

Altered AMP-activated protein kinase activity and pathologic cardiac disease

Michael H. Gollob, Martin S. Green and John P. Veinot
Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada;
Department of Pathology, Ottawa Civic Hospital, Ottawa, Ontario, Canada

Correspondence: Dr Michael Gollob, Arrhythmia Research Laboratory and Division of Cardiology, University of Ottawa Heart Institute, Room H350, 40 Ruskin St, Ottawa, Ontario, Canada K1Y 4W7.
Tel: +1 613 761 5016; fax: +1 613 761 5060; e-mail: mgollob@ottawaheart.ca

Abstract

AMP-activated protein kinase (AMPK) regulates vital metabolic pathways in the cell. Although downstream substrates are abundant, a major role of AMPK is to preserve “energy homeostasis”, particularly in highly metabolically active cells such as skeletal and cardiac myocytes. The biologic importance of AMPK in regulating cellular metabolism is confirmed by the observation that genetic defects in the gamma regulatory subunit of this heterotrimeric protein lead to pathologic skeletal and cardiac disease.

■ *Heart Metab.* 2006;32:28–31.

Keywords: AMP-activated protein kinase (or AMPK), Wolff–Parkinson–White, arrhythmia, glycogen storage disease, hypertrophy, genetics

Case report

In 1985, a 23-year-old man experienced a sudden loss of consciousness, with a spontaneous recovery and without adverse clinical sequelae. Cardiovascular examinations identified ventricular pre-excitation (Wolff–Parkinson–White) on the 12-lead electrocardiogram (*Figure 1*). Two-dimensional echocardiography demonstrated significant left ventricular hypertrophy (septal thickness 20 mm) and a diagnosis of hypertrophic obstructive cardiomyopathy was made.

Three years later, the patient experienced a recurrent loss of consciousness. Emergency personnel documented severe bradycardia (heart rate 20–30 beats/min). Following this event, a permanent pacemaker was implanted. At the age of 31 years, the patient was pacemaker-dependent, and had persistent atrial flutter progressing to permanent atrial fibrillation.

In recent years, the patient has developed progressive and severe left ventricular dilatation and dysfunction. A multigated nuclear scan has documented a left

ventricular ejection fraction of 15% (normal >50%). His clinical course has been further complicated by renal and splenic infarcts, despite a therapeutic international normalized ratio for the coumadin that he was receiving as treatment for permanent atrial fibrillation. Transesophageal echocardiography confirmed a left atrial appendage thrombus. Surgical excision of the left atrial appendage was performed and histologic examination of atrial tissue was completed (*Figure 2*). At the age of 43 years, the patient is awaiting cardiac transplantation. Genetic testing had previously confirmed that he patient harbors an Arg302Gln amino acid substitution in the gamma-2 regulatory subunit (PRKAG2) of AMPK [1].

Discussion

The case presented exemplifies the characteristic features of the PRKAG2 cardiac syndrome, which we have described previously [2]. Typically, affected

