

The Natural History of Asymptomatic Ventricular Pre-Excitation

A Long-Term Prospective Follow-Up Study of 184 Asymptomatic Children

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- Objectives** The aim of this study was to describe the natural history of asymptomatic ventricular pre-excitation in children and to determine predictors of potentially life-threatening arrhythmic events.
- Background** Sudden death can be the first clinical manifestation in asymptomatic children with ventricular pre-excitation, but reduction of its incidence by prophylactic ablation requires the identification of subjects at high risk.
- Methods** Between 1995 and 2005 we prospectively collected clinical and electrophysiologic data from 184 children (66% male; median age 10 years; range 8 to 12 years) with asymptomatic ventricular pre-excitation on the electrocardiogram. After electrophysiologic testing, subjects were followed as outpatients taking no medications. The primary end point of the study was the occurrence of arrhythmic events. Predictors of potentially life-threatening arrhythmias were analyzed.
- Results** Over a median follow-up of 57 months (min/max 32/90 months) after electrophysiologic testing, 133 children (mean age 10 years; range 8 to 12 years) did not experience arrhythmic events, remaining totally asymptomatic, while 51 children had within 20 months (min/max 8/60 months) a first arrhythmic event, which was potentially life-threatening in 19 of them (mean age 10 years; range 10 to 14 years). Life-threatening tachyarrhythmias resulted in cardiac arrest (3 patients), syncope (3 patients), atypical symptoms (8 patients), or minimal symptoms (5 patients). Univariate analysis identified tachyarrhythmia inducibility ($p < 0.001$), anterograde refractory period of accessory pathways (APERP) ≤ 240 ms ($p < 0.001$), and multiple accessory pathways ($p < 0.001$) as risk factors for potentially life-threatening arrhythmic events. Independent predictors by multivariate analysis were APERP ($p = 0.001$) and multiple accessory pathway ($p = 0.001$).
- Conclusions** These findings are potentially relevant in terms of early identification of high-risk asymptomatic children with ventricular pre-excitation. Subjects with short APERPs and multiple pathways are at higher risk of developing life-threatening arrhythmic events and are the best candidates for prophylactic ablation. (J Am Coll Cardiol 2009;53:275–80) © 2009 by the American College of Cardiology Foundation

It is well known that subjects with ventricular pre-excitation on the electrocardiogram (ECG) are at a small but real risk of sudden death, and catheter ablation of accessory pathways (APs) can definitively eliminate the risk. Based on this concept, current guidelines support liberal indications for catheter ablation in patients with Wolf-Parkinson-White (WPW) syndrome while in the asymptomatic subjects, who also are at real risk of sudden death, this “liberal” indication is not clearly

defined (1). Currently, as ablative techniques have significantly improved with success rates approaching 100% without major complications in many centers worldwide, asymptomatic subjects with the WPW ECG pattern are increasingly being referred for electrophysiologic evaluation, with radiofrequency ablation in those arbitrarily considered to be at high risk (2–6).

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Therefore, in the absence of accurate predictors, identification of the asymptomatic child at risk continues to be a growing clinical challenge considering that sudden cardiac death can be the first presenting symptom of the syndrome (1). We report

Abbreviations and Acronyms

- AF** = atrial fibrillation
- AP** = accessory pathway
- APERP** = anterograde effective refractory period of the accessory pathway
- EPT** = electrophysiologic testing
- VF** = ventricular fibrillation
- WPW** = Wolff-Parkinson-White

here the results of a prospective long-term electrophysiology-based follow-up study in a large series of asymptomatic children incidentally found with asymptomatic ventricular pre-excitation on the ECG.

Methods

Study design. Between January 1995 and September 2005, children with an incidental WPW syndrome on the ECG, who

were considered to be asymptomatic based on an accurate history, were enrolled and followed for at least 24 months after electrophysiologic testing (EPT) in the absence of antiarrhythmic drug therapy. Subjects <5 or >18 years of age or those participating in other investigational protocols were excluded from this study. Physicians from all over Italy were told of this study and asked to look for and refer all children with asymptomatic ventricular pre-excitation to our center for risk stratification. Parents or their legal guardians provided written informed consent for participation after the study design had been approved by the ethics committee.

