Should catheter ablation be performed in asymptomatic patients with Wolff-Parkinson-White syndrome?

When to Perform Catheter Ablation in Asymptomatic Patients With a Wolff-Parkinson-White Electrocardiogram

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What to do when a person without any cardiac complaint shows a Wolff-Parkinson-White (WPW) pattern on the ECG has been an important question for more than 2 decades. Recent articles by Pappone et al1–3 make it necessary to revisit that question.

Background

Epidemiological data indicate that 0.1% to 0.3% of the general population have ECG findings suggesting that during sinus rhythm, in addition to AV conduction over the AV node His pathway, there is also AV conduction over an accessory AV pathway (AP).4 This means that each year ≈4 new cases are found in a population of 100,000. It is also known that there is a 4-fold increase of this finding in family members of WPW patients.5

The WPW patient is often symptomatic because of cardiac arrhythmias. When arrhythmias are present, the disorder is called the WPW syndrome. The 2 most common types of arrhythmia in the WPW syndrome are (1) a circus movement tachycardia (CMT), also called an AV reentrant tachycardia, in which AV conduction goes by way of the normal AV conduction system and VA conduction over the AP and (2) atrial fibrillation (AF).6

AF can be a life-threatening arrhythmia in the WPW syndrome if the AV AP has a short anterograde refractory period (RP), allowing many atrial impulses to be conducted to the ventricle. That will result in very high ventricular rates with possible deterioration into ventricular fibrillation (VF) and sudden death.7,8

A CMT that in general is well tolerated by the patient when additional heart disease is absent may deteriorate into AF, and the ventricular rate and risk for VF will depend on the anterograde RP of the AP. Therefore, the most important question in the asymptomatic WPW patient in whom the typical ECG accidentally is recorded is whether he or she is at risk for VF when AF supervenes. This risk is dependent on the anterograde RP of the AP during AF.

Recognizing the Risk for Dying Suddenly

As indicated, the presence of a short anterograde RP of the AP carries the potential risk of sudden death. A long anterograde RP of the AP does not exclude the possibility of a CMT, but the patient is not at risk when the CMT deteriorates into AF. As shown in Table 1, information about the anterograde RP of the AP can be obtained by noninvasive and invasive testing.

Noninvasive Testing

Sudden Block in the AP During Exercise

The best indicator of low risk, first described by Levy et al,9 is the sudden disappearance of pre-excitation during exercise. This indicates a long anterograde RP of the AP. Sympathetic...
stimulation occurring during exercise will shorten the duration of the RP of the AP. When the RP of the AP is reached during exercise, as manifested by sudden block in the AP, one knows that the patient is not at risk for AF even during sympathetic stimulation. One must be careful, however, to distinguish true block in the AP from diminution of the degree of pre-excitation over the AP produced by sympathetic stimulation during exercise, which will shorten the trans-AV nodal conduction time. This is more likely to occur when the AP is left sided. Therefore, several leads should be taken simultaneously, and special attention should be given to the sudden occurrence of block in the AP during exercise and to the ECG after exercise because, in exercise-induced block in the AP, a sudden marked change in the ECG takes place on resumption of AV conduction over the AP. An example of block in the AP during exercise is shown in Figure 1.

### Intermittent Pre-Excitation

Intermittent pre-excitation is present when, during sinus rhythm, some QRS complexes show pre-excitation and are followed by QRS complexes showing AV conduction over the normal AV conduction pathway. That finding, shown in Figure 2, indicates a long anterograde RP of the AP. This has to be differentiated from a bigeminal ventricular rhythm with a long coupling interval (Figures 3 and 4).

In the patient with intermittent pre-excitation, 1-to-1 conduction over the AP may occur during exercise because of shortening of the RP of the AP by sympathetic stimulation. However, there is never such shortening that a dangerously short RP of the AP develops.

### Block in the AP After Drug Administration

When during sinus rhythm the intravenous injection of ajmaline (1 mg/kg body weight given in 3 minutes) or procainamide (10 mg/kg body weight over a 5-minute period) results in complete block of the AP, a long anterograde RP (>270 ms) of that structure is likely. Figure 5 shows block in the AP after administration of 600 mg procainamide. Using a modified ajmaline test, Chimienti et al showed that the amount of ajmaline required to block conduction over the

**TABLE 1. Findings Identifying the Low-Risk Patient**

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<td>An anterograde RP of the AP &gt;270 ms during intracardiac or esophageal stimulation</td>
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**Figure 1.** Sudden block in the AV AP during exercise testing. As shown, pre-excitation is present on the left. On reaching a heart rate of 150 bpm, there is sudden block in anterograde conduction over the AP. After occasional conduction over the AP, complete block is present on the right.

**Figure 2.** Example of intermittent pre-excitation. Three QRS complexes showing pre-excitation are followed by 6 QRS complexes showing AV conduction over the AV node–His pathway only.
AP correlates with the duration of the anterograde RP of the AP. Because ajmaline and procainamide also prolong the RP of the His-Purkinje system, these tests should be done in an area in which the possible complication of complete AV block can be appropriately managed.

The weak aspect of pharmacological testing is that the drugs are given at rest. The test does not indicate what the drug will do on RP duration during sympathetic stimulation such as exercise, emotion, anxiety, and “recreational” drug use. However, by combining the different noninvasive tests, we usually can identify patients at low risk for sudden death because of a relatively long anterograde RP of the AP. Some authors have questioned the sensitivity and specificity of these noninvasive markers because of the low incidence of future adverse events.

### Invasive Evaluation of the Anterograde RP of the AP

As shown 30 years ago, in patients with the WPW syndrome, there is good correlation between the value of the anterograde RP of the AP obtained during atrial single-test
stimulation and atrial pacing at increasing rates and the ventricular rate during AF. Such an investigation may therefore be considered in situations in which noninvasive testing does not lead to the conclusion that a relatively long anterograde RP is present.

