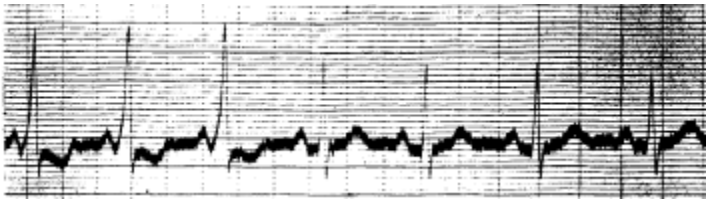
The WPW Syndrome: Current Concepts and Controversies



Nikhil V. Munshi, M.D., Ph.D.

University of Texas Southwestern Medical Center

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Nikhil V. Munshi, M.D., Ph.D., Assistant Professor of Medicine, Cardiology Division

Research and Clinical Interests

My laboratory focuses on understanding the molecular underpinnings of cardiac conduction system formation and how these mechanisms impact normal and pathological cardiac rhythms. My clinical interests include management of coronary care unit (CCU) patients and the genetics of cardiovascular disease.

Purpose and Overview

The pathophysiology of Wolff-Parkinson-White (WPW) syndrome has been ascribed to the developmental persistence of accessory pathways that electrically couple the atria and ventricles outside of the normal cardiac conduction system. Furthermore, the diagnosis and management of WPW syndrome have been well-established through a combination of clinical studies and expert consensus opinion. Interestingly, recent genetic studies have revealed that WPW syndrome can also result from abnormal glycogen storage, providing a potentially new avenue for pharmacological treatment. Moreover, controversies remain over which patients with asymptomatic WPW are at risk for sudden death and whether these individuals should undergo prophylactic ablation.

Educational Objectives

1) To review the pathophysiology of the WPW syndrome highlighting recent advances in the clinical genetics of this disorder
2) To summarize the management of acute and chronic arrhythmias associated with the WPW syndrome
3) To provide an evidence-based rationale for the current strategies employed to treat patients with the WPW EKG pattern in the absence of symptoms

PATHOPHYSIOLOGY OF THE WPW SYNDROME

History, Epidemiology, and Clinical Definitions

In 1930, Wolff, Parkinson, and White described a series of eleven patients who presented with tachyarrhythmias associated with bundle-branch block and a short PR interval on their EKGs[1]. These patients were particularly prone to symptomatic paroxysms of regular or irregular tachycardia. Interestingly, these clinicians also noted that several of their patients had intermittent ventricular pre-excitation or pre-excitation that resolved with exercise. The most concerning aspect of the so-called WPW syndrome, however, was that it occurred in young, otherwise healthy individuals in the absence of clinically-evident organic heart disease. Thus, even from the initial description of this disease, it was recognized that the WPW syndrome could potentially cause symptomatic arrhythmias in healthy, young adults.

From a clinical standpoint, one must distinguish the WPW pattern from the WPW syndrome. The WPW EKG pattern consists of a short PR interval (<120 msec), a wide QRS (>120 msec), slurring of the QRS complex (delta wave), and secondary ST-T wave changes. However, this EKG pattern can occur even in the absence of overt symptoms. Therefore, the WPW syndrome comprises the WPW EKG pattern in addition to either symptoms consistent with or EKG evidence of supraventricular tachycardia (SVT).

In general, EKG evidence of ventricular pre-excitation is relatively rare in the general population based on retrospective epidemiological studies with the caveat that many of these studies are fraught with referral and/or ascertainment bias. One of the largest cohorts for which EKGs were performed on a routine basis was a group of 122,043 potential flyers in the US Air Force with ages ranging from 16 to 50[2]. In this study, the authors retrospectively analyzed EKGs for the WPW pattern (i.e. short PR interval, wide QRS, and delta wave) and found the incidence to be 1.5 per 1000 individuals (0.15%), which correlates with similar epidemiological studies performed in smaller cohorts. In a separate study[3], these authors analyzed 126 individuals with the WPW pattern in more detail during long-term follow-up. Interestingly, 13.3% of these men developed paroxysmal tachycardias during the follow-up period.

Cardiac conduction, accessory pathways, and developmental considerations

In order to understand the etiology of arrhythmias associated with the WPW syndrome, it is instructive to consider the anatomy of the normal cardiac conduction system (Figure 1). This system is a specialized tract of cardiac myocytes that is responsible for impulse generation and propagation within the heart[4]. The sinus node, located in the right atrium, is the site of the normal cardiac pacemaker. Once initiated, the impulse travels through atrial myocytes before undergoing a characteristic delay in propagation through the atrioventricular node (AVN), the only connection between the

atria and the ventricles in the normal adult heart. From the AVN, the impulse passes through the His Bundle (HB), left and right bundle branches, and the Purkinje fiber network to direct depolarization and contraction of ventricular myocytes.

