

## Impact of Clinical History and Electrophysiologic Characterization of Accessory Pathways on Management Strategies to Reduce Sudden Death Among Children With Wolff-Parkinson-White Syndrome

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**Objectives.** This study sought to determine whether the clinical and electrophysiologic criteria developed in adults also identify children with Wolff-Parkinson-White syndrome at risk for sudden death.

**Background.** In adults with Wolff-Parkinson-White syndrome, a shortest RR interval <220 ms during atrial fibrillation is a sensitive marker for sudden death. However, because reliance on the shortest RR interval has a low positive predictive value, the clinical history has assumed a pivotal role in assessing risk. This approach has not been evaluated in children.

**Methods.** We retrospectively evaluated 60 children  $\leq 18$  years old who underwent comprehensive electrophysiologic evaluation between 1979 and 1989 before undergoing operation for Wolff-Parkinson-White syndrome. Clinical and electrophysiologic data were analyzed after patients had been grouped by their clinical presentation: high risk (cardiac arrest), intermediate risk (syncope or atrial fibrillation) or low risk (orthodromic reciprocating tachycardia alone).

**Results.** Ten children had a clinical cardiac arrest (high risk);

only one had a prior history of syncope or atrial fibrillation. Compared with the intermediate ( $n = 19$ ) and low risk groups ( $n = 31$ ), there were no differences in age ([mean  $\pm$  SD]  $14.8 \pm 0.6$  vs.  $14.7 \pm 0.6$  vs.  $14.5 \pm 1.7$  years), duration of symptoms ( $1.9 \pm 0.5$  vs.  $4.1 \pm 1.1$  vs.  $5.2 \pm 0.8$  years), incidence of congenital heart disease (30% vs. 26% vs. 32%), presence of multiple pathways (28% vs. 16% vs. 16%) or accessory pathway location. A shortest pre-excited RR interval <220 ms was found in 7 of 7 high risk patients (sensitivity 100%), 14 of 19 intermediate risk patients and 11 of 31 low risk patients (prevalence 35%).

**Conclusions.** Cardiac arrest was the only distinguishing clinical feature between high and low risk groups and the first manifestation in 80% of the children of an accessory pathway that can precipitate a life-threatening arrhythmia. In this series, the largest reported to date of children with Wolff-Parkinson-White syndrome having a cardiac arrest, a shortest pre-excited RR interval <220 ms was more sensitive than clinical history for identifying those at risk for sudden death.

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Wolff-Parkinson-White syndrome is a common cause of symptomatic arrhythmias in children (1). Orthodromic supraventricular tachycardia is the most frequent arrhythmia producing symptoms but is generally benign in otherwise healthy children. Atrial fibrillation with rapid anterograde conduction over an accessory pathway is less common but may be a catastrophic event leading to sudden death (2,3). Reduction in the incidence of sudden death in children with Wolff-Parkinson-White syndrome requires accurate identification of those at risk for life-threatening ventricular rates during atrial fibrillation.

In adults with Wolff-Parkinson-White syndrome, virtually all patients experiencing ventricular fibrillation have inducible atrial fibrillation with a shortest pre-excited RR interval <220 ms (2,3). Unfortunately, the positive predictive value of

a shortest pre-excited RR interval <220 ms in adults is only 19% to 38% (2,3), a finding that reduces clinical enthusiasm for interventions in individual patients believed to be potentially at risk but who have not yet had a cardiac arrest. Consequently, management strategies in adults are influenced, at least in part, by clinical history. There is a consensus that patients experiencing a clinical cardiac arrest are at high risk for a recurrence. Syncope or spontaneous atrial fibrillation with a rapid ventricular rate is regarded as a warning arrhythmia. Adults with only paroxysmal palpitations or documented orthodromic supraventricular tachycardia, or both, are generally regarded as having a benign condition.

Assessing the risk of sudden death in children with Wolff-Parkinson-White syndrome has been hampered by limited data characterizing the clinical profile of those who have experienced life-threatening arrhythmias. The natural history of Wolff-Parkinson-White syndrome in children is poorly defined. A paucity in the number of natural history studies in infants and children is further limited by short follow-up, small sample size and selection bias (4-6). Despite the disturbing prospect of sudden death in children with Wolff-Parkinson-

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White syndrome, no guidelines have been endorsed for its prevention.