Programmed electrical stimulation of the atrium can be performed by the transesophageal route, and the value of the anterograde RP of the AP can be determined.19

The Risk of Dying Suddenly
Following the reports by Dreifus et al7 and Klein et al,8 several authors described sudden death in the WPW syndrome based on AF with a high ventricular rate deteriorating into VF. But, as discussed by Todd et al,20 longitudinal natural history studies, either electrophysiology or population based, suggest very low risk of sudden death during follow-up in the asymptomatic WPW patient.21–33 Thus, it is important to recognize certain features that have been reported in WPW patients with cardiac arrest who were successfully resuscitated and subsequently studied electrophysiologically.

Characteristics of the WPW Patient With Cardiac Arrest
Previously published articles8,34–36 reported the following 4 risk factors associated with the development of VF: (1) male gender; (2) a very rapid ventricular rate during AF because of a short anterograde RP of the AP; (3) a history of previous supraventricular tachycardias (SVTs), especially AF; and (4) the presence of multiple APs.

Although Timmermans et al36 could not confirm multiple APs as a risk factor for VF, they found a high incidence of septal APs in their VF patients. Another interesting finding in the Timmermans et al study was that sudden death usually occurred during increased adrenergic tone such as during emotion and/or physical stress. Table 2 summarizes the characteristics of the WPW patient dying suddenly. Both Torner34 and Timmermans36 showed that, in about half of the patients resuscitated from VF, this arrhythmia was the first symptomatic arrhythmia they ever experienced.

Management of the Asymptomatic Patient
When confronted with the asymptomatic patient showing a WPW ECG, the first step is to perform the noninvasive tests outlined above to recognize the low-risk patient. For the low-risk patient, no measures are advised other than an explanation to the patient of the ECG findings. It is advisable to give the patient a copy of his or her ECG and a short note about the fact that the WPW syndrome is present to prevent the misdiagnosis of myocardial infarction and to explain the basis of cardiac arrhythmias in case they develop later.

Until now, if noninvasive testing suggested a short anterograde RP of the AP, the decision to advise an invasive study and catheter ablation of the accessory AP was made individually, depending on the age of the patient, the location of the AP, and social and professional factors. If RF catheter ablation were a totally risk-free procedure, one would logically advise such a procedure to the asymptomatic WPW patient with a short anterograde RP. However, certain risks are associated with RF ablation. They include the general risks of any cardiac catheterization such as thromboembolic complications, infection, bleeding, cardiac perforation with or without cardiac tamponade, valvular damage, and radiation damage. In addition, there are specific risks in patients with APs, eg, in small children in whom the catheter ablation lesion is relatively large because of the size of the heart.

Risk may also be related to the location of the AP. For example, ablation of a para-Hissian AP carries the risk of complete AV block. In epicardially located posteroseptal or left posterior APs in which ablation has to be performed from the coronary venous system, there is the risk of damage to the coronary artery or perforation of the venous system, leading to cardiac tamponade. In addition, in right free wall APs, the right coronary artery may be damaged. Three registry studies37–39 reported the complications of RF ablation in symptomatic patients with APs. Although rare, deaths were reported in all 3 studies, along with other complications such as complete AV block, cardiac perforation with and without tamponade, and cerebrovascular accidents.

These studies were done in the early 1990s. Unfortunately, we do not have more recent information about the current complication rate of catheter ablation in patients with APs with the exception of the pediatric group.40 Kugler et al40 compared 1991 to 1995 with 1996 to 1999 and found an increased success rate of catheter ablation of APs but no significant change in complications.

The Role of Invasive Testing
Recent publications by Pappone and coworkers1–3 make it necessary to revisit our ideas about the management of asymptomatic WPW.

In the first study,1 asymptomatic WPW patients were studied invasively. Ages ranged from 7 to 63 years, with 50%
of patients in the third and fourth decades. During the electrophysiological study, the anterograde RP of the AP was determined and initiation of tachycardia was attempted by atrial and ventricular pacing, including atrial burst pacing to induce AF. Arrhythmias were considered sustained if they lasted >1 minute. One hundred sixty-two patients were studied twice. During follow-up (mean, 37.7 months), only 4 of 115 noninducible patients developed symptomatic SVT. In contrast, 29 of 47 inducible patients developed either SVT ($n=21$) or AF ($n=8$). Inducible patients were younger, had shorter anterograde RPs of their AP, and more often had multiple APs compared with patients who remained asymptomatic. Of the 8 patients with symptomatic episodes of AF and inducible sustained AF, 2 had resuscitated cardiac arrest, and 1 died suddenly. All 3 were inducible for AV reentrant tachycardia and AF and had multiple APs.

Shortly thereafter, Pappone et al$^2$ published a randomized study of prophylactic catheter ablation in asymptomatic patients with the WPW syndrome. Of 224 asymptomatic patients who underwent an AP study similar to that used in the previous publication,$^1$ 72 patients with inducible arrhythmias were randomized to radiofrequency catheter ablation of their APs (37 patients) or no treatment (35 patients). During follow-up, 2 of the 37 patients who underwent ablation had an arrhythmic event (median follow-up, 27 months). In contrast, 21 of the 35 patients in the control group had an arrhythmic event (median follow-up, 21 months), with 1 patient successfully resuscitated from VF.

