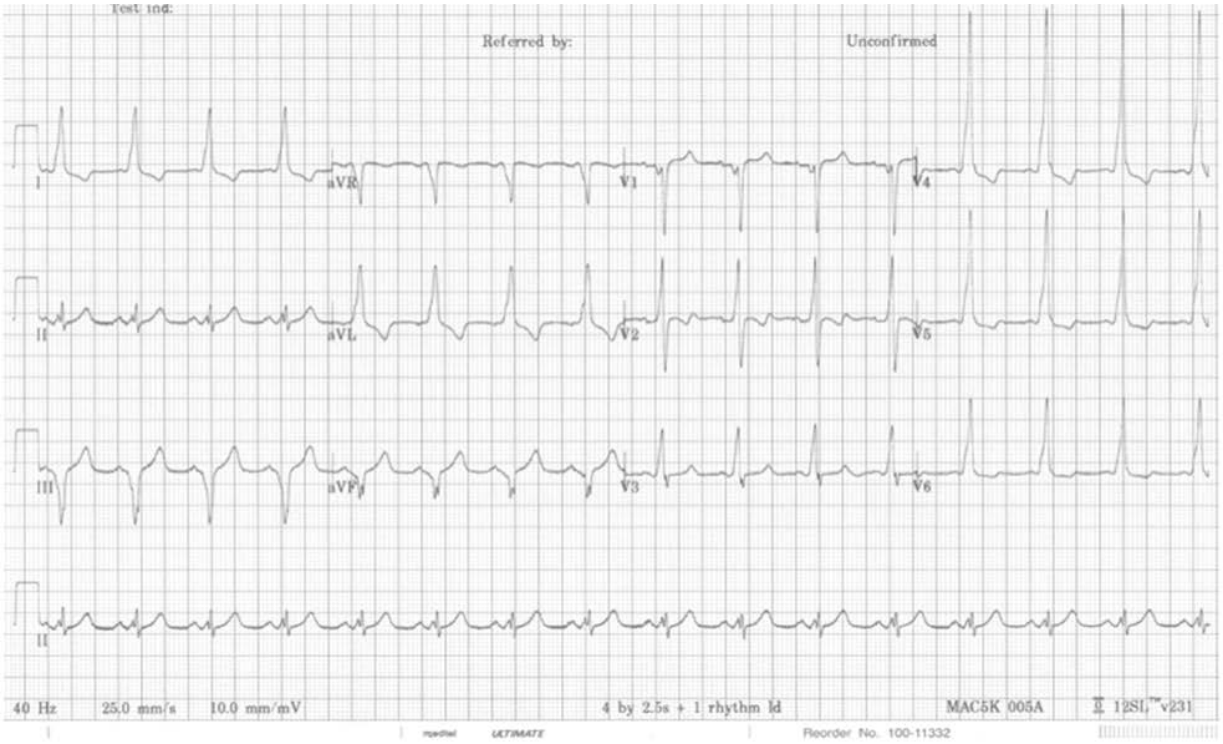

Figure 2A. Current ECG showing a short PR interval and a delta wave in all ECG leads.

