In 1930, Dr Louis Wolff, Sir John Parkinson, and Paul Dudley White described a case series of 11 patients with a syndrome that now bears their name. The first patient with a short PR interval, ventricular preexcitation, and supraventricular tachycardia was described by Cohn and Fraser in 1913.1 Wood et al postulated the accessory pathway (AP) as its anatomic substrate in 1942, and a large population series reported the prevalence of preexcitation to be 0.15% in 1962.2 Reports in 1971 and 1979 described sudden cardiac death (SCD) in patients with Wolff-Parkinson-White (WPW) syndrome related to atrial fibrillation (AF) that was conducted rapidly over the AP with a short refractory period that deteriorated into ventricular fibrillation (VF).3,4 The first operative ablation of an AP was performed by Sealy in 1967,1 whereas Weber and Schmitz described the first endocardial catheter ablation of an AP in 1983.1

The evolution of curative catheter ablation has clearly become the treatment of choice in the patient with substantive symptoms. A continuing controversy has been the use of this therapy in the asymptomatic or less symptomatic individual, and the central looming theme is the incidence of SCD as part of the natural history of this entity and our ability to predict it. The incidence of SCD in symptomatic patients with WPW syndrome was initially reported in the late 1960s and is estimated to be in the range of 0.25% per year, or 3% to 4% over a lifetime.5

A number of risk factors for development of SCD have emerged,6 including (1) shortest preexcited RR interval (SPRRI) during AF and its surrogate, the antegrade effective refractory period (ERP) of the AP; (2) multiple APs; (3) male gender7; (4) a history of or inducibility of atrioventricular nodal tachycardia (AVRT); (5) age; and (6) syncope.

In a large, early series of patients resuscitated from VF related to WPW syndrome, a SPRRI of >250 ms was not observed, and a range of 200 ms or less was the norm.4 Most patients in this series had inducible AVRT, and others reported vulnerability to AF and inducible AVRT as risk factors.7 Although a SPRRI <250 ms has been virtually uniformly present in patients with VF, many more patients never destined to have sudden death also have this risk factor, which gives it a poor positive predictive value (PPV) with a high negative predictive value (NPV).8 Thus, a SPRRI of <250 ms and its surrogate, an antegrade ERP of <250 ms, have virtually 100% NPV but poor PPV.9 A SPRRI <250 ms remains the pivotal risk factor without which VF related to AF would be rare indeed. Requiring the presence of multiple risk factors in combination would be expected to improve specificity but at the risk of loss of sensitivity.

The only uncontestable and meaningful end point for accurate risk assessment is the SCD rate, which fortunately is very low. Nonetheless, this low event rate challenges the accuracy of any predictor, including electrophysiological studies. A high NPV reported for risk stratifiers is not meaningful in this context, and it must be borne in mind that a coin toss will also have excellent NPV if the event rate is sufficiently low. Assessment of antegrade conduction properties of the AP with isoproterenol will clearly increase the number of false-positive results without any proven improvement in sensitivity given the low SCD rate.

In the current issue of Circulation, Pappone et al10 report on 369 WPW patients not undergoing ablation for a variety of reasons after electrophysiological studies, 142 of them simply refusing ablation. Patients were followed up with medical therapy or no therapy (98%) at the discretion of the referring physician. Although there were no deaths, a conservative and inclusive surrogate of death was used as the primary end point: combined events of presyncope, syncope, hemodynamic collapse, or AF of at least 1-minute duration with SPRRI <250 ms, collectively termed malignant arrhythmia. The majority of WPW syndrome patients remained asymptomatic or had only a “benign” recurrence of arrhythmia over a 5-year period (92%), with the majority no longer taking antiarrhythmic medications (98%). Four patients (1.1%) experienced hemodynamic collapse (preexcited AF in 3 and VF in 1) that required cardiopulmonary resuscitation and/or defibrillation (the circumstances and precipitating factors before hemodynamic collapse are not reported). An additional 25 patients experienced presyncope or syncope during follow-up. Multivariate analysis demonstrated that the antegrade ERP of the AP and AVRT that degenerated to preexcited AF during electrophysiological studies predicted the occurrence of the primary end point. Although the specificity and PPV of AF that resulted from AVRT for predicting the primary end point can be calculated to be 99% and 82%, respectively, this was only observed in 31% (sensitivity) of patients. Other studies11,12 have demonstrated sustained AF to have a PPV of

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only 18% and an NPV of 100% (with use of more rigorous end points). The inducibility of AVRT has been reported to have PPVs that vary widely between 0% and 70%, with PPVs >95% for prediction of subsequent AVRT. To be clear, of the 29 patients in the present study with the end point, 3 had rapid AF and 1 developed VF. Although the latter were not specifically identified, all but 3 of the total group of 29 patients had an AP ERP $\leq$ 250 ms (2 with 270 ms, 1 with 260 ms). If analyzed with the 4 cases of hemodynamic collapse alone (given that SCD is exceptionally rare, and the surrogate end point in this study is a collective that includes presyncope and syncope), the PPV of a short ERP from this study is at best 15%, and NPV is 100%.

The merits of including presyncope or syncope as an end point need to be considered. The association of supraventricular tachycardia with high vagal tone has been reported to result in syncope. Syncope has not been found to be a clinical predictor of VF, and the occurrence of syncope had low sensitivity and specificity for predicting rapid heart rates. Another study demonstrated that AVRT per se was a common cause of syncope, even though the maximum rate over the AP was not higher in patients with syncope than in those without it. Paul et al reported a syncpe incidence of 19% (n = 14) in 74 patients with WPW syndrome and noted that AF with SPRRI was more frequent in patients with syncope (9 of 14 patients). In another study, patients with syncope differed from asymptomatic patients by a higher incidence of inducible AVRT, inducible AF, and had shorter SPRRI.

In the final analysis, the major limitation of the present study by Pappone et al and other studies purporting to predict risk in the WPW syndrome is the very low event rate, especially in those with no or minimal symptoms. The selection of the primary end point is germane to this. At one extreme, the only indisputable end point in our context is SCD or VF. If one sticks to this end point, it is not possible to demonstrate any meaningful risk stratification that provides both high sensitivity and high PPV. One can circumvent this problem by adding other parameters to achieve more end points. Unfortunately, other end points added, such as presyncope, syncope, or any nonsustained arrhythmia, are of more debatable clinical significance.

What can be taken from the present study? It is certainly a large and well-executed study and is likely the closest that will be achievable to a “natural history” study of the patient presenting with symptoms in the modern era. It verifies the very low mortality in general in the WPW syndrome, even in patients with a short ERP. It supports the contention that both medical therapy and no therapy are reasonable options, even in the symptomatic patient who is clearly told of the therapeutic options, along with the pros and cons of ablation, and who elects not to have ablation. It verifies that the group “at risk” is that with a measure of short AP refractoriness. The study does not circumvent the inherent major limitation of attempting accurate risk stratification with so few meaningful end points. 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.

Disclosures

None.

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Risk of Sudden Death in Wolff-Parkinson-White Syndrome: How High Is the Risk?
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