Most recently, Pappone et al$^3$ described invasive testing and catheter ablation in children with asymptomatic WPW. Of 165 eligible children 5 to 12 years of age, 60 were determined, after an AP study, to be at high risk for arrhythmias and were invited to participate in a randomized study of catheter ablation of the AP or no treatment. The parents of 13 children withdrew them from the study; of the remaining children, 20 underwent prophylactic ablation, and 27 had no treatment. During follow-up (median, 34 months for the ablation group and 19 months for the control group), no patient from the ablation group had recurrence of ventricular pre-excitation, and only 1 patient had an SVT using an additional concealed posteroseptal AP. In contrast, all controlled patients continued to have ventricular pre-excitation, and 7 had symptomatic arrhythmias. In addition, in 5 apparently asymptomatic patients in the control group, follow-up Holter monitoring documented silent episodes of sustained AF, remaining asymptomatic despite extremely rapid ventricular responses over their APs. Three children in the control group had VF, which led to the death of 1 child.

**Problems**

The 3 articles by Pappone et al$^1–3$ suggest that the ability to induce a sustained arrhythmia (SVT or AF) in the asymptomatic patient with a WPW ECG is a marker of risk and should be followed by catheter ablation of the AP. They put less emphasis on the length of the anterograde RP of the AP as a risk factor, although in asymptomatic WPW patients, a short duration identifies risk for a high ventricular rate in case of AF. In addition, the risk of dying suddenly with SVT is not the same as the risk when AF occurs in a patient with a short anterograde RP of the AP.

The electrophysiological properties of both the AP and normal AV conduction system may change over time, often unpredictably.$^{21,26,41}$ In patients with a short anterograde RP of their AP ($<260$ ms), however, it is rare to see marked lengthening of that value during an AP study years later, whereas such lengthening, even complete block, in the AP is not unusual in patients not having a short anterograde RP of their AP.

Another important point is that the inability to induce an arrhythmia now is no guarantee that arrhythmia will be noninducible years from now. For example, in the patient with a short anterograde RP of the AP, arrhythmia may not be inducible at a young age, but AF may develop when the patient is in his or her 60s. Thus, I am reluctant to accept the suggestion by Pappone et al that the asymptomatic WPW patient is at low risk when >35 years of age.

A major problem is that the studies by Pappone et al$^1–3$ report a much higher incidence of (serious) arrhythmias than previous natural history publications.$^{21–33}$ As discussed elsewhere,$^{42}$ it may not be easy to identify the asymptomatic WPW patient. This seems to be especially difficult in children. In view of the prevalence of the WPW ECG, to find 165 children between 5 and 12 years of age with asymptomatic WPW (the number reported by Pappone et al), you have to obtain $\approx 200,000$ ECGs in asymptomatic children. Apparently, ECGs are performed in asymptomatic children frequently in Italy, but this practice is unusual in other countries. In balancing risk and benefits of catheter ablation in asymptomatic patients, one should know the success and complication rates of the center to which the patient is referred. As indicated earlier, that information is often not available.

**Current Guidelines**

The most recent guidelines of the American College of Cardiology and the European Society of Cardiology on the management of asymptomatic WPW patients suggest restricting catheter ablation of APs to those in high-risk occupations and professional athletes—ie, to advise on the basis of individual considerations.$^{43}$ Catheter ablation in asymptomatic pre-excitation was classified as a IIA indication with a B level of evidence.

According to the NASPE Expert Consensus Conference, asymptomatic WPW pattern on the ECG without recognized tachycardia is a class IIb indication for catheter ablation in children >5 years of age and a class III indication in younger children.$^{44}$

**Conclusions**

Recent publications and recommendations by Pappone et al force us to look again at the management of the asymptomatic
patient with a WPW ECG. A problem with these studies is the much higher incidence of (serious) arrhythmic complications than in previous natural history studies on asymptomatic patients. Other difficulties are the identification of asymptomatic patients and the risks of invasive studies and catheter ablation. In view of those risks, one should start with noninvasive studies (exercise, Holter, effect of a pharmacological intervention) to identify the low-risk patient because of a long anterograde RP of the AP. In patients not showing block in their AP during these noninvasive studies, esophageal pacing can be performed to determine the anterograde RP of the AP and the ability to induce sustained arrhythmias. If arrhythmias can be induced, benefits and risk of an invasive investigation and catheter ablation should be based on individual considerations such as age, gender, occupation, and athletic wishes. This should be discussed with the patient or, in the case of a child, with the parents. Because knowledge about the success and complication rate at the electrophysiological center plays a major role in decision making, that information should be made available so that the appropriate place for invasive diagnosis and treatment can be selected.

References


Ablation in Asymptomatic WPW

Catheter Ablation Should Be Performed in Asymptomatic Patients With Wolff-Parkinson-White Syndrome

Carlo Pappone, MD, PhD; Vincenzo Santinelli, MD

Although the clinical presentation and natural history of people with accessory pathways (APs) are largely unknown, previous studies have found asymptomatic Wolff-Parkinson-White (WPW) to be associated with a good prognosis.1–11 Subjects with ventricular pre-excitation on the ECG but who are asymptomatic and have no clinical arrhythmias are usually described as having “ventricular pre-excitation” or “WPW ECG pattern.” In our experience, asymptomatic WPW patients are also those who have totally silent tachyarrhythmias that occasionally may be life-threatening, as documented during Holter monitoring.12 Silent tachyarrhythmias frequently occur in young WPW patients who may experience ventricular fibrillation (VF), cardiac arrest, or sudden cardiac death (SD) as their first clinical presentation.13 Recognizing silent or minimally symptomatic life-threatening arrhythmias despite extremely rapid ventricular rates in apparently asymptomatic patients is a new concept that has attracted considerable attention and recent confirmation.13,14

