

ORIGINAL ARTICLE

Radiofrequency Ablation in Children with Asymptomatic Wolff–Parkinson–White Syndrome

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ABSTRACT

BACKGROUND

Ventricular fibrillation can be the presenting arrhythmia in children with asymptomatic Wolff–Parkinson–White syndrome. Deaths due to this arrhythmia are potentially preventable.

METHODS

We performed a randomized study in which prophylactic radiofrequency catheter ablation of accessory pathways was compared with no ablation in asymptomatic children (age range, 5 to 12 years) with the Wolff–Parkinson–White syndrome who were at high risk for arrhythmias. The primary end point was the occurrence of arrhythmic events during follow-up.

RESULTS

Of the 165 eligible children, 60 were determined to be at high risk for arrhythmias. After randomization, but before any ablation had been performed, the parents withdrew 13 children from the study. Of the remaining children, 20 underwent prophylactic ablation and 27 had no treatment. The characteristics of the two groups were similar. There were three ablation-related complications, one of which led to hospitalization. During follow-up, 1 child in the ablation group (5 percent) and 12 in the control group (44 percent) had arrhythmic events. Two children in the control group had ventricular fibrillation, and one died suddenly. The cumulative rate of arrhythmic events was lower among children at high risk who underwent ablation than among those at high risk who did not. The reduction in risk associated with ablation remained significant after adjustment in a Cox regression analysis. In both the ablation and the control groups, the independent predictors of arrhythmic events were the absence of prophylactic ablation and the presence of multiple accessory pathways.

CONCLUSIONS

In asymptomatic, high-risk children with the Wolff–Parkinson–White syndrome, prophylactic catheter ablation performed by an experienced operator reduces the risk of life-threatening arrhythmias.

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NATURAL-HISTORY STUDIES IN CHILDREN with the Wolff–Parkinson–White syndrome have been limited by short follow-up, small sample size, and selection bias.^{1–4} Although the incidence of sudden death in children with the Wolff–Parkinson–White is unclear,⁵ the lifetime incidence is estimated to be about 3 to 4 percent.^{6–8} Ventricular fibrillation can be the presenting arrhythmia, and the consequences of a “missed” sudden death in children are devastating.^{4,9–11} Recently, it was reported that high-risk, asymptomatic ventricular preexcitation is associated with a poor prognosis.¹² Prophylactic ablation improves outcome in high-risk adult patients,¹³ emphasizing the need to readdress guidelines in this setting.¹⁴ Accordingly, the goal of the current, randomized study was to evaluate whether prophylactic ablation of accessory pathways is of benefit in preventing arrhythmic events in asymptomatic children at high risk for arrhythmias.

METHODS

STUDY DESIGN

This study was conducted between January 1999 and January 2004. We recruited asymptomatic children, 5 to 12 years of age, who were found on routine medical examination to have ventricular preexcitation on 12-lead electrocardiography. Exclusion criteria were participation in other study protocols, concomitant disease, or congenital heart disease. Written informed consent was obtained from the children’s parents or guardians, and the hospital ethics committee approved the study design. Psychological counseling was uniformly performed one week before the procedure and one week after the procedure to reduce emotional stress.

ELECTROPHYSIOLOGICAL TESTING

The patients underwent electrophysiological testing after receiving propofol for anesthesia. Lead shielding was used to minimize radiation exposure to the pelvis. The electrophysiological-testing procedures have been described in detail previously.^{12,13} Diagnostic catheters were introduced through separate sheaths and positioned at the high right atrium, the bundle of His, the coronary sinus, and the right ventricular apex. Bilateral femoral venous access was used, with the ablation catheter inserted through a sheath in the right femoral vein or artery. Induction of atrial fibrillation was attempted with ramp pacing starting at a cycle length of 300 msec and decreasing to a minimum

of 100 msec over a period of 20 seconds; pacing was stopped once refractoriness had been attained or atrial fibrillation induced. Atrial fibrillation was considered abnormal if it lasted more than 30 seconds. Arrhythmias were considered sustained if they lasted more than one minute. Preexcited QRS morphology and the shortest RR interval between preexcited beats were determined during sustained atrial fibrillation, when inducible. Intravenous isoproterenol (1 to 4 μ g per minute) was used to facilitate induction of arrhythmias.