Electrophysiologic study. All subjects underwent a baseline electrophysiologic study, as described previously (4-6). They also received propofol for anesthesia, and lead shielding was used to minimize radiation exposure to the pelvis. Briefly, atrial and ventricular extrastimulation with progressively shorter coupling intervals was performed at drive-cycle lengths of 400 and 350 ms to induce atrioventricular re-entrant tachycardia until the effective refractory periods of the atrium and ventricle were achieved. Induction of atrial fibrillation (AF) was attempted by ramp pacing starting at a cycle length of 300 ms over a period of 20 s; pacing was stopped once atrial refractoriness had been attained or AF induced. Inducible arrhythmias were defined as sustained if they lasted more than 1 min. Inducibility was also assessed at baseline and/or after isoproterenol infusion (1 to 4 $\mu\text{g}/\text{min}$) and defined as reproducible induction of sustained atrioventricular re-entrant tachycardia and/or AF. An episode of atrioventricular re-entrant tachycardia was terminated by rapid pacing 3 min after its onset. The anterograde effective refractory period of the accessory pathway (APERP) was defined as the longest coupling interval at which anterograde block in the bypass tract was observed. Multiple pathways were diagnosed by change in morphology during induced AF and accurate endocardial mapping by multiple catheters during induced tachyarrhythmias or ventricular pacing.

Definitions. A potentially life-threatening arrhythmia was defined as an episode of documented sustained (>1 min) pre-excited AF with a shortest pre-excited RR interval <250 ms. Cardiac arrest was defined as a condition requir-

ing cardiopulmonary resuscitation and/or electrical defibrillation, which was not associated with an acute myocardial infarction or other transient factors. Inducibility was defined as reproducible induction of sustained tachyarrhythmias.

End point. The primary end point of the study was the occurrence of a first arrhythmic event. Predictors of potentially life-threatening arrhythmias for risk stratification were analyzed.

Follow-up. The follow-up started after EPT and was conducted in an outpatient setting up to September 2007. Follow-up visits were scheduled every 6 months for a clinical evaluation, 12-lead ECG recording, and 24-h Holter monitoring regardless of symptoms. Key elements of the approach to managing these patients, their parents, or family members included careful instruction about the importance of immediately reporting any new symptom, conducting frequent follow-up visits according to the proposed protocol, and obtaining serial Holter monitoring to evaluate arrhythmic event occurrence even in the absence of symptoms. Subjects were asked to report the following symptoms: palpitation, asthenia, nausea, resting or exercise dyspnea, dizziness, chest oppression, blurred vision, syncope, or any transient sensation of feeling unwell. The circumstances of arrhythmic events occurrence were obtained from subjects, the patient's physicians, and/or patient's family.

Statistical analysis. The Mann-Whitney *U* test was used to analyze differences between respective comparison groups for continuous variables. For discrete variables, the chi-square test was performed, unless the Fisher exact test was required for frequency tables when >20% of the expected values were <5. Factors that predicted life-threatening arrhythmic events were identified by univariate and multivariate analyses using the Cox proportional hazards model. To avoid overfitting of the multivariate model, the convention of limiting the number of independent variables entered to approximately 10% of the number of events was followed. In our analysis, independent variables for entry into the model were selected according to their weight on univariate testing (*p* values and shorter 95% confidence intervals); consequently, 2 variables were eligible for this analysis: multiple APs (no/yes = 0/1) and baseline refractory period of the APs ≤ 240 ms (no/yes = 0/1). Two-sided *p* values <0.05 were considered to indicate statistical significance. Statistical tests were performed with SPSS software, version 16.0.2 (SPSS Inc., Chicago, Illinois).

Results

Study population. The baseline characteristics of the overall sample are shown in Table 1. Among 244 screened subjects, 60 declined entry into the study and were lost to follow-up. Accordingly, a total of 184 children, median age at diagnosis 10 years, were included into the study and prospectively followed after EPT. Individuals were referred for WPW electrocardiographic pattern found incidentally

Table 1 Clinical and Electrophysiologic Characteristics of 184 Children With Asymptomatic Ventricular Pre-Excitation

Variable	All Children (n = 184)	Arrhythmic Events			Potentially Life-Threatening Arrhythmias		
		Yes (n = 51)	No (n = 133)	p Value	Yes (n = 19)	No (n = 165)	p Value
Median age, yrs (IQR)	10 (8–12)	12 (10–14)	10 (8–12)	0.001	10 (10–14)	10 (8–12)	0.671
Male	122 (66.3)	39 (76.5)	83 (62.4)	0.071	16 (84.2)	106 (64.2)	0.081
Median anterograde APERP, ms (IQR)	270 (240–290)	250 (230–260)	270 (250–290)	<0.001	230 (220–250)	270 (250–290)	<0.001
Anterograde APERP ≤240 ms	48 (26.1)	25 (49)	23 (17.3)	<0.001	14 (73.7)	34 (20.6)	<0.001
Multiple accessory pathways	32 (17.4)	24 (47.1)	8 (6.0)	<0.001	11 (57.9)	21 (12.7)	<0.001
Arrhythmia induction	77 (41.8)	43 (84.3)	34 (25.6)	<0.001	18 (94.7)	59 (35.8)	<0.001

Values are expressed as n (%) unless otherwise indicated.
APERP = accessory pathway effective refractory period; IQR = interquartile range.

