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Impact of growth on electrophysiological properties of ventricular pre-excitation in paediatric athletes

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Abstract

Aim: Risk stratification is recommended for patients with ventricular pre-excitation, particularly when sports eligibility is required. Few studies have examined the changes in the electrophysiological properties of the accessory pathway during growth. This study investigates the evolution of electrophysiological properties of the ventricular pre-excitation in young athletes referred for sports eligibility. *Methods:* Between January 2011 and July 2022, 44 paediatric patients (32 males; mean age, 10 ± 2.42) with ventricular pre-excitation underwent an electrophysiological study, both at rest and during adrenergic stress at two different times (T0 and T1) within a minimal interval of 2 years. Transcatheter ablation was not performed between the two electrophysiological studies. Electrophysiological data were collected and compared. *Results:* Electrophysiological study under basal conditions showed a significant decrease in the anterograde accessory pathway effective refractory period and 1:1 conduction over the accessory pathway from T0 to T1. The shortest pre-excited R-R interval during atrial fibrillation did not significantly change at the basal condition; however, it decreased during the stress test. Furthermore, six patients (13.6%) changed the risk profile of their accessory pathway: two "high-risk" patients at T0 became "low-risk" and four "low-risk" patients became "high-risk" at T1. Atrioventricular re-entry tachycardia inducibility did not differ significantly between the two electrophysiological studies. *Conclusions:* This study highlights the importance of repeating electrophysiological study (transesophageal or intracardiac) in paediatric athletes with ventricular pre-excitation because significant and clinically relevant changes in the conduction and refractoriness of accessory pathway can occur. This could influence risk stratification for sports eligibility and the correct indication and timing for accessory pathway ablation.

Introduction

Ventricular pre-excitation carries a low but lifetime risk of sudden cardiac death (up to 2.8 per 1000 patient-years), which is apparently higher in symptomatic patients. However, patients with ventricular pre-excitation sometimes remain asymptomatic during childhood and may become symptomatic during adolescence; moreover, sudden cardiac death can be the first manifestation of the disease.[1–7]

In this regard, management of asymptomatic children with pre-excitation remains debated. An electrophysiological study can be used for the risk stratification of these patients, especially when sports eligibility for competitive athletes is required.[8–10] Indeed, physical activity on a competitive level has been associated with increased risk of arrhythmic events in these patients.[11]

Moreover, the electrophysiological properties of accessory pathways may vary during growth. However, only a few studies have analysed the changes in accessory pathway properties over time,[12–14] but they included both children and adults or performed transcatheter ablation between the two electrophysiological studies.

Therefore, the aim of this study was to assess changes in electrophysiological characteristics of accessory pathways and atrial vulnerability in paediatric patients with manifest ventricular pre-excitation who were referred for sports eligibility.

Methods

Study design and population

This was a retrospective, single-centre, observational study and complied with the Declaration of Helsinki.

Written informed consent was obtained from the parents of all the patients prior to the procedure.

The study enrolled all paediatric athletes (<18 years) with ventricular pre-excitation (32 males, 12 females) who were repeatedly evaluated through an electrophysiological study for sports eligibility between January 2011 and July 2022.

The definition adopted for "athlete" was: "an individual of young or adult age, either amateur or professional, who is engaged in regular exercise training and participates in official sports competition," according to the European Society of Cardiology indications.[10]

In all patients, transcatheter ablation was not performed between the two evaluations due to parents' choice, use of antiarrhythmic drugs, or accessory pathway's locations at risk of procedural complications (i.e. anterior septal accessory pathways or probable epicardial location).

Transesophageal or endocavitary electrophysiological study evaluation was performed at two different life periods (T0 and T1) within a minimal interval of 2 years.

All antiarrhythmic drugs were discontinued for at least five half-lives before the procedure to ensure complete pharmacological washout.

The electrophysiological and clinical data were collected and compared.

