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Treatment of Patients with Asymptomatic Ventricular Pre-Excitation Results of a Tiered Non-Invasive Electrocardiographic and Invasive Electrophysiological Risk Stratification Approach

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Abstract

Aims: Treatment of asymptomatic Wolff-Parkinson-White (aWPW) patients has been a controversial issue, with approaches ranging from only follow up to ablation of all Accessory Pathways (APs). We aimed to assess the ability of a stepwise, non-invasive and invasive risk stratification approach to detect and manage high risk aWPW patients.

Methods: The first step was the detection of low-risk APs with intermittent pre-excitation (pre-excitation disappearance - PED - on 12-lead ECG, on 24-hour Holter recording, or during an exercise stress test). In cases of no PED, invasive Electrophysiological Study (EPS) was pursued in order to determine the Effective Refractory Period (ERP) of the AP, and, should it be found ≤250msec, endocardial ablation was offered.

Results: Eighty-five aWPW patients were included (55 male, mean age 29 years), in 32 of whom PED was noted. The remaining 53 patients were submitted to EPS revealing at least one AP (23 were located at the left ventricular free wall, 24 at the posterior septal area, 2 were anteroseptal, and 5 were located at the right ventricular wall - a single patient had 2 APs - mean ERP was 302msec). Ablation of the AP was offered to 10 high-risk patients with one of them declining. All procedures were successful with pre-excitation disappearance. During a prolonged follow up period (171±90months), no sudden cardiac deaths were observed, with all patients remaining asymptomatic.

Conclusion: A tiered, mixed non-invasive electrocardiographic and invasive electrophysiological risk stratification approach leading to ablation of high-risk APs is safe and effective among aWPW patients.

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Introduction

Patients with symptomatic Wolff-Parkinson-White (WPW) syndrome are at increased risk of sudden cardiac death, this reaching 4% over lifetime, while catheter ablation is undoubtedly the treatment of choice [1-3]. A continuing controversy though has been the use of ablation in asymptomatic WPW patients. In large-scale population studies electrocardiographic pre-excitation affects about 0.1% to 0.3% of the general population [4]. Asymptomatic patients with WPW electrocardiographic pattern have a good prognosis, and may not develop any arrhythmia related to ventricular pre-excitation throughout their lives [5]. However, the management of asymptomatic WPW patients remains a challenge for electrophysiologists, as the risk of sudden cardiac death, although small, does exist and has been reported to be up to 0.02% per patient-year [6]. The mechanism of sudden cardiac death is mostly attributed to rapid antegrade conduction of atrial fibrillation through the Accessory Pathway (AP), resulting in ventricular fibrillation. Identification though of the truly asymptomatic WPW patient is not easy, and only incidentally discovered as a result of ECG screening for sports participation or surgical procedures. At present, it is estimated that more than half of adolescents and 40% of individuals over 30 years with a WPW pattern on a resting ECG are asymptomatic [1,7]. Factors associated with increased risk for sudden cardiac death include male sex, younger age, inducibility of Atrioventricular-Reciprocating Tachycardia (AVRT) during Electrophysiological Study (EPS), the presence of multiple accessory pathways and the ability of the accessory pathway to allow rapid conduction to the ventricles [1,8]. Thus, the identification of high risk features that will lead to prophylactic catheter ablation in patients with asymptomatic pre-excitation is crucial. Indeed, we have to take into account that the procedural complication risk over a small risk due to the natural history of the disease along with lack of cost-effectiveness data from a broad screening program with EPS, may counterbalance the use of catheter ablation as a first choice in these subjects [9]. The purpose of the present study was to prospectively examine the ability of a tiered, mixed non-invasive and invasive risk stratification process to detect high risk asymptomatic WPW patients in predicting the occurrence of symptomatic arrhythmic events over a prolonged follow up period.

Materials and Methods

Population and data collection

This is a prospective 20-year study designed to evaluate the long term outcomes in patients with asymptomatic WPW. From 2000 to 2020 eighty-five asymptomatic WPW patients referred to the arrhythmiologic department of our hospital for further assessment, were consecutively enrolled in our study. A stepwise approach was followed in order to identify low risk accessory pathways. High-risk occupation or competitive athletes were excluded from the study. Patients with intermittent pre-excitation, meaning either pre-excitation disappearance on 12-lead ECG, on 24-hour ECG recording or during exercise stress test, were deemed low risk and were followed regularly at prespecified time points. Those without pre-excitation disappearance, underwent EPS, in order to assess the Effective Refractory Period (ERP) of the accessory pathway. In case ERP was found >250msec, serial follow up was offered, otherwise endocardial ablation was pursued. The registry has been frequently updated with the use of electronic clinical records and by telephone encounters. The study protocol was approved by the institutional review board of our hospital, and each subject provided written and verbal informed consent for participating in the study.

