Noninvasive Risk Stratification for Sudden Death in Asymptomatic Patients With Wolff-Parkinson-White Syndrome

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Sudden cardiac death (SCD) as the first clinical manifestation of Wolff-Parkinson-White (WPW) syndrome is a well-documented, although rare occurrence. The incidence of SCD in patients with WPW ranges from 0% to 0.39% annually. Controversy exists regarding risk stratification for patients with preexcitation on surface electrocardiogram (ECG), particularly in those who are asymptomatic. This article focuses on the role of risk stratification using exercise and pharmacologic testing in patients with WPW pattern on ECG.

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KEY WORDS

Wolff-Parkinson-White syndrome • Sudden cardiac death • Risk stratification • Preexcitation

Sudden cardiac death (SCD) as the first clinical manifestation of Wolff-Parkinson-White (WPW) syndrome is a well-documented, although rare occurrence. The incidence of SCD in patients with WPW ranges from 0% to 0.39% annually.[1-3] Although there is general agreement that the overall incidence of SCD in patients with WPW is quite low, controversy exists regarding risk stratification for patients with preexcitation on surface electrocardiogram (ECG), particularly in those who are asymptomatic. This article focuses on the role of risk stratification using exercise and pharmacologic testing in patients with WPW pattern on ECG who are asymptomatic upon presentation.

Epidemiology

The exact prevalence of WPW within the general population has varied in different studies, depending upon the population being studied and the duration of follow-up. One challenge is that the epidemiology of WPW syndrome is different than the epidemiology of the WPW pattern. What distinguishes WPW syndrome from the WPW pattern is that WPW syndrome encompasses patients with

the WPW pattern on surface ECG with an associated arrhythmia. The prevalence of a WPW pattern on surface ECG has been estimated to fall between 0.13% and 0.25% of the general population.[4,5] The prevalence of the actual WPW syndrome is substantially lower, involving only approximately 1.0% to 1.8% of those patients with a WPW pattern on ECG. It has been reported that the incidence of newly diagnosed ventricular preexcitation in a cohort of 22,500 healthy aviation personnel was 0.25%, only 1.8% of whom had documented arrhythmia.[6] Kobza and colleagues[1] described an overall prevalence of 0.13% in young male conscripts.

Multiple tachyarrhythmias have been reported in patients with WPW. The most common arrhythmia is atrioventricular reentrant tachycardia (AVRT), accounting for approximately 80% of tachyarrhythmias associated with WPW syndrome.[5] Between 15% and 30% of patients have atrial fibrillation (AF), and approximately 5% of those manifest atrial flutter. It is now well recognized that the primary mechanism of SCD in patients with WPW is the rapid conduction of AF down an accessory pathway (AP), as initially described by Dreifus and colleagues.[7] However, SCD can be the first presenting symptom of WPW. Pappone and associates[8] reported 3 cases of SCD in 162 patients who were initially asymptomatic, and all 3 patients developed symptomatic AF prior to the episode of SCD. Furthermore, Basso and associates[9] reported that ventricular preexcitation accounted for 3.6% of SCD in young people and was not preceded by symptoms in 40%. Klein and colleagues[10] found 3 of 25 patients with WPW and SCD who had ventricular fibrillation (VF) as the presenting symptom, whereas, in a study by Timmermans and colleagues[11] 8 of 15 patients with WPW and SCD had VF as the first presenting symptom. Further, Klein and colleagues[10] showed that VF is a particularly rare presentation in patients over age 30 years. Many experts think the true incidence of VF in asymptomatic patients with WPW is lower than the aforementioned statistic, suggesting that these studies suffer from selection bias. Despite the differences in the incidence of life-threatening arrhythmias from these studies, they all underscore the potential for VF as the presenting symptom of WPW.

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Santinelli and coworkers[3] prospectively followed 293 asymptomatic patients with evidence of preexcitation on their ECGs using the occurrence of a first arrhythmic event as the primary endpoint. None of the 293 patients had suffered a cardiac arrest during the median span of 67-month follow-up.