Transesophageal electrophysiological study

A transesophageal electrophysiological study was performed as a screening test according to Italian guidelines for sports participation.[8]

Children were considered non-collaborative or collaborative based on their age, capability, and/or willingness to perform exercise testing.

In non-collaborative patients, transesophageal electrophysiological study was performed under deep sedation (60% O2, 39.8% N2O 0.8% sevoflurane). In collaborative patients, local anaesthesia with 1% nasal and oral lidocaine spray was established prior to the insertion of the oesophageal catheter. A 7-French tetrapolar oesophageal catheter (FIAB Esoflex 4S; Vicchio-Florence, Italy) was advanced through the nose into the oesophagus at an appropriate depth, where the maximal amplitude of the bipolar atrial potential was recorded. Cardiac stimulation was performed with a programmable stimulator (FIAB 8817) using a pulse width of 10 ms and a stimulus current amplitude that was slightly in excess, resulting in consistent atrial capture (15–20 V).

At rest, stimulation was performed at a fixed cycle length (600 or 450 ms, according to the spontaneous sinus rate) with one, two, or three extra stimuli. Bursts of decreasing cycle length (600–150 ms by reducing 50 ms every 5 s) were delivered and repeated thrice.

The same stimulation protocol was repeated under intravenous isoproterenol infusion (0.02-0.08 mg/kg/min) or

Accessory pathway effective refractory period was defined as the longest A1–A2 interval that failed to conduct through the accessory pathway and conducted through the atrial-ventricular node. The 1:1 conduction over the accessory pathway was measured during incremental atrial pacing.

The shortest pre-excited R-R interval during atrial fibrillation was measured in milliseconds during induced atrial fibrillation.

Accessory pathways were considered "high-risk" in case of shortest pre-excited R-R interval ≤ 250 ms during incremental atrial pacing of induced atrial fibrillation and/or an accessory pathway effective refractory period ≤ 250 ms obtained by programmed atrial stimulation protocol, performed at baseline or during adrenergic stress.[15–17]

The duration and cycle length of the induced atrioventricular re-entry tachycardia and atrial fibrillation were recorded in seconds and defined as non-sustained when they lasted < 30 s. In cases of sustained arrhythmia associated with hemodynamic intolerance, sinus rhythm was restored by burst pacing or external electrical cardioversion.

In patients without inducible atrioventricular re-entry tachycardia/atrial fibrillation and/or with non-high-risk resting electrophysiological parameters, the pacing protocol was repeated during exercise testing with a cycle ergometer or under isoproterenol infusion (0.04–0.08 mcg/kg/min), in order to reach at least a 50% increase of heart rate and/or a target heart rate of 140–150 bpm.

The same stimulation protocol was applied at T0 and T1.

Intracardiac electrophysiological study

Intracardiac electrophysiological study was performed only in young athletes for whom a transcatheter ablation was initially planned and in agreement with patients' parents.

The procedure was performed under general anaesthesia with endotracheal intubation, induced with sevoflurane or propofol, and maintained with sevoflurane. A thermal mattress was used to maintain a normal body temperature.

Surface electrocardiogram leads and endocardial potentials were recorded and stored on a multichannel recorder (Bard Electrophysiology, Billerica, MA, USA). The bipolar bandwidth filter was set in the range of 30–300 Hz.

The same electrophysiological parameters analysed in the transesophageal electrophysiological study were also assessed during the electrophysiological study.

Statistical analysis

Descriptive statistics were reported as mean ± standard deviation or median and interquartile range for continuous variables, as appropriate; the results are presented as frequencies for categorical variables. A preliminary analysis and subsequently the Kolmogorov-Smirnov test were performed to test the normality of the continuous data. Although a model assumption of normality was documented in some situations, we considered the non-normality of the distribution of the studied variables owing to the small sample size, and nonparametric models were used. For statistical analysis, continuous variables were compared using the Mann–Whitney test. Categorical variables were analysed using a contingency table with a Chi-squared test. Differences were considered statistically significant at a P-value < 0.05. Data analysis was performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

Patients characteristics

There were 44 children with manifest ventricular pre-excitation, who were evaluated for sports eligibility [32 (73%) males, mean age 10 ± 2.42 years at T0 and 14.11 ± 2.11 years at T1].