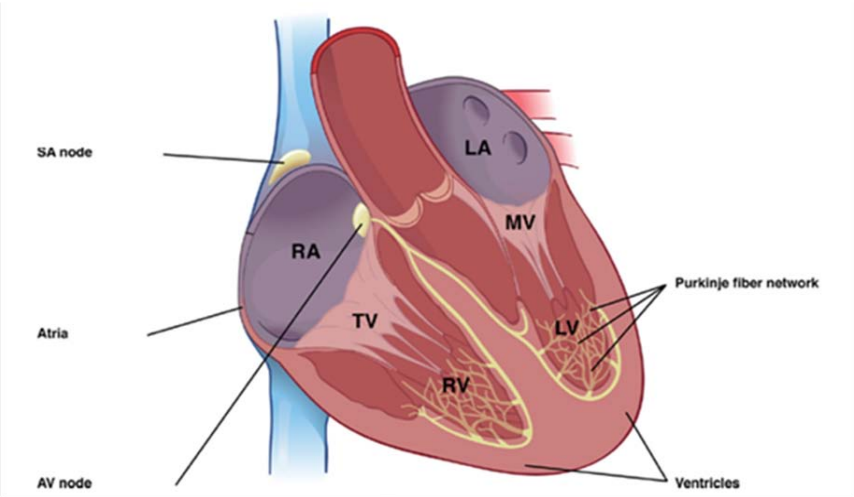

Figure 1

Additional atrioventricular accessory pathways are the hallmark of the ventricular pre-excitation syndromes, including WPW. Interestingly, Kent originally described a group of fibers in the right free wall that he proposed as the physiological connection between atria and ventricles[5]. We now know that the bundles of Kent may in fact have been potential accessory pathways providing the substrate for the arrhythmias associated with the WPW syndrome. In reality, accessory pathways in WPW can be found on the left or the right, either in the septum or free wall[5]. Accessory pathways that either originate or end in any component of the cardiac conduction system are referred to as Mahaim fibers, which are the substrate for Mahaim tachycardias, which will not be discussed further in the current protocol.

Although anatomists and pathologists had described accessory pathways in humans, it was not until clinicopathological correlations were made that these pathways were directly implicated in the WPW syndrome. In a small study of 7 individuals[6], for which prior EKGs and autopsy specimens were available, the authors identified potential bypass tracts in all 7 patients, and 5 out of 7 were predicted by the EKG. This important study demonstrated that there was a correlation between the site of ventricular pre-excitation on the EKG and the anatomical site of the accessory pathway, and it suggested a cause and effect relationship.

While accessory pathways provide a potential substrate for arrhythmia, the functional properties of a particular pathway vary from one individual to another. For example, whether an accessory pathway is identifiable by its ability to cause ventricular pre-excitation on a surface EKG (manifest conduction) depends upon both the location and the specific electrical properties of the bypass tract[7]. Accessory pathways that have rapid anterograde conduction are typically associated with a delta wave, since a significant proportion of ventricular myocardium is activated via the bypass tract. However, despite the rapidity of conduction over a particular pathway, if it is located distant from the sinus node (e.g. left lateral), then conduction will preferentially occur through the AVN, resulting in the absence of ventricular pre-excitation on surface EKG.

Thus, even rapid-conducting and potentially life-threatening accessory pathways can be missed by surface EKG. Furthermore, certain pathways can conduct in only one direction (e.g. retrograde), resulting in "concealed" conduction.

Depending upon the exact characteristics of an accessory pathway (e.g. speed and direction of conduction, localization, etc.), several arrhythmias can be observed in patients with WPW syndrome[8]. In sinus rhythm, patients with an accessory pathway may or may not have EKG evidence of pre-excitation depending upon the factors outlined above. A well-placed premature beat can generate a circus-movement tachycardia known as atrioventricular re-entrant tachycardia (AVRT) that results in either a narrow-complex or wide-complex tachycardia. In the majority of patients with WPW (70%), the accessory pathway makes up the retrograde limb of the re-entrant circuit, resulting in a narrow-complex tachycardia known as orthodromic AVRT. In contrast, 10% of patients will utilize the accessory pathway as the anterograde part of the re-entrant circuit leading to a wide-complex tachycardia referred to as antidromic AVRT. In the remaining 10% of patients with WPW, pre-excited atrial fibrillation (AF), where rapid and irregular impulses are generated in the atria and conducted in a 1:1 fashion, is the predominant arrhythmia.

In order to understand the genesis of abnormal atrioventricular (AV) connections, we must consider how the pattern of AV excitation is established during embryogenesis. The early embryonic heart forms through a process of looping morphogenesis such that common atria and ventricles are formed prior to septation[9]. Although the separation of pulmonary and systemic circuits has not yet been completed, a mechanism is already established to propel blood in a unidirectional fashion. Thus, the AV canal (AVC), or the region between the atria and the ventricles, subserves this function in the early embryonic heart to coordinate contraction in the absence of a distinctive AVN. Consistent with this observation, the impulse is propagated from atria to ventricles over the epicardium, leading to a distinctive base-to-apex direction of ventricular contraction and blood flow[10]. After septation occurs, the AVN matures concomitant with apoptosis of specific AVC myocytes, and the atria and ventricles become electrically insulated by the annulus fibrosus. At this point, electrical activation propagates preferentially via the AVN down the HB and bundle branches to stimulate contraction in an apex-to-base pattern for blood to be expelled through the outflow tracts[10]. Interestingly, the early embryonic AVC, which provides the basis for AV delay during early development, is precisely the anatomical location of the accessory pathways found in the WPW syndrome[11]. Thus, the ring of tissue that surrounds the tricuspid and mitral valves, collectively known as the AV ring, provides a potential substrate for pre-excitation if this tissue is not appropriately eliminated or the fibrous insulation is inadequate.