Risk Stratification

Klein and colleagues[12] demonstrated that patients with an R-R interval < 250 ms between consecutive beats during induced AF in the electrophysiology laboratory had the shortest AP effective refractory periods (ERP) and were, therefore, at greatest risk for SCD. Noninvasive testing (including Holter monitoring, pharmacologic agents, and exercise testing) has also been studied as a risk stratification technique in patients with preexcitation on resting ECG. Abrupt loss of preexcitation during graded exercise is thought to predict a longer AP ERP and, therefore, a low risk of SCD. The sudden disappearance of the δ wave during exercise testing suggests a complete block in the AP, thus indirectly suggesting a long anterograde ERP and low risk of SCD if one should develop AF; the gradual disappearance of the δ wave is considered less reliable in this context.[8]

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Exercise and Pharmacologic Testing for Risk Stratification

Sharma and colleagues[13] assessed the sensitivity and specificity of the electrophysiologic (EP) study compared with exercise testing in 67 patients with WPW (including 9 patients with a history of VF) using both EP and exercise testing; 55 of these patients were referred because of arrhythmias related to the AP and 12 patients who were asymptomatic were referred for SCD risk assessment. During EP testing, risk was defined as an R-R interval during induced AF ≤ 250 ms. This parameter correctly identified seven of the nine patients who had a history of VF yielding a sensitivity of 78%. The authors concluded that EP testing had a specificity of 48.3% for SCD; 28 of the 58 patients with a history of cardiac arrest without VF had a negative test result when using the ≤ 250 ms cutoff to identify patients at risk for SCD.

The authors then studied 56 of the aforementioned 67 patients with exercise testing, including 6 patients with a history of SCD. Continuous

preexcitation with exercise was observed in 34 patients (61%) with a mean shortest R-R interval of 236 ± 64 ms, gradual loss of preexcitation was observed in 9 (16%) with a mean shortest R-R interval of 242 ± 37 ms, and sudden loss (ie, a negative test result) was observed in 13 patients (23%) with a mean shortest R-R interval of 410 ± 148 ms. Sensitivity and specificity for detecting SCD was then calculated. In this calculation, patients with a gradual loss of preexcitation were excluded based on the premise that preferential conduction over the atrioventricular (AV) node during periods of sympathetic drive could confound the results. The authors determined that sudden loss of the δ wave during exercise testing could identify patients who are at low risk for SCD. The results show that continuous preexcitation with exercise had a sensitivity of 80% and a specificity of 28.6% for detecting patients at risk of SCD.[13]

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Thus, the authors concluded both invasive and noninvasive testing have a good sensitivity but low specificity for identifying patients with WPW syndrome and SCD.[13] R-R intervals ≥ 250 ms during AF and apparent block of AP conduction during exercise testing were associated with a low risk of SCD in this patient population.

Gaita and associates[14] demonstrated similar findings when they studied 65 patients with permanent preexcitation on the resting ECG, 50 of whom were symptomatic with palpitations, syncope, or both. They studied 46 men and 19 women with a mean age of 28 ± 14 years (range, 8-61 y). All of these patients underwent exercise testing using the Bruce protocol with a goal of maximal physical capacity. An ECG was generated at 1-minute intervals and only a sudden and complete loss of the δ wave was considered in these patients. Prior to exercise testing, these patients underwent EP testing and were subsequently divided into two groups (groups A and B). Patients in group A (24 patients) were found to have an R-R interval or an ERP of the AP ≤ 250 ms between preexcited beats during AF that was either induced or sustained using rapid atrial pacing. Group B patients (41 patients) were found to have an R-R interval and an anterograde ERP of the AP > 250 ms during preexcited beats during induced or sustained AF. The EP study was then used as a reference standard to assess the sensitivity, specificity, and predictive values of noninvasive testing.