From 1990 to 2004: More Than a Decade of Insights and Progress

The study of asymptomatic ventricular pre-excitation has a long history in our laboratory, beginning as a pilot study with the first 20 patients who performed sequential transesophageal electrophysiological testing (EPT) to assess a potential relationship between inducibility and outcome.15 From 1990 to 1999, we continued to collect asymptomatic patients with a WPW ECG pattern from all over Italy for invasive EPT and risk stratification. At present, we have accumulated sufficient data from a total of 477 asymptomatic untreated patients (median age, 26 years; interquartile range, 12 to 38 years) that, by virtue of their magnitude, will be useful in delineating the natural history of the disease and revisiting current practice guidelines. Interest was centered on the usefulness of EPT to stratify the risk, focusing on inducibility, distribution of induced arrhythmias, and the presence of multiple AP as predictors of arrhythmic events. In 2003, we reported the first 3 cases of VF from which 2 asymptomatic patients were resuscitated.12 High-risk patients were identified as those ≤35 years of age in whom sustained arrhythmias were reproducibly induced by EPT; low-risk subjects were noninducible and/or >35 years of age. Soon thereafter, for the first time, a durable and strong benefit of prophylactic percutaneous radiofrequency (RF) catheter ablation was demonstrated in a “high-risk” group, and the results were recently published in the *New England Journal of Medicine*.13,14

Historical Background

In the early 1980s, surgical ablation of APs was the only alternative to pharmacological treatment despite its significant risks, complications, and costs. Arrhythmia surgery,
however, was recommended as a last resort only for highly symptomatic WPW patients whose arrhythmias were refractory to drug treatment or were life-threatening. In contrast, among asymptomatic WPW patients, no risk stratification by EPT was attempted in the absence of an alternative to surgery, and a conservative approach was quite appropriately, recommended. In the 1990s, technologies in the electrophysiology laboratory evolved substantially with the introduction of percutaneous RF ablation and sophisticated mapping systems. Indeed, since 1992, RF catheter ablation has eliminated the need for surgical ablation in almost all patients and the need for antiarrhythmic drug therapy in many patients.21,22 Subsequently, the high success rates of RF ablation and the very low incidence of serious complications acted as a strong stimulus for some pediatric electrophysiologists to perform EPT and ablation of AP in selected asymptomatic children, despite conservative guideline recommendations.23

Magnitude of the Problem

The high preoccupation for the intrinsic risk of a potentially preventable SD in an otherwise healthy individual is not difficult to understand because WPW is one of the few syndromes with a mechanism that is clearly understood and can be easily confirmed and definitively and safely eliminated by catheter ablation. Treatment of asymptomatic patients, however, is complicated by incomplete information on the natural history of the disease and by insufficient data on the electrophysiological characteristics of APs. This article is intended to describe the progress in our understanding of SD in asymptomatic WPW, focusing on the usefulness of EPT in identifying high-risk patients and on the results of prophylactic ablation in high-risk patients aimed at preventing such deaths.

Natural History of the WPW Syndrome: Risk Assessment

Several natural history studies of the WPW syndrome have reported low SD rates (0.0% to 0.6% per year), but most had relatively small numbers and limited follow-up, providing underpowered data for risk assessment. Leitch et al reported no cases of SD in a group of 75 initially asymptomatic subjects followed up for a mean of 4.3 years. Munger et al reported that 30% of initially asymptomatic subjects developed symptoms related to arrhythmias over a 12-year follow-up. They also reported 2 SDs over 1338 patient-years of follow-up, but neither occurred in patients who were asymptomatic at diagnosis. In the Munger et al study, no symptoms developed during follow-up in any individual >40 years of age who was asymptomatic at diagnosis, and up to 33% of asymptomatic people lost the capacity to conduct anterogradely. In contrast, a third of those <40 years of age became symptomatic.

Kitada et al reviewed palpitations and arrhythmias by questionnaire in 397 responding school children. They found that those with WPW syndrome had only a fair prognosis in terms of repeated arrhythmic events rather than mortality or serious cardiovascular complications. Fitzsimmons et al reported that among asymptomatic military aviators with intermittent or continuous pre-excitation, 28 of 187 (15.3%) had supraventricular tachycardia (SVT) during long-term follow-up, but among those with continuous pre-excitation, 23% experienced SVT. Other investigators have reported lower rates of symptom development (0% to 8%) with variable follow-up periods, confirming that the length of follow-up is indeed crucial because some patients may become symptomatic after many years and may have SD as their first presenting symptom. Among 241 relatively unselected WPW patients, Pietersen et al identified 26 who had developed atrial fibrillation (AF). Over a mean of 15 years (range, 1 to 37 years) of follow-up, 2 of these 26 patients died suddenly. Their shortest RR intervals during induced AF had been short (<220 ms). In contrast, 2 of the remaining 215 patients (ie, those in whom AF had not occurred) died suddenly, but this difference was not statistically significant. Taken together, these findings provide evidence that ventricular pre-excitation is not such a benign condition as once might have been thought; 4 SDs from a total of 241 WPW patients represent a 2% mortality over the follow-up period.

Results of the 3 largest published series of WPW patients with VF demonstrated that VF was the first presentation in 3 of 25 patients, 6 of 23 patients, and 8 of 15 patients. Klein et al raised concern for asymptomatic patients by documenting VF in 3 pediatric patients 8 to 16 years of age who presented with cardiac arrest. Montoya et al reported clinical and electrophysiological data of 23 WPW patients with spontaneous VF collected in a multicenter retrospective study in 7 European centers. VF was the first manifestation of the syndrome in 6 patients. No significant differences were found between those with VF and without VF in age, complaints of palpitations, syncope, and presence of structural heart disease. Timmermans et al reported that 15 of 690 patients (2.2%) with WPW syndrome who were referred to their hospital over a 16-year period had an aborted SD, and VF was the first clinical manifestation in 8 patients. From our results and those of previous reports, it seems that aborted SD and SD occur more frequently in young, otherwise healthy male subjects and that VF is a rare initial presentation in patients >30 years of age. We documented VF in 7 healthy, young patients (6 male patients); 5 were successfully resuscitated, and 2 died suddenly. Tragically, patients with VF had had asymptomatic life-threatening Holter-documented tachyarrhythmias, but they declined RF ablation on the grounds that they have been asymptomatic. Two of them (1 child) died suddenly, and the others were ablated only after experiencing cardiac arrest. None of these patients had a family history of SD.

