



The Risk of Sudden Death Associated with Symptomatic and Asymptomatic Ventricular Pre-excitation in Athletes

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Abstract

Sudden death (SD) in athletes is a potential avoidable dramatic scenario. When done regularly, cardiological evaluation increases the chances of diagnosing ventricular pre-excitation. Consequently, the following question arises: what is the real incidence of SD risk in athletes with Wolff-Parkinson-White (WPW) syndrome/pattern? This study included 84 consecutive patients diagnosed with WPW and was designed as a retrospective analysis of data acquired between 2011 and 2021 to answer this question. The patients were evaluated using a 12-lead electrocardiogram (ECG), echocardiography, stress test, and electrophysiological study (EPS). The SD risk linked to WPW was defined as ≥ 1 of the following: the anterograde effective refractory period (AERP) of the accessory pathway (AP) ≤ 250 ms, atrial fibrillation (AF) with the shortest RR pre-excited interval ≤ 250 ms, syncope during AF or atrioventricular reentry tachycardia. The athletes with WPW pattern ($n=25$) or syndrome ($n=59$) at risk of SD were identified and treated with radiofrequency ablation (RFA). The mean age was 19.83 (10-29) years; 66.6% were men. Seventeen athletes ($n=17$; 20.23%) were found with SD risk: 15 ($n=15$; 17.85%) in the WPW syndrome group and 2 ($n=2$; 2.38%) in the WPW pattern group. During the EPS, $n=4$ developed syncope: 1 during antidromic tachycardia and 3 during pre-excited AF. RFA was curative in 96.42% of cases. The EPS is mandatory to identify athletes with short AERP APs linked to an increased risk of SD. RFA is the intervention that settles the patients into a risk-free area, allowing resumption of sports shortly afterward.

Keywords

athletes, sudden cardiac death, Wolff-Parkinson-White syndrome, atrial fibrillation, electrophysiological study, catheter ablation

Rezumat

Moartea subită (MS) la sportivi este un scenariu dramatic potențial evitabil. Atunci când se face în mod regulat, evaluarea cardiologică crește șansele de a diagnostica preexcitația ventriculară. În consecință, apare următoarea întrebare: care este incidența reală a riscului SD la sportivi cu sindrom/model Wolff-Parkinson-White (WPW)? Acest studiu a inclus 84 de pacienți consecutivi internați cu WPW și a fost conceput ca o analiză retrospectivă a datelor obținute între 2011 și 2020 pentru a răspunde la această întrebare. Pacienții au fost evaluați folosind ECG cu 12 derivații, ecocardiografie, test de stres și studiu electrofiziologic (EPS). Riscul SD legat de WPW a fost definit ca ≥ 1 dintre următoarele: perioada refractară efectivă anterogradă (AERP) a căii accesorii (PA) ≤ 250 ms, fibrilație atrială (FA) cu cel mai scurt interval RR preexcitat ≤ 250 ms, sincopă în timpul FA sau tahicardie de reintrare atrioventriculară. Sportivii cu pattern WPW ($n=25$) sau sindrom ($n=59$) cu risc de SD au fost identificați și tratați cu ablație cu radiofrecvență (RFA). Vârsta medie a fost de 19,83 (10-29) ani; 66,6% erau bărbați. S-au găsit șaptesprezece sportivi ($n=17$; 20,23%) cu risc SD, cincisprezece ($n=15$; 17,85%) în grupul cu sindrom WPW și doi ($n=2$; 2,38%) în grupul cu pattern WPW. În timpul EPS, $n=4$ au dezvoltat sincopă: 1 - în timpul tahicardiei antidromice și 3 - în timpul FA cu preexcitație. RFA a fost curativă în 96,42% din cazuri. EPS este obligatoriu pentru a identifica sportivii cu AERP cu cale accesorie scurtă și risc crescut de SD. RFA este intervenția care așează pacienții într-o zonă fără riscuri, permițând reluarea sportului la scurt timp după.

Cuvinte cheie

sportivi de performanță, sindrom Wolff-Parkinson-White, fibrilație atrială, studiu electrofiziologic, catheter-ablație

Introduction

Sudden death (SD) in athletes is an ongoing dilemma for practitioners worldwide. Since the beginning of the 19th century, the topic has been addressed on numerous occasions and has continuously sparked debates owing to a lack of consensus. One of the most significant problems is insufficient action regarding screening, prevention, and early treatment measures. Over time, it has been agreed that SD should be defined as death owing to unknown causes occurring 1 hour after the onset of the first pathognomonic symptom in a patient without any known fatal condition [1]. Sudden cardiac death in young athletes may be potentiated by physical activity [2]. Moreover, the risk of death due to rhythm disorders is higher in asymptomatic children than in adults, making it even more serious [3].

