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Titolo della tesi

INTERMITTENT VENTRICULAR PRE-EXCITATION IN SYMPTOMATIC ADULTS: ALWAYS A MARKER OF LOW RISK?

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ABSTRACT

Background: Intermittent ventricular pre-excitation was considered a low-risk marker for sudden death. However, to date, some studies do not exclude the existence of accessory pathways (APs) with high-risk intermittent antegrade conductive properties. According to current European Guidelines, high-risk features of APs are antegrade pathway conduction ≤250 msec in baseline or during the adrenergic stimulus, inducibility of atrioventricular reciprocating tachycardias (AVRT), inducibility of pre-excited atrial fibrillation (AF), and presence of multiple APs. For all of these transcatheter ablation is recommended.

The aim of our study was to evaluate the existence of differences in risk characteristics between patients with intermittent pre-excitation (IPX) and those with persistent pre-excitation (PPX), from a sample of adults with ventricular pre-excitation and symptoms like palpitations.

Methods: 293 adults [IPX: 51 (17.4%); PPX: 242 (82.6%)] underwent electrophysiological (EP) study and then catheter ablation of their APs if arrhythmia inducibility (AVRT/AF) was noted, or, conversely, if it was appreciated a fast AP antegrade conduction, in baseline or during intravenous isoproterenol infusion, or if multiple APs were detected.

Results: There were no statistically significant differences in demographic characteristics of age [IPX: mean age 37.23±16.89 years *vs* PPX: mean age 39.03±16.19; *p-value* = 0.21] and gender [IPX male: 31 (60.8%) *vs* PPX male: 152 (62.8%); *p-value* = 0.28]. Also EP features like AVRT/AF inducibility [IPX: 27 (52.9%) vs PPX: 100 (41.3%); p-value = 0.13], antegrade conductive properties [IPX: mean ERP 260±45.8 msec vs PPX: mean ERP 267.7±59.6msec; p-value = 0.5], prevalence of multiple APs (p-value = 0.56), and APs locations (p-value = 0.32) did not demonstrate any significant differences between IPX and PPX patients.

Conclusions: In our study, patients with IPX did not show significant differences in clinical and electrophysiological features *vs* PPX patients.

CONTENTS

Abbreviations and acronyms

AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
AP	Accessory pathway
AV	Atrioventricular
AVN	Atrioventricular node
AVNRT	Atrioventricular nodal re-entrant tachycardia
AVRT	Atrioventricular re-entrant tachycardia
b.p.m.	Beats per minute
COCIS	Italian protocol for sports activity
DHP	Dihydropyridine
ECG	Electrocardiogram
EPS	Electrophysiology study
ERP	Effective refractory period
ESC	European Society of Cardiology
EST	Exercise Stress test
IPX	Intermittent ventricular pre-excitation
PPX	Persistent pre-excitation
SCD	Sudden cardiac death
SPERRI	Shortest pre-excited RR interval during atrial fibrillation
RF	Radiofrequency
SD	Standard deviation
VF	Ventricular fibrillation
WPW	Wolff-Parkinson-White

1. Wolff-Parkinson-White syndrome (WPW)

Wolff-Parkinson-White syndrome (WPW) is characterized by the association of an atrio-ventricular accessory pathway (AP), which can – generally – conduct the impulse faster than the normal conduction pathway and symptoms like palpitations due to arrhythmias related to AP.[1-3] The abnormal pathway electrically connects the atria to the ventricles – and viceversa – and allows an impulse generated in one chamber (atria or ventricles) to reach the other one, bypassing the normal atrio-ventricular conduction pathway represented by AV node and His bundle.[1-3]

This abnormal connection can be single or multiple and it can be located anywhere at the level of the mitral or tricuspid annulus, although left pathways and more specifically the left lateral ones are more prevalent (figure 1).[1-3] Rarely, the pathways may be located near the nodal-hisian system: the so called para-hisian bundles.[1-3]

The accessory pathway can activate part of the ventricular myocardium with variable extent before it is reached by the impulse travelling along the phisiological conduction pathway. This area of the ventricle is therefore "pre-excited". Preexcitation is possible because the accessory pathways are made up of fast sodium-dependent fibres that conduct quickly, unlike the AV node, which is made up of slow calcium-dependent fibres that are responsible for the physiological delay of the supraventricular impulse.[1-3]

1.1 Embryogenesis

In the early stages of heart development, the atrium and the primitive ventricle are not electrically separated but are continuously connected.[2] Only later, as the fibrous skeleton of the heart grows, the atria electrically separate from the ventricles and any pre-existing muscular connection degenerates and disappears, giving way to the fibrous tissue that forms the trigone and the two atrioventricular anuli.[2] For this reason, the supraventricular impulse is conducted almost simultaneously to both ventricles by the specialized conduction system that includes the AV node and the His-Purkinje fibers.[2] Sometimes, bundles of muscle which originally connected the

atria and the ventricles do not disappear: these fascicles constitute the accessory pathways.[2]

1.2 Accessory pathways classification

There are two different types of accessory pathways, depending on their cardiomyocites type[2]:

- Na^+ dependent – non-decremental fibers, divided in:
  - common Kent's accessory pathways, which directly connect the atria to the ventricles and capable of antegrade, retrograde or both conduction properties;
  - rare (true) Mahaim's accessory pathways, which connect the AV node directly to the right bundle or right ventricular myocardium (named nodo-fascicular and nodo-ventricular accessory pathways, respectively)[4];
- rare Ca^{2+} dependent – decremental fibers, divided in:
  - antegradely conducting: inappropriately know as Mahaim's fibers[4];
  - retrogradely conducting: the so called Coumel's fibers and responsible of the homonymous tachycardia[2-3].

Na^+-dependent fibers have high conduction velocity because and a shorter refractory period than that of the physiological atrioventricular pathway.

Conduction through the Kent bundle is independent of heart rate and occurs in an on/off mode. This means that the conduction time remains the same regardless of frequency and an impulse can be conducted or blocked, but if conduction does occur, there is no slowing down along the accessory pathway regardless of the prematurity of the impulse. The sinus impulse is usually able to reach the ventricles via the accessory pathway more quickly than via the normal conduction pathway, so that part of the ventricle is pre-excited.[2-3] A Kent bundle may conduct the impulse in both directions (60%), but there may be cases of only retrograde conduction (45%) and, exceptionally, only anterograde conduction (5%). If the conduction is only retrograde, there is no ventricular pre-excitation and it is defined

concealed accessory pathwway. Conversely, the evidence of ventricular pre-excitation, due to a Kent bundle with antegrade conductive properties, is named **manifest** ventricular pre-excitation. However, even if the accessory pathway has antegrade conduction properties, there is not always evidence of ventricular preexcitation during sinus rhythm. This may be due to a longer activation time through the accessory pathway than through the normal pathway – usually seen for left lateral APs which are located further away than AVN from the sinus node -, or to intermittent antegrade impulse block in the normal pathway. In some subjects, the pre-excitation is intermittent and disappears for long periods. The latter is defined **intermittent** ventricular pre-excitation.[2]

Most Kent bundles can conduct the impulse rapidly, but there is a minority of people in whom the accessory pathway conducts the impulse very slowly. These 'slow' accessory pathways are not usually associated with ventricular pre-excitation because the ventricles have already been activated by the impulse travelling through the AV node before the accessory pathway can initiate depolarization of the ventricles.