RISK STRATIFICATION AND RANDOMIZATION

Patients in whom atrioventricular reciprocating tachycardia or atrial fibrillation was reproducibly induced were considered to be at high risk and were randomly assigned to either radiofrequency ablation of accessory pathways (the ablation group) or no ablation (the control group). Patients in whom arrhythmias were not induced were considered to be at low risk. Randomization was performed by means of envelopes containing computer-generated numbers. No stratification was used. Because of the sensitive nature of the protocol, parents were given the opportunity to withdraw consent after randomization.

ABLATION THERAPY

After electrophysiological evaluation, a 6-French deflectable electrode catheter with a 4-mm tip was introduced by way of the femoral artery or vein, as previously described.¹³ Left-sided accessory pathways were ablated by the retrograde approach or by transseptal puncture. The ablation protocol included precautions to minimize damage to the normal conduction tissues. One precaution was the use of low-power “test” applications, set initially at 15 W for a maximum of five seconds. If preexcitation disappeared, a “therapeutic” application at a power of up to 40 W for 30 to 60 seconds with a temperature limit of up to 60°C was delivered. Another precaution was the use of expiratory apnea for up to 60 seconds during radiofrequency application to decrease the motion of the catheter tip in intubated patients. All the ablation procedures were performed by a single experienced operator. We diagnosed multiple pathways if any of the following were found: intermittent anterograde conduction through multiple pathways in sinus rhythm, preexcited atrial fibrillation with variable morphology and activation, or variable activation patterns during antidromic tachycardias.

The stimulation protocol was repeated after 30

minutes. Echocardiography was scheduled to be performed immediately after the procedure, at the time of hospital discharge, and seven days after discharge to rule out pericardial effusion or valvular damage. Major complications were defined as those that required treatment or prolonged hospitalization.

FOLLOW-UP EVALUATIONS

Follow-up evaluations were prespecified and included clinical examination, electrocardiography, echocardiography, and Holter monitoring at one, three, and six months; thereafter, the patients were seen annually or more often if symptoms or arrhythmias occurred. Parents were asked to report any symptoms they observed in their children. The primary end point was the occurrence of an arrhythmic event, including supraventricular tachycardia, atrial fibrillation, and ventricular fibrillation. To ensure uniformity in the ascertainment of the end point, events were reviewed by an independent, blinded committee.

STATISTICAL ANALYSIS

The sample size was determined according to the anticipated frequency of arrhythmic events. On the basis of our own experience, we predicted that the rate of arrhythmic events over a three-year observation period among the high-risk patients would be 60 percent and that ablation would result in a 95 percent reduction in the frequency of arrhythmic events. On this basis, we then predicted that 20 subjects per group would be required in order for the study to have 95 percent power to detect an absolute difference between the groups of 40 percent, with a two-sided alpha value of 0.05. To account for withdrawals, it was decided that a total of 60 subjects should be enrolled. We anticipated that enrollment and follow-up would take five years.

Continuous variables were compared by the Mann-Whitney U test. For categorical variables, Fisher's exact test and exact method were applied. Freedom from arrhythmic events was calculated by the Kaplan-Meier method, with the time to a first arrhythmic event as the outcome variable. The statistical significance of differences in outcomes between the two randomized groups was assessed by the log-rank test. Data were censored if a patient died, reached the end of the study period, or was lost to follow-up before any arrhythmic event had occurred. In addition, covariate-adjusted analysis of outcomes among the high-risk patients (both those who underwent ablation and those who did

not) was performed with use of a Cox proportional-hazards model. Covariates included in this analysis were age, sex, anterograde refractory period of accessory pathways before and after isoproterenol, presence of single or multiple accessory pathways, and type of inducible arrhythmia. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Statistical tests were performed with SPSS software, version 12.0.1.

RESULTS

PATIENTS

Of 172 screened children, 165 were eligible for the study and underwent diagnostic electrophysiological testing. One hundred five patients were determined to be at low risk for arrhythmias and entered the follow-up phase of the study. Sixty patients were determined to be at high risk for arrhythmias and were randomly assigned to either the ablation group or the control group (Fig. 1). Of these 60 patients, 13 (10 in the ablation group and 3 in the control group) were not included in the analyses because their parents withdrew consent after randomization; however, they remained under clinical observation. Thus, 20 patients in the ablation group and 27 in the control group completed the study protocol. No significant differences were found between these two groups (Table 1).

