Asymptomatic ventricular preexcitation: A long-term prospective follow-up study of 293 adult patients

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V. Santinelli: Natural history of asymptomatic ventricular preexcitation

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Abstract

Background. Sudden cardiac death can be the first clinical presentation of asymptomatic ventricular preexcitation.

Methods and Results. From 1995 to 2005 we prospectively collected clinical and electrophysiologic data among 293 adults with asymptomatic ventricular preexcitation (61.4% males; median age, 36 years; interquartile range (IQR, 28-47.5). After electrophysiologic testing, patients were prospectively followed taking no drugs. Primary end point of the study was the occurrence of a first arrhythmic event. Predictors of arrhythmic events were analyzed by univariate and multivariate Cox models. Over a median follow-up of 67 months (min-max, 8-90) after electrophysiologic testing, 262 patients (median age, 37 years; IQR, 30-48) did not experience arrhythmic events, remaining totally asymptomatic, while 31 patients (median age, 25 years; IQR, 22-29; median follow-up 27 months, min-max 8-55) had a first arrhythmic event, which was potentially life-threatening in 17 of them (median age, 24 years; IQR, 20-28.5; median follow-up 25 months, min-max 9-55). Potentially life-threatening tachyarrhythmias resulted in resuscitated cardiac arrest (1 patient), pre-syncope (7 patients) syncope (4 patients), or dizziness (5 patients). In multivariate analysis age (p=0.004), inducibility (p=0.001) and anterograde effective refractory period of the accessory pathway ≤250 ms (p=0.001) predicted potentially life-threatening arrhythmias.

Conclusions. These results indicate that prognosis of adults who present with asymptomatic ventricular preexcitation is good and the risk of a significant event is small. Short anterograde effective refractory period of the accessory pathway and inducibility at baseline are independent predictors of potentially life-threatening arrhythmic events and the risk decreases with increasing age.

Key words: Wolff-Parkinson-White; sudden death; syncope; catheter ablation.
The natural history of asymptomatic ventricular preexcitation in the pediatric and adult population does not necessarily imply parity of disease in terms of pathophysiology, mechanisms, outcomes, predictors, and management. Children have a different electrophysiologic function of both the accessory pathway and the AV node as well as a considerably higher incidence of multiple pathways than adults and this can influence outcome and predictors (1). Recently, we have demonstrated that in children aged between 5 and 18 years, incidentally found with asymptomatic ventricular preexcitation, the outcome is not as benign as previously supposed (2). Multiple accessory pathways and short refractory periods were identified as independent predictors of potentially life-threatening arrhythmic events (2). We report here additional data on outcome and predictors of arrhythmic events in asymptomatic patients older than 18 years to extend our knowledge on the natural history of asymptomatic ventricular preexcitation beyond childhood.

Methods

Study design
Between July 1995 and December 2005, subjects older than 18 years with an incidental WPW syndrome on the ECG, who were considered to be asymptomatic based on an accurate history, were enrolled and followed after electrophysiologic testing (EPT) in the absence of antiarrhythmic drug therapy. Patients participating to other investigational protocols were excluded from the study. Patients provided written informed consent for participation after the study design had been approved by the ethics committee.

Electrophysiologic study
All patients underwent a baseline EPT, as described previously (2-5). Briefly, atrial and ventricular extrastimulation with progressively shorter coupling intervals was performed at drive-cycle lengths of 400 and 350 msec to induce atrio-ventricular reentrant tachycardia (AVRT) 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 msec over a period of 20 seconds;
pacing was stopped once atrial refractoriness had been attained or AF induced. Inducible arrhythmias were defined as sustained if they lasted more than one minute. Inducibility was also assessed at baseline and/or after isoproterenol infusion (1 to 4 µgr/min) and defined as reproducible induction of sustained AVRT and/or AF. An episode of AVRT was terminated by rapid pacing three minutes 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 minute) preexcited AF with a shortest preexcited 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 AVRT and/or AF.