Human genetics of the WPW syndrome

Several case reports had demonstrated that WPW syndrome could be inherited within families, but the heritability of WPW had not been systematically analyzed to draw any rigorous conclusions. In 1987, Vidaillet and colleagues conducted a study[12] on the first-degree relatives of 456 consecutive patients under their care for ventricular pre-excitation due to accessory pathways documented by an electrophysiology study (EPS). EKGs were analyzed for first-degree relatives of 383 of the 456 patients, and the prevalence of the WPW EKG pattern in this cohort was compared with the general population. From this dataset, these authors demonstrated that the prevalence of pre-excitation by EKG was higher in first-degree relatives of WPW patients than the general population (0.55% vs. 0.15%; $p<0.0001$). Furthermore, the likelihood of having a first-degree relative with EKG evidence of pre-excitation was even higher for individuals with multiple accessory pathways, and the mode of inheritance appeared consistent with an autosomal dominant disorder.

Building on the fundamental hypothesis that WPW syndrome could be inherited as a dominant Mendelian disorder, two groups independently collected multiple pedigrees involving several affected individuals to identify a potential causative mutation[13-15]. In the first study published in 2001 by Gollob and colleagues, two families were identified with familial WPW, and an Arginine to Glutamine substitution was found at position 302 of the PRKAG2 gene that segregated with the disease in both families. Interestingly, the clinical presentation of both families was unique from sporadic WPW in that a high percentage of affected individuals presented with atrial fibrillation or flutter (44% in Family 1 and 38% in Family 2), many affected individuals (76%) required permanent pacemaker implantation for conduction disease, and left ventricular hypertrophy was uncovered in 26% of affected family members. The following year, Arad and colleagues published their findings on 6 families with autosomal dominant transmission of WPW syndrome, and they found 2 additional mutations (Thr400Asn and Asn488Ile) in the PRKAG2 gene, thus independently confirming this association. Moreover, these authors showed that cardiac pathological analysis was consistent with myocyte enlargement rather than myofibrillar disarray, the hallmark of inherited hypertrophic cardiomyopathies, and that glycogen-filled granules were present, suggestive of a myocardial metabolic storage disease.

PRKAG2 encodes the gamma-2 regulatory subunit of the AMP-activated protein kinase (AMPK). AMPK has three subunits, and the gamma subunit is known to mediate the energy-dependent modulation of AMPK kinase activity[16]. Although the exact role of AMPK in the pathogenesis of WPW syndrome remains enigmatic, the authors of the initial study hypothesized that AMPK was likely to be a critical hub in the regulation of various energy-dependent processes within cardiomyocytes[14]. Over the last decade, in addition to myriad roles in regulating whole-body metabolism, AMPK has been implicated in various aspects of cardiac physiology and pathophysiology, including

angiogenesis, cell growth, metabolism, and fibrosis[17]. Aside from its potential role in regulating cardiac energy balance to influence accessory pathway formation, it has also been demonstrated that AMPK can directly phosphorylate voltage-gated sodium channels to affect their conduction properties[16]. Thus, mutation of PRKAG2 is likely to influence multiple aspects of cardiac physiology to ultimately result in accessory pathway formation and concomitant ventricular pre-excitation.

In order to strengthen the cause and effect relationship between PRKAG2 mutations and WPW syndrome, transgenic mouse models over-expressing the human mutant proteins were generated and characterized by both groups that described the original mutations in humans[18, 19]. Arad and colleagues demonstrated that a transgenic mouse overexpressing an N488I mutant PRKAG2 developed LVH and hypertrophic cardiomyopathy with pathological evidence of myocyte enlargement and glycogen deposition, reminiscent of the human pathology. From an electrophysiology standpoint, these mice manifested ventricular pre-excitation by surface EKG, they were particularly susceptible to paroxysmal SVT, and they had reduced survival compared with wild-type littermates. Importantly, detailed histological analysis revealed the presence of continuous AV muscular connections outside of the normal conduction system, consistent with human correlates of ventricular pre-excitation.

Characterization of these mouse models not only provided strong evidence for a causative role of PRKAG2 mutations in WPW syndrome, but it offered a glimpse into a fascinating connection between inherited glycogen storage diseases and ventricular pre-excitation[20]. Several case reports and clinical series have been published demonstrating that patients with Pompe disease, Danon disease, and Tuberous sclerosis can have accessory pathways, thus supporting the idea that anomalous AV connections may result from myocardial metabolic storage disease (Table 1). Perhaps this concept provides a unifying principle for the clinical manifestations of PRKAG2-associated WPW syndrome, hypertrophic cardiomyopathy, and conduction disease. Moreover, WPW syndrome is strongly associated with Ebstein's anomaly, and it has

Disease Category	Example
Congenital Heart Disease	Ebstein's anomaly
Hypertrophic Cardiomyopathy (HCM)	Sarcomeric mutations (AD)
WPW + HCM + Conduction Disease	γ2 AMPK mutations (AD)
Metabolic Myopathies and Storage Disorders	Pompe disease (AR)
	Danon disease (XL)
	Tuberous sclerosis (AR)
Mitochondrial Syndromes	Leber's hereditary optic neuropathy (M)
	tRNA mutations (M)

Table 1

been reportedly linked with certain sarcomeric mutations that cause hypertrophic cardiomyopathy and specific mitochondrial syndromes, including Leber's hereditary optic neuropathy and those associated with tRNA mutations.