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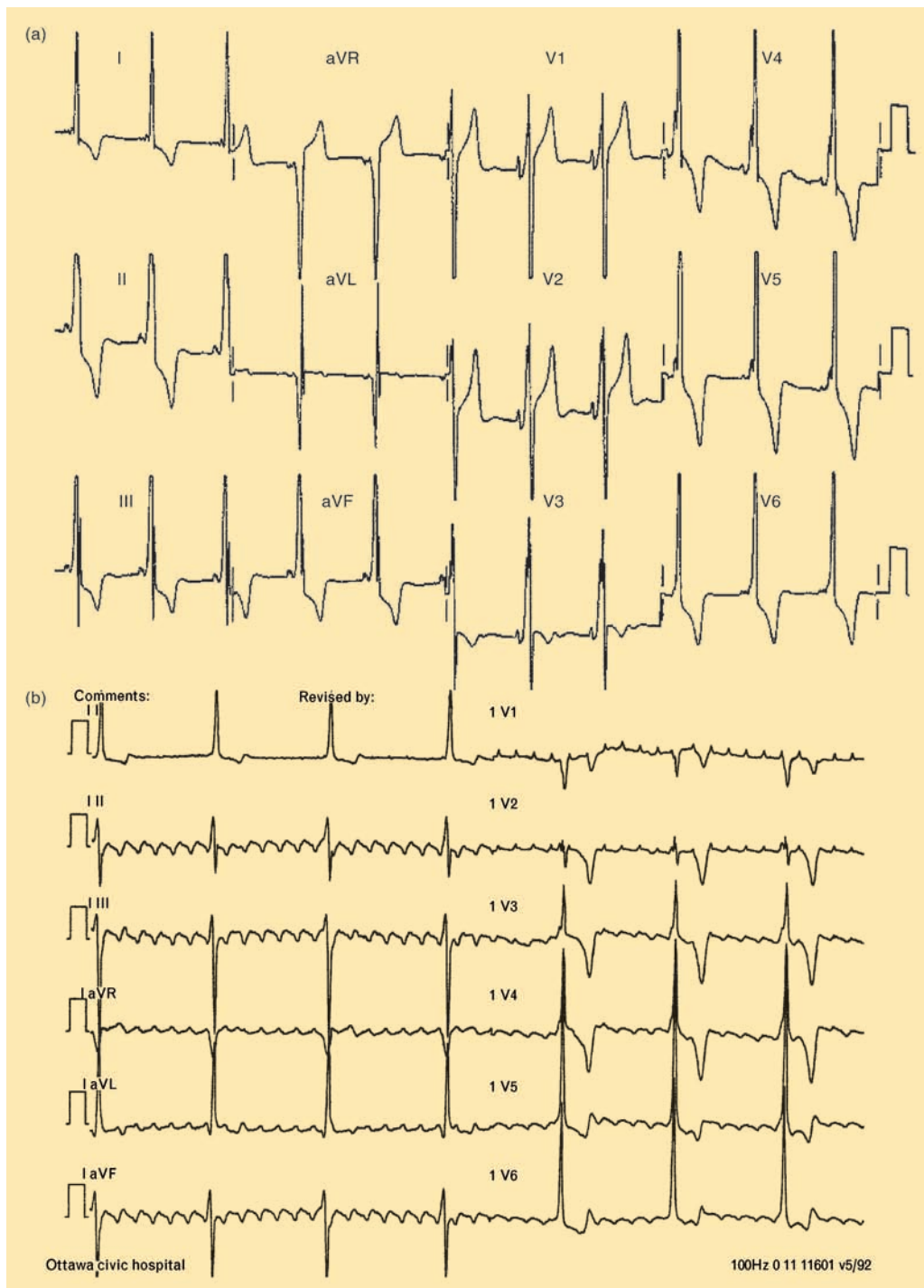


Figure 1. Progressive 12-lead electrocardiographic changes in the PRKAG2 (γ -2 regulatory subunit of AMPK) cardiac syndrome. (a) Baseline 12-lead electrocardiogram (ECG) of the patient at age 23 years, demonstrating a short P–R interval and broad QRS with slurred upstroke, consistent with ventricular pre-excitation. (b) ECG at age 26 years, showing atrial flutter with a slow ventricular response as a result of poor atrioventricular node conduction. The patient was not receiving any medications.

patients present in late adolescence with symptomatic palpitations and documented supraventricular tachycardias. Progressive disease is usual, with the paradoxical development of cardiac conduction system disease, including sinus node dysfunction and impaired atrioventricular node conduction, leading to the onset of bradycardic heart rhythms.

Presumably, the impaired cellular metabolism caused by altered AMPK activity over decades is progressively toxic to cardiac myocytes and conductive tissue.

More than 70% of our patients harboring the Arg302Gln mutation have required a permanent pacemaker during or before their 4th decade of life. In excess of 80% of patients develop either

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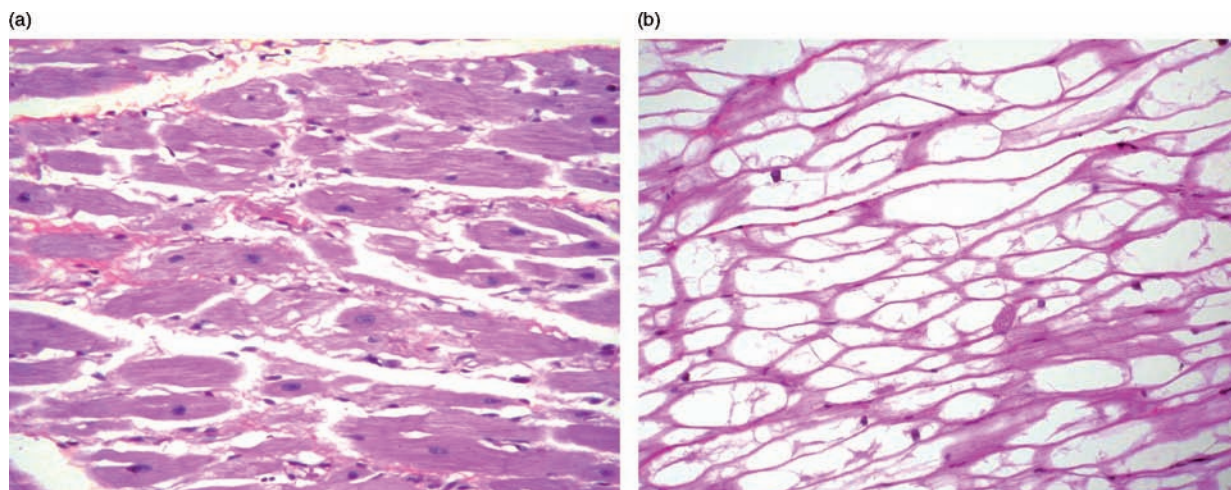