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The incidence of sudden cardiac death in athletes varies from 1 in 200,000 [4] to 2 in 100,000 [1], and overall mortality reaches approximately 1.83 deaths per 10 million athlete-years [5]. The leading causes of SD differ depending on the patient's age. At a younger age, the arrhythmogenic substrate and regulatory and triggering factors predominate, whereas in older patients, atherosclerosis and subsequent coronary artery disease are more common scenarios [1,4].

Physical training has significant benefits to the heart and blood vessels, especially to blood pressure and arterial stiffness parameters [6], but the precise, intrinsic body adjustments to exercise are less precisely known [7,8]. Systematic athletic training can lead to structural and functional modifications of the heart [9]. These changes are known as exercise-induced cardiac remodeling [10]. The most common changes found in the athletes are the following: left ventricle enlargement, concentric or eccentric hypertrophy of the left ventricle [11], enlarged right ventricle primarily associated with endurance sports, enlargement of the aortic root, and, the most important in patients with pre-excitation, enlargement and fibrosis of the left atria [9]. Remodeling the left atria or the presence of a myocarditis condition combined with the underlying pathological electrical substrate (Kent fibers) can lead to a perfect storm of life-threatening arrhythmias [12].

The Kent fiber, also known as the accessory pathway (AP), is the morphological basis of pre-excitation. The AP is an additional bypass tract with particular conduction properties, a myocyte with modified electric properties [13,14]. Atrial fibrillation (AF) is the most common arrhythmia globally: 1 in 3 middle-aged adults in the United States and Europe will develop AF during their lifetime [15]. The consequences of athletic conditioning will result in 40% of the athletes having an abnormal ECG, which may implicate left atrial dilation, a secondary cause of AF [16].

All the aspects mentioned above provide extra support for the theory that AF incidence is higher in athletes than in the general population. It can be even higher in athletes with ventricular pre-excitation than in athletes without pre-excitation. Moreover, the incidence of AF rises significantly in the presence of multiple accessory pathways [17]. The adrenergic discharge can modify atrial, ventricular, and AP electric properties during training and competition, making AF associated with a short anterograde effective refractory period (AERP) AP, which is potentially life-threatening in the general population and particularly dangerous in athletes [18].

According to the international guidelines, the 2 most common noninvasive investigations to evaluate and establish the resumption or cessation of sports activities in professional athletes are ECG and echocardiography [19]. However, the gold standard method for assessing the risk of SD in patients with pre-excitation is electrophysiological study (EPS) [20]. The programmed atrial stimulation, including progressively increasing frequency stimulation and extra stimulus testing at baseline, is the most accurate method for revealing the AP's AERP and the intrinsic atrial vulnerability, a secondary cause of AF. In addition to programmed atrial stimulation, programmed ventricular stimulation helps assess the induction of reentry arrhythmias associated with pre-excitation: atrioventricular

orthodromic reentry tachycardia (AVORT) and atrioventricular antidromic reentry tachycardia (AVART) [21].

The current research focuses on evaluating sudden death associated with Kent fibers in athletes.

Materials and Methods

The study included patients admitted to the Institute of Cardiovascular Diseases of Timișoara, Romania, between 2011 and 2021. This research was conducted with the approval of the hospital's ethics committee and under the Declaration of Helsinki [22].

We defined the Wolff-Parkinson-White (WPW) pattern as ventricular pre-excitation without symptoms and WPW syndrome as ventricular pre-excitation with symptoms or documentation of arrhythmia (reentry tachycardia and/or AF/aborted SD) [23].

We defined the athlete as an individual participating on an organized team or in individual sport, engaging in competitions regularly, and systematically deploying a high level of training.

The proportion of patients belonging to different standard categories established by age in our country is presented in Table 1. The mean age was 19.83 (10-29) years, and 66.6% were men.

Study design

All the athletes addressed with WPW pattern or syndrome between January 2011 and September 2021 were identified and included. Patients diagnosed with WPW pattern/syndrome were referred to our hospital by the Institute of Athletic Medicine or another national hospital for further cardiovascular and electrophysiological evaluation and treatment.

None of the patients was under any antiarrhythmic medication.

The patients' assessment followed a noninvasive pattern, including anamnesis (history of palpitations, syncope, and family history of SD evaluation), physical examination, and investigations (blood tests, ECG, exercise stress testing, echocardiography).

