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# 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) $\leq$240 ms ($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 Wolff-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

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**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 $\mu$g/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 requiring 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

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