Long-Term Natural History of Adult Wolff–Parkinson–White Syndrome Patients Treated With and Without Catheter Ablation

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Background—There are a paucity of data about the long-term natural history of adult Wolff–Parkinson–White syndrome (WPW) patients in regard to risk of mortality and atrial fibrillation. We sought to describe the long-term outcomes of WPW patients and ascertain the impact of ablation on the natural history.

Methods and Results—Three groups of patients were studied: 2 WPW populations (ablation: 872, no ablation: 1461) and a 1:5 control population (n=11 175). Long-term mortality and atrial fibrillation rates were determined. The average follow-up for the WPW group was 7.9±5.9 (median: 6.9) years and was similar between the ablation and nonablation groups. Death rates were similar between the WPW group versus the control group (hazard ratio, 0.96; 95% confidence interval, 0.83–1.11; P=0.56). Nonablated WPW patients had a higher long-term death risk compared with ablated WPW patients (hazard ratio, 2.10; 95% confidence interval: 1.50–20.93; P<0.0001). Incident atrial fibrillation risk was higher in the WPW group compared with the control population (hazard ratio, 1.55; 95% confidence interval, 1.29–1.87; P=0.0001). Nonablated WPW patients had lower risk than ablated patients (hazard ratio, 0.39; 95% confidence interval, 0.28–0.53; P<0.0001).

Conclusions—Long-term mortality rates in WPW patients are low and similar to an age-matched and gender-matched control population. WPW patients that underwent the multifactorial process of ablation had a lower mortality compared to nonablated WPW patients. Atrial fibrillation rates are high long-term, and ablation does not reduce this risk. (Circ Arrhythm Electrophysiol. 2015;8:1465-1471. DOI: 10.1161/CIRCEP.115.003013.)

Key Words: adult ■ atrial fibrillation ■ catheter ablation ■ mortality ■ Wolff-Parkinson-White syndrome

The long-term natural history of Wolff–Parkinson–White syndrome (WPW) is relatively unknown, as curative catheter ablation has emerged as an upfront therapy for both symptomatic and asymptomatic patients.1–3 Early curative treatment is advocated as a means to reduce symptoms, resolve circuit-mediated tachycardias, and potentially lower the risk of atrial fibrillation (AF) and sudden death. Recently, reported long-term data have supported the early use of catheter ablation by demonstrating very low rates of ventricular fibrillation or other malignant ventricular arrhythmias.5

In patients, who present with AF and WPW, ablation of the accessory pathway is considered a curative means to treat both the accessory pathway and AF, particularly, in the absence of other structural heart disease. The sentiment reflects a nearly 30% to 40% incidence of AF in WPW patients compared with long-term rates in non-WPW patients that are <10%.3,6,8 However, now that catheter ablation for WPW has been used for multiple decades, an understanding of very long-term outcomes is possible, including risk of AF. In our center, we have observed many patients with prior ablation for WPW returning for management of AF. This clinical observation suggests that WPW is a syndrome not only consisting of an accessory pathway but may also involve an underlying atrial myopathy conducive toward AF. The possibility of an inherited atrial myopathy was supported by a recent study of 362 WPW patients, which showed that despite catheter ablation the risk of AF remained high. Compared with a control group without WPW, long-term risk of AF was significantly elevated in patients with the WPW syndrome (hazard ratio [HR], 4.77; 95% confidence interval [CI], 3.05–7.43).6

Therefore, we sought to determine the effect of ablation in WPW on long-term incidence of AF and mortality compared with the general population and WPW patients who did not undergo ablation.
WHAT IS KNOWN

- Patients with Wolff-Parkinson-White (WPW) syndrome are at higher risk of developing supraventricular tachycardia and atrial fibrillation, and when antegrade conduction over the accessory pathway is rapid, sudden death.
- Catheter ablation is advocated as a curative therapy for patients with WPW syndrome and as such, atrial fibrillation in the setting of WPW may be a reversible disease manifestation.

WHAT THE STUDY ADDS

- Long-term mortality in adult patients with WPW syndrome is low and similar to control patients without WPW.
- Long-term rates of atrial fibrillation in adult patients that present with WPW remain high despite ablation.
- Trends of increased risk of atrial fibrillation in ablated WPW patients suggest that mechanisms other than those directly related to the presence of an accessory pathway may play a role in atrial fibrillation genesis.