This study aimed to identify the electrophysiological properties, triggers, and structural modifications of the heart associated with SD risk in individuals with WPW pattern/syndrome performing competitive sports. The athletes showing persistent pre-excitation during the exercise stress testing were further referred for EPS. The EPS was conducted at baseline for all patients (no isoproterenol challenge was used). The inclusion and exclusion criteria are presented in Table 2. All of the patients had associated ventricular pre-excitation appearance on the 12-lead surface ECG. A significant proportion of the patients also had typical symptoms, including documented arrhythmias, a history of sudden onset and termination of palpitations, aborted SD, or syncope. The exclusion criteria were as follows: missing data, radiofrequency ablation (RFA) performed or attempted in other centers, patient's refusal to undergo invasive exploration/radiofrequency catheter ablation, or informed consent signing.

Table 1 - Distribution of patients by age-standardized groups

Category	Age	n (%)
Children	10-11	8 (9.52)
Cadets	12-13	7 (8.33)
Junior	14-16	6 (7.14)
Youth	17-18	9 (10.71)
Seniors	>18	54 (64.28)

Table 2 - Inclusion and exclusion criteria

Inclusion criteria
1. ECG showing a WPW pattern (mandatory)
2. ECG documented arrhythmia +/- structural heart disease
3. Aborted SD or syncope
4. Typical symptoms (sudden onset and termination of palpitations) alone or associated with sudden familial death with or without ECG-tracing documentation
Exclusion criteria
1. Missing data
2. Ablation procedures performed or attempted in other centers
3. Patient's refusal to undergo invasive exploration/radiofrequency catheter ablation or to sign the informed consent

All the patients signed the informed consent; for athletes under 18 years, the parents/legal guardian's informed consent was obtained.

The standard evaluation sequence consisted of physical examination, blood tests, 12-lead resting ECG, and echocardiography during hospitalization. The EPS was performed in all patients regardless of the presence of symptoms.

The EPS was carried out in the electrophysiology laboratory; double peripheral venous access was obtained for each patient before the procedure. A continuous 12-lead surface ECG tracing was available during the intervention. A monitor recorded vital parameters such as blood pressure, heart rate, and oxygen saturation of the arterial blood. Permanent access to an external defibrillator was provided during the procedure. The ablation generator's indifferent electrode was placed in the patient's thoracic area before the procedure in the event that RFA would have to be performed. Right groin local anesthesia was achieved with 5 ml Lidocaine 1%. Three femoral vein punctures were obtained using the modified Seldinger technique.

The essential equipment used for the EPS and RFA were a General Electric CardioLab EP Recording System, which served for acquisitions of the intracardiac electrograms and surface ECG; a GE OEC 9800 x-ray imaging system, used for fluoroscopic incidences acquisition and used to guide catheter positioning; a Micropace EPS320B/T StimCor external programmable cardiac stimulator; and a Biosense-Webster Stockert 70 Cardiac Ablation RF Generator F48.

The right femoral venous punctures were used to place the diagnostic catheters in standard positions: a 6F quadripolar catheter with 5-5-5-mm electrode spacing was placed at the right ventricular apex, a 5F steerable quadripolar catheter with 2-2-2-mm spacing recording the signal from the His bundle, and a quadripolar catheter with 5-5-5-mm electrode spacing was located on the lateral wall of

the right atrium. A 12-electrode steerable catheter with 2-8-2-mm consecutive spacing was used for coronary sinus cannulation.

Primary electrophysiology data were recorded. The standard intervals were measured at baseline during sinus rhythm at a stable heart rate before stimulation. The intervals measured were the following: the PP interval (between 2 consecutive P waves of sinus rhythm), the PA interval (between the onset of the surface P wave and the earliest atrigram recorded endocavitary), the AH interval (between the atrial electrogram recorded on the His catheter and the onset of the His electrogram), the H-delta interval (between the onset of the His electrogram and the delta wave) and the HV interval (between the His deflection and the ventricular electrogram).

The standard EPS consisted of incremental atrial and ventricular stimulation and atrial and ventricular extra-stimulus testing. The extra-stimulus testing was performed consecutively with 1, 2, and/or 3 extra stimuli.

RFA was performed in selected cases and aimed to restore a risk-free status as needed for sports resumption.

Standard nonirrigated 6 French (F) and 7F Biosense-Webster ablation catheters and a Biosense-Webster Stockert 70 Cardiac Ablation RF Generator F48 were used. The radiofrequency was applied with power variations between 40W and 50W, depending on the properties of the target area. The power was adjusted during the radiofrequency applications to achieve the target temperature (55–60 °C) for conventional ablation. The length of the radiofrequency application at the targeted site varied between 30 and 120 seconds.