1.2.1 Manifest pre-excitation

In manifest pre-excitation, we have a corresponding electrocardiographic implication represented by a shortening of the PR interval and the presence of the δ wave with associated QRS widening. The short PR interval, generally < 0.12 seconds, is due to Kent bundle conduction faster than the nodo-Hisian pathway, so that activation of the ventricles begins earlier than when the impulse is only conducted through the AV node. Wide QRS, on the other hand, is due to the ventricles being electrically activated partly by the normal AV conduction system and partly by the accessory pathway, creating a 'fusion' complex.[2]

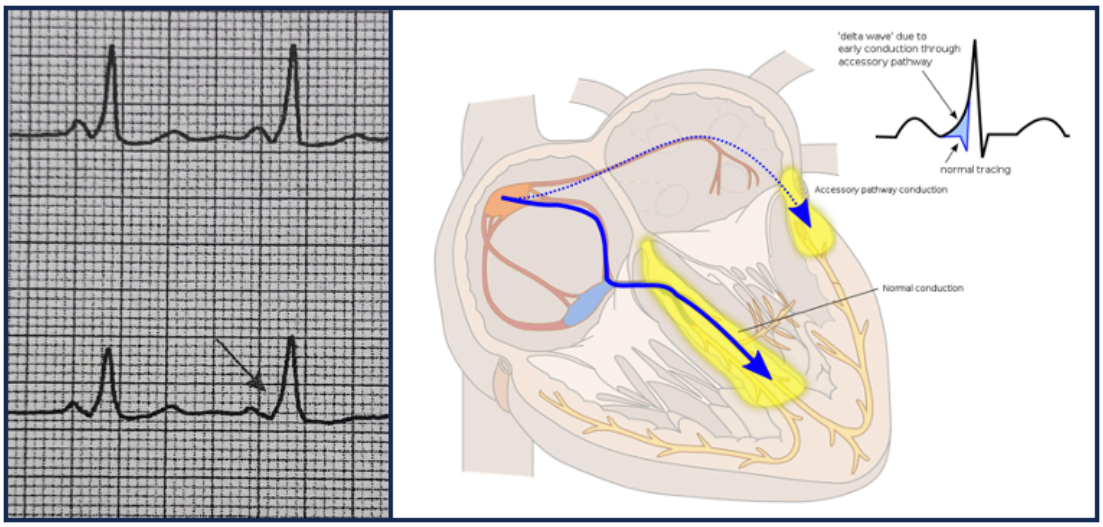

Figure 1. Right panel. Manifest pre-excitation signs: short PQ duration (≤0,12 sec); δ wave (arrow) and wide QRS. Left panel. Representation of ventricular activation in presence of an accessory pathway: QRS activation and morphology derive from a variable grade of fusion between conduction over physiological pathway and accessory one. The part of ventricle pre-excited is electrically represented by the δ wave (shown in detail).

Generally speaking, the initial activation is due to Kent's bundle, which conducts more rapidly, whereas in the later stages of depolarization both pathways contribute. The potential for an accessory pathway to activate part of the ventricles depends firstly on the location of the abnormal bundle: if its atrial insertion is far from the sinus node, it will take a longer time for the sinus impulse to reach the atrial insertion of the accessory pathway, whereas a Kent bundle close to the sinus node will be reached by the sinus impulse in a shorter time.[3] A left accessory pathway is less likely to pre-excite a large amount of ventricular tissue than a right accessory pathway because the impulse from the sinus node must activate the right atrium and then trasmitted to the left before reaching the left accessory pathway. The extent of pre-excitation also depends on the conduction properties of the AVN: if it conducts rapidly, it is likely that a large part of the ventricular mass will be activated by the physiological pathway, whereas the Kent bundle will only pre-excite a limited ventricular area, so the pre-excitation will be modest.[3] The opposite phenomenon occurs when conduction through the node is slowed so that most or all the ventricular mass is activated by the Kent bundle. When, even in the presence of an accessory pathway capable of anterograde conduction, the ventricular mass is activated only by the normal pathway without signs of pre-excitation, this is termed

non-manifest pre-excitation.[3] If, in this context, AVN conduction-depressing maneuvers are performed, ventricular pre-excitation may be seen. AV node conduction depression or block may be obtained by vagal maneuvers (like Valsavae ora carotid sinus massage) or administration of AV node blocking drugs (like adenosine, beta-blockers, non-DHP-calcium blockers).[3]

1.2.2 Concealed accesory pathways

Concealed accessory pathways can conduct only retrogradely (from ventricles to atria), so the ECG in sinus rhythm shows no evidence of pre-excitation. The presence of a concealed accessory pathway can only be deducted from the analysis of the surface ECG in case of an orthodromic AV re-entrant tachycardia, a supraventricular narrow QRS regular tachycardia characterised by a RP'<P'R and RP'≥90 msec.[1] A phenomenon that leads to the suspicion of an occult accessory pathway is the recurrence of episodes of paroxysmal atrial fibrillation in a young person without heart disease: in this situation, the triggering of the atrial fibrillation is often associated with the presence of a Kent bundle that is only capable of retroconduction.[1-3] Occult Kents should not be confused with the non-manifest forms, in which there is no evidence of pre-excitation during sinus rhythm, but which may be induced by manoeuvres that slow nodal conduction or during atrial fibrillation. The diagnosis of occult preexcitation is straightforward during electrophysiological study, as non-decremental (eccentric or not) atrial retroactivation is observed during ventricular pacing and orthodromic AV re-entry tachycardia can also be induced.

1.3 12 lead ECG accessory pathways localization

The accessory pathway can be accurately localised only by electrophysiological study. However, a careful evaluation of the basal 12-lead ECG is essential in the location of the pathway, which may be anterior (or superior), posterior (or inferior),

lateral (right or left sided), or septal, and sometimes it helps in the recognition of the presence of multiple accessory pathways.[1-3]

1- There are different algorithms for the localization of an accessory pathway basing on 12 lead ECG and following there are the main features included in them:δ wave and QRS analysis during sinus rhythm, with or without full ventricular pre-excitation

2- Retrograde P-wave morphology/axis analysis during atrioventricular re-entry tachycardia

3- Changes in orthodromic tachycardia cycle lenght associated with onset of ipsilateral functional bundle branch block (Coumel's sign).

Following, there are pictured in figure 2-4 some examples of algorithms for 12-lead ECG APs localization.

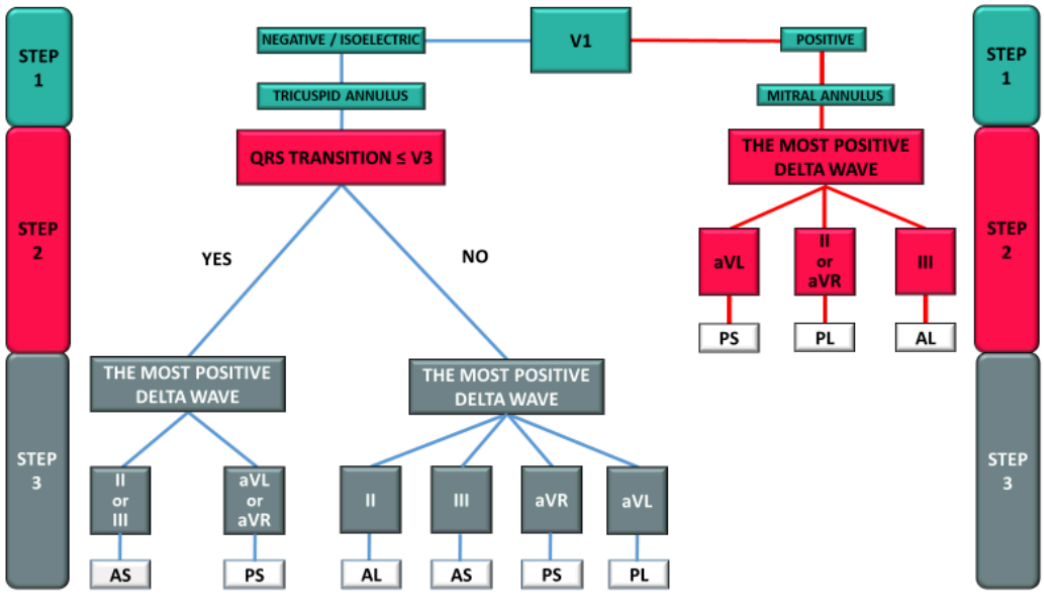

Figure 2. EASY-WPW: a novel ECG-algorithm for easy and reliable localization of accessory pathways in children and adults.[5]

