PERSPECTIVE

High-Risk Patients with Ventricular Preexcitation — A Pendulum in Motion

Bruce B. Lerman, M.D., and Craig T. Basson, M.D., Ph.D.

Since they were first described, preexcitation syndromes have intrigued physicians. The interest derives in part from the myriad bizarre electrocardiographic abnormalities associated with these syndromes and from the variety of complex arrhythmias that may be manifested in affected patients. Symptomatic tachycardias develop in patients with the Wolff–Parkinson–White syndrome because there is conduction over an accessory (extranodal) atrioventricular pathway consisting of working myocardium. Since an impulse arising from the sinus node can activate the atrioventricular node and the more rapidly conducting accessory pathway in parallel, the ventricle ipsilateral to the site where the accessory pathway enters the myocardium is excited prematurely. The consequent classic electrocardiographic triad is a short PR interval, a slurred QRS upstroke ("delta" wave), and a prolonged QRS complex. The estimated prevalence of the Wolff–Parkinson–White pattern is 0.1 to 0.3 percent.

Continued fascination with the Wolff–Parkinson–White syndrome rests on two compelling findings. First, the most common arrhythmia associated with this syndrome, atrioventricular reciprocating tachycardia, represents the clearest clinical paradigm of functional and anatomical reentry, and second, sudden death from ventricular fibrillation may occur in young, previously asymptomatic persons.

Orthodromic atrioventricular reciprocating tachycardia is composed of a circuit in which the normal atrioventricular conduction system serves as the anterograde limb and the accessory pathway serves as the retrograde limb. The electrocardiogram shows a narrow QRS complex and a retrograde P wave inscribed shortly after the QRS complex. The reversal of this circuit, antidromic atrioventricular reciprocating tachycardia, is far less common and presents as tachycardia with a wide QRS complex. Either form of atrioventricular reciprocating tachycardia can degenerate into atrial fibrillation, which can be particularly ominous. In the normal heart, the atrioventricular node protects the ventricles from extremely rapid and potentially destabilizing atrial conduction because there is an inverse relation between the atrial rate and the conduction velocity in the atrioventricular node. However, no such safety net exists with regard to the accessory pathway. As a result, the capacity to conduct rapidly over the accessory pathway allows atrial fibrillation to precipitate ventricular fibrillation and sudden death.

A patient's arrhythmia may be reproduced by programmed stimulation in the invasive-electrophysiology laboratory, and the properties of the reentrant arrhythmia can be characterized. The electrophysiologist can introduce a premature atrial beat by means of a catheter placed in the right atrium or coronary sinus. If the refractory period of the accessory pathway is longer than that of the atrioventricular node, the impulse will proceed only over the slowly conducting atrioventricular node. However, if excitability in the accessory pathway recovers, the impulse can engage the pathway from the ventricle in a retrograde fashion and then reenter the atria to repeat the sequence continuously.

Several measurements are obtained during electrophysiological evaluation to assess the risk of a potentially lethal arrhythmia. These include the anterograde refractory period of the accessory pathway, a surrogate marker for the rate of conduction over the pathway during atrial fibrillation, as well as the mean and shortest RR intervals during preexcited atrial fibrillation. Studies can be performed during the infusion of a catecholamine, such as isoproterenol, to simulate the conditions observed during exercise, and the results can be compared with base-line measurements. The rate at which 1:1 conduction proceeds over the accessory pathway during atrial pacing is also assessed. Septal locations of accessory pathways and the presence of multiple pathways have both been thought to increase the

risk of ventricular fibrillation. Unfortunately, because there is considerable overlap of measured variables between patients in whom life-threatening arrhythmias develop and those in whom they do not, the positive predictive value of such measures is low. Findings suggestive of a low likelihood of sudden death include preexcitation that is intermittent, the ability to produce anterograde conduction block with drugs such as procainamide, and the disappearance of preexcitation during exercise.

