Invasive electrophysiological evaluation and ablation in patients with asymptomatic ventricular pre-excitation persistent at exercise stress test

Roberto De Ponti*, Raffaella Marazzi, Lorenzo A. Doni, Valentina Cremona, Jacopo Marazzato, and Jorge A. Salerno-Uriarte

Department of Heart and Vessels, Ospedale di Circolo e Fondazione Macchi, University of Insubria, Viale Barri, 57, Varese IT-21100, Italy

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Aims
In patients with asymptomatic ventricular pre-excitation (VPE) persistent at exercise stress test, this study evaluates the proportion of cases with adverse conduction properties of the atrioventricular accessory pathway (AP) at invasive electrophysiological study and the long-term follow-up after they received treatment according to pre-determined criteria.

Methods and results
Over 10 years, asymptomatic patients with VPE persistent at exercise stress test referred for invasive electrophysiological evaluation including isoproterenol (IPN) infusion were included. Ablation was planned if they had at least one of the following criteria: (i) shortest pre-excited R–R interval (SPERRI) ≤ 250 ms and/or (ii) inducible atrioventricular re-entrant tachycardia (AVRT). Cryoablation was electively used in para-hisian and mid-septal APs. Patients not eligible for ablation received no therapy. Sixty-three patients (45 males; mean age 26 ± 14 years) underwent electrophysiological evaluation: 7 had fasciculo-ventricular fibres and were excluded, whereas 56 had 58 APs. Thirty-one patients (55%) were eligible and underwent successful ablation: 87% had at least the SPERRI ≤ 250 ms and 61% had at least inducible AVRT. In 15 cases (48%) the ablation criteria were met only during IPN infusion. During follow-up (73 ± 33 months), one patient was successfully retreated for resumption of VPE in the ablation group, whereas no event was observed in the group of patients who received no treatment.

Conclusion
In this subset of patients with asymptomatic VPE, invasive electrophysiological evaluation shows fast antegrade conduction over the AP and/or inducible AVRT in about half of the cases. Patients who received no therapy because of a benign electrophysiological profile had an event-free follow-up.

Keywords
Asymptomatic Wolff–Parkinson–White electrocardiographic pattern • Electrophysiological study • Isoproterenol • Catheter ablation

Introduction
In patients with ventricular pre-excitation (VPE), lack of symptoms does not necessarily identify subjects with no arrhythmic events during follow-up.1 In symptomatic and asymptomatic children with VPE, the electrophysiological parameters related to the risk of sudden death are comparable.2 In the Wolff–Parkinson–White syndrome, sudden death is dramatic, but rare.3 More frequently, these patients suffer from atrioventricular re-entrant tachycardia (AVRT) and/or non-fatal pre-excited atrial fibrillation, which may cause disabling symptoms and affect their quality of life. In addition, in some countries, asymptomatic VPE excludes from competitive sports, if not adequately risk stratified and treated.4 Similarly, asymptomatic individuals with VPE are, in general, not eligible for jobs with an increased occupational risk.

Although ablation is effective and safe,5 the widespread use of this therapy as a prophylactic treatment in an unselected population of asymptomatic patients with VPE seems unjustified, both on a risk/benefit6 and cost/effectiveness7 ratio. On the other hand, non-invasive and invasive methods to risk stratify this population8,9 are used differently among European centres.10

Recently, ablation in asymptomatic subjects with VPE, especially in children, has been widely debated11,12. Due to the lack of definitive evidence on the best strategy to manage these cases, the PACES/HRS...
What’s new
- In a population of patients with a wide range of age and asymptomatic ventricular pre-excitation persistent at exercise stress test, invasive electrophysiological evaluation including isoproterenol infusion shows adverse conduction properties of the atrioventricular accessory pathway in 55.4% of the cases.
- The remaining patients (44.6%), who receive no treatment because of a benign electrophysiological profile, have no event during a long-term follow-up.

expert consensus statement proposed a management algorithm. According to this algorithm, the patients with persistent or uncertain loss of VPE at exercise stress test, in whom the risk of arrhythmias remains undefined, may undergo electrophysiological evaluation and catheter ablation can be proposed if the shortest pre-excited R–R interval (SPERR) is ≤ 250 ms (class IIA indication) or a supraventricular tachycardia is induced (class IIb indication). Similar to what is recommended in the European guidelines, the Italian cardiological guidelines for sports eligibility state that athletes with asymptomatic VPE are disqualified from sports practice if at electrophysiological testing fast antegrade conduction over the atrioventricular accessory pathway (AP) is observed and AVRT induced, unless catheter ablation results in permanent cure; in borderline cases, electrophysiological study should be repeated periodically. In our country, this results in a specific referral of competitive athletes and even of individuals who practice non-competitive physical activity for electrophysiological evaluation, after an exercise stress test has failed to show loss of VPE.