**End point**

The primary end point of the study was the occurrence of a first arrhythmic event. Predictors of arrhythmic events and potentially life-threatening arrhythmias were analyzed.

**Follow-up**

The follow-up began after EPT and was conducted in an outpatient setting up to December 2007. Follow-up visits were scheduled every 6 months for a clinical evaluation, 12-lead ECG recording, and 24-hour Holter monitoring regardless of symptoms. Patients were instructed to immediately report any new symptom, conduct frequent follow-up visits with serial 24-h Holter recording to evaluate potential arrhythmic events 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 accurately obtained.

**Statistical Analysis**

For continuous variables the Mann-Whitney U test was used to analyze differences between patients with or without arrhythmic or potentially life-threatening events. 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 time to total arrhythmic events and potentially life-threatening events were identified by univariate and multivariate analyses using the Cox proportional hazards models. In this analysis, independent variables for entry into the model were selected according to their weight on univariate testing (p<0.001): age, refractory period of the accessory pathways ≤ 250 ms (no/yes= 0/1), and tachyarrhythmia inducibility (no/yes= 0/1). Two-sided p values of less than 0.05 were considered to indicate statistical significance. Statistical tests were performed with SPSS software, version 17.0.0.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Study population**

The baseline characteristics of the study population are shown in Table 1. Among 343 screened subjects, 50 declined entry into the study and were lost to follow-up. Accordingly, a total of 293 patients, median age at diagnosis 36 years (IQR, 28-47.5), were included into the study and prospectively followed after baseline EPT (Figure 1). Patients were referred for WPW electrocardiographic pattern found incidentally (n=180) or before starting sport activities (n=113). According to electrocardiographic criteria (6), 42 % of patients had left-sided, 30.4 % right-sided, 26.6 % postero-septal, and 1 % antero-septal accessory pathways. Associated diseases were found in 34 patients (11.6%) and there was a predominance of male subjects (61.4%).
Follow-up after electrophysiologic testing

The baseline clinical and electrophysiologic characteristics of the patients who did or did not experience arrhythmic events or potentially life-threatening arrhythmic events are listed in Table 1. Seventy-nine patients (27%, mean age 48±5 years) had spontaneous disappearance of the delta wave during the follow-up. The median duration of follow-up after EPT for the entire study population was 67 months (min-max, 8-90). Among the 262 patients who did not experience arrhythmic events the median follow-up duration was 69 months (min-max, 39-90). Total arrhythmic events occurred within a median follow-up of 27 months (min-max, 8-55) and potentially life-threatening during a median follow-up of 25 months (min-max, 9-55). The first arrhythmic event was documented as sustained atrio-ventricular reentrant tachycardia (18 patients), which degenerated into AF in 4 patients and AF (13 patients) (Figure 1). As compared with patients who had no events, those who did were younger, had shorter anterograde refractory period of accessory pathways, and more frequently were found multiple pathways (Table 1). In addition, among patients who developed potentially life-threatening events, EPT showed that AF was triggered by AVRT in 12 patients and by burst pacing in 2 patients with a shortest preexcited RR interval of 227.5±8.7 ms (range, 215-240). By contrast, among patients who did not experience life-threatening events, AF was triggered by AVRT in 2 patients and by burst pacing in 5 patients with a shortest preexcited RR intervals of 234.2±9.7 ms (range, 220-250). There was no difference in shortest preexcited RR intervals between patients with and without potentially life-threatening events (p=0.899). Isoproterenol facilitated tachyarrhythmias induction in 2 patients with potentially life-threatening events and in 6 without life-threatening events. Subjects who experienced arrhythmic events had baseline intact retrograde conduction over accessory pathways.