Non-invasive testing

Patients underwent non-invasive evaluation with 12-lead ECG, ambulatory monitoring or exercise stress test in order to assess the conductive properties of the accessory pathway. A sudden disappearance of the pre-excitation during exercise was indicative of a long refractory period, rendering the patient low risk [1,10]. Intermittent pre-excitation is present when during sinus rhythm, some QRS complexes show delta wave and followed by QRS complexes showing Atrioventricular (AV) conduction over the normal AV conduction pathway [1]. Intermittent pre-excitation either in 12-lead ECG or 24-hour ECG monitoring was also suggestive of a long refractory period of the accessory pathway, thus these patients were deemed low risk.

Invasive evaluation

Electrophysiological Study (EPS)

Standard electrode catheters were positioned in high right atrium, His bundle area and right ventricular apex. A multipolar electrode catheter was placed into the Coronary Sinus (CS), and multiple bipolar recordings were established along its length. The stimulation protocol consisted of atrial and ventricular incremental pacing up to a minimal cycle length maintaining atrioventricular or ventriculoatrial 1:1 conduction and programmed atrial and ventricular stimulation at drive cycle length of 550ms and 400ms [2,3]. The Anterograde Effective Refractory Period of the Accessory Pathway (AP-AERP) was defined as the longest coupling interval at which anterograde block in the bypass tract was observed. If Atrial Fibrillation (AF) was not induced by atrial extra stimuli, atrial burst pacing at fast cycle lengths was performed [2,3]. Pre-excited QRS morphology, mean ventricular rate, and the Shortest RR Interval between two consecutive pre-excited QRS complexes (SPERRI) were calculated during sustained AF, when inducible. Inducible arrhythmias were defined as sustained if they lasted >1 minute. Isoproterenol infusion was not used at the time of EPS in our study protocol.

Catheter ablation procedure

Mapping and ablation catheter were inserted through the femoral artery or transeptal puncture for left sided APs, or through the femoral vein for the right sided APs, driven with manual navigation [2,3]. Electro anatomic mapping system was used occasionally. For left sided and poster septal APs a non irrigated radiofrequency catheter ablation (RFA) was performed in temperature-controlled mode targeting up to 60 ^{0}C and up to 50 W. Occasionally, an irrigated tip ablation catheter was used for paraseptal APs, where RFA was delivered carefully at lower energy settings and for shorter duration periods in order to avoid advanced Atrioventricular Block (AVB) [3]. Selective venography of the CS was also used in some cases in order to achieve successful ablation. The endpoint of the ablation procedure was defined as the absence of anterograde and retrograde AP conduction on repeat electrophysiology testing after a 30-min waiting period prior to termination of the procedure [2,3]. Patients who underwent ablation were prescribed either aspirin 100mg or direct oral anticoagulants for up to 3 months.

Follow up

Patients were followed closely at pre-specified time points, at one, three and six months. Physical examination and 12-lead ECG were performed at each visit. Thereafter, patients were seen annually, or whenever they reported symptoms suggestive

of arrhythmic events. In specific, patients were asked to report palpitations, dizziness, chest pain, dyspnoea or syncope. The primary endpoint of our study was the occurrence of symptomatic arrhythmic events, including AVRT, atrial fibrillation, and ventricular fibrillation, leading to sudden cardiac death. Major complications were defined as those that required intervention or prolonged hospitalization.

Results

Eighty-five consecutive asymptomatic WPW patients were included in our study and followed over a 20-year period. Patients' mean age at the time of enrolment was 29 years; there were 55 (64.7%) male patients (Table 1). The majority of the study participants were referred to the electrophysiology department of our hospital as a result of accidental finding of pre-excitation on ECG (Table 1).

Clinical and electrophysiological characteristics

Pre-excitation disappearance was noted in 32 (37.6%) patients. In specific, 7 patients presented intermittent pre-excitation on ECG, 11 on 24-hour ECG monitoring and 14 patients on exercise stress test. No patient had underlying structural heart disease. The remaining 53 patients were submitted to invasive EPS, revealing at least one accessory pathway, of which 23 APs were located at the left ventricular free wall, 24 at the posterior septal area, 2 were anteroseptal, and 5 were located at the right ventricular wall. A single patient had 2 accessory pathways. Mean effective refractory period was estimated at 302msec (range 180-360msec). Atrial fibrillation was induced in 2 patients and AVRT in 5 patients (Table 2).

