K<sub>ATP</sub> Channel Openers, Myocardial Ischemia, and Arrhythmias—Should the Electrophysiologist Worry?

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Myocardial ATP-sensitive potassium (K<sub>ATP</sub>) channels and their modulation have been extensively studied in various experimental models. K<sub>ATP</sub> channels, which open when the intracellular ATP-concentration decreases, constitute an endogenous myocardial protective mechanism. K<sub>ATP</sub> activation during ischemia postpones the onset of irreversible damage and reduces the size of the area of myocardial infarction (reviewed in [1]). Blockade of K<sub>ATP</sub> channels by sodium 5-hydroxydecanoate (5-HD) and sulfonylurea derivatives abolishes these cardioprotective effects [1]. The latter drugs are commonly used in diabetics, who are often also suffering from ischemic heart disease. The potential harmful effects of these drugs in terms of more rapid development of irreversible damage and enlarged infarcts have only been studied recently [2]. However, over the years much attention has been focused on the proarrhythmic potential of K<sub>ATP</sub> openers (KCOs), which may constitute an important drawback of this new and promising class of drugs in the treatment of ischemic heart disease. However, both proarrhythmic and antiarrhythmic effects of KCOs have been described [3,4]. These apparent discrepancies may result from the large variation in experimental models used and, more importantly, the different electrophysiological mechanisms of the particular arrhythmia studied.

In this article, we will first describe the electrophysiology of the different types of ischemia-related arrhythmias. Next, we will discuss the electrophysiological effects of K<sub>ATP</sub> channel modulation and the implications for arrhythmogenesis during myocardial ischemia. Finally, we will comment on the available literature concerning the clinical aspects of this issue.

**Electrophysiological Changes and Arrhythmias During Myocardial Ischemia**

Cessation of myocardial blood flow and subsequent shortage of oxygen and substrate leads to a cascade of metabolic and electrophysiological changes in the deprived myocardium (reviewed in [5] and [6]). Within minutes, the potassium concentration in the extracellular space rapidly rises due to an increase in efflux of potassium ions from myocardial cells presumably compensating for an influx of cations such as sodium [7]. More importantly, inhomogeneity in [K<sup>+</sup>]<sub>e</sub> develops during regional ischemia, both within the border zone between the ischemic and normal myocardium and in the central ischemic zone (see [6]). Also, extracellular acidification occurs due to accumulation of protons and lactate generated by anaerobic glycolysis and ATP hydrolysis. In rabbits, the extracellular potassium concentration ([K<sup>+</sup>]<sub>e</sub>) reaches a plateau phase after about 8 minutes of ischemia, and a third phase (second rise in [K<sup>+</sup>]<sub>e</sub>) is observed after about 16–18 minutes of ischemia, correlating with the onset of irreversible myocardial damage [5,8]. At this stage, anaerobic glycolysis is exhausted and the extracellular pH does not decrease further.

Electrically, cells in the ischemic area depolarize within minutes, i.e., the resting membrane potential decreases, at least partly due to the alterations in extracellular potassium concentrations (reviewed in [5]).

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Secondary to the depolarization, the conduction velocity decreases. Another important electrophysiological effect of ischemia is progressive shortening of the action potential duration (APD), caused by the increased activity of outward potassium currents. In particular, opening of KATP channels seems to be involved [9]. It is ultimately followed by a progressive decrease in amplitude of the action potential and inexcitability, changes in the refractory period, and slowing of conduction velocity [5]. Epicardial cells are more susceptible to action potential shortening than endocardial cells, giving rise to spatial inhomogeneities in action potential duration. Indeed, it is thought that the spatial dispersion in ischemia-induced electrophysiological changes (i.e., slow conduction and altered refractoriness) is the most important trigger for reentrant arrhythmias during early myocardial ischemia [6].

