

Uniwersytet Jagielloński
Collegium Medicum

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The role of electrocardiogram as a diagnostic tool in
Wolff-Parkinson-White syndrome

Rola elektrokardiogramu jako narzędzia diagnostycznego
w zespole Wolffa-Parkinsona-White'a

Praca doktorska

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I. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

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- Autorzy:** Paweł Moskal, Marek Jastrzębski, Maciej Pitak, Kamil Fijorek, Piotr Weryński, Danuta Czarnecka
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II. WSTĘP

Zespół Wolffa-Parkinsona-White'a (WPW) charakteryzują napadowe zaburzenia rytmu serca oraz obecność preekscytacji w elektrokardiogramie (EKG). Do preekscytacji dochodzi, gdy komory serca są aktywowane wcześniej, niż gdyby aktywacja zachodziła fizjologicznie przez węzeł przedsionkowo-komorowy oraz układ Hisa-Purkiniego. Dodatkowy front depolaryzacji jest obserwowany w EKG pod postacią fali delta. [1]

W zespole WPW przyczyną preekscytacji jest obecność drogi dodatkowej łączącej tkankę przedsionka i komory serca z pominięciem węzła przedsionkowo-komorowego. Droga dodatkowa jest zdolna do przewodzenia impulsów elektrycznych, co sprawia że może być elementem pętli nawrotnej i prowadzić do powstania arytmii. Każdy epizod częstoskurczu nawrotnego w zespole WPW wiąże się z ryzykiem wystąpienia preekscytowanego migotania przedsionków lub migotania komór, które mogą prowadzić do zatrzymania krążenia i zgonu pacjenta. [1] W dotychczas opublikowanych pracach zaproponowano cechy elektrokardiograficzne, takie jak najkrótszy preekscytowany odstęp RR (SPRRI), indukcja częstoskurczu podczas badania elektrofizjologicznego czy lokalizacja drogi dodatkowej, które obok cech klinicznych mogą pomóc w diagnostyce i identyfikacji pacjentów o wysokim ryzyku wystąpienia złośliwych arytmii. Wyniki tych badań, ze względu na ograniczenia metodologiczne i różnice populacyjne, nie pozwalają na wyciągnięcie jednoznacznych wniosków dotyczących wartości diagnostycznej wybranych cech elektrokardiograficznych.

Wprowadzenie zabiegu przezskórnej ablacji prądem o wysokiej częstotliwości (RF) umożliwiło wyeliminowanie drogi dodatkowej prowadząc do trwałego wyleczenia pacjenta. [2,3] Warunkiem skutecznego i bezpiecznego wykonania ablacji jest precyzyjna lokalizacja drogi dodatkowej w rejonie pierścienia włóknistego serca. [4] Analiza morfologii preekscytacji w spoczynkowym 12-odprowadzeniowym EKG umożliwia określenie przybliżonego położenia drogi dodatkowej przed zabiegiem, co pozwala na wstępne zaplanowanie procedury. Manifestacja elektrokardiograficzna drogi dodatkowej zależy od jej umiejscowienia w sercu oraz wielkości aktywowanego przez nią obszaru mięśnia komory. Skrajną sytuacją jest maksymalna preekscytacja, w której praktycznie cała masa mięśniówki komór zostaje aktywowana przez drogę dodatkową. [1]

Stworzono ponad 20 algorytmów pozwalających na przybliżone określenie lokalizacji drogi dodatkowej na podstawie wybranych cech elektrokardiograficznych, takich

jak kierunek fali delta (algorytm Arrudy) [5], polarność zespołów QRS (algorytm d'Avila) [6] czy stosunek wielkości załamka R do S (algorytm Taguchiego) ocenianych w spoczynkowym badaniu EKG. [7] W badaniach walidujących większość algorytmów miała niską precyzję w lokalizacji drogi dodatkowej. Jedną z możliwych przyczyn trudności w stworzeniu uniwersalnego algorytmu jest duża zmienność nasilenia cech preekscytacji w spoczynkowym EKG. Drogi lewostronne często posiadają jedynie subtelne zmiany w morfologii zespołów QRS, natomiast drogi prawostronne wykazują wyraźniejszą preekscytację. Podczas maksymalnej preekscytacji, w której przewodzenie zachodzi głównie szlakiem dodatkowym, możliwe jest zaobserwowanie wszystkich cech elektrokardiograficznych właściwych dla danej drogi dodatkowej. Maksymalną preekscytację można uzyskać podczas zabiegu elektrofizjologicznego poprzez: wykonanie szybkiej stymulacji przedsionkowej, indukcję częstoskurczu nawrotnego przedsionkowo-komorowego antydromowego albo podanie adenozyiny — leku blokującego łącznie przedsionkowo-komorowe. Do tej pory zależność między nasileniem preekscytacji w elektrokardiogramach a precyzją algorytmów lokalizujących drogę dodatkową nie została systematycznie zbadana.

Kolejnym problemem związanym ze zjawiskiem preekscytacji jest różnicowanie preekscytowanego częstoskurczu nadkomorowego od częstoskurczu komorowego. Jest to istotny problem kliniczny, ponieważ patofizjologia oraz postępowanie np. w preekscytowanym trzepotaniu przedsionków będzie inne niż w częstoskurczu komorowym. Z uwagi na podobieństwo morfologiczne tych arytmii dostępne algorytmy do różnicowania częstoskurczów z szerokimi zespołami QRS, oparte o pojedyncze kryterium, nie pozwalają na skuteczne ich odróżnianie. Co więcej, w większość opublikowanych badań wykluczano pacjentów z preekscytacją lub umieszczano ich w grupie pacjentów z częstoskurczem komorowym. Nowe podejście do analizy elektrokardiogramów z wykorzystaniem skali punktowej — ventricular tachycardia score (VT score), może pozwolić na lepsze różnicowanie tych arytmii. Wymaga to jednak walidacji tego algorytmu na dużej bazie zapisów EKG z maksymalną preekscytacją oraz porównania go z dotychczas stosowanymi algorytmami takimi jak algorytm Brugady, algorytmu aVR czy algorytmem Steurera. [8–10]

W niniejszej pracy doktorskiej zbadano rolę elektrokardiogramu jako narzędzia diagnostycznego w zespole Wolffa-Parkinsona-White'a.

III. CELE PRACY

Celem pracy było określenie roli elektrokardiogramu jako narzędzia diagnostycznego w zespole Wolffa-Parkinsona-White'a

Cele szczegółowe pracy:

1. Określenie cech elektrokardiograficznych związanych z wysokim ryzykiem wystąpienia złośliwych arytmii w przebiegu zespołu Wolffa-Parkinsona-White'a.
2. Określenie wpływu nasilenia preekscytacji w elektrokardiogramie na dokładność algorytmów lokalizujących położenie drogi dodatkowej.
3. Porównanie dokładności tradycyjnych algorytmów lokalizujących położenie drogi dodatkowej.
4. Analiza wartości diagnostycznej algorytmu lokalizującego stworzonego dla elektrokardiogramów z maksymalną preekscytacją.
5. Porównanie specyficzności pojedynczych kryteriów elektrokardiograficznych oraz algorytmów elektrokardiograficznych (skala ventricular tachycardia score, algorytm Brugady, algorytm aVR, algorytm Steurera) w różnicowaniu częstoskurczów komorowych od preekscytowanych częstoskurczów przedsionkowo-komorowych.

IV. METODOLOGIA

Badania miały charakter retrospektywnej analizy zabiegów ablacji dróg dodatkowych wykonanych w latach 2002–2019. Do badań byli włączani pacjenci skierowani do szpitala z powodu rozpoznanego zespołu Wolffa-Parkinsona-White'a lub z bezobjawową preekscytacją. Analizie poddano dokumentację szpitalną, opisy zabiegowe, zapisy z systemu elektrofizjologicznego, obrazy z fluoroskopii z położeniem elektrody ablacyjnej oraz zapisy 12-odprowadzeniowego EKG.

Podczas badania elektrofizjologicznego wykonywano rejestrację wysokiej jakości spoczynkowego EKG stosując przesuw 25 mm/s oraz filtrację sygnału w zakresie 0.01–100 Hz. Zapis EKG z maksymalną preekscytacją otrzymano stosując:

1. szybką stymulację z elektrody umieszczonej w prawym przedsionku,
2. indukcję częstoskurczu przedsionkowo-komorowego antydromowego,
3. indukcję migotania przedsionków z szybką akcją komór.

Położenie drogi dodatkowej było określone na podstawie położenia elektrody ablacyjnej w projekcji lewej przedniej skośnej oraz prawej przedniej skośnej w miejscu skutecznej ablacji. Badanie elektrofizjologiczne było przeprowadzone u pacjentów niebędących pod wpływem leków antyarytmicznych. Użycie izoprenaliny zależało od decyzji operatora.

Szczegółowa metodyka każdego z badań znajduje się w sekcji „Methods” w załączonych publikacjach.

V. TEKSTY OPUBLIKOWANYCH PRAC NAUKOWYCH BĘDĄCYCH
PODSTAWĄ PRACY DOKTORSKIEJ

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

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KEY WORDS

ablation, accessory pathway, malignant atrial fibrillation, sudden cardiac arrest, Wolf–Parkinson–White syndrome

EDITORIAL

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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.

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

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

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.

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	
SPRRRI, 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.

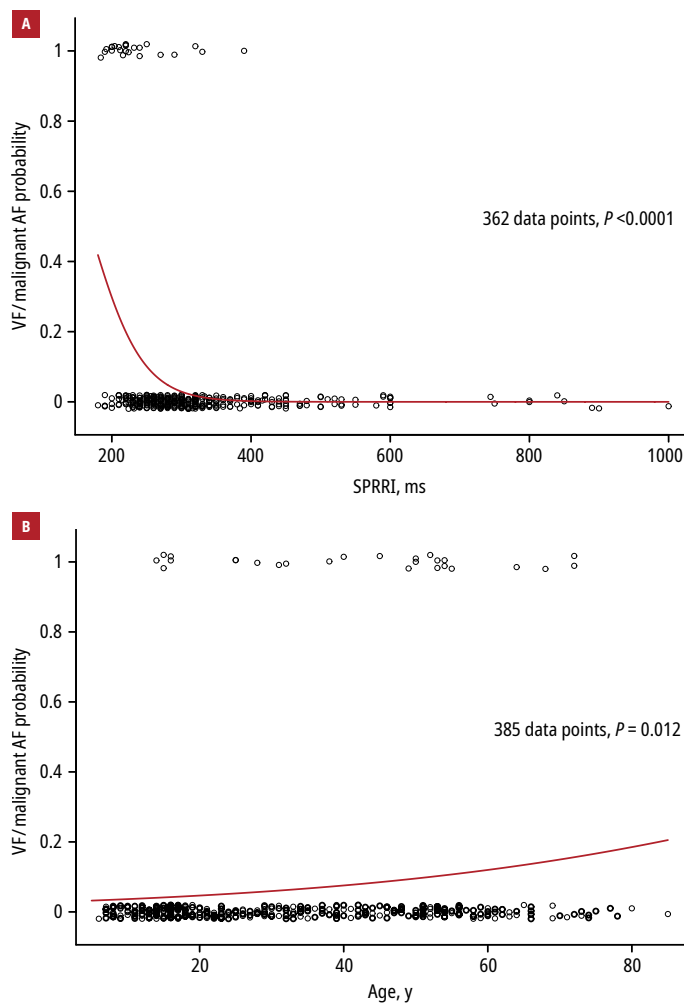


FIGURE 1 Logistic regression fit: **A** – the risk of ventricular fibrillation (VF) or malignant atrial fibrillation (AF) is reduced with a decrease in the accessory pathway’s ability to conduct fast (longer shortest preexcited RR interval [SPRRI]); **B** – the risk of VF or malignant AF increases with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

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}

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 al²⁴ 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 al²⁵ 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 al²⁸ 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 al³⁰ 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

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.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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Increased pre-excitation in ECG improves accuracy of algorithms for accessory pathway localization in Wolff–Parkinson–White syndrome

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Increased pre-excitation in ECG improves accuracy of algorithms for accessory pathway localization in Wolff–Parkinson–White syndrome

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What's New?