In 1993, Russel et al described 256 pediatric patients, 6 of whom had presented with life-threatening events as the first
manifestation of their pre-excitation syndrome. Among these 256 patients, 60 (23.4%) were asymptomatic. In 1995, Deal et al reported 42 patients with WPW syndrome who experienced cardiac arrest. Twenty had cardiac arrest as the initial presenting symptom. In 1996, Bromberg et al reported 60 patients who had surgical ablation of the AP. Ten children had experienced a clinical cardiac arrest; of this group, only 1 had a history of syncope or AF.

Dubin et al reported on 100 pediatric patients with WPW syndrome who underwent EPT for risk stratification and demonstrated that asymptomatic patients had statistically the same recognized EPT risk profile as the symptomatic patients.

Recently, in a 15-year follow-up study, among 98 asymptomatic WPW children, 1 child 8 years of age whose parents refused to perform EPT died of SD. In our series, the incidences of VF, SD, and life-threatening syncopal arrhythmias were 0.3%, 0.1%, and 1.3% per year, respectively.

Mechanism of VF and SD
Although increased ventricular vulnerability in patients with WPW syndrome is reported, the generally postulated mechanism for SD in WPW is the onset of AV reciprocating tachycardia (AVRT), which degenerates into AF and subsequently VF. The ability to conduct rapidly over at least 1 AP with a short refractory period may allow AF to degenerate into VF and SD, particularly if the ventricular rates exceed 300 bpm. In our series, patients who experienced VF had rapid conduction and short refractory period of both the AV node and AP with inducible AVRT triggering AF. Although the presence of a short effective refractory period of AP (ERPAP), in combination with a short AV node refractory period, usually dictates a narrow excitable gap, making spontaneous arrhythmia induction unlikely, these patients are at high risk of extremely rapid ventricular rates during pre-excited AF if the correct electrophysiological circumstances arise to permit the induction and maintenance of sustained arrhythmias. The presence of multiple pathways also plays an important role in precipitating AF and then VF. Therefore, it appears that the inducibility of rapid AVRT and the presence of multiple AP, not the short ERPAP per se, convey risk of VF or SD. It has been reported that patients with WPW who were resuscitated after VF have usually had (1) clinical AF with rapid ventricular rates, (2) clinical SVT, (3) inducible AVRT or AF with rapid ventricular response or both, (4) an anterograde AP refractory period <270 ms, and/or (5) multiple pathways. These observations are in agreement with our results and confirm the role of EPT in assessing inducibility, the number and location of APs, and the electrophysiological characteristics of both the AV node and bypass tract to identify high-risk patients. In our experience, the anatomic distribution and the number of APs were predictive of arrhythmic events, and the most common location was in the left free wall (42%), followed by the right free wall (24%) and the posteroseptal region (23%). The least common location was the anteroseptal region (2%). Multiple pathways have previously been reported in up to 20% of patients with pre-excitation syndromes. Patients resuscitated from VF have an increased prevalence of multiple AP, but their location determines only the likely procedural success rate and the potential risk of AV block with catheter ablation. In our experience, patients with multiple APs were more likely to experience arrhythmic events than those with a single AP.

The Need to Identify High-Risk Patients: EPT
EPT is usually recommended for symptomatic patients to elucidate the pathophysiological basis of their arrhythmias and for asymptomatic individuals with high-risk occupations because the positive predictive value of EPT has been considered too low to justify its routine use in asymptomatic patients. Because of the rarity of arrhythmic events reported among asymptomatic subjects, the negative predictive value of EPT has been considered excellent. Most asymptomatic patients identified as high risk on the basis of the shortest pre-excited RR interval during induced AF or short ERPAP alone actually do reasonably well during relatively short follow-up. Conversely, asymptomatic patients labeled low risk by these tests are truly at low risk. Inducibility of sustained or nonsustained tachyarrhythmias varied from 6% to 51%. Prior electrophysiology-based studies demonstrated inducibility of AVRT in 15.7% (range, 7.5% to 20%) of patients and AF in 18.1% (range, 3% to 31%). Milstein et al described the difficulty in inducing AVRT in most of the 42 asymptomatic WPW patients. In 1990, Leitch et al reported that among 75 asymptomatic patients with ventricular pre-excitation (mean age, 34 years) who underwent EPT, 12 patients had inducible sustained AVRT, 10 patients had inducible nonsustained AVRT, and 23 patients had inducible sustained AF. No patient died suddenly during a median follow-up of 4.3 years. Of them, 6 (8%) became symptomatic with SVT, of whom 2 underwent surgical ablation of their APs. In this study, inducible sustained or nonsustained AVRT did not predict future arrhythmic events. The authors also found that a considerable number of asymptomatic patients lost their capacity for anterograde conduction over the AP; these data are in agreement with our experience. Indeed, among 115 noninducible patients, 21 (18.2%) lost anterograde conduction over AP and 35 had retrograde conduction. Subjects who lost ventricular pre-excitation were older and showed longer ERPAP than patients in whom pre-excitation persisted. Satoh et al confirmed the inducibility of AVRT and sustained AF before and after isoproterenol in 18% and 6% of 34 asymptomatic WPW patients (mean age, 36 years). Klein et al have broken up the risk of SD on the basis of the shortest RR interval during AF as follows: (1) definite risk, shortest pre-excited RR interval <220 ms; (2) probable risk, shortest pre-excited RR interval <250 but >220 ms; (3) possible risk, shortest pre-excited RR