Over a 10-year period, 62 children with Wolff-Parkinson-White syndrome were referred for surgical division of an accessory pathway. Among them were a disproportionate number who survived a clinical cardiac arrest before referral. Virtually all underwent comprehensive electrophysiologic procedures as a part of their preoperative evaluation. To our knowledge, this group includes the largest number of children with Wolff-Parkinson-White syndrome reported who have experienced a near-sudden-death episode, affording a unique opportunity to characterize the clinical and electrophysiologic profile in this subgroup. Accordingly, the purpose of this study was to determine the extent to which the clinical and electrophysiologic criteria developed in and applied to adults would successfully identify children with Wolff-Parkinson-White syndrome at risk for sudden death.

### Methods

**Patients.** The records of 91 children  $\leq 18$  years of age undergoing arrhythmia surgery at Washington University between 1984 and 1989, as well as those operated on by one of the authors (J.L.C.) while at Duke University from 1979 to 1984, were reviewed. Sixty-two children had manifest pre-excitation on a 12-lead electrocardiogram (ECG) and were included in the initial analysis. Two patients with ventricular pre-excitation were excluded from further analysis because the accessory pathways were divided concurrently with congenital heart surgery. Neither child had symptoms of an arrhythmia. The remaining 60 patients form the basis of this study.

**Preoperative electrophysiologic evaluation.** A comprehensive preoperative electrophysiologic study was performed in each patient as described previously (7). Induction of atrial fibrillation for measurement of the shortest RR interval between pre-excited QRS complexes was attempted by burst atrial pacing in 58 patients. This was deferred in two patients because of ECG documentation of atrial fibrillation immediately precipitating ventricular fibrillation. Anterograde effective refractory periods of the bypass tract and shortest RR interval during atrial burst pacing were determined as well. The electrophysiologic studies were performed without isoproterenol and, with one exception, in the absence of antiarrhythmic drugs. One patient was studied during treatment with amiodarone because of recurrent ventricular fibrillation.

Patients were assigned an electrophysiologic risk for sudden death based on the shortest RR interval between pre-excited QRS complexes measured during induced atrial fibrillation. Those in whom either atrial fibrillation was noninducible or the shortest RR interval was  $>220$  ms were assigned to a low risk group. A shortest RR interval between pre-excited QRS complexes  $<220$  ms classified a patient as high risk.

**Clinical classification.** Patients were stratified as follows: *Group I (high risk)* = documented ventricular fibrillation or asystole; *Group II (intermediate risk)* = syncope or spontaneous atrial fibrillation/flutter with rapid anterograde conduc-

**Table 1.** Patient Profile According to Clinical Risk for Sudden Death

Clinical Risk	Age (yr) (p = 0.97)	Symptom Duration (yr) (p = 0.019)	Congenital Heart Disease (p = 0.78)
Group I (n = 10)			
Mean $\pm$ SD	14.8 $\pm$ 0.6	1.9 $\pm$ 0.5	n = 3 (30%)
Range	0-18	0-12	
Group II (n = 19)			
Mean $\pm$ SD	14.7 $\pm$ 0.6	4.1 $\pm$ 1.1	n = 5 (26%)
Range	13-18	1-16	
Group III (n = 31)			
Mean $\pm$ SD	14.5 $\pm$ 1.7	5.2 $\pm$ 0.8	n = 10 (32%)
Range	11-17	0-14	

Group I = high risk; Group II = intermediate risk; Group III = low risk.

tion; *Group III (low risk)* = orthodromic supraventricular tachycardia but no history of syncope or atrial fibrillation.

The three clinical groups were compared for differences in age, duration of symptoms, congenital heart disease, presence of multiple pathways, pathway location, shortest RR interval during atrial fibrillation and during atrial burst pacing and the anterograde accessory connection effective refractory period. The sensitivity of the shortest RR interval was calculated for Group I, as was the frequency of a shortest RR interval  $<220$  ms in Groups II and III.

**Statistics.** Continuous variables were reported as mean value  $\pm$  SD for each clinical group and compared by analysis of variance (ANOVA) and Tukey's multiple comparison test if the variances were equal. The exception was for comparison of the shortest pre-excited RR interval during atrial fibrillation, where the variances among clinical groups were unequal. In that case, the Kruskal-Wallis one-way ANOVA was utilized, and multiple comparisons performed with Dunn's correction. Discrete variables were compared by chi-square analysis. Significance refers to a value of  $p < 0.05$ .

