Procainamide infusion test: inability to identify patients with Wolff-Parkinson-White syndrome who are potentially at risk of sudden death

LAMEH FANANAPAZIR, M.D., DOUGLAS L. PACKER, M.D., LAWRENCE D. GERMAN, M.D., G. STEPHEN GREER, M.D., JOHN J. GALLAGHER, M.D., JOYCE C. PRESSLEY, M.P.H., AND ERIC N. PRYSTOWSKY, M.D.

ABSTRACT Persistence of preexcitation in sinus rhythm with procainamide infusion has been reported to occur in patients with a short anterograde accessory pathway effective refractory period (AERPAP) and this test has been proposed as a reliable noninvasive method to identify patients with the Wolff-Parkinson-White syndrome who are at risk of sudden death. However, sudden death correlates best with a shortest preexcited RR interval during atrial fibrillation (SRRPE) of 260 msec or less. We infused 10 to 12 mg/kg procainamide to 56 patients to determine whether persistence or loss of preexcitation in sinus rhythm identified patients with SRRPEs of 260 or less or greater than 260 msec, respectively. Atrial fibrillation was induced in 53 patients. Of these, 32 patients had persistence of preexcitation with procainamide infusion and SRRPE in this group of patients was shorter than that in patients in whom preexcitation was lost (194 ± 44 vs 235 ± 55 msec, p < .05). However, preexcitation persisted after procainamide infusion in only 31 of 46 (67%) patients with SRRPEs of 260 msec or less. Furthermore, 15 of 21 patients who lost preexcitation had SRRPEs of 260 msec or less and two of these patients had a history of ventricular fibrillation. The correlation between AERPAP and SRRPE was studied in a separate group of 79 patients with single accessory pathways. There was a significant (p < .001) but poor (r = .58) correlation between these two variables. Thus, the procainamide test regarding accessory pathway refractoriness often cannot be extrapolated to SRRPE. We conclude that the procainamide infusion test does not reliably predict SRRPE and is therefore of limited value as a noninvasive method to identify patients with Wolff-Parkinson-White syndrome who are at potential risk of sudden death.


PATIENTS with Wolff-Parkinson-White syndrome who have rapid preexcited ventricular rates during atrial fibrillation are at risk of sudden death from ventricular fibrillation.1-9 Persistence of preexcitation in normal sinus rhythm with procainamide infusion has been proposed10 to occur in patients with a relatively short (<270 msec) anterograde effective refractory period of the accessory pathway (AERPAP). Since these investigators previously noted a close correlation between AERPAP and the shortest preexcited RR interval during atrial fibrillation (SRRPE),11 they proposed that the procainamide test identifies patients who are most likely to have rapid preexcited ventricular rates during atrial fibrillation. However, SRRPE and not AERPAP correlates best with a history of ventricular fibrillation,9 and the correlation of AERPAP and SRRPE remains controversial.9, 11-14

The purpose of the present investigation was two-fold: first, to test the hypothesis that loss of preexcitation in sinus rhythm with procainamide infusion reliably predicts SRRPE, and second, to reexamine the relationship between AERPAP and SRRPE and thus determine whether AERPAP can be used as a reliable guide for SRRPE.

Methods

Patient population. Patients were investigated after written informed consent was obtained in accordance with the Human Institutional Review Board. Three patient groups were studied: (1) SRRPEs were compared in 45 consecutive patients with a history of ventricular fibrillation and 206 consecutive patients without a history of ventricular fibrillation. (2) The ability of the procainamide infusion test to identify patients with relatively short AERPAPs (<270 msec) and SRRPEs (<260 msec) was assessed in 59 patients with a single accessory atrioventricular pathway capable of anterograde conduction. An SRRPE of 260
msec was selected to dichotomize patients, since all patients with a history of ventricular fibrillation had a SRRPE of 260 msec or less (see Results). The clinical characteristics of the patients are presented in Table 1. (3) The relationship of AERPAP to SRRPE was studied in 113 consecutive patients with single accessory pathways capable of anterograde conduction.

Electrophysiologic study. All patients underwent electrophysiologic study in the fasting nonsedated state when they were at least five half-lives free of any antiarrhythmic therapy. A quadripolar electrode was introduced percutaneously into the subclavian vein and advanced under fluoroscopic guidance to the distal coronary sinus. Similarly, three multipolar electrode catheters were introduced into the femoral vein and positioned in the high right atrium, right ventricular apex, and His bundle area. Programmed atrial and ventricular stimulation was performed as previously described. The site of accessory pathway was determined by endocardial mapping and surface electrocardiographic characteristics.

Atrial fibrillation was induced by rapid atrial pacing if it did not occur spontaneously. The duration of atrial fibrillation was 30 sec in three patients and was sustained (requiring procainamide or electrical cardioversion) in the remaining patients.