ELECTROPHYSIOLOGICAL TESTING AND ABLATION

In the ablation group of high-risk patients, all accessory pathways were successfully ablated via the retrograde approach except in one patient, in whom the transseptal approach was used because the accessory pathway was close to the left atrial appendage. The median number of radiofrequency applications was 4 (range, 3 to 7) in patients with a single pathway and 6 (range, 5 to 10) in those with multiple pathways. The mean fluoroscopy time was 12.3 ± 7.2 minutes for those with a single pathway and 20.1 ± 10.2 minutes for those with multiple pathways. Of the patients determined to be at low risk, only 17 percent had inducible nonsustained atrial fibrillation, which lasted from 5 to 20 seconds (Table 2).

COMPLICATIONS

Anesthesia-related complications occurred in 5 of the 165 eligible patients (3 percent). Transient respiratory arrest occurred in one patient during induction of anesthesia, and nausea and vomiting occurred in three others during recovery from an-

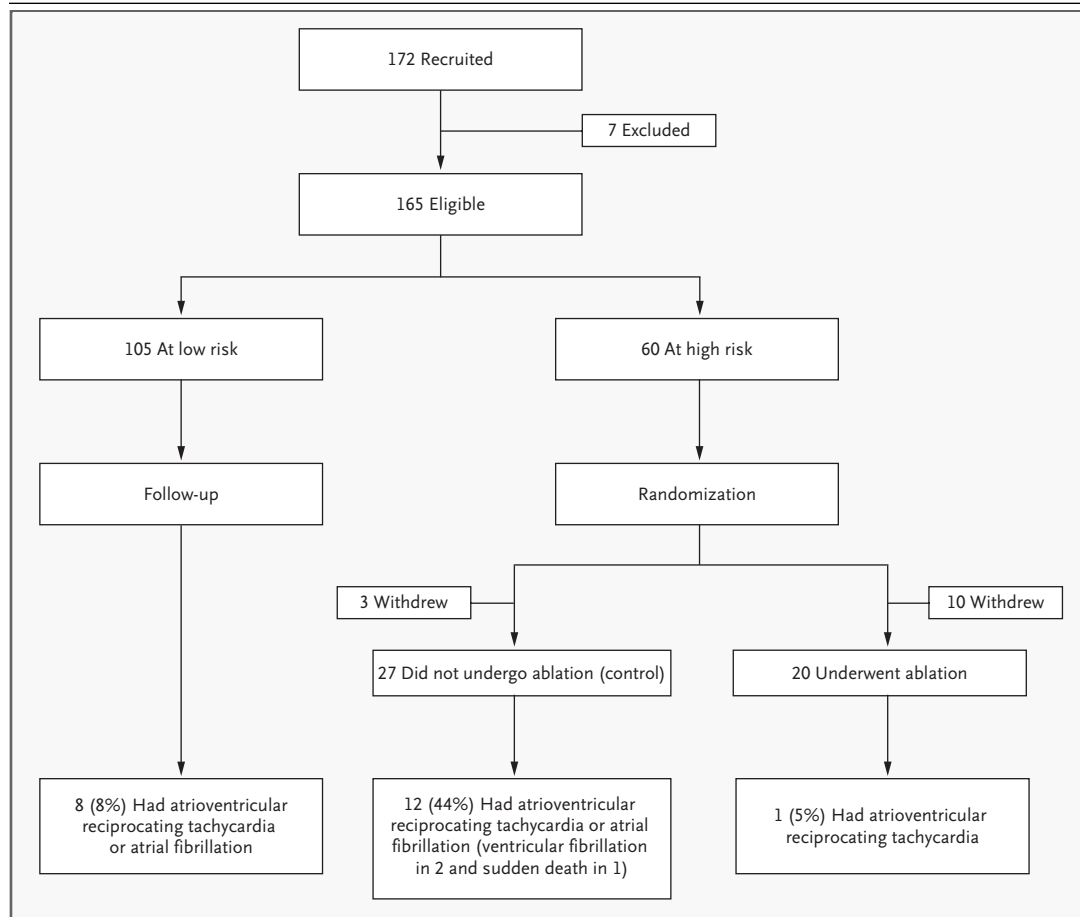


Figure 1. Study Protocol.