### Results

**Clinical profile.** Ten children were judged to be at high risk for sudden death because of documented ventricular fibrillation or asystole (Group I). Nineteen were classified at intermediate risk because of a history of syncope or spontaneous atrial fibrillation with rapid anterograde conduction (Group II). The remaining 31 children were assessed as having low risk for sudden death because none had experienced syncope, and their only documented arrhythmia was orthodromic supraventricular tachycardia. No patient had clinical atrial fibrillation with a slow ventricular response. There were no significant differences among groups according to age at the time of surgery, duration of symptoms, or presence of congenital heart disease (Table 1). Of the 18 patients with congenital heart disease, 5 had Ebstein's anomaly, 5 had cardiomyopathy, and 4 had mitral valve prolapse.

**Electrophysiologic profile.** Complete electrophysiologic testing was performed in 58 of the 60 patients (Table 2). Atrial

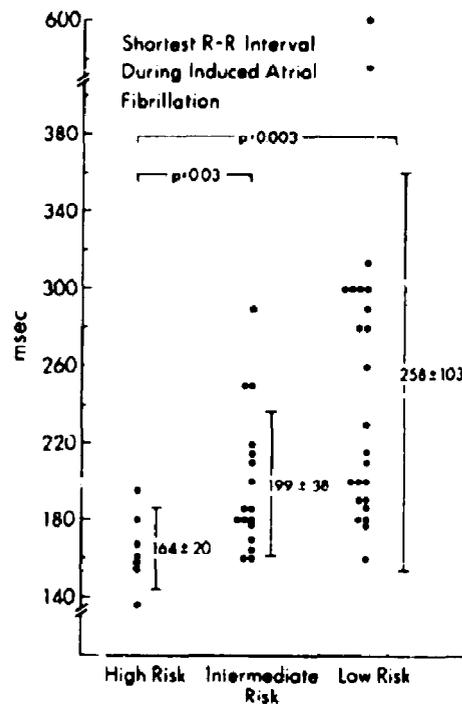
**Table 2. Anterograde Conduction of Accessory Pathways During Attempted Induced Atrial Fibrillation\***

Clinical Risk	SRRI < 220 ms	SRRI ≥ 220 ms	NA
Group I	7	0	3
Group II	14	3	2
Group III	11	10	10

\*Induction of atrial fibrillation was not attempted in 2 of 10 patients in Group I because of prior hemodynamic collapse. A third patient was taking amiodarone at the time of electrophysiologic study because of prior cardiac arrest and consequently did not have inducible atrial fibrillation. There were 12 patients in Groups II and III in whom atrial fibrillation either could not be induced or in whom the QRS configuration was narrow during atrial fibrillation. All patients in Groups II and III were studied in a drug-free state. NA = not applicable; SRRI = shortest pre-excited RR interval during atrial fibrillation; other abbreviations as in Table 1.

fibrillation was induced in 7 of 10 Group I patients. Of the remaining three patients, one was on amiodarone at the time of the electrophysiology study, and induction of atrial fibrillation was not attempted in two patients because of previous hemodynamic collapse. Seventeen of the 19 Group II patients (89%) and 22 of the 31 Group III patients (66%) were inducible into atrial fibrillation, during which they exhibited ventricular pre-excitation. One patient in Group II and two patients in Group III had only a narrow QRS response during atrial fibrillation. All patients with clinical ventricular fibrillation or asystole (Group I) in whom atrial fibrillation was induced had a shortest RR interval < 220 ms (Fig. 1). Among the 17 patients in Group II with inducible atrial fibrillation, a shortest RR interval < 220 ms was present in 14 (74% of the total). In the group of patients classified at low risk (Group III), 11 had a shortest RR interval < 220 ms. Thus, in the patients judged clinically to be at low risk for sudden death (Group III), electrophysiologic evidence of risk for a life-threatening arrhythmia was observed in 35% of the total group and in 50% of those in whom atrial fibrillation was induced. One patient in this group experienced hemodynamic collapse at the time of the electrophysiology study when atrial fibrillation was induced, and direct current cardioversion was necessary. In each of the eight patients in this group in whom atrial fibrillation could not be induced, the effective refractory period of the accessory pathway was > 260 ms.