The purpose of this study is to assess in patients with asymptomatic VPE persistent at exercise stress test and consecutively referred for electrophysiological evaluation: (i) the proportion of patients with fast antegrade conduction over the atrioventricular AP and/or inducible AVRT at invasive electrophysiology study, who, according to the guidelines, can be considered for ablation and (ii) the rate of events during follow-up in the subgroup of patients with a benign electrophysiological profile who received no therapy.

Methods

Population selection
Patients with asymptomatic and stable VPE were included in this retrospective cohort study and underwent invasive electrophysiological evaluation between 1 January 2003 and 31 May 2012 if: (i) VPE persisted or no sudden loss of VPE was observed during maximal exercise stress test; (ii) their age was ≥ 10 years; (iii) arrhythmia-related symptoms alternative to palpitations, such as dizziness, syncope, or dyspnoea, could be clearly excluded; (iv) no asymptomatic arrhythmia was previously documented at 12-lead ECG or Holter monitoring; and (v) after counselling at our centre, the patients or their parents/legal guardians gave informed consent to undergo invasive electrophysiological testing and catheter ablation according to the protocol shown in Figure 1. Transthoracic echocardiogram was performed to assess or exclude structural heart disease. Before electrophysiological evaluation, in cases with antero-septal VPE, adenosine test was performed to diagnose fasciculo-ventricular fibres and exclude these subjects from invasive evaluation. Nevertheless, electrophysiology testing was performed if the adenosine test was contraindicated or not diagnostic. This study conformed to the Declaration of Helsinki on human research and was approved by the Institutional Review Board at our University.

Electrophysiological study
No patient had previously taken antiarrhythmic drug therapy. The procedure was carried out in the fasting non-sedated state by placing multipolar catheters in the high right atrium, coronary sinus, His bundle area, and right ventricular apex. Antegrade and retrograde conduction properties of the AP and induction of AVRT were tested at baseline and during continuous isoproterenol (IPN) infusion (Figure 2). In all patients, IPN was initially infused at 4 μg/min until a 50% increase of the baseline heart rate was stably obtained; afterwards, the infusion rate was maintained or reduced down to 1 μg/min as required to stably maintain the 50% increase of the baseline heart rate. The shortest value of antegrade effective refractory period (ERP) of the AP was determined by programmed stimulation from distal coronary sinus for the left free wall APs or from the high right atrium for the other AP locations. Induction of antidromic/orthodromic AVRT was tested by using multiple extrastimuli and burst pacing with progressive shortening of the pacing cycle length until the 1:1 atrial capture was lost to use induce atrial fibrillation. If atrial fibrillation was not inducible, the SPERR was calculated during rapid atrial pacing. The diagnosis of fasciculo-ventricular fibres was based on the following criteria: (i) antero-septal VPE with a short, positive, and constant H-delta interval and (ii) during incremental atrial pacing, decremental atrioventricular conduction with progressive increase in the stimulus-delta interval corresponding to the prolongation of the A–H interval while the H-delta interval and degree of VPE on surface ECG remained unchanged.

Catheter ablation
Both electrophysiological testing and catheter ablation were performed by two experienced operators. As shown in Figure 1, catheter ablation was performed in the same procedure, if at least one of the following criteria was met at baseline or during IPN infusion: (i) SPERR ≤ 250 ms and (ii) induction of orthodromic or antidromic AVRT. Subjects who did not meet any of these criteria were discharged with no therapy.

Ablation of left-sided APs was performed byelective transseptal catheterisation. Ablation was performed using a 4-mm tip steerable catheter to deliver radiofrequency energy in temperature-controlled mode. For mid-septal and para-hisian APs, cryoablation was electrovully used with a dedicated console (Cryoconsole, Medtronic CryoCath LP) and a 4 or a 6 mm tip steerable catheter (Freezor or Freezor Xtra, Medtronic CryoCath LP). Cryoablation was performed at −75°C up to 480 s. In case of inadvertent modification of conduction over the normal atrioventricular conduction pathway during cryoablation, it was immediately terminated and resumption of the baseline conduction properties was assessed. After successful ablation, absence of conduction resumption over the AP was assessed for 45 min.