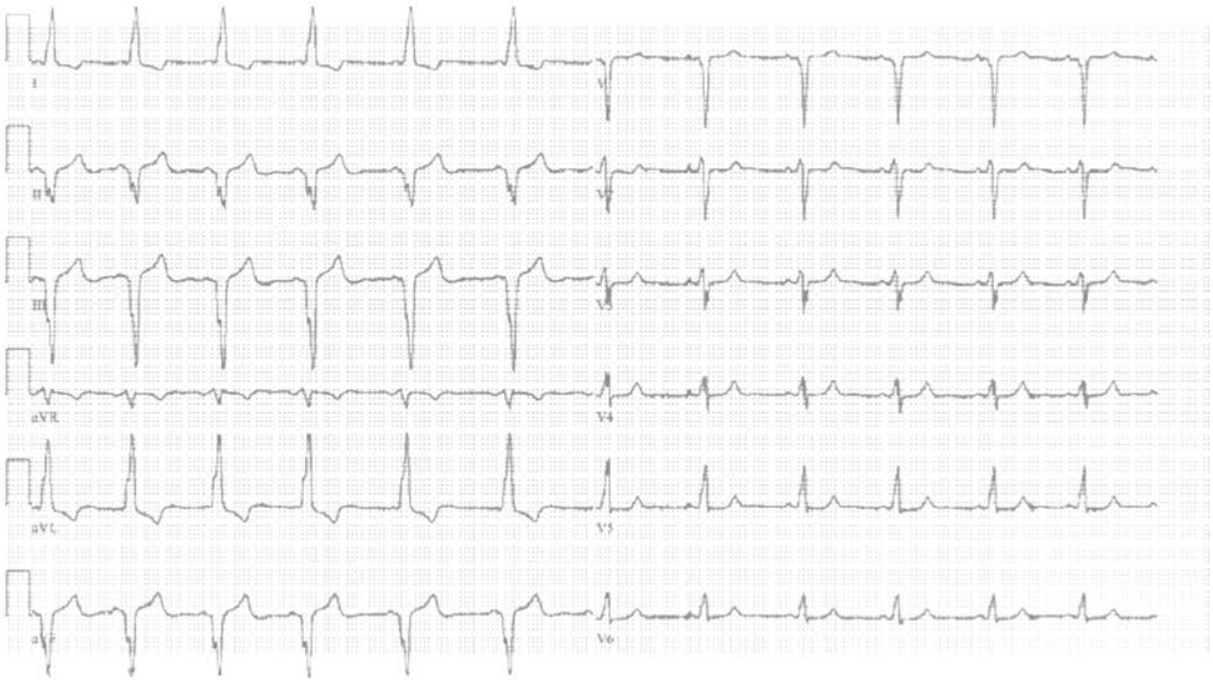

Figure 2B. ECG record after de sudden death episode suffered at 4 month old. Again it revealed a short PR with delta wave in 4 limbs leads.

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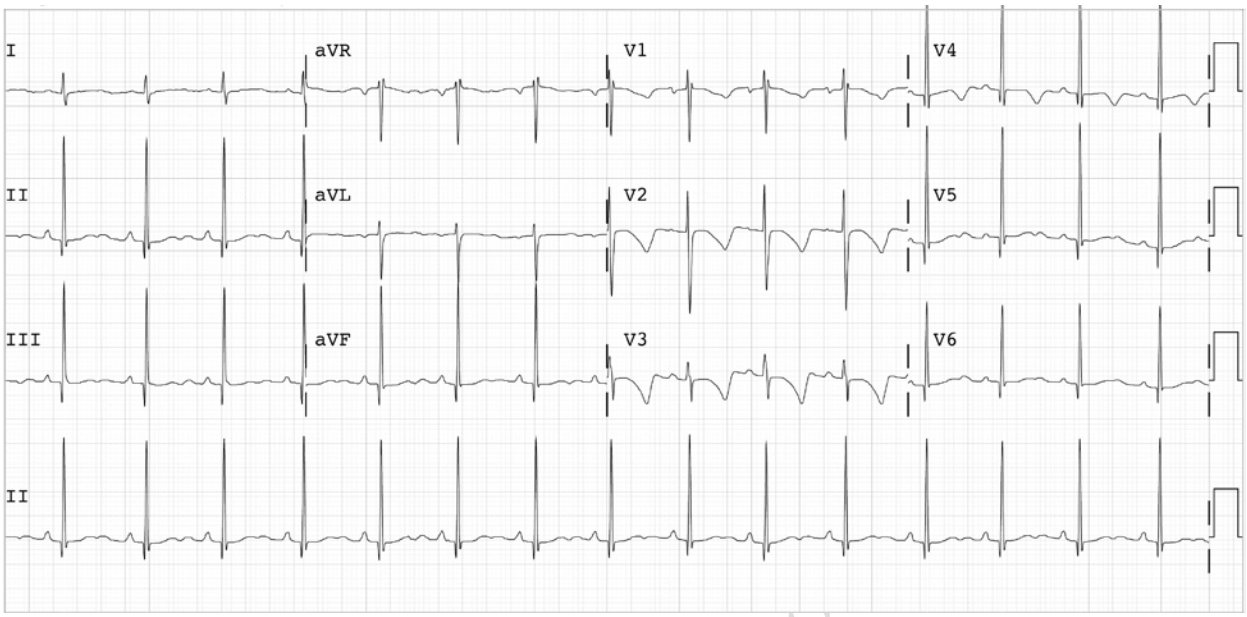