Aside from PRKAG2 transgenic mice, additional mouse models have recently emerged that manifest ventricular pre-excitation. Cardiac-specific knockout of the Tbx2 transcription factor, for example, causes mis-patterning of the embryonic AVC and results in left lateral accessory pathways[21]. Similarly, cardiac-specific overexpression of the Notch intracellular domain perturbs normal development of the AVC and also results in the persistence of accessory pathways and ventricular pre-excitation[22]. We recently demonstrated that the Gata4 transcription factor plays a role in AVN formation and establishing normal AV delay. Interestingly, aside from short PR intervals, a subset of Gata4 heterozygous mice and humans carrying a dominant G295S mutation have notching of their QRS complex suggestive of an accessory pathway in the absence of full-fledged WPW syndrome[23]. Additional work with all of these animal models will be aimed at uncovering the molecular mechanisms involved in accessory pathway persistence as a stepping-stone towards developing novel pharmacological approaches for the WPW syndrome.

As an important proof-of-concept that the pathways regulating accessory pathway formation and persistence are modifiable, a transgenic mouse was generated that expresses the mutant PRKAG2 protein only in the presence of an inducer[24]. Using this animal model, Wolf and colleagues showed that the amount of glycogen deposited in cardiac tissue is proportional to the length of exposure to the mutant protein. Most importantly, however, when the mutant PRKAG2 was removed after an age when accessory pathways typically form, the mice resolved their ventricular pre-excitation and demonstrated histological evidence of an intact AV junction. This remarkable study shows that the molecular mechanisms regulating accessory pathway formation are at least theoretically druggable for potential therapeutic benefit.

Conclusions

Taken together, epidemiological studies demonstrate that the prevalence of the WPW EKG pattern is approximately 0.15% in the general population. Pathological, histological, and embryological studies suggest that ventricular pre-excitation results from accessory AV pathways that are normally eliminated during development. Interestingly, a genetic syndrome of WPW, hypertrophic cardiomyopathy, and conduction disease is associated with gain-of-function mutations in the PRKAG2 subunit of the AMPK protein kinase. Finally, mouse models of PRKAG2 WPW syndrome recapitulate many aspects of the human disease and suggest that reversibility of disease is theoretically possible.

ESTABLISHED TREATMENT STRATEGIES FOR WPW SYNDROME

Medical management of WPW

Given the substantial improvements in percutaneous treatment options to potentially cure patients with symptoms associated with accessory pathways (see below), current guidelines no longer advocate the use of anti-arrhythmic drugs for chronic management of patients with WPW syndrome[25]. As detailed in the most recent guidelines, anti-arrhythmic drugs previously used for long-term treatment, such as flecainide, propafenone, sotalol, amiodarone, and beta blockers, have been given a IIa recommendation, while the nodal blocking agents verapamil, diltiazem, and digoxin are absolutely contra-indicated (class III). Thus, medical management of the WPW syndrome has been relegated to acute treatment of the associated arrhythmias.

Although drug treatment of the acute arrhythmias associated with WPW syndrome have largely been established by expert consensus opinion, several small studies provide some guidance for the choice of anti-arrhythmic for pre-excited AF (Table 2). Perhaps the most well-established anti-arrhythmic in clinical practice for this indication is procainamide, which is known to preferentially slow conduction through the accessory pathway. In a study of 55 patients with prior EKG evidence of anterograde pre-excitation[26], Boahene et al. evaluated their response to procainamide (n=30) versus propafenone (n=25) during acute AF. In this small cohort of patients that included 42 men and 13 women with a mean age of 32, AF was successfully terminated in 65% of the procainamide group versus 46% in the propafenone group. In a separate study[27], the efficacy of ibutilide for pre-excited AF was assessed in 22 patient (18 men and 4 women; mean age 31) with previous evidence of an accessory pathway. In this single-arm clinical trial, AF was successfully terminated in 95% of patients after a mean duration of 8 minutes following ibutilide infusion. Finally, a third study[28] enrolled 15 patients (all men; mean age 34) with the WPW syndrome, and they were treated with dofetilide versus placebo for pre-excited AF in an escalating dosing regimen. In this small study with multiple cross-over events, AF was successfully terminated in 71% of the patients who received dofetilide versus 20% of those who received placebo. Taken together, these small studies suggest that procainamide, ibutilide, and dofetilide are reasonable first-line anti-arrhythmic drugs for the acute treatment of pre-excited AF.