Results

Our study included athletes (n=84) with ventricular pre-excitation from the following age categories: seniors, youth, juniors, cadets, and children according to the classification established by the Romanian Ministry of Youth and Sports [21].

The incidence of WPW calculated over 10 years using the number of recognized athletes registered annually in the national yearbook of sports was 0.014%. This incidence was compatible with the range of ventricular pre-excitation incidence described in the general population [21].

The distribution of athletes by WPW type showed 59 (70.23%) patients in the WPW syndrome and 25 (29.76%) patients in the WPW pattern group. The mean age of patients was 19.83 (10-29) years.

The athletes included in our study participated in various sports, including endurance sports. Seven (n=7) of 38 athletes (n=38; 45.23%) in the endurance sports group (i.e., cycling, swimming, rugby, and cross country running) were found to be at risk of SD (5 with WPW syndrome and 2 with WPW pattern). The athletes performing other sports had the following distribution: football 25 (29.76%), judo 5 (5.5%), handball 5 (5.95%), basketball 4 (4.76%), kayaking/canoeing 3 (3.57%), gymnastics 2 (2.38%), outdoor climbing 1 (1.19%), and ice skating 1 (1.19%). The distribution of patients by the type of sport is summarized in Table 3.

Table 3 - The distribution of athletes by endurance/nonendurance sports

Sports, n (%)		Total
Endurance Sports	Cycling	12 (14.28)
	Cross country/ marathon running	18 (21.40)
	Swimming	6 (7.14)
	Rugby	2 (2.38)
	Football	25 (29.76)
	Judo	5 (5.95)
Nonendurance Sports	Handball	5 (5.95)
	Basketball	4 (4.76)
	Kayaking	3 (3.57)
	Gymnastics	2 (2.38)
	Outdoor climbing	1 (1.19)
	Ice skating	1 (1.19)
		38 (45.23%)
		46 (54.76%)

Table 4 - Distribution of accessory pathways according to localization

Localization of the APs	n (%)
Left-sided	39 (46.42)
Right-sided	36 (42.84)
Midseptal & anteroseptal	9 (10.71)
Multiple pathways (4LS, 3 LR, 2 RS)	9 (10.71)

Note. AP: accessory pathway, LS: left septal, RS: right septal, LR:

Table 5 - Dimensions of the left heart structures in athletes with WPW syndrome/pattern

Echographic Findings in Athletes with WPW, Mean Values	
LV end-diastolic diameter	4.53 ± 0.60 cm
LV end-systolic diameter	2.70 ± 0.57 cm
IVS	1.00 ± 0.15 cm
PWLV	0.96 ± 0.16 cm
EFLV	65.39 ± 6.96%
LA surface	17.42 ± 2.71 cm ²

Note. WPW: Wolff-Parkinson-White, LV: left ventricle, IVS: interventricular septum, PWLV: posterior wall of the left ventricle, EFLV: ejection fraction of the left ventricle, LA: left atrium

The ECG was the first noninvasive investigation performed at admission for each patient. The ECG changes were not judged based on the International Consensus Standard for ECG Interpretation in Athletes before the RFA ablation procedure because of the ventricular depolarization and repolarization disturbances caused by the AP/APS. However, the only reliable ECG changes observed and used for analysis during sinus rhythm were sinus bradycardia (48p; 57.14%), short PR interval, and delta wave in all patients.

The Arruda algorithm for AP localization was used for the initial assessment of the ventricular insertion of APs based on the delta wave morphology [24]. The algorithm accurately reproduced the position of the APS, confirmed by intracavitary electrogram recording during the EPS. There were 39 patients (n=39; 46.42%) with free wall left-sided APs, 36 patients (n=36; 42.84%) with free wall right-sided APs, 9 patients (n=9; 10.71%) with midseptal and anteroseptal APs and 9 patients (n=9; 10.71%) with multiple pathways, 4 (n=4)

patients with left and septal pathways, 3 (n=3) patients with left and right pathways and 2 (n=2) patients with right and septal APs.

The ECG recording evaluated after ablation showed changes in 31 patients, other than "memory" T waves (n=31; 36.9%). One month after the successful catheter ablation, the International Consensus Standard for ECG Interpretation in Athletes was applied; the ECGs showed modifications in athletes performing endurance sports such as marathon running and canoeing. The changes consisted of a Sokolov-Lyon index above 40 mm found in 29 patients (34.52%) and in V1, V2, and V3 T wave inversion found in 3 patients (3.57%) performing endurance sports, with mild ventricular hypertrophy confirmed at echography.

