ORIGINAL ARTICLE

Malignant ventricular arrhythmias and other complications of untreated accessory pathways: an analysis of prevalence and risk factors in over 600 ablation cases

Paweł Moskal[1*], Marek Jastrzębski[1*], Maciej Pitak[2], Kamil Fijorek[3], Piotr Weryński[2], Danuta Czarnecka[1]

1 1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
2 Department of Cardiology, Institute of Paediatrics, Jagiellonian University Medical College, Kraków, Poland
3 Department of Statistics, Cracow University of Economics, Kraków, Poland

EDITORIAL
by Giaccardi, see p. 177

ABSTRACT

BACKGROUND   The presence of accessory pathways (APs) is a risk factor for sudden cardiac death and other clinical complications.

AIMS   We aimed to characterize all adverse events likely related to the presence of APs in patients referred for AP ablation and to identify risk factors for malignant arrhythmias.

METHODS   We performed a retrospective analysis of consecutive patients referred for AP ablation from 2002 to 2017. Electrocardiograms, electrophysiological system records, and hospital discharge notes were reviewed. We collected data concerning symptoms before ablation, occurrence of ventricular fibrillation or malignant atrial fibrillation (AF), as well as other complications related to APs.

RESULTS   We identified 602 patients with APs. Serious AP-related events were observed in 41 patients, including 14 sudden cardiac arrests (1 death) and 16 pre–cardiac arrest events. Other complications included strokes, pulmonary edema, heart failure, and unnecessary device implantation. The risk of malignant arrhythmias decreased with a longer shortest preexcited RR interval (per 10 ms: odds ratio [OR], 1.3; 95% CI, 1.16–1.47) and increased with age (per 10 years: OR, 1.29; 95% CI, 1.06–1.57). The presence of inducible AF, but not sole atrioventricular reentrant tachycardia, increased the risk for malignant arrhythmias when compared with patients without any inducible arrhythmias.

CONCLUSIONS   Patients with APs referred for ablation commonly present with various adverse events. The predictive value of clinical risk factors for malignant arrhythmias is too low to prevent devastating consequences. When high safety and efficacy of AP ablation are ensured, even a low risk of sudden death is unacceptable and a lower threshold for prophylactic ablation should be used to prevent AP-related adverse events.

Correspondence to:
Paweł Moskal, MD,
1st Department of Cardiology,
Interventional Electrocardiology
and Hypertension, Jagiellonian
University Medical College,
ul. Jakubowskiego 2,
30-688 Kraków, Poland,
phone: +48 12 424 73 00,
email: pawel@moskal.in

* PM and MJ contributed equally
  to this work.

INTRODUCTION   Accessory atrioventricular connections were described in the late 19th/early 20th century. They are responsible for Wolf–Parkinson–White (WPW) syndrome, which manifests with a plethora of symptoms (heart palpitations, presyncope/syncope, dyspnea), various arrhythmias (ortho- and antidromic atrioventricular reentrant tachycardia [AVRT], atrial fibrillation [AF], preexcited AF, ventricular fibrillation [VF]) and several clinical consequences (eg, sudden cardiac death, stroke, syncope, heart failure).

Indications for accessory pathway (AP) ablation are based on AVRT-related symptoms and a long-term risk of other consequences of untreated APs, especially the risk of sudden cardiac

WHAT'S NEW?

For the first time, a comprehensive evaluation of typical (ventricular fibrillation, preexcited atrial fibrillation, sudden cardiac death) as well as unusual consequences of the untreated accessory pathway (AP) was performed in a sizeable cohort of patients undergoing AP ablation. Our study suggests that the occurrence of various adverse events, some of them devastating, in patients referred for AP ablation is not uncommon. Therefore, when high safety and efficacy of AP ablation are ensured, a low threshold for prophylactic ablation should be used.

arrest.[1] In asymptomatic or mildly symptomatic patients, the issue of prophylactic ablations of APs has long been a matter of scientific debate.[2-5]

Several clinical and electrophysiological parameters have been proposed and investigated as risk factors for sudden cardiac death, including age, sex, history of heart palpitations, inducibility of AVRT or AF, the shortest preexcited RR interval (SPRRI), AP effective refractory period, and AP location.[6-10] However, the published data are not entirely consistent, and differences between local populations are possible. Furthermore, although VF is the most feared adverse event, other severe

consequences of untreated APs are likely. However, there are scarce data concerning the occurrence of such events.

