Editorial

Wolff-Parkinson-White Syndrome
A Genetic Disease?

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The history of the Wolff-Parkinson-White (WPW) syndrome is a 50-year-long tale of speculation and discussion among physiologists, anatomists, and clinicians about how to explain the frequently occurring tachycardias in patients showing a strange ECG. That riddle was solved in 1967 in Amsterdam when Durrer and associates showed that the WPW syndrome was based on a second connection between the atrium and ventricle apart from the normal AV node–His pathway. The presence of conduction over such an accessory AV pathway was demonstrated by epicardial mapping during sinus rhythm. The crucial role of that structure in the tachycardia mechanism was proven by programmed electrical stimulation of the heart and mapping of cardiac activation by intracardiac catheters. It was shown that an impulse circulating in a circuit (consisting of atrium–AV node–His pathway–ventricle–accessory AV pathway) was responsible for the tachycardias usually found in these patients. Essential for initiation of the tachycardia is a difference in the electrophysiological properties of the 2 AV connections, which allows the occurrence of unidirectional block in 1 of the 2 structures. This difference can be exposed not only by critically timed atrial and ventricular premature beats but also by changes in the sinus rate (eg, during exercise). For perpetuation of the tachycardia, the circulation time of the impulse in the tachycardia circuit must be longer than the duration of the refractory period of the different parts of the tachycardia circuit.

It also became clear that the anterograde refractory period of the accessory AV pathway determines the ventricular rate during atrial fibrillation. This helps to identify WPW patients at risk for dying suddenly when atrial fibrillation supervenes. The demonstration that an accessory AV pathway is an essential link both in the reentrant tachycardia mechanism and the ventricular rate during atrial fibrillation has been the basis for successful treatment. Interruption of conduction over the accessory AV pathway, initially by surgery and later by catheter ablation, results in cure of the tachycardias.

Almost 60 years ago, Öhnell stated that there is “a hereditary influence in some preexcitation cases.” Vidaillet et al found that 13 of 383 patients with WPW syndrome also had documentation of accessory pathways in 1 or more first-degree relatives, a prevalence almost 4 times higher than that of the general population. Their data suggested a hereditary contribution to the development of accessory AV pathways in an autosomal dominant pattern.

Molecular Genetics

In the present issue of Circulation and also in a previous article, Gollob et al described families with extensive cardiac disease, characterized by conduction disturbances often requiring pacemaker implantation, atrial arrhythmias, and presence or absence of ventricular hypertrophy, who also showed electrocardiographic features suggestive of the WPW syndrome. In these families, Gollob et al identified mutations in the AMP-activated protein kinase γ-2 subunit (PRKAG2) gene. It is important to note that these patients had a cardiac phenotype that clearly was different from most patients with the WPW syndrome. The majority of WPW patients, apart from their accessory AV pathway, have no other cardiac abnormalities. They may be identified as having “simple” WPW, in contrast to the families described by Gollob et al, in whom a “complex” WPW is present. There is another category of WPW patients who can be classified as complex. Those are patients with congenital heart disease and an accessory AV pathway, with Ebstein’s disease being the most common. We have no information about the genetic background of the accessory pathway in the latter category nor in the isolated simple WPW cases. It is obvious that in the complex cases, the incidence and risk of tachycardias is determined not only by the electrophysiological properties of the accessory AV pathway (most importantly, the refractory period in anterograde direction) but also by the presence of additional cardiac abnormalities.

The families described by Gollob et al raise a number of questions. First, the information about the electrophysiological properties of the atrium, ventricle, normal AV conduction system, and accessory AV pathway is limited. What looks like preexcitation (eg, in hypertrophic cardiomyopathy) may not be the consequence of conduction over an accessory AV pathway but rather of abnormal intraventricular conduction. In the first 2 families, it was found that in 5 of the 8 patients in whom an electrophysiological study was performed, conduction over the accessory AV pathway showed decremental properties. We assume that this was the case in anterograde direction, which is an unusual finding in accessory AV pathways. Also, the finding of ventricular hypertrophy, atrial arrhythmias, and sino-atrial and atrioventricular conduction abnormalities at a young age suggest extensive histological changes in the hearts of these patients. Therefore,
important.14 In contrast, isoform 3 is only expressed with high levels in heart, placenta, liver, and testis, is indispensable and potentially would protect against myocardial dysfunction. One could also hypothesize that a gain of function of the AMP-activated protein kinase complex. The AMP-activated protein kinase complex has been shown to limit the consumption of ATP and to promote metabolism due to failure to conserve and produce ATP for vital functions would impair myocyte contractile function and easily could induce hypertrophic responses and eventually cardiac failure. One could also hypothesize that a gain of function would make the cardiomyocyte function more efficient and potentially would protect against myocardial dysfunction.