This study analysed the accuracy of five accessory pathway localising algorithms using resting and maximally pre-excited 12-lead electrocardiogram (ECG). We found that the increased pre-excitation improved the accuracy of all investigated algorithms. Pambrun algorithm based on maximally pre-excited ECGs has the best accuracy. Our main finding is that maximally pre-excited ECGs should be preferably used in clinical practice to facilitate the ablation procedure.

Abstract

Background: Several electrocardiographic (ECG) algorithms were developed for localization of accessory pathways (AP) in Wolff-Parkinson-White syndrome. However, their accuracy may be related to the manifested degree of pre-excitation in ECG.

Aims: Our goal was to assess the influence of the degree of pre-excitation on the accuracy of four traditional AP localizing algorithms and to compare them with the algorithm specifically designed for maximally pre-excited ECGs (Pambrun).

Methods: The study included 300 patients who underwent successful ablation of an overt atrioventricular accessory pathway. Resting and maximally pre-excited ECGs obtained during incremental atrial pacing were assessed using four traditional AP localizing algorithms: Xie, d'Avila, Iturralde and Taguchi. Maximally pre-excited ECGs were additionally assessed with Pambrun algorithm. We compared the precision of the algorithms to predict accurate or anatomically adjacent AP localization.

Results: Overall accuracy of traditional AP localizing algorithms using resting ECG ranged between 26 – 53.7% and improved to 47.3 – 69.7% when adjacent locations were accepted. When used with maximal pre-excitation, all algorithms had significantly higher accuracy, with a mean improvement of 14.3 and 15.6 percentage points for precise and adjacent sites. Pambrun algorithm for maximally pre-excited ECGs had the highest precision for both accurate and adjacent locations of APs (89.7 and 97%).

Conclusions: Greater pre-excitation in ECG improved the accuracy of the traditional AP localizing algorithms. The algorithm designed to use maximally pre-excited ECG has the best accuracy. Preferably maximally pre-excited ECGs should be used in clinical practice to facilitate the ablation procedure.

Keywords: accessory pathway, algorithms, pre-excitation, maximal pre-excitation, Wolf-Parkinson-White syndrome

Introduction

Ventricular pre-excitation caused by an accessory pathway (AP) is a typical feature of Wolff-Parkinson-White syndrome (WPW). The electrocardiographic hallmark of pre-excitation is the QRS complex that is distorted, prolonged and often with altered polarity. The radiofrequency catheter ablation of an accessory pathway is a standard treatment in WPW. [1] Preprocedural localization of AP facilitates the success of ablation and allows pre-procedural risk assessment. Over 20 different algorithms were created to localize AP based on the resting 12-lead electrocardiogram (ECG) features: delta wave morphology, QRS polarity or R/S amplitude ratio of QRS complexes. However, most of these algorithms had low accuracy in validation studies. [2–6] This discrepancy might be related to a different degree of pre-excitation in the initial sets of ECGs and in the validation cohorts. The majority of the AP localizing algorithms were designed to be used with resting ECG, where QRS morphology results of a fusion of ventricular activation through the His-Purkinje conduction system and an accessory pathway. [7] Fused QRS morphology is influenced mainly by two factors: 1) conduction via atrioventricular node/His bundle and bundle branches, and 2) AP localization. However, during a provoked or spontaneous maximal pre-excitation, we observe ventricular activation accomplished almost exclusively by AP, with QRS morphology almost completely depending on AP localization (Figure 1). [8]

Variability in the degree of pre-excitation in QRS morphology can explain the difficulty in creating an accurate and universal algorithm. Pambrun et al. proposed a new AP localizing algorithm designed for ECGs with maximal pre-excitation that aims to have better predictive value, but it has not been validated so far by independent studies. [9]

This study aimed to assess the influence of the degree of pre-excitation in resting ECG on the accuracy of four AP localizing algorithms designed for resting ECGs and to compare

them to the recently introduced algorithm specifically designed for maximally pre-excited ECGs.

Methods

We retrospectively analysed 340 consecutive ablation procedures from 2002 to 2019 in patients with overt pre-excitation. The ablation outcomes, success rate and risk factors analysis for malignant arrhythmias of this cohort were reported by us previously. [10,11] For the current study, we excluded patients with structural heart disease, multiple APs, atriofascicular (“Mahaim pathways”) and fasciculo-ventricular pathways, failed ablation and without high-quality 12-lead ECGs with resting and maximally pre-excited patterns.

From the electrophysiological recording system, we printed 12-lead surface ECG (25 mm/s) with baseline pre-excitation — observed at the beginning of the procedure. The second ECG was obtained during the electrophysiological study (EPS) when maximal pre-excitation was provoked by either incremental fast atrial pacing, induction of antidromic atrioventricular re-entry tachycardia or induction of rapid atrial fibrillation. The accessory pathway localization was assessed using right and left anterior oblique views according to the position of the ablation catheter at the successful ablation site.

To compare the accuracy of AP prediction, we analysed each pair of resting and maximally pre-excited ECGs with four traditional algorithms: Xie et al., d'Avila et al., Iturralde et al. and Taguchi et al. [12–15] They were designed to use with resting 12-lead ECG and do not require subjective delta wave assessment. Iturralde, d'Avila and Xie algorithms predict AP location at 5 to 9 sites along mitral and tricuspid annulus, using mainly the polarity and morphology of the QRS complexes in leads II, III, aVF, aVL, V1 and V2. Taguchi algorithm uses the R/S ratio in leads V1, V2 and aVF to predict the location of AP at five sites.

In addition, we analysed maximally pre-excited ECGs with the recently published algorithm by Pambrun et al. To localize the AP at nine sites it uses the polarity of lead V1 and V3, the number of overall positive inferior leads (II, III, aVF), ratio of R waves in V1 and lead I and morphology of lead II. [9] The summary of algorithms criteria is presented in Supplementary Table S1.

The number of possible AP locations in chosen algorithms ranges from 5 to 9, and different terminology was used to describe them. To facilitate comparison of algorithms, we adapted a unified classification of AP locations as it was done in previous studies. [4,6] We used Pambrun et al. AP sites as a reference and translated locations given in other algorithms as described in Table 1.

We defined the predictions of the algorithm as (1) accurate – predictions matched precisely the AP location established during EPS; (2) adjacent – predictions were anatomically adjacent to the actual AP location; (3) inaccurate – predictions did not match the above definitions.

In the secondary analysis, we wanted to investigate the performance of traditional algorithms in patients divided according to the degree of pre-excitation in resting ECG. We measured resting QRS duration (QRSd) using global QRS method. [16] and used terciles to split ECGs into three groups according to manifested pre-excitation: (1) low — QRSd < 123 ms, n = 109; (2) moderate — QRSd 123–138 ms, n = 92; (3) high — QRSd > 138 ms, n = 99,

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

Statistical analysis

We performed statistical analyses using STATA 16.1 (StataCorp, Texas, USA). The accuracy of algorithm was defined as the percent of patients with a correct prediction of

successful ablation site. We used a chi-square test for the comparison of categorical variables and McNemar's test to compare algorithm accuracy between baseline and maximally pre-excited ECGs. We used a Mann-Whitney test to compare a median QRS duration between left and right-sided AP. We considered a P value of less than 0.05 as statistically significant.

Results

The final study group included 300 patients. We presented the basic demographic data and AP locations according to the successful ablation site during the electrophysiological study in Table 2. Left free-wall APs were more prevalent than septal or right free-wall APs (44%, 38% and 18% respectively). In resting ECG, the median QRS duration for left-sided AP was significantly shorter than for right-sided AP (median 127 vs 132 ms, $P = 0.01$).

Accuracy for resting and maximally pre-excited ECGs

We presented the overall accuracy of the algorithms in Table 3. For the ECGs with resting pre-excitation, Taguchi and Iturralde algorithms had the most accurate predictions (53.7% and 53.3%, respectively). When adjacent localizations were accepted, then the accuracy of all algorithms improved, but d'Avila, Iturralde and Taguchi algorithms were significantly better than Xie ($P < 0.001$).

For the ECGs with maximal pre-excitation, all traditional algorithms had an increase in accuracy, with a mean improvement of 14.3 percentage points for precise locations and 15.6 percentage points for adjacent locations. Pambrun algorithm achieved the most accurate predictions in precise and adjacent sites.

The performance of algorithms according to the degree of pre-excitation in resting ECG

Figure 2 shows the accuracy of the algorithms in patients with low, moderate and high resting pre-excitation. The precision of all traditional algorithms improved with the increase of pre-excitation, with mean improvement from low to high of 14.3 percentage points for

accurate locations and 10 percentage points for adjacent sites. Xie algorithm had the lowest accuracy independently of the degree of pre-excitation.

Accuracy in distinguishing left-sided and right-sided accessory pathways

The accuracy of the traditional algorithm in predicting left and right-sided locations of APs using resting ECG ranged between 62.7% – 86.0% (Figure 3). Using the maximally pre-excited ECGs the accuracy of Xie, d'Avila, Iturralde and Taguchi algorithms increased to 83.7–95%. Pambrun algorithm was the most accurate (98%).

Analysis of errors in Pambrun algorithm

In our cohort, 33% of parahisian APs manifested the overall negative polarity of the QRS complex in lead V3 during maximal pre-excitation and were subsequently incorrectly predicted as right anterior or right lateral AP. There were four epicardial/deep coronary vein APs. None of them met the criteria of Pambrun algorithm (Supplementary Table S1). The three cases the QRS pattern were typical for right posteroseptal AP. In one there were notched QS complexes in the lead II. The fourth case had positive QRS in lead V1 but did not have notched QS complex in the lead II.

Discussion

Our analysis of a large cohort of WPW patients showed that the accuracy of traditional algorithms in localizing accessory pathways improved with the increase of pre-excitation in the resting ECG. Moreover, the traditional algorithms had better accuracy when applied to maximally pre-excited ECG obtained at the beginning of an electrophysiological study. In line with this, we found that the Pambrun algorithm, specifically designed for maximally pre-excited ECGs had the highest accuracy of all analysed methods.