The echocardiographic measurements (Table 4) in the study population revealed that the mean end-diastolic diameter of the left ventricle (LV) was 4.53 ± 0.60 cm, the mean end-systolic diameter of the LV was 2.70 ± 0.57 cm, the interventricular septum was 1.00 ± 0.15 cm, the posterior wall of the LV was 0.96 ± 0.16 cm, an ejection fraction of the LV was 65.39 ± 6.96%, and the left atrial surface was 17.42 ± 2.71 cm² (Table 5). The LV diameters and walls were within normal range in 38 patients (n=38; 45.23%) at the superior limit of the normal values, indicating incipient LV hypertrophy and LA dilatation. The athletes with modified echocardiographic parameters were identified exclusively in the endurance sports group (i.e., cycling, natation, rugby, and marathon running).

APS properties and sudden death risk evaluation

Following the standard evaluation sequence, the EPS proved to be the primary investigation to establish the SD risk. Seventeen athletes (n=17; 20.23%) were found with SD risk: 15 (n=15; 17.85%) belonging to the WPW syndrome group and 2 (n=2; 2.38%) to the WPW pattern group.

Four patients (n=4; 4.76%) presented with syncope during the EPS. Syncope was determined by AF conducted over a short effective anterograde refractory period (EARP) AP in 3 patients (2 belonging to the WPW syndrome group and 1 to the WPW pattern group). AVART anterogradely mediated over 2 distinct APs; both with short AERP also were associated with syncope in 1 patient from the WPW pattern group.

Multiple APs were present in 9 athletes (n=9; 10.7%), from which 2 patients were found at risk of SD linked to short AERP of at least 1 of the APs, AF, or syncope.

The decision for RFA was made based on the properties of the AP/APs and the patient's request if the EPS showed no risk of SD at baseline. Eighty-one (n=81; 96.4%) athletes with AP/APs were treated with RFA, with recurrence in 2 patients who underwent successful ablation in a repeated procedure over the next 3 months following the first ablation. The remaining 3 patients decided not to undergo RFA after the EPS showed AP properties outside the danger area.

The invasive screening of the patients showed another category of patients with SD risk with short AP AERP or multiple AP in the

Table 6 - Distribution of patients with sudden death risk criteria

Parameters	WPW syndrome n (%)	WPW pattern n (%)	Total n (%)
Short EARP AP<250 ms	15 (17.85)	2 (2.38)	17 (20.23)
Minimal pre-excited RR interval during AF <250 ms	2 (2.38)	1 (1.19)	3 (3.57)
Reentry tachycardia with hemodynamic collapse and syncope	0 (0)	1 (1.19)	1 (1.19)
Syncope during pre-excited AF	2 (2.38)	1 (1.19)	3 (3.57)

Note. WPW: Wolff-Parkinson-White, EARP: effective anterograde refractory period, AP: accessory pathway, AF: atrial fibrillation, RR: two R-waves

absence of AF or syncope: 12 (n=12; 14.28%) had short AP AERP (<250 ms), and 6 had multiple accessory pathways from which 4 had at least 1 AP with short AERP.

The SD risk was assessed in both WPW groups: patients already diagnosed with WPW syndrome and athletes with WPW patterns without any history of arrhythmia. This was defined by the presence of at least 1 of the following (Table 6): short EARP <250 ms, minimal pre-excited RR interval during AF <250 ms, tachycardia with hemodynamic collapse, or syncope during tachycardia/atrial fibrillation. The majority of patients (n=15; 88.23%) with risk criteria for SD were men. All patients with minimal pre-excited RR <250 ms, reentry tachycardia (antidromic) causing hemodynamic collapse, respectively, with syncope during pre-excited AF had at least 1 short EARP AP.

Programmed atrial stimulation led to sustained AF in 11 patients (n=11; 13.09%), uncovering a great SD risk in 3 patients in which pre-excited AF produced hemodynamic collapse with the need for external electrical conversion to sinus rhythm. Right and left atrial fragmentation signals (displayed by the right atrial and coronary sinus recordings) were obvious during sinus rhythm in 38% of patients.

Seven (n=7; 8.33%) patients with SD risk were endurance athletes, representing 46.6% of all patients at risk of SD. Twenty-three patients (n=23; 27.38%) had Kent fibers presenting with anterograde conduction only, from which 1 was found with SD risk generated by AF conducted down a short AERP AP, necessitating cardioversion.

There were no complications related to the EPS or RFA.