During exercise, sudden anterograde block in the AP occurred in 1 of the 24 patients within group A (4%). In group B, sudden anterograde block of conduction over the AP occurred in 7 of the 41 patients (17%). In 10 patients studied (2 in group A and 8 in group B), loss of the δ wave was gradual; thus, they were not considered to have block in the AP. Using the EP study as a reference standard in this study, exercise testing had a sensitivity of 96% and a specificity of 17%; its positive predictive value was 40% and its negative predictive value was 88%. Thus, the authors concluded that exercise testing had a high negative predictive value in the setting of sudden, complete loss of the δ wave during exercise testing in patients with a low risk of SCD. However, in patients with incomplete or gradual loss of the δ wave during exercise, we cannot reliably predict whether they are at high risk of SCD.

Pharmacologic tests were also done in patients of the same cohort. Procainamide was administered intravenously and a 12-lead ECG was performed at 1-minute intervals during the administration and up to 10 minutes after cessation of the infusion. Propafenone was also administered intravenously using the same protocol. Anterograde block occurred with procainamide in 1 group A patient (4%) and in 21 group B patients (51%). Using EP testing as a reference standard, the procainamide test had a sensitivity of 96% and a specificity of 51%. The positive predictive value was 53% and negative predictive value was 95%. The propafenone test provided the same results as the procainamide test, except in two patients; the propafenone test yielded the same sensitivity, specificity, and positive and negative predictive values. The authors similarly concluded that pharmacologic testing had a high negative predictive value in the setting of loss of the δ wave. Pharmacologic testing did not, however, offer any additional information compared with exercise testing in identifying patients who may be at increased risk of SCD in this study.

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Daubert and colleagues[15] studied patients with documented orthodromic reciprocating tachycardia. Four of these patients had AF or atrial flutter, six had permanent preexcitation on their resting ECG, and the other four had intermittent

preexcitation. The patients underwent bicycle exercise testing using the Bruce protocol with grading every 3 minutes. Of the 10 patients studied, 6 patients had total loss of their δ wave, 4 had gradual loss, and 2 had sudden loss; 3 patients had a partial loss of their δ wave. The point of δ wave disappearance of the R-R interval was between 340 and 895 ms. However, when these patients were subjected to EP testing, of the six patients whose δ wave completely disappeared during exercise, only two patients had a good correlation between the estimated ERP from exercise compared with the recorded ERP during EP testing. In the other four cases, there was no correlation of the ERP between exercise and EP testing.

Given disparate findings in the above studies, we identified 163 patients in 5 other studies in whom the δ wave behavior was characterized. In 74 of these patients (45%), there was either gradual or sudden loss of the δ wave during exercise; 35 patients (21%) had sudden loss of their δ wave, 30 patients (18%) had a gradual loss, and 16 patients (9%) had incomplete disappearance of their δ wave. These studies examined mostly patients with a documented history of arrhythmia in the presence of preexcitation.

In 1987, Critelli and associates[16] began questioning the usefulness of exercise testing when performed while patients are in normal sinus rhythm. They studied 13 patients ranging in age from 18 to 60 years with WPW who had documented rapid preexcited ventricular response during atrial flutter and/or AF and were therefore considered to be at high risk of SCD. Two of these patients were resuscitated from SCD. All patients had undergone EP study prior to exercise testing. Of the 13 patients with a preexcitation pattern on their resting ECG, 11 had a stable preexcitation pattern, 1 had an intermittent preexcitation pattern, and 1 patient had a latent one. All of these patients were subjected to exercise testing and the characteristics of their preexcitation pattern were observed.