Radiofrequency ablation

Endocardial ablation of the accessory pathway was offered to 10 patients deemed as high-risk (Figure 1) with one of them declining. All procedures were successful with pre-excitation disappearance. There were no complications related to the EP study or radiofrequency ablation.

Long term follow up

During a prolonged follow up period (171±90months), no sudden cardiac deaths were observed, with all patients remaining totally asymptomatic.

Table 1: Patients' clinical characteristics (n=85).

Mean age, years	29
Male gender, [n (%)]	55 (64.7)
Reasons for further investigation	
Incidental finding, [n (%)]	58 (68.2)
Chest pain, [n (%)]	2 (2.4)
Syncope, [n (%)]	6 (7.1)
Palpitations, [n (%)]	14 (16.5)
Relatives with WPW, [n (%)]	1 (1.2)
Evaluation prior to sports participation, [n (%)]	4 (4.7)
Structural heart disease, [n (%)]	0

Discussion

This is a long prospective follow up registry assessing the long term outcomes of treated and untreated asymptomatic WPW patients. Following a stepwise approach in risk stratifying asymptomatic WPW patients with both non-invasive and

Table 2: Electrophysiological characteristics.

Pre-excitation disappearance, [n (%)]	32 (37.6)
ECG, [n (%)]	7 (21.9)
24-hour ECG monitoring, [n (%)]	11 (34.4)
Exercise stress test, [n (%)]	14 (43.8)
Patients undergoing EPS, [n (%)]	53 (62.4)
Location of the accessory pathway	
Left ventricular free wall	23 (42.6)
Posterior septal area	24 (44.4)
Anteroseptal	2 (3.7)
Right ventricular free wall	5 (9.3)
Inducible arrhythmias during EPS	
Atrial fibrillation, [n (%)]	2 (3.8)
Atrioventricular re-entry tachycardia, [n (%)]	5 (9.4)
Effective refractory period (msec), mean (range)	302 (180-360)
Endocardial ablation, [n (%)]	9 (10.6)

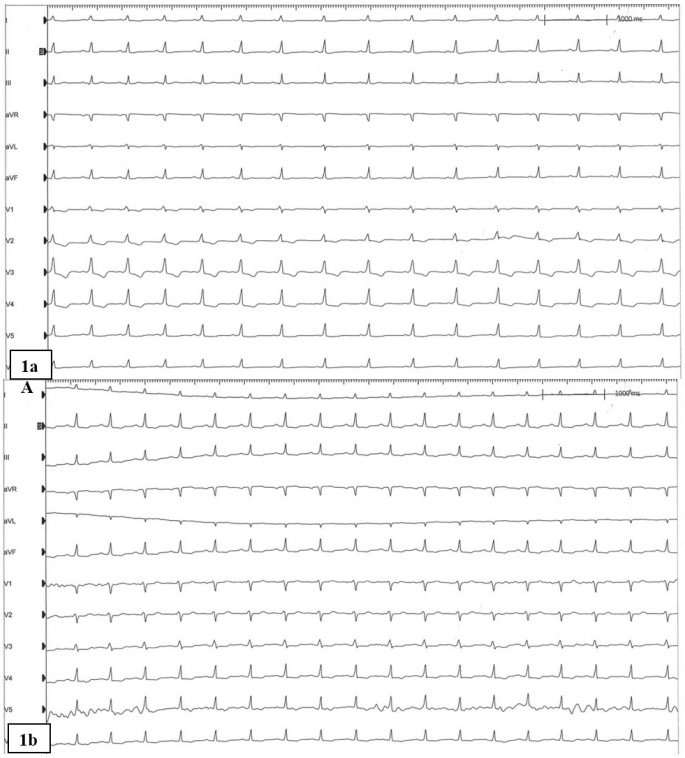

Figure 1: Left posteroseptal tract with a short ERP at 180msec in an asymptomatic 18-year-old girl with WPW electrocardiographic pattern consistent with a left posteroseptal tract **(A)** Surface electrocardiogram at baseline **(B)** Surface electrocardiogram post ablation treatment.
Abbreviations: WPW: Wolff-Parkinson-White; ERP: Effective refractory period.

invasive tests, we were able to identify the truly low risk patients, where regular clinical follow up was preferred over ablation therapy. In our study, 38% of asymptomatic WPW patients referred to the arrhythmiologic department for clinical assessment of WPW electrocardiographic pattern, presented pre-excitation disappearance either on ECG, or 24-hour ECG monitoring or exercise stress test. The remaining of our study population underwent EPS in order to assess high risk features of the accessory pathway, of whom nine patients were successfully treated with ablation therapy. Notably, none of the low risk patients

who were untreated experienced an arrhythmic event, and everyone remained asymptomatic and alive along a prolonged follow up period.

