The ATP-sensitive potassium channel in the heart. Functional, electrophysiological and molecular aspects
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**Chapter 4**

**K_{ATP} channel openers, myocardial ischemia and arrhythmias – should the electrophysiologist worry?**

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Chapter 4

Introduction

Myocardial ATP-sensitive potassium (K\textsubscript{ATP}) channels and their modulation have been extensively studied in various experimental models. K\textsubscript{ATP} channels, which open when the intracellular ATP-concentration decreases