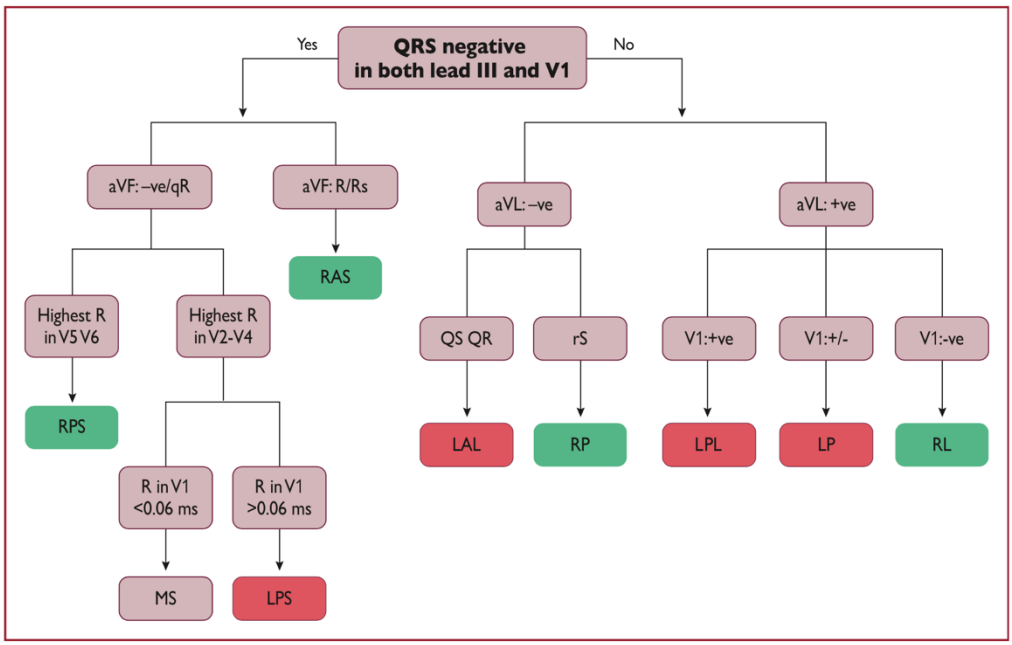

Figure 3. The St George's algorithm for the localization of accessory pathways +ve= positive QRS complex; -ve = negative QRS complex; +/- = isoline QRS complex.[1]

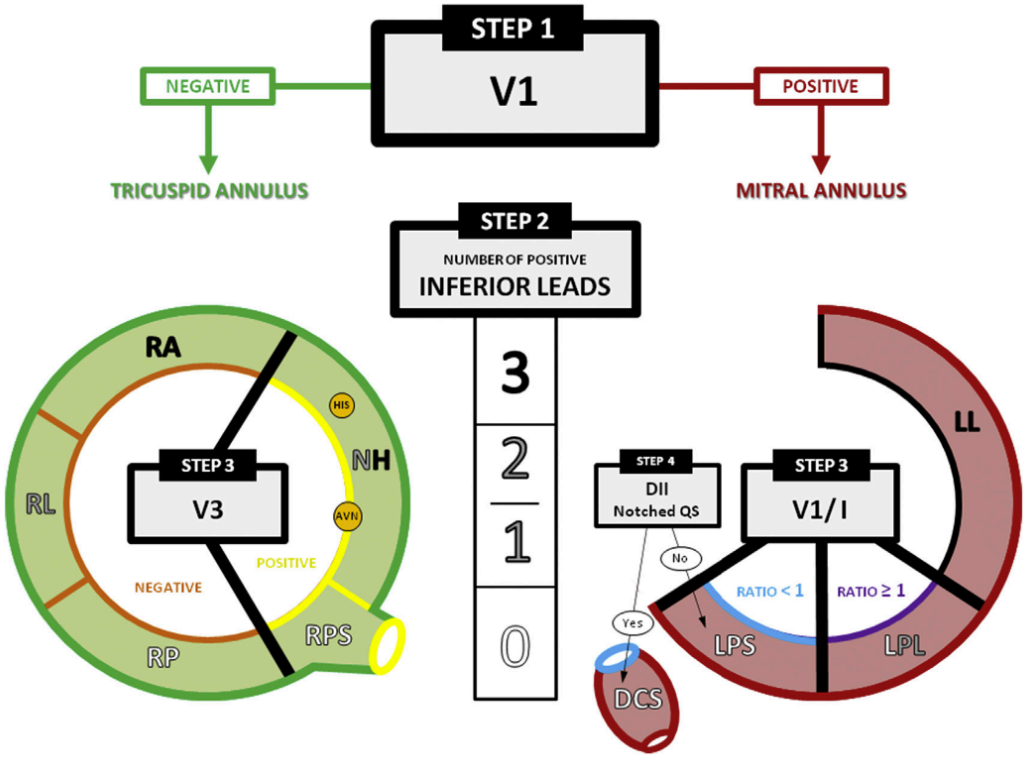

Figure 4. Pambraun's et algorithm for localization of accessory pathway in the presence of maximum (spontaneous or evoked) pre-excitation. Accessory pathway locations are green when right-sided and red when left-sided. Left posterolateral accessory pathways can have 0,1 or 2 inferior leads with positive polarity, whereas nodo-Hisian accessory pathways can have1, 2, or 3 inferior leads with positive polarity. Right-sided accessory pathways are framed orange or yellow when the V3 lead is negative or positive, respectively. Left posterior accessory pathways are framed blue when the V1/1 ratio is <1 or purple when V1/l ratio is ≥ 1.[6]

1.4 Electrophysiological study in pre-excitation

An endocavitary electrophysiological study (EPS) is an invasive diagnostic test that assesses the electrical properties of the heart and its susceptibility to developing different types of arrhythmia. The goal of EPS is to identify the type of arrhythmia being studied. A variable number of catheters are inserted through the venous system and placed in different locations in the heart. Generally speaking, an ablation catheter is then inserted into the right or left heart if an ablation is needed.[3]
It is based on:

- Simultaneous recording of the ECG and intracavitary electrocardiograms obtained through diagnostic and/or mapping catheters inserted into the heart cavities.
- Electrical stimulation applied at different points in the atria or ventricles. The information provided by intracavitary recordings combined with artificial pacing defines the electrical phenomena of the heart with greater precision than is possible with conventional 12 lead ECG, Holter monitoring, transesophageal EPS, and so on.

Surface ECG is also continously monitored during all the steps of the procedure.
In the specific case of an EPS carried out for the evaluation of an AP, the purposes are:

1 Define the antegrade and retrograde atrioventricular conduction;
2 Measure the anterograde effective refractory period (ERP) of the Kent bundle, in baseline and during adrenergic stimulus (iv. isoproterenol infusion);
3 Induce AV re-entry tachycardia and/or atrial fibrillation (AVRT/AF), in baseline and during adrenergic stimulus;
4 Determine the number and the precise location of the accessory pathway(s).

Point 2 to 4 are mandatory to be checked because of, in case of an asymptomatic patient, they are crucial in the decision to perform or not AP ablation.[1]
Risk features of accessory pathway requiring ablation are:[1]

- ERP≤250 msec (in baseline or during adrenergic stimulus),

- AVRT induction,
- Fast conducting AF (SPERRI≤250 msec – see later),
- Multiple accessory pathways.

1.5 Localization of the accessory pathways with endocavitary mapping

The ECG may suggest the location of the AP, but should be reiterated that it can be accurately mapped only during an endocavitary EPS. The atrioventricular ring is mapped to define the specific location of Kent's bundle and the point at which the shortest A-V interval is recorded during anterograde conduction or atrial pacing or where the shortest V-A interval is seen during ventricular pacing or orthodromic AVRT. The catheter is placed at the right or left AV annulus in contact with the endocardium and is progressively advanced until the shortest conduction interval (named “fused” AV or VA signal) is found or, better, where an AP potential is seen or unmasked during differential pacing.[3]
An accurate mapping is crucial for ablation success and prevention of recurrence.