Figure 2C. ECG record after radiofrequency ablation showing normal sinus rhythm.

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3. Discussion and Review of the Literature

The best clinical approach to managing patients with AWPWS has yet to be established. The clinical benefit of identifying and treating these patients at risk of SCD has been debated since RFA became effective and safe even in small children.

3.1. Real risk of sudden cardiac death in asymptomatic patients

Traditionally the management depends entirely on the patient's clinical picture because symptomatic patients have a higher risk of SCD, and a more aggressive approach is preferred for them. The general incidence of SCD in WPWS is reported to be between 0%-0.6% per year[2-4]. In symptomatic patients, the risk is 3–4 % over a lifetime (approximately 0.25 % per year). Although most asymptomatic patients have a good prognosis, there is also a lifetime risk of malignant arrhythmias and SCD, estimated to be 0.1 % per patient-year, that is a very low incidence of SCD (similar to that observed in the general population). A recent meta-analysis has shown that the risks associated with an invasive procedure such as RFA are similar to the risk of SCD in asymptomatic individuals[11]. This argues against routine invasive management in most

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asymptomatic individuals with the Wolff-Parkinson-White ECG pattern. Recently there have been advocates for performing invasive electrophysiologic assessment and catheter ablation therapy in asymptomatic individuals based on the finding by some investigators (Italian studies) of higher mortality rates in these individuals[12,13]. Thus, conflicting opinions are reported depending on the risk of SCD deemed, with some physicians aiming at the conservative approach and others advocating the first ablation approach.

Particular care must be taken with infants, in whom it is challenging to determine the absence of symptoms and therefore, to determine the real risk by the clinical history alone remains a dilemma. Remarkably, the incidence of SCD seems to be higher in pediatric than adult patients (1.93 versus 0.86 per 1,000 person-years)[11], and SCD may be the initial symptom in up to 53% of cases[5-8,14,15]. Also, it is essential to bear in mind that the unavailability of ECG during resuscitation could underestimate the low incidence of infants presenting with SCD. So the absence of symptoms did not necessarily connote low risk in infants, and risk-stratification in this population is a matter of concern.

In 2012, the PACES position statement for risk stratification in the young (aged 8–21 years) AWPWS patients[16] recommended an EPS 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. Catheter ablation is a Class IIA (level of evidence B/C) indication for young patients (aged 8–21 years) with AWPWS when high-risk electrophysiological properties of the AP at an electrophysiological study (EPS) are observed, whatever the risk of the procedure have been taken into account. Of note, no clear recommendations were given for infants.

3.2. Risk factors for sudden cardiac death

In absence of any test some clinical variables such as male sex, younger age, familiar history o WPWS, structural heart disease and septal localisation of AP, have been associated with a higher risk of SCD[2-4,14,15]. However all them have a modest power to identify these patients, and therefore, risk stratification has focused on the electrophysiological properties of the AP[17-19]. As mentioned previously, the obligatory condition for VF is an AP with short antegrade refractory period, as reflected by the shortest R-R interval between preexcited (SPERRI) QRS complexes during AF ≤220 ms or the AERP measured during EP study ≤250 ms. Inducibility (the ability to sustain an atrioventricular reciprocating tachycardia or AF) for >1 minute), and the presence of multiple AP are other electrophysiological risk-factors.