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interval <300 but >250 ms; and (4) negligible risk, shortest pre-excited RR interval <300 ms. Contrasting with these observations are the results of recent data from our laboratory that demonstrated that the shortest pre-excited RR interval does not predict arrhythmic events.\cite{12-14} Teo et al\cite{42} reported that the combined finding of multiple AP and shortest pre-excited RR interval <250 ms lowers the sensitivity (88% to 29%) but increases the specificity (36% to 92%) and positive predictive value (9% to 22%). Brembilla-Perrot and Ghavi\cite{6} reviewed 40 asymptomatic WPW patients (mean age, 35 years) and found that at intracardiac or transesophageal EPT, 22 patients were noninducible. Sustained AVRT was induced in 3 patients (8%), nonsustained AVRT in 4 patients (10%), and sustained atrial tachyarrhythmias in 12 patients (30%) (atrial flutter in 4, AF in 9). Atrial pacing at cycle lengths down to 40 ms in 1 patient directly induced VF. After a mean follow-up of 1.8 years, 2 of the previously asymptomatic patients became symptomatic with reciprocating tachycardia. Both had had AVRT provoked by EP testing. No patient had SD during a follow-up ranging from 1.3 to 7.5 years. Munger et al\cite{7} reported that of 11 initially asymptomatic patients who became symptomatic, 4 underwent EPT; in this group, arrhythmias induced included AF in 4 and orthodromic reentrant tachycardia in 2, suggesting the usefulness of EPT. We have recently demonstrated the crucial role of EPT in stratifying high-risk patients for prophylactic percutaneous RF ablation.\cite{12-14} In our first experience, 33 initially asymptomatic patients (20.4%) became symptomatic.\cite{12} At the initial EPT, 29 of the 33 patients (88%) who became symptomatic had inducible AVRT, which degenerated into pre-excited AF in 11 patients. After the onset of symptoms, spontaneous arrhythmias were documented in all 33 patients: SVT in 25 patients and AF in 8 patients. All patients with spontaneous AF had both inducible AVRT and pre-excited AF during the initial EPT. Only 1 of the 30 patients with inducible AVRT at the initial study remained asymptomatic, and of the 115 noninducible patients, only 3.4% developed symptoms during follow-up. The occurrence of nonsustained AF after rapid atrial pacing at the initial EP study was not a good predictor of future symptoms. VF occurred in 3 patients who had both AVRT and AF at the time of the initial EP study. The sensitivity, specificity, and positive and negative predictive values of short anterograde ERPAP (<250 ms) and positive EPT in predicting arrhythmic events were 71.9%, 72.6%, 44.2%, and 89.5% and 87.9%, 86%, 61.7%, and 96.5%, respectively. The combination of short anterograde refractory period of AP and inducibility was associated with a sensitivity of 93.7% and a specificity of 67.6%, with positive and negative predictive values of 46.9% and 97.3%.\cite{12} Kaplan-Meier survival analysis showed that the cumulative risk of developing arrhythmias was significantly higher for patients with a positive EPT. Inducibility was the strongest predictor of arrhythmic events, with positive and negative predictive values of >90% and >85%. In addition, EPT was able to identify other predictive factors such as the presence of multiple pathways. Conversely, a short anterograde effective refractory period of the AP was a much weaker predictor than multiple pathways or inducible AVRT, with positive and negative predictive values of 35% and 93%. Therefore, from our data, EPT is useful for evaluation of the number, sites, conduction properties of AP, and mechanism of tachycardia and is unequivocally the gold standard for determining risk in asymptomatic patients with WPW. Our protocol for inducibility includes atrial and ventricular stimulation and burst pacing. Induction of AF is
attempted with ramp pacing, starting at a cycle length of 300 ms, decreasing to a minimum of 100 ms over 20 seconds, and stopping once refractoriness is attained or AF is induced. AF is considered abnormal if the arrhythmia lasts ≥30 seconds. Arrhythmias are considered sustained if they last ≥1 minute. Intravenous isoproterenol (1 to 4 μg/min) is used to facilitate arrhythmia induction.

In experienced centers, the complication rate from RF ablation appears to be very low (<1% in older patients with structural heart disease). Early reports focused on the new and evolving modality, before its widespread application and before significant improvements in technology, and thus do not represent current results, which have reported no deaths in >2900 ablations in a pediatric population of 0 to 16 years of age.43 Similarly, in our experience, complications of both EPT and ablation were infrequent, minor, and not life-threatening.

What Can Be Done?
From the above discussion, in the final analysis, asymptomatic ventricular pre-excitation is not a benign condition, and recent extensive data report no fatal complications from EPT and RF ablation in experienced centers.12–14,43 EPT has high specificity and sensitivity for the identification of high-risk asymptomatic patients.12 Thus, prophylactic ablation of APs in high-risk subjects may be justified but is not an acceptable option for low-risk subjects.

Results of Prophylactic Ablation for High-Risk Asymptomatic WPW Patients
The effectiveness of prophylactic ablation among high-risk asymptomatic WPW patients has recently been reported in 2 randomized studies.13,14 In the first study, among 220 asymptomatic patients referred to our laboratory (≥12 years of age), 37 high-risk subjects were randomized to prophylactic ablation, and 35 received no treatment.13 Ablation was successful in all patients without any complications. The 5-year Kaplan-Meier estimates of the incidence of arrhythmic events were 7% among patients who underwent ablation and 77% among control subjects (P<0.0001); the risk reduction with ablation was 92% (relative risk, 0.08; 95% CI, 0.02 to 0.33; P<0.001). Compared with controls, patients undergoing ablation had a relative risk of arrhythmic events of 0.016 (95% CI, 0.002 to 0.104; P<0.001).