The number of children recruited for the study and assigned to a study group are shown. Seven children were excluded initially because their parents declined to have them participate (in four cases) or because their physician did not refer them to the study (in three cases).

esthesia. Postoperative respiratory depression developed in one patient but resolved within a few minutes. There were no septic complications. Complications related to electrophysiological testing occurred in 5 of the 165 patients (3 percent). Four of them had transient catheter-induced, first-degree atrioventricular block or right bundle-branch block (i.e., catheter bumping). One had femoral venous thrombosis, which was a major complication.

Three of the 20 patients who underwent ablation (15 percent) had complications related to the ablation procedure. Mobitz type II atrioventricular block and right bundle-branch block occurred in a patient who underwent ablation of a posteroseptal pathway but resolved within a few minutes. Permanent right bundle-branch block developed in

another patient, who had right free-wall and posteroseptal accessory pathways. A small, asymptomatic pericardial effusion requiring prolongation of hospitalization developed in a third patient, who had left and right free-wall pathways. Patients between 5 and 10 years of age had more complications related to cardiac catheterization than did older patients.

FOLLOW-UP

After ablation, patients were followed for a median of 34 months (range, 19 to 44). Serial echocardiograms showed no damage to the valvular apparatus. No patient had recurrence of ventricular preexcitation on electrocardiography. Twenty-one months after the ablation of two accessory path-

Table 1. Characteristics of the 47 Asymptomatic Children with the Wolff-Parkinson-White Syndrome Who Were at High Risk for Arrhythmias.*

Variable	Ablation Group (N=20)	Control Group (N=27)
Age (yr)		
Median	10	10
Interquartile range	10-12	10-12
Male sex (%)	41	59
Structural heart disease (%)	0	0
Anterograde refractory period of accessory pathways (msec)		
Before isoproterenol		
Median	240	240
Interquartile range	233-260	230-270
After isoproterenol		
Median	200	200
Interquartile range	200-220	200-210
Multiple accessory pathways (%)	25	22
Location of single accessory pathways (%) †		
Left free wall	53	57
Right free wall	33	33
Posteroseptal	13	5
Anteroseptal	0	5
Location of multiple accessory pathways (%) ‡		
Left free wall and posteroseptal	40	33
Left free wall and right free wall	40	33
Right free wall and posteroseptal	20	33
Induced arrhythmias (%)		
Nonsustained atrial fibrillation	0	7
Atrioventricular reciprocating tachycardia	65	74
Atrioventricular reciprocating tachycardia, triggering atrial fibrillation	35	19
Length of cycle in atrioventricular reciprocating tachycardia (msec) §		
Median	255	250
Interquartile range	230-299	230-265
Shortest preexcited RR interval during sustained atrial fibrillation (msec) ¶		
Median	230	230
Interquartile range	220-230	215-230
Hospital stay (days)		
Median	2	2
Range	2-5	2-5

* Because of rounding, not all percentages total 100. There were no significant differences between the groups.

† Data are from 15 children who underwent ablation and 21 controls.

‡ Data are from five children who underwent ablation and six controls.

§ Data are from 20 children who underwent ablation and 25 controls.

¶ Data are from seven children who underwent ablation and two controls.

Table 2. Characteristics of the 105 Asymptomatic Children with the Wolff–Parkinson–White Syndrome Who Were at Low Risk for Arrhythmias.

Variable	Value
Age (yr)	
Median	9
Interquartile range	7–11
Male sex (%)	61
Structural heart disease (%)	7
Anterograde refractory period of accessory pathways (msec)	
Before isoproterenol	
Median	280
Interquartile range	260–295
After isoproterenol (msec)	
Median	220
Interquartile range	210–230
Multiple accessory pathways (%)	7
Location of single accessory pathways (%)*	
Left free wall	58
Right free wall	19
Posteroseptal	21
Anteroseptal	2
Location of multiple accessory pathways (%)†	
Left free wall and posteroseptal	43
Left free wall and right free wall	43
Right free wall and posteroseptal	14
Induced arrhythmias (%)	
Nonsustained atrial fibrillation	17
Atrioventricular reciprocating tachycardia	0
Atrioventricular reciprocating tachycardia, triggering atrial fibrillation	0

* Data are from 98 patients.