The goal of risk-stratification is to identify individuals with these high-risk AP features[17-19]. Non-invasive and invasive tests are used for this purpose, but none alone is the best option for

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infants. Then, the problem in infants focuses on how in the best strategy to asses these EP properties and therefore, to avoid the very low but definite risk of mortality.

3.3. Invasive risk- stratification

EPS: EPS is the examination that offers the best cost/benefit ratio for risk stratification in asymptomatic patients. During the EPS, the inducibility of tachycardias is assessed as well as the conduction characteristics (SPERRI and AERP) of the AP. Long anterograde AERP/SPERRI (>250 ms) of the accessory pathway indicates limited capability of anterograde conduction via accessory pathway and indicates low risk for VF and SCD. The sensitivity and negative predictive value is high and well established (near 100%), but the specificity and positive predictive values of predicting SCD are low[11,15-19]. The very low event rates of VF challenge the accuracy of EPS to predict SCD, so many patients would be unnecessarily treated and exposed to the risks of EP study and RFA if all such asymptomatic patients were treated.

According to recent surveys, most pediatric electrophysiologists (84%) used some form of EP study to risk-stratify asymptomatic children with WPWS, with high rates of successful RFA (>90%)[16-19]. In asymptomatic patients, ablation of the AP decreases the incidence of potential future symptomatic arrhythmias[20]. A randomised clinical trial that evaluated the results of prophylactic catheter ablation in children (aged 5–12 years) with AWPWS showed that the absence of prophylactic ablation was an independent predictor of arrhythmic events[12]. However, EPS is an invasive procedure with a risk of complications (5%-15%), with major ones reported in 0.9%-4.2% (death 0.12%), being higher in infants less than 15kg of weight or 18 months of age[5-8,16-19]. Also, prolonged exposure to radiation and high recurrence rates of arrhythmia after successful procedures (7%-17%) are of particular concern[5-8,16-19]. So, uniform referral of every infant for an EPS or RFA could result in severe and potentially life-threatening complications, that possibly surpass the number of deaths caused by untreated disease, and usually AWPWS infants (less than 15 Kg) are not considered to be an indication for invasive risk stratification or RFA[21]. An EPS to stratify risk and RFA procedure should only be considered in small infants when accepted high-risk factors determined non-invasively are present and whenever the risk of complications, judged mainly by localisation and body surface area of the patient, is low.

Transesophageal EPS (TEPS): TEPS is still considered in current guidelines as a suitable option for evaluating asymptomatic WPWS[16-19]. 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[22-24]. 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 could make considering

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TEPS before EPS and ablation a favorable risk-stratification approach in small infants. However, some limitations must be taken into consideration when using TEPS for risk stratification[22-24]. First, the accuracy of TEPS to locate the AP and to discern multiple APs is low. Second, 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 in risk stratification for WPW pattern using TEPS; this would lead to the determination of risky WPW patients with a higher sensitivity.

Isoproterenol challenge: Observational data have shown that isoproterenol can modify the EP properties of APs and inducibility of supraventricular arrhythmia in patients with ventricular pre-excitation[25,26]. 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[25]. Thus, use of intravenous infusion of isoproterenol during EPS or TEPS in children has been advocated as a possible surrogate of adrenergic stimulation, and it would be used as a pharmacologic stress test in infants who are not able to perform an exercise test looking for an abrupt loss of preexcitation.

3.4. Non-invasive risk-stratification (ECG, Holter Monitoring, Treadmill Testing)

In general, these tests look for evidence of an AP that fails to be able to conduct at rapid rates, either in sinus rhythm or during AF[16-19, 23,24]. Intermittent preexcitation is present when 2 consecutive sinus beats show the presence and absence of preexcitation. This finding indicates a long antegrade refractory period of the accessory pathway resulting in very low risk of sudden cardiac death. The appearance of different preexcited morphologies on an ECG or Holter monitoring is suggestive of multiple AP, which has been identified as a risk factor for ventricular fibrillation and SCD[16-19,23,24]. The best indicator of low risk is the sudden disappearance of pre-excitation during exercise, that indicates a long antegrade effective refractory period of the accessory pathway[16-19, 23,24]. Sympathetic stimulation occurring during exercise will shorten the duration of the AERP of the AP. When the AERP is reached during exercise, as manifested by sudden block in the accessory pathway and normalization of the ECG, it is a good indicator that the patient is not at risk for VF even during sympathetic stimulation. The inability to clearly demonstrate the sudden and absolute loss of manifest preexcitation during exercise warrants invasive EPS.