The mean shortest RR interval during atrial fibrillation in Group I was significantly shorter than the mean value calculated for Group II patients,  $164 \pm 20$  versus  $199 \pm 38$  ms ( $p = 0.03$ ) and for Group III,  $258 \pm 103$  ( $p = 0.003$ ). Mean values of other measures of accessory pathway conduction were not significantly different among the clinical risk groups (Table 3). The anterograde accessory connection effective refractory period was  $256 \pm 58$  ms in Group I versus  $272 \pm 83$  ms in Group II and  $293 \pm 65$  ms in group III ( $p = 0.4$ ). In Group I, the shortest pre-excited RR interval during atrial burst pacing was  $283 \pm 51$  ms compared with  $324 \pm 110$  ms for Group II and  $313 \pm 85$  ms for Group III ( $p = 0.6$ ). No differences were found among the groups for the presence of multiple pathways or pathway location.



**Figure 1.** Shortest pre-excited RR intervals during induced atrial fibrillation plotted as a function of each patient's clinical risk for sudden death.

**Sudden death.** The clinical features of the 10 children with documented clinical ventricular fibrillation are summarized in Table 4. Six had a resultant encephalopathy; three had permanent sequelae. In three others, atrial fibrillation deteriorated to ventricular fibrillation after the patient reached the hospital, where prompt defibrillation almost certainly prevented neurologic injury. Ventricular fibrillation was the first manifestation of Wolff-Parkinson-White syndrome in two patients. Seven patients had a 6-month to 4-year history of palpitations or known orthodromic supraventricular tachycardia, but only one had a prior history of syncope. None had subjective or objective evidence of atrial fibrillation.

## Discussion

**Risk of sudden death.** Sudden death is the most serious consequence for any patient, child or adult, with Wolff-Parkinson-White syndrome. In the surgical era of definitive treatment for Wolff-Parkinson-White syndrome, the generally conservative approach to children was based on two assumptions: 1) Sudden death in patients with Wolff-Parkinson-White syndrome is rare. 2) Children at risk for sudden death will have a warning event such as syncope, presyncope or atrial fibrillation before cardiac arrest.

The incidence of sudden death in children with Wolff-Parkinson-White syndrome is unknown. In the prospective analysis of a mostly adult population by Munger et al. (8),

**Table 3. Electrophysiologic Profile According to Clinical Risk for Sudden Death**

Clinical Risk	Multiple Pathways (p = 0.95)	Pathway Location (p = 0.15)			SRR1 (p = 0.001) (mean ± SD and range)	ACERP (p = 0.4) (mean ± SD)	A Burst (p = 0.6) (mean ± SD)
		Right	Septal	Left			
Group I	2/10 (20%)	1	6	6	164 ± 20 132-195 n = 7	256 ± 58	283 ± 51
Group II	2/19 (16%)	4	5	15	199 ± 38 160-250* n = 17	272 ± 83	324 ± 110
Group III	5/31 (16%)	11	8	16	258 ± 102 190-600† n = 21	293 ± 65	313 ± 85

\*p = 0.03, †p = 0.003 versus Group I. Atrial fibrillation could not be induced in 2 patients in Group II and in 10 patients in Group III. A Burst = shortest pre-excited RR interval during atrial burst pacing; ACERP = anterograde accessory connection effective refractory period; SRR1 = shortest pre-excited RR interval during induced atrial fibrillation (excludes three patients in Group I in whom induction of atrial fibrillation was either not attempted or was elicited during antiarrhythmic treatment; see text for details); other abbreviations as in Table 1.

there were no deaths among 53 asymptomatic patients with Wolff-Parkinson-White syndrome. However, among the 60 patients with symptoms of palpitations, two patients (3.5%) aged 23 and 32 years died suddenly. Flensted-Jensen (9) reported 2 sudden deaths among 47 symptomatic patients (4%) followed for 23 to 34 years. Therefore, even if there were no sudden deaths in childhood, the lifetime incidence of sudden death in a symptomatic child with Wolff-Parkinson-White syndrome appears to be in the range of 3% to 4% (8-10). If older age selects for those at lower risk for sudden death, and because most natural history studies draw on largely adult populations, the lifetime incidence of sudden death for children may potentially be substantially underestimated.