In our study, Xie and Iturralde algorithms had the accuracy in predicting AP locations similar to the results of previous studies. [2,5,6] Teixeira et al. and Maden et al. reported that

d'Avila algorithm was significantly worse than other algorithms, but in our research, its performance was comparable. [5,6] Taguchi algorithm has not been validated so far. We found that it was not better than Iturralde algorithm, similarly designed to predict AP at five sites with only three criteria. The performance of all four traditional algorithms in discriminating left-sided from right-sided AP was poor with 14 – 37.1% error rate.

The association between the degree of pre-excitation and the accuracy of the AP localizing algorithms was intuitively accepted but not proven so far. Our study confirmed this clinical assumption. Low pre-excitation in resting ECG hampered predictive value of traditional algorithms. On the other hand, the accuracy of algorithms was significantly better when applied to ECGs with maximal pre-excitation. For over two decades it was a routine practice in our electrophysiology laboratory to use d'Avila algorithm, albeit with the modification that we used fully pre-excited ECG obtained at the beginning of EP study instead of required resting ECG. This study confirms that it was the right approach, as the accuracy of this algorithm increased from 64% to 79%. Similarly, approximately 15% more cases were correctly diagnosed by other algorithms when fully pre-excited ECG was analysed instead of ECG with baseline pre-excitation. We believe that these results are firmly rooted in basic electrophysiology and electrocardiography. More pre-excited QRS contains more information regarding the impact of an accessory pathway on ventricular depolarization. The more information we have – the more accurate the ECG analysis can be in localizing the accessory pathway insertion around mitral and tricuspid annuli.

In the secondary analysis, we observed that the performance of algorithms depended on the degree of pre-excitation in resting ECG. This could be explained by the fact that the sensitivity of algorithms varies for different AP location, which in turn is the primary determinant of the degree of pre-excitation. [4–6] Ability of algorithms to locate AP is the

worst in low pre-excitation. Therefore, clinician should be especially cautious when trying to predict the AP location in this group of patients.

Our study provides the first external validation of Pambrun algorithm on a large cohort. We confirmed its high accuracy for precise locations of AP (89.7%), matching the accuracy reported by the authors (90%). [9] However, we found two recurring errors in node-His (midseptal and parahisian area) and deep coronary sinus AP locations that need to be addressed. First, Pambrun et al. reported that they did not have enough cases of AP localized in coronary sinus (CS) pouch to fully assess the criterion for deep coronary sinus location (notched QS complex in lead II). In our cohort, there were 4 epicardial AP, from which 3 were localized in the CS diverticulum. In all cases, the maximal pre-excitation pattern was similar to right posteroseptal AP, with deep negative QS complexes in leads II, III, aVF. Interestingly, in one of these cases, the criterion for deep coronary sinus location was present. We believe that this feature should also be assessed for right posteroseptal localization to predict a location closer to the epicardium. Second, Pambrun et al. used positive QRS in lead V3 as a criterion to differentiate mid-septal and parahisian AP location (or node-His using Pambrun terminology) from the right lateral and right anterior AP. However, in our cohort, we found that almost 33% of true parahisian APs had overall negative QRS in lead V3 during maximal pre-excitation, therefore, this feature cannot be reliably used to exclude this particular location.

Although prediction of AP location is better when based on maximally pre-excited ECG, clinicians usually have only resting ECG available. However, more pre-excited ECG can be easily obtained, either using vagal manoeuvres, short-acting drugs that slow conduction in the atrioventricular node or by analysing 12-lead Holter monitoring, as the degree of pre-excitation in ECG often changes during the day. During the

electrophysiological study, maximally pre-excited ECG should be obtained at the beginning of the procedure to verify resting ECG data.

Limitations

First, this is a retrospective, single-centre study. Despite a large number of patients, population-related differences could influence the accuracy of the tested algorithms. Second, resting ECGs were acquired at the beginning of the procedure, and the altered sympathetic/parasympathetic tone could affect the degree of basal pre-excitation.

Conclusions

Our study confirms that the accuracy of traditional algorithms is related to the degree of pre-excitation in the resting ECG. Among all investigated algorithms, Pambrun algorithm, designed explicitly for maximally pre-excited ECG, had the best accuracy for localizing accessory pathways and should be preferred for this task. When other algorithms are used, then the fully pre-excited ECG should be analysed to maximize their performance.

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Table 1. Unified classification of accessory pathway nomenclature between algorithms.

AP location in Pambrun algorithm — reference	Algorithms			
	Xie	d'Avila	Iturralde	Taguchi
Right anterior	RAS	AS	RA	RAS/ RA/RL
Right lateral	RL	RL		
Right posterior	RP	RPS	RIP/RI	RPL/ RP
Right posteroseptal	RPS	PS		MS/PS
Deep coronary sinus				
Node-His	MS	MS		
Left posteroseptal	LPS	LPS	LIP/LI	
Left posterolateral	LP LPL	LP	LPL/ LAS	LP/LPL
Left lateral	LAL	LL		LA/LL

Abbreviations: AP, Accessory pathway; RA, right anterior; RL, right lateral; RP, right posterior; RPS, right posteroseptal; NH, node-His; DCS, deep coronary sinus; LPS, left posteroseptal; LPL, left posterolateral; LL, left lateral; RAS, right anteroseptal; MS, midseptal; LP, left posterior; LAL, left anterolateral; AS, anteroseptal; PS, posteroseptal; RIP/RI, right inferior paraseptal and right inferior; RASP, right anterosuperior paraseptal; LIP/LI, left inferior paraseptal and left inferior; LPL/LAS, left posterolateral and left anterosuperior

Table 2. Clinical characteristics of the study group

Parameter		Value	
Patients, n		300	
Age, y, mean (SD)		32.0 (18.4)	
Male sex		178 (59.2)	
QRS duration in resting ECG, ms, mean (SD)		130.4 (21)	
Accessory pathway localization, n	Left free-wall	Left lateral	71 (23.67)
		Left posterolateral	61 (20.33)
	Septal	Left posteroseptal (left paraseptal)	17 (5.67)
		Right posteroseptal	64 (21.33)
		Parahisian / midseptal (node-His)	29 (9.67)
		Epicardial (deep coronary sinus)	4 (1.33)
	Right free-wall	Right anterior	24 (8.0)
		Right posterior	19 (6.33)
		Right lateral	11 (3.67)

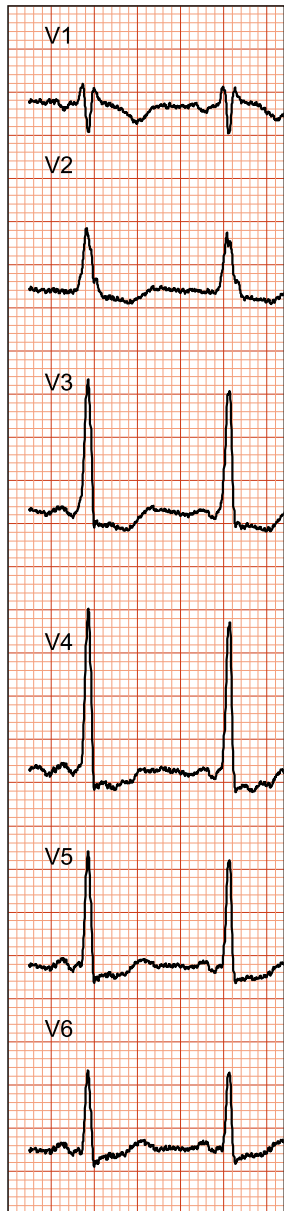
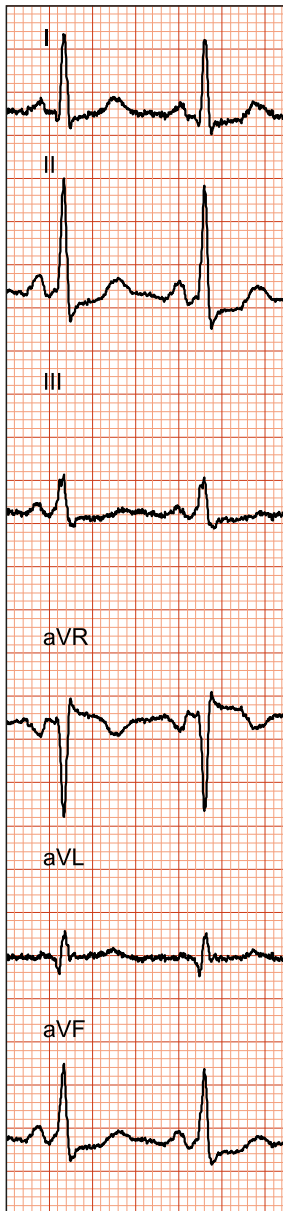
Data are presented as number (percentage) of patients unless otherwise indicated

Table 3. Overall accuracy of the accessory pathway localizing algorithms in resting and maximally pre-excited ECGs.

Algorithms	Resting ECG		ECG with maximal pre-excitation		<i>P</i> value resting vs maximal pre-excitation	
	Accuracy (%)	Adjusted ^a accuracy (%)	Accuracy (%)	Adjusted ^a accuracy (%)	Accuracy	Adjusted accuracy
Xie	26.0	47.3	32.7	62.7	< 0.001	< 0.001
d'Avila	40.0	64.3	54.7	79.0	< 0.001	< 0.001
Iturrlade	53.3	69.7	67.7	86.3	< 0.001	< 0.001
Taguchi	53.7	65.3	75.0	81.0	< 0.001	< 0.001
Pambrun	—	—	89.7	97.0	—	—

^a predictions were anatomically adjacent to the actual AP location; Abbreviation: ECG, electrocardiogram

RESTING ECG



MAXIMALLY PRE-EXCITED ECG

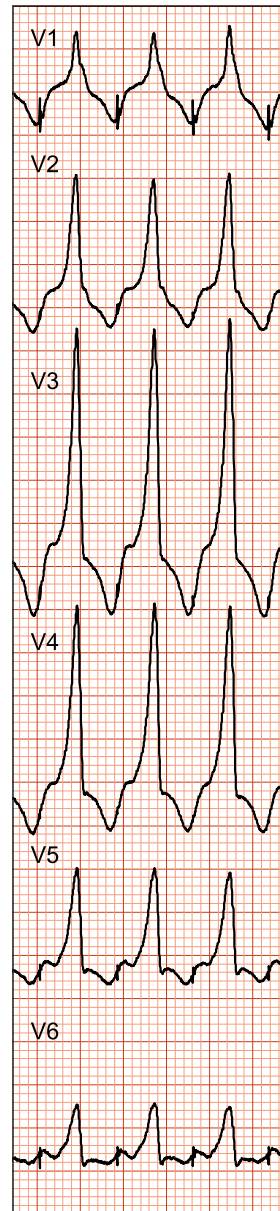
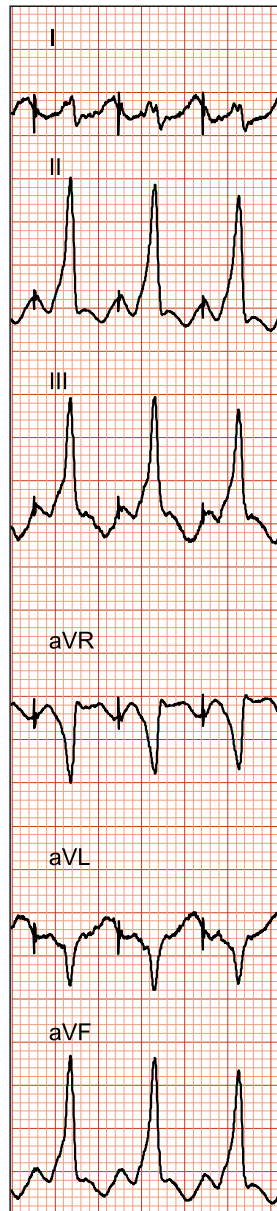


Figure 1. The example of resting and maximally pre-excited ECGs recorded from the patient with a left lateral accessory pathway. The predictions of traditional algorithms were: right lateral by Xie, anteroseptal by d'Avila, midseptal/posteroseptal by Taguchi and right anterosuperior paraseptal by Iturralde. Using maximally pre-excited ECG, Pambrun and all traditional algorithms made a correct prediction of left lateral location.