Our study findings are in accordance with previous studies supporting a benign prognosis in asymptomatic WPW patients [7,12-14]. For example, Santinelli et al, in a large prospective electrophysiology based study of 293 patients with asymptomatic ventricular pre-excitation reported good overall prognosis and small risk of arrhythmic events over a median follow up of 67 months [13]. In specific, ≈90% of the study population experienced no arrhythmic events remaining totally asymptomatic and 30% of them had pre-excitation disappearance. Only a minority of younger adults developed a potentially significant arrhythmic event. The authors concluded that the combination of younger age at the time of diagnosis, short anterograde ERP of the accessory pathway and inducibility at baseline were independent predictors of potentially life-threatening arrhythmic events [13]. Recently released guidelines on the management of supraventricular tachyarrhythmias by European Society of Cardiology suggest in case of asymptomatic WPW patients the performance of EPS to risk stratify individuals with high risk occupation or competitive athletes [1]. In every other case an invasive (IIa B) or a non-invasive (IIb B) approach is recommended in order to identify the low risk population [1]. Loss of delta wave during exercise testing or following drug administration (procainamide, propafenone, disopyramide) indicates a low risk accessory pathway [10]. Similarly, intermittent disappearance of pre-excitation on ECG or ambulatory monitoring suggests a long ERP characterising the bypass tract [15]. Persistent pre-excitation at maximum exercise was used as a risk stratifying tool in 85 asymptomatic WPW young individuals, designating the group of patients who will be further assessed with EPS [16]. A meta-analysis of studies including asymptomatic untreated WPW patients indicated a low incidence of sudden cardiac death, advising against a routine invasive risk stratification approach [14].

On the contrary, publications of Papone and co-workers suggest the reappraisal of asymptomatic WPW patients' management. Given that sudden cardiac death may be the first clinical manifestation of WPW syndrome in a previously asymptomatic individual and that lifetime sudden cardiac death risk is truly unpredictable regardless of the presence of symptoms, Papone et al. examined the long term outcomes of both treated and untreated WPW patients in a large prospective study including 2169 participants [8]. The authors propose the routine use of EPS as risk stratification strategy, as the only predictors of future adverse arrhythmiologic events and sudden cardiac death were intrinsic electrophysiological properties of the AP, such as shorter AP-AERP and AVRT triggering AF, rather than the presence or absence of symptoms [8]. In a previous randomized controlled trial asymptomatic high risk WPW patients were assigned to RFA of all APs or no treatment [17]. Prophylactic RFA of APs resulted in a risk reduction of 92% over a five-year follow up period. Of note, according to the authors, high risk for developing future adverse arrhythmias were those patients 35 years old or younger in whom arrhythmias were induced [17].

Ablation therapy is effective at eliminating the risk of sudden cardiac death, however, the procedure itself carries risk of complications even in high volume experienced centres [3,8]. Catheter-induced complete AVB and need for permanent pacing related to the location of the AP [3], thromboembolic phenomena, femoral hematoma, cardiac perforation with or without cardiac tamponade have been reported [2,18]. Current data do not support the use of EPS as a broad screening strategy in asymptomatic WPW patients, not suggesting prophylactic ablation of all APs. Low mortality rate, low WPW prevalence in the general population, potential harm and high cost of the invasive procedures are reasons arguing against an aggressive approach in asymptomatic patients. Focusing on non-invasive variables identifying the truly low risk subjects would be more prudent for this group of patients. Besides, up to 31% of adults and 26% of children lose pre-excitation over 5 years of follow-up, pointing towards an initial non-invasive risk stratification approach in asymptomatic patients [19].

Limitations

Our observations should be interpreted in the light of the following limitations. First, the observational design of our study along with the small sample size and the absence of control group should be taken into consideration. Furthermore, provocative drug testing during the first step of non-invasive evaluation was not performed as well as isoproterenol infusion during the second step of EPS. Also, despite the long-term follow up, it is unknown whether our study population will remain asymptomatic throughout their life, as the mean age of the patients included is rather young. However, both the patients' mean age and the follow up period was similar to other studies [6,8,13,17]. Our study findings, although may not seem to add to current knowledge, corroborate recently published ESC guideline recommendations for evaluation and treatment of asymptomatic patients with pre-excitation and the role of invasive EPS.

Conclusion

Management of patients with asymptomatic WPW has long been a field of debate among electrophysiologists. Our study provides data supporting a tiered approach using non-invasive tests and EPS in order to identify the truly low risk asymptomatic WPW patients who over a prolonged follow up period did not develop any life-threatening arrhythmias, rendering prophylactic ablation a non beneficial option for this group of patients.

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