† Data are from seven patients.

ways, an 11-year-old girl had an episode of supraventricular tachycardia due to an additional, concealed posteroseptal pathway.

In the control group of high-risk patients, the median duration of follow-up was 19 months (range, 8 to 58). None of the 27 patients in this group lost ventricular preexcitation on the electrocardiogram during follow-up. After a median follow-up of 19 months (range, 16 to 22), seven patients (26 percent; median age, 10 years), six of

whom were boys, had symptomatic arrhythmias, including supraventricular tachycardia leading to syncope (in one patient), presyncope (in four patients), and atrial fibrillation with rapid ventricular responses over accessory pathways, leading to presyncope (in two patients).

In five apparently asymptomatic patients in the control group, follow-up Holter monitoring documented silent episodes of sustained atrial fibrillation, which remained asymptomatic despite extremely rapid ventricular responses over accessory pathways. The parents of these children were consulted, but they declined radiofrequency ablation on the grounds that their children did not have symptoms. Subsequently, one of these children, who was 10 years old, died suddenly; the rhythm was not documented. Another presented with ventricular fibrillation, and another with absence-like episodes found to be due to atrial fibrillation resulting from preexcitation, which degenerated into ventricular fibrillation on one occasion. All three of the latter children had multiple pathways, inducible atrioventricular reciprocating tachycardia, and atrial fibrillation, and all three were boys. Accurate retrospective evaluation showed that loss of appetite, nausea, and tiredness were nonspecific symptoms that may have been associated with these arrhythmias. Overall, 12 of the 27 high-risk patients in the control group (44 percent) had life-threatening tachyarrhythmias, and 1 of these 12 patients died. Subsequently, the other 11 patients underwent ablation. In one, who had an anteroseptal accessory pathway, a permanent right bundle-branch block developed after radiofrequency application.

The 105 low-risk patients were followed for a median of 34 months (range, 8 to 60). None lost preexcitation during follow-up. Eight of these patients (8 percent; median age, eight years), six of whom were boys, had arrhythmic events leading to palpitations (supraventricular tachycardia in six patients and atrial fibrillation in two); all eight subsequently underwent successful ablation.

Figure 2 shows the cumulative rate of survival free of arrhythmic events among the high-risk patients, according to whether or not they were randomly assigned to undergo ablation. The benefit in terms of event-free survival associated with ablation remained significant after adjusted Cox regression analysis. The number of high-risk patients needed to treat to prevent arrhythmic events in one of these patients was 2.0 (95 percent confidence interval, 1.4 to 3.1). For all the high-risk patients, the

independent predictors of arrhythmic events were the absence of prophylactic ablation (hazard ratio, 69.4; 95 percent confidence interval, 5.1 to 950.0; $P=0.001$) and multiple accessory pathways (hazard ratio, 12.1; 95 percent confidence interval, 1.7 to 88.2; $P=0.01$). Patients in the control group who had single accessory pathways were more likely to be free of arrhythmias than those with multiple pathways (Fig. 3).

DISCUSSION

This study demonstrates that among children with asymptomatic Wolff-Parkinson-White syndrome who are at high risk for arrhythmias, the significant and durable benefits of prophylactic catheter ablation of all accessory pathways outweigh the procedural risks; many (44 percent) of the high-risk patients who did not undergo prophylactic ablation had arrhythmic events, including cardiac arrest or sudden death, during the first two years of follow-up. More than 90 percent of the low-risk patients remained asymptomatic during follow-up.

Radiofrequency catheter ablation has become the treatment of choice for children with symptomatic tachyarrhythmias.¹⁵⁻²¹ Ventricular fibrillation or sudden death has been reported in several large series of children without symptoms, and in a large proportion of the cases, ventricular fibrillation was the presenting arrhythmia.⁹⁻¹¹ Despite guideline recommendations to adopt a conservative approach, most pediatric cardiac electrophysiologists are currently performing invasive studies to stratify children with asymptomatic Wolff-Parkinson-White syndrome according to risk, selecting those for whom radiofrequency ablation is appropriate.²²

The current study demonstrates that the presence of multiple pathways, which are more common in children at high risk for arrhythmias than in children at low risk, is a predictor of arrhythmic events, including sudden death. Therefore, among children at high risk, prophylactic ablation of all accessory pathways can greatly reduce the risk of arrhythmic events, including life-threatening arrhythmias.