Programmed stimulation was performed at twice the diastolic threshold, at a rectangular pulse width of 2 msec. AERPAP was defined as the longest A1-A2 coupling interval that failed to conduct with preexcitation measured at a site closest to the accessory pathway, determined at pacing cycle lengths of 600, 500, or 400 msec. The AERPAP value obtained at the shortest pacing cycle length was used for purposes of comparison and statistical analysis.

Procainamide infusion test. After control data were obtained, procainamide was given intravenously as a 100 mg bolus followed by 50 mg/min during sinus rhythm until preexcitation was lost or a total dose of 10 to 12 mg/kg body weight was infused (15 patients), or during atrial fibrillation until sinus rhythm was restored and preexcitation was lost or 10 to 12 mg/kg body weight was infused (41 patients). Direct-current shock restored sinus rhythm in patients in whom atrial fibrillation persisted after procainamide infusion. Continuous electrocardiographic (ECG) leads I, II, III, V1, and V6 and a 12-lead electrocardiogram were recorded before and after procainamide infusion. In addition, before and after procainamide infusion AERPAP, determined at the same pacing cycle length, and SRRPE were obtained. Although procainamide was infused in patients in sinus rhythm or atrial fibrillation, determinations of persistence or loss of preexcitation with procainamide infusion were made only during normal sinus rhythm.

Statistics. The Mann-Whitney U test was used to test for significant differences between two independent samples and the Spearman rank order test was used to test for correlation between two variables. A \( p < .05 \) was considered to indicate a significant difference.

### TABLE 1

<table>
<thead>
<tr>
<th>Procainamide study population</th>
<th></th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>59</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>47</td>
</tr>
<tr>
<td>Age (mean ( \pm 1 ) SD yr)</td>
<td>28 ± 10</td>
</tr>
<tr>
<td>Location of accessory of pathway</td>
<td></td>
</tr>
<tr>
<td>Left free wall</td>
<td>28</td>
</tr>
<tr>
<td>Posteroseptal</td>
<td>11</td>
</tr>
<tr>
<td>Right free wall</td>
<td>15</td>
</tr>
<tr>
<td>Right anteroseptal</td>
<td>5</td>
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</tbody>
</table>

### Results

Correlation of SRRPE with risk of sudden death. The distribution of SRRPEs in patients with a history of ventricular fibrillation and in patients without a history of cardiac arrest or ventricular fibrillation are compared in Figure 1. Patients with a history of ventricular fibrillation had a significantly (\( p < .001 \)) shorter SRRPE (190 ± 36 msec, mean ± 1 SD) compared with patients without a history of ventricular fibrillation (235 ± 62 msec). All patients with a history of ventricular fibrillation had a SRRPE of 260 msec or less.

Effect of procainamide on AERPAP and SRRPE. Three patients were excluded from this analysis due to absence of preexcitation in normal sinus rhythm during the control period. These patients nonetheless had rapid preexcited ventricular rates during atrial fibrillation (SRRPE 115, 150, and 160 msec) and two of these
patients had a history of ventricular fibrillation (figure 2). Of the remaining 56 patients, 22 patients lost preexcitation and in 34 patients preexcitation in normal sinus rhythm persisted after procainamide infusion. The clinical characteristics of these two groups are presented in table 2. No differences were noted between the two groups.

**AERPAP.** The distributions of control values of AERPAP in patients who subsequently lost preexcitation and in patients in whom preexcitation in normal sinus rhythm was present after procainamide infusion are shown in figure 3. Refractory period data were available in 18 patients who lost preexcitation and in 29 patients who did not lose preexcitation with procainamide infusion. Twelve patients with AERPAP of less than 270 msec and two of five patients with a history of ventricular fibrillation lost preexcitation with procainamide infusion. Furthermore, in six patients with exact AERPAP determinations, preexcitation in normal sinus rhythm persisted with procainamide infusion despite relatively long AERPAPs of 270 to 375 msec. Thus, the abilities of the procainamide infusion test to discriminate between patients with relatively long and short AERPAPs were poor (table 3). There were insufficient numbers of patients in whom the exact values of AERPAP before and after procainamide therapy were available to test the correlation between changes in AERPAP due to procainamide infusion and initial duration of AERPAP.