**Mechanism and occurrence of arrhythmias during ischemia**

The incidence and time distribution of ventricular arrhythmias during myocardial ischemia is dependent on the experimental model used and the electrophysiological changes induced. In dog and pig models of early regional ischemia, ventricular arrhythmias occur in two distinct phases (reviewed in [6]). The first phase (phase 1a) occurs between 2 and 10 minutes after the onset of ischemia. Following an arrhythmia-free interval, the second early phase (phase 1b) starts at about 15 to 20 minutes and lasts until 30 minutes after coronary occlusion. In contrast, other species such as rats, guinea pigs, and rabbits show a unimodal rather than a bimodal distribution of arrhythmias in the first 30 minutes of both regional and global ischemia, with a peak incidence at 10 minutes or longer. It has been suggested that the arrhythmias observed in smaller hearts correspond to the phase 1b arrhythmias of larger hearts.

Phase 1a arrhythmias are considered to be caused by reentry, since they occur when slowing of conduction and delayed activation are most prominent [10]. Mapping experiments, using simultaneous electrogram recordings from multiple myocardial sites, have demonstrated that circus movement reentry occurs during the 1a phase of ischemic arrhythmias [6]. The electrophysiological basis of phase 1b arrhythmias is less clear. Their time course suggests that they may be related to the onset of irreversible myocardial damage, since they occur at roughly the same time as the second rise in [K+]o and the rise in extracellular resistance [11,12]. Uncoupling of cells may provide favorable conditions for (micro-) reentry. In addition, the endogenous release of catecholamines in the myocardium, also occurring around this time [13], may contribute to the occurrence of arrhythmias. Involvement of catecholamines may be pertinent to all electrophysiological mechanisms.

During the later, subacute stage of myocardial ischemia, delayed ventricular arrhythmias occur about 12–18 hours after the onset of ischemia. These so-called phase 2 arrhythmias are based on abnormal automaticity [6]. During the following weeks and years, surviving fibers within the infarct area may provide an anatomical substrate for reentrant pathways, leading to late ventricular tachycardia or degeneration into late fibrillation.

**KATP Channels and Ischemia: Electrophysiology and Effects on Arrhythmias**

**Electrophysiological effects of KATP activation during ischemia**

When the intracellular ATP concentration decreases, as occurs during ischemia and hypoxia, KATP channels are activated, resulting in increased potassium conductance. However, it is still unclear exactly when and at what level of intracellular ATP ([ATP]) during ischemia these channels become activated (discussed in [14]). KATP channel sensitivity to [ATP] is altered during ischemia, and intracellular compartmentalization of ATP may occur. It has been suggested that KATP channel activation is regulated by ATP produced by oxidative phosphorylation and not by ATP produced by anaerobic glycolysis [15], but this issue has not been settled yet.

Pretreatment with KATP channel blockers such as glibenclamide reduces but does not abolish potassium loss from ischemic myocardium [16]. Concomitant with a decrease in [K+]o, the decrease in conduction velocity is attenuated and conduction block is prevented [17]. In contrast, KATP channel openers (KCOs) do not enhance either the rate of increase in [K+]o or the concentration of potassium in the extracellular space during ischemia [16]. However, the rate of action potential shortening is enhanced in the presence of KCOs and is decreased by KATP blockers (see [1]).

From the functional point of view, KATP channel activation during ischemia is beneficial, and pretreatment with KCOs postpones the onset of contracture and electrical uncoupling (i.e., the onset of irreversible myocardial damage) and may diminish infarct size [18].

The concept of a cardioprotective effect of KCOs is further supported by the observation that the KATP blocker glibenclamide reverses this effect, leading to an acceleration of onset of irreversible damage and an increase in eventual infarct size [1,18]. For several years, the action potential shortening and subsequent decreased influx of calcium into the cell, resulting in reduced contractility and less calcium overload, was considered pivotal to the cardioprotective potential of KCOs. However, a low dose of the KCO bimakalim was equally effective in reducing infarct size without affecting action potential duration, suggesting that other (sub-) cellular mechanisms may be involved in the cardioprotection process [19]. One such mechanism may be activation of KATP channels in the mitochondrial