The Asymptomatic Wolff-Parkinson-White Patient:

Time to be More Proactive?

Running title: Obeyesekere et al.; Asymptomatic WPW: Time to be More Proactive?

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It is well known by now that sudden cardiac death (SCD) may occur even in the asymptomatic individual with Wolff-Parkinson-White (WPW) pattern. This is related to the occurrence of atrial fibrillation (AF) with a rapid ventricular response leading to ventricular fibrillation (VF). The essential and critical risk factor is the presence of an accessory pathway(s) (AP) with critically short antegrade refractoriness. The most common numeric in the literature reflecting this is shortest RR interval between pre-excited cycles <250 ms (SPRRI) in AF. The risk of SCD in the individual with asymptomatic WPW has been estimated to be low, in the range of 0.05-0.2% per year, a risk that can obviously be eliminated with successful, uncomplicated catheter ablation. These facts are not in dispute. The controversy that remains is related simply to the fact that population wide electrophysiological assessment and ablation cannot be carried out without risk of complications and even mortality that can mitigate the benefit and broad screening and electrophysiologically based management would be very costly. Current guidelines reflect this by suggesting that electrophysiological assessment with a view to ablation is reasonable when a well-informed patient chooses the small risk of ablation over a small risk due to the natural history (2A recommendation) depending on their individual circumstances. Further, there is little advocacy in the guidelines for large-scale population screening. Do we now have evidence to support improved clinical outcomes for electrophysiological assessment with a view to ablation in all individuals with the WPW pattern in the general population?

The data presented in the manuscript in the current issue of Circulation titled “The natural history of WPW syndrome in the era of catheter ablation, insights from a registry study of 2,169 patients”, by Pappone et al reports outcomes in 1,001 WPW patients (550 asymptomatic and 451 symptomatic) having undergone electrophysiology testing and followed without ablation. The authors contend that the management of asymptomatic WPW is based on
the perceived influence of symptoms on prognosis and raise the notion that symptomatic status unduly influences the management of the asymptomatic individual. In reality, the management of the symptomatic individual is not related to the management of the asymptomatic individual since the former is done primarily for symptom control with benefit abundantly clear while the latter would be done purely to prevent SCD, an unproved hypothesis. Thus, the presented symptomatic control group has no relevance to the discussion of the asymptomatic individual and one may well consider this as a typical “attacking of a straw man”. The supremacy of AP conduction properties prognostically is hardly a new concept. Further, the symptomatic patients in this study were those having refused ablation after electrophysiological assessment for a variety of reasons not clarified but arguably informed by knowledge of AP refractoriness and accordingly can’t be truly considered as even representing the “natural history” of the WPW patient with symptoms. The relevance and validity of this group as a comparator to asymptomatic individuals with WPW is at best questionable and we will focus most of our comments on the asymptomatic group, which is really at the heart of any management controversy in this syndrome.

VF occurred in 15 patients of whom 13 were grouped as asymptomatic, all aged between 10 to 14, mean 11 years (2.4% over a median of 75 months, a crude estimate of 0.38% per year). Although it is well appreciated that VF is not a trivial endpoint, one must also emphasize that in this well documented registry, no symptomatic or asymptomatic patient of over 1,000 studied followed over an overall median of 96 months actually died or had residual adverse sequelle while complications related to catheter ablation included complete AV block leading to a lifetime exposure to permanent pacing and left bundle branch block in 3 with unknown longer term consequences. This in the hands of a very experienced high volume center. These findings
are similar to outcomes observed elsewhere\(^1\), namely a small incidence of VF (aborted in a majority) almost exclusively observed in the pediatric population. Due to the absence of fatalities, the registry data in reality reinforce the failure of an effort to screen and ablate patients to improve hard outcomes of preventing death.

One might pause and consider further. None died! This is a truly extraordinary statistic, that is, 15 clinical VFs without any mortality or sequelae in anyone! All 15 patients with VF (13 initially grouped as asymptomatic) experienced symptoms prior to VF (pre-syncope in 10 and dizziness in 5) allowing for medical attention. VF is NOT immediate in the great majority of WPW patients and the lag time of intermediate arrhythmias results in patients coming to medical attention due to tachycardia related symptoms. Indeed, the authors acknowledge that “patients and parents have been well educated and alarmed to immediately reach hospital or emergency services at beginning of symptoms.” In fact, 8 patients had VF in hospital and many had premonitory symptoms. The registry argues for VF associated with WPW as being fundamentally dissimilar to VF associated with potentially more malignant entities (e.g., coronary disease, LQTS etc).

