Electrophysiology Testing and Catheter Ablation Are Helpful When Evaluating Asymptomatic Patients with Wolff-Parkinson-White Pattern

The Con Perspective

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KEYWORDS

• Electrophysiology • Catheter ablation • Wolff-Parkinson-White syndrome • Sudden cardiac death

KEY POINTS

- The association between asymptomatic Wolff-Parkinson-White (WPW) syndrome and sudden cardiac death (SCD) has been well documented.
- The inherent properties of the accessory pathway determine the risk of SCD in WPW, and catheter ablation essentially eliminates this risk.
- There is no substitute for an approach to WPW syndrome that incorporates the patient's individualized considerations into the decision making.
- Patients must understand that there is a trade-off of a small immediate risk of an invasive approach for elimination of a small lifetime risk of the natural history of asymptomatic WPW.
- Clinicians can further minimize the invasive risk by only performing ablation for patients with at-risk pathways. If this approach is taken, discipline must be maintained to withhold ablation in most pathways; a discipline with which practicing electrophysiologists may struggle.

Case history

A 32-year-old woman presents with atypical chest pain and is found to have Wolff-Parkinson-White syndrome on the 12-lead electrocardiogram. The chest pain evaluation is unremarkable. Transthoracic echocardiography shows no structural heart disease. The patient has no symptoms suggestive of supraventricular tachycardia. The clinician recommends proceeding with electrophysiologic testing and ablation.

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INTRODUCTION

Clinicians are asked to assess adult patients with truly asymptomatic Wolff-Parkinson-White (WPW) syndrome in the setting of a structurally normal heart. The debate is whether all asymptomatic patients with preexcitation should undergo invasive assessment and subsequent ablation, or whether there is a more selective approach. In this article, the evidence relevant to this decision making is discussed and put into context, and a coherent argument is made for an individualized, patient-oriented selective approach.

The association between asymptomatic WPW syndrome and sudden cardiac death (SCD) has been well documented, with an estimated risk between 0.5 and 2 per 1000 patient-years of follow-up.[1] Competing risks of sudden death in the young depend on age, but range from 0.09 per 1000 patient-years (age 0–35 years) to 0.13 per 1000 patient-years (age 35–49 years).[1–5] Unlike patients without WPW, atrial fibrillation (AF) in the presence of a rapidly conducting accessory pathway (AP) can result in a rapid ventricular response and ultimately degeneration to ventricular fibrillation (VF) with hemodynamic collapse. Thus, it is the inherent properties of the AP that determine the risk estimated by the shortest preexcited RR intervals during AF (SPRRI) or the AP effective refractory period (ERP) less than 250 milliseconds as the best known measures of risk.[6–9] In addition, catheter ablation, by eliminating AP conduction, essentially eliminates this risk.[8,9] With these well-documented facts, it can be argued that all patients with electrocardiogram (ECG) evidence of preexcitation, regardless of symptomatic state, should undergo catheter ablation.

Before widespread screening for WPW and widespread invasive AP assessment and ablation can be advocated, the evidence for such a strategy, the quality of the evidence to support it, and the competing risks of an invasive strategy need to be considered. When this is done, it is not clear that an aggressive strategy for catheter ablation of asymptomatic WPW is recommended in all patients.[10,11] As noted in most recent guidelines, such a strategy is reasonable only when a well-informed patient chooses a small immediate risk of ablation rather than a small ongoing risk of the natural history of the condition based on their individual circumstances (IIA recommendation).[8]

TRADITIONAL KNOWLEDGE

Almost as early as electrophysiologic testing was developed, assessment of the risks for SCD in patients with WPW was investigated. Several measures were identified to better define risk, including measures of the AP refractory period, using either the ERP or the SPRRI greater than 250 milliseconds, loss of preexcitation during treadmill testing, or intermittent preexcitation, all identifying low risk individuals.[6,12–14] In addition to AP characteristics, there seemed to be a difference in risk in symptomatic and asymptomatic patients. In one of the early cohorts, Klein and colleagues[6] reported on 25 patients with WPW who presented with VF, 22 of whom were symptomatic before presentation. The only previously asymptomatic patients were all children, aged 8, 9, and 16 years. Subsequent cohort studies have confirmed that most patients with WPW resuscitated from SCD have had prior symptoms,[6,15,16] suggesting that symptomatic and asymptomatic patients have inherently different risks. Mechanistically the increased risk in symptomatic patients is presumed to be caused by an increased propensity to preexcited AF associated with the presence of recurrent atrioventricular reentrant tachycardia (AVRT). It has been well documented clinically and in animal models that rapid atrial rates associated with recurrent supraventricular tachycardia (SVT),[17–20] or atrial pacing in the case of animal models, result in an increased susceptibility to AF.[21,22]