Study	Patients	Sex	Age	Treatment Groups	Successful AF Termination	P-value
Boahene et al., 1990	55	42M/13F	32	Procainamide (n=30) vs. Propafenone (n=25)	65% 46%	NS
Glatter et al., 2001	22	18M/4F	31	Ibutilide (n=22)	95% (mean duration 8 min)	ND
Krahn et al., 2001	15	15M/0F	34	Dofetilide (n=14) vs. Placebo (n=5)	71% 20%	<0.05

Table 2

As outlined in the recent guidelines, nodal blocking agents (e.g. calcium-channel blockers, beta blockers, digoxin, and adenosine) should be avoided in the treatment of SVT involving an accessory pathway given the risk of precipitating pre-excited AF[25]. Nevertheless, adenosine is routinely used in the emergency department to terminate SVT in young individuals without a prior EKG. Thus, the actual risk of precipitating AF in this treatment group remains to be quantified. In order to address this question, Strickberger and colleagues studied 200 consecutive patients (74 men and 126 women; mean age 43) with paroxysmal SVT referred for an EPS[29]. During their study, 12mg of IV adenosine was administered after SVT induction to assess their response. Although SVT was terminated in 98% of the cohort, AF or AFL was precipitated in 12%. Interestingly, an APC was observed immediately preceding the onset of AF or AFL in 100% of these patients but only in 58% of patients that did not develop AF or AFL. The authors concluded from this study that if the mechanism of SVT is unknown, adenosine should be administered only if a defibrillator is readily available.

An algorithm for the diagnosis and management of WPW-associated arrhythmias can be summarized as follows (Figure 2)[30]. Patients with tachycardia and a pulse who are unstable should be immediately cardioverted. In those who are stable, the QRS width should be assessed. A narrow complex tachycardia in the presence of an accessory pathway is most likely orthodromic AVRT, and adenosine can be administered. If the QRS is wide and the rhythm is regular, then it is most likely antidromic AVRT, and adenosine can be given. An irregular wide-complex tachycardia in the presence of an accessory pathway should always be considered pre-excited AF unless proven otherwise. In this setting, procainamide is a reasonable first-line agent, although ibutilide, dofetilide, or amiodarone could also be used in the appropriate setting. Finally, nodal blocking agents should be avoided, and a

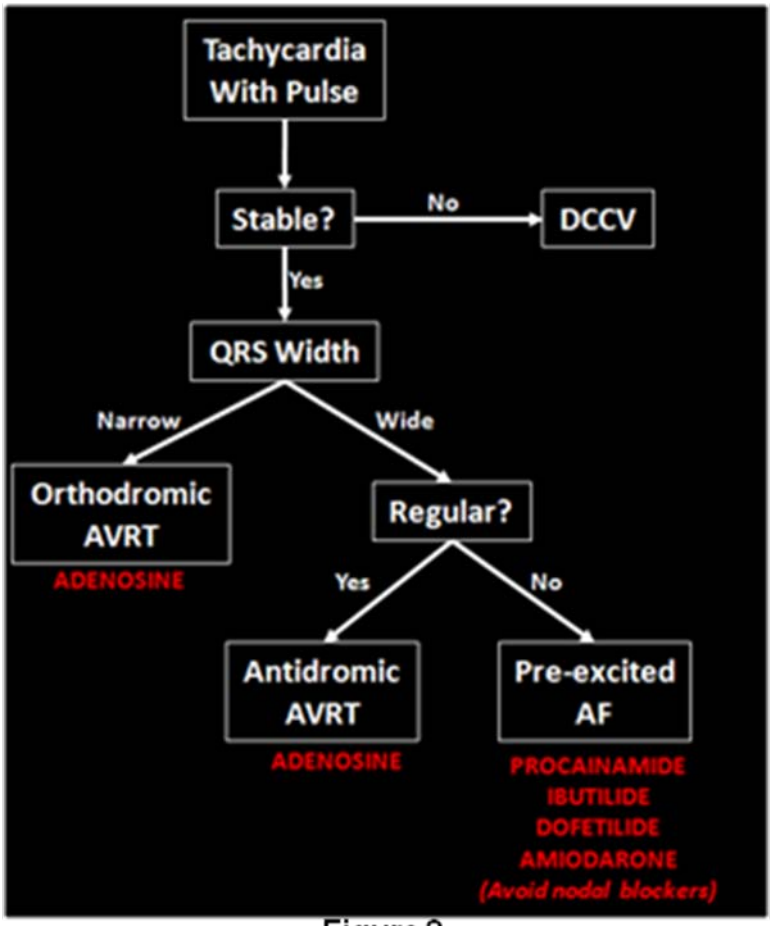

Figure 2

defibrillator must be available while administering all of these anti-arrhythmic treatments.

Catheter ablation approaches for WPW

While percutaneous management of accessory pathways had been reported in sporadic case reports, the first large case series were published in the early 1990s by three independent groups (Table 3). Jackman and colleagues reported on 168 patients[31] with an average age of 32 who underwent ablation of an accessory pathway for the WPW syndrome. In their series, the majority of patients had a left free wall pathway (64%) followed by posteroseptal (26%), right free wall (9%), and anteroseptal (8%). These authors reported a success rate of 99%, a recurrence rate of 9%, and a complication rate of 1.8% (complete AV block, pericarditis, and cardiac tamponade). In a second series published concurrently, Calkins and colleagues described 40 patients with WPW syndrome[32] out of a cohort of 116 patients with SVT (49 men and 57 women; average age 43). The distribution of ablated accessory pathways was remarkably similar to the previous study, and they reported a success rate of 93%, a recurrence rate of 10%, and a complication rate of 2.5% (left circumflex artery occlusion and complete AV block). Similarly, Kuck and colleagues reported on their series of 105 patients with WPW syndrome[33] (66 men and 39 women; average age 40) referred for ablation, and they demonstrated a success rate of 89%, a recurrence rate of 22%, and a complication rate of 3% (thrombotic occlusion of the femoral artery, groin puncture AV fistula, and cardiac tamponade).