1.5.1 Multiple accessory pathways

In some subjects with pre-excitation (10-15% of cases), more than one accessory pathway is present.[1] The data show that the presence of multiple accessory pathways is more common than one might think in clinical practice; some of these pathways do not conduct the impulse and are non manifest or concealed. The presence of more than one accessory pathway increases the incidence of symptoms and is also associated with an increased risk of sudden death from atrial fibrillation converting to ventricular fibrillation.[1] It has been observed that patients with pre-excitation who have suffered a cardiac arrest have a significantly higher incidence of multiple pathways than controls who have not had cardiac arrest.[1-3]

Using the following criteria, multiple accessory pathways can be observed on the ECG

a) Two different pre-excited morphologies in atrial fibrillation.
   The atrial rate is very high and the two abnormal pathways compete with each other and with the nodal pathway to deliver the impulse to the ventricles. A change in the morphology of the pre-excited QRS shows that the atrial impulse reaches the ventricles using different pathways. For example, the diagnosis of a dual accessory pathway requires the presence of two different types of QRS complexes, each perfectly having characteristic of a particular location of the Kent bundle. It is possible to find beats with an intermediate morphology, expressing a fusion between the two different activation modes. Notably, the variability of the pre-excited QRS morphology in AF is not sufficient for the diagnosis of multiple accessory pathways, because it may depend on the fusion between the impulse conducted by an accessory pathway and that conducted by the His bundle. Only the presence of two distinct and different pre-excited morphologies establishes the diagnosis.
b) Mismatch between the location of the accessory pathway determined from P'-wave polarity during orthodromic tachycardia and that inferred from δ wave/QRS morphology during sinus rhythm or atrial fibrillation.
c) Two different P waves during different episodes of orthodromic AVRT. Retrograde P morphology variation is not possible if the accessory pathway is only one, and if the tachycardia is orthodromic, conduction to the atria cannot take place via the AV node, which is used for anterograde conduction.
d) Rapid transition from an orthodromic tachycardia to an antidromic tachycardia or vice versa The transition from an orthodromic to an antidromic tachycardia without interruption of the tachycardia necessarily requires two accessory pathways. During orthodromic tachycardia, Kent's bundle is used to conduct the impulse from the ventricle to the atrium and an accessory pathway cannot suddenly reverse the direction of conduction. An orthodromic tachycardia can become an antidromic tachycardia if there is a second abnormal pathway capable of conducting the impulse anterograde and if the first accessory pathway conducts in the retrograde direction.

1.6 Arrhythmias in pre-excitation

The most common arrhythmias in pre-excitation are AV re-entry tachycardia and atrial fibrillation.[1] In particular, there are two forms of AVRT:

- Ortodromic (more frequent)
- Antidromic (less frequent)

1.6.1 Orthodromic atrio-ventricular reciprocating tachycardia

Orthodromic AV reciprocating tachycardia is characterized by narrow QRS complexes, while the antidromic form necessarily has wide, fully pre-excited QRS complexes, each of which corresponds to a "pure" δ wave. In the antidromic tachycardias, the activation of the ventricles depends exclusively on the accessory pathway. Orthodromic tachycardia can be given by a manifest AP or a concealed one. Therefore, orthodromic AV re-entrant tachycardia may be present both in subjects with WPW syndrome (manifest pre-excitation) and in subjects in whom no signs of ventricular pre-excitation are present in sinus rhythm. Antidromic tachycardia can not be possible if the accessory pathway is not capable of antegrade conduction.

AVRT may be induced by an atrial or ventricular extra-beat (Figure 5).

The 12 lead ECG features of orthodromic AV reentrant tachycardia are:

a) If there is no aberrant conduction or pre-existing bundle branch block, QRS is narrow, with regular RR cycles, and rate between 120 and 250 bpm, but more often around 170-200 bpm.
b) The P wave can usually be observed in the ST segment or in the T wave. P wave morphology suggests retrograde eccentric atrial activation (except for septal APs);
c) RP'≥90 msec and RP'≤'PR;
d) Vagal nerve stimulation can stop the tachycardia with AV block so we usually see blocked retrograde P wave;

e) There may be ECG changes (ST depression in multiple leads) which do not express myocardial ischemia, but this is a not specific finding (it can be seen in different kind of paroxysmal SVTs).

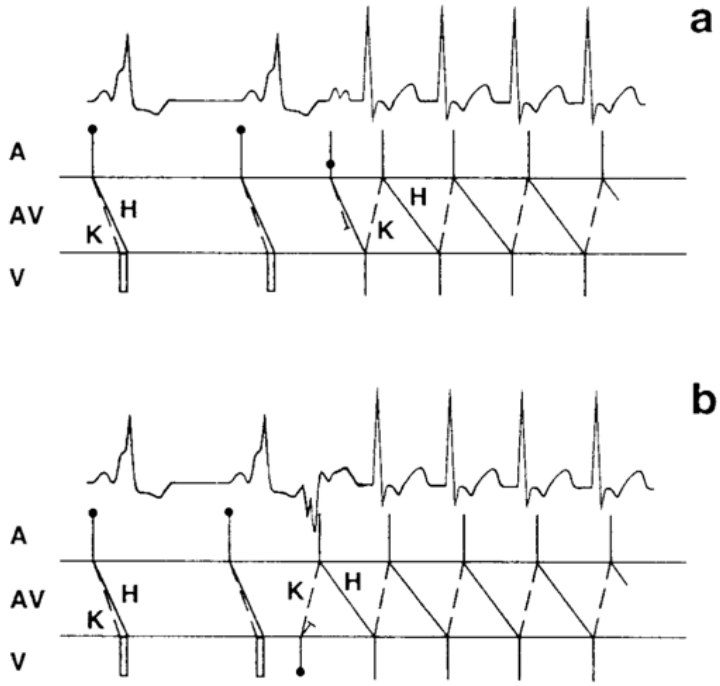

Figure 5. Atrial extrasystole (a) or ventricular extrasystole (b) inducing orthodromic atrioventricular re-entry tachycardia

1.6.2 Atrial fibrillation

Atrial fibrillation is far to be uncommon in the patients with APs, and in pre-excited patients sometimetimes it may represent a particularly dangerous arrhythmia.[1]
It is always a paroxysmal atrial fibrillation, because the chronic form is not very frequent without organic heart disease. One of the most shared theories is that the presence of the accessory pathway allows an impulse to reach the atria after a very short time from the previous depolarization. This would make it possible for a premature impulse to fall during the vulnerable phase of the atria, triggering atrial fibrillation. It occurs mainly in subjects with AV reentrant tachycardia and more often the orthodromic one. Different mechanisms can lead to the transformation of

re-entrant tachycardia into atrial fibrillation. For example, the high frequency leads to a reduction of the atrial refractory period and in this case a premature atrial impulse can fall more easily in the vulnerable period. In some subjects with pre-excitation and atrial fibrillation, electrophysiological studies have allowed us to see abnormalities of atrial excitability and conduction, expressed by an increase in intra-atrial conduction time and increased atrial vulnerability to electrical stimulation of the atria. It is possible that the accessory pathway represents only an element that favors the triggering of fibrillation if an adequate substrate is present.[3] Surgical interruption with transcatheter ablation of the accessory pathway is associated with a dramatic reduction in the incidence of atrial fibrillation, but it is unclear whether this positive result is due to the elimination of Kent's bundle or the absence of AV re-entry tachycardia. Atrial fibrillation associated with pre-excitation usually presents with wide QRS. The difference between pre-excited atrial fibrillation and the one with aberrant conduction or with pre-existing bundle branch block is based on two elements:

1. the morphology of the ventricular complexes is characteristic of conduction through a Kent's bundle, while in the other it is typical of an intraventricular conduction disorder;
2. in pre-excited AF, narrow QRS are not infrequently observed, expressing sudden block in the accessory pathway with exclusive conduction through the AV node. The narrow beats are not always so late as to suggest the disappearance of tachycardia-dependent aberrancy but may occur at the end of relatively short R-R intervals, which allows the mechanism of QRS widening to be recognized in pre-excitation.

Pre-excited atrial fibrillation is very important because the accessory pathway can allow many atrial impulses to reach rapidly the ventricles, resulting in a very high ventricular rate, with possible degeneration into ventricular fibrillation. Antegrade effective refractory period is the most important factor in determining the risk of atrial fibrillation being associated with high ventricular rates, and so SCD risk. Antegrade effective refractory period can be evaluated with an electrophysiological study, but also atrial fibrillation allows it to be assessed by measuring the shortest R-R interval (SPERRI) between two consecutive pre-excited beats. Pre-excited

atrial fibrillation is also of diagnostic importance because it allows the location of the accessory pathway to be determined with high reliability because QRS complexes are almost always an expression of AV conduction through the accessory pathway only. Atrial fibrillation also aids the detection of multiple accessory pathways.

1.7 Pre-excitation syndrome treatment

In patients with pre-excitation, treatment can be directed towards four different goals:[1]

1. treat the condition for symptoms (e.g. palpitations) relief,
2. prevent the risk of sudden death,
3. in patients with incessant – high burden – tachycardia, we must prevent or treat the deterioration of ventricular function,
4. to allow the performance of potentially dangerous activities in pre-excited subjects (eg. professional athlets and high-risk occupation subjects).