(n = 21) or before starting sport activities at any level as required by Italian laws (n = 163). According to electrocardiographic criteria (7), 35.1% of patients had left-sided, 30.7% right-sided, 23.9% posteroseptal, and 1.5% antero-septal APs. Associated diseases including mitral valve prolapse and hypertrophic cardiomyopathy were found in 2 and 1 subjects, respectively. A predominance of male subjects was observed (66%).

Follow-up after EPT. The baseline clinical and electrophysiologic characteristics of the children who did or did not experience arrhythmic events are listed in Table 1. No patient had disappearance of the delta wave during the follow-up on Holter monitoring. The median duration of follow-up after EPT was 57 months (min/max 32/90 months) for the patients who did not experience arrhythmic events, 20 months (min/max 8/60 months) for the patients who had arrhythmic events, and 19 months (min/max 9/53 months) for those in whom the arrhythmic event was potentially life-threatening (19 children). The first arrhythmic event was documented as sustained atrioventricular re-entrant tachycardia in 29 patients (15.8%) and AF in 22 patients (12%) (Fig. 1). Compared with children who had no events, those who did had a different electrophysiologic profile characterized by shorter anterograde refractory pe-

riod of APs and the presence of multiple APs and inducible tachyarrhythmias found more frequently (Table 1). In addition, subjects who experienced arrhythmic events had baseline intact retrograde conduction over APs while 41 of 133 (30.8%) of those who did not experience events showed no retrograde conduction over APs at baseline.

Potentially life-threatening arrhythmias. Potentially life-threatening arrhythmias were due to a pre-excited AF with a mean ventricular rate of 280 ± 15 beats/min and occurred in 19 children at rest (11 nonathletic subjects and 8 participating in moderate sport activities). They had a median age of 10 years, most were male, and all but 1 had inducible tachyarrhythmias with shorter APERP (Table 1). Tachyarrhythmias led to ventricular fibrillation (VF) with resuscitated cardiac arrest without neurologic sequelae (3 subjects), syncope (3 patients), or producing atypical symptoms (8 patients) or minimal symptoms on occasional Holter monitoring, which were retrospectively referred to as a sensation of just feeling unwell (5 patients). Atypical symptoms were characterized by nausea (5 children), sudden tiredness with anxiety (1 child), abdominal pain with swelling (1 child), and lack of concentration and irritability while playing (1 boy), all of which alarmed parents to seek prompt medical attention that allowed tachyarrhythmia

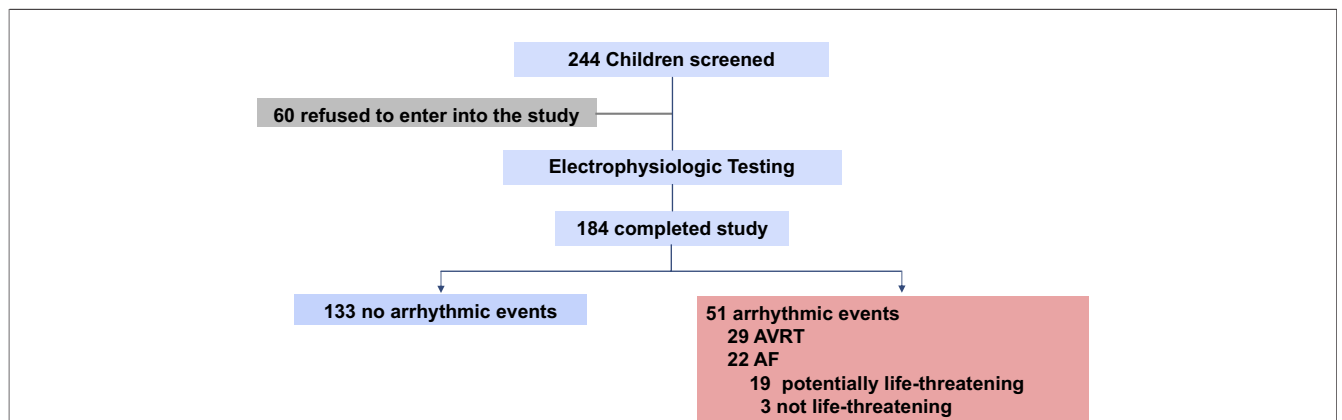


Figure 1 Flow Chart of the Study Population, Including Study Protocol and Outcome