Study	Patients	Sex	Age	Accessory Pathways	Success Rate	Recurrence Rate	Complication Rate
Jackman et al., 1991	166	?	32	LFW: 106 (64%) AS: 13 (8%) PS: 43 (26%) RFW: 15 (9%)	164 (99%)	15 (9%)	3 (1.8%)
Calkins et al., 1991	40 (116)	(49M/57F)	43	LFW: 27 (68%) AS: 2 (5%) PS: 8 (20%) RFW: 3 (7.5%)	33 (93%)	4 (10%)	1 (2.5%)
Kuck et al., 1991	105	39F/66M	40	LFW/AS: 79 (71%) RFW/PS: 32 (29%)	93 (89%)	23 (22%)	3 (3%)

Table 3

Despite these promising initial results, long-term follow-up on larger cohorts did not become available for another ten years (Table 4). Calkins and colleagues reported on their experience with 500 patients[34], revealing a success rate of 93%, a recurrence rate of 7.8%, and a complication rate of 1.4%. Similarly, Sheinman and Huang described a series of 654 patients[35] with a success rate of 94%, a recurrence rate of 4.6%, and a complication rate of 2%. Thus, even after considering large groups of patients that underwent catheter-based ablation of an accessory pathway,

percutaneous ablation is safe and effective with a minimal recurrence rate in the hands of an experienced operator.

Study	Patients	Sex	Age	Success Rate	Recurrence Rate	Complication Rate
Calkins et al., 1999	500	290M/ 210F	27	93%	7.8%	1.4%
Scheinman and Huang, 2000	654	353M/ 301F	36	94%	4.6%	2.0%

Table 4

In addition to being efficacious, ablation for the long-term management of the WPW syndrome is cost-effective in high-risk patients. Hogenhuis and colleagues performed a computer simulation to determine the cost-effectiveness of radiofrequency ablation versus other treatment strategies for the WPW syndrome[36]. In their model, they assumed the existence of 4 groups with progressively decreasing risk: 1) patients who survived a prior arrest, 2) patients with paroxysmal SVT or AF with hemodynamic compromise, 3) patients with paroxysmal SVT or AF without hemodynamic compromise, and 4) asymptomatic patients. Furthermore, their algorithm incorporated 5 separate management strategies: 1) observation, 2) observation until cardiac arrest followed by ablation, 3) drug therapy, 4) ablation, and 5) surgery. Based on their computer simulation, these authors found that ablation yields a life expectancy greater than or equal to the other strategies regardless of the patient risk group. In arrest survivors and patients with hemodynamically significant paroxysmal SVT or AF, ablation prolongs survival and saves resources. Finally, ablation in asymptomatic patients was not cost effective, and the benefit in patients with paroxysmal SVT or AF without hemodynamic compromise was unclear. Thus, from the perspective of resource utilization, ablation appears reasonable in patients with symptomatic WPW but not in those without symptoms. Collectively, the efficacy, safety, and cost-effectiveness of ablation make it a class I guideline recommendation for any patient with symptomatic WPW, while ablation in asymptomatic patients remains a class IIa recommendation[25].

Conclusions

In summary, medical management of the WPW syndrome is reserved for acute treatment of the associated arrhythmias. In general, procainamide is the anti-arrhythmic of choice for pre-excited AF, and nodal blocking agents must be avoided. For long-term treatment of the WPW syndrome, accessory pathway ablation is safe, effective, and potentially curative. Finally, ablation should be offered as first-line therapy for all patients with symptomatic WPW.

MANAGEMENT OF ASYMPTOMATIC PATIENTS WITH THE WPW EKG PATTERN

Ventricular pre-excitation, sudden death, and the natural course of WPW

While previous human studies provided strong evidence that accessory pathways contributed to the pathophysiology of ventricular pre-excitation, the notion that pre-excited AF was a potential cause of sudden death in young individuals relied largely on anecdotal evidence and case reports. The results from a large series of 273 unexplained sudden deaths in children and young adults (age<35) were used to substantiate the idea that pre-excited AF could cause sudden death[37]. In Northeastern Italy, all unexplained sudden deaths in children and young adults are examined post-mortem as part of an ongoing systematic evaluation. Basso and colleagues analyzed 10 of these patients (3.6%) with ventricular pre-excitation on a prior EKG and pathological evidence of an accessory pathway. In 90% of these patients, sudden death occurred at rest, and 60% of them had previous symptoms. Furthermore, the majority of sudden deaths associated with ventricular pre-excitation involved left-sided pathways (70%), and, interestingly, 40% were found to have pathological evidence of atrial myocarditis. Taken together, this study demonstrated that 1) sudden death can be associated with ventricular pre-excitation, although it is relatively uncommon, 2) 40% of these sudden deaths occurred without premonitory symptoms, and 3) atrial myocarditis may act as a trigger for AF that leads to sudden death.