Potentially life-threatening arrhythmias

Potentially life-threatening arrhythmias were due to a preexcited AF with a mean ventricular rate of 250±18 bpm and occurred at rest. Patients with potentially life-threatening arrhythmias were young adults (median age, 24 years), the majority of them were male, and most had inducible
tachyarrhythmias with shorter APERP (Table 1). Inducible tachyarrhythmias were characterized by AVRT triggering AF in 12/14 patients without isoproterenol and AF in the remaining 2 patients after isoproterenol. No patient had inducible AVRT and ERP of accessory pathway > 250 ms. Tachyarrhythmias led to ventricular fibrillation with a resuscitated cardiac arrest (1 subject), pre-syncope (7 patients), syncope (4 patients) or dizziness (5 patients). Transition from rapid preexcited AF to cardiac arrest was documented at the emergency room and was not preceded by symptoms. In most patients life-threatening arrhythmias were recorded during presentation to emergency room (13 patients) or incidentally during routine Holter (6 patients). All patients were successfully ablated.

Predictors of total arrhythmic events and life-threatening tachyarrhythmias

By univariate Cox analysis predictors of arrhythmic events or potentially life-threatening events were age, anterograde refractory period of accessory pathways ≤250 ms, and inducibility (Table 2). Moreover, multiple pathways were significantly associated with shorter time to event only for total arrhythmic events. Multivariate Cox analysis demonstrated that younger age, anterograde refractory period of accessory pathways ≤250 ms and inducibility were predictors of total arrhythmic events and potentially life-threatening events (Table 3). Sensitivity, specificity, positive predictive values of risk factors, alone and in combination, are reported in Table 4. A high predictive positive value (80%) is obtained when all 3 factors are combined (Table 4).

Discussion

Main findings

The results of the present long-term follow-up study demonstrate that among patients in whom ventricular preexcitation has been found incidentally at age of >18 years only a minority experienced arrhythmic events and almost all remained asymptomatic over a median follow-up of 67 months. These data suggest that in adult patients who present with asymptomatic ventricular preexcitation the prognosis is good and the risk of a significant event is small decreasing with
increasing age. Younger age at diagnosis, tachyarrhythmia inducibility and short refractory period of accessory pathways are independent risk factors for potentially life-threatening arrhythmic events and their combination results in a high positive predictive value.

**The natural history of asymptomatic ventricular preexcitation from childhood to adulthood**

Ventricular preexcitation has been noted in subjects of all ages and its clinical presentation and natural history is highly variable (2-5, 7-18). The WPW ECG pattern may be incidentally found from childhood to adulthood suggesting that initially asymptomatic subjects may have different ages at diagnosis, which may result in different prognosis and predictors. Prior electrophysiology or population-based studies (19-29) have reported that asymptomatic population with ventricular preexcitation, as a whole, has a benign prognosis although it is well known that sudden death can be the first clinical manifestation of the syndrome in a previously asymptomatic subjects (2-5, 8-11). Although the association of sudden death in the WPW syndrome with AF with a rapid response and short ERP has been reported, no clinical or electrophysiologic variables have been demonstrated by univariate or multivariate analysis to predict which patients are at greater risk from within the larger pool of asymptomatic people with WPW pattern (19-29). In the present long-term electrophysiology-based study, a total of 293 adult patients (61.4% were male) with a median age of 36 years underwent a baseline electrophysiologic study. Subjects 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 competitive sports. During a median follow-up of 67 months after electrophysiologic testing, about 90% of them had no arrhythmic events remaining totally asymptomatic and 30% of them had delta wave disappearance. Only a minority of young adult patients (10%; median age 25 years) developed a first arrhythmic event, which was potentially life-threatening in approximately 5% (median age, 24 years), but no one died. Although this relatively good prognosis suggests that an aggressive population based ablative strategy may not be justified in the adult population who present with asymptomatic ventricular preexcitation, a close follow-up with prophylactic ablation in selected young subjects at risk may be considered as an acceptable
option. Compared to patients who experienced potentially life-threatening events, those who did not showed a characteristic electrophysiological profile (i.e., older age, lower tachyarrhythmia inducibility, longer anterograde refractory period of accessory pathways and many of them had no baseline retrograde AP conduction or multiple accessory pathways). These data indicate that, unlike children (2), only a minority of adults has multiple bypass tracts (4.4%), which suggests that from childhood to adulthood multiple pathways can disappear in many subjects decreasing the risk of life-threatening events or alternatively, that children with multiple pathways are more likely to become symptomatic and therefore not present as an asymptomatic adult. Disappearance of ventricular preexcitation on the ECG occurred in as many as 30% of older subjects (>45 years), perhaps further decreasing the risk of life threatening events over years. These findings suggest that increasing age may be associated with changes of both number and electrophysiological proprieties of accessory pathways which ultimately may expose adult older patients to less risk of life-threatening arrhythmias and sudden death. Understanding pathophysiology, mechanisms, and clinical course over years can better clarify the natural history of asymptomatic ventricular preexcitation from childhood to adulthood in order to find the most acceptable therapeutic option.