There are three different therapeutic approaches: antiarrhythmic drugs, transcatheter ablation, surgical ablation of the accessory pathway.[1]

1.7.1 Antiarrhythmic drugs

Anti-arrhythmic drugs can be used for both the treatment and prevention of arrhythmic episodes. Interruption of paroxysmal AV re-entry tachycardia can be performed with vagal stimulation maneuvers and intravenous administration of drugs acting on the AV node and accessory pathway to increase refractoriness in a critical area of the circuit.

Adenosine should be used with caution for the treatment of AVRT because of potential induction of atrial fibrillation that can be conducted to the ventricles only by the AP given the just blocked AV node. Drug therapy could be directed at one of the components of the circuit: the AVN is targeted during ortodromic AVRT

(e.g. beta-blockers, diltiazem, verapamil, or etripamil), and the accessory pathway is targeted during antidromic AVRT (e.g. propafenone, flecainide, procainamide). Antidromic AVRT may be associated with malignant WPW syndrome in case of a very fast-conducting accessory pathway, and drugs acting mainly on the accessory pathway should be preferred. In addition, in case of antidromic AVRT with APs representing both the anterograde and retrograde limb, drugs acting on the AVN are ineffective. In drug-refractory antidromic AVRT, amiodarone may also be considered. AF with fast ventricular conduction could also induce ventricular fibrillation, therefore electrical cardioversion should always be available. Conduction of electrical impulses can occur preferentially via the AP due to its shorter ERP compared with the atrioventricular node. Accordingly, any AVN-modulating agents (adenosine, verapamil, diltiazem, beta-blockers, or digoxin) should be avoided in pre-excited AF as they may contribute to a risk of ventricular fibrillationdevelopement facilitating AV conduction over the AP rather than phisiological pathway. The role of prophylactic drug therapy in individuals with WPW syndrome is therefore rather limited because:

a) the drugs are not always effective;

b) side effects can sometimes make it impossible their administration;

c) in a prophylactic treatment it is theoretically necessary for the patient to take his or her therapy for life, which is not always acceptable, especially for young subjects;

d) the progress of transcatheter ablation now makes it possible to radically solve the problem of pre-excitation with negligible risk and a very high success rate (high benefit/risk ratio).

1.7.2 Transcatheter ablation

Transcatheter ablation consists of delivering radiofrequency energy (and less often cryoenergy) through an intracavitary catheter placed close to the accessory pathway to permanently treat pre-excited patients. This procedure has very limited risks with a high success rate and low incidence of recurrence. Catheter ablation is the

treatment of choice for patients with WPW syndrome (signs of pre-excitation plus symptoms) and APs with risk features. For asymptomatics, therapeutic decisions should be balanced between the overall risks and benefits of the invasive nature of ablation vs long-term commitment to pharmacological therapy. Once again, ablation of the accessory pathway has a high acute success rate and is associated with a low complication rate depending on the pathway location. Major complications include cardiac tamponade and complete AV block, the latter in patients in whom ablation of septal APs is attempted. When targeting septal pathways and applying cryoenergy, the incidence of AV block is lower compared with radiofrequency energy. However, recurrence of previously blocked pathways has been reported to be significantly higher when cryoenergy is applied.[3]
Finally, surgical resection of AP has very strict indications which are limited to previous failure(s) of transcatheter approach and rare cases of epicardial Kent.

1.7.3 Chronic terapy

If ablation is not desirable or feasible in patients with APs and AVRT, and in whom structural or ischaemic heart disease has been excluded, class Ic antiarhythmic drugs act mainly on the AP and can be used in antidromic tachycardia. In cases of pre-excited AF, caution should be taken not to transform it into atrial flutter and induce 1:1 conduction. Apart from class Ic drugs, beta-blockers, diltiazem, or verapamil may also be considered in case of orthodromic tachycardias if no signs of pre-excitation are observed on the resting ECG.[1]

1.7.4 Electrical therapy

Electrical therapy in pre-excitation syndrome is based on cardioversion, which can be used in the treatment of pre-excited atrial fibrillation and exceptionally also in AV re-entry tachycardia, and on atrial or ventricular electrostimulation, which can be used to interrupt a re-entry tachycardia.[1]

2. Arrhythmic risk in ventricular pre-excitation

Arrhythmias related to ventricular preexcitation could be dangerous in rare cases.[1] These arrhythmias are AVRT and AF. AVRT in itself is a non-life threatning arrhythmia, but it may trigger AF. On the other hand, AF may degenerate in ventricular fibrillation if it is rapidly conducted to the ventricles through an AP with high antegrade conductive properties. For sure the risk of this kind of event is rare, but it exists. Generally speaking, this is the reason why APs should be evaluated by an EP study. There were identified risk factors for SCD. Among these there were hystorically included:[1]

- Presence of arrhythmias related to AP (AVRT and/or AF). They can be spontaneously documented (in symptomatic patients) or induced during EPS;
- Presence of multiple APs;
- Septal APs;
- High anterograde pathways conduction properties;
- Presence of symptoms;
- Younger age.

As for pathway conduction, this parameter grossly inludes: effective refractory period (ERP) and shoortest pre-excited R-R interval during AF (SPERRI). According to last European Guidelines[1], an AP is at higher risk if ERP or SPERRI are ≤250 msec in baseline or during adrenergic stimulus (like intraprocedural intravenous isoproterenol administration). These are quitely recent recognized risk parameters in the international guidelines, but they were already recognized in the past by the Italian protocol for sports activity (COCIS)[7]. In particular, COCIS is always been more restrictive on the cut off of these two parameter, but at this point it is out from our discussion.

Patients with WPW may be completely asymptomatic and have no event related to their ventricular preexcitation, but rarely SCD may be the first manifestation of the disease, so asymptomatic patients need attention.[1] Catheter ablation is still recommended for symptomatic WPW, while no treatment was recommended for asymptomatic WPW, limiting ablation to people with high-risk occupations and

professional athletes.[1] This approach assumed that asymptomatic people with WPW have little or no risk of sudden death and that patients with ventricular fibrillation have had previous episodes of atrial fibrillation or paroxysmal supraventricular tachycardia.

However, the risk of death essentially depends on the electrophysiological properties of the accessory pathways rather than presence or not of symptoms.

In children, the syndrome is not as benign as previously thought and asymptomatic children have a higher risk of death than asymptomatic adults. Ablation could be considered in children over 5 years of age, whereas children under 5 years of age are not treated.[8]

Admitting that younger are at higher risk than older ones means that there is a sort of risk reduction with aging. This could be reasonable if an older subject with pre-excitation was been always asymptomatic. But we must consider 2 things: 1) symptomaticity is related to a personal perception and should be proved with arrhythmia recording, and 2) one subject could become symptomatic later, especially if we consider that AF incidence increase with ageing.[9] In the latter extent, what could be happen in a patient with AF – always asymptomatic before – and high antegrade conductive accessory pathway?

The last european Guidelines[1] did a step backward about the age in risk stratification and, so, according to them, the risk characteristics of ventricular pre-excitation, for which catheter ablation of the accessory pathway is recommended, are:

- ERP/SPERRI ≤250 msec (in baseline conditions or during adrenergic stimulus);
- inducibility of APs-related tachycardias (AVRT/AF);
- The presence of multiple accessory pathways.

As already stated before, pre-excitation may be persistent or intermittent. The phenomenon of intermittent pre-excitetion is poorly understood but is thought to be related to the refractory period of the AP and cell connectivity within the pathway resulting in variable conduction between the AV node and the AP. It has long been considered a generally benign condition with an almost negligible risk of SCD.[10]

As for intermittent ventricular pre-excitation, the last European Guidelines, state as following. “Loss of pre-excitation on resting ECG or ambulatory monitoring has also been associated with APs with longer ERPs and has been accepted as a credible risk stratification tool. However, several recent studies, including both symptomatic and asymptomatic patients, have shown that more than one fifth of patients with intermittent pre-excitation have AP ERPs <250 ms. Thus, intermittent pre-excitation is now recognized as an imperfect marker of low-risk AP.”[1]

Although this admission from last guidelines, they do not give precise reccomendation on how to manage intermittent ventricular pre-excitation.

The belief that intermittent pre-excitation detected during sinus rhythm indicates the presence of an accessory pathway (AP) with poor anterograde conduction - which does not pose a risk of rapid ventricular response during atrial fibrillation and subsequent development of ventricular fibrillation - is mainly based on expert opinion.[1] The literature search does not reveal any large trials about intermittent APs in relation to the long-term risk of developing ventricular fibrillation.