We aimed to characterize all adverse events likely related to the presence of AP as well as to identify risk factors for VF or malignant preexcited AF in patients referred for AP ablation.

METHODS We performed a retrospective cohort study of consecutive patients referred for AP ablation at 3 centers, from 2002 to early 2017. Ablation procedure descriptions, digital electrophysiological system records, hospital discharge notes, and 12-lead electrocardiograms (ECGs) of all patients scheduled for ablation were carefully reviewed. Pertinent clinical data were collected, such as the presence of symptoms before ablation, occurrence of cardiac arrest, occurrence of malignant AF (defined as a need for emergency cardioversion or syncope/presyncope symptoms and ECG with the shortest RR intervals <250 ms), history of stroke and AF, or other consequences considered to be related to the presence of an AP. The following electrophysiological data were obtained: 1) AP location, based on the archived fluoroscopic images of a successful ablation site in anteroposterior and left anterior oblique views; 2) shortest preexcited RR interval (measured either during incremental atrial pacing or during AF—the shortest SPRRI was recorded); and 3) inducibility of AVRT or AF. Electrophysiological studies were performed in a fasting and drug-free state (antiarrhythmic drugs stopped at least 5 half-times before the procedure). Isoproterenol use was at the physician's discretion.

The study protocol was approved by the ethics committee. Patient consent was not required in this study.

Statistical analysis All statistical analyses were performed using R version 3.2 (Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as counts and percentages, and continuous variables, as mean (SD) or median with quartiles as appropriate. For continuous variables, the significance of differences in 2 independent groups was assessed using the Mann–Whitney test. For categorical variables, the Fisher exact test was used. The association between the binary and continuous variable was estimated using a logistic regression model. A *P* value of less than 0.05 was considered significant. No adjustment for multiple comparisons was made. Whenever missing data were encountered, the pairwise deletion was used.

TABLE 1 Clinical and electrophysiological characteristics of the study group

Parameter		Value
Patients, n		570
APs, n		630
Ablation procedures, n		610
Age, y, mean (SD)		33 (18.9)
Male sex		320 (56.1)
Asymptomatic patients		94 (16.5)
AP location	Left free wall	319 (50.6)
	Posteroseptal (right and left)	123 (19.6)
	Right free wall	64 (10.2)
	Midseptal (right and left)	49 (7.8)
	Right anteroseptal	33 (5.3)
	Parahisian	20 (3.1)
	Epicardial	11 (1.8)
	Fasciculoventricular (true Mahaim)	8 (1.3)
	Aortomitral continuity	1 (0.16)
	Atriohisian (James)	1 (0.16)
AP functional types	Overt	427 (67.8)
	Concealed	187 (29.7)
	Concealed slow / decremental (Coumel)	7 (1.1)
	Atriofascicular (pseudo-Mahaim)	9 (1.4)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: AP, accessory pathway

RESULTS We identified 602 consecutive patients scheduled for an electrophysiological study or AP ablation. A total of 659 electrophysiological

TABLE 2 Serious events related to untreated accessory pathways

Event	Value
Sudden cardiac arrest (ventricular fibrillation)[a,b]	14 (3.1)
Malignant atrial fibrillation / near cardiac arrest[a]	16 (4.1)
Pulmonary edema	2 (0.35)
Stroke	2 (0.35)
Placental abruption	1 (0.17)
Heart failure	2 (0.35)
Recurrent syncope	2 (0.35)
Unnecessary ICD implantation	1 (0.17)
Unnecessary coronary angiogram	1 (0.17)