The vast majority of the WPW population indeed have an excellent prognosis, as reaffirmed by the registry data\(^4\). The reported low VF incidence of 1.9 per 1,000 patient years of follow-up in the asymptomatic population is comparable with other publications, reporting SCD (a majority aborted) in asymptomatic WPW patients of 1.25 per 1,000 person-years (95% confidence interval [CI], 0.57-2.19)\(^1\). The paediatric population has been reported to have a SCD rate of 1.9 (95% Confidence Interval (CI); 0.6–4.1) compared with 0.9 (95% CI; 0.3–1.8) in adults per 1,000 patient years of follow-up (\(P=0.07\))\(^1\). This fortunately low overall risk has frustrated our ability to identify the truly at risk patient accurately which again resonated in this
registry. An abbreviated SPRRI of <250ms has been long accepted as the best predictor of VF but the vast majority of individuals even with this characteristic (and with a short AP effective refractory period (ERP)), will not experience SCD (low PPV). The study by Pappone indeed resonated with previous reports by reporting a PPV for the AP-ERP <230ms at predicting VF of 42.4% and a negative predictive value of 100%. An end point that includes AF (>1 minute) with a SPRRI <250ms (classified as potential malignant arrhythmia), fails to recognize that a SPRRI <250ms has a poor PPV for identifying the patient likely to experience VF (although without a SPRRI<250ms or AP-ERP<230ms VF would be extraordinarily rare). All 78 patients experiencing so-called potential malignant arrhythmias also experienced symptoms, highlighting the importance of symptoms as an impetus to re-evaluate treatment options and that even the truly asymptomatic patient generally presents to medical attention prior to VF.

Comparison of the asymptomatic group to the symptomatic group shows as expected the traditional predictors of VF in both groups albeit with a higher prevalence in asymptomatic individuals. In the symptomatic group, the decision of a minimally or moderately symptomatic patient NOT to undergo ablation would be informed by knowing that the ERP of the AP was long and hence this group might be expected to be composed largely of patients screened by electrophysiology study to be low risk. This biases the multivariate analysis that did not demonstrate symptom status as an independent predictor of events. Indeed, there seems no rational reason why a symptomatic individual patient should have lower risk than an asymptomatic one! Additionally the large number screened (11,237 patients) in this registry and the small number ultimately included (2169) raises the possibility of selection bias.

As reported by Pappone et al, there is a low albeit not zero complication rate associated with AP ablation, even in high volume experienced centres. It is probable that the incidence of
complications/death associated with AP ablation is indeed variable in the community and that those complications may be under reported. Registry data of un-enrolled patients compared with enrolled patients have been reported to have higher risk and receive poorer quality of care with subsequent poorer outcomes. Similarly, the outcome data from those selected for reporting in this registry (2,169 from >11,000 patients) arguably has the potential to misrepresent the real world. In 2 large studies reporting on >1300 adult patients, complications included venous thrombosis (1%), pulmonary emboli (0.3-1.6%), thrombophlebitis (0.6%), infection (0.8%), and catheter induced permanent complete AV block (0.1%). The registry also reported a 0.08% third degree AV block, with approximately 2% overall complication rate (including pneumothrax, femoral hematoma, fistula, left or right bundle branch block and pericardial effusion). Death has been reported in paediatric patients due to cardiac perforation, coronary or cerebral thromboembolism and ventricular arrhythmia. The overall incidence reported in this early large cohort of paediatric patients was 0.22%

Current data including the present study cannot justify a broad screening program for asymptomatic WPW patients, nor can it justify a more aggressive ablation approach in the asymptomatic WPW patient. A number of variables argue against the efficacy of a screening program and not surprisingly is further reinforced by the current registry data, including, low mortality/morbidity rate of asymptomatic WPW, potential for harm by screening and subsequent EP testing and ablation, sensitivity and specificity of risk stratifiers (poor accuracy of SPRRI and AP-ERP), practicality and cost-effectiveness. Ablation provided at the asymptomatic stage has not been demonstrated to produce outcomes superior to those of early treatment at the symptomatic stage (notably all cases of VF were preceded by symptoms and all were resuscitated, allowing for radio-frequency ablation). Although ablation is overall safe and
effective in high volume centers, it is yet to be convincingly demonstrated as superior in the real world to the natural history in asymptomatic WPW patients. A low WPW prevalence in the population is also a barrier to cost-effectiveness.

As highlighted by many publications, risk factors for identifying the truly high-risk patient lack accuracy. However, the identification of factors generally associated with a favorable long-term outcome is somewhat easier. The abrupt and complete loss of pre-excitation during sympathetic stimulation identifies APs which are incapable of rapid antegrade conduction, and thus at low risk of causing VF. Similarly, intermittent pre-excitation generally suggests that rapid antegrade conduction is unlikely. Up to 31% of adults and 0-26% of children lose pre-excitation over 5 years of follow-up, thus highlighting the importance of guideline recommendations to pursue initial non-invasive risk stratification in asymptomatic patients. Indeed the registry data further support the observation of the longer AP-ERP in those who lose pre-excitation compared to those who have persistent pre-excitation (mean AP-ERP 300ms vs. 270ms, p<0.001). Non-invasive variables that identify lower risk asymptomatic individuals, although not the focus of this manuscript may be underexploited and help clinical management.

**Conclusion**

Catheter ablation in the symptomatic patient is not relevant to the management of asymptomatic individuals with WPW since it is fundamentally done to relieve symptoms while ablation in the asymptomatic is done for preventing SCD. The notion that AP refactoriness is pivotal prosthetically is well known. Ultimately this registry verifies what others have shown, namely a very low expected mortality, especially in adults. This does not convincingly argue for population screening or routine invasive testing with a view to ablation that arguably may cause
more harm than good, especially in the “real world” outside of the higher volume centers. The potential for complications from ablation make it difficult to make an unreserved recommendation for a primary electrophysiological assessment and ablation strategy in asymptomatic individuals. The current practice of fair and reasonable discussion of options/risks with the patient is verified and a class IIA indication for ablation when the patient chooses this option remains reasonable3.

**Conflict of Interest Disclosures:** None.

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