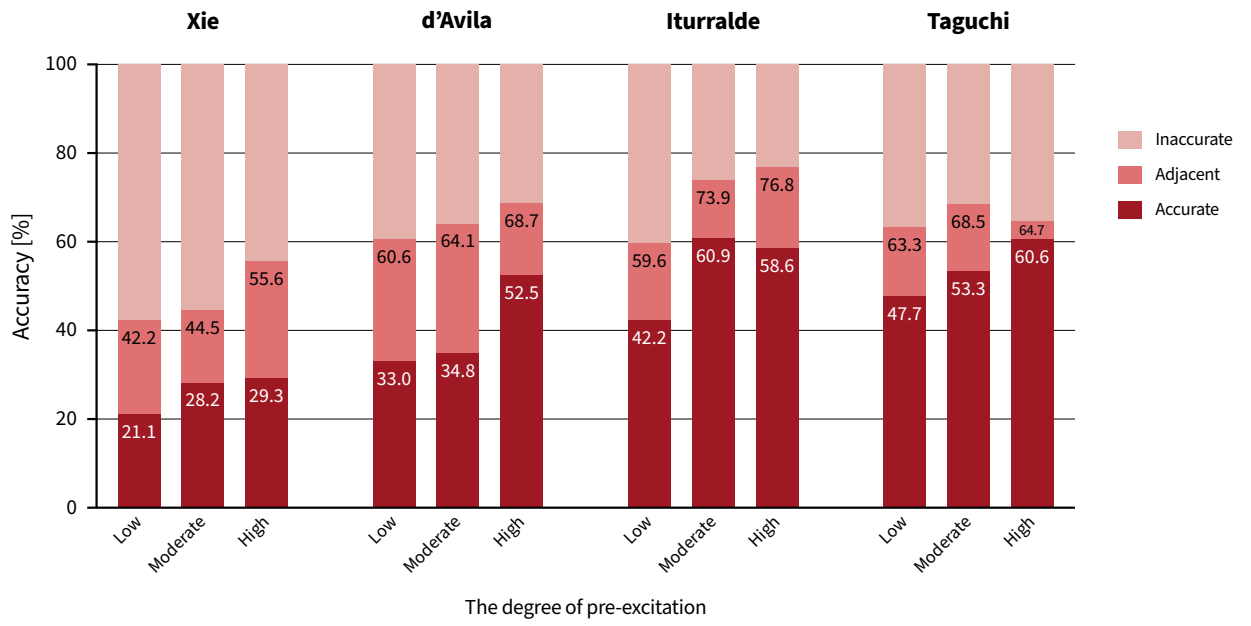


Figure 2. The accuracy of the traditional algorithms according to the degree of manifested pre-excitation in resting ECG. Low, QRSd < 123 ms; moderate, QRSd 123–138 ms; high, QRSd > 128 ms.

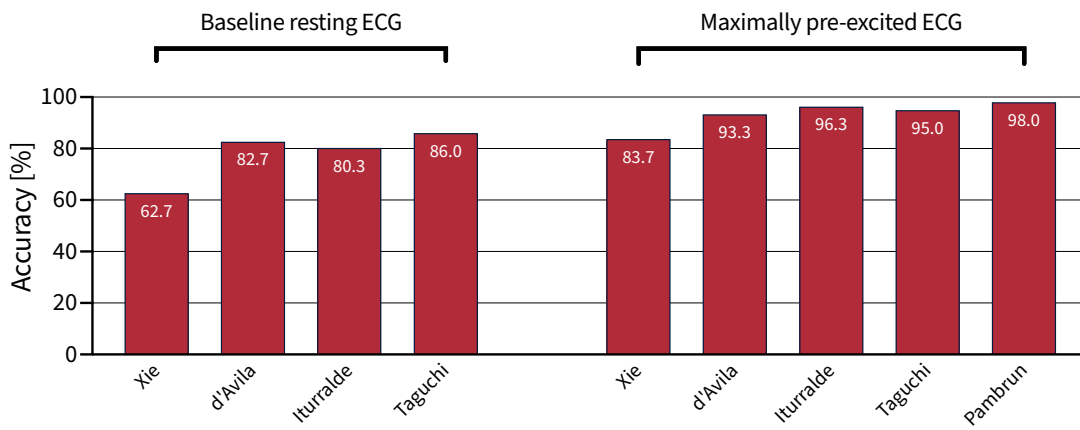


Figure 3. The accuracy of the algorithms to predict left-sided and right-sided accessory pathways using baseline ECG and maximally pre-excited ECG.

Supplementary material

Moskal P, Bednarski A, Kielbasa G, et al. Increased pre-excitation in ECG improves accuracy of algorithms for accessory pathway localization in Wolff–Parkinson–White syndrome. Kardiologia Pol. 2020.

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Supplemental table 1.

Algorithm	Criteria for specific accessory pathway locations									
Pambrun et al. (2018) (requires maximally pre-excited ECG)	RA	RL	RP	RPS	NH	DCS	LPS	LPL	LL	
	V1 –	V1 –	V1 –	V1 –	V1 –	V1 –	V1 +	V1 +	V1 +	V1 +
	3 positive inferior leads	1-2 positive inferior leads	0 positive inferior leads	0 positive inferior leads	1-3 positive inferior leads	1-2 positive inferior leads	1-2 positive inferior leads	1-2 positive inferior leads or	1-2 positive inferior leads	3 positive inferior leads
	V3 –	V3 –	V3 –	V3 +	V3 +	V1/I ratio < 1 II notched QS +	V1/I ratio < 1 II notched QS –	0 positive inferior leads and V1/I ratio ≥ 1		
Xie et al. (1994)	RAS	RL	RP	RPS	MS	see RPS	LPS	LP	LPL	LAL
	III – & V1 – aVF R/Rs morph.	III + and/or V1 + aVL + V1 –	III + and/or V1 + aVL – with rS	III – & V1 – aVF –/qR morph. RWH in V5 or V6	III – & V1 – aVF –/qR morph. RWH in V2–V4 RW < 0.06 ms		III – & V1 – aVF –/qR morph. RWH in V2–V4 RW > 0.06 ms	III + and/or V1 + + aVL + V1 ±	III + and/or V1 + + aVL + V1 +	III + and/or V1 + aVL – with QS or QR morph.
d'Avila et al. (1995)	AS	RL	RPS	PS (paraseptal)	MS	see PS	LPS	LP		LL
	1. V1 –	V1 –	V1 –	V1 –	V1 –		V1 + or ±	V1 + or ±		1. V1 + or ±
	III ±	III –	III –	III –	III – & Qrs morph.		III –	III ±		III +
	2. V1 –	II + or –	II +	II –						2. V1 –
	III + aVL +	V2 –	V2 +	V2 +						III + aVL –
Iturralde et al. (1996)	RA	see RA	RIP/RI	see RIP/RI	RASP	see RIP/RI	LIP/LI	LPL/LAS		see LPL/LAS
	III – or ±		III – or ±		III +		III – or ±	III +		
	V1 – or ±		V1 – or ±		V1 –		V1 +	V1 +		
	V2 –		V2 +							
Taguchi et al. (2014)	RAS/RA/RL	see RAS/RA/RL	RPL/RP	MS/PS	see MS/PS	see MS/PS	see MS/PS	LP/LPL		LA/LL
	V1 R/S ratio < 0.5		V1 R/S ratio < 0.5	V1 R/S ratio < 0.5				V1 R/S ratio ≥ 0.5		V1 R/S ratio ≥ 0.5
	V2 R/S ratio < 0.5		V2 R/S ratio < 0.5	V2 R/S ratio ≥ 0.5				aVF R/S ratio < 1		aVF R/S ratio ≥ 1
	aVF R/S ratio ≥ 1		aVF R/S ratio < 1							

Abbreviations: RA, right anterior; RL, right lateral; RPS, right posteroseptal; NH, node-His; DCS, deep coronary sinus; LPS, left posteroseptal; LPL, left posterolateral; LL, left lateral; RAS, right anterosseptal; MS, midseptal; LP, left posterior; LAL, left anterolateral; AS, anterosseptal; PS, posteroseptal; RIP/RI, right inferior paraseptal and right inferior; RASP, right anterosuperior paraseptal; LIP/LI, left inferior paraseptal and left inferior; LPL/LAS, left posterolateral and left anterosuperior; RWH, the highest R wave recorded in precordial lead

Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation

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Background: Despite substantial progress in the field of differentiation between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with wide QRS complexes, differentiation between VT and preexcited SVT remains largely unresolved due to significant overlap in QRS morphology. Our aim was to assess the specificities of various single ECG criteria and sets of criteria (Brugada algorithm, aVR algorithm, Steurer algorithm, and the VT score) for diagnosis of VT in a sizable cohort of patients with preexcitation.

Methods: We performed a retrospective study of consecutive accessory pathway ablation procedures to identify preexcited tachycardias. Among 670 accessory pathway ablation procedures, 329 cases with good quality ECG with either bona fide preexcited SVT ($n = 30$) or a surrogate preexcited SVT (fast paced atrial rhythm with full preexcitation, $n = 299$) were identified. ECGs were analyzed with the use of wide QRS complex algorithms/criteria to determine specificities of these methods.

Results: The Steurer algorithm and VT score (≥ 3 points), with specificities of 97.6% and 96.1%, respectively, were significantly ($p < .01$) more specific for the diagnosis of VT than Brugada algorithm, aVR algorithm, and Pava criterion with specificities of 31%, 11.6%, and 57.1%, respectively. The first step of the Brugada algorithm and the first step of the aVR algorithm had also high specificities of 93.3% and 96.0%, respectively.

Conclusion: There are sufficient electrocardiographical differences between VT and preexcited SVT to allow electrocardiographic differentiation. VT score, Steurer algorithm, and some single criteria do not overdiagnose VT in patients with preexcitation.