Predictors of potentially life-threatening tachyarrhythmias

Predicting clinical outcome is one of the major issues in patients incidentally found with asymptomatic ventricular preexcitation. At present, risk assessment in such population has not been well defined remaining a considerable clinical challenge (7). In the present study, the event rate of potentially life-threatening events was low. Univariate and multivariate analysis demonstrated that younger age at diagnosis, tachyarrhythmia inducibility and short refractory period of accessory pathways are independent risk factors for arrhythmic events as well as for potentially life-threatening arrhythmic events. The odds ratio of 0.851 indicates the protective effect per year of increase in the age at diagnosis. These findings demonstrate that the greater risk of potentially lethal events is limited to early adulthood decreasing with increasing age. Inducibility and short refractory period of accessory pathways were important predictors which confirms previous studies (2-5).
Finally, potentially life-threatening tachyarrhythmias occurred about 2 years after baseline EPT, which suggests that in young adults tachyarrhythmia inducibility is a marker of future serious arrhythmia occurrence.

**Study limitations**

Patients who declined to enter into the study were lost to follow-up, which might result in a potential selection bias. A potential overfitting due to the low number of life-threatening arrhythmic events cannot be completely excluded.

**Conclusions**

The results of the present study increase our knowledge on the natural history of asymptomatic ventricular preexcitation and verify that the risk of potentially life-threatening tachyarrhythmias in adults incidentally found with asymptomatic ventricular preexcitation on the ECG is indeed small and decreases with increasing age. Young age at diagnosis, tachyarrhythmia inducibility and short refractory period of accessory pathways at baseline are independent predictors of potentially life-threatening arrhythmic events. In young adults at risk catheter ablation can offer lifetime benefits that overcome the minimal risk of the procedure.

**Sources of Funding**

There are no sources of funding for this study.

**Disclosures**

None.
References


Legend to Figure

**Figure 1.** Patients enrolment and outcomes.
Table 1. Characteristics of 293 asymptomatic adult patients with ventricular preexcitation with and without arrhythmic events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 293)</th>
<th>Arrhythmic events</th>
<th>p-value</th>
<th>Potentially life-threatening arrhythmias</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n=31)</td>
<td>No (n=262)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (IQR), years</td>
<td>36 (28-47.5)</td>
<td>25 (22-29)</td>
<td>37 (30-48)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>180 (61.4)</td>
<td>21 (67.7)</td>
<td>159 (60.7)</td>
<td>0.445</td>
<td></td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms, n (%)</td>
<td>39 (13.3)</td>
<td>22 (71)</td>
<td>17 (6.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multiple accessory pathways (%)</td>
<td>13 (4.4)</td>
<td>4 (12.9)</td>
<td>9 (3.4)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Inducibility (%)</td>
<td>47 (16.0)</td>
<td>22 (71.0)</td>
<td>25 (9.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