Data are presented as number (percentage) of patients.

a   Calculated for patients with overt accessory pathways (n = 385)

b   Resulting in permanent serious brain damage in 2 patients and death in 1 patient (0.8% of the population)

Abbreviations: ICD, implantable cardioverter-defibrillator

TABLE 3 Risk factors for ventricular fibrillation or malignant atrial fibrillation

Variable		Patients free of VF / malignant AF[a] (n = 359)	Patients with VF / malignant AF[a] (n = 26)	P value
Age, y, median (IQR)		27 (16–48)	47 (26–54)	0.01
Male sex		202 (56.3)	18 (69.2)	0.22
AP location	Posteroseptal	83 (23.6)	7 (26.9)	0.64
	Left free wall	165 (46.9)	14 (53.8)	0.55
	Right free wall	42 (11.9)	1 (3.8)	0.34
	Other septal	62 (17.6)	4 (15.4)	0.99
Symptoms		274 (76.3)	22 (84.6)	0.47
SPRRI, ms, median (IQR)		300 (260–350)	220 (203–242)	<0.001
Inducibility	None	142 (40)	6 (24)	0.14
	AVRT	165 (46.5)	7 (28)	0.1
	AF	24 (6.8)	5 (20)	0.03
	AF + AVRT	24 (6.8)	7 (28)	0.002

Data are presented as number (percentage) of patients unless otherwise indicated.