A second assumption that influenced management strategies in the surgical era was that most children at risk would have a warning event before cardiac arrest. However, a recent multicenter study indicated that no prior rhythm had been documented in 48% of the children who had Wolff-Parkinson-White syndrome and a cardiac arrest (11). This assumption also was not supported by the data acquired in this study. Only

1 of the 10 children in Group I had a history of syncope, and an infant in the intensive care unit had atrial fibrillation before cardiac arrest. Ventricular fibrillation was the first manifestation of Wolff-Parkinson-White syndrome in two patients. The other six children in Group I had only symptoms or documentation of orthodromic supraventricular tachycardia. Even if all of the patients in Group II would eventually have experienced a sudden death episode if not for surgery (n = 19), the sensitivity of the clinical history for sudden death was only 72% (2/10 in Group I plus 19/19 in Group II). The sensitivity would be even lower (67%) if the patients in Group II who either had a long shortest RR interval or did not have inducible atrial fibrillation during electrophysiology study were excluded. Other clinical descriptors such as age, duration of symptoms or coexisting congenital heart disease were similar among the three patient groups.

**Sensitivity and predictive value of electrophysiologic testing.** Electrophysiologic testing has been evaluated as a method to stratify risk of sudden death in patients with Wolff-Parkinson-White syndrome. On the basis of data acquired from adults, measurement of the shortest pre-excited RR interval is a sensitive approach for distinguishing a group of patients with a history of near sudden death (2,3). The sensitivity of this approach in children was confirmed by our study. All of the Group I patients with a prior cardiac arrest who were tested in a drug-free state were inducible into atrial fibrillation and had a shortest RR interval <220 ms (sensitivity 100%). Estimating the predictive value of inducible atrial fibrillation and a shortest RR interval <220 ms is difficult because the natural history of the disease in the children studied was altered by operation. However, if we assume that all patients with spontaneous atrial fibrillation or syncope would eventually experience a cardiac arrest, the positive predictive value of a shortest RR interval <220 ms was 68% (7 of 7 in Group I plus 14 of 14 in Group II plus 3 of 10 in Group III).

One-third of the children in the ostensibly low risk group

**Table 4. Clinical Profile of Children With Wolff-Parkinson-White Syndrome Experiencing Cardiac Arrest**

Age (yr)	SVT		CNS Sequela
	Duration (yr)	Previous Syncope	
18	0	No	Hypoxic encephalopathy
15	4	No	Hypoxic encephalopathy
18	2	No	Recent memory loss
16	0	No	Hypoxic encephalopathy, transient
14	1	No	Hypoxic encephalopathy, transient
14	3	No	Hypoxic encephalopathy, transient
01	01	Yes	Died; failed to wean from bypass
17	3	No	None; arrest in hospital
18	3	No	None; arrest in hospital
17	3	Yes	None; arrest in hospital

CNS = central nervous system; SVT = supraventricular tachycardia.

had an electrophysiologic substrate characteristic of patients who have survived sudden death (i.e., inducible atrial fibrillation and a shortest RR interval < 220 ms). The only indication for electrophysiologic study in this low risk group was impending operation for orthodromic tachycardia. The data acquired are not sufficient to determine whether these Group III patients are correctly classified in a low risk group on the basis of their clinical profile or whether they are at high risk for a future catastrophic event on the basis of shortest RR interval. One child required cardioversion during the study when induced atrial fibrillation and a rapid ventricular response led to hemodynamic instability. Moreover, had the Group I patients been studied and undergone surgical division for orthodromic tachycardia before their cardiac arrest, 8 of 10 of their electrophysiologic study results would have been classified as false positive.

**Evolving indications for definitive treatment.** The risk of death or permanent neurologic sequelae reinforces the need to develop and evolve definitive management strategies in children with Wolff-Parkinson-White syndrome. We believe the data acquired from this study support the concept that children with Wolff-Parkinson-White syndrome should be treated more aggressively, even though, on the basis of studies in adults, most will never have a life-threatening event (8-10). The decision to proceed prophylactically with definitive treatment should be determined by the balance of risks and benefits. In the past, when surgery offered the only curative option, there was a reluctance to recommend intervention because of the attendant morbidity, mortality and cost. Radiofrequency catheter ablation has become the definitive treatment of choice for patients with Wolff-Parkinson-White syndrome. Successful ablation can be achieved in 90% of patients, with virtually no morbidity and at substantially less cost than operation (12,13). Multiple centers have demonstrated that the procedure can be safely performed in children (14-16).