In this study, 1 patient with multiple pathways in both the right

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ablation Group (n=57)</th>
<th>Control Group (n=62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median), y (IQR)</td>
<td>15 (16)</td>
<td>14 (11)</td>
<td>0.41</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>43 (48.3)</td>
<td>46 (51.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>Structural heart disease (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anterograde ERPAP (median), ms (IQR)</td>
<td>240 (30)</td>
<td>240 (33)</td>
<td>0.58</td>
</tr>
<tr>
<td>Anterograde ERPAP after isoproterenol (median), ms (IQR)</td>
<td>200 (15)</td>
<td>200 (10)</td>
<td>0.69</td>
</tr>
<tr>
<td>Multiple accessory pathways, n (%)</td>
<td>18 (51.4)</td>
<td>17 (48.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Location of single AP, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left free wall</td>
<td>20 (51.3)</td>
<td>21 (46.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Right free wall</td>
<td>14 (35.9)</td>
<td>17 (37.8)</td>
<td></td>
</tr>
<tr>
<td>Posteroseptal</td>
<td>4 (10.3)</td>
<td>5 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>1 (2.6)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Location of multiple APs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left free wall and posteroseptal</td>
<td>6 (33.3)</td>
<td>6 (35.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Left free wall and right free wall</td>
<td>7 (38.9)</td>
<td>5 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Right free wall and posteroseptal</td>
<td>5 (27.8)</td>
<td>6 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Inducibility, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained AF</td>
<td>14 (24.6)</td>
<td>5 (24.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>AVRT</td>
<td>28 (49.1)</td>
<td>34 (54.8)</td>
<td></td>
</tr>
<tr>
<td>AVRT triggering AF</td>
<td>15 (26.3)</td>
<td>13 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Length of AVRT cycle (median), ms (IQR)</td>
<td>280 (50)</td>
<td>260 (40)</td>
<td>0.46</td>
</tr>
<tr>
<td>Shortest pre-excited RR interval during sustained AF (median), ms (IQR)</td>
<td>240 (30)</td>
<td>230 (30)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

*Data pooled from studies cited in References 13 and 14.
TABLE 2. Multivariate Cox Proportional-Hazards Model Among High-Risk Asymptomatic WPW Patients*

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3.82</td>
<td>1.75–8.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>0.99–1.12</td>
<td>0.065</td>
</tr>
<tr>
<td>Multiple APs</td>
<td>5.03</td>
<td>1.83–13.82</td>
<td>0.002</td>
</tr>
<tr>
<td>Anterograde ERPAP before isoproterenol</td>
<td>0.98</td>
<td>0.97–1.00</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Type of inducible arrhythmia†

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVRT</td>
<td>14.71</td>
<td>3.47–62.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AVRT + AF</td>
<td>13.06</td>
<td>2.50–68.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Ablation</td>
<td>49.33</td>
<td>13.07–186.20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Final model of covariate-adjusted analysis of outcomes (arrhythmic events) among high-risk patients (data pooled from studies cited in References 13 and 14) was performed with use of a Cox proportional-hazards model with stepwise backward method for variable selection (Wald). Covariates included in this analysis were sex, age, presence of single or multiple APs, anterograde ERPAP before and after isoproterenol, and type of inducible arrhythmia and ablation procedure.

†Nonsustained AF was chosen as the reference category.

and left sides of the septum randomized to the conservative arm subsequently had a VF arrest, suggesting that multiple pathways are an important target for ablation to prevent VF and SD. All arrhythmic events occurred within the first 2.5 years of follow-up in patients with inducible AVRT, whereas more than half of those with inducible nonsustained AF remained asymptomatic at 5 years. We found that the risk of spontaneous arrhythmias significantly and persistently decreased over time after ablation: The event-free survival curves for patients at high risk who underwent ablation and those who did not continued to diverge over the duration of the follow-up. In the second study, RF catheter ablation of AP was compared with no treatment in 165 asymptomatic high-risk children 5 to 12 years of age.14 To collect these data, we estimate that \( \approx 150,000 \) ECGs had to be obtained. One of 20 children (5%) in the ablation group and 12 of 27 (44%) in the control group had arrhythmic events. Three children in the control group had VF as the first presenting arrhythmia, and 1 of them died suddenly. The other 2 patients were successfully resuscitated and were subsequently ablated. The independent predictors of arrhythmic events were absence of prophylactic ablation (hazard ratio, 69.4; 95% CI, 5.1 to 950.0; \( P = 0.001 \)) and the presence of multiple pathways (hazard ratio, 12.1; 95% CI, 1.7 to 88.2; \( P = 0.01 \)).

Pooling Data Analysis for Risk Stratification and Treatment

Individual studies may be limited by small sample sizes for end points with relatively low incidences. If all available data are synthesized, pooling data analysis allows a more precise estimate than that obtained from the results of a single individual study. Combined data from our 2 recent randomized studies13,14 showed that there were 119 high-risk and 253 low-risk patients. Overall, 69 of 315 untreated subjects (22%) developed arrhythmic events during follow-up, of which the greatest proportion (77%) occurred up to 25 years (Figure 1). There was an age-related effect on outcome in that more than a half of subjects <25 years of age became symptomatic as opposed to the 20% of those 25 to 35 years of age (Figure 2). Among older patients (ie, those >35 years of age), there was
little, if any, risk of arrhythmic events. In the high-risk group, 57 patients underwent prophylactic ablation, and 62 did not (Table 1). Arrhythmic events occurred earlier in high-risk nonablated patients with induced AVRT, whether or not it triggered AF, than in those with induced nonsustained AF (Figure 3), whereas prophylactic ablation among high-risk patients was of strong benefit (Figure 4).