Figure 2. Tissue pathology in the PRKAG2 (gamma-2 regulatory subunit of AMPK) cardiac syndrome. (a) Normal left atrial myocardium, with normal myocyte myofiber staining and content, from a patient without cardiomyopathy. (b) Grossly abnormal vacuolated, cleared myocytes, glycogen-filled and with scarce myofiber contents, in the PRKAG2 cardiac syndrome.

paroxysmal or permanent atrial fibrillation, commonly during their 20s. Although our patient described developed severe cardiomyopathy, evidence of cardiac hypertrophy, dilatation, or dysfunction is observed in only 40% of patients harboring the Arg302Gln mutation. Clinical penetrance of this autosomal dominant genetic disease is 100%, as we have never observed carriers of a clinically silent mutation in adulthood.

The known role of AMPK in regulating key cellular metabolic pathways, particularly glucose metabolism, led to our original hypothesis that the cellular basis for the observed cardiac hypertrophy in many cases was secondary to abnormal glycogen storage in myocytes [2,3]. This hypothesis was supported after the development of transgenic mouse models expressing known disease-causing PRKAG2 mutations [4,5]. The histology presented in Figure 2 in this report confirms that the cellular enlargement and cardiac hypertrophy in affected humans are secondary to glycogen-filled vacuoles, and not a result of the presence of an increase in sarcomeric units, as occurs in the more common form of hypertrophic cardiomyopathy seen in adulthood. The mechanism by which altered AMPK activity results in accessory atrioventricular connections, the anatomic substrate for ventricular pre-excitation, remains unclear. Nevertheless, these accessory atrioventricular connections behave in a fashion similar to that observed in patients with Wolff–Parkinson–White syndrome but without this genetic disease. We have documented atrioventricular re-entrant tachycardia in patients with the Arg302Gln PRKAG2 mutation and confirmed the use of the accessory atrioventricular connection in the tachycardia circuit. In addition, we have performed successful radiofrequency ablation on accessory atrioventricular connections in such patients.

The propensity for frequent atrial arrhythmias in patients implies that AMPK may have a direct role in regulating cardiac ion channels, perhaps through phosphorylation. Evidence suggests that cardiac sodium channels may be a substrate of AMPK [6].

Although the genetic basis of this complex cardiac phenotype has been elucidated, the precise biochemical mechanism of the disease remains controversial. The biochemical effects on AMPK activity of known disease-causing mutations in PRKAG2 has been studied by various methodologies. Mutant AMPK activity has been measured by in-vitro assays, ex-vivo assays of transgenic mice heart extracts, and after expression in various mammalian cell types. Directly conflicting results have been reported, suggesting either a constitutive gain-of-function induced by PRKAG2 mutations, or a significant loss-of-function [4,5]. Recently, Burwinkel et al [7] obtained data suggesting that both a loss-of-function and a gain-of-function may be imposed by PRKAG2 mutations. The presence of the mutation abolished AMP-induced activation of AMPK, hence loss of function. However, the basal state of phosphorylation and activity of AMPK were increased in the presence of the mutation studied, resulting in a constitutive gain-of-function in the cell, independent of the need of AMP for activation [7]. These opposing data sets illustrate the challenges in understanding biochemical phenomena in experimental systems. It is hoped that future studies, perhaps through novel methodologies, will resolve the current controversy.

Conclusion

In view of the significant function of AMPK under conditions of myocardial ischemia and in regulating

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glucose metabolism, this enzyme has been considered as a potential target for drugs. However, the observation that genetically induced perturbations in AMPK activity may lead to a severe cardiac pathology must be considered in the context of the future development of drugs targeting this protein. ■

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