KEYWORDS

preexcitation, ventricular tachycardia, VT score, wide QRS complex tachycardia, WPW syndrome

1 | INTRODUCTION

Several ECG-based methods for wide QRS complex tachycardia (WCT) diagnosis were developed over the last 50 years, leading to substantial progress in the field of differentiation between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with wide QRS complexes (Brugada, Brugada, Mont, Smeets, & Andries, 1991; Griffith, Garratt, Mounsey, & Camm, 1994; Jastrzebski, Kukla, Czarnecka, & Kawecka-Jaszcz, 2012a; Jastrzebski et al., 2016; Kindwall, Brown, & Josephson,

1988; Lau et al., 2000; Marriott, 1970; Sandler & Marriott, 1965; Swanick, LaCamera, & Marriott, 1972; Verecke, Duray, Szenasi, Altemose, & Miller, 2008). However, most of the available criteria/methods seem to be capable only of differentiation between VT and SVT with aberrant conduction, while differentiation between VT and preexcited SVT remains largely unresolved. Most of the published studies either excluded patients with preexcitation, or did not report if such patients were included, or even grouped preexcited SVT patients with VT patients (Jastrzebski et al., 2012a; Verecke & Miller, 2012). Preexcitation unquestionably warrants



FIGURE 1 Twelve-lead ECG showing full preexcitation via mid-septal accessory pathway during atrial pacing. A slow initial ventricular depolarization is present in both limb and precordial leads. The RS interval in V_6 is >100 ms, the V_i/V_t in aVR is <1 , and the RWPT in lead II is >50 ms—these results in misdiagnosis of this preexcited SVT as a VT by the Brugada algorithm, the aVR algorithm, and the Pava criterion. In contrast, the VT score of 1 point does not make the diagnosis of VT. Paper speed is 25 mm/s

differentiation from VT as there is a clear difference between, for example, a preexcited atrial flutter and a ventricular tachycardia in terms of pathophysiology and management (Jastrzebski & Kukla, 2012). Some believe that neither traditional nor novel QRS morphologic criteria are capable of differentiation between preexcited SVT and VT, as in both cases, depolarization of the ventricles begins in the working myocardium, outside of the His-Purkinje system, giving rise to an initially slow ventricular depolarization—a phenomenon from which multiple ECG criteria for differentiation are derived (Figure 1) (Vereckei & Miller, 2012; Vereckei et al., 2008). However, there is little published data to either support or refute this view. Our previous studies suggest that some methods might be better at differentiating preexcited SVT from VT (Jastrzebski et al., 2012a; Jastrzebski et al., 2016). However, this might be difficult to prove in studies involving general WCT population as preexcited SVT generally constitute only a small percentage of WCT cases.

2 | AIM

To assess the specificity of a wide spectrum of ECG criteria and sets of criteria (Brugada algorithm, aVR algorithm, Steurer algorithm, and the VT score) for diagnosis of ventricular tachycardia in a sizable cohort of patients with overt preexcitation.

3 | METHODS

3.1 | Studied cohort

All consecutive ablation procedures in patients diagnosed with an overt accessory pathway from years 2002 to 2016 were retrospectively

analyzed to obtain a good quality 12-lead ECGs with either bona fide preexcited SVT (antidromic atrioventricular tachycardia, preexcited atrial flutter, or other preexcited regular supraventricular tachycardia) or with maximal obtainable preexcitation induced by incremental atrial pacing (just before block in accessory pathway was observed), considered a good surrogate for preexcited SVT.

3.2 | Analysis of ECGs

All preexcited electrocardiograms recorded with standard amplification and at a paper speed of 25 mm/s were analyzed by two observers (a cardiology specialist and a cardiology resident) and in a case of conflicting results, by a third doctor (an electrophysiologist) who made the final verdict in these cases.

The following QRS morphologic criteria/algorithms/methods were analyzed:

1. Brugada algorithm criteria (lack of an RS complex in leads V_1 – V_6 ; presence of an RS interval >100 ms; atrioventricular (AV) dissociation, presence of VT morphologic criteria in both V_1 and V_6) (Brugada et al., 1991).
2. Presence of aVR algorithm criteria (monophasic R in aVR; initial r/q >40 ms in aVR; notched S in aVR, initial to terminal QRS velocity ratio (V_i/V_t) ≤ 1 (Vereckei et al., 2008).
3. The R-wave peak time (RWPT) criterion. The RWPT represents the interval from the beginning of the QRS to the first visible change in direction of the initial polarity, from ascending to descending or vice versa, that is, to R-wave peak or S-wave nadir or any notch on the descending limb of the S wave or the ascending limb of the R; RWPT ≥ 50 ms is diagnostic for VT (Pava et al., 2010).

4. Steurer algorithm criteria (predominantly negative QRS complexes from V_4 to V_6 , qR complex in any of V_2 - V_6 , AV dissociation) (Steurer et al., 1994).
5. The ventricular tachycardia score method criteria as defined and described in detail recently (Jastrzębski, Kukla, & Czarnecka, 2017; Jastrzebski et al., 2016). Briefly, the VT score is a novel approach to VT diagnosis which provides a graded response from 0 to 8 points, rather than a “yes or no” type of answer from WCT algorithms. This allows the physician to know how much he can trust the obtained diagnosis of VT. With each point, the probability of VT diagnosis increases and a firm diagnosis of VT can be made when 3 or more VT score points are obtained. Following QRS, morphologic criteria were assigned one point: initial R wave in V_1 , initial $r > 40$ ms in V_1 or V_2 , notched S in V_1 , initial R wave in aVR, lead II RWPT ≥ 50 ms, and lack of RS complex in leads V_1 - V_6 , AV dissociation (including fusion/capture beats and partial dissociation) was assigned two points.

3.3 | Statistics

Each analysis method was assessed in terms of the presence of a particular criterion during preexcited SVT, that is, the amount of false-positive results, as there were no true VT included, thus leading to the calculation of specificity of a criterion/method for VT diagnosis. Calculated specificity values were compared using McNemar test (Fijorek, Fijorek, Wisniowska, & Polak, 2011). For all analyses, a p value $< .05$ was considered to indicate a significant difference. Statistical analyses were performed using “R”—a language and environment for statistical computing (<http://www.R-project.org>).

4 | RESULTS

We analyzed 670 consecutive accessory pathway ablation procedures. Among these, 329 cases with good quality ECG with either bona fide preexcited SVT ($n = 30$) or a surrogate preexcited SVT ($n = 299$) were identified. Remaining patients had either concealed accessory pathway or poor/intermittent antegrade accessory pathway conduction. All antiarrhythmic drugs were stopped at least 3 days before the study. The studied group ($n = 329$) has basic clinical characteristics: males, 57%; average age, 34 ± 12 years; organic heart disease (coronary heart disease, heart failure, cardiomyopathy, etc.) present in 4.8% of cases.

We found that several criteria were very specific for VT diagnosis: no RS complex in V_1 - V_6 , dominant R in aVR, AV dissociation, VT score ≥ 3 , VT score ≥ 4 , and S notch in aVR. Negative QRS V_4 - V_6 and QR in any of V_2 - V_6 were in seen in only 6.4%, 4%, 0%, 3.9%, 0%, 5.5%, 0.3%, and 1.5% of preexcited tachycardias, respectively. This resulted in good overall specificity of two methods—the VT score and the Steurer algorithm, which were significantly more specific for VT diagnosis than other methods ($p < .0001$). On the other hand, several differentiation criteria/algorithms, both classic and novel, were found to be unsuitable for differentiation of VT from preexcited SVT due to

TABLE 1 Various criteria and methods: specificity for ventricular tachycardia diagnosis in patients with preexcited tachycardias

Criterion/Method	SP (%)	p^*
VT score criteria	-	-
R in V_1	61.4	.0000
$r > 40$ ms in V_1/V_2	82.7	.0000
S notch in V_1	88.5	.0003
No RS in V_1 - V_6	93.3	.1237
R in aVR	96.0	.7893
AV dissociation	100	.0009
Lead II RWPT ≥ 50 ms	57.1	.0000
VT score ≥ 1	22.2	.0000
VT score ≥ 2	60.8	.0000
VT score ≥ 3	96.1	-
VT score ≥ 4	100	.0009
aVR algorithm criteria ^a		
S notch in aVR	94.5	.4725
$r/q > 40$ ms in aVR	89.1	.0017
aVR V_i/V_t	14.9	.0000
aVR algorithm	11.5	.0000
Brugada algorithm criteria ^a		
V_1 - V_6 RS > 100 ms	46.8	.0000
4th step ($V_1 + V_6$) criteria	74.8	.0000
Brugada algorithm	31.0	.0000
Steurer algorithm criteria		
Negative QRS V_4 - V_6	99.7	.0033
QR in any of V_2 - V_6	98.5	.0990
Steurer algorithm	97.6	.3827

* p calculated versus VT score ≥ 3 .

^aonly criteria not already included in the VT score are listed, however, calculation of specificity of the whole algorithms included all pertinent criteria as explained in the Methods.

very low specificity, and this included aVR algorithm, aVR V_i/V_t criterion, VT score ≥ 1 , and Brugada algorithm. Detailed data concerning specificities of all assessed criteria and whole algorithms are presented in Table 1.

Distribution of VT scores in the studied cohort with preexcited SVT was significantly ($p < .001$) different from that observed previously in patients with VT (Table 2) (Jastrzebski et al., 2016).

5 | DISCUSSION

This is the first study that assesses specificities of wide selection of criteria and algorithms for WCT diagnosis with regard to their ability to differentiate between preexcited SVT and VT. The major finding of the study is that some of these methods (the VT score, the Steurer algorithm, and selected criteria from other algorithms) are capable of high specificity for VT diagnosis in this setting.

WCT type	VT score					
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	≥5 (%)
VT ^a	6.2	16.6	19.9	24.8	18.9	13.7
Preexcited SVT	22.2	38.6	35.3	3.9	0	0

$p < .001$.

^aVT distribution data from Jastrzebski et al. (2016).

Despite valid theoretical considerations that a preexcited SVT and a VT might lead to identical depolarization of the ventricles (i.e., depolarization that begins in the working myocardium, outside of the His-Purkinje system) and hence indistinguishable QRS complexes we have shown that there are often significant differences in QRS morphology between these two arrhythmia types. We believe that there are three main sources of these differences: (1) no AV dissociation in preexcited tachycardias, (2) obligatory basal to apical depolarization during preexcitation, and (3) lack of myocardial scar or fibrosis-related ECG features in preexcited SVT patients. Recent data support the notion that several of the classic morphologic criteria for VT are not related to VT per se (or to initial slow depolarization outside of the His-Purkinje system) but to the presence of organic heart disease (e.g., fibrosis, scars, and ventricle dilatation), as they are absent in idiopathic VT, yet present during supraventricular rhythm in heart failure patients with left bundle branch block (Jastrzebski, Kukla, Czarnecka, & Kawecka-Jaszcz, 2012b; Wijnmaalen et al., 2011). The same applies to preexcited VTs—as these also mostly occur in healthy hearts, and bear resemblance to a rare VT subtype only: an idiopathic annular VT. This is why VT-specific ECG criteria resulting mainly from the presence of a scar (qR in V_2 – V_6 , S-wave notch in V_1 /aVR) or from grossly abnormal vector of depolarization (monophasic R in aVR, no RS in V_1 – V_6) are very rare in preexcited SVT. In consequence, while a preexcited SVT can exhibit some VT-specific features, an organic heart disease based VT will usually have much more such features. Therefore, a method that makes a diagnosis on the basis of the concomitant presence of several such features (VT score ≥ 3) or on the presence of features truly very rare in preexcited QRS (Steurer algorithm) will be able to differentiate between preexcited SVT and VT.