VF or a cardiac arrest may be the initial presentation, particularly in children.[6,23] The age of presentation as well as the presence of multiple APs have been noted as higher risk features, although with time AP characteristics (APERP, SPRRI) have become generally accepted with SPRRI as the best single risk factors.[24] In the surgical era, invasive assessment was often used to identify risk for patients, because surgery was only used for those at highest risk given the obvious barriers to widespread patient acceptance in low-risk groups. However, with the advent and advancements of the catheter ablation era, the thresholds for performing an invasive strategy and subsequent ablation have become lower. Data reevaluating an invasive strategy in the current catheter ablation era have been limited given the widespread acceptance of catheter ablation. Nonetheless, it is an informative exercise to review the most current data.

A Reevaluation of Data in the Modern Catheter Ablation Era: Symptomatic Patients

Pappone and colleagues[25] should be congratulated for their ongoing efforts to provide clarity on this problem in the modern catheter era. Recently they reported on the medium-term (40 months) follow-up of a cohort of 369 patients

who declined catheter ablation among a larger cohort of 8575 patients (4.3%) who had symptomatic SVT. How this cohort was selected and the reasons for declining ablation were not clear. Nonetheless, over 5 years of follow-up, risk factors for the development of malignant arrhythmia were determined. Over 40 months, 29 malignant arrhythmia episodes were found, defined as presyncope/syncope (25), hemodynamic collapse (3), and VF (1).

Of the remaining 340 patients, 168 were asymptomatic for 5 years despite minimal antiarrhythmic drug therapy (3 on drugs). The remaining 172 had a benign course with recurrence of AVRT or AF (40) without sequelae. Patients with malignant arrhythmia had degeneration of AVRT into preexcited AF more often (9 [31%] versus 2 [1.2%]), multiple APs (7 [24.1%] vs 5 [2.9%]) and shorter AP ERPs (239.7 $\pm$ 14 milliseconds vs 264.8 $\pm$ 16.7 milliseconds). On multivariate analysis AVRT degenerating into AF and AP ERP remained independently associated with malignant arrhythmia. SPRRI was not evaluated.

In this modern-era cohort, it is reassuring that traditional risk factors, namely AP ERP and its variants, have been reconfirmed as important. However, several factors need to be discussed when considering the quality of these data. This cohort is highly selected, representing 4% of a large symptomatic WPW population. The investigators provide few data as to why ablation was not performed, but pathway location and characteristics, including ERP and patient preferences, likely informed the decision, limiting this group as a natural history. More importantly, SCD is rare in any cohort of patients with WPW. The primary end point in this cohort study was enriched with 25 of 29 of patients defined as having a malignant course because of presyncope or syncope alone. Syncope at the initiation of benign arrhythmias, including SVT, has been well described and is commonly vagally mediated, especially in young patients, and benign in nature.[26–28] Only 4 so-called hard end points were recorded in this cohort, including only 1 with VF over 5 years (0.8%/y). Herein lies the challenge in defining further risk factors in this population. Hard end points are few, made worse by intervention in those of highest risk. Adding softer end points allows for more robust statistical analyses, but the resulting risk factors have very low positive predictive value for the outcome of SCD. Despite a well-constructed, longitudinal cohort study, it remains difficult to circumvent the inherent major limitation of attempting accurate risk stratification with so few meaningful end points. It is clear that most symptomatic patients with WPW do well, even those with a malignant arrhythmia as defined in this cohort in which 25 of 29 had syncope or presyncope only. As a result, management will always be based on the preference of a well-informed patient who balances a very small immediate ablation risk with a very small longer-term risk without ablation.