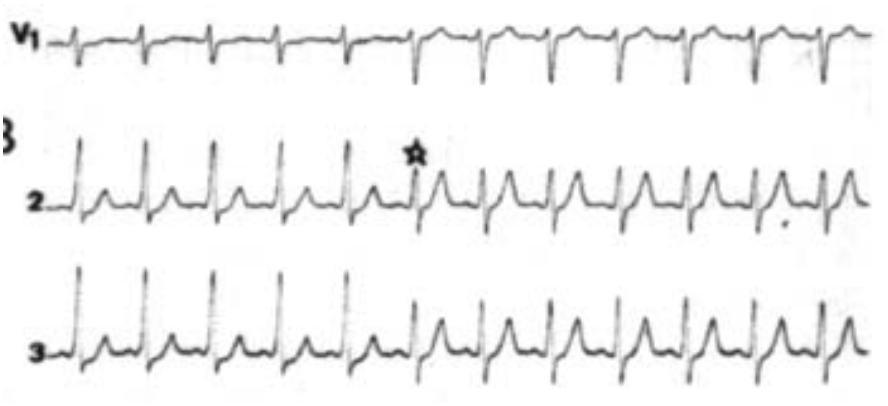

Figure 1. Cessation of conduction down the accessory pathway—and thus abolition of the δ wave (*asterisk*)—with ajmaline. Reprinted with permission from Eshchar Y et al.[17]

Of the 11 patients with a preexcitation pattern, 1 patient had a disappearance of the preexcitation during exercise and ajmaline administration, and therefore demonstrated apparent block of the AP conduction, despite having been capable of sustaining AF with rapid ventricular response (≤ 250 ms). The authors found that continuous preexcitation during exercise testing (and pharmacologic testing with ajmaline) identified 12 of the 13 patients who were deemed to be at high risk of SCD, yielding a sensitivity of 92%. However, these patients were deemed to be at high risk, some of whom were SCD survivors, meaning that one of these patients would have been falsely identified as low risk using exercise testing alone. EP testing, conversely, managed to identify all 13 of these patients when using the shortest R-R interval of ≤ 250 ms as a cutoff of high risk, yielding a sensitivity of 100% in this study.[16]

In 1986, Eshchar and coworkers[17] studied 24 patients with WPW syndrome using EP, exercise, and ajmaline testing. Ajmaline blocked anterograde conduction in 15 of the 24 patients studied; the ERP of the AP in these 15 patients ranged from 250 to 600 ms (mean, 350 ± 110 ms). In the nine patients in whom ajmaline did not block anterograde conduction down the AP, the ERP was 180 to 250 ms (mean, 227 ± 13 ms). An example of cessation of conduction down the AP with administration of ajmaline is shown in Figure 1. The authors concluded that failure of ajmaline to block conduction down the AP was predictive of a short ERP of the AP in their cohort. This small study did not include clinical patient outcomes, and the sensitivity and specificity of the ajmaline test were not calculated. Studies comparing noninvasive testing with invasive EP studies are summarized in Table 1.

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TABLE 1

Sensitivity and Specificity in Studies Utilizing Noninvasive Testing

Study	Patients (N)	Modality	Outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sharma AD et al[13]	56	ETT	Continuous preexcitation	80	29	—	—
Gaita F et al[14]	65	ETT	Loss of δ wave	96	17	40	88
Gaita F et al[14]	65	Pharmacologic	Loss of δ wave	96	51	53	95
Critelli G et al[16]	13	ETT	Loss of δ wave	92	—	—	—

ETT, exercise tolerance test; NPV, negative predictive value; PPV, positive predictive value.

Transesophageal Pacing

Transesophageal pacing has been studied as an effective means for inducing arrhythmias in patients with WPW in order to test the ERP and risk stratify asymptomatic patients. In 1996, Fenici and colleagues[18] studied the reproducibility of inducing arrhythmias in patients with WPW using transesophageal pacing. A total of 74 patients with WPW (64% of whom were symptomatic) were studied transesophageally. Atrial pacing (through the AV node and AP) was successful in all patients, and AP-refractory periods were reproducible in the same patients in two studies performed 3 months apart. The coefficient of reproducibility was low at < 30 ms between studies, but the studies were done with varying autonomic conditions, including supine, upright, and exertional states. This study indicates that transesophageal pacing is consistent in evaluating the ERP through the AV node and AP, although no direct comparison was made between transesophageal studies and intracardiac EP studies in these patients.