Methods

Patient Populations

Intermountain Healthcare is composed of 22 hospitals and 185 clinics that are all electronically integrated. A system-wide screen of electronic medical records over the past 25 years was performed to include all WPW patients >18 years of age verified by an ECG, regardless of ablation treatment, receiving care at an Intermountain Healthcare facility. Intermountain Healthcare is the largest health-care provider in the Intermountain West serving the needs of Utah and Southeastern Idaho residents. Three cohorts of patients were studied: (1) WPW patients who underwent ablation (n=872), (2) WPW patients without ablation (n=1461), and (3) 5:1 age (±2 years)-matched and sex-matched control population without WPW (n=11 175). Patients were also matched on cardiovascular and valve disease history. Because WPW is an uncommon disorder, we wanted to include all identified WPW patients; however, not every patient was able to provide 5 matches to control for multiple demographics. The WPW populations were matched ±2 years, to minimize temporal discrepancies. However, as ablation practice increased newer patients were more likely to receive ablation as a therapy. In the overall patient population, WPW patients were matched ±6 months to non-WPW patients. Here are the date ranges for each group—non-WPW: September 23, 1992, to November 7, 2014; WPW, nonablation: June 19, 1992, to October 28, 2014; and WPW, ablation: December 2, 1992, to October 28, 2014. The Intermountain Healthcare Urban Central Institutional Review Board approved this study.

Demographics and Clinical Assessments

In addition to age and sex, other clinical characteristics collected included diabetes mellitus, hypertension, hyperlipidemia, smoking, renal failure, coronary artery disease, heart failure, cardiomyopathy, sleep apnea, prior ventricular tachycardia, prior stroke, transient ischemic attack, and myocardial infarction. The presence of these characteristics was determined by International Classification of Diseases, Ninth Revision codes. The use of statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, diuretics, digoxin, antiplatelet agents, anticoagulants, aspirin, and calcium-channel blockers was also documented.

WPW was first determined by International Classification of Diseases, Ninth Revision (426.7) and Tenth Revision (I48.7) codes with confirmation by review of the system-wide ECG database. The ECG database is automated in diagnosis with review and verification typically provided by a cardiologist. In this regard, the diagnosis of WPW represented all potential preexcited syndromes. Electrophysiology study characteristics of the WPW ablation patients were not available in this system-wide analysis. The ablative treatment spanned several decades and reflects different approaches in mapping and ablative technologies. No standardized treatment protocol was used.

Patient Follow-Up and Event Assessment

Clinical outcomes evaluated included death and AF. AF was determined through the review of International Classification of Diseases, Ninth Revision (427.31) and Tenth Revision (I480, I481, I482, I489) codes and the ECG and ambulatory cardiac monitor databases. Deaths were determined by hospital records, Utah State Health Department records (death certificates), and through the Social Security death records. When available, deaths were subsequently classified as cardiac or cardiac arrest. Patients not listed as deceased in any registry were considered to be alive.

Statistical Analysis

The Student t test, ANOVA, and the χ2 statistic were used to evaluate baseline and clinical characteristics among the patient groups. For the WPW groups, demographics were collected at the time of first diagnosis. To confirm associations determined by univariable analysis, multivariable Cox hazard regression (SPSS, version 22.0, Chicago, IL; SAS, version 9.3, Cary, NC) was performed to determine HRs. Kaplan–Meier survival estimates and the log rank test were used to determine initial associations with the end points. An interaction term between time and treatment was included in the Cox analysis, wherever the proportionality assumption seemed to be violated. A subsequent propensity analysis was performed in the WPW patients to minimize variance in confounding baseline demographics. To estimate the propensity score, a logistic regression model was used in which ablation status among WPW patients was regressed on the baseline characteristics listed in Table 1. Patients were then matched 1:1 on propensity score (±0.02) and index date (±2 years). Subsequent analysis of these populations was similar to those described above, with the HR taking into account paired matching and the stratified log-rank being reported. Variables used in the multivariable models included baseline characteristics, comorbidities, and medications (see Table 1 for list). However, final models entered only significant (P<0.05) and confounding (10% change in HR) variables. Two-tailed P values of <0.05 were designated to be nominally significant.