In the current study, the three boys who had ventricular fibrillation, sudden death, or both had had life-threatening tachyarrhythmias that were silent despite extremely rapid heart rates. Similarly, other patients in the control group had only tiredness, nausea, or loss of appetite during these

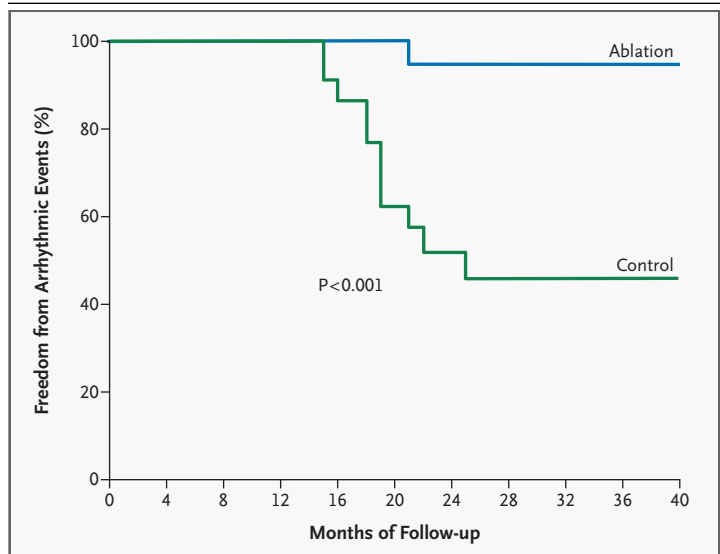
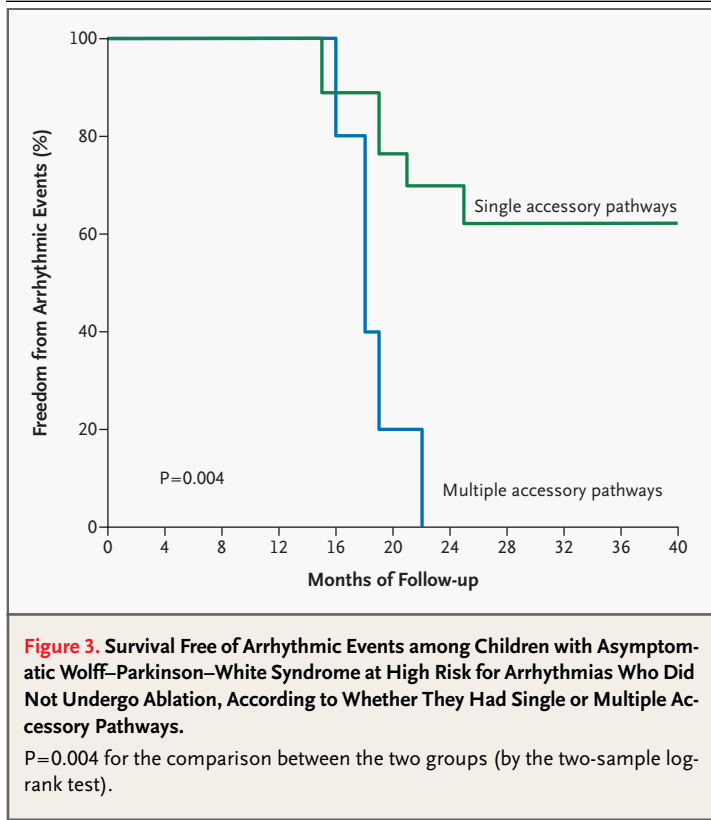


Figure 2. Survival Free of Arrhythmic Events among Children with Asymptomatic Wolff-Parkinson-White Syndrome at High Risk for Arrhythmias, According to Whether They Underwent Prophylactic Accessory-Pathway Ablation or No Ablation (Control).

$P<0.001$ for the comparison between the ablation group and the control group (by the two-sample log-rank test).

arrhythmias. This underlines the absence of correlation between classic symptoms and the risk of life-threatening tachyarrhythmias among children; moreover, the absence of symptoms does not necessarily indicate a low risk. Therefore, children with asymptomatic Wolff-Parkinson-White syndrome should be stratified on the basis of electrophysiological-test results to select high-risk patients for ablation.