The second electrophysiological evaluation (T1) was performed at a minimum interval of two years (mean interval 4.11 ± 2.27 years) in all patients.

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Table 1. Electrophysiological study at rest

	EPS at T0	EPS at T1	P value
Patients (n)	44	44	
Age ± SD (years)	10.01 ± 2.42	14.11 ± 2.11	
Male (n, %)	32 (73)	32 (73)	
Female (n, %)	12 (27)	12 (27)	
AV nodal ERP (ms)	245 (230–280)	250 (230–280)	0.56
WCL (ms)	275 (260–290)	260 (240–285)	0.15
APERP (ms)	300 (280–320)	280 (260–300)	**0.0039**
Induced ARVT (n, %)	9 (20.5)	14 (31.8)	0.33
1:1 conduction over AP (ms)	280 (260–295)	260 (240–285)	**0.0182**
Induced AF (n, %)	7 (15.9)	16 (36.4)	0.05
SPERRI (ms)	295 (265–310)	290 (245–300)	0.37

P value < 0.05 is considered as statistically significant.
AF = Atrial fibrillation; AP = accessory pathway; APERP = Accessory pathway effective refractory period; ARVT = atrioventricular re-entry tachycardia; AV = atrioventricular; ERP = effective refractory period; EPS = electrophysiological study; SPERRI = shortest pre-excited R-R interval; WCL = Wenckebach cycle length.

Table 2. Electrophysiological study during adrenergic stress

	EPS at T0	EPS at T1	P value
Patients (n)	44	44	
Age ± SD (years)	10.01 ± 2,42	14.11 ± 2.11	
Male (n, %)	32	32	
Female (n, %)	12	12	
AV nodal ERP (ms)	180 (160–200)	205 (190–225)	**0.0011**
WCL (ms)	190 (180–210)	210 (180–220)	0.16
APERP (ms)	220 (200–230)	220 (200–235)	0.52
Induced ARVT (n, %)	15 (37.5)	17 (41.5)	0.89
1:1 conduction over AP (ms)	210 (180–220)	210 (195–240)	0.52
Induced AF (n, %)	12 (30)	11 (26.8)	0.94
SPERRI (ms)	230 (220–275)	210 (185–230)	**0.0274**

P value < 0.05 is considered as statistically significant.
AF = Atrial fibrillation; AP = accessory pathway; APERP = Accessory pathway effective refractory period; ARVT = atrioventricular re-entry tachycardia; AV = atrioventricular; ERP = effective refractory period; EPS = electrophysiological study; SPERRI = shortest pre-excited R-R interval; WCL = Wenckebach cycle length.

Electrophysiological data

Transesophageal electrophysiological study was performed on 40 patients (90.9%) at T0 and 41 (93.2%) at T1. The remaining patients underwent intracardiac electrophysiological study.

No procedure-related complications occurred.

The stimulation protocol was performed during adrenergic stress (isoproterenol infusion or exercise stress testing) in 90.9% and 97.7% of patients at T0 and T1, respectively.

Under the baseline condition, a significant reduction in the accessory pathway effective refractory period and 1:1 conduction over the accessory pathway was observed between T0 and T1 (see Table 1). However, no significant differences in these parameters were observed during adrenergic stress (see Table 2).

Both atrioventricular re-entry tachycardia and atrial fibrillation were inducible in a not negligible proportion of patients (see Tables 1 and 2). Atrioventricular re-entry tachycardia inducibility was not significantly different between T0 and T1, although an upward trend was observed (see Tables 1 and 2).

