Prognostic Value of Electrophysiology Testing in Asymptomatic Patients With Wolff-Parkinson-White Pattern

James W. Leitch, MBBS, George J. Klein, MD, FRCP(C), FACC, Raymond Yee, MD, FRCP(C), FACC, and Challon Murdock, MBBS, FRACP

The prognostic value of electrophysiology testing was studied in 75 asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. All patients underwent electrophysiology testing at entry to the study and were followed up annually for a total of 348 patient-years (median, 4.3 years). There were 44 male and 31 female patients, and age at enrollment ranged from 7 to 77 years (mean, 34±14 years). The median effective refractory period of the accessory pathway was 293 msec (interquartile range, 280–310 msec), and the median shortest RR interval between preexcited beats during atrial fibrillation was 274 msec (240–320 msec). Twenty-three patients had an SRR of 250 msec or less and eight patients had a median shortest SRR interval of 200 msec or less. Twelve patients had inducible sustained reciprocating tachycardia, 10 patients had inducible nonsustained reciprocating tachycardia, and 23 patients had inducible sustained atrial fibrillation. Twenty patients (27%) lacked retrograde conduction over the accessory pathway. No patient died suddenly during a median follow-up of 4.3 years. Six patients (8%) became symptomatic with documented supraventricular tachycardia, of whom two underwent operative ablation of their accessory pathways. No patient with absent retrograde accessory pathway conduction during the electrophysiology study became symptomatic. Inducible sustained or nonsustained reciprocating tachycardia at electrophysiology study did not predict the development of subsequent symptomatic supraventricular tachycardia. Nine patients lost preexcitation during follow-up. Age at enrollment (relative risk/decade, 1.4; 95% confidence interval, 1.0–1.8) and anterograde accessory pathway refractory period (relative risk, 1.06/10 msec; 95% confidence interval, 1.0–1.12) were independent predictors of loss of preexcitation. This study confirms the good short-term prognosis in asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. Electrophysiology testing was of limited benefit in this group of patients owing largely to the low incidence of adverse events. (Circulation 1990;82:1718–1723)

Asymptomatic patients with the Wolff-Parkinson-White (WPW) electrocardiographic pattern have been considered at risk for sudden death according to studies that found that 12–27% of patients were asymptomatic before their episode of ventricular fibrillation. Patients with the WPW pattern resuscitated from sudden cardiac arrest have been found to have a specific electrophysiological profile, and this has raised the possibility that electrophysiology testing may be used to identify asymptomatic patients at risk of sudden death. Consequently, we prospectively studied 75 asymptomatic patients with the WPW pattern on the surface electrocardiogram to determine the prognostic value of electrophysiology testing.

Methods

Patients

Consecutive asymptomatic patients with the WPW pattern on the surface electrocardiogram were enrolled in this study. Patients were referred after ventricular preexcitation was found either as an incidental finding at routine medical examination (n=14), during investigation of chest pain (n=13), palpitations, or irregular heart beat (n=16), or during investigation of other medical problems (n=32). Patients with palpitations were considered asymptomatic.

From the Department of Medicine, University Hospital, London, Ontario, Canada. Supported by the Heart and Stroke Foundation of Ontario, Toronto, Canada. G.J.K. is a Distinguished Research Professor of the Heart and Stroke Foundation of Ontario. Address for correspondence: Dr. G.J. Klein, University Hospital, 339 Windermere Road, London, Ontario, Canada N6A 5A5. Received January 5, 1990; revision accepted July 19, 1990.
tomatic if the palpitations were transient (lasting seconds only) and consistent with isolated ectopic beats. All patients underwent symptom-limited exercise stress testing and 24-hour Holter monitoring and were excluded from the trial if supraventricular tachycardia was documented at any time. Other specific exclusions were intermittent preexcitation either at rest or during exercise testing and unwillingness to undergo electrophysiology testing. Nine patients with intermittent preexcitation were enrolled in the study before this finding was made a specific exclusion in 1983. These patients were excluded from this analysis. Three asymptomatic patients who elected to undergo surgical ablation of their accessory pathways immediately after electrophysiology study were also excluded from this study. (Two patients requested operative treatment in order to continue in their occupations as professional pilot and athlete, and ablation was performed in the third patient at the time of coronary artery bypass surgery.) This cohort includes patients previously reported.6

Study Design

After informed consent was obtained, patients underwent clinical assessment, symptom-limited treadmill exercise testing, echocardiography, 24-hour ambulatory monitoring, and electrophysiology testing. The results of the investigations were communicated to the patient and referring physician. Antiarrhythmic medication or operative intervention were not advised, irrespective of the results of the investigations. Follow-up was conducted annually by telephone or clinic visits. In the event of symptoms, full clinical reassessment was performed, and patients were provided with a transtelephonic recorder to record palpitations. Patients were considered to have become symptomatic when supraventricular tachycardia was documented by telephonic recording or on hospital admission.

