Cardiovascular Topics

Assessment of P- to delta-wave interval and its relationship with accessory pathway properties in patients with pre-excitation

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Abstract

Background: The first clinical manifestation of the Wolff–Parkinson–White syndrome in previously asymptomatic individuals may be sudden cardiac death. The options for non-invasive risk stratification are limited in the current era beyond ambulatory rhythm monitoring and an exercise stress test. In our study, we sought to investigate whether there was a relationship between the shortest measured P- to delta-wave time interval (PDI) on the conduction properties of surface electrocardiogram and accessory pathways expressed as antegrade effective refractory period (APERP).

Methods: Demographic data, symptom status, electrocardiograms (ECG) and intra-cardiac recordings of invasive electrophysiology testing of 103 patients who underwent accessory pathway ablation procedures were collected. Exclusion criteria were: (1) intermittently occurring pre-excitation, which was detected in previous ECGs, (2) delta-wave resolution on treadmill test, (3) presence of multiple accessory pathways, and (4) accessory pathway locations other than the septum. The PDI was measured as the time interval from the beginning of the P wave to the earliest upstroke or downstroke of the delta wave on V1 and V2 derivations of the surface ECG, and the shortest measurement was recorded.

Results: Patients were grouped into two groups: group I, if APERP was < 240 ms and group II if APERP was ≥ 240 ms. PDI was significantly shorter in group II. By correlation analysis, a positive and moderate correlation between PDI and APERP (r = 0.598, p < 0.001) and PDI and age (r = 0.800, p < 0.001) was found, and a negative and moderate correlation between PDI and inducible AF (r = –0.492, p < 0.001). The best cut-off value for PDI to predict APERP ≥ 240 was 90.5 ms with a sensitivity of 80% and a specificity of 83%.

Conclusion: Our results demonstrate that there was a strong correlation between the P- to delta-wave interval and universally accepted risk factors, such as low age, low APERP and atrial fibrillation inducibility. Further studies with larger patient groups and follow-up data are needed to appraise its predictive value.

Keywords: delta wave, pre-excitation, electrocardiogram

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The Wolff–Parkinson–White (WPW) pattern, which is demonstrated by a typical pre-excitation on surface electrocardiogram (ECG), is estimated to show a prevalence of 0.1%. The first clinical manifestation of the WPW syndrome in previously asymptomatic individuals may be sudden cardiac death. According to the latest guidelines, the WPW syndrome is considered to carry a risk of increased life-threatening arrhythmic events when the following factors are observed: young age, effective refractory period of the accessory pathway (APERP) < 240 ms, inducibility of atrioventricular re-entrant tachycardia on electrophysiological study (EPS) and multiple accessory pathways.

Although risk stratification in asymptomatic patients with invasive electrophysiological procedures has been extensively discussed, there is a lack of data in the literature utilising non-invasive surface ECG on this subject. The intermittent appearance of delta waves on surface ECG seems to be a marker of lower risk in this patient group; however its predictive value is debatable.

We hypothesised that the time interval from the beginning of the P wave to the beginning of the earliest delta wave (PDI) on ECG may provide a clue about the conduction property of the accessory pathway. Therefore, we sought to investigate whether there was a relationship between the shortest measured PDI on precordial V1 and V2 derivations and conduction properties, expressed as APERP.

Methods

Patient records of the Electrophysiology Department, Samsun Training and Research Hospital, were retrospectively analysed. Demographic data, symptom status, ECGs and intra-cardiac recordings of invasive electrophysiological testing of 103 patients who underwent accessory pathway ablation procedures were collected. Patients were deemed symptomatic if they had a documented tachycardia episode or they complained about episodes of palpitation, dizziness or syncope. Exclusion criteria were: (1) intermittently occurring pre-excitation that was detected in previous ECGs, (2) delta-wave resolution on a treadmill test,
(3) presence of multiple accessory pathways, and (4) accessory pathway locations other than the septum.

A 12-lead surface ECG (Nilon Kohden Corporation, Cardiofax M Model ECG-1250, Tokyo, Japan) was performed in the supine position, with a 25-mm/s paper speed and a voltage of 10 mm/s. ECGs were recorded after 15 minutes’ resting. All the ECG papers were scanned and transferred to the digital media, and the digital records were analysed under × 400% magnification in a personal computer. The shortest measured P- to delta-wave interval from V1 and V2 (shorter one acquired) on 12-lead ECG was recorded for each patient (Fig. 1). Measurement started from the beginning of the P wave to the first upstroke (or downstroke if it was negative) of a delta wave.