Given that pre-excited AF can cause sudden death and many of these patients have no previous symptoms, it would be beneficial to have a sense for how common these events are in individuals with the WPW EKG pattern in the absence of symptoms. In order to address this question, several groups have reported on the natural history of the WPW EKG pattern, specifically assessing for arrhythmic symptoms and sudden death (Table 5). In the study with the longest follow-up period, 19 officers in the Royal Canadian Air Force were identified with the WPW EKG pattern and followed for a mean of 28 years[38]. During this period, 58% developed symptoms of arrhythmia while 0% had sudden death. In a larger cohort of WPW patients from Olmstead County in Minnesota over a 12-year follow-up period[39], 63% had arrhythmic symptoms and 1.8% died

Study	Patients	Location	Sex	Age (yrs)	Follow-up (yrs)	Symptoms of Arrhythmia	Sudden Death
Krahn et al., 1992	19	Manitoba, Canada (RCAF)	19M/ 0F	31	28	11/19 (58%)	0/19 (0%)
Munger et al., 1993	113	Olmstead Co., Minnesota	75M/ 38F	0-77	12	71/113 (63%)	2/113 (1.8%)
Goudevenos et al., 2000	157	Northwest Greece	108M/ 49F	49	4.6	80/157 (51%)	0/157 (0%)
Fitzsimmons et al., 2001	238	Brooks AFB, Texas	232M/ 6F	34	22	69/228 (30%)	1/128 (0.4%)

Table 5

suddenly. In a cohort of 157 WPW patients from Northwestern Greece over a nearly 5-year follow-up period[40], 51% had arrhythmic symptoms and there were no sudden deaths. Finally, Fitzsimmons and colleagues analyzed a cohort of 238 Air Force officers with the WPW EKG pattern during 22 years of follow-up[41] and demonstrated that 30% developed arrhythmic symptoms with only 1 sudden death (0.4%). Taken together, these natural history studies suggest that 30-60% of patients with asymptomatic WPW will develop symptoms consistent with arrhythmia over the long-term, while the rate of sudden death (0-1.8%) in asymptomatic individuals is extremely low.

Risk factors for sudden death and non-invasive risk stratification

Despite the fact that sudden death is a rare event in asymptomatic WPW, the ability to stratify the risk of individual patients would have tremendous clinical implications. In order to address this issue, Klein and colleagues retrospectively studied 25 patients with the WPW EKG pattern and a history of ventricular fibrillation (VF) compared with 73 control patients with the WPW EKG pattern without a history of VF[42]. Perhaps not surprisingly, a history of previous AF and AVRT was the risk factor that best distinguished individuals that developed VF versus those that did not (56% vs. 24.7%; p=0.004). In addition, the presence of multiple accessory pathways and a shortest RR interval less than 250 msec during AF were also independent predictors of VF.

Taking this approach one step further, Timmermans and colleagues retrospectively evaluated 15 patients with the WPW syndrome that had had an aborted sudden death versus 675 individuals with the WPW syndrome in the absence of a sudden death history[43]. From their analysis, the authors showed that 87% of sudden death survivors were men, 73% had a septal accessory pathway, and 67% had elevated adrenergic tone (e.g. exercise or emotional stress) just prior to sudden death. In summary, these two studies established several potential risk factors for VF and sudden death: 1) prior history of AF or AVRT, 2) multiple accessory pathways, 3) short RR interval during AF, 4) male sex, and 5) high adrenergic state.

For patients that present with the WPW EKG pattern in the absence of arrhythmic symptoms, a strategy of initial non-invasive risk stratification seems prudent. The EKG provides a simple, non-invasive test to quickly assess the predilection for a particular patient to conduct rapidly over their accessory pathway in an anterograde fashion. Intermittent pre-excitation or block in the accessory pathway during exercise suggests a low risk of sudden death[44]. More provocative testing that involves infusion of procainamide or ajmaline to assess for loss of pre-excitation also confers a lower risk of sudden death, although these tests remain controversial and have fallen out of favor. In contrast, young age and male sex are risk factors that confer an elevated risk of sudden death in patients with truly asymptomatic WPW and are the only high-risk characteristics that can be assessed non-invasively[44].

Invasive risk stratification and prophylactic ablation

Asymptomatic WPW patients at intermediate risk based on non-invasive assessment may require further risk stratification by EP testing. Before considering the utility of invasive testing, however, one must ensure that invasive assessment is reproducible over time. In order to address this important question, Klein and colleagues performed a longitudinal study on 29 patients with asymptomatic WPW who were invasively assessed by 2 EP studies performed at least 3 years apart[45]. Interestingly, 31% of these patients lost the ability to conduct anterograde over the accessory pathway, and these patients had bypass tracts with longer refractory periods on the initial assessment compared with patients who had persistent pre-excitation. Aside from this subset of the cohort, the remainder of the patients had electrophysiological measurements that were remarkably similar between the two studies. Thus, with the caveat that certain individuals with slower accessory pathways will lose the ability to conduct anterograde, invasive assessment remains stable over time.