The decision-making process for prophylactic radiofrequency ablation in high-risk children should be determined by balancing risks and benefits. Ablation is associated with several hazards in children: general anesthesia, electrophysiological testing, and the ablation procedure itself. In this study, we performed 165 electrophysiological tests; five patients had complications of anesthesia, and five had transient conduction defects due to catheter bumping. One patient had a femoral venous thrombosis. Of the 20 patients who went on to undergo ablation, an additional 3 had complications: in 2, the complications (transient Mobitz type II atrioventricular block and transient right bundle-branch block in 1 patient and permanent right bundle-branch block in another) were directly related to the ablation procedure, and in the third, the com-



plication (a small pericardial effusion that did not require aspiration) was in all probability due to ablation, although it could have developed during diagnostic electrophysiological testing.

Thus, substantial risk was associated with electrophysiological testing and anesthesia (which led to complications in 10 of 165 patients [6 percent]), and additional risk was associated with the ablation procedure (which led to complications in 3 of 20 patients [15 percent]), although the complications associated with ablation were relatively minor. Nonetheless, if our study groups are representative of the overall population of children with asymptomatic Wolff–Parkinson–White syndrome, we need to use ablation to treat between one and three high-risk children in order to prevent an arrhythmic event in one child.

The echocardiograms obtained during follow-up did not show damage to the valvular apparatus, but such damage might become manifest only after years. Because there was only one patient with an anteroseptal pathway (in the control group), our data may underestimate the procedural risk associated with heart block.

An analysis of data from the Pediatric Radio-frequency Catheter Ablation Registry²¹ showed that there have been significant decreases in complication rates, associated with improved success rates and decreased mean fluoroscopy times, in recent years. The fluoroscopy time in our study was shorter than that in the registry, although our complication and success rates were similar. The risk of a fatal procedural complication has been estimated to be up to 0.3 percent; however, the rate of death in otherwise healthy children or adolescents might be considered lower.

Our data suggest that children without inducible arrhythmias or those with inducible atrial fibrillation lasting less than 30 seconds do not require prophylactic ablation, since they will probably remain asymptomatic for many years. Children with reproducible induction of atrioventricular reciprocating tachycardia or atrial fibrillation (of more than 30 seconds' duration) or both should undergo detailed mapping and prophylactic ablation of all accessory pathways, since life-threatening tachyarrhythmias and sudden death may occur during follow-up, especially in those with multiple pathways and silent tachyarrhythmias. In the current study, there was a tendency for serious arrhythmias to occur more often in boys than in girls, although because the patient groups were small, this difference did not reach statistical significance. In such children, prophylactic catheter ablation of all accessory pathways substantially reduces the probability of arrhythmic events, including life-threatening arrhythmias, with a favorable risk–benefit ratio and a low number needed to treat. The need for ablation has financial implications, but cost per quality-adjusted year of life will be comparatively low.

Our results were achieved at an institution where a large number of ablation procedures are performed in adolescents, children, and infants; therefore, the results may not be directly applicable to the entire electrophysiology community. Our definition of multiple pathways is based on our ability to differentiate changes in activation during mapping. The presence of multiple pathways becomes more apparent during ablation because activation patterns change after successful ablation of a pathway. Therefore, the true incidence of multiple pathways in patients who underwent only the diagnostic study may have been slightly underestimated if pathways were located close to one another. The complication rate might be expected to be higher

in children with anteroseptal pathways or complex congenital heart disease, or those less than five years of age. We cannot completely rule out potential valvular damage over longer follow-up periods, especially in younger children with multiple pathways. Wolff-Parkinson-White syndrome is more commonly diagnosed in men than in women, although this sex difference is not observed in children.²³ In our study, there was a nonsignificant preponderance of girls in the group of children at

high risk who were randomly assigned to ablation. Six of the seven life-threatening arrhythmias occurred in boys, although it is unclear why these events occurred more often in boys than in girls.

The findings of this study should reassure physicians and parents alike that in children with the Wolff-Parkinson-White syndrome who are at high risk for arrhythmias, ablation is an appropriate option. We hope that future technological developments will further reduce complication rates.

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