The ability to define the precise anatomical location of an accessory pathway through catheter-mapping techniques led to the development of a surgical cure for the Wolff–Parkinson–White syndrome in 1968. Subsequently, various endocardial and epicardial surgical approaches evolved to divide accessory pathways successfully. In the 1980s, endocardial-catheter techniques performed with the use of radio-frequency energy emerged; these techniques have usurped the role in pathway ablation that previously belonged to surgery (see Figure). Antiarrhythmic therapy began to be reserved for patients with infrequent and well-tolerated episodes. Some antiarrhythmic drugs can directly suppress conduction over the accessory pathways, but all of these drugs may also be proarrhythmic. Thus, the high success rate of radio-frequency catheter ablation (approximately 95 percent) and its low com-

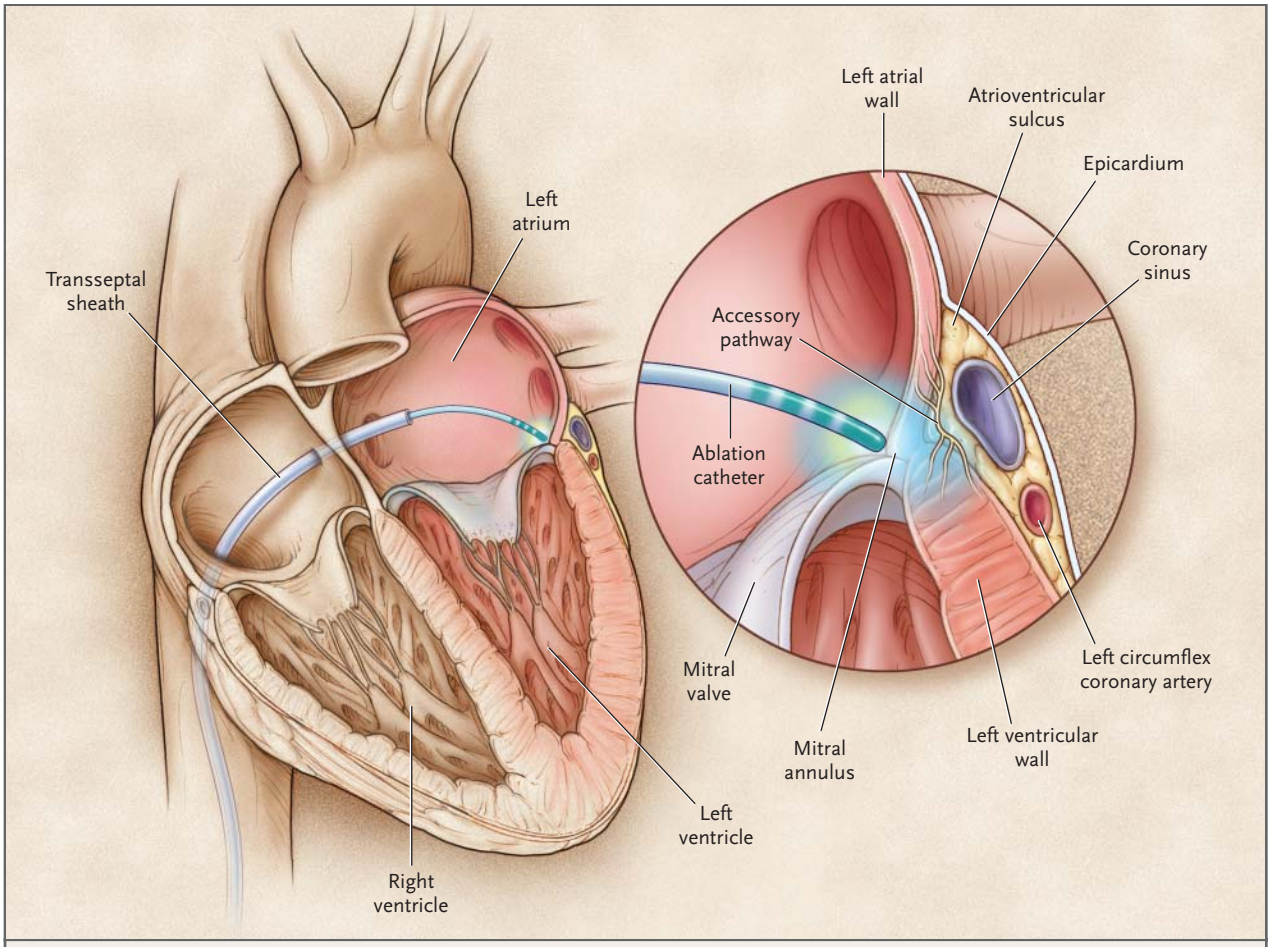

Figure. Ablation of an Accessory Pathway.