Atrial fibrillation induction was different at rest but not during adrenergic stress, whereas the shortest pre-excited R-R interval during adrenergic stress decreased significantly (see Tables 1 and 2).

The electrophysiological study showed "high-risk" properties in thirty-five children and "low-risk" properties in three patients both at T0 and T1. Six patients (13.6%) changed the risk profile of accessory pathway: two "high-risk" patients at T0 became "low-risk" and four "low-risk" patients became "high-risk" (see Table 3).

During the study period, accessory pathway anterograde conduction was preserved in all patients, but one child with a constant ventricular pre-excitation on ECG developed an intermittent form.

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Table 3. Electrophysiological characteristic of patients changing risk category between the evaluations (T0 and T1)

	Age	*Sex*	*Symptoms*	*AP localisation*	*TEE/EPS*	*Baseline SPERRI (ms)*	*ISO/exercise SPERRI (ms)*	*Baseline AP ERP (ms)*	*ISO/exercise AP ERP (ms)*	*AVRT inducibility*	*At risk of SCD*
Patient 1 at T0	7	F	Yes	Right Septal	TEE	250	180	300	200	Yes	**Yes**
Patient 1 at T1	15		No		TEE	290	255	300	260	No	**No**
Patient 2 at T0	9	F	No	Left Lateral	EPS	460	400	400	350	No	**No**
Patient 2 at T1	12		No		TEE	380	320	290	230	Yes	**Yes**
Patient 3 at T0	9	M	No	Left Posterior	TEE	NA	260	NA	260	No	**No**
Patient 3 at T1	13		No		TEE	245	205	250	200	No	**Yes**
Patient 4 at T0	10	F	No	Left Lateral	TEE	410	350	350	280	Yes	**No**
Patient 4 at T1	16		Yes		TEE	250	230	280	250	Yes	**Yes**
Patient 5 at T0	11	M	No	Right Septal	TEE	NA	NA	NA	NA	No	**No**
Patient 5 at T1	15		No		TEE	380	330	270	240	No	**Yes**
Patient 6 at T0	15	M	Yes	Right Septal	EPS	260	220	310	240	Yes	**Yes**
Patient 6 at T1	17		No		TEE	265	260	300	260	Yes	**No**

NA = in case of intermittent VP, when AP conduction is not visible at the time of EPS or AP refractory period > CL of stimulation.
AP = accessory pathway; EPS = intracavitary electrophysiological study; ERP = effective refractory period; SCD = sudden cardiac death; SPERRI; shortest pre-excited R-R interval; TEE = transoesophageal study.

None of our patients presented with documented life-threatening or poorly tolerated arrhythmic events (atrial fibrillation or ventricular tachycardia/ventricular fibrillation).

Discussion

The role of electrophysiological study to evaluate the pre-excitation syndrome-related risks of adverse events has been proven in previous studies.[4,6,7,18,19] In this regard, all the recent guidelines suggest performing an electrophysiological study on all young athletes with ventricular pre-excitation.[8,10,15]

However, the evolution of electrophysiological properties of accessory pathway during life has been reported in a few papers.[12–14,20,21]

The Italian screening programme for sports eligibility requires a cardiovascular assessment to be performed every year and the electrophysiological study for risk stratification of ventricular pre-excitation can be repeated at the discretion of the sports physicians.[8,9,22]

Consequently, our study population affected by ventricular pre-excitation was repeatedly evaluated using the electrophysiological study to obtain sports eligibility, especially focusing on arrhythmic vulnerability and changes in accessory pathway anterograde conduction.

Our results showed that significant changes in electrophysiological data could occur during growth. Indeed, we observed a significant modification in the conduction properties of the accessory pathways.

Specifically, the accessory pathway effective refractory period and 1:1 conduction over the accessory pathway significantly decreased at rest, whereas shortest pre-excited R-R interval decreased during the adrenergic stress test.