Electrograms (EGM) were retrospectively analysed from recorded procedural data in an electrophysiology stimulator (EP-TRACER, Schwarzer Cardiotek GmbH, Germany). All ECG and EGM measurements were taken separately by two different cardiologists who were blinded to the clinical signs and ECG and EGM measurements were taken separately by two different cardiologists who were blinded to the clinical signs of the patients, and the mean values were transferred to the database. The inter- and intra-observer coefficients of variation were 3.2 and 2.4%, respectively.

The institutional protocol for electrophysiological testing was as follows:

- Incremental atrial pacing was performed until the highest rate was conducted 1/1 through the accessory pathway and/or the atrioventricular (AV) node.
- Programmed atrial stimulation in two different drives (at basic cycle lengths of 400 and 500 ms) was performed: one atrial extra-stimulus was delivered after eight paced atrial stimuli at a cycle length of 400 or 500 ms from 390 or 490 ms until the accessory pathway (AP) refractory period or the atrial effective refractory period (ERP) was achieved with decreases of 10 ms.
- Briefly, atrial and ventricular extra-stimulation with progressively shorter coupling intervals was performed to induce AV re-entrant tachycardia (AVRT) until the effective refractory periods of the atrium and ventricle were achieved.

- The disappearance of the pattern of pre-excitation was indicated when the APERP was reached. The longest atrial decremental pacing interval that failed to conduct at the atria was considered the effective APERP. This protocol was reproduced again after several minutes to study the reproducibility of the measurement of the antegrade effective refractory period. Inducible arrhythmias were defined as sustained if they lasted more than one minute. Tachyarrhythmia inducibility was defined as reproducible induction of sustained AVRT, or atrial fibrillation (AF), or AVRT conversion to AF.

- All interventions listed above were done under conscious sedation with midazolam and phentanyl.

Statistical analysis

All analyses were performed using SPSS V 22.0 for Windows (SPSS Inc, Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to determine the distribution of continuous variables. The Student’s t-test or Mann–Whitney U-test was used to compare two means according to whether the data were normally distributed. Chi-squared or Fisher’s exact tests were used to examine categorical variables. Continuous variables are represented as mean ± SD and categorical variables as counts and percentages. A p-value < 0.05 was considered statistically significant.

The Spearman correlation coefficient was used for correlation analysis to evaluate relationships between the following parameters: PDI, AF inducibility, APERP and age. Receiver operating characteristic (ROC) curve analysis was applied to determine the sensitivity and specificity with a 95% confidence interval (CI) for the PDI to detect the presence of APERP ≥ 240 ms and AF triggering tachycardia at the cut-off values. The association of different variables with APERP was calculated in univariate analysis. Logistic regression analysis was used to find independent predictors of APERP < 240 ms.

Results

Baseline demographic, clinical and electrophysiological properties of the study group are listed in Table 1. Among V1 and V2, 71 patients’ PDI were measured shorter on V1 (68%). A total of 103 patients were grouped by APERP. Individuals with APERP < 240 ms were included in group I (n = 29) and individuals with APERP ≥ 240 ms were included in group II (n = 74).

Patients in group I were significantly younger, more symptomatic and more of them had inducible AF in EPS (Table

### Table 1. Demographical and clinical data

<table>
<thead>
<tr>
<th>Parameters</th>
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<tr>
<td>Age, years</td>
<td>42.6 ± 14.4</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>32 (31.1)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Symptomatic patients, n (%)</td>
<td>57 (55.3)</td>
</tr>
<tr>
<td>PDI, ms</td>
<td>98.4 ± 9.28</td>
</tr>
<tr>
<td>APERP, ms</td>
<td>283.2 ± 35.7</td>
</tr>
<tr>
<td>AF triggering tachycardia, n (%)</td>
<td>30 (28.8)</td>
</tr>
<tr>
<td>AF: atrial fibrillation, APERP: accessory pathway antegrade effective refractory period, PDI: P- to delta-wave interval</td>
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Furthermore, when patients were grouped into two groups, according to having inducible AF or not, individuals who experience AF episodes \((n = 30)\) had significantly shorter PDI \((91.3 \pm 7.9 \text{ vs } 101.3 \pm 8.1, p < 0.001)\). It was similar when the study group was divided into two according to symptom status; symptomatic patients \((n = 57)\) had significantly shorter PDI than the others \((96.4 \pm 9.79 \text{ vs } 100.93 \pm 8.03, p = 0.012)\).