Follow-up
At discharge, no antiarrhythmic drug was prescribed. For patients who underwent ablation, repeated standard 12-lead ECG, Holter monitoring, and a visit were scheduled in the first 2 months to assess persistent absence of VPE and symptoms. For subjects who did not undergo ablation, a yearly visit was scheduled for 2 years. All patients were invited to refer to our centre or to the referring cardiologist in case of any symptom possibly of cardiovascular origin. In November 2012, a phone contact was performed to assess the clinical status of each patient and to exclude that in the group of subjects who did not undergo ablation any antiarrhythmic
drug was prescribed by other physicians during late follow-up. To prolong the follow-up in this specific subgroup, a phone call was repeated in August 2014 for the group of subjects who received no therapy.

**Statistics**
All continuous variables were tested for normal distribution with D’Agostino–Pearson test: if normally distributed, they are expressed as mean ± standard deviation; otherwise, they are given as median and percentiles. All categorical data were confronted with $\chi^2$ test with Yates correction or Fisher’s exact test as appropriate according to sample size. Mann–Whitney $U$ test was used to confront continuous variables. A subgroup analysis to evaluate the correlation between the ERP and SPERRI according to AP location was made, dividing AP location into three subgroups: septal, postero-septal, and free wall (both left and right). All data were analysed using MedCalc version 9.3.7.0 (MedCalc Software).

**Results**

**Population**
Sixty-six patients with asymptomatic VPE persistent at stress effort test were referred for electrophysiological evaluation. One patient refused the consent to undergo the electrophysiology procedure and was excluded. Adenosine test was diagnostic of fasciculo-ventricular fibres in two subjects, who were also excluded. The other 63 patients (45 males, 18 females, mean age 26 ± 14 years, range 10–49 years) entered the study and underwent electrophysiological evaluation. Eight patients (13%) were ≤ 12 years of age and 18 (29%) were > 18 years of age. Five patients (8%) had minor structural heart disease: bicuspid aortic valve (1 patient), mild aortic valve stenosis and regurgitation (1 patient), mild mitral valve regurgitation (1 patient), and mitral valve prolapse (2 patients). Twenty-five (40%) patients were competitive athletes.

**Electrophysiological evaluation**
The results of the electrophysiological study are reported in Figure 3. In seven subjects with antero-septal VPE, fasciculo-ventricular fibres were diagnosed and no arrhythmia induced. Therefore, they were excluded from further analysis. Twenty-five (45%) out of the 56 patients with an AP had a SPERRI ≥ 250 ms and no inducible AVRT. Conversely, the remaining 31 patients (55%) met at least one criterion for ablation: 87% (27 of 31) had at least fast antegrade conduction over the AP and 61% (19 of 31) had at least inducible AVRT (orthodromic in 18 patients and antidromic in 1). Fifteen cases (48%) had a SPERRI ≤ 250 ms and/or inducible AVRT only during IPN infusion. In this group, as well as in patients who did not meet any of the criteria for ablation, IPN infusion significantly decreased the SPERRI and the antegrade ERP of the AP, as shown.

![Figure 1](https://academic.oup.com/europace/article-abstract/17/6/946/2398570)
in Table 1. All patients with retrograde conduction over the AP had also inducible orthodromic AVRT at baseline or during IPN infusion.

The SPERRI was evaluated during atrial fibrillation in 25 cases and during fast atrial pacing in the remaining 31 cases because atrial fibrillation was not induced even during IPN infusion. The SPERRI was 239 ± 28 ms in those who met at least one criterion for ablation vs. 326 ± 36 ms in those who did not meet any of the criteria for ablation (P < 0.001). There was a statistically significant correlation between the SPERRI and the antegrade ERP of the APs (r 0.77, CI 0.63–0.86, P < 0.0001).