Discussion

Easily revealed by surface ECG, the prevalence of WPW pattern in the general population ranges from 0.15% to 0.25%, increasing to 0.55% among first-degree relatives of patients with Kent fibers [25]. WPW syndrome is responsible for at least 1% of SD in athletes. The percentage might be even more significant, which may account for many deaths for which the autopsy was negative because of the challenges in establishing the postmortem diagnosis of WPW syndrome [26].

The AP or the Kent fiber is different from the physiological atrioventricular conduction system in terms of electrical properties. The AP is a direct electrical connection between the atria and the ventricles and competes with the physiological atrioventricular connection, conducting electrical impulses in a fast and nondecremental pattern. In most of the reported cases, the histology of an AP showed that the atrioventricular connection is composed of "working" myocardium but also may be composed of "specialized" myocardial cells [27].

The presence of APs is responsible for 3 types of arrhythmia: AVART, AVORT, and pre-excited AF. AVORT is the most common reentrant tachycardia associated with WPW syndrome. It uses the atrioventricular node anterogradely and the AP retrogradely for closing the reentry circuit. During AF, the AP acts as a bystander conducting the atrial impulses quickly and in proportion to the capacity of conduction recovery, respectively, to the value of the AERP.

The AVART uses the Kent bundle anterogradely and the normal atrioventricular conduction pathway as the circuit's retrograde loop. Morphologically it is a wide QRS tachycardia that occurs much less frequently than the AVORT. The AVART has been documented in about 5% of patients with WPW syndrome. It is more likely associated with syncope than AVORT and may be induced in less than 10% of patients with APs during the EPS [28].

The present study assessed all significant SD risk parameters in patients with anterograde-conducting Aps. Death results from AF conducted down an AP with a short AERP, arrhythmia, which may easily degenerate into ventricular fibrillation. The conditions contributing to the modification of SD risk are the following: AERP ≤250 ms, corresponding to the shortest RR pre-excited interval during AF, the degree of adrenergic charge proportional to the permeabilization of the AP, and presence of multiple Aps.

The parameters establishing the risk of SD in our study are as follows:

- short EARP (i.e., <250 ms)
- minimal pre-excited RR interval during AF <250 ms (Figure 1)
- AVART with a hemodynamic collapse in 1 patient
- syncope during tachycardia/AF.

The present research revealed a noticeable difference between the number of patients at risk of SD belonging to the WPW syndrome and WPW pattern groups (17.85% vs. 2.38%).

Although a significant proportion of our patients were men, being male is linked to the type of sport they engaged in, so we cannot assume, based exclusively on this study, that being male is a risk factor for SD. Intense physical activity usually induces adaptive changes to the heart. The most frequent activity-induced cardiac modifications are increased left ventricular and right ventricular size, left ventricular hypertrophy, and left atrial dilation and fibrosis. The heart remodeling is reflected in both ECG and echocardiography. In the presence of Kent fibers, hypertrophy and ischemia cannot be judged based on surface ECGs. Thus, the authors used echocardiography exclusively at inclusion to assess structural changes. In our study, the majority of athletes presenting



Figure 1 - Atrial fibrillation was conducted over a Kent bundle with a short anterograde refractory period associated with a minimal pre-excited RR interval of ~200 ms. At the end of the ECG recording, AF degenerates into ventricular fibrillation.

Note. RR: two R-waves, ECG: electrocardiogram, AF: atrial fibrillation

with echocardiographic hypertrophy of the left ventricular and left atrial enlargement was associated with endurance sports (i.e., cycling, natation, rugby, and marathon running). Left atrial enlargement linked to enhanced filling pressures and volume of the LV is a generator of atrial ectopic beats, which explains how AF due to atrial remodeling may be caused by intense physical activity. The mechanisms producing AF in athletes are speculative. However, the combined effects of exercise-induced left atrial remodeling and inflammation increased sympathetic activity during exercise, and parasympathetically mediated slow resting heart rates potentiating atrial escape have been incriminated as potential factors [29]. Another theory that may explain the occurrence of AF in patients with ventricular pre-excitation is the presence of multiple APs. Sharma et al. demonstrated that AF occurs in more than one-third of patients with WPW syndrome regardless of age [30]. Patients with WPW and AF have a higher association of multiple, posteriorly, and epicardial-situated AP, producing a vulnerable atrial state [31]. Various mechanisms are responsible for AF in patients with anterograde conducting AP, mainly the AP's electrophysiological properties, the AP insertion's effects on the atrial architecture, the intrinsic atrial vulnerability, and the degeneration of AVART into AF [32]. Jackman et al. emitted micro reentry theory. Reentries within the AP strands' branching networks can be the basis of the genesis of atrial flutter or fibrillation [33]. Following this hypothesis, one can assume that the higher the number of APs, the higher the incidence of AF linked to pre-excitation.