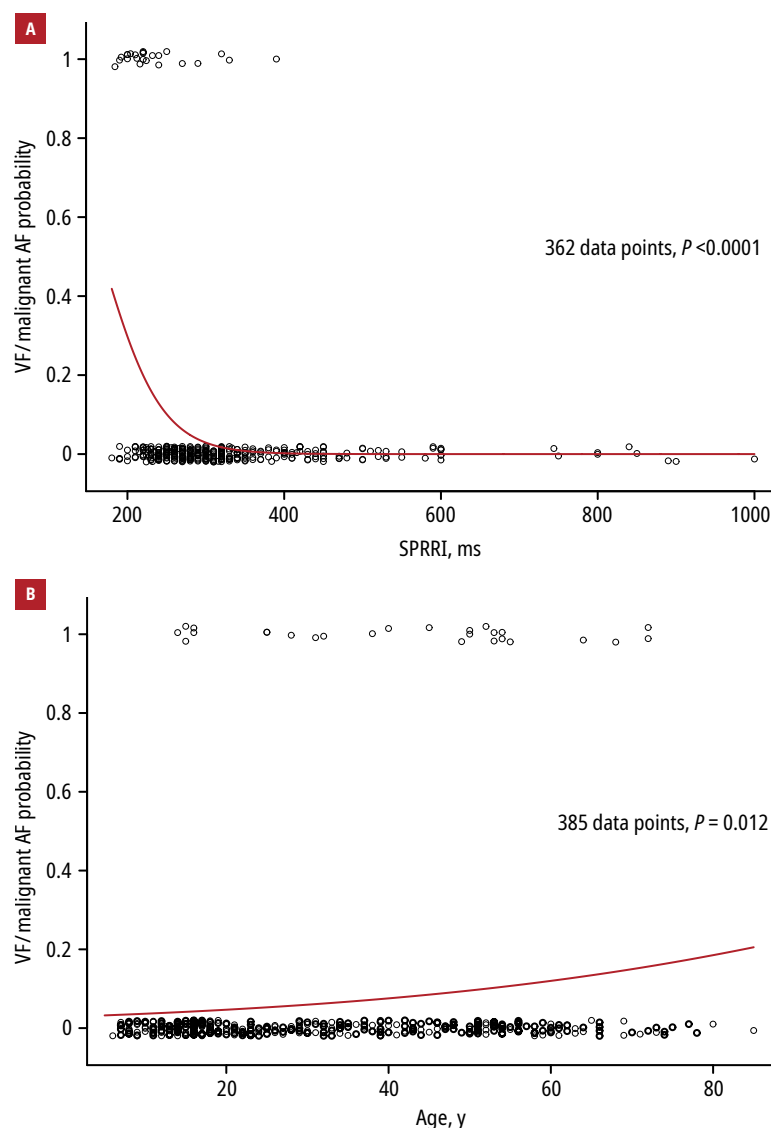a   Only patients with an overt AP

Abbreviations: AF, atrial fibrillation; AVRT, atrioventricular reentrant tachycardia; IQR, interquartile range; SPRRI, shortest preexcited RR interval; VF, ventricular fibrillation; others, see TABLE 1

studies and 639 ablation procedures were performed from 2002 to 2017; 21 patients had more than one AP, and there were 41 redo procedures. The study population consisted of 500 adults and 102 pediatric patients (age, 7–17 years). Ablation outcomes in this cohort were reported elsewhere.[11] Basic clinical and demographic data, as well as AP locations and AP types, some of which were also described previously, are presented in TABLE 1.[12-14]

Serious AP-related events were observed in 41 patients (7.2%), including 14 sudden cardiac arrests (2 resulting in permanent severe brain damage and 1 in death) and 16 pre–cardiac arrest events (TABLE 2). It is noteworthy that one of the cardiac arrests occurred in a patient with a concealed AP. The event was triggered by a very fast, hemodynamically unstable AVRT. Two patients with cardiac arrest were referred for implantable cardioverter-defibrillator (ICD) implantation, and one was actually implanted with the device (later explanted in our institution, after the diagnosis of WPW syndrome was established). Moreover, AP-related complications were not limited to arrhythmic events but included strokes (considered to be most likely caused by AF episodes secondary to AVRT), pulmonary edema with cardiogenic shock (prolonged fast AVRT attack), chronic congestive heart failure due to incessant tachycardia, placental abruption in pregnant woman (prolonged AVRT attack), and others (TABLE 2). Importantly, 27% of sudden cardiac arrests, including those with the worst consequences, occurred in previously asymptomatic patients and the rest in minimally symptomatic patients who did not consider symptoms of occasional palpitations bothersome enough to undergo ablation (which they had perceived as a risky procedure).

Characteristics related to the occurrence of VF or malignant AF are presented in TABLE 3. The median age, SPRRI, as well as AF and AVRT + AF inducibility differed significantly between patients with and without VF or malignant arrhythmia. The risk of VF or malignant arrhythmia decreased with a longer SPRRI (per each 10 ms: odds ratio [OR], 1.30; 95% CI, 1.16–1.47; P <0.001) and increased with age (per 10 years: OR, 1.29; 95% CI, 1.06–1.57; P = 0.01). Data are presented in FIGURE 1. Inducibility of AF or AF + AVRT (OR, 4.85; 95% CI, 1.42–16.56; P = 0.01 and OR, 6.62; 95% CI, 2.10–20.81; P <0.001, respectively), but not sole AVRT inducibility (OR, 1.00; 95% CI, 0.34–2.93; P = 0.997), increased the risk of VF or malignant arrhythmia when compared with patients without any inducible arrhythmia.

DISCUSSION The very good safety profile and efficacy of the AP ablation procedure[11,15] stands in stark contrast to the multiple severe and often devastating complications of untreated APs that were observed in 7.2% of all studied patients, including VF or malignant AF seen in 7% of the patients with overt preexcitation. Moreover, in 1.93% of the patients, we noted various non–VF or nonmalignant arrhythmic events with serious consequences. These complications were rarely investigated in cohort studies, as they are usually reported as case reports or case series.

FIGURE 1 Logistic regression fit: **A** – the risk of ventricular fibrillation (VF) or malignant atrial fibrillation (AF) is reduced with a decrease in the accessory pathway's ability to conduct fast (longer shortest preexcited RR interval [SPRRI]); **B** – the risk of VF or malignant AF increases with age.