AF = atrial fibrillation; AVRT = atrioventricular re-entrant tachycardia.

documentation as a cause of the reported symptoms. Before cardiac arrest, all children had documented pre-excited AF with rapid ventricular response, which precipitated into VF just before (1 patient) or at hospital admission (2 patients). All of them were not participating in any sports activity at baseline; all were male; and all had short anterograde refractory periods of APs, inducible tachyarrhythmias, and multiple pathways. The characteristics of these 3 patients are summarized in Table 2. Children who became symptomatic and those who had documented potentially life-threatening tachyarrhythmias or cardiac arrest were successfully ablated.

Predictors of potentially life-threatening arrhythmias. In the univariate analysis, tachyarrhythmia inducibility, APERP, and multiple APs at baseline were significantly associated with development of life-threatening arrhythmic events (Table 3). Multivariate analysis confirmed APERP and multiple APs as independent predictors of life-threatening arrhythmic events (Table 4).

Discussion

Based on the vast clinical experience accumulated over the last 20 years, catheter ablation is considered first-line therapy for symptomatic WPW syndrome, while its use in asymptomatic ventricular pre-excitation remains controversial (1). Indeed, catheter ablation is still limited to asymptomatic subjects with ventricular pre-excitation who are athletes or who are considered in higher-risk occupations (1). Recently, we suggested extending prophylactic ablation to asymptomatic patients arbitrarily considered at high risk based on inducibility alone (4–6). The results of the present prospective follow-up study for the first time demonstrate that there are many independent risk factors of life-threatening arrhythmic events, and it is useful to limit prophylactic ablation to those at risk. Among 244 screened children, 184 subjects with a median age of 10 years were enrolled for this prospective electrophysiologic-based study.

Variable	Patient #1	Patient #2	Patient #3
Age, yrs	10	8	12
Sex	Male	Male	Male
Structural heart disease	No	No	No
APERP, ms	210	220	210
Multiple APs	Yes	Yes	Yes
Location of multiple APs	LFW + PS	LFW + PS	LFW + PS
Arrhythmia induction	Yes	Yes	Yes
AVRT triggering AF	Yes	Yes	Yes
Cycle length of AVRT (ms)	220	230	220
Shortest pre-excited RR interval during sustained AF (ms)	200	190	200

AF = atrial fibrillation; AP = accessory pathway; APERP = accessory pathway effective refractory period; AVRT = atrioventricular re-entrant tachycardia; LFW = left free wall accessory pathway; PS = posteroseptal accessory pathway.

Variables	Coefficient	HR (95% CI)	p Value
Age	0.050	1.052 (0.911–1.214)	0.491
Sex	1.091	2.978 (0.867–10.225)	0.083
Multiple APs	2.372	10.720 (4.247–27.061)	<0.001
Anterograde APERP ≤240 ms	2.406	11.091 (3.968–30.999)	<0.001
Inducibility	3.629	37.676 (4.999–283.965)	<0.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

Children were totally asymptomatic at the time of diagnosis, which was made incidentally either at a routine medical examination or on a screening ECG before admission to sports in the majority of cases. Subjects underwent a baseline electrophysiologic study and then were followed as outpatients in the absence of antiarrhythmic therapy. During the follow-up, no child lost pre-excitation, more than 70% had no arrhythmic events, and about 30% developed a first arrhythmic event, which was potentially life-threatening in <10%. Compared with children who experienced potentially life-threatening tachyarrhythmias, those who did not showed a characteristic electrophysiologic profile (i.e., lower tachyarrhythmia inducibility, longer anterograde refractory period of APs, and many of them had no baseline retrograde AP conduction or multiple APs).

Potentially life-threatening tachyarrhythmias as first clinical manifestation of the syndrome. Potentially life-threatening tachyarrhythmias occurred at rest in 19 of 184 children and frequently (13 of 19 children) were associated with atypical or minimal symptoms, like the sensation of feeling unwell, which in most cases was occasionally detected. After their recognition, catheter ablation was performed successfully in all cases. These findings indicate that the natural history of asymptomatic children with ventricular pre-excitation is not as benign as previously supposed, since onset of potentially life-threatening tachyarrhythmias can be unsuspected in many cases. Indeed, frequently symptoms may be less specific or poorly articulated and, if unrecognized, can lead to rapid AF and VF as first clinical manifestation of the syndrome as it was for 3 patients in this series. Thus, it is imperative to identify children at risk as soon as possible since they have a longer time frame of exposure to risk of sudden death.