APERP = Accessory Pathway Effective Refractory Period.
Table 2. Univariate Cox’s regression analysis in 293 asymptomatic adults with ventricular preexcitation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>HR (95 % CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total arrhythmic events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>-0.137</td>
<td>0.872 (0.825-0.921)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.254</td>
<td>1.290 (0.607-2.739)</td>
<td>0.508</td>
</tr>
<tr>
<td>Multiple AP</td>
<td>1.358</td>
<td>3.887 (1.360-11.112)</td>
<td>0.011</td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms</td>
<td>3.061</td>
<td>21.349 (9.800-46.505)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inducibility</td>
<td>2.838</td>
<td>17.079 (7.844-37.188)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Potentially life-threatening arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>-0.190</td>
<td>0.827 (0.753-0.907)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.110</td>
<td>1.117 (0.413-3.020)</td>
<td>0.828</td>
</tr>
<tr>
<td>Multiple AP</td>
<td>1.240</td>
<td>3.457 (0.790-15.121)</td>
<td>0.100</td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms</td>
<td>4.124</td>
<td>61.783 (14.083-271.046)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inducibility</td>
<td>3.437</td>
<td>31.084 (8.901-108.548)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The Hazard Ratio for age is per 1 year increase.

AP = Accessory Pathway; APERP = Accessory Pathway Effective Refractory Period; B = Coefficient; CI = Confidence Interval; HR = Hazard Ratio.
Table 3. Multivariate Cox analysis in 293 asymptomatic adults with ventricular preexcitation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total arrhythmic events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>-0.112</td>
<td>0.894 (0.838-0.953)</td>
<td>0.001</td>
</tr>
<tr>
<td>Inducibility</td>
<td>1.902</td>
<td>6.700 (2.893-15.515)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms</td>
<td>1.860</td>
<td>6.422 (2.771-14.884)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Potentially life-threatening arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>-0.161</td>
<td>0.851 (0.762-0.951)</td>
<td>0.004</td>
</tr>
<tr>
<td>Inducibility</td>
<td>2.180</td>
<td>8.850 (2.311-33.895)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms</td>
<td>2.743</td>
<td>15.529 (3.290-73.287)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* The Hazard Ratio for age is per 1 year increase.

Abbreviations as in Table 2.
Table 4. Diagnostic accuracy of the risk factors for potentially life-threatening arrhythmic events, alone and in combination, in asymptomatic adults with ventricular preexcitation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>88.24% (63.56% to 98.54%)</td>
<td>74.28% (68.69% to 79.33%)</td>
<td>17.44% (10.1% to 27.13%)</td>
</tr>
<tr>
<td>Inducibility</td>
<td>82.35% (56.57% to 96.2%)</td>
<td>88.04% (83.62% to 91.63%)</td>
<td>29.79% (17.34% to 44.89%)</td>
</tr>
<tr>
<td>Anterograde APERP ≤ 250 ms</td>
<td>88.24% (63.56% to 98.54%)</td>
<td>91.3% (87.34% to 94.35%)</td>
<td>38.46% (23.36% to 55.38%)</td>
</tr>
<tr>
<td>Age + Inducibility + Anterograde APERP</td>
<td>70.59% (44.04% to 89.69%)</td>
<td>98.91% (96.86% to 99.78%)</td>
<td>80% (51.91% to 95.67%)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval; PPV = positive predictive value; APERP = Accessory Pathway Effective Refractory Period.

* To categorize this variable, ROC curve defining an optimal age cut-off value to distinguish patients with potentially life-threatening arrhythmic events from those without these events was performed. The cut-off values obtained by ROC curve analysis was 29 years of age.
343 adult subjects screened

50 refused to enter into the study

Electrophysiologic Testing

293 completed study

262 no arrhythmic events

31 total arrhythmic events
14 AVRT
17 potentially life-threatening
   4 AVRT + AF
13 AF
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