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

Running title: Obeyesekere et al.; Predicting risk of sudden death in WPW syndrome

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Journal Subject Codes: Electrophysiology [106], Epidemiology [8]

Key words: editorials, atrial fibrillation, electrophysiology test, sudden death, Wolff-Parkinson-White syndrome
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\(^1\). The first patient with a short PR interval, ventricular pre-excitation and supraventricular tachycardia (SVT) was described by Cohn and Fraser in 1913\(^1\). Wood et al postulated the accessory pathway (AP) as its anatomical substrate in 1942 and a large population series reported the prevalence of pre-excitation to be 0.15% in 1962\(^2\). Reports in 1971 and 1979 described sudden cardiac death (SCD) in WPW patients related to atrial fibrillation (AF) conducting 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\(^1\) while 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 utilization 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 1960's and is estimated to be in the range of 0.25% per year or 3-4% over a lifetime\(^5\).

A number of risk factors for development of SCD have emerged\(^6\) including; 1) Shortest pre-excited RR intervals (SPRRI) during AF\(^4\) and its surrogate, the antegrade effective refractory period (ERP) of the AP, 2) Multiple APs, 3) Male gender\(^7\), 4) A history of, or inducibility of atrio-ventricular re-entrant tachycardia (AVRT), 5) Age and 6) Syncope.

In a large, early series of patients resuscitated from VF related to WPW, a SPRRI of greater than...
250ms was not observed and a range of 200ms or less was the norm. Most patients in this series also had inducible AVRT while others reported vulnerability to AF and inducible AVRT as risk factors. Although a SPRRI less than 250ms has been virtually uniformly present in patients with VF, many more patients never destined to have sudden death also have this risk factor, rendering it a poor positive predictive value (PPV) with a high negative predictive value (NPV). Thus, SPRRI of less than 250ms and its surrogate, an antegrade ERP of less than 250ms have virtually 100% NPV but poor PPV. The SPRRI <250ms 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 endpoint 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 (EPS). 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. Assessing antegrade conduction properties of the AP with isoproterenol will clearly increase the number of false positives without any proven improvement in sensitivity given the low SCD rate.

In the current issue of Circulation, Pappone et al report on 369 WPW patients not undergoing ablation for a variety of reasons after EPS, 142 of them simply refusing ablation. Patients were followed with medical or no therapy (98%) at the discretion of the referring physician. Although there were no deaths, a conservative and inclusive surrogate of death was utilized 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 off anti-arrhythmic medications (98%). Four patients (1.1%) experienced hemodynamic collapse (pre-excited AF in 3 and VF in 1) requiring cardiopulmonary resuscitation and/or defibrillation (the circumstances and precipitating factors prior to hemodynamic collapse are not reported). An additional 25 patients experienced presyncope or syncope during follow-up. Multivariate analysis demonstrated the antergrade ERP of the AP and AVRT degenerating to pre-excited AF during EPS to predict the occurrence of the primary end point. Although the specificity and PPV of AF resulting from AVRT at predicting the primary end point can be calculated to be 99% and 82%, respectively, this was only observed in 31% (sensitivity) of patients. Other studies have demonstrated sustained AF to only have a PPV of 18% and a NPV of 100%\cite{11,12} (by utilizing more rigorous end points). The inducibility of AVRT has been reported to have PPVs that vary widely between 0%\cite{12} to 70%\cite{13} and NPVs >95%\cite{12-14} at predicting subsequent AVRT. To be clear, of the 29 patients with the end point, 3 had rapid AF and one developed VF. Although the latter were not specifically identified, all but 3 of the total group of 29 had an AP ERP ≤250ms (2 with 270ms, 1 with 260ms). 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 pre-syncope or syncope as an end point need to be considered. The association of SVT with high vagal tone has been reported to result in syncope\cite{15}. Syncope has
not been found to be a clinical predictor of VF\textsuperscript{16} and the occurrence of syncope had low sensitivity and specificity for predicting rapid heart rates\textsuperscript{17}. Another study demonstrated that AVRT per se was a common cause of syncope\textsuperscript{18} even though the maximum rate over the AP was not higher in patients with syncope compared to those without. Paul et al\textsuperscript{19} reported a syncope incidence of 19\% (n=14) in 74 patients with WPW syndrome and they noted that AF with SPRRI was more frequent in patients with syncope (9/14). In another study patients with syncope differed from asymptomatic patients by a higher incidence of inducible AVRT, inducible AF, and had shorter SPRRI\textsuperscript{18}.

In the final analysis, the major limitation of this 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. \textit{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 non-sustained arrhythmia, are of more debatable clinical significance.

What can be taken from this study? It is certainly a large and well-executed study and it 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 medical therapy or no therapies 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 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 endpoints. 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.

Conflict of Interest Disclosures: None

References:


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Circulation, published online January 3, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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