Predictors of potentially life-threatening tachyarrhythmias and risk stratification. Risk assessment in asymptomatic children with ventricular pre-excitation has not

Variables	Coefficient	HR (95% CI)	p Value
Multiple AP	1.638	5.143 (1.905–13.887)	0.001
Anterograde APERP ≤240 ms	1.847	6.342 (2.092–19.222)	0.001

Abbreviations as in Tables 2 and 3.

been defined and remains a considerable clinical challenge (8–24). Information on clinical and electrophysiologic parameters assessing the risk of VF has largely been gathered from case series of adult patients resuscitated from sudden cardiac death. Unfortunately, there are very limited data about children who have experienced life-threatening arrhythmias or aborted sudden death (16,21–23). In the present study, univariate analysis showed that tachyarrhythmia inducibility, APERP, and multiple pathways were predictors of life-threatening arrhythmic events. In multivariate analysis, which included only 2 of the 3 predictors because of the low life-threatening event rate, APERP and multiple APs were still independent predictors, confirming and expanding the classical concept that in adults the risk includes the duration of the refractory period and/or presence of multiple APs (8,9,25,26). Although there is no difference in atrioventricular re-entrant tachycardia inducibility on comparing VF patients to symptomatic WPW patients without VF, in this study tachyarrhythmia inducibility was a strong predictor. On the basis of data acquired from adults, virtually all patients resuscitated from VF have inducible AF with the shortest RR intervals <220 ms (26), and many of them have multiple pathways (8,25). In the present study, subjects who developed potentially life-threatening tachyarrhythmias had a baseline electrophysiologic profile characteristic of adult patients who have survived sudden death (8,25,26). Of note, potentially life-threatening tachyarrhythmias occurred about 2 years after baseline EPT suggesting that tachyarrhythmia inducibility, short anterograde refractory period of APs, and multiple pathways are a marker of imminent tachyarrhythmia development. Therefore, asymptomatic children with this characteristic electrophysiologic profile should be considered the best candidates for prophylactic ablation.

Comparison with previous studies. The present study represents one of the largest electrophysiologic-based follow-up studies on asymptomatic children with ventricular pre-excitation. The documentation of potentially life-threatening tachyarrhythmias by an intensive monitoring, while confirming alarming reports in very young previously asymptomatic children (3–6,8–20), indicates that the incidence of life-threatening tachyarrhythmias is higher in children than in adults (27–38), which underestimated risk in the pediatric age population conferring a “benign” prognosis to the asymptomatic population as a whole. On the other hand, the true incidence of sudden death and/or life-threatening arrhythmic events in children with WPW syndrome has not been well defined as many natural history studies have drawn data from the adult population, who have by definition survived to adulthood and may, therefore, be at lower risk. A multicenter study indicated that no prior arrhythmias had been documented in 48% of the children who had WPW syndrome and a cardiac arrest (12). The general rule that the larger the study population, the more intensive the monitoring, the more clinical events are found is true for tachyarrhythmias, including silent or minimally

symptomatic tachyarrhythmias, in the same way it is for other clinical entities. In the present study, potentially life-threatening tachyarrhythmias produced atypical or minimal symptoms in the majority of children, which suggests that, in the absence of an intensive monitoring, their presence could have been missed in many cases. These findings are in agreement with a recent retrospective study in which it has been reported that many resuscitated adult patients with WPW syndrome, before cardiac arrest, were never sufficiently alarmed by symptoms to seek medical attention (39).

Clinical implications. Our study for the first time demonstrates that EPT can identify asymptomatic subjects at risk of developing potentially life-threatening tachyarrhythmias. Predictors of such events are crucial to select high-risk children for prophylactic ablation, which offers a lifetime benefit against a minimal acute or no risk of the procedure (5,6).

Study limitations. Children who declined to enter into the study were lost to follow-up, which might result in a potential selection bias. To avoid overfitting due to the low event rate of life-threatening arrhythmic events, only 2 independent predictors were considered as the maximum in the multivariate analysis.

Conclusions

This study reports new information on the natural history of children with asymptomatic ventricular pre-excitation and on predictors of risk of potentially life-threatening arrhythmias. Anterograde refractory period of APs and multiple APs are independent predictors of future life-threatening arrhythmic events. These parameters can be used to select children for prophylactic catheter ablation, which can offer lifetime benefits that overcome the minimal risk of the procedure.

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Key Words: Wolff-Parkinson-White syndrome ■ sudden death ■ syncope ■ catheter ablation.