Results

The baseline demographics of the WPW groups stratified by ablation status and compared with a 5:1 control population are displayed in Table 1. The patients who underwent ablation were younger and less likely to have hypertension, diabetes mellitus, renal failure, and coronary artery disease. Ablation patients were also less likely to be treated with an ACE inhibitor or a diuretic. WPW patients were less likely to have hyperlipidemia, diabetes mellitus, prior stroke, or have sleep apnea but had higher rates of coronary artery disease. Compared with the control population, WPW patients were more likely to be treated with an angiotensin receptor blocker and β-blocker. In the WPW patients, who underwent ablation, the accessory pathway was successfully ablated in 93% of the patients. Table 2 displays the
results of a propensity analysis matched 1:1 among WPW patients to account for baseline demographic variance noted in Table 2. In 35.9% of the WPW patients, supraventricular tachycardia was also diagnosed during their initial electrophysiology evaluation.

The average follow-up for the WPW group was 7.9±5.9 (median: 6.9) years. Similar follow-up times were observed for the ablation versus the no ablation groups (ablation: 7.9±5.4 [median: 7.2] years versus no ablation: 7.9±6.2 [median: 6.7] years). The average length of follow-up for the control population was 7.5±5.5 (median: 6.8) days.

Incidence of death, AF, cardiac death, and cardiac arrest are displayed in Table 3 among the different study groups.

Long-term death rates were similar between the total WPW group versus the control group (adjusted HR, 0.96; 95% CI, 0.83–1.11; P=0.56; Figure 1). Long-term cardiac arrest deaths were also similar between the WPW and control groups (adjusted HR, 0.81; 95% CI, 0.47–1.40; P=0.45). However, when we stratified WPW patients by ablation status, nonablation patients had a higher risk of long-term death compared with ablation patients (HR, 2.66; 95% CI, 1.92–3.67; P<0.0001; Figure 1). Cardiac arrest deaths were statistically similar between the WPW, no ablation group versus the ablation group (adjusted HR, 1.49; 95% CI, 0.47–4.72; P=0.50), as well as cardiac deaths (adjusted HR, 1.22; 95% CI, 0.75–1.98; P=0.43). However, both death types trended toward more events in the nonablation-treated WPW group.

Next, we examined long-term rates of AF. Multivariate adjusted long-term rates of incident AF were higher in the total WPW group compared with the control population (HR, 1.55; 95% CI, 1.29–1.87; P<0.0001; Figure 3). Interestingly, in the WPW no ablation group, long-term incident AF rates were found to be lower than the WPW ablation group (HR, 0.35; 95% CI, 0.25–0.48; P<0.0001), even after adjustment.
(HR, 0.39; 95% CI, 0.28–0.53; P < 0.0001; Figure 4). Despite higher AF long-term rates in the WPW groups, stroke and heart failure hospital rates were similar among all groups.

Table 3 displays outcomes in the propensity analysis population. The same mortality and AF trends noted in the general population comparison remained in the analysis of the propensity-matched sample of WPW patients. The multivariate adjusted risk of mortality was lower in the WPW ablation group compared with the WPW no ablation group (HR, 0.51; 95% CI, 0.38–0.70; P < 0.0001; Figure 5). The risk of AF was significantly higher in the WPW ablation group compared with the WPW no ablation group (HR, 2.68; 95% CI, 1.83–3.92; P < 0.0001; Figure 6).

**Discussion**

In this large system-wide study of WPW patients, several important findings were found. First, in general long-term mortality rates are similar between WPW and non WPW patients. However, among WPW patients, there is a reduction in long-term mortality in those treated with catheter ablation that is not fully accounted for by reducing cardiac arrests alone. Next, long-term AF rates are significantly elevated in WPW patients compared with non-WPW patients. The long-term risk of AF is not reduced by catheter ablation.