Electrophysiology Testing

The electrophysiology protocol has been detailed elsewhere.6 Briefly, two quadripolar and one tripolar catheters were introduced into the right femoral vein and positioned in the high right atrium, right ventricular apex, and His bundle recording position, respectively. Intracardiac electrocardiograms were recorded simultaneously with surface leads I, II, III, V1, and V6 on a Siemens mingograph (Salne, Sweden) at a paper speed of 100 mm/sec. Programmed stimulation was performed at two to four times diastolic threshold with 2-msec square wave pulses. Atrial and ventricular extrastimulus testing was performed at two cycle lengths until refractoriness was reached, and atrial and ventricular incremental pacing was performed until atrioventricular and ventriculoatrial block occurred, respectively. If atrial fibrillation did not occur during this protocol, we attempted to induce it by pacing the right atrium at a cycle length of 50 to 200 msec for 1 minute. Intervals in atrial fibrillation were measured during a 1-minute sample. If atrial fibrillation was not sustained after termination of atrial pacing, ventricular intervals were measured during atrial fibrillation sustained by pacing. Localization of the accessory pathway was determined by electrocardiographic criteria.7

Atrial fibrillation was considered sustained if it persisted for more than 5 minutes after either incidental or deliberate induction. Reciprocating tachycardia was considered sustained if it persisted for more than 30 seconds and was considered nonsustained if it persisted for more than 3 beats but less than 30 seconds. Pharmacological interventions were not routinely used in an attempt to induce reciprocating tachycardia if it was not inducible in the baseline state. Only tachycardias inducible in the drug-free state were considered in this analysis.

If atrial or ventricular refractoriness did not allow exact determination of the refractory period of the accessory pathway, the value obtained before atrial or ventricular refractoriness was used as an approximation. If there were no adjacent preexcited beats during atrial fibrillation, the longest RR interval measured was used to approximate the shortest preexcited RR interval during atrial fibrillation (SRR).

Statistical Analysis

The distributions of the electrophysiological variables were positively skewed, and therefore, these variables are expressed as median and interquartile range. Electrophysiological variables were compared with the Wilcoxon's ranked sum test, and patient ages were compared with an unpaired t test.8 Frequencies were compared with the \( \chi^2 \) test.8 The probability of remaining arrhythmia free was calculated by the Kaplan-Meier product-limit method, and comparison between subgroups was performed with the log rank test.9 The Cox proportional hazards model was used to determine predictors of loss of preexcitation during follow-up.9

Results

Between February 1980 and October 1988, 87 consecutive asymptomatic patients with the WPW pattern were enrolled in the study. After excluding nine patients with intermittent preexcitation and three patients who underwent surgical ablation, 75 patients remained in this study. Patient ages at the time of enrollment ranged from 7 to 77 years (mean, 34±13), and there were 44 male and 31 female patients. Five patients had associated cardiac disease (one coronary artery disease, two cardiomyopathy, one valvular heart disease, and one Ebstein's anomaly of the tricuspid valve).

No patient was lost to follow-up. The total follow-up time was 348 patient-years, and median follow-up was 4.3 years (range, 1–9 years).

Electrophysiology Testing

The results of electrophysiology testing are summarized in Table 1, and accessory pathway location is shown in Table 2. The median effective refractory
Table 1. Electrophysiology Findings in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterograde ERP AP</td>
<td>72</td>
<td>293</td>
<td>280–310</td>
</tr>
<tr>
<td>SCL 1:1 AP</td>
<td>60</td>
<td>300</td>
<td>255–360</td>
</tr>
<tr>
<td>Retrograde ERP AP*</td>
<td>45</td>
<td>288</td>
<td>240–320</td>
</tr>
<tr>
<td>SRR</td>
<td>72</td>
<td>274</td>
<td>240–325</td>
</tr>
<tr>
<td>ARR</td>
<td>72</td>
<td>408</td>
<td>370–451</td>
</tr>
</tbody>
</table>

*Patients with absent retrograde accessory pathway conduction excluded.

ERP, effective refractory period; AP, accessory pathway; SCL 1:1, shortest cycle length with 1:1 anterograde conduction; SRR, shortest RR interval between preexcited beats during atrial fibrillation; ARR, mean ventricular interval during atrial fibrillation.

The period of the accessory pathway was 293 msec (interquartile range, 280–310 msec), and the median SRR was 274 msec (interquartile range, 240–325 msec). Twenty-three patients had an SRR of 250 or less, and eight patients had an SRR of 200 msec or less (Figure 1). There was no significant relation between age and either accessory pathway refractory period or SRR values.