Spearman correlation analysis (Fig. 2) revealed a positive and moderate correlation between PDI and APERP \((r = 0.598, p < 0.001)\), a positive and moderate correlation between PDI and age \((r = 0.800, p < 0.001)\), a negative and moderate correlation between PDI and inducible AF \((r = -0.492, p < 0.001)\), a positive and moderate correlation between age and APERP \((r = 0.552, p < 0.001)\), a negative and moderate correlation between age and inducible AF \((r = -0.445, p < 0.001)\), and a negative and moderate correlation between APERP and inducible AF \((r = -0.425, p < 0.001)\).

Univariate analysis showed that PDI was an independent predictor of APERP \((\text{OR: } 1.211, 95\% \text{ CI: } 1.076–1.363; p = 0.002)\). In the ROC curve analysis, the value for PDI to detect APERP \(\geq 240\) ms with a sensitivity of 80% and a specificity of 83% was 90.5 \((\text{the area under the curve was } 0.85, p < 0.001)\). The best cut-off value for PDI to detect AF triggering tachycardia was 110.5, with a sensitivity of 97% and a specificity of 83% \((\text{the area under the curve was } 0.187, p < 0.001)\) (Fig. 3).

**Discussion**

We found that the non-invasive electrocardiographic PDI parameter was correlated with invasive risk-stratification parameters. Its use may provide additional information as an easily applicable non-invasive ECG parameter.

In 1913, Kent demonstrated that AV connection was not singular and limited to the AV node.\(^{6,7}\) In 1930, Wolff, Parkinson and White described a distinct pattern of surface ECG with short PR interval and right bundle branch block (RBBB) pattern in patients with paroxysmal supraventricular tachycardia (PSVT).\(^{8}\) Years later, the term ‘pre-excitation’ was introduced as...
a phenomena whereby, in relation to atrial events, the whole or part of the ventricular muscle is activated earlier by the impulse originating in the atrium than would be expected if the impulse reached the ventricles by way of the normal conduction system.3

WPW remains the most common variety of pre-excitation syndrome. The classic ECG in the WPW syndrome is characterised by a short PR interval (< 120 ms) and a prolonged QRS duration. The initial slurring of the upstroke of the QRS complex (delta wave) represents the anomalous excitation of the ventricle, with muscle–muscle conduction bypassing the normal pathway.

Clinical features of the WPW syndrome are variable among patients; a spectrum occurs that manifests from no symptoms to sudden cardiac death. Both atrial and ventricular arrhythmias may occur in this group of patients. If atrial disorganised high-frequency electrical impulses transmit to the ventricle through the accessory pathway during AF episodes, sudden cardiac death due to ventricular fibrillation is inevitable. Therefore, AF inducibility is one of the risk factors for WPW patients.7

In recent studies, AF inducibility was investigated in both animal and human heart models.8,10 Authors have emphasised c-Jun N-terminal kinase (JNK) in their work. Advancing age and other stresses, such as excessive alcohol use, obesity and inflammation, drive JNK activation and the JNK/CaMKII interaction is likely a critical mechanism that couples arrhythmia and these stresses (Ca2+/calmodulin directly phosphorylates CaMKII proteins, driving CaMKII pro-arrhythmic effects on diastolic-dependent kinase II). Activated JNK2 decreases SR Ca2+ handling.

Authors have shown that in JNK-challenged animal models, AF propensity was eliminated by JNK2 ablation or CaMKII inhibition. Beyond obesity and excessive alcohol consumption, the literature is not rich on the relationship between augmented JNK2 activity and other pro-arrhythmic conditions such as co-existing accessory pathways and genetic mutations (long-QT syndromes). Furthermore, it has not been studied whether emotional or physical stress (endurance sport) affect JNK activity in the same way as the other stresses mentioned. At this point, JNK is worth investigating to explain AF inducibility in young WPW patients.

Another reason for sudden cardiac death is ventricular arrhythmias, ventricular fibrillation in particular. Idiopathic ventricular fibrillation and other malignant arrhythmias are not rare in these patients and they may occur spontaneously without preceding AF.12 To understand the mechanism at play here, a basic model would be helpful.11

Hypothetically, an antegrade fusion beat uses both AV node and accessory pathways, which bring non-physiological delay between ventricular depolarisation kick off. This delay may even be intraventricular and between different regions of the same ventricle. Non-uniform prolongation of the action potential duration may be pro-arrhythmic by increasing dispersion of repolarisation or refractoriness and changing the electrical gradients.