Toni and Blaufax[19] more recently studied 23 asymptomatic pediatric patients with WPW who underwent both transesophageal pacing and intracardiac EP study. There was no difference in the anterograde minimum ERP found between transesophageal pacing and intracardiac pacing (312 ± 51 ms vs 316 ± 66 ms; $P = .5$) in this group of patients. The authors concluded that transesophageal pacing is as effective as intracardiac EP study in determining the anterograde minimum ERP. Risk stratification in asymptomatic patients with WPW can therefore be performed with transesophageal pacing, potentially without the complications associated with an invasive procedure such as an EP study, although this modality is not as well studied as invasive EP testing.

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Invasive Testing as a Screen for SCD

Invasive testing as a method of screening patients with WPW for risk of SCD has also been studied extensively. There have been a number of studies looking at the natural history of WPW in patients who are asymptomatic who underwent EP testing and were followed longitudinally. We identified 153 patients in 4 studies of asymptomatic patients who had an EP study.[10,11,20,21] AVRT was induced in 17.75% of patients; 19.5% of patients had AF with a shortest preexcited R-R interval of < 250 ms and were thus considered high risk. However, after a median of 4.4 years of follow-up between all studies, there were no reported deaths.

These findings support those published in 2003 by Pappone and associates.[8] The authors studied a cohort of 212 patients who were asymptomatic at the time of recruitment, thus looking at a different patient population than previous studies.[8] Evidence of preexcitation was found incidentally in all patients studied, mostly from screening ECGs. It should be noted that 50 of the 212 patients were

excluded from the final analysis, thus giving a final number of 162 patients. All patients underwent a baseline EP study and a follow-up EP study 5 years later (or earlier if symptoms developed). Over a period of 5 years, 33 of the 162 patients (20%) became symptomatic. Of note, 29 of these 33 patients had inducible AVRT during their initial EP study. In 11 of these 29 patients, the AVRT degenerated into AF with a mean shortest R-R interval of 223 ms. Of the 33 patients who eventually developed symptoms, 8 had documented spontaneous AF and 25 had SVT. All eight patients with spontaneous AF had both inducible AVRT and preexcited AF during their EP studies. In addition, it should be noted that three patients who suffered a VF arrest had both inducible AVRT and AF at the time of their initial EP study, which, retrospectively, seemed to identify all of the patients at high risk of SCD.

Aside from a patient's inducibility of tachycardia in the EP laboratory, there were other factors that the authors concluded connoted risk for SCD. Among these was the presence of multiple pathways. Of the 33 patients who became symptomatic, 15 were found to have multiple APs, compared with only 1 patient of the remaining 129 asymptomatic patients ($P < .0001$). This suggests that patients with multiple APs have a much higher likelihood of becoming symptomatic. Moreover, all three patients who suffered VF had multiple APs.

Given the above findings, the authors concluded that an initial EP study in asymptomatic patients with preexcitation on ECG should be considered. They suggested that a negative EP study result, initially, identifies those patients who are at low risk of future arrhythmic death. They concluded that a positive EP study has a positive predictive value of 88% for future arrhythmic events and that a negative EP study has a negative predictive value of 86%. AF was induced in only 17% of these patients.

Santinelli and colleagues[3] studied 293 asymptomatic adults with ventricular preexcitation who underwent EP testing who were subsequently followed as outpatients without taking medication for a median time frame of 67 months. Over that time span, 31 patients had an arrhythmic event and 17 had a potentially life-threatening arrhythmia, as defined in this study as AF with a mean rate $\geq 250 \pm 18$ per minute. However, none of the 293 patients died. Using multivariate analysis, the authors concluded that life-threatening arrhythmias could be predicted using a combination of age, inducibility of tachycardia (either AVRT or AF), and an ERP of the AP of ≤ 250 ms. However, the authors ultimately concluded that the overall risk of SCD in this patient population was small.