Sustained reciprocating tachycardia was induced in 12 patients (16%), and nonsustained reciprocating tachycardia was induced in 10 patients (13%). Single or multiple atrial echocardiographic beats were induced in 43 patients (57%). In 20 patients, retrograde conduction over an accessory pathway was considered to be absent, either because there was no ventriculoatrial conduction or because ventriculoatrial conduction was clearly decremental without orthodromic atrial echocardiographic cycles at any time. Patients with demonstrable retrograde conduction over an accessory pathway were considered to have an intact orthodromic tachycardia circuit irrespective of the inducibility of tachycardia at electrophysiology testing. By this definition, 55 patients had an intact orthodromic tachycardia circuit. Patients with an intact orthodromic tachycardia circuit had shorter SRR values than did patients without an intact orthodromic tachycardia circuit (median, 270 msec compared with 285 msec; p=0.04) and tended to have inducible atrial fibrillation more frequently (median, 37% compared with 15%; p=0.08).

Overall, sustained atrial fibrillation was induced in 23 patients (31%). Compared with the patients without sustained atrial fibrillation, those with sustained atrial fibrillation had shorter SRR values (median, 255 compared with 279 msec; p=0.01) and shorter accessory pathway effective refractory periods (median, 287 compared with 300 msec; p=0.01), but they did not have different atrial effective refractory periods (median, 200 compared with 200 msec; p=0.8) or age (mean, 30 compared with 34 years; t=1.3, p=0.20).

Clinical Outcome

Mortality. Three patients died, one of lung carcinoma, one of chronic lung disease, and one of head injuries received as a passenger in a motor vehicle accident. Arrhythmias were not a contributing factor in death in any of these patients. One patient died suddenly after initial consultation but before electrophysiology testing could be performed. Autopsy did not reveal a cause for death, and the mode of death was presumed to be a cardiac arrhythmia. Because electrophysiology study was not performed, this patient was not included in the study.

Operative intervention. Two patients underwent surgical ablation of their accessory pathways after recurrent symptomatic supraventricular tachycardia.

Development of arrhythmias. During the course of the study, six patients became symptomatic with either reciprocating tachycardia (five patients) or atrial fibrillation (one patient). Electrophysiology findings in these patients are shown in Table 3, and the probability of remaining arrhythmia free for the study group is shown in Figure 2.

All patients who lacked an intact orthodromic tachycardia circuit remained asymptomatic. The probability of remaining arrhythmia free for the patients with and without an intact orthodromic tachycardia circuit is shown in Figure 3. Despite an absence of events in the group without an intact orthodromic circuit, the difference between the groups was not significant (p=0.1). The presence of nonsustained or sustained reciprocating tachycardia at electrophysiology study did not differentiate patients who remained asymptomatic from those who became symptomatic (Figure 4). Only one patient developed clinical atrial fibrillation despite the induction of sustained atrial fibrillation in 23 patients at electrophysiology testing.
Table 3. Electrophysiology Findings and Clinical Arrhythmias in the Six Patients Who Became Symptomatic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical arrhythmia</th>
<th>EP finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>RT</td>
</tr>
<tr>
<td>2</td>
<td>RT</td>
<td>RT</td>
</tr>
<tr>
<td>3</td>
<td>RT</td>
<td>Nonsustained RT*</td>
</tr>
<tr>
<td>4</td>
<td>RT</td>
<td>Atrial echo†</td>
</tr>
<tr>
<td>5</td>
<td>RT</td>
<td>No RT or atrial echo beats</td>
</tr>
<tr>
<td>6</td>
<td>AF</td>
<td>AF repeatedly induced by catheter placement and single APC Unable to test for RT</td>
</tr>
</tbody>
</table>

*Tachycardia terminated spontaneously with block in the accessory pathway.
†Atrial echocardiographic cycles blocked in the atroventricular node.
EP, electrophysiology; study; RT, reciprocating tachycardia; AF, atrial fibrillation; APC, atrial premature complex.

Antiarrhythmic medication was prescribed in eight patients. Three asymptomatic patients required β-adrenergic blocking agents for hypertension or symptomatic sinus tachycardia, two asymptomatic patients were treated with class I antiarrhythmic medication for ventricular ectopic beats, and three patients who became symptomatic were treated with class I agents for control of symptomatic supraventricular tachycardia.