A Reevaluation of Data in the Modern Catheter Ablation Era: Asymptomatic Patients

The major focus of management of asymptomatic patients with WPW is managing a perceived risk of sudden death. Unlike symptomatic patients, who benefit from catheter ablation because of elimination of symptoms, asymptomatic patients do not. As such, the only element of value is determination of factors related to SCD. This has key implications for natural history studies on WPW because symptomatic patients often undergo ablation to resolve symptoms alone. Those who do not undergo ablation have undergone electrophysiologic assessment and likely a well-informed decision has been made based on severity of symptoms, AP ERP and risk of ablation overall, including AP anatomic location. Thus a true comparator group for the asymptomatic population remains equally elusive.

Nevertheless, Pappone and colleagues[9] have recently published an 8-year prospective cohort of patients, both symptomatic and asymptomatic with WPW. Among 2169 included in the cohort, 1001 (550 asymptomatic and 451 symptomatic) did not undergo ablation after routine electrophysiology (EP) testing based on patient refusal or referring physician's request. Importantly, 1168 patients underwent ablation, including 206 asymptomatic patients and 962 with symptoms. Complications included complete atrioventricular block leading to permanent pacing in 1 and left bundle branch block in 3 with unknown longer-term consequence. Over a median follow-up of 96 months, 15 patients had VF: 13 previously asymptomatic and 2 previously symptomatic. All patients with VF were successfully resuscitated without neurologic sequelae and all had warning symptoms, including presyncope in 10 and dizziness in 5 others, occurring in hospital in 8 and before hospital in 7. All underwent subsequent successful ablation without complication. All but 1 patient had an AP ERP of less than 230 milliseconds. Three-quarters (73%) had inducible AVRT triggering preexcited AF and only one-quarter had multiple APs. Multivariate analysis showed AP-ERP and AVRT-triggered AF as independently associated with VF. Of the 15 patients with VF, 13 were asymptomatic and 11 were young, between

9 and 14 years of age. Only 2 were adults (both aged 32 years). Age at enrollment trended as a predictor of VF, but was not statistically significant on multivariate analysis ($P = .09$). Thirteen of the asymptomatic patients (2.4%) had VF over 75 months resulting in a crude rate of 0.38%/y (3.8 per 1000 patient-years).

These newest data are not substantially different from previously published data reported in a recent meta-analysis.[1] We performed a systematic review of all English-language cohort studies reporting SCD in patients with asymptomatic WPW. Twenty published studies reported data on 1869 asymptomatic patients with WPW with 11,722 person-years of follow-up.[7,29–47] Follow-up ranged from 15 months to 21.8 years. There was 1 randomized controlled trial, 14 prospective cohort studies, and 5 retrospective cohort studies. Ten SCDs were reported in 6 studies (5 originating from Italy), resulting in a range of 0.7 to 4.5 per 1000 person-years. The unadjusted risk of SCD was 0.85 per 1000 patient-years. Mild heterogeneity was seen. In a random effects model the risk was 1.25 (95% confidence interval [CI], 0.57–2.19) per 1000 patient-years. Eight of the 9 for whom the sex was known were male.

Estimates for SCD differed in the adult and pediatric populations. Among children, 5 SCDs occurred in 2900 person-years of follow-up, resulting in an adjusted risk of 1.93 (95% CI, 0.57–4.14) per 1000 person-years. Five SCDs occurred in adults, among 8822 person-years of follow-up in 14 studies. The adjusted risk of SCD was 0.86 (95% CI, 0.28–1.75). Despite the small numbers, the risk of SCD was numerically higher and trended to be statistically higher in children, although the test of interaction was $P = .07$. Many of the studies reporting SCD in this systematic review were Italian; 7 studies originated in Italy and reported 9 SCDs. A widespread ECG screening program may account for this observation. In addition, it may be that individual SCDs were included in more than 1 cohort study, resulting in an overestimation of the risk of SCD. Sensitivity analysis, using lost to follow-up as a variable, suggested rates as high as 3.66 to 3.98 per 1000 patient-years of follow-up. Regardless, the best estimate of the incidence of SCD seems to be very low (0.9–1.9 per 1000 patient-years); so low as to make accurate measures challenging.