**Risk stratification.** The sequelae of a "missed" sudden death are devastating. In this study, electrophysiologic testing would have excluded two-thirds of the low and intermediate risk patients, either because atrial fibrillation could not be induced or because the shortest RR interval exceeded 220 ms. Because the best available data indicate a lifetime risk for sudden death of ~4% among symptomatic patients (8-10), excluding the two-thirds of this group who lack the electrophysiologic substrate increases the risk among those remaining patients to 12%.

Several noninvasive measures have been described for ascertaining the antegrade conduction properties of the bypass tract in patients with Wolff-Parkinson-White syndrome. These include exercise testing (17), procainamide infusion (18) and transesophageal pacing (19). Our results indicate that the variables most readily measured by transesophageal pacing, the antegrade accessory connection effective refractory period and the shortest pre-excited RR interval during atrial burst pacing, do not readily distinguish those patients at risk for sudden death. The sensitivity of a procainamide infusion has also been questioned (20). Therefore, at our institution, if

we cannot exclude the risk of sudden death by exercise testing, we recommend an intracardiac electrophysiologic study in children >12 years of age. For those who exhibit a shortest RR interval <220 ms, we advocate radiofrequency catheter ablation because our analysis suggests that those patients may face a lifetime risk of ventricular fibrillation as high as 12%. The attendant risk of neurologic injury or death seems unacceptable when compared with the 2% incidence of serious morbidity or mortality associated with radiofrequency catheter ablation (12-16). In the absence of a warning event, we use 12 years of age as the cutoff for evaluation. Sudden death appears to be a rare event in younger children. With the exception of the infant with an underlying cardiomyopathy, the youngest child in this study to have a cardiac arrest was 14 years old.

It should be emphasized that our results support this approach only in symptomatic patients with manifest pre-excitation. Studies of adults with only electrocardiographic evidence of Wolff-Parkinson-White syndrome and no symptoms have demonstrated that the risk of sudden death is low (8,21-23). Although the follow-up in these studies was relatively short, and one 30-year old man died suddenly while awaiting evaluation (23), taken together, they are reassuring that the prognosis is benign in asymptomatic adults. The triggering role of orthodromic supraventricular tachycardia in atrial fibrillation has been well described (24,25) and may explain the low incidence of sudden death in asymptomatic patients.

We recognize that even strict adherence to the management principles outlined will not entirely eliminate sudden death in Wolff-Parkinson-White syndrome. Ventricular fibrillation may be the first manifestation of Wolff-Parkinson-White syndrome as it was for two patients in this series. Furthermore, there are occasional reports in the literature of sudden death in very young children (26,27). On the other hand, radiofrequency ablation is not without potential risks, including myocardial infarction, aortic and atrioventricular valve injury (28), stroke (29) and death (16). Unanswered questions remain about the long-term effects of radiofrequency ablation, particularly in children (30).

**Study limitations.** The surgical nature of the study cohort skewed the sample toward those at high risk. Thus, inferences cannot be made from this study regarding the frequency of sudden death in children with Wolff-Parkinson-White syndrome or the predictive value of electrophysiologic testing in an unselected population. Patients seeking surgical treatment tend to have more frequent or prolonged episodes of orthodromic tachycardia, which may be a risk factor for sudden death. These issues could only be addressed in a large, unselected and untreated population that was screened with ECGs on entry into grade school and followed up for at least two to three decades. Such a study would be difficult to justify ethically in light of current treatment alternatives.

**Conclusions.** The present study reviews a 10-year experience of children with Wolff-Parkinson-White syndrome in whom a comprehensive electrophysiologic evaluation was routinely performed. The referral nature of this surgical cohort

resulted in a disproportionate number of children who survived a cardiac arrest, providing to our knowledge the largest clinical and electrophysiologic experience in this subset of patients with manifest pre-excitation. Our analysis suggests that electrophysiologic testing is more sensitive than the clinical history for identifying children with Wolff-Parkinson-White syndrome who are at risk for sudden death.

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