**SRRPE.** Control SRRPEs were available in 32 patients in whom preexcitation persisted with procainamide infusion and in 21 patients who lost preexcitation. The SRRPE was shorter in patients in whom preexcitation persisted than in those who lost preexcitation (194 ± 44 vs 235 ± 55 msec, p < .05), but 15 of 21 patients who lost preexcitation had SRRPEs of 260 msec or less and of these, two patients had a history of ventricular fibrillation (figure 4). Additionally, only 31 of 46 patients (67%) with SRRPEs of 260 msec or less had persistence of preexcitation in sinus rhythm with procainamide infusion. Thus, the ability

<table>
<thead>
<tr>
<th>Preexcitation with procainamide infusion</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Age (mean ± 1 SD yr)</td>
<td>26 ± 10</td>
<td>30 ± 11</td>
</tr>
<tr>
<td>Accessory pathway site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left free wall</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Posteroseptal</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Right free wall</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Right anteroseptal</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>HV interval (msec)</td>
<td>14 ± 23</td>
<td>14 ± 17</td>
</tr>
<tr>
<td>Procainamide dose (mg)</td>
<td>925 ± 282</td>
<td>956 ± 235</td>
</tr>
</tbody>
</table>

**FIGURE 2.** Absence of preexcitation during the control period in a patient with a history of ventricular fibrillation and with an SRRPE of 115 msec.

**FIGURE 3.** Distribution of control values of AERPAP in patients with and without persistence of preexcitation in normal sinus rhythm (NSR) after procainamide infusion. AFRP = atrial functional refractory period.
TABLE 3
Ability of persistence of preexcitation in sinus rhythm with procainamide infusion test to identify patients with an SRRPE of 260 msec or less and an AERPAP of less than 270 msec

<table>
<thead>
<tr>
<th>SRRPE ≤ 260 msec</th>
<th>AERPAP &lt; 270 msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>86</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>67</td>
</tr>
<tr>
<td>False-positive rate (%)</td>
<td>33</td>
</tr>
<tr>
<td>False-negative rate (%)</td>
<td>14</td>
</tr>
</tbody>
</table>

of the procainamide infusion test to identify patients with relatively short preexcited intervals during atrial fibrillation was poor (table 3).

**Correlation of control SRRPE with SRRPE recorded after procainamide infusion.** In 31 patients who did not lose preexcitation after procainamide infusion, atrial fibrillation was induced after procainamide. There was a significant \( p < 0.01 \) correlation between SRRPE determined after procainamide infusion and the control value (figure 5). Control values for SRRPE, however, did not reliably \( r = 0.61 \) predict the effect of procainamide on this interval (figure 5).

**Correlation of AERPAP with SRRPE.** Estimation of AERPAP was limited by atrial refractoriness in 34 of 113 (30%) patients, regardless of the use of multiple atrial paced rates. In 79 patients in whom exact AERPAP measurements were made, a significant \( p < 0.001 \) correlation existed between AERPAP and SRRPE (figure 6). The relationship between AERPAP

**FIGURE 4.** Distribution of control values of SRRPE in patients with and without persistence of preexcitation in normal sinus rhythm after procainamide infusion.

**FIGURE 5.** Correlation of SRRPE after procainamide infusion with control SRRPE.

**FIGURE 6.** Correlation of AERPAP determined at pacing cycle lengths (PCL) of 600 to 400 msec with SRRPE. Each point represents a separate patient. Unfilled squares are PCL 600 msec, unfilled circles are PCL 500 msec, and filled are PCL 400 msec.
and SRRPE, however, was subject to a great deal of patient variation \(r = .58\), and the correlation between these two variables was poor for each pacing cycle length tested (pacing cycle length 600 msec, \(r = .70\); 500 msec, \(r = .45\); 400 msec, \(r = .62\)). It is noteworthy that of 60 patients with relatively short SRRPEs \((\leq 260\) msec), 24 patients had relatively long AERPAPs \((\geq 270\) msec), and of 19 patients with relatively long SRRPEs \((> 260\) msec), three had relatively short AERPAPs \((< 270\) msec). Conversely, of 39 patients with relatively short AERPAPs \((< 270\) msec), three patients had relatively long SRRPEs \((> 260\) msec) and of 40 patients with relatively long AERPAPs \((\geq 270\) msec), 24 patients had relatively short SRRPEs \((\leq 260\) msec).)

**Discussion**

In normal hearts, ventricular rates during atrial fibrillation are limited by the electrophysiologic properties of the atrioventricular node. In patients with Wolff-Parkinson-White syndrome, rapid ventricular rates may occur during atrial fibrillation due to conduction over the accessory pathway and this may result in syncope or sudden death.\(^1\)\(^-\)\(^9\) Klein et al.\(^9\) reported that an SRRPE of 250 msec or less occurred in patients with Wolff-Parkinson-White syndrome who had a history of ventricular fibrillation. The SRRPE interval was more useful in this respect than the average ventricular response during atrial fibrillation, the shortest atrial-paced cycle length with 1:1 conduction over the accessory pathway, or AERPAP.\(^9\) The present study confirms the close connection between SRRPE and a history of cardiac arrest, and all 45 patients who had clinical ventricular fibrillation had an SRRPE of 260 msec or less.