Follow-up electrocardiograms were available in 63 patients for a total follow-up time of 232 patient-years (median, 3.6 years) (Figure 5). In nine patients, the WPW pattern disappeared (14%). Age at enrollment (relative risk/decade, 1.4; 95% confidence interval, 1.0–1.8; p=0.03) and antegrade accessory pathway refractory period (relative risk, 1.06/10 msec; 95% confidence interval, 1.0–1.12; p=0.04) were identified as significantly independent predictors of loss of preexcitation in the Cox proportional hazards model. The SRR had borderline significance when assessed alone (relative risk/10 msec, 1.04; 95% confidence interval, 1.0–1.08; p=0.07) and was not significant (p=0.17) when entered into the model with the other variables because of the strong linear correlation between SRR and antegrade accessory pathway refractory period (r=0.76, p<0.001). In one patient, loss of preexcitation coincided with the deve-
opment of clinical reciprocating tachycardia, and retrograde conduction over the accessory pathway was demonstrated at repeated electrophysiology study.

**Discussion**

Sudden death may be the first manifestation of the Wolff-Parkinson-White syndrome, but this is likely to be a rare event according to previous studies of the natural history of the WPW syndrome. Thus, use of electrophysiological criteria to screen asymptomatic patients is associated with serious obstacles owing to the low incidence of adverse events and the relatively poor positive predictive value for positive results. This study confirms the generally good prognosis of asymptomatic patients with the WPW pattern. Only 8% of the patients developed symptoms during a median follow-up of 4.3 years, resulting in an incidence of onset of arrhythmic events of 1.7/100 patient-years. In the minority of patients (27%) who lacked an intact orthodromic tachycardia circuit, electrophysiology testing was of significant benefit because it demonstrated that subsequent symptom development was unlikely. The converse, however, was not true. Fifty-five patients had an intact orthodromic tachycardia circuit, of whom only six became symptomatic. Thus, an intact orthodromic circuit did not reliably predict the development of clinical arrhythmias during follow-up.

There were no clinical or electrophysiological properties that clearly identified patients who subsequently became symptomatic with supraventricular tachycardia. However, in one patient, onset of tachycardia coincided with loss of preexcitation. This suggests that changes in anterograde accessory pathway conduction relative to atrioventricular nodal conduction may be important in the development of clinical tachycardia.

Over the relatively short follow-up period, no patient in this study died suddenly. This confirms the findings of earlier studies indicating a very low incidence of sudden death in asymptomatic or mildly symptomatic patients. Because no arrhythmic deaths occurred, the findings of SRR values of 250 msec or less in 31% and of 200 msec or less in 11% of the patients were nonspecific. Because patients resuscitated from sudden cardiac arrest usually have inducible reciprocating tachycardia, as well as rapid ventricular rates during atrial fibrillation, it is likely that only patients with both these findings are at significant, though small, risk of sudden death. Thus, the finding of an SRR of 250 msec or less in patients without a substrate for orthodromic reciprocating tachycardia may be of less significance, and screening of asymptomatic patients by merely inducing atrial fibrillation may be potentially misleading.

In Figure 6, the frequency distribution of the SRR values in this cohort is compared with the frequency distribution of the SRR values in the patients who experienced ventricular fibrillation reported by Klein et al in 1979. Clearly, these populations are significantly different, but unfortunately, a large overlap occurs that includes a substantial number of patients in both populations. This demonstrates the difficulty in relying on a single parameter, such as SRR values, to determine prognosis and to guide therapy.

Nine patients in this study lost preexcitation during follow-up. Preexcitation was lost earlier in patients with poor antegrade accessory pathway conduction and advanced age. This suggests that spontaneous resolution of antegrade conduction over the accessory pathway is less likely to occur in patients considered at high risk of sudden death because of short accessory pathway refractory periods and SRR values.

**Limitations and Clinical Implications**

This study has a limited ability to detect very low rates of sudden death owing to the relatively short
follow-up. Using the method proposed by Hanley and Lippman-Hand\textsuperscript{15} for interpreting zero numerators, we found that the 95% confidence interval for the risk of sudden death ranges from 0% to 4% of the study population during the median 4.3-year follow-up. Furthermore, some patients required intervention, which may have reduced the specificity of the electrophysiology findings. Nonetheless, the low rate of events in this study argues against routine use of electrophysiology testing as a screening procedure. Electrophysiology testing may be indicated in selected asymptomatic individuals who find even a small risk of arrhythmias unacceptable.

Acknowledgments

We thank Sheila Doan for preparation of the manuscript and the Health Care Research Unit, UWO, for assistance with the statistical analysis.

References


Key Words • Wolff-Parkinson-White syndrome • atrial fibrillation • electrophysiology testing
Prognostic value of electrophysiology testing in asymptomatic patients with Wolff-Parkinson-White pattern.
J W Leitch, G J Klein, R Yee and C Murdock

Circulation. 1990;82:1718-1723
doi: 10.1161/01.CIR.82.5.1718

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/5/1718