Similar to prior WPW studies, long-term death rates are relatively low, and in this large population of WPW patients, general mortality rates were similar to non-WPW patients. However, among WPW patients those treated with ablation had lower mortality rates compared with those not treated with ablation. We do not have electrophysiological data about the accessory pathway characteristics. This registry includes patients diagnosed with WPW before and during the era of routine use of catheter ablation. Symptoms likely prompted
Ablation in the majority of patients, although this approach evolved to be considered an upfront therapy. In that regard, symptomatic patients with WPW who underwent ablation had lower rates of long-term mortality. However, decisions to undergo an invasive approach are more complex and also include patient preferences, willingness to seek additional care, socioeconomic status, and referring physician interest in cardiovascular diseases. Patients who undergo ablation also have now seen a cardiologist and as such may receive more attention toward other cardiovascular diseases and risk factors of heart disease. This same paradigm of symptom-driven outcomes was found in a large recent registry that reported higher rates of ventricular fibrillation in asymptomatic WPW patients not treated with catheter ablation compared with symptomatic patients. This registry was a nonrandomized study, but all patients underwent an electrophysiology study as part of the care. However, the use of an electrophysiology study introduces an important outcomes bias as pathway characteristics likely influenced ablation use. In general, given favorable long-term results of catheter ablation, an invasive strategy independent of symptoms in adult patients may be considered. Nonetheless, without randomized trial data, this will remain a controversial topic as all current data have been generated from observational analysis. In pediatric patients, symptomatic and asymptomatic WPW patients have similar long-term sudden death risks. In general, these data that suggest an overall low mortality rate and those from a meta-analysis of 10 studies of asymptomatic WPW patients do not support broad screening programs to reduce community cardiac arrest rates.

Recent studies have challenged the role of catheter ablation in WPW modulating the risk of AF particularly in adult patients. Our data are consistent with these studies, showing persistently higher rates of AF in WPW patients compared with the general population despite catheter ablation. It is plausible that in certain WPW patients that the pathway is part of
a syndrome that also consists of an atrial myopathy. In a study of 31 patients with WPW, those with AF had shorter effective refractory periods of the pulmonary veins and greater veno-
atrial conduction delay. Accessory pathway characteristics associated with a higher risk of symptomatic supraventricular and ventricular arrhythmias also correlated with inducibility of AF. This would also explain our data, which showed that symptomatic patients undergoing ablation had the highest long-term rates of AF. Another plausible explanation is that WPW patients who received an ablation were more likely to receive additional cardiac care and evaluation later in life that led to a diagnosis of AF. Regardless of mechanism, these data do suggest in WPW patients that long-term surveillance for AF may be warranted to early arrhythmia detection to mini-
mize disease-related morbidity.

Limitations
This study has several important limitations to consider. First, this is a system-wide retrospective analysis. As a consequence, many potent confounding variables that can influence out-
comes are introduced. However, given the current broad applica-
tion of ablation in patients with WPW, other study designs will be challenging to pursue. As a consequence, we think that the historical data provide valuable insight. Also, given the retrospective design, we do not have details about the electrophysiology characteristics or locations of the accessory pathway(s). As discussed previously, these characteristics are helpful in determining risk of both atrial and ventricular arrhythmias. However, this study is a large population of adult patients, including many that were diagnosed before routine catheter ablation was offered, which allows for an understanding of the natural history of WPW and the potential impact of catheter ablation on that history. AF diagnosis was based on nonprotocol and symptom-driven electrocardiograms and ambulatory event monitors and as such subclinical AF events will be missed and as a consequence the true long-term incidence of AF underestimated. In addition, we did not estimate the risk of AF according to ablation status after adjusting the competing events like cardiac arrest or cardiac death. Results should be interpreted accordingly.

Finally despite attempting to match based on age and sex, there were still demographic variables that were dif-
cering between groups that may have influenced long-term outcomes. We sought to minimize these with a subsequent propensity analysis, which also confirmed the same outcomes trends. Finally, although this is a system-wide analysis, WPW patients are often seen relatively early in their lives. Although mortality events acquisition is relatively robust, long-term AF outcomes can be influenced by individuals that are more prone to seek care and evaluation, loss of these people to other healthcare systems, or movement out of the region. Nonetheless, these data provide important insight into real world outcomes in a large healthcare network involving large populations of WPW patients.

Conclusions
Long-term mortality rates in WPW patients are low and simi-
lar to an age-matched and sex-matched control population. AF rates are high long-term, and ablation of the accessory pathway does not reduce risk suggestive of a potential underly-
ing inherited atrial myopathy. Trends of increased risk of AF in ablated WPW patients suggest that mechanisms that likely promote symptoms and severity of symptoms may also play a role in AF genesis.

Disclosures
Dr Jared Bunch served on the advisory board for Boston Scientific in 2014 and received minor compensation. Dr Osborn served as a consultant or on the speakers bureau and received minor compensa-
tion from Medtronic, St. Jude Medical, Boston Scientific, Cook, and Spectrornetics. Dr Weiss served as a consultant or on the speakers bureau and received minor compensation from Biosense Webster, St. Jude Medical, and Stereoxis. The other authors report no conflicts.

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