From simple organisms such as yeast (Saccharomyces cerevisiae), we learned that the AMP-activated protein kinase is composed of α, β, and γ subunits.12 Whereas the α protein contains the catalytic site, β is required for assembly of the protein complex, and γ is the regulatory protein because it contains the AMP binding site. So far, 3 different isoforms of the γ subunit (1, 2, and 3) have been cloned.13 The 3 isoforms suggest high-level activity on binding of isoforms 1 and 2 and reduced activity with isoform 3.

Amino acid comparison of part of the 3 γ isoforms of the AMP-activated protein kinase (PRKAG). The 2a and 2b proteins are alternately spliced products, identical at the site of the mutations. For comparison, the porcine PRKAG3 isoform is included, in which an identical R-Q mutation was described by Milan et al.15 Note the high homology at the mutated sites.

A careful electrophysiological study should be performed, and information from cardiac biopsy also should be helpful. What about the relation between the genetic findings and the described cardiac abnormalities? One can explain cardiac hypertrophy or cardiac failure as a phenotype caused by loss of function of the AMP-activated protein kinase protein complex. The AMP-activated protein kinase complex has been shown to limit the consumption of ATP and to promote production on binding of AMP. AMP binding depends on changes in the AMP/ATP concentration ratio. A defect in cell metabolism due to failure to conserve and produce ATP for vital functions would impair myocyte contractile function and easily could induce hypertrophic responses and eventually cardiac failure. One could also hypothesize that a gain of function would make the cardiomyocyte function more efficient and potentially would protect against myocardial dysfunction.

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From the PRKAG2 gene, 3 differently sized transcripts have been identified.14 Thus far, 2 proteins have been identified: The PRKAG2a protein is based on the full transcript (exons 1 to 16; 569 amino acids), and PRKAG2b is considerably shorter (exons 5 to 16; 328 amino acids). The first 4 exons are missing in PRKAG2b and contain several myrisylation sites and 1 glycosylation domain, which suggests a membrane-bound position for the PRKAG2a protein. Whether the 2a and 2b proteins have counteractive functions in the heart is unclear. The expression pattern of PRKAG2, with high levels in heart, placenta, liver, and testis, is important.14 In contrast, isoform 3 is only expressed is skeletal muscle.15 Functional studies of the various PRKAG isoforms suggest high-level activity on binding of isoforms 1 and 2 and reduced activity with isoform 3.

An interesting observation was made in purebred Hampshire pigs. In these pigs, a dominant mutation is associated with high muscular glycogen content, which has detrimental effects on processing of the meat. This so-called RN − mutation was identified and seemed to be a R200Q mutation in the PRKAG3 protein. Functional studies in pig skeletal muscle showed a 3-fold difference in AMP kinase activity, with reduced values in the presence of the RN− mutation.15 Loss-of-function mutations in the homologous gene in yeast (SNF4) caused defects in glucose metabolism, including glycogen accumulation. This could be based on impaired recruitment of glycogen for ATP formation because of lack of function of AMP-activated protein kinase complex.

Protein comparison (Figure) of the pig PRKAG3 and human PRKAG2 reveals a perfect match with the R302Q (exon 7) previously identified by Gollob et al16 in familial cardiac disease associated with WPW (Figure). In the present issue of Circulation, an additional mutation is described10 in PRKAG2 (R513G, exon 15) with an early phenotype (at age 2). The striking finding in this small family is the lack of hypertrophy, despite the early onset of hypertension. No mutations in the conserved domain of the PRKAG2 protein, including amino acid 513, have been described previously, and the function of the affected protein domain has not been elucidated.

The question arises as to whether the combination of cardiac abnormalities described by Gollob et al is a variant of a cardiac-specific glycogen accumulation–related disease. To prove this hypothesis, histology of patient material would be most informative.

The possible involvement of glycogen metabolism does not explain the extensive cardiac abnormalities, nor does it tell us whether they lead to disturbances at the channel or gap junction level. However, the association of hypertrophy in combination with the WPW syndrome had already been described in 1978 in a patient with Pompe’s disease.16 In Pompe’s disease, deficiency of the acid-α-glucosidase gene leads to a combined phenotype of cardiac and skeletal muscle disease. This phenotype is mimicked in an acid-α-glucos-
dase–deficient mouse model, showing a marked cardiac phenotype. Again, the identification of a mutation causing a specific disease is just the starting point for interesting new studies to try to unravel pathophysiology. Focusing on glucose and glycogen handling could be a fruitful consideration to guide further studies in the families described by Gollob et al.10,11

Conclusion
Although the observations by Gollob et al are of interest, we should not extrapolate the results uncovered in these unique families with complex arrhythmias and conduction disturbances to the general population of patients with the WPW syndrome or atrial fibrillation. For the majority of WPW patients, we do not have a basis for their arrhythmias other than the presence of an accessory AV pathway. Their therapy is straightforward: complete block in the accessory AV pathway, preferably by catheter ablation. For management of WPW patients, it is important, therefore, to classify them into simple or complex cases. More information from careful electrophysiological, histological, and molecular genetic studies is required to arrive at the best treatment for the complex familial cases.

References

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