Stress hormones adrenaline and noradrenaline concentrations may increase during exercise between 1.5 to > 20 times, depending on the effort's duration and intensity [34].

RFA is a therapeutic option that, if successful, allows resuming sports after a maximum of 3 months.

Explicit statements and guidelines regarding the management and treatment of patients with WPW patterns have lacked for a long time. The 2015 European Society of Cardiology (ESC) Guidelines for the Management of Sudden Death recommended ablation in patients with WPW syndrome resuscitated from sudden cardiac arrest caused by AF conducted down the AP and degenerating into ventricular fibrillation [35]. This strategy carried out an enormous risk, especially for athletic individuals. However, the following published guideline touching on this subject, the 2019 ESC Guidelines for the Management of Patients with Supraventricular Tachycardia, has a more cautious approach regarding WPW patients, recommending accurate EP testing in patients with persistent pre-excitation and the ablation of the AP in symptomatic athletes [36].

This study pointed out the importance of complex assessment of anterograde conducting APs in athletes. It proposed an algorithm for SD risk factors screening, which may reduce the lifetime risk of SD in this specific population.

The potential limitations of this research are single-center experience and the relatively small number of included patients. Also, this study did not evaluate strategies using pharmacologic testing for risk stratification [37,38]. The importance of the study emphasizes

the need for complex and careful evaluation, even in asymptomatic athletes, because SD could be the first symptom of ventricular pre-excitation [39].

Conclusions

The SD risk factors among athletes are more frequent than initially thought. This study revealed that 20.23% of the patients had pre-excitation-related sudden death risk factors (short EARP AP <250 ms). Furthermore, in 4.76% of the athletes, the imminence of death was caused by minimal pre-excited RR interval during AF <250 ms, tachycardia with hemodynamic collapse, and syncope during tachycardia/AF.

A complex electrophysiological evaluation is highly recommended in all patients with pre-excitation, regardless of arrhythmia.

Safe ablation should be mandatory in patients with reentry tachycardia, APs with EARP equal to or lower than 250 ms with or without AF, with the possibility of resuming sports in a maximum of 1 month after RFA.

Perspectives. Athletes are a particular category of patients with WPW; they may have changes in the AP's electrical properties in

the sense of permeabilization and decreasing the EARP under the influence of stress hormones. In this category of patients, AF occurs more often, sometimes at a young age, and depends on the sport's degree of difficulty and endurance. The fact that athletes consume high-dose caffeine or other energizers before competitions can result in further changes in atrial and ventricular myocardium properties, becoming electrically vulnerable. These aspects often place the athlete in the middle of a multitude of factors that can trigger a perfect storm of SD in the presence of an AP. Further research is needed to establish the degree of risk for these patients.