The utility of invasive risk stratification was directly tested in a prospective study of 162 patients with the WPW EKG pattern[46]. This cohort consisted of 105 men and 57 women with an average age of 36, and they all had EP studies performed upon entry to the study. Out of the 162 patients in the cohort, 29% were inducible for AF or AVRT and the remaining 71% were not inducible. In general, inducible patients were younger and had multiple accessory pathways with shorter anterograde refractory periods. Importantly, inducible patients had a 17.9-fold higher risk of developing arrhythmic symptoms compared with non-inducible patients over a mean follow-up period of 38 months. Thus, inducibility during invasive EP testing identifies asymptomatic individuals with the WPW pattern who are at higher risk of subsequently developing arrhythmic symptoms.

Building on the potential utility of invasive testing to identify individuals at risk for arrhythmic events, Pappone and colleagues prospectively randomized high-risk asymptomatic WPW patients (inducibility + age<35) to ablation (n=37) versus observation (n=35)[47]. Arrhythmic events occurred in 7% of patients who underwent ablation versus 77% in controls ($p<0.001$), which translates to a 92% relative risk reduction. Interestingly, subgroup analysis suggested that high-risk patients could be further risk-stratified based on the arrhythmia that was induced during the EP study, with non-sustained AF carrying the lowest risk and AVRT triggering AF conferring the greatest risk. Collectively, this study demonstrates that prophylactic ablation can reduce the frequency of arrhythmia in selected high-risk asymptomatic individuals and raises the issue of whether further risk stratification based on the inducible arrhythmia might be feasible.

Since children represent some of the highest-risk individuals with asymptomatic WPW, Pappone and colleagues also tested the hypothesis that prophylactic ablation

would similarly benefit high-risk children[48]. In their study, they randomized asymptomatic children with the WPW EKG pattern deemed to be at high-risk based on inducibility during EP testing to ablation (n=20) versus observation (n=27). Arrhythmic events occurred in 5% of patients who underwent ablation versus 44% of controls ($p<0.001$), amounting to an 89% relative risk reduction. In their subgroup analysis, multiple accessory pathways again emerged as an independent predictor of arrhythmic events in high-risk individuals. In summary, this study shows that prophylactic ablation can reduce the frequency of arrhythmia in high-risk asymptomatic children.

Special populations

As mentioned above, children represent a select population requiring special consideration. In general, children have more rapid anterograde accessory pathway conduction and a longer exposure to the risk of sudden death, while invasive testing and ablation carry higher complication rates and exposure to radiation. Furthermore, it has become apparent that accessory pathway conduction velocity tends to decrease with time, thus complicating risk-stratification at an early age. Given these considerations and based largely on consensus opinion, the Heart Rhythm Society (HRS) gives a class IIb recommendation for prophylactic ablation in children over the age of 5 and a class III recommendation for children below age 5[49].

Athletes are another population requiring special consideration, since epidemiological studies have associated a higher risk of VF and sudden death with exercise. Based on expert consensus opinion from the Bethesda Conference[50], an echocardiogram and exercise treadmill test is recommended in all athletes with the WPW EKG pattern in the absence of symptoms. If both are negative, and the athlete is older than 20-25 years old, then they are allowed to participate in competitive sports. Even if both are negative, and the athlete is under the age of 20, then additional EP testing should be performed and ablation should be offered if multiple accessory pathways exist or the ventricular rate is greater than 240 bpm during isoproterenol infusion.

Finally, individuals with high-risk occupations require special consideration since even an infinitesimal risk of sudden death has profound implications on numerous additional individuals[51]. In the case of pilots, the United States Air Force disqualifies any individual with the WPW EKG pattern from flying unless an ablation is performed. The Federal Aviation Administration (FAA) does not take such a hard-line on this issue, but it requires further invasive risk stratification in any individual with the WPW EKG pattern in the absence of symptoms.

Conclusions

Sudden death is a rare manifestation in patients who are truly asymptomatic with the WPW EKG pattern. Intermittent pre-excitation and exercise-induced accessory

pathway block identify low-risk patients, while male gender, young age, and high adrenergic state associate with patients at a higher risk of sudden death. Prophylactic ablation in high-risk asymptomatic children and adults with the WPW EKG pattern reduces arrhythmic symptoms. Although prophylactic ablation does not specifically prevent sudden death, it may be considered on an individual basis and in certain special populations, including children, athletes, and patients with high-risk occupations.

While prevention of sudden death by prophylactic ablation has not been evaluated in high-risk asymptomatic individuals with the WPW EKG pattern, a recent meta-analysis provides a more accurate risk assessment in this patient population[52]. Obeyesekere and colleagues performed a meta-analysis of 20 studies involving 1869 patients who had the WPW EKG pattern in the absence of symptoms and did not undergo ablation. These authors found that sudden death was reported in 0.5% of this population, and 90% of these deaths occurred in Italian cohorts. Additionally, SVT was reported in 10% of this population, and the rates of both sudden death and SVT were higher in children compared with adults. Taken together, this study demonstrates that the rate of sudden death is low in asymptomatic WPW patients, and the fact that nearly all sudden deaths occurred in Italian cohorts suggests a particularly malignant form of WPW in this geographic region. Overall, these findings support the notion that observation in adults with asymptomatic WPW is reasonable, although children warrant close observation.

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