Recently, a link between preexcitation (mainly due to an anteroseptal AP) and increased risk of AF (hazard ratio [HR], 3.12) and heart failure (HR, 2.11) was reported in a large ECG study using a database from a primary care cohort. Moreover, patients aged 65 years or older had a significantly higher risk of death (HR, 1.85) when compared with patients without preexcitation.[23]

Stec et al[24] reported a case series of patients with asymptomatic preexcitation with dyspnea and exercise intolerance. No organic disease in the cardiopulmonary system was found. However, all patients had abnormal spirometry results. After radiofrequency ablation, a significant improvement in exercise capacity was observed in all cases.

The presence of AP can lead to inappropriate ICD implantation (one case in our cohort). Song et al[25] reported the case of a 13-year-old girl with refractory VF who required extracorporeal life support due to malignant left parahisian AP. Surprisingly, the decision was made not to ablate the AP and the ICD was implanted instead. In a study by Becker et al,[26] including 462 patients with a clinical diagnosis of sustained VT or cardiac arrest referred for ICD implantation, 6 patients (1.3%) were diagnosed with WPW syndrome, which prevented the unnecessary device implantation. On the other hand, the presence of AP can mask the underlying complete atrioventricular block and delay pacemaker implantation.[27]

Ling et al[28] reported a patient with WPW syndrome and an inferior-wall ST-segment elevation myocardial infarction, in whom the preexcitation pattern masked typical ECG changes of the occluded right coronary artery. In other scenarios, overt preexcitation can mimic ischemia on ECG, which can result in unnecessary coronary angiography (1 case in our cohort), or when AP is in an atypical location, it can resemble ventricular tachycardia.[29]

Finally, in patients with an untreated AP, potential side effects of drugs could be more serious. Inci et al[30] reported a patient with untreated WPW syndrome who developed preexcited AF and subsequently VF after ingestion of sildenafil.

Risk factors for malignant ventricular arrhythmias Only 3 AP and clinical characteristics were identified as risk factors for VF or malignant arrhythmia. They include a shorter SPRRI, AF or AVRT inducibility, and, surprisingly, older age. Both AF or AVRT inducibility and a shorter SPRRI were identified by several previous studies as related to malignant arrhythmias (TABLE 4). However, importantly, in 3 survivors of VF, we observed SPRRI that was longer than the recommended cutoff value of 250 ms for prophylactic AP ablation. Perhaps this reflects poor sensitivity of SPRRI to identify patients with WPW syndrome at risk for sudden

Unusual consequences of untreated accessory pathways Overt preexcitation causes chronic ventricular desynchrony, the deleterious effect of which was reported in both adult and pediatric populations. In most cases, it is usually limited to regional wall motion abnormality that correlates with local myocardial fibrosis and wall thinning on magnetic resonance imaging or computed tomography. However, regional wall motion abnormality usually persists after AP ablation.[16] When the AP is located in the septal or right free wall, which causes left bundle branch block–like QRS morphology, there is an increased risk for global systolic dysfunction and dilated cardiomyopathy that can progress to chronic heart failure.[16-20] The systolic heart function usually recovers after AP ablation. Other possible mechanisms for heart failure due to tachycardia-induced cardiomyopathy are chronic AF with preexcitation and incessant AVRT (2 cases in our cohort).[21,22]

TABLE 4 Risk factors for sudden cardiac death in patients with Wolf–Parkinson–White syndrome