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Given the low incidence of adverse events of WPW and the relatively low sensitivity and specificity of exercise testing cited in the above studies, it is a challenge to assess the future risk of the development of VF in patients with WPW. Moreover, invasive measures within the electrophysiology laboratory seem to have a better negative predictive value but also lack a unifying physiologic measure that has both adequate sensitivity and specificity. Using the ≤ 250 ms cutoff during sustained induced AF is a sensitive but not specific measure. We saw this in the study by Sharma and colleagues[13] in which EP testing carried only 48% specificity when using this physiologic parameter. One could argue that the generally accepted mechanism of SCD in these patients is the development of AVRT that degenerates into AF which, in turn, degenerates into VF. It could be argued, then, that the presence of inducible AVRT would be a more specific marker of a future VF risk. In the study by Pappone and associates,[8] AVRT that was induced and subsequently degenerated into AF occurred in all three patients who subsequently had VF. However, the fact remains that rapid preexcited AF (≤ 250 ms) is an almost universal finding in patients with WPW and VF and is, therefore, most commonly used as a risk factor.

Conclusions

Given the low overall incidence of SCD associated with ventricular preexcitation, and considering questions regarding the usefulness of noninvasive testing as a screening test for risk of SCD in asymptomatic patients with ventricular preexcitation who are in sinus rhythm,[9] the cardiology community has become divided on how to approach asymptomatic patients who have documented ventricular preexcitation. Considering the sensitivity and specificity of the response of preexcitation on the exercise ECG, up to 20% of patients who are truly at high risk of future VF may be missed on noninvasive testing. In addition, given the low specificity of the exercise test, up to 70% of those who have continuous preexcitation may be unnecessarily sent for EP testing. With respect to EP testing as a screen for SCD, current guidelines do not recommend routine EP testing in patients with asymptomatic WPW.[22,23]

The optimal approach to asymptomatic WPW remains unclear, but the preponderance of evidence

suggests that these patients should not undergo testing (if asymptomatic). In light of studies such as those from Santinelli and colleagues,[3] we agree with current guidelines. However, if we are compelled to offer a test to reassure the anxious patient with preexcitation—in light of the data from Pappone and associates[8]—we can offer exercise testing, or perhaps pharmacologic testing, given their respectable sensitivity. This will avoid unnecessary invasive procedures in a large number of patients who would not benefit; however, this strategy will still leave a very small number of potentially high-risk patients without accurate risk stratification. Every patient and practitioner should jointly decide which method of risk stratification, if any, is warranted. ■

The authors report no real or apparent conflicts of interest.

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MAIN POINTS

- Sudden cardiac death (SCD) as the first clinical manifestation of Wolff-Parkinson-White (WPW) syndrome is a well documented, albeit rare occurrence. Although there is general agreement that the overall incidence of SCD in patients with WPW is quite low, controversy exists regarding risk stratification for patients with preexcitation on surface electrocardiogram, particularly in those who are asymptomatic.
- The primary mechanism of SCD in patients with WPW is the rapid conduction of atrial fibrillation down an accessory pathway, leading to ventricular fibrillation (VF). However, SCD can be the first presenting symptom of WPW.
- Both invasive and noninvasive testing have a good sensitivity but low specificity for identifying patients with WPW syndrome and SCD.
- Transesophageal pacing has been studied as an effective means for inducing arrhythmias in patients with WPW in order to test the effective refractory periods and risk stratify asymptomatic patients.
- Given the low incidence of adverse events of WPW and the relatively low sensitivity and specificity of exercise testing cited in numerous studies, it is a challenge to assess the future risk of the development of VF in patients with WPW.
- Every patient and practitioner should jointly decide which method of risk stratification, if any, is warranted.