Notably, in our study population, 13.6% of the patients had changes in accessory pathway properties, with a consequent switch between the risk categories. Furthermore, in the resting condition, atrioventricular re-entry tachycardia and atrial fibrillation showed an increasing trend of inducibility at T1.

Consequently, we believe that a repeated electrophysiological study during growth may improve the risk stratification for sudden cardiac death in young athletes with ventricular pre-excitation. Indeed, patients at "low-risk" may become at "high-risk" and vice versa, and tachycardia inducibility may vary with time according to different conduction properties of atrioventricular node and accessory pathways with the growth of patients and their hearts. Moreover, when a transoesophageal electrophysiological study can be performed, the risks connected to the electrophysiological evaluation are minimal.

Differently from our study, Brembilla–Perrot,[20] describing the follow-up (6.3 ± 4.8 years) of 47 children with ventricular pre-excitation (mean age 12.2 ± 4.3 at first evaluation), reported that there were no significant changes in clinical and electrophysiological study data. In this regard, we believe that these different findings could be due to the younger age of our patients at T0 (10.01 ± 2.42 years) with consequent different periods of the paediatric age analysed.

Interestingly, in the Brembilla–Perrot's study, most children with spontaneous/inducible atrioventricular re-entry tachycardia at the time of initial electrophysiological study still had inducible tachycardia at the time of the second electrophysiological study. In this regard, Vignati and Drago[14] reported that the tachycardia disappeared in approximately 50% of the patients during the first year of life and atrioventricular re-entry tachycardia very rarely disappears in patients who develop the tachycardia after 12 years of age.

Our data confirm that atrioventricular node effective refractory period increases with age,[23] with different but not significant atrioventricular re-entry tachycardia inducibility. On the contrary, the accessory pathway effective refractory period decreased in contrast to the "impedance mismatch" theory (22–24), according to which the relatively small accessory pathway current can be easily blocked by the larger mass of the ventricular myocardium, which is expected to grow during the paediatric age.

Our data also revealed a larger number of "high-risk" patients than in the Brembilla–Perrot's study, probably because our definition of "high risk" is in accordance with the latest European guidelines available and the Italian Recommendation for sport eligibility.[8,15]

Notably, the accessory pathway anterograde conduction was preserved in all but one patient in our study population even if Milstein[24] reported that a considerable number of asymptomatic patients can lose their capacity for anterograde conduction over the accessory pathway.

Lastly, none of our patients presented with a documented life threatening or poorly tolerated arrhythmic event (neither atrial fibrillation nor ventricular tachycardia/ventricular fibrillation), despite the high prevalence of so-called high-risk accessory pathways.

Future studies with a long-term follow-up are expected to establish whether our results can be confirmed in larger populations. In addition, our risk stratification protocol with a repeated electrophysiological study during growth could be compared to the present standard of care to investigate if it can improve outcomes in these patients.

Limitations

This was a retrospective single-centre study with a small number of patients; therefore, the results could be influenced by the population selection and characteristics.

The definition of athletes may vary in different countries and/or hospitals. In this paper, athletes were defined as reported in the most recent European Society of Cardiology guidelines.[10]

Lastly, it has been already described that measurements of refractoriness and conduction properties of accessory pathway can be not reproducible also during the same electrophysiological procedure.[26]

Conclusion

This study highlights the importance of repeating electrophysiological study (transesophageal or intracardiac electrophysiological study) in paediatric athletes with ventricular pre-excitation, because significant and clinically relevant changes in the conduction and refractoriness of accessory pathway can occur. This could influence risk stratification for sports eligibility and the correct indication and timing for accessory pathway ablation that is essential to avoid sudden cardiac death in young athletes potentially at risk. For this purpose, the use of isoproterenol infusion or exercise testing during the stimulation protocol further increases the sensitivity of electrophysiological testing and possibly its predicting value in athletes.

Data availability statement. The data that support the findings of this study are available on reasonable request from the corresponding author.

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Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of our Institution.

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