5.1 | Ventricular tachycardia score

The VT score results indicate that a preexcited SVT bears some, albeit limited, resemblance to a VT. Preexcited SVT very often (74% of cases) exhibits one or two VT-like features. However, VT score of 3 is present in only <4% of preexcited SVTs and VT score ≥ 4 in none (Table 2). This is a significant difference that allows firm differentiation between most VTs and preexcited SVTs. This corroborates results of our prior VT score validation study, based on a 786 ECGs, where VT score misclassified only one WCT, indeed, a preexcited SVT as a VT (Jastrzebski et al., 2016). This misclassified SVT had VT score of 3 as the only one of 38 preexcited SVTs included in that study. This would point to 2.6% real-life preexcited SVTs that can be misclassified by the VT score and is quite similar to the results of the current study,

TABLE 2 Distribution of VT scores in the currently studied cohort of preexcited SVT and in a real-life VT cohort

which included almost 10 times more preexcited tracings, where 3.9% of preexcited SVTs were misclassified.

5.2 | Brugada algorithm

The first step of the Brugada algorithm (lack of RS criterion) is very specific for VT diagnosis, both in general cohort of patients (Jastrzebski et al., 2016), and as shown by the current results, also in patients with preexcited WCT. Of note, this criterion encompasses former the Marriott criterion of positive/negative QRS concordance and Coumel criterion of qR in the precordial leads (Marriott, 1970; Coumel et al., 1984). While negative concordance and qR are not observed during preexcitation, positive concordance is—slightly lowering specificity of this criterion. In contrast to the first step, the second step criterion (RS > 100 ms) is very nonspecific, fulfilled in every second preexcited tachycardia. In addition, the final step of this algorithm is rather nonspecific. The net result is a 31% specificity of the whole method. In other words, two out of the three preexcited tachycardias will be diagnosed by the Brugada algorithm as VT. In the original publication by Brugada et al. that introduced this popular algorithm, there is no information concerning inclusion or exclusion of patients with preexcited SVT (Brugada et al., 1991). Therefore, one might assume that this algorithm is universal, that is, tested on a general cohort of WCTs and suited for all patients, including preexcited SVT patients. Despite subsequently published opinions that Brugada algorithm might not be able to differentiate VT from preexcitation (Steurer et al., 1994; Vereckei & Miller, 2012), this algorithm and its criteria were never properly studied in this regard. The current study provides data which show that while Brugada algorithm as a whole is unable to differentiate preexcitation from ventricular ectopy, some of its criteria might be very useful.

5.3 | The aVR algorithm

The first three criteria of this algorithm being basically Marriott and Kindwall morphologic criteria applied to lead aVR instead of lead V_1 are relatively specific in the setting of preexcitation (specificity of 89%–96%). Especially, the first criterion, a monophasic R in aVR is seen only in 4 out of 100 preexcited SVTs. However, the final step of this algorithm (V_i/V_t criterion) being the inventive contribution of Vereckei, Duray, Szenasi, Altemose, & Miller (2007); to the field of WCT differentiation is incapable of differentiating between preexcited SVT and VT; it is fulfilled in almost every preexcited QRS due to the presence of initial slow depolarization known as the delta wave. Consequently, the whole algorithm misclassifies 89% of preexcited

SVTs. The authors of this algorithm have already suggested that this algorithm might not be capable of VT/preexcited WCT differentiation (Vereckei et al., 2008), and later even revealed they grouped preexcited SVTs with VTs, considering diagnostic mistakes (e.g., preexcited sinus tachycardia diagnosed as VT) as correct answers, thus questionably increasing specificity and accuracy of the method (Jastrzebski & Kukla, 2012; Vereckei & Miller, 2012). Our data corroborate the opinion of Vereckei et al. (2008) that the whole aVR algorithm cannot differentiate preexcitation from ventricular ectopy and that only the monophasic R in aVR criterion (the first step of the aVR algorithm) is useful for this task.

5.4 | Steurer algorithm

This is the only algorithm designed specifically to deal with the problem of VT versus preexcited SVT differentiation (Antunes, Brugada, Steurer, Andries, & Brugada, 1994; Steurer et al., 1994). Our results confirm the very high specificity of both criteria and of the whole algorithm. Steurer et al. found it to be 100% specific while our results, based on a three times bigger cohort of preexcited SVT patients, point to a slightly lower specificity of 97.6%. The major limitation preventing the application of this algorithm is not its unquestionable high specificity in this specific subpopulation, but its sensitivity and overall accuracy in a general population. Importantly, in contrast to other WCT algorithms and the VT score method, this little-known algorithm was never validated on a general cohort of WCT patients. Steurer et al. (1994) assessed its performance only on a rather artificial group of patients consisting of 149 VTs (mainly postinfarction) and 118 preexcited SVTs, excluding the usual wide complex SVTs, that is, SVTs with functional or preexistent bundle branch block. In a sibling publication concerning this algorithm, coauthored by Brugada and Brugada, there is a suggestion that this algorithm should be used post main Brugada algorithm; that is after differentiation between VT versus SVT with aberration was already completed (Antunes et al., 1994). Such resulting seven-step method was also never validated on a real-life cohort of patients. It seems likely that the low sensitivity of the Steurer criteria would significantly impact on the overall accuracy of such approach.

6 | LIMITATIONS

Majority of analyzed ECGs were recorded during fast atrial pacing with maximal obtainable preexcitation. Most likely, such ECGs correspond in vast majority of cases with preexcitation that would be observed during bona fide preexcited SVT or antidromic atrioventricular reentrant tachycardia. However, some differences in QRS morphology cannot be excluded. Atrial pacing site was either in the high right atrium or proximal coronary sinus and some merging of the paced p wave with QRS was possible, similarly as during true preexcited SVT. Moreover, we believe that simultaneous recording of all 12 ECG leads helped to precisely delineate the beginning of the QRS.

All observers interpreting the ECGs knew that there were no true VTs included. This might have promoted bias in assessment of some criteria, especially in case of criteria that are dependent on ascertainment of QRS onset and offset.

7 | CONCLUSION

This is the first study that assesses the performance of various single ECG criteria and complex ECG-based methods for wide QRS complex tachycardia differentiation in patients with ventricular preexcitation dispelling the myth that preexcitation cannot be differentiated from ventricular ectopy.

Despite significant overlap in QRS morphology between preexcited and ectopic QRS complex, there are usually sufficient electrocardiographic differences to allow electrocardiographic differentiation. In contrast to other methods, VT score and Steurer algorithm do not overdiagnose VT in patients with preexcitation. Perhaps these two methods or selected single criteria that were found to be specific for VT should be preferred in patients more likely to have preexcitation.

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VI. WYNIKI

Publikacja 1

Spółród 385 pacjentów z jawną preekscytacją, u 26 pacjentów stwierdzono epizod migotania komór lub złośliwej szybkiej arytmii przedsionkowej, w tym jeden zgon i dwa przypadki ciężkiego uszkodzenia neurologicznego. U pacjentów, u których doszło do wystąpienia arytmii, mediana najkrótszego preekscytowanego odstępu RR (SPRRI) była niższa niż u pacjentów bez epizodu arytmii (220 vs 300 ms, $P < 0.001$). W analizie regresji logistycznej stwierdzono wzrost ryzyka migotania komór lub złośliwej arytmii wraz ze skróceniem parametru SPRRI (na każde 10 ms: OR 1.30, 95% CI 1.16–1.47, $P < 0.001$). U 3 pacjentów SPRRI było dłuższe niż 250 ms, co jest zalecanym punktem odcięcia dla profilaktycznej ablacji. U pacjentów z epizodem ciężkiej arytmii stwierdzono częstszą indukowalność migotania przedsionków (AF) lub migotania przedsionków i częstoskurczu przedsionkowo-komorowego (AF + AVRT). Iloraz ryzyka w analizie logistycznej dla indukowalności AF i AF+ AVRT wynosił odpowiednio: 4.85; 95% CI, 1.42–16.56; $P = 0.01$ oraz OR 6.62; 95% CI, 2.10–20.81; $P < 0.001$.

Publikacja 2

Spółród 4 ocenianych algorytmów opartych o polarność zespołu QRS, algorytmy Taguchiego oraz Iturralde pozwalały na najbardziej precyzyjną lokalizację drogi dodatkowej (odpowiednio 53.7% i 53.3%). Wykorzystanie elektrokardiogramów z maksymalną preekscytacją zwiększało precyzję wszystkich analizowanych algorytmów o średnio 14.3 punkty procentowe. Algorytm Pambruna, stworzony do stosowania w EKG z maksymalną preekscytacją był precyzyjniejszy niż klasyczne algorytmy (89.7%).

Publikacja 3

Zaobserwowano wysoką specyficzną niektórych kryteriów EKG w rozpoznawaniu częstoskurczu komorowego: brak zespołów RS w V1-V6, dominujący załamek R w aVR, rozkojarzenie przedsionkowo-komorowe, VT score ≥ 3 , VT score ≥ 4 oraz zazębiony załamek S w odprowadzeniu aVR. Algorytm VT score oraz algorytm Steurera były bardziej specyficzne niż pozostałe algorytmy w odróżnianiu częstoskurczu komorowego od preekscytowanego częstoskurczu nadkomorowego. Algorytm Brugady, aVR oraz kryteria aVR V_i/V_t i VT score ≥ 1 posiadały niską specyficzną, czyniąc je nieprzydatnymi w różnicowaniu częstoskurczu komorowego od nadkomorowego z preekscytacją.

VII. WNIOSKI

Badanie opisane w *Publikacji 1* potwierdziło znaczenie elektrokardiograficznego parametru najkrótszego preekscytowanego odstępu RR (SPRRI) oraz indukowalności arytmii podczas badania elektrofizjologicznego w wykrywaniu pacjentów z grupy wysokiego ryzyka migotania komór lub złośliwej arytmii nadkomorowej. Jednak wartość predykcyjna tych parametrów nie pozwala na identyfikację wszystkich pacjentów z podwyższonym ryzykiem ciężkich powikłań. W erze bezpiecznych i skutecznych zabiegów ablacji, nawet niewielkie ryzyko istotnych powikłań drogi dodatkowej nie powinno być akceptowane, a próg decyzyjny dla ablacji profilaktycznej powinien być niski.