For a better understanding, in vivo left ventricular hypertrophy models would be helpful. In these studies, it was shown that epicardial action potentials are more prolonged than those in the endocardium, altering the endo–epicardial gradient seen in normal hearts and associated with increased inducibility of polymorphic ventricular tachycardia or ventricular fibrillation.14,16

Generally, radiofrequency ablation of the accessory pathway is recommended for symptomatic patients and/or individuals who undertake competitive/endurance sport and/or whose occupation is accepted to bear high risk (pilot, bus driver). A major problem for clinicians is predicting the clinical outcome in patients incidentally found with asymptomatic ventricular pre-excitation. Current guidelines recommend single or combined utilisation of risk factors such as young age, AF inducibility and short antegrade AP ERP.8 However, non-invasive methods for risk stratification are limited.

The intermittent appearance of delta waves on a surface ECG or Holter monitor is accepted to be a low-risk predictor. It was postulated that disappearance of delta waves may be due to acceleration-dependent block (phase 3 block) when an impulse reaches a conduction fibre during its repolarisation phase. It may also occur when an impulse reaches a conduction fibre during a time of slow diastolic depolarisation (automaticity), referred to as phase 4 block.7

Exercising and catecholamine discharges cause an increase in the sinus rates as well as enhanced conduction through both the accessory pathway and the AV node. This may lead to different degrees of ventricular pre-excitation on the surface ECG and mask persistent pre-excitation. Abrupt and complete loss of pre-excitation during exercise has been shown to correlate with a long antegrade AP ERP and consequently lower risk for sudden death. However, sensitivity is low for non-rapid conducting accessory pathways and there is a need for another tool for risk stratification.15

Furthermore, two studies retrospectively analysed a large group of asymptomatic paediatric pre-excitation patients,8,9 and demonstrated that there was no difference in the prevalence of high-risk accessory pathways between patients with persistent pre-excitation, those with intermittent pre-excitation on baseline ECG, and those with loss of pre-excitation on Holter or exercise.

With this background, we sought to find a new non-invasive risk marker for decision making in asymptomatic patients. We hypothesised that faster conduction in the accessory pathway would be the shorter measurable time interval on surface ECG. If we use a model of sinus fast-pathway conduction in a slow–fast AV re-entry model, we would expect the time interval from the occurrence of the sinus impulse (beginning of the P wave) to depolarisation of the first myocardial mass (beginning of the delta wave) (PDI) would be shorter in some ECG derivations. These derivations supposedly directly record the axis of accessory pathway conduction, which is V1 and V2 in our case. Positive–negative or negative–positive delta-wave couples are classic for septal accessory pathways.

Therefore we hypothesised that PDI measurements would be more appropriate and are expected to be shorter in the above ECG derivations. When patients were grouped by AP ERP < 240 ms or having inducible AF or symptom status, the PDI was significantly shorter in individuals who had a shorter AP ERP, had inducible AF and were symptomatic. We demonstrated a strong positive correlation between PDI duration and AP ERP and AF inducibility in adult WPW patients.

Limitations
The main limitation of our study is the absence of isoproterenol in the electrophysiology protocol. A nationwide shortage of this drug prevented us from utilising the shortening effect of isoproterenol's
refractory period. Previous studies have shown that isoproterenol will reliably shorten all markers of risk assessment.\textsuperscript{11-12} One of the minor limitations is the autonomic effects on heart rate and refractory periods. We tried to abolish the autonomous effect by mild (conscious) sedation during the invasive procedure. One of the least cardio tropic agents, midazolam, was the only agent utilised in the procedures and the mean dose was quite low (1.7 ± 0.2 mg).

Finally, the absence of a control group of WPW patients who did not undergo ablation, and lack of follow-up data are also limitations due to the retrospective study design. However, our aim was merely to investigate whether there was a correlation between PDI and established invasive risk factors. Clinical replications are the subject of further research.

Conclusions

Our results demonstrate that there was a strong correlation between the P- to delta-wave interval and universally accepted risk factors, such as low APERP and AF inducibility. To reach definite conclusions about the predictive value of this surface ECG parameter, long-term follow up of asymptomatic patients who did not undergo ablation is needed. Future studies with larger patient groups would shed more light on our primary work.

References