AMPK and the Atrial Response to Metabolic Inhibition*

Grace E. Kim, PhD, Lawrence H. Young, MD

AMP-activated protein kinase (AMPK) is a molecular energy sensor that is essential to the stress response in the heart (1). AMPK is activated during energy imbalance, when the ADP- or AMP-to-ATP ratio increases. Because few proteins have adenine nucleotide binding domains, the activation of a protein kinase, which phosphorylates numerous downstream proteins, amplifies the energy stress response. AMP and ADP binding to AMPK enhances the phosphorylation of the critical Thr172-activating site by promoting the activity of the upstream kinase liver kinase B1 (LKB1), which is also present in the heart. When activated, AMPK signals the cell to generate ATP through substrate metabolism and to conserve energy by limiting anabolic pathways (1).

The LKB1-AMPK axis has emerged as a master metabolic regulator with pleiotropic actions in the heart. During ischemia, there is rapid and robust activation of endogenous left ventricular (LV) AMPK, which limits energy depletion by stimulating glucose uptake and glycolysis and increases autophagy and inhibits protein synthesis (1). Mice with genetically inactivated AMPK are predisposed to ischemia-reperfusion injury with exaggerated necrosis and apoptosis (2,3). Conversely, small-molecule AMPK activators prevent myocardial injury during ischemia-reperfusion (4). Furthermore, agents that activate AMPK may also have benefit in experimental heart failure (5).

In this issue of the Journal, Harada et al. (6) provide initial evidence that atrial AMPK is activated during atrial fibrillation (AF). Using a canine model, they demonstrate increased phosphorylation of the AMPK Thr172 site in left atrial tissue after 1 week of rapid pacing-induced AF. They also found that pacing isolated atrial myocytes at 2 Hz increased the AMP/ATP ratio compared to that in quiescent cells. Increases in the AMP/ATP ratio have also been seen in experimental AF models (7), reflecting alterations in metabolic pathways and the increased energy use required to maintain ionic gradients during rapid atrial rhythm. In addition to changes in energetics, novel mechanisms might also contribute to AMPK activation in AF, as is the case in the ischemic heart, where secreted cytokines amplify AMPK activation (8,9).

The physiological and cell signaling consequences of AMPK activation in AF are all important but were not examined in this study. However, the effects of AMPK inhibition and activation during metabolic stress were explored in canine atrial myocytes, as a possible window into understanding the role of AMPK in AF. Myocytes were incubated with pyruvate as the sole exogenous fuel source and a very high concentration of deoxyglucose, which is not metabolized beyond deoxyglucose-6-phosphate. Such conditions force cells to rely on nonglycolytic metabolism and to deplete the inorganic phosphate needed for cellular ATP synthesis. Metabolic inhibition reduced atrial calcium transients and cell contractility, which partially recovered unless AMPK was inhibited with the pharmacological kinase inhibitor compound C. Although kinase inhibitors lack specificity (10), these results suggest that AMPK activation is an important adaptive mechanism during metabolic imbalance in atrial cells.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut; and the Departments of Internal Medicine (Cardiovascular Medicine) and Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut. Dr. Young has received research grant support from Merck Research Laboratories through Yale University. Dr. Kim has reported that she has no relationships relevant to the contents of this paper to disclose.
Reductions in calcium transients and contractility during AMPK inhibition were associated with a reduced NCX and L-type Ca$^{2+}$ (Cav1.2) channel activity. Cav1.2 and NCX1 were identified in macromolecular complexes that also contained AMPK, raising the question as to whether AMPK might phosphorylate these channels. Kinases recognize stereotypic amino acid sequences within proteins, and AMPK prefers serine residues that are flanked by hydrophobic amino acids (11). Because neither Cav1.2 nor NCX1 contains a classical AMPK phosphorylation sequence, it is more likely that indirect mechanisms were responsible for the physiological effects observed.

The decreased Cav1.2 channel activity likely contributed to the reduction of contractility observed during metabolic inhibition in isolated cardiomyocytes treated with compound C. How these changes might contribute to AF development is less clear. Cav1.2 channel expression is normal in paroxysmal but decreased in persistent AF patients (12), whereas NCX channel expression is increased in paroxysmal but normal in persistent AF patients (13). The authors postulate that intrinsic AMPK activation during AF might prevent shortening of the atrial action potential duration, which could promote re-entry and the perpetuation of AF.

The hypothesis that AMPK inactivation contributes to the development or perpetuation of AF is consistent with prior findings that spontaneous AF occurs in mice with inactive AMPK due to genetic deletion of the upstream kinase LKB1. These mice also develop substantial atrial fibrosis, LV hypertrophy and LV contractile dysfunction (14,15). LKB1 deletion also severely affects early atrial electrophysiology, with chamber-specific neonatal reduction in the atrial expression of Nav1.5, Cx 40 and 43, as well as atrial conduction slowing, before the onset of AF (16). Because LKB1 also regulates 12 other AMPK-related kinases, the extent to which AMPK is primarily responsible for these electrophysiological findings requires further investigation.

Mutations in human AMPK are also known to cause AF as part of the familial PRKAG2 syndrome. Some of these mutations cause a gain-of-function change in AMPK activity (17), which would appear to contradict the antifibrillatory effects of AMPK proposed by Harada et al. (6). However, mutations in PRKAG2 have a continuously high level of AMPK activation, promoting glucose uptake in excess of metabolic demand and inhibiting glucose oxidation, which shunts glucose into glycogen. The consequent glycogen overload leads to persistence of atrial-ventricular muscle bridges during cardiac development, resulting in the Wolff-Parkinson-White syndrome. It also leads to post-natal atrial and ventricular remodeling, conduction system disease and atrial arrhythmias. Interestingly, atrial glycogen buildup is also associated with pacing-induced AF in goats (18), raising the possibility that more long-term AMPK activation induced by AF might contribute to secondary glycogen deposition.

How do these results relate to human AF? The authors also assessed AMPK phosphorylation in right atrial appendage tissue excised from patients with either paroxysmal or chronic AF undergoing cardiac surgery. Although the fraction of phosphorylated AMPK was increased in paroxysmal AF, it was decreased in chronic AF. Whether these initial findings are associated with changes in AMPK activity or lead to alterations in downstream pathways is important to understand and requires further investigation.

AMPK is emerging as a physiological regulator with important roles in type 2 diabetes and cancer. Potent pharmacological AMPK activators are being developed for therapeutic purposes, and it will be of interest to determine whether these agents might be effective in the treatment or prevention of atrial arrhythmias in patients with metabolic disease.

**REFERENCES**


KEY WORDS AMPK, atrial fibrillation, cell calcium handling, myocardial energy metabolism