W badaniu opisanym w *Publikacji 2* po raz pierwszy potwierdzono zależność precyzji elektrokardiograficznych algorytmów lokalizujących drogę dodatkową od nasilenia cech preekscytacji w EKG. Algorytm Pambruna stworzony dla elektrokardiogramu z maksymalną preekscytacją posiadał najwyższą dokładność i powinien być preferowany. Jeżeli inne algorytmy są wykorzystywane, to należy używać elektrokardiogramów z najbardziej nasilonymi cechami preekscytacji dla optymalizacji wyników algorytmów.

Obserwacje zawarte w *Publikacji 3* podważyły powszechny pogląd, że nie można odróżnić preekscytacji od ektopii komorowej. Pomimo podobieństwa cech morfologicznych w obu tych zjawiskach, EKG z reguły zawiera wystarczającą liczbę cech pozwalających na ich zróżnicowanie. Algorytm VT score lub algorytm Steurera powinny być preferowane u pacjentów z wyższym prawdopodobieństwem preekscytacji, u których wystąpił częstoskurcz z szerokimi zespołami QRS.

Od pierwszego opisu elektrokardiograficznych cech zespołu Wolffa-Parkinsona-White'a mija w 2020 roku 90 lat. Mimo upływu czasu, EKG pozostaje podstawowym narzędziem diagnostycznym w zespole preekscytacji. Cykl publikacji będących podstawą rozprawy doktorskiej potwierdził wartość diagnostyczną opisanych wcześniej cech EKG, jak również pokazał nowe zastosowania elektrokardiografii, które mogą być przydatne w codziennej praktyce klinicznej.

VIII. STRESZCZENIE

Nieprawidłowe drogi dodatkowe łączące przedsionki i komory serca zostały opisane na przełomie XIX i XX wieku i są przyczyną zespołu Wolffa-Parkinsona-White'a (WPW). Typowymi objawami zespołu WPW są kołatania serca, omdlenia oraz duszność, które są spowodowane występowaniem różnego rodzaju arytmii takich jak częstoskurcz przedsionkowo-komorowy (AVRT), migotanie przedsionków (AF), preekscytowane AF oraz migotanie komór (VF), które mogą prowadzić do wielu ciężkich powikłań (nagły zgon sercowy, udar mózgu, utrata przytomności, niewydolność serca). Obecność drogi dodatkowej powoduje preekscytację w elektrokardiogramie (EKG). Główną cechą preekscytacji jest obecność fali delta na ramieniu wstępującym zespołu QRS, która powoduje jego zniekształcenie i wydłużenie czasu trwania. Jest to spowodowane zsumowaniem dwóch frontów depolaryzacji komórek serca: z prawidłowej depolaryzacji przez układ Hisa-Purkiniego oraz aktywacji przez drogę dodatkową. Jeżeli miokardium jest zdepolaryzowane wyłącznie przez drogę dodatkową, to dochodzi do maksymalnej preekscytacji, podczas której zespół QRS przypomina pobudzenie komorowe, a jego morfologia w większości wynika z lokalizacji drogi dodatkowej.

W praktyce klinicznej EKG w zespole WPW jest wykorzystywane do rozpoznawania preekscytacji, oceny ryzyka złośliwych arytmii, określenia przybliżonego położenia drogi dodatkowej wokół pierścienia trójdzielnego i mitralnego, a także do różnicowania częstoskurczy z szerokimi zespołami QRS.

Celem pierwszej pracy z cyklu była ocena wartości diagnostycznej EKG do diagnozowania cech wysokiego ryzyka wystąpienia migotania komór lub złośliwego preekscytowanego migotania przedsionków. Do badania włączono 385 pacjentów z jawną preekscytacją. Przeanalizowano opis zabiegów ablacji, zapis z systemów elektrofizjologicznych oraz zapis 12-odprowadzeniowego EKG wszystkich pacjentów skierowanych do wykonania badania elektrofizjologicznego oraz ablacji drogi dodatkowej. Na podstawie dokumentacji medycznej oceniono objawy arytmii przed ablacją, występowanie incydentów zatrzymania krążenia, złośliwego migotania przedsionków, udaru niedokrwiennego mózgu oraz innych powikłań, które mogą być związane z obecnością drogi dodatkowej. Złośliwe AF zdefiniowano jako: (1) konieczność pilnej kardiowersji elektrycznej lub (2) omdlenie/stan przedomdleniowy z najkrótszym preekscytowanym

interwałem RR (SPRRI) ≤ 250 ms. Podczas badania elektrofizjologicznego zmierzono SPRRI przy szybkiej stymulacji przedsionkowej lub po indukcji szybkiego migotania przedsionków. Oceniono również indukowalność AVRT oraz AF. Ciężkie powikłania spowodowane obecnością drogi dodatkowej stwierdzono u 26 pacjentów: 14 zatrzymań krążenia (w tym 1 zgon oraz 2 przypadki ciężkiego uszkodzenia neurologicznego) oraz 16 epizodów złośliwego migotania przedsionków. W analizie regresji logistycznej stwierdzono wzrost ryzyka migotania komór lub złośliwego migotania przedsionków wraz ze skróceniem parametru SPRRI (na każde skrócenie o 10 ms: iloraz szans [OR] 1.30, 95% przedział ufności [95% CI] 1.16–1.47, $P < 0.001$). Indukowalność migotania przedsionków lub migotania przedsionków i częstoskurczu przedsionkowo-komorowego było związane z wyższym ryzykiem wystąpienia złośliwych arytmii. U 3 pacjentów, którzy przeżyli epizod migotania komór, parametr SPRRI był dłuższy niż 250 ms, co jest aktualnym zalecanym punktem odcięcia dla profilaktycznej ablacji drogi dodatkowej. Wyniki badania sugerują, że parametr SPRRI jest pomocny w identyfikacji pacjentów z wysokim ryzykiem złośliwych arytmii, ale jego wartość predykcyjna jest niewystarczająca. Przy zapewnieniu wysokiego bezpieczeństwa i skuteczności zabiegu ablacji, próg decyzyjny dla ablacji drogi dodatkowej powinien być niski, aby zapobiegać powikłaniom zespołu WPW.

Celem drugiej pracy była ocena wpływu nasilenia preekscytacji na dokładność czterech elektrokardiograficznych algorytmów lokalizujących drogę dodatkową oraz porównanie ich do algorytmu zaprojektowanego dla EKG z maksymalną preekscytacją (algorytm Pambruna). Do badania włączono 300 pacjentów, którzy mieli wykonaną skuteczną ablację jawną drogi dodatkowej. Przeanalizowano zapisy spoczynkowego EKG oraz EKG z maksymalną preekscytacją uzyskaną jedną z metod: (1) szybką stymulacją przedsionków, (2) indukcją antydromowego częstoskurczu przedsionkowo-komorowego, oraz (3) indukcją szybkiego migotania przedsionków. Do analizy wybrano cztery tradycyjne algorytmy elektrokardiograficzne: Xie, d'Avila, Iturralde oraz Taguchi. Algorytmy te stworzono do analizy zapisów EKG ze spoczynkową preekscytacją i nie wymagają subiektywnej oceny fali delta. Zapisy EKG z maksymalną preekscytacją były również przeanalizowane za pomocą algorytmu Pambruna. Porównano precyzję algorytmów w określaniu położenia drogi dodatkowej (zarówno dokładnego położenia jak i sąsiadującego anatomicznie). Precyzja tradycyjnych algorytmów lokalizujących wynosiła od 26% do 53.7%, a dla lokalizacji sąsiadujących anatomicznie ulegała popra-

wie do 47.3%–69.7%. Jeżeli algorytmy zastosowano w EKG z maksymalną preekscytacją, to precyzja wszystkich algorytmów ulegała istotnej poprawie, ze średnim wzrostem dokładności o 14.3 punktu procentowego. Algorytm Pambruna miał najwyższą dokładność, zarówno dla dokładnej lokalizacji, jak i anatomicznie sąsiadujących (odpowiednio 89.7% i 97%). Badanie to udowodniło zależność precyzji elektrokardiograficznych algorytmów lokalizujących drogę dodatkową od nasilenia cech preekscytacji w EKG. Algorytm Pambruna, stworzony dla EKG z maksymalną preekscytacją, był najprecyzyjniejszy ze wszystkich przeanalizowanych algorytmów. W codziennej praktyce klinicznej należy poddawać analizie EKG z najbardziej nasilonymi cechami preekscytacji w celu ułatwienia zabiegów ablacji.

Celem trzeciej pracy było określenie specyficzności pojedynczych kryteriów elektrokardiograficznych oraz wybranych algorytmów EKG: algorytm Brugadów, algorytm aVR, algorytm Steurera oraz algorytmu ventricular tachycardia score (VT score) do diagnozowania częstoskurczu komorowego w populacji pacjentów z jawną preekscytacją. Do badania włączono 329 pacjentów: 30 z zarejestrowanym preekscytowanym częstoskurczem nadkomorowym oraz 299 z ekwiwalentem preekscytowanego częstoskurczu nadkomorowego, uzyskanego za pomocą szybkiej stymulacji przedsionkowej. Zapisy EKG przeanalizowało dwóch niezależnych obserwatorów. Zaobserwowano wysoką specyficzność niektórych kryteriów EKG w rozpoznawaniu częstoskurczu komorowego. Należą do nich brak zespołów RS w odprowadzeniach V1-V6, dominujący załamek R w odprowadzeniu aVR, rozkojarzenie przedsionkowo-komorowe, VT score ≥ 3 , VT score ≥ 4 oraz ząbiony załamek S w odprowadzeniu aVR. Stwierdzono wysoką specyficzność dwóch narzędzi diagnostycznych — VT score oraz algorytmu Steurera. Algorytm Brugadów, aVR, kryterium aVR V_i/V_t oraz VT score ≥ 1 z uwagi na niską specyficzność okazały się mało przydatne do różnicowania VT od preekscytowanych SVT. Wyniki badania sugerują, że w zapisie EKG preekscytowanego częstoskurczu nadkomorowego obecna jest wystarczająca liczba cech pozwalających na różnicowanie go z częstoskurczem komorowym. Algorytm VT score oraz algorytm Steurera, a także wybrane pojedyncze kryteria EKG nie powodują nadrozpoznowania częstoskurczu komorowego w populacji pacjentów z preekscytacją.

Cykl publikacji będących podstawą rozprawy doktorskiej potwierdził wartość diagnostyczną opisanych wcześniej cech EKG, jak również pokazał nowe zastosowania elektrokardiografii, które mogą być przydatne w codziennej praktyce klinicznej.

IX. SUMMARY

Accessory atrioventricular anomalous conduction pathways were described in the late 19th / early 20th century. They are responsible for Wolff–Parkinson–White syndrome (WPW), which manifests with diverse symptoms such as heart palpitations, syncope, dyspnea, various arrhythmias (atrioventricular reentrant tachycardia [AVRT], atrial fibrillation [AF], preexcited AF, ventricular fibrillation [VF]) which may lead to several clinical consequences (e.g., sudden cardiac death, stroke, syncope, heart failure). An accessory pathway (AP) causes ventricular pre-excitation, which manifest in electrocardiography (ECG). The electrocardiographic hallmark of pre-excitation is the delta wave that distorts and prolongs the QRS complex. This is caused by the fusion of ventricular activation from two sources: through the native His-Purkinje conduction system and an accessory pathway. When ventricular activation is accomplished exclusively by AP (maximal pre-excitation), then the QRS morphology almost completely depends on AP localization and resembles ventricular ectopic beat.