Regarding the pediatric population there are retrospetive studies which evaluated electrophysiological properties of intermittent-conducting APs, and which will be analyzed in the next chapter.[11-13] Conversely, for the adult population there are only case reports of patient with intermittent pre-excitation with high risk features or with cardiac arrest, which inspired the step backward of the recent ESC guidelines about this topic.[1,10,14-15]

Our study inserts in this context aiming to discover if there are differences in arrhytmic risk features between adults with persitent and intermittent pre-excitation submitted to EPS.

3. OUR STUDY - Intermittent ventricular pre-excitation in symptomatic adults: always a marker of low risk?

3.1 INTRODUCTION

Intermittent ventricular preexcitation (IPX) on either a resting electrocardiogram (ECG) or ambulatory Holter monitoring has long been viewed as a generally benign condition with a nearly negligible risk of sudden cardiac death (SCD).[16] Historically, risk factors for SCD have included patients with multiple accessory pathways (APs), septal APs, atrioventricular (AV) reciprocating tachycardias (AVRT) and/or atrial fibrillation (AF), and antegrade pathway conduction ≤250 msec.[17–21] The phenomenon of IPX is poorly understood, but it is likely related to the refractory period of the AP as well as cellular connectivity within the pathway resulting in variable conduction between the AV node and the AP. Although IPX has been considered a predictor of poor antegrade AP conduction,[16,22-25] it has been observed on rare occasions in some patients with cardiac arrest. In addition, there are some recent data in the literature reporting IPX patients, both symptomatic and asymptomatic, with high-risk features.[10,14-15] For these reasons, current European Guidelines on the management of supraventricular arrhythmias do recognize IPX as an imperfect marker of a low-risk AP.[1]

Given that current European Guidelines recommend APs ablation in case of fast antegrade conduction [defined as an effective refractory period/shortest pre-excited RR interval (ERP/SPERRI) ≤250 msec in baseline or during adrenergic stimulus], AVRT/pre-excited AF (spontaneous or triggered), or presence of multiple APs,[1] the aim of our monocentric retrospective study was to evaluate the existence of differences in the risk features between patients with IPX and those with persistent pre-excitation (PPX), from a sample of adults with ventricular pre-excitation evaluated for palpitations (Wolff-Parkinson-White Syndrome).

3.2 MATERIAL AND METHODS

3.2.1 Study population

Adults (≥18 yo) with ventricular preexcitation were retrospectively enrolled from Policlinico Casilino EP lab to investigate their clinical and electrophysiological features. All of them were referred for an outpatient visit for palpitations. This represented an indication to submit each patient to an electrophysiological study (EPS) to obtain APs arrhythmic risk stratification and, thus, catheter ablation if needed, regardless of the risk assessment related to sporting and/or professional activity. Patients with syncope potentially related to tachyarrhythmia were excluded as they were already considered at high risk. Based on the pre-procedural evaluation, patients were divided into 2 groups: those with IPX and those with PPX. IPX was defined as the sudden loss of delta wave at resting 12-lead ECG and/or at Holter monitoring, not related to heart rate modifications or ongoing treatment with anti-arrhythmic drugs (AADs). **Figure 7** shows an example of IPX.
All patients gave their written informed consent before EPS and also for the use of their data for scientific purposes. EPSs were performed by expert operators (more than 100 WPW ablation cases each). The study was carried out in accordance with Helsinki Declaration. Figure 8 depicts the study design.

3.2.2 EP Study and Ablation

All AADs were discontinued at least five half-lives before the procedure. The surface ECGs and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system [LabSystem PRO (Bard Electrophysiology, Lowell, MA, USA)]. The bipolar electrograms were filtered from 30 to 500 Hz. A 6-Fr 10-pole catheter was inserted through the right femoral vein and positioned in the coronary sinus for pacing and recording. A 6-Fr 4-pole catheter was inserted through the left femoral vein and placed at the His bundle

region and in the right ventricle for pacing and recording. The EPS workflow included ventricular programmed stimulation to check retrograde conduction properties, atrial programmed stimulation to check APs ERP and atrial incremental pacing in order to check 1:1 conduction over the APs. Moreover, atrial bursts and all these maneuvers were performed also during intravenous infusion of isoproterenol (0.1-mcg/kg bolus over 1 minute, followed by a 0.01–0.02-mcg/kg/min infusion) if AVRT/AF were not inducible in basal condition. During EP study and mapping, APs locations were checked and annotated paying attention to multiple ones. In particular, patients with multiple APs were excluded from both groups to avoid bias during the comparison of APs site distribution. APs locations were considered as follows: right free-wall (right-sided); left free-wall (left-sided) and septal (including antero-septal, mid-septal, and right- and left-postero-septal). According to the Guidelines, APs ablation was performed in case of: 1) AVRT/AF inducibility, or 2) fast antegrade conduction (ERP ≤250 msec in basal, or ≤210 msec during the adrenergic stimulus, according to the Italian protocol in force when each EP study was performed), and/or 3) multiple APs documentation.[27-29] APs ablation were performed via radiofrequency or cryoenergy delivery, according to the operator's preferences and choosing case by case (a detailed description of the ablation procedure is beyond the purposes of this paper). A 12-18 mg i.v. adenosine bolus was administered at the end of ablations, except in patients with asthma. After discharge, all patients underwent an outpatient follow-up visit (1 to 3 months later) with 12-lead ECG and Holter monitoring showing no APs recurrences in any case.

3.2.3 Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) value. The differences in the continuous variables between the two (IPX and PPX) groups were compared by *t*-test per data with normal distribution. Categorical variables were expressed as numbers and percentages and their differences were investigated with a *Chi-square* test or *Fisher's exact* test. *P-value* <0.05 was considered statistically significant.

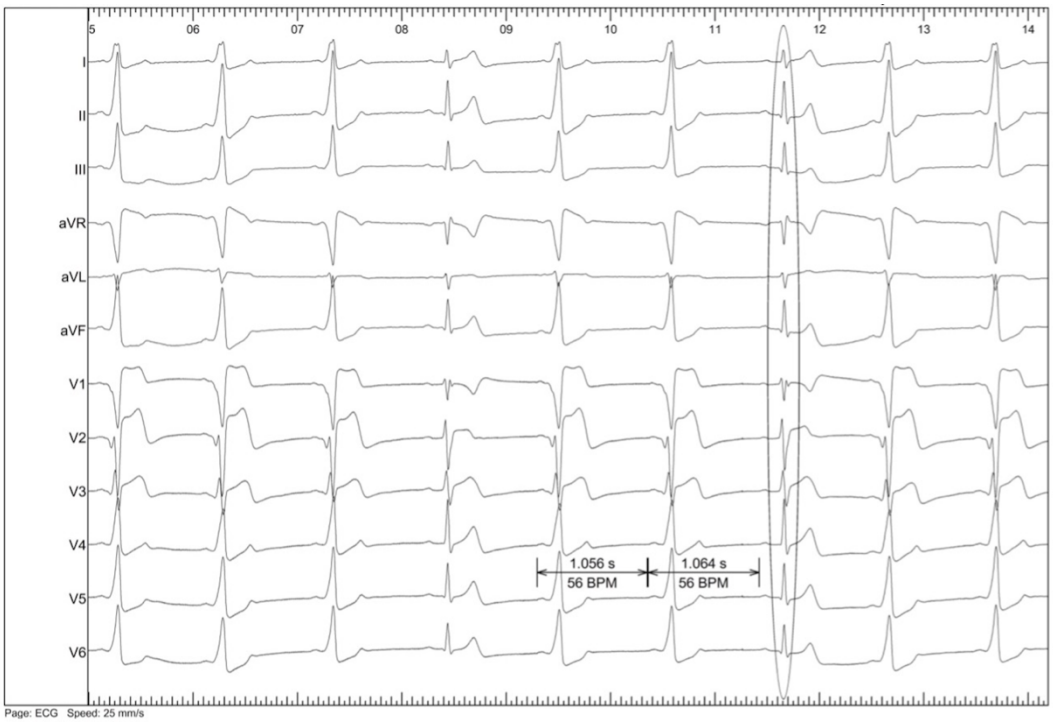

Figure 7. A case of intermittent pre-excitation. All the QRS complexes, except for the 4◦ and the 6◦ , are wide and show an initial δ wave. δ wave is negative in V1-V2, with early transition in V3, and positive in D1, aVL and D2-D3-aVF, thus suggesting a right-sided antero-septal AP. The 4◦ and 6◦ beats abruptly show normal PQ, no δ wave and narrow QRS with normal morphology (physiological septal activation testified by the small q wave in V5-V6). This is an emblematic case of intermittent pre-excitation because of the abrupt disappearance of δ wave is not related to heart rate variation (the heart rate is fixed at 56 bpm). In particular, this is the 12-lead ECG of a 21 yo male referred for palpitations - without previous documentation of AVRT/AF - with an AP ERP < 250 ms at EP study. He was successfully cryo-ablated. AVRT, atrioventricular reciprocating tachycardias; AF, atrial fibrillation; AP, accessory pathway; ERP, effective refractory period.