Although these techniques have been reasonably applied as a part of routine clinical practice for risk assessment in WPW patients, non-invasive risk assessment itself may be problematic in infants for many reasons. First, it was recently observed that intermittent preexcitation in children does not connote a lower risk AP by EP criteria[12,13]. Second, abrupt and complete loss of

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preexcitation during exercise occurred in only 15% of a predominantly pediatric group of patients. Third, in children with subtle preexcitation, an exercise test may be difficult to interpret. Finally, the child must be old enough to comply with the exercise test. Remarkably, they are not as successful as the TEPS or EPS to predict EP AP properties, and up to 40% of patients with intermittent preexcitation on Holter and up to 30% of patients with sudden loss of preexcitation on an exercise test, will have high-risk accessory pathway conduction at TEEPS or EPS[23,24]. Therefore, risk stratification with non-invasive methods is relatively nonspecific, nonsensitive, incomplete and difficult to perform in infants, and better methods are warranted.

3.5. Prophylactic pharmacological approach

Because the well-known SCD risk in young patients with symptomatic WPWS, it makes sense to treat symptomatic patients with antiarrhythmic drugs until ablation of the AP can be performed. Flecainide, an IC class antiarrhythmic drug, has proven to be safe and effective in controlling supraventricular arrhythmias in children, even infants, neonates and fetus[27-29]. 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 paroxysmal AF[27-29]. Thus, its use in patients with WPW can prevent SVT and AF episodes, and, if AF develops, its effects on the properties of the AP can prevent fast ventricular responses and therefore VF. 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[29]. So an echocardiographic study previously to start flecainide is warranted in these patients. In asymptomatic infants, that can develop a potentially life-threatening arrhythmic events during follow-up and are not able to verbalize symptoms, the low accuracy of non-invasive methods, 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 centers, make difficult an appropriate risk-stratification. In this context an alternative and judicious approach could be to initiate prophylactic treatment with flecainide (1-2 mg/Kg/day), to minimise the risk of malignant arrhythmias at least until the age at which the patient can describe well the presence of symptoms and can comply with an exercise-test, or a TEPS or EPS can be performed safely. The choice to observe asymptomatic infants should be preceded by the parents being informed of the small but real risk of life-threatening arrhythmias developing in the absence of treatment.

4. Conclusion

AWPWS in infants is a non-rare and challenging condition that implies a very low but real risk of SCD, which is very difficult to determine accurately with diagnostic methods currently available. The main argument against studying and treating asymptomatic patients has been the

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poor predictive accuracy (low specificity and low positive predictive value) of non-invasive and invasive risk stratified due to the low event rate of SCD.

Non-invasive risk-stratification are of limited value in infants, so it is not recommendable to take decisions based on these tests.

Invasive risk-stratification through EPS is the most accuracy method but it is a high-risk procedure in infants. When the complications of both electrophysiological studies are considered, an accurate risk determination in infants with WPWS pattern by using only TEPS with isoproterenol challenging and higher cut-off values of the refractory period of the AP, is the desired situation. EPS and RFA should follow TEPS for the cases considered with high-risk during TEPS. The cases considered to be without risk by applying TEPS only should undoubtedly be followed-up. It may be favorable to reevaluate these patients with EPS in the presence of clinical necessities.

If it is not possible or safe to perform an invasive risk-stratification, prophylactic treatment with Flecainide could be started to minimise the risk of malignant arrhythmias. The choice to observe without treatment asymptomatic infants should be preceded by the parents being informed of the small but real risk of life-threatening arrhythmias developing in the absence of treatment.

5. Footnotes

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