Study	Cases, n	Identified risk factors
Klein et al[6]	98	History of AVRT and AF, multiple APs, short SPRRI (180 ms vs 240 ms in the control group)
Santinelli et al[7]	98	Multiple AP: HR, 5.14; 95% CI, 1.91–13.88 AP-ERP ≤240 ms: HR, 6.34; 95% CI, 2.09–19.22
Pappone et al[8]	369	Age: HR, 0.94; 95% CI, 0.875–1.01 AP-ERP: HR, 0.922; 95% CI, 0.9–0.944 AVRT / AF inducibility: HR, 5.01; 95% CI, 2.1–11.95
Orczykowski et al[9]	1007	Overt preexcitation: OR, 3.54; 95% CI, 1.63–7.97 Male sex: OR, 2.3; 95% CI, 1.23–4.3 Multiple APs: OR, 2.05; 95% CI, 1.1–3.5
Pappone et al[10]	1004	Age: HR, 0.91; 95% CI, 0.81–1.02 AP-ERP: HR, 0.86; 95% CI, 0.82–0.91 AVRT/AF inducibility: HR, 27.16; 95% CI, 5.29–139.4
Moskal et al (current study)	385	Age: OR, 1.29; 95% CI, 1.06–1.57 per 10-year increase SPRRI: OR, 1.30; 95% CI, 1.16–1.47 per 10-ms shortening AVRT only inducibility: OR, 1; 95% CI, 0.34–2.93 AF only inducibility: OR, 4.85; 95% CI, 1.42–16.56 AVRT + AF inducibility: OR, 6.62; 95% CI, 2.1–20.81

Abbreviations: AP-ERP, accessory pathway antegrade effective refractory period at baseline; HR, hazard ratio; OR, odds ratio; others, see TABLES 1 and 3

death. Of note, the value of 250 ms was based on an early study involving a rather small series of patients.[31] In a contemporary study by Orczykowski et al,[9] who presented the results for the largest group of patients with WPW after cardiac arrest investigated so far, several patients had an SPRRI longer than 250 ms, as can be inferred from the reported mean (SD) value of 205 (27) ms. The limitation of SPRRI as a risk-stratifying tool is supported by a recommendation included in the recent European Society of Cardiology guidelines that ablation may be considered in patients with low-risk asymptomatic preexcitation in experienced centers (class IIb, level of evidence C).[1]

The increase in the risk of developing malignant arrhythmia with age, as observed in our study, could have resulted from a known increase in the prevalence of AF with age. This observation is corroborated both by Orczykowski et al,[9] who reported the second peak in malignant arrhythmic episodes in patients with preexcitation around the age of 50, and by Brembilla-Perrot et al,[32] who conducted a transesophageal stimulation study in patients with asymptomatic preexcitation and found that older patients remained at high risk of malignant arrhythmias. These observations are in contrast to the popular belief and results of studies that reported the occurrence of VF only in children and adolescents.[5,10]

Sudden cardiac arrest We observed 1 death, which occurred just 14 days before the scheduled prophylactic ablation in a previously asymptomatic individual due to confirmed VF; all other patients survived malignant arrhythmia episodes. However, we believe that the relatively high percentage of survivors seen both in our and in other studies on preexcitation cannot be considered as an argument in favor of withholding ablation in asymptomatic patients, as suggested by some investigators.[2,5] Two of our sudden cardiac arrest survivors suffered severe irreversible brain damage, and both were previously asymptomatic. Moreover, some permanent cognitive and psychological consequences of sudden cardiac arrest or malignant AF episode were likely present in the remaining patients, although this was not assessed either in our or in any other study on WPW syndrome. However, this was observed in the survivors of sudden cardiac arrest.[33]

Limitations The limitations of this study are typical of retrospective observations, with a potential referral bias. In addition, over the study period, there were some changes in isoproterenol use, which influences the SPRRI. At first, isoproterenol infusion could be omitted if the AP was symptomatic. Later, it was always used when an SPRRI was longer than 250 ms, as recommended in the guidelines.[1]

Conclusion Our study suggests that the occurrence of various adverse events, some of them devastating, in patients with WPW syndrome referred for an AP ablation procedure is not uncommon. Although risk factors for malignant arrhythmias can be identified, their predictive value does not seem satisfactory. We believe that in the era of high safety and efficacy of AP ablation, even a low risk of sudden death is unacceptable and that there should be a lower threshold for prophylactic ablation to prevent AP-related adverse events.

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