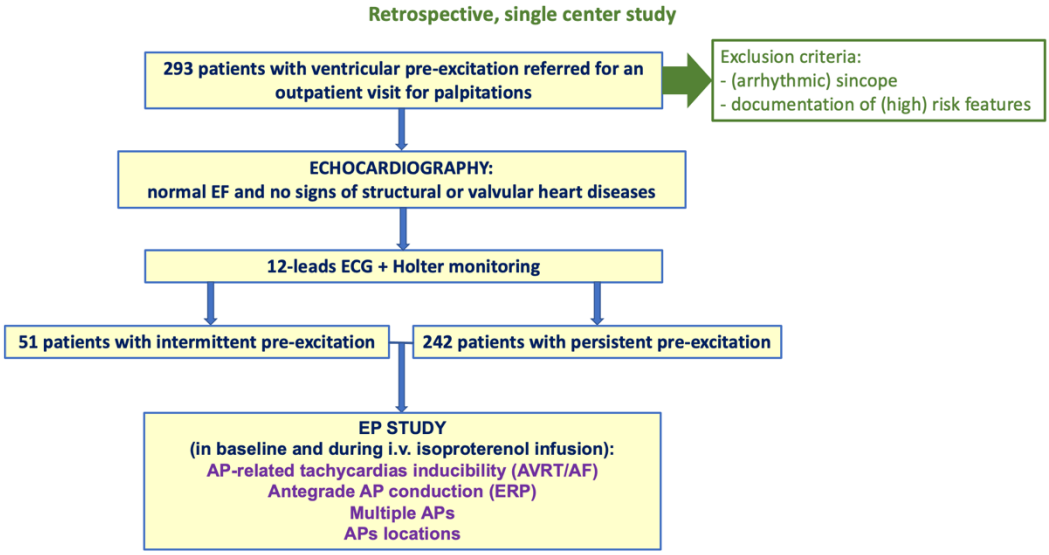

Figure 8. Study design.

3.3 RESULTS

3.3.1 Patients population

In the sample of 293 WPW adults, 51 patients (17.4%) had IPX and 242 patients (82.6%) had PPX.

All patients had normal ejection fraction and no sign of structural or valvular heart diseases at transthoracic cardiac ultrasound. The 2 groups of patients did not show statistically significant differences in age at the time of the EP study [IPX: mean age 37.23±16.89 years *vs* PPX: mean age 39.03±16.19; *p-value* = 0.21] and gender [IPX male: 31 (60.8%) *vs* PPX male: 152 (62.8%); *p-value* = 0.28].

3.3.2 EP-study findings

Table 1 represents the results in detail.

When measured, there were no statistically significant differences regarding APs ERP [IPX: mean ERP 260±45.8 msec *vs* PPX: mean ERP 267.7±59.6msec; *p-value* = 0.5] (Figure 9). Samely, the inducibility of arrhythmias related to AP (AVRT/AF) did not show statistically significant differences [IPX: 27 (52.9%) *vs* PPX: 100 (41.3%); *p-value* = 0.13]. In particular, arrhythmia inducibility was not statistically different in the 2 groups (IPX and PPX) when each was split into 2 subgroups according to ERP value (≤250 msec and >250 msec, respectively). Table 2 details those results. Multiple accessory pathways were found in 2 patients of the IPX group (3.9%), both females (100%) and in 6 patients of the PPX group (2.5%), of which 2 females (33.3%), not showing statistically significant differences (*p-value* = 0.56). There were 49 patients in the IPX group with a single AP so distributed: 3 right-sided, 21 septal, 25 left-sided; while in the PPX group, there were 235 patients with a single AP so distributed: 17 right-sided, 126 septal, 92 left-sided. Also, APs site distribution in both groups did not show statistically significant differences (*p-value* = 0.32).

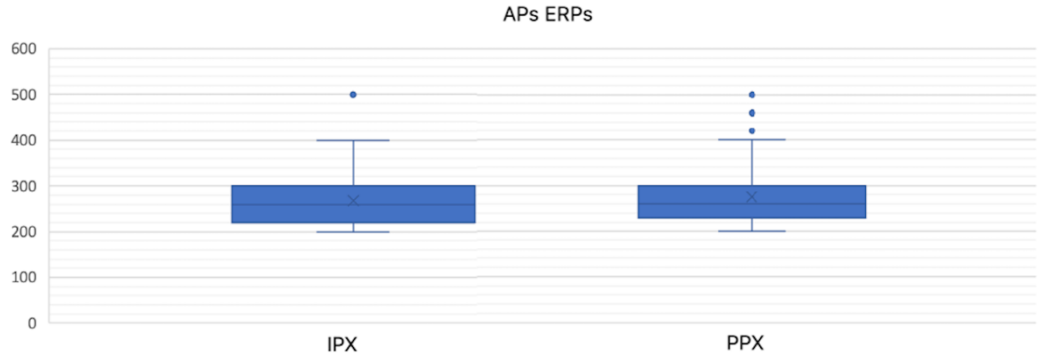

Figure 9. Box plot. In the picture are represented in a box plot the values in ms of ERPs of the APs of the two groups: intermittent ventricular pre-excitation patients (IPX) and persistent ventricular pre-excitation patients (PPX).

Table 1. Study population features.

	IPX	**PPX**	*p-value*
N (%)	51 (17.4)	242 (82.6)	*(<0.05)*
Age (y±DS)	37.23±16.89	39.03±16.19	*0.21*
Sex, male(%)	31(60.8)	152 (62.8)	*0.28*
ERP (msec±SD)	260±45.8	267±59.6	*0.5*
AVRT and/or AF inducibility (%)	27 (52.9)	100 (41.3)	*0.13*
• AF only	4 (7.8)	18 (7.4)	*0.9*
• AVRT only	20 (39.2)	74 (30.6)	*0.23*
• AVRT+AF	3 (5.9)	8 (3.3)	*0.38*
APs location[a]			***0.32***
• Right-sided (%)	3 (6)	17 (7)	*0.78*
• Septal (%)	21 (43)	126 (54)	*0.17*
• Left-sided (%)	25 (51)	92 (39)	*0.12*
Multiple APs (%)[b]	2 (3.9)	6 (2.5)	*0.56*

Note: The table summarizes the variables compared in the study sample. Data are expressed as the means ± standard deviation or number (%). p-value was significant at < .05. aComparison between APs locations was performed keeping in count patients with only a single AP. b Multiple APs: ≥2 APs.

Table 2. Arrhythmias inducibility in IPX and PPX groups split into two subgroups according to ERP ≤250 ms e > 250 ms, respectively.

	IPX (n = 51)	PPX (n = 242)	*p-value (<0.05)*
ERP available in	11 (21.6)	86 (35.5)	*0.07*
≤250 msec	5 (9.8)	38 (15.7)	*0.4*
not inducible	4 (7.8)	22 (9.1)	*1*
AVRT	1 (2)	9 (3.7)	*1*
AF	0 (0)	8 (3.3)	*0.36*
>250 msec	6 (11.8)	48 (19.8)	*0.2*
not inducible	5 (9.8)	32 (13.2)	*0.6*
AVRT	2 (3.9)	15 (6.2)	*0.7*
AF	0 (0)	2 (0.8)	*1*

Note: Values are expressed in n (%).