In clinical practice, ECG is used to diagnose pre-excitation, evaluate the risk of malignant arrhythmias, estimate the location of the accessory pathway around tricuspid and mitral annulus and differentiate wide QRS complex tachycardia.

The aim of the first study was to assess the value of ECG to diagnose patients with a high risk of developing VF or malignant pre-excited AF. Three hundred eighty-five patients with overt pre-excitation were included in the study. Ablation procedure descriptions, digital electrophysiological system records, hospital discharge notes, and 12-lead ECGs of all patients scheduled for ablation were carefully reviewed. Clinical data were collected, such as the presence of symptoms before ablation, the occurrence of cardiac arrest, the occurrence of, history of stroke or other consequences considered to be related to the presence of an AP. Malignant AF was defined as (1) a need for emergency cardioversion or (2) syncope/presyncope symptoms associated with ECG with the shortest RR intervals ≤ 250 ms. During the electrophysiological study, the shortest pre-excited RR interval was measured either during incremental atrial pacing or during fast AF, and the inducibility of AVRT or AF was recorded. Serious AP-related events were observed in 26 patients, including 14 sudden cardiac arrests (1 death and 2 cases of severe neurological deficits) and 16 pre-cardiac arrest events. The risk of malignant arrhythmias increased with a shorter SPRRI (per 10 ms:

odds ratio [OR], 1.3; 95% CI, 1.16–1.47). The presence of inducible AF or AF and AVRT increased the risk of malignant arrhythmias. In three survivors of VF, recorded SPRRI was longer than the currently recommended cut-off value of 250 ms for prophylactic AP ablation. The results of this study suggest that SPRRI can be helpful to identify patients with a high risk of malignant arrhythmias; however, its predictive value does not seem satisfactory. Therefore, when high safety and efficacy of AP ablation are ensured a lower threshold for prophylactic ablation should be used to prevent WPW-related adverse events.

The second study aimed to assess the influence of the degree of pre-excitation on the accuracy of four traditional electrocardiographic AP localizing algorithms and to compare them with the algorithm specifically designed for maximally pre-excited ECGs (Pambrun algorithm). The study included 300 patients who underwent successful ablation of an overt atrioventricular accessory pathway. Resting and maximally pre-excited ECGs obtained during either incremental fast atrial pacing, induction of antidromic atrioventricular re-entry tachycardia or induction of rapid atrial fibrillation were assessed using four traditional AP localizing algorithms: Xie, d'Avila, Iturralde and Taguchi. These algorithms were designed to use with resting 12-lead ECG and do not require subjective delta wave assessment. Maximally pre-excited ECGs were additionally assessed with Pambrun algorithm. The precision of the algorithms to predict accurate or anatomically adjacent AP localization were compared. The overall accuracy of traditional AP localizing algorithms using resting ECG ranged between 26%–53.7% and improved to 47.3%–69.7% when adjacent locations were accepted. When used with maximal pre-excitation, all algorithms had significantly higher accuracy, with a mean improvement of 14.3 percentage points for a precise site. Pambrun algorithm had the highest precision for both accurate and adjacent locations of APs (89.7% and 97%). The study showed that greater pre-excitation in ECG improves the accuracy of the traditional AP localizing algorithms. Pambrun algorithm designed to use with maximally pre-excited ECG had the best overall accuracy. Preferably maximally pre-excited ECGs should be used in clinical practice to facilitate the ablation procedure.

The aim of the third study was to assess the specificities of various single ECG criteria and sets of criteria (Brugada algorithm, aVR algorithm, Steurer algorithm, and ventricular tachycardia score [VT score]) for diagnosis of ventricular tachycardia in a

cohort of patients with overt preexcitation. Three hundred twenty-nine cases of ECG with either bona fide pre-excited supraventricular tachycardia (n = 30) or a surrogate pre-excited supraventricular tachycardia (fast-paced atrial rhythm with maximal preexcitation, n = 299) were identified. Recordings were analysed by two independent observers. Several criteria were found very specific for ventricular tachycardia diagnosis: no RS complex in V1-V6, dominant R in aVR, AV dissociation, VT score ≥ 3 , VT score ≥ 4 and S notch in aVR. This resulted in good overall specificity of two methods — the VT score and Steurer algorithm. Brugada algorithm, aVR algorithm, aVR V_i/V_t criterion, VT score ≥ 1 were found unsuitable for differentiation of VT from pre-excited SVT due to very low specificity. The results of the study suggest that there are sufficient electrocardiographic differences between VT and preexcited SVT to allow electrocardiographic differentiation. VT score, Steurer algorithm, and some single criteria do not overdiagnose VT in patients with preexcitation.

This collection of articles, on which PhD thesis is based, confirms the value of previously described ECG features, as well as highlights possible its new clinical utility.

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XI. OŚWIADCZENIA WSPÓŁAUTORÓW

Kraków, 26.05.2020

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OŚWIADCZENIE

Jako współautor pracy „Malignant ventricular arrhythmias and other complications of untreated accessory pathways: analysis of prevalence and risk factors in over 600 ablation cases”, Kardiologia Polska, 2020, 78: 203-208, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 50% i polegał na: opracowaniu koncepcji i hipotezy badania, zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, analizie statystycznej danych, opracowaniu i interpretacji wyników, przygotowaniu pracy w formie publikacji.



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Kraków, 26.05.2020

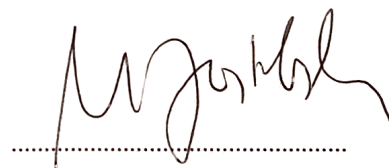
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Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lekarza Pawła Moskala jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lekarza Pawła Moskala polegający na: opracowaniu koncepcji i hipotezy badania, zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, analizie statystycznej danych, opracowaniu i interpretacji wyników, przygotowaniu pracy w formie publikacji.



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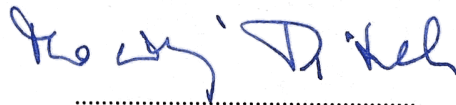
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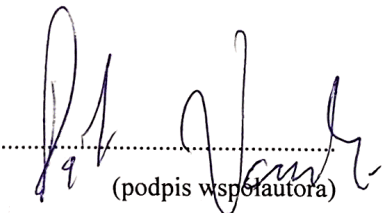
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OŚWIADCZENIE

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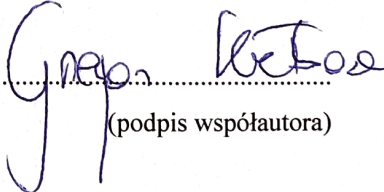
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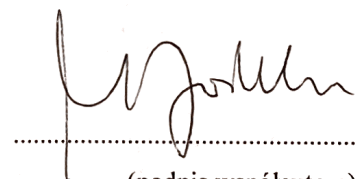
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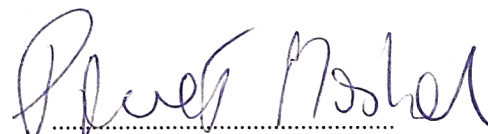
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Nadciśnienia Tętniczego

OŚWIADCZENIE

Jako współautor pracy „Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation”, *Annals of Noninvasive Electrocardiology*, 2018, 23: e12493, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 30% i polegał na: udziale w zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, opracowaniu i interpretacji wyników, udziale w przygotowaniu pracy w formie publikacji, krytycznej analizie manuskryptu.



(podpis współautora)

Kraków, 25.05.2020

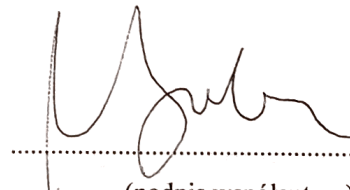
dr hab. med. Marek Jastrzębski, prof. UJ
Uniwersytet Jagielloński Collegium Medicum
Klinika Kardiologii, Elektrokardiologii oraz
Nadciśnienia Tętniczego

OŚWIADCZENIE

Jako współautor pracy „Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation”, Kardiologia Polska, 2018, 23: e12493, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 45% i polegał na: opracowanie założeń badania, nadzorze nad wykonaniem, zebranie materiału do badania, ocenie EKG, udziale w opracowaniu manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lekarza Pawła Moskala jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lekarza Pawła Moskala polegający na: udziale w zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, opracowaniu i interpretacji wyników, udziale w przygotowaniu pracy w formie publikacji, krytyczna analiza manuskryptu.



(podpis współautora)

Kraków, 22.05.2020

dr hab. med. Piotr Kukła
Szpital Specjalistyczny im.
H. Klimontowicza w Gorlicach

OŚWIADCZENIE

Jako współautor pracy „Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation”, Annals of Noninvasive Electrocardiology, 2018, 23: e12493, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5% i polegał na: udziale w ocenie EKG oraz krytycznej analizie manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lekarza Pawła Moskala jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lekarza Pawła Moskala polegający na: udziale w zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, opracowaniu i interpretacji wyników, udziale w przygotowaniu pracy w formie publikacji, krytyczna analiza manuskryptu.

Dr hab. n. med. Piotr Kukła
SPECJALISTA KARDIOLOG
specjalista chorób wewnętrznych
tel 48 906 478 082
3567897 980626302

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(podpis współautora)

dr n. med. Roksana Kisiel

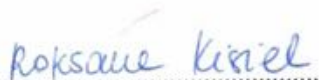
Oddział Kardiologii i Kardioonkologii
Beskidzkie Centrum Onkologii w Bielsku - Białej

OŚWIADCZENIE

Jako współautor pracy: „Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation”, *Annals of Noninvasive Electrocardiology*, 2018; 23: e12493, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5% i polegał na ocenie zapisów EKG oraz krytycznej analizie manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Pawła Moskala jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lekarza Pawła Moskala polegający na: udziale w zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, opracowaniu i interpretacji wyników, udziale w przygotowaniu pracy w formie publikacji, krytyczna analiza manuskryptu.



(podpis współautora)

Kraków, 26.05.2020

Prof. dr hab. med. Danuta Czarnecka
Uniwersytet Jagielloński Collegium Medicum
Klinika Kardiologii, Elektrokardiologii oraz
Nadciśnienia Tętniczego

OŚWIADCZENIE

Jako współautor pracy „Specificity of wide QRS complex tachycardia criteria and algorithms in patients with ventricular preexcitation”, *Annals of Noninvasive Electrocardiology*, 2018, 23: e12493, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 10% i polegał na: krytyczna analiza manuskryptu, współudział w prezentacji wyników, dyskusji i tworzeniu manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lekarza Pawła Moskala jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lekarza Pawła Moskala polegający na: udziale w zbieraniu materiału do badania, wykonaniu analizy elektrokardiogramów, opracowaniu i interpretacji wyników, udziale w przygotowaniu pracy w formie publikacji, krytycznej analizie manuskryptu.



(podpis współautora)