The image at the left shows a coronal view of a heart with a left-sided accessory pathway. The transseptal sheath and ablation catheter are introduced through a percutaneous puncture in the femoral vein. The sheath and catheter are advanced through the fossa ovalis with the ablation catheter extended along the circumference of the mitral annulus in order to map the site of the accessory pathway electrically. Once the appropriate site has been identified, radio-frequency energy is applied from the distal electrode of the ablation catheter to a reference transcutaneous electrode positioned on the patient's back (not shown). The magnified inset shows the relation between the ablation catheter and the accessory pathway, which forms a nexus between the atrial and ventricular myocardium.

plication rate (about 2 percent)[1] have made it the treatment of choice for patients with frequent, symptomatic episodes.

However, the appropriate strategy for persons with asymptomatic Wolff–Parkinson–White patterns on the electrocardiogram has been controversial. Although ventricular fibrillation leading to sudden death may be the first manifestation of the Wolff–Parkinson–White syndrome, it is rare. In at least five population-based studies[2] in which more than 600 asymptomatic patients were followed for 5 to 20 years, only two sudden deaths overall were recorded. As a result, the pendulum swung from initial concern about the need to develop aggressive treatment strategies for asymptomatic patients to a consensus that electrophysiological evaluation and ablation should not be recommended for such patients. Exceptions have been made for patients who have high-risk occupations, such as airline pilots and firefighters. The risk of a fatal arrhythmia must be weighed against the risk of death due to ablation (approximately 0.1 percent).[1,3]

In a prospective study reported in this issue of the *Journal*, Pappone and colleagues (pages 1803–1811) randomly assigned asymptomatic "high-risk" patients (patients ≤35 years of age in whom arrhythmias were inducible during electrophysiological study) to undergo ablation or to receive no therapy. The patients who underwent ablation had significantly fewer symptomatic episodes during follow-up. In one high-risk, asymptomatic patient who was randomly assigned to the control group, ventricular fibrillation subsequently developed. It is important to note that the development of symptomatic episodes due to atrioventricular reciprocating tachycardia is not the same as sudden death. Moreover, markers of high risk remain controversial. Certainly, the delineation of genetic factors underlying the pathogenesis of the Wolff–Parkinson–White syndrome or malignant responses to stochastic environmental stressors that may precipitate symptomatic arrhythmias, sudden death, or both would contribute to our clinical armamentarium. However, genetic causes have thus far been identified only for rare, complex forms of the Wolff–Parkinson–White syndrome that include hypertrophic cardiomyopathy or glycogen storage disease,[4,5] and even in these unusual cases, the genetic causes have not yet been correlated with outcomes. Whether prophylactic ablation for the prevention of symptomatic episodes will gain wide acceptance remains to be seen. What is certain is that these new data will animate debate on a critical question that was thought to have been put to rest.

From the Cardiology Division, Department of Medicine, Weill Medical College of Cornell University, New York.

1. Scheinman MM. NASPE survey on catheter ablation. Pacing Clin Electrophysiol 1995;18:1474-8.
2. Todd DM, Klein GJ, Krahn AD, Skanes AC, Yee R. Asymptomatic Wolff-Parkinson-White syndrome: is it time to revisit guidelines? J Am Coll Cardiol 2003;41:245-8.
3. Calkins H, Yong P, Miller JM, et al. Catheter ablation of accessory pathways, atrioventricular nodal reentrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. Circulation 1999;99:262-70.
4. Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. J Clin Invest 2002;109:357-62.
5. Vaughan CJ, Hom Y, Okin DA, McDermott DA, Lerman BB, Basson CT. Molecular genetic analysis of PRKAG2 in sporadic Wolff-Parkinson-White syndrome. J Cardiovasc Electrophysiol 2003;14:263-8.

Have We Seen the Last Variant of Severe Combined Immunodeficiency?

Alain Fischer, M.D.

Over the past 15 years, deciphering of the molecular defects in primary immunodeficiencies has spawned a stream of information on how the immune system works. These advances have been facilitated by the development of powerful new tools that make possible the analysis of the genome and genetic errors. During this time of advances in knowledge of basic immunology, we have also improved medical services for patients with genetically disabled immune systems. Today, accurate diagnosis, precision in prognostication, sophisticated genetic counseling, and new treatments have im-