3.4 DISCUSSION

3.4.1 Current intermittent ventricular pre-excitation panorama

Although the current European Guidelines on the management of supraventricular arrhythmias clearly outline the indications for the EPS (and therefore for the risk stratification and possible treatment) of the APs responsible for persistent ventricular pre-excitation, both in the symptomatic and asymptomatic, they do not give precise indications regarding the evaluation of the APs responsible for intermittent ventricular pre-excitation.[1] More precisely, historically the intermittent loss of ventricular pre-excitation has been considered a benign feature of the APs, so much so that PACES/HRS have expressed themselves about the pediatric population by issuing clear indications for subjects with intermittent ventricular pre-excitation. They stated that the disappearance of ventricular pre-excitation during the stress test is sufficient to consider the pathway as low-risk, especially in asymptomatic subjects.[8] In support of this indication, even if *"a posteriori"*, there are two retrospective studies on pediatric populations that examined overall 623 patients with ventricular pre-excitation, of which 80 (12.5%) with intermittent pre-excitation. These studies revealed that APs ERPs were >250 msec and on average longer in asymptomatic patients with intermittent pre-excitation than in those with persistent pre-excitation.[11,12] In 2020, Escudero et al[13] showed from the largest multicenter retrospective study that 13% of pediatric patients with IPX met high-risk criteria at EPS, even if likewood of high conduction properties was lower in the IPX group than PPX one. Some IPX patients experienced SCD or rapid-conducting AF. Moreover, this study demonstrated that non-invasive evaluation may miss IPX patients with high-risk features at EPS, and those latter were detected also in some asymptomatics. The conclusions were the non-perfect reliability on non-invasive tests during evaluation of IPX and on IPX itself in conferring freedom from arrhythmic risk.[13]

This excursus on pediatric studies is far from being a criticism of them, but it is a means of analyzing the adult population. In fact, even in adults asymptomaticity is questionable, not only because it is linked to the perception of the individual (in

cases where there has been no objective documentation of a previous arrhythmia related to an AP) but also because the risk of AF correlates with aging and for this reason, an asymptomatic subject today (and therefore not considered at risk today), could become symptomatic tomorrow and therefore could potentially be at risk in the future. In line with the concepts set out so far, even age should appear to be unreliable in risk assessment. Together with the known factors: ERP/SPERRI ≤250 msec, AVRT/AF, and multiple APs, young age has been indicated as a risk factor,[30-32] which is equivalent to saying that there is some sort of risk reduction with aging. As already stated, AF - which may have a great weight in the arrhythmic risk - has a direct correlation with aging. Furthermore, the evolution of the APs properties over time is not absolutely predictable and, moreover, we must not forget that the presence of an AP in itself can increase the risk of AF since it increases the intra-atrial refractoriness dispersion;[33] thus APs represent an excellent ablative target in the context of tailored AF treatment.[34]

So far we have made some speculations on the pediatric population on which we have considerable studies, which however are lacking on the adult population. For the latter, we have only reports showing cases of patients with intermittent ventricular pre-excitation and APs with high-risk characteristics or even cardiac arrest from VF.[10,14-15] And based on these data, as already mentioned at the beginning of the discussion, the recent European Guidelines have taken a step backward on the hot topic of intermittent ventricular pre-excitation, on whose risk stratification they do not express themselves at all.[1]

3.4.2 Remarks from our study: what should we do?

In this setting, our study reports the largest series of patients with intermittent pre-excitation compared to patients with persistent pre-excitation in an adult population.

In our study, the two populations appear homogeneous: the demographic characteristics of age and gender did not show statistically significant differences between the two groups. Similarly, it was for the antegrade conduction properties,

AVRT/AF inducibility, as well as the number of APs and their location. As for the ERP, even if it was not available in each patient, its value did not seem to correlate with arrhythmias inducibility. There were no patients with inducible-AF in the IPX group with ERP ≤250 msec, but this is not enough to absolutely infer a negligible risk in such a subset. This result may depend on the small sample size and should be taken into account that AF non-inducibility at EPS does not exclude its appearance in the future.

Even if in absolute terms APs responsible for intermittent pre-excitation were found to be more left-sided (51%; versus 39% in the persistent pre-excitation group) rather than septal (43%; versus 54% in the persistent pre-excitation group), this difference was not statistically significant (**Fig. 9**). Probably, the left atrial location of an AP is not enough to explain its intermittent manifestation, particularly by invoking the theory that greater anatomical distance from the sinus node favors conduction along the AV node-hisian pathway and consequently a less marked pre-excitation.[34,35]

In this regard, conversely, the EPS proves to be fundamental in risk stratification. But is it necessary or can we rely on other less invasive assessments, such as the exercise stress test (EST)?[36] As known, pathway conduction ≤250 msec is a risk indicator. Provocatively, we can state that, during the stress test, it is necessary to reach heart rates ≥240 bpm and contextually observe the stable disappearance of ventricular pre-excitation to surely consider such a patient as low risk. It is obvious that it is impossible for an adult to reach these heart rates during effort-mediated sinus tachycardia. Although previous studies showed that the majority of benign APs disappear considerably below this heart rate, one must consider the rare phenomenon of supernormal conduction for which some APs can paradoxically recover their conductive properties at higher heart rates.[37-40]

In conclusion, we are not trying to say that all the APs should be subjected to an EPS to perform an ablation to reduce any possible risk,[7,41-42] but that, given the already exposed limits of the non-invasive evaluation and of some clinical criteria, the APs responsible for intermittent pre-excitation may be better evaluated with an EPS, at baseline and during i.v. infusion of isoproterenol.

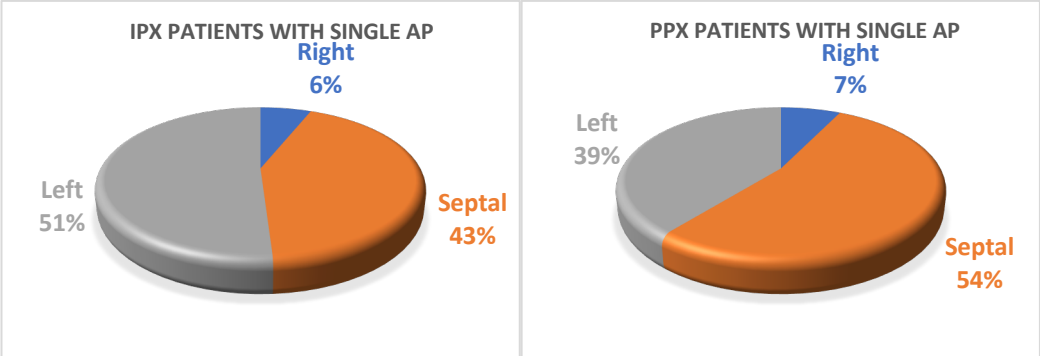

Figure 9. Anatomical distribution of the APS sites in the 2 groups. Relative percentages did not show any statistically significative differences.

3.4.3 Limitations

Limitations inherent in this study include its moderate-sized patient sample from a single institution and its retrospective design.

Another limitation of this study is that it considers patients with pre-excitation and palpitations. The latter presence in anamnesis was crucial to justify an EPS, regardless of whether it was necessary for the risk assessment related to sporting and/or professional activity.[7] For this reason, we have to consider our sample of adults as symptomatic. However, should be reiterated how symptoms like palpitations not supported by any arrhythmia documentation it may not be enough to judge that patient as surely "symptomatic" and therefore at greater risk. This not net subdivision in true symptomatic versus true asymptomatic (based on objective recordings) may represent a bias in the study design.

Another limitation is the lack of data from EST. We are not able to explore if there were any correlation between pre-excitation behavior at EST and its characteristics during EPS.

Finally, larger and possible prospective studies are needed to deeply investigate the undiscovered panorama of intermittent ventricular pre-excitation. But these kinds of studies need a sample of intermittent ventricular pre-excitation due to AP with high-risk features that should be split into 2 arms: the first submitted to catheter ablation and the second not submitted to catheter ablation but only followed up. It

is hard to accept to not submit to catheter ablation high-risk APs only to follow up on their clinical evolution over time.

3.5 CONCLUSIONS

In our single-center cohort of symptomatic adults with ventricular pre-excitation, we did not find significant differences in demographic and electrophysiological features among those with intermittent ventricular pre-excitation and those with persistent pre-excitation.

These results may be interesting given that they add new evidence about intermittent ventricular pre-excitation in the adults whose management, still today, represents a grey area in the current guidelines.

To the best of our knowledge, our study is the first exploring demographic and electrophysiological features of an adult population with intermittent pre-excitation and – despite its limitations – it, in particular, enforces isolated findings from case reports speaking against the previous belief according to which intermittent ventricular pre-excitation was a benign condition.

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