AGE OF PRESENTATION

Is it important that the patient in question is an adult? Despite the limitations of natural history studies as noted earlier, it seems that the risks of pediatric patients and adults differ, with the incidence of life-threatening symptoms in asymptomatic children with a WPW ECG pattern being much higher than in adults.[1] Although most patients with WPW resuscitated from SCD have had prior symptoms,[6,15,16] VF or a cardiac arrest may be the presenting event, particularly in the pediatric population,[6,23,48] which may be because all asymptomatic adults with a WPW ECG pattern by definition have survived childhood without any symptoms, and therefore have a lower risk. Most life-threatening arrhythmia, both in adults and the pediatric population, is aborted.[41,49] In addition, up to 31% of adults may lose the ventricular preexcitation and anterograde conduction over a 5-year period.[34]

THE IMPACT OF RISK FACTORS IN ASYMPTOMATIC PATIENTS

As in patients with symptomatic WPW, the very low incidence of SCD makes accurately defining high-risk groups a considerable challenge. Historically, an SPRRI during AF of less than 250 milliseconds has been used as a marker for SCD.[6,24] As noted earlier, the negative predictive value is very useful. In contrast, the positive predictive value is generally poor. As noted in the literature, patients with WPW in general do well, with rare exceptions, which must be kept in mind when considering a strategy that recommends ablation only for those with high-risk features. All patients will have been subjected to the risk of an invasive procedure and many will undergo ablation even if not destined to have VF, let alone SCD.

The Impact of Catheter Ablation

It is not intuitively clear, and has not been definitively shown, that catheter ablation can meaningfully /affect SCD in asymptomatic WPW. In the most recent cohort study from Pappone and colleagues,[9] there were no deaths in patients undergoing catheter ablation. In contrast, 3 large series have reported rates of death attributable to catheter ablation as 0.7 per 1000, 1.3 per 1000, and 1.9 per 1000 person-years.[50–52] Procedure-related complications were reported in 18, 44, and 82 per 1000 patients.[1,50–52] Recurrence rates of up to 8% were also noted. It is possible that the rates in the community vary widely and that rates of serious complication and procedure-related death are under-reported.

On balance, do these data support a widespread approach for screening and subsequent invasive evaluation of all asymptomatic patients with WPW? To use the latest cohort as an example, there were 15 episodes of VF among 1001 untreated patients over 75 months of follow-up (2.4 per 1000 patient-years) that were potentially preventable

with catheter ablation. In contrast, it is important to reflect carefully on these data. VF is an important end point, but clearly, as in implantable cardioverter-defibrillator populations, it is not coincident with SCD. None of the 15 patients who developed VF died. Among 1001 patients with WPW who were untreated over 8 years, there were no patient deaths among symptomatic or asymptomatic patients. Other registries have found similar findings; that is, a small number of episodes of VF, many aborted, observed almost exclusively among the pediatric population. This finding is remarkable and strongly suggests that VF in the setting of preexcited AF seems distinct in mechanism from that associated with other malignant settings like acute myocardial infarction and inherited arrhythmia. This phenomenon may be caused by the well-documented and presumably tachycardia-related premonitory symptoms in this cohort such that patients sought medical attention during the tachycardia stage before VF. This tendency may have been reinforced by patient and parent education provided by the EP team, as described by the investigators. Thus, it has not been proved that an aggressive screening and invasive approach to asymptomatic WPW, especially in the adult population, can alter outcomes. It is certain that complications can occur from this approach. Even in this large-volume single-center cohort, AV block and long-term permanent pacing, bundle branch block of unknown consequence, and a low rate of access complications were seen.

SUMMARY

How do clinicians put all these data together for their patients? There is no substitute for an approach that incorporates patients' individualized considerations into the decision making. Patients must understand that there is a trade-off of a small immediate risk of an invasive approach for elimination of a small lifetime risk of the natural history of asymptomatic WPW. An approach can be advocated to further minimize the invasive risk by only performing ablation for those with at-risk pathways. If this approach is taken, discipline must be maintained to withhold ablation in most pathways; a discipline with which practicing electrophysiologists may struggle. Ongoing concerns for the potential for harm in a widespread invasive approach are reflected in the current guidelines. It is unlikely that the latest data will alter this recommendation.

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