Some investigators\(^1\)\(^1\)\(^,\)\(^12\) have advocated, as a result of data from small series of patients, estimation of AERPAP as an indirect guide to ventricular rates during atrial fibrillation. Recently, however, Klein et al.\(^9\) reported a poor correlation \((r = .49)\), and Rowland et al.\(^14\) no correlation between AERPAP and SRRPE. In our study, determination of AERPAP was limited by atrial refractoriness in about 30% of patients. In patients in whom exact AERPAP data were available, there was a significant but not close correlation between AERPAP and SRRPE at drive cycle lengths of 600 to 400 msec. Of note, 41% of patients with relatively long AERPAPs \((\geq 270\) msec) had short SRRPEs \((\leq 260\) msec). Since AERPAP is affected by pacing cycle length,\(^16\) it is possible that AERPAP determined at drive cycle lengths less than 400 msec might show a better correlation with SRRPE. Nonetheless, the critical information needed is SRRPE, which should be determined by induction of atrial fibrillation.

There are several theoretical reasons for the poor reliability of AERPAP as a guide to SRRPE. These may include electrophysiologic and anatomic determinants of atrioaccessory pathway and accessory pathway-ventricular connections, anterograde and retrograde concealed conduction into the accessory pathway, and ventricular refractoriness. Furthermore, during atrial fibrillation, rapid ventricular rates and changes in autonomic nervous system activity may affect conduction and refractoriness of the accessory pathway.

Attempts have been made to correlate effects of class I antiarrhythmic drugs on anterograde conduction over the accessory pathway with control values of AERPAP, assuming that AERPAP correlates closely with SRRPE.\(^10\)\(^,\)\(^17\)\(^-\)\(^20\) In this context, Wellens et al.\(^10\)\(^,\)\(^17\) reported that anterograde block in the accessory pathway with ajmaline or procainamide infusion reliably separated patients with relatively long from those with short AERPAPs. Nineteen of 20 patients with AERPAPs of 270 msec or greater lost preexcitation in sinus rhythm, but in 18 or 19 patients with AERPAPs of less than 270 msec and in all patients with AERPAPs of less than 250 msec, preexcitation in sinus rhythm persisted with procainamide infusion.\(^10\) Some investigators,\(^21\)\(^,\)\(^22\) however, have reported that patients with relatively long AERPAPs (for example, AERPAP of 350 msec) or anterograde accessory pathway block after ajmaline therapy nevertheless had rapid preexcited ventricular rates during atrial fibrillation in the control period. In our study, the majority of patients who lost preexcitation in sinus rhythm after procainamide infusion had relatively short AERPAPs of less than 270 msec (10 of 18 patients had AERPAP of \(<250\) msec) and SRRPEs of 260 msec or less. That loss of preexcitation in sinus rhythm with procainamide infusion does not identify patients who are free of risk of ventricular fibrillation is underlined by the occurrence of this arrhythmia in two patients in this category (figure 4).

The design of our study differed from that reported by Wellens et al.\(^10\) in several aspects. In the study of Wellens et al., up to 10 mg/kg body weight of procainamide was infused in patients only during sinus rhythm and in the absence of any indwelling cardiac catheters. In our study, most patients received procainamide during atrial fibrillation. Although it is possible for cardiac catheters to traumatize accessory pathways, and hence affect the electrophysiologic properties,\(^24\) this occurs rarely and in only selected areas of the heart and
was not noted throughout the study. Furthermore, observations on loss or persistence of preexcitation were made only during sinus rhythm, not during atrial fibrillation. In our study, procainamide was infused over an average of 15 min, because infusion of large doses of procainamide over 5 min may be associated with side effects due to hypotension, which may in turn affect the properties of the entire conduction system by increasing sympathetic nervous system activity. Six of 39 patients in the study reported by Wellsen et al. developed such side effects. It is to be noted, however, that most of our patients who lost preexcitation after procainamide infusion had relatively short SRRPEs (≤260 msec). This group included two patients who had a history of ventricular fibrillation. In essence, the differences between our results and those of Wellsen et al. cannot be explained on the basis of the quantity of procainamide given or on the infusion rate, since the test in our experience was limited by large false-positive and false-negative rates. The patients included in our series, however, had shorter AERPAPs and SRRPEs. These constitute, in our opinion, the most important differences between the two studies. Yet, it is precisely patients with short AERPAPs and SRRPEs that the procainamide infusion test is designed to identify. A further limitation of the procainamide infusion test is its inapplicability in patients in whom preexcitation in sinus rhythm during the control period is absent due to short atrioventricular nodal conduction times associated with left-sided pathway locations. The test would thus not have identified three patients in our series who had rapid preexcited ventricular rates during atrial fibrillation, including two patients with a history of ventricular fibrillation.

We conclude that the procainamide infusion test cannot be recommended as a reliable method of assessing patients with Wolff-Parkinson-White syndrome who are at potential risk of sudden death. Atrial fibrillation should be induced when risk stratification and assessment of protective therapy are considered.

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