Figure 2 Example of marked increase in the antegrade conduction properties of a postero-septal atrioventricular accessory pathway in a 49-year-old patient. In both panels, from top to bottom, surface electrocardiogram, bipolar recordings from the coronary sinus catheter (CS1–CS5, from distal to proximal), bipolar recordings from the His bundle catheter (HBEd–HBEp, from distal to proximal), and the bipolar recording from the high right atrium catheter (Sited) are shown. (A) At baseline, the shortest pre-excited R–R interval is 320 ms and 2:1 conduction occurs over the accessory pathway during atrial pacing with a shorter cycle length. (B) During IPN infusion, the shortest pre-excited R–R interval decreases to 210 ms. Neither intra-atrial conduction delay nor decremental conduction over the accessory pathway is observed during rapid atrial pacing.
In these 56 patients, 58 APs where located as follows: postero-septal in 20 cases, septal (mid-septal or antero-septal) in 16, left free wall in 14, and right free wall in 8. Interestingly, as shown in Table 2, no significant difference as to the age, sex distribution, and location of the AP was noted between the group of patients eligible for ablation and the group of patients who did not qualify for ablation. Moreover, as also shown in Table 2, while the SPERRI was significantly shorter in the patients eligible for ablation for every subgroup of AP location, the antegrade ERP of the AP was similarly shorter in the subgroups of postero-septal and septal APs, but not in the subgroup of free wall AP, in which there is a considerable overlap of ERP values in the two groups.

**Catheter ablation**

The 31 patients who were eligible for catheter ablation underwent successful ablation of 33 APs: one patient had both a para-hisian and mid-septal AP and another one had both a para-hisian and a right postero-septal AP. Radiofrequency energy was used in 21 patients and cryoablation was used in nine to ablate five para-hisian and five mid-septal APs; in one patient, both cryothermal and radiofrequency energy were used to ablate a para-hisian and a right postero-septal AP, respectively. No complication was observed in any case. Overall, skin-to-skin procedure duration was 163 ± 43 min, fluoroscopy time was 17 ± 10 min, and dose area product was 61 ± 44 Gy cm².

**Follow-up**

The follow-up durations for the patients who received ablation and for those who received no therapy are 60 ± 32 and 85 ± 29 months, respectively. The results of this long-term follow-up are shown in Figure 3. In the first month of follow-up, one patient with both a para-hisian and a mid-septal AP had resumption of conduction over the para-hisian AP and was retreated successfully and permanently by cryoablation. No other patient had events, both in the group of patients who received ablation and in the one of patients who received no treatment.

**Discussion**

**Main findings**

In the population considered, invasive electrophysiological testing including IPN infusion identifies individuals who have a SPERRI > 250 ms and no inducible AVRT in 45% of the patients; in this subset no event is observed during an off-drug long-term follow-up. This subgroup is not identified by any of the clinical variables. The remaining 55% of the cases shows fast antegrade conduction over the AP.
Electrophysiological evaluation in asymptomatic VPE

Table 2 Clinical and electrophysiological characteristics of the 56 patients with an AP

<table>
<thead>
<tr>
<th>Location of AP</th>
<th>Patients with criteria for catheter ablation</th>
<th>Patients without criteria for catheter ablation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postero-septal</td>
<td>13 (39%)</td>
<td>7 (28%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Antegrade ERP (ms)</td>
<td>230 (220–240)</td>
<td>320 (280–327.5)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SPERRI (ms)</td>
<td>240 (220–252.5)</td>
<td>330 (307.5–355.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal</td>
<td>8 (24%)</td>
<td>8 (32%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Antegrade ERP (ms)</td>
<td>230 (220–240)</td>
<td>320 (280–327.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SPERRI (ms)</td>
<td>240 (225–250)</td>
<td>330 (307.5–355)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Free wall</td>
<td>12 (37%)</td>
<td>10 (40%)</td>
<td>1</td>
</tr>
<tr>
<td>Antegrade ERP (ms)</td>
<td>240 (210–265)</td>
<td>265 (225–325)</td>
<td>0.24</td>
</tr>
<tr>
<td>SPERRI (ms)</td>
<td>250 (240–265)</td>
<td>320 (305–357.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
*The SPERRI and ERP values are expressed as median and interquartile range.