Conflict of Interest

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References

- Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *J Am Med Assoc* 2006;296:1593–1601. doi:10.1001/jama.296.13.1593.
- Futerman LG, Myerburg R. Sudden death in athletes. An update. *Sport Med* 1998;26:335–50.
- Rao AL, Salerno JC, Asif IM, Drezner JA. Evaluation and management of Wolff-Parkinson-White in athletes. *Sport health* 2014;6:326–32. doi:10.1177/1941738113509059.
- Ferreira M, Santos-Silva PR, de Abreu LC, Valenti VE, Crispim V, Imaizumi C, Filho CF, Murad N, Meneghini A, Riera ARP, et al. Sudden cardiac death athletes: a systematic review. *Sports Med, Arthrosc, Rehab, Ther Technol* 2010;2:19.
- Endres BD, Kerr ZY, Stearns RL, Adams WM, Hosokawa Y, Huggins RA, Kucera KL, Casa DJ. Epidemiology of sudden death in organized youth sports in the United States, 2007–2015. *J Athlet Train* 2019;54:349–55. doi:10.4085/1062-6050-358-18.
- Iurciuc S, Avram C, Turi V, Militaru A, Avram A, Cimpean AM, Iurciuc M. Physical training, hemodynamic parameters, and arterial stiffness: friends or foes of the hypertensive patient? In vivo (Athens, Greece) 2016;30.
- Crimi E, Ignarro LJ, Cacciatore F, Napoli C. Mechanisms by which exercise training benefits patients with heart failure. *Nat Rev Cardiol* 2009;6:292–300.
- Silverman MN, Deuster PA. Biological mechanisms underlying the role of physical fitness in health and resilience. *Interface Focus* 2014;4.
- Mihl C, Dassen WRM, Kuipers H. Cardiac remodelling: concentric versus eccentric hypertrophy in strength and endurance athletes. *Neth Heart J* 2008;16:129–33.
- Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Int Med* 1975;82:521–24. doi:10.7326/0003-4819-82-4-521.
- Pelliccia A, Maron MS, Maron BJ. Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete's heart from pathologic hypertrophy. *Prog Cardiovasc Dis* 2012;54:387–96. doi:10.1016/j.pcad.2012.01.003.
- Crîșan S, Tint D, PL. Therapeutic advances in emergency cardiology: a focus on acute myocarditis. *Am J Ther* 2019;26. doi:10.1097/MJT.0000000000000921.
- Fujita S, Fujii E, Sugiura S, Ito M. Atrioventricular accessory pathway with anterograde decremental conduction property. *BMJ Case Reports* 2013;2013. doi:10.1136/bcr-2013-009814.
- Gupta A, Al-Ahmad A. Wolff-Parkinson-White syndrome. In *Cardiac Electrophysiology: Clinical Case Review*. Springer International Publishing, 2020, 267–69. ISBN 9783030285333.
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Euro Heart J* 2020;1–126. doi:10.1093/eurheartj/ehaa612.
- Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. *Ochsner J* 2009;9:191–96.
- Zachariah JP, Walsh EP, Triedman JK, Berul CI, Cecchin F, Alexander ME, Bevilacqua LM. Multiple accessory pathways in the young: the impact of structural heart disease. *Am Heart J* 2013;165:87–92. doi:10.1016/j.ahj.2012.10.025.
- Brugada J, Keegan R. Asymptomatic ventricular pre-excitation: between sudden cardiac death and catheter ablation. *Arrhythm Electrophysiol Rev* 2018;7:32–38. doi:10.15420/aer.2017.51.2.
- Grazioli G, Sanz M, Montserrat S, Vidal B, Sitges M. Echocardiography in the evaluation of athletes. *F1000 Research* 2015;4:151.
- Wackel P, Irving C, Webber S, Beerman L, Arora G. Risk stratification in Wolff-Parkinson-White syndrome: the correlation between noninvasive and invasive testing in pediatric patients. *PACE—Pacing Clin Electrophysiol* 2012;35:1451–57. doi:10.1111/j.1540-8159.2012.03518.x.
- Negru AG, Alzahrani T. *Electrophysiologic Testing*. StatPearls Publishing, 2020.
- World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA: J Am Med Assoc* 1997;277:925–26. doi:10.1001/jama.1997.03540350075038.
- Iqbal AM, Ghazni MS, Mubarik A, Zubair N, Jamal SF. The conversion of Wolff-Parkinson-White (WPW) pattern into WPW syndrome in the presence of ischemia: a case report. *Cureus* 2019;11:e4147. doi:10.7759/cureus.4147.
- Arruda MS, McClelland JH, Wang X, Beckman KJ, Widman LE, Gonzalez MD, Nakagawa H, Lazzara R, Jackman WM. Development and validation of an ECG algorithm for identifying accessory pathway ablation site

in Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 1998;9:2–12. doi:10.1111/j.1540-8167.1998.tb00861.x.

25. Santinelli V, Radinovic A, Manguso F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Ciconte G, Sacchi S, Sala S, et al. The natural history of asymptomatic ventricular pre-excitation. A long-term prospective follow-up study of 184 asymptomatic children. *J Am Coll Cardiol* 2009;53:275–80. doi:10.1016/j.jacc.2008.09.037.

26. Rao AL, Salerno JC, Asif IM, Drezner JA. Evaluation and management of Wolff-Parkinson-White in athletes. *Sports Health* 2014;6:326–32. doi:10.1177/1941738113509059.

27. Waller BF, Gering LE, Branyas NA, Slack JD. Anatomy, histology, and pathology of the cardiac conduction system—Part V. *Clin Cardiol* 1993;16:565–69. doi:10.1002/clc.4960160710.

28. Ali R, Tahir A, Nadeem M, Shakhathreh MI, Faulkner B. Antidromic atrioventricular reentry tachycardia with Wolff Parkinson White syndrome: a rare beast. *Cureus* 2018;10:e2642. doi:10.7759/cureus.2642.

29. Baggish AL, Wood MJ. Athlete's heart and cardiovascular care of the athlete | EndNote Click Available online: <https://kopernio.com/>