The number of high-risk patients needed to treat, calculated according to the method by Altman and Anderson, to prevent arrhythmic events in 1 high-risk patient was 7.6 at 1 year, 2.3 at 2 years, and 1.8 at 4 years (Figure 5). Therefore, performing ablation in high-risk asymptomatic patients would lead to 1 event-free patient at 2 years for every 2.3 patients ablated. These results are clinically important because they demonstrate that ablation among high-risk asymptomatic patients is of durable benefit and not harmful at any point during follow-up. Multivariate analysis showed that independent predictors of arrhythmic events were inducibility, presence of multiple AP, and sex (Table 2).

One can argue that the risk of any arrhythmia and the risk of SD should be distinguished. Indeed, combining data from our 3 consecutive trials indicates that asymptomatic high-risk ablated patients were less likely to experience VF than high-risk patients who did not undergo ablation (Figure 6). Taken together, these data indicate that ablation should be performed as early as possible in young male asymptomatic subjects determined to be at high risk, particularly in the presence of multiple APs.

**Moving Forward: Need for a New Consensus Development**

At present, the available data with high level and type of evidence are sufficient to revisit current guidelines. We believe that in light of the recently published data, RF ablation can be safely and appropriately extended to asymptomatic high-risk patients and that this choice should be made by expert physicians, not by inexpert patients. Low-risk patients may choose prophylactic ablation at the time of EPT when the catheters are in place, but our data demonstrate that in a low-risk group, prophylactic ablation is unjustified because complication rates may exceed potential benefit, particularly in the case of septal APs. Nevertheless, we do not

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Arrhythmic event–free survival plots according to whether the high-risk asymptomatic WPW patients received treatment with prophylactic AP ablation. Proportion of patients remaining asymptomatic during follow-up is plotted also for low-risk subjects.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Number needed to treat at various times after treatment for 119 WPW patients at high risk for arrhythmic events ablated and nonablated. Note the number of patients at risk at each follow-up point, along with corresponding estimates of number needed to treat and 95% CIs.
know whether our results in terms of benefits and risks may be extended to the general electrophysiology community. These results are from a single center with a high volume of ablation procedures. In addition, most of the procedures have been performed by a single operator, especially for the pediatric population, which is at higher risk of serious complications.

References


44. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319:1492–1495.
Response to Pappone and Santinelli

Hein J. Wellens, MD

The data from Drs Pappone and Santinelli are of great interest. I do admire the results, but can their approach be adopted by the cardiological community at large? I do not think so. There are 3 important reasons.

First, the risk for developing life-threatening arrhythmias in the asymptomatic patient, as discussed earlier, is, in the experience of most investigators, much smaller than in the series reported by Pappone and coworkers.

Second, ECG screening of the population for asymptomatic WPW would be costly. For example, as pointed out before, in view of the prevalence of the WPW ECG, to find 165 children between 5 and 12 years of age with asymptomatic WPW (the number reported by Pappone et al), ECGs of ≈200,000 children would have to be made, assuming that 100% of parents would consent to having their child undergo an invasive procedure.

Third, I am afraid that with our current invasive techniques, a diagnostic investigation and catheter ablation performed by the average clinical electrophysiologist carries a higher risk than the natural history of asymptomatic WPW. A mandatory catheter ablation registry is needed to assess that possibility. Results and risks obtained by Dr Pappone and coworkers cannot automatically be extended to the general electrophysiological community.

I believe that at this point in time, carefully executed noninvasive studies can identify the low-risk patient and that the decision to perform an invasive procedure, especially catheter ablation of the AP, should be based on individual considerations that take into account age, gender, occupation, athletic wishes, and information from long-term ECG recordings.

Response to Wellens

Carlo Pappone, MD, PhD; Vincenzo Santinelli, MD

Noninvasive studies may identify asymptomatic WPW subjects who are unlikely to develop VF, which, unfortunately, can be the presenting arrhythmia of the syndrome. In our experience, the mere presence of APs, regardless of symptoms, can predispose from childhood to tachyarrhythmias. We prospectively collected data on 477 asymptomatic untreated WPW subjects of all ages. In a total observation time of 2070 patient-years, 80 patients (16.8%) became symptomatic, and 26 of them (median age, 11.5 years) had life-threatening arrhythmias, including VF, from which 5 subjects were resuscitated and 2 subjects died. Among the 7 patients with VF, 6 were male; all were between 10 and 22 years of age, had multiple pathways, and had been inducible for sustained AVRT triggering AF. Although refractory periods of APs are short in children or younger patients, making inducibility of AVRT difficult, if triggered, the arrhythmia can be fast and degenerate into rapid AF, which predisposes to life-threatening events. Younger age, inducibility, and multiple pathways independently predicted arrhythmic events, whereas anterograde ERPAP or shortest pre-excited RR interval did not. Younger subjects (≤25 years of age), if inducible and with multiple pathways, were at highest risk (87%). Older patients, if inducible, were at high risk (60%), but if noninducible, they were at lowest risk (2%). Because previous longitudinal natural history studies enrolled mostly older subjects, it is not surprising that they reported a much lower incidence of life-threatening events, probably missing the peak of events that usually occur in younger patients. To define the true natural history of the disease, larger numbers of asymptomatic subjects, particularly children, are required. Although we agree with Wellens’ conclusions that noninvasive studies may be the first step to identify the low-risk patient, our data provide sufficient evidence that it will be beneficial to address the role of invasive testing in future guidelines to identify high-risk subjects for prophylactic catheter ablation.
When to Perform Catheter Ablation in Asymptomatic Patients With a Wolff-Parkinson-White Electrocardiogram
Hein J. Wellens

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