Electrophysiological profile in patients with asymptomatic VPE persistent at stress effort test

A recently published retrospective study reported that invasive electrophysiological evaluation in children and adolescents with asymptomatic VPE persistent at maximal exercise stress test shows a SPERRI ≤ 250 ms or inducible AVRT in the same proportion of cases observed in our series, in which also adults are included. This finding deserves two considerations. First, about half of the cases with asymptomatic VPE persistent at stress effort test has fast antegrade conduction over the AP and/or inducible AVRT, and, according to the PACES/HRS expert consensus document, can be candidate for ablation with a class IIA or IIB indication. This underlines the usefulness of electrophysiological testing in a population with an undefined risk of AP-related arrhythmias after a stress effort test has failed to show loss of VPE. In fact, similar to what has been previously reported, our data show that in this population the non-invasive variables do not identify patients with adverse conduction properties of the AP. As observed in another series, in our cohort study, the distribution of AP locations and the prevalence of multiple APs were not significantly different from the ones in asymptomatic Wolff–Parkinson–White patients undergoing catheter ablation in the same time interval in our centre. Second, adverse AP properties in patients with no symptom are not necessarily observed only in the paediatric age, but can be encountered later in life. Therefore, subjects with asymptomatic VPE persistent at stress effort test should not be excluded by electrophysiological evaluation based only on age.

Isoproterenol infusion and exercise test improve the conduction properties of the AP and increase the probability of arrhythmia induction both in symptomatic and asymptomatic children and both in asymptomatic children and adolescents under general anaesthesia or sedation. The PACES/HRS expert consensus document reports that, since the prognostic value of the addition of IPN for risk stratification has not been adequately studied, the risk profile is generally determined at baseline. On the other hand, the Italian guidelines for sports eligibility recommend that in asymptomatic VPE the conduction properties of the AP and the induction of arrhythmias are assessed also during exercise or, as a surrogate, during IPN infusion. Our data show that also in the non-sedated state β-adrenergic stimulation can crucially improve the AP conduction properties during invasive electrophysiological evaluation in 38% of the patients with a SPERRI > 250 ms and no inducible AVRT at baseline. More importantly, patients who had a SPERRI > 250 ms and no AVRT inducible during IPN infusion experienced no event during an off-drug long-term follow-up. This underlines the negative predictive value of electrophysiological test with IPN infusion and leads us to consider ablation not justified in this subset at no risk for AP-related arrhythmias.

Catheter ablation in asymptomatic ventricular pre-excitation

In the general population with asymptomatic VPE, the ‘ablate all’ strategy is questionable both on a risk/benefit and cost/effectiveness ratio. As proposed by the PACES/HRS expert consensus document, after non-invasive screening with effort stress test electrophysiological evaluation identifies patients who might develop AP-related arrhythmias and in whom ablation can be considered. As previously reported, in young asymptomatic patients, radiofrequency energy ablation is usually deferred when the AP location is in proximity to the atrioventricular node. Cryoablation can be instrumental in avoiding complications related to inadvertent modifications of atrioventricular conduction, less tolerable in this subset of patients.
Limitations
This is a single-centre retrospective cohort study with data collection over 10 years in a relative small cohort.

Secondly, the SPERRI was evaluated during atrial fibrillation in 45% of the cases and in the rest of the patients it was determined during fast atrial pacing because atrial fibrillation could not be induced even during IPN infusion. Although the evaluation of antegrade conduction over the AP during a sustained episode of atrial fibrillation could be more indicative of what could happen clinically, the SPERRI determined during rapid atrial pacing is considered a reasonable surrogate.13

Thirdly, the overall population with asymptomatic VPE screened by exercise stress test from which the study population was extrapolated cannot be well defined, since some patients were referred from other centres after an exercise test failed to provoke sudden loss of VPE. This does not affect the data quality of our study, which has the aim to define the electrophysiological profile in patients with a positive stress effort test, but does not allow us to determine precisely the proportion of patients with asymptomatic VPE which requires invasive evaluation after non-invasive screening.

Fourthly, to reach a definite conclusion on the usefulness of IPN to predict future events in patients who met the criteria for ablation only during IPN infusion, these patients should have been randomised to predict future events in patients who met the criteria for ablation only during IPN infusion, these patients should have been randomised to

Conclusion
In a population of patients ageing between 10 and 49 years with asymptomatic VPE persistent at exercise stress test, 55% of the patients shows adverse conduction properties of the AP at invasive electrophysiological evaluation with IPN challenge. The remaining 45% has a benign form of VPE with no event during a long-term off-drug follow-up, although this group has non-invasive characteristics similar to the ones of the group with adverse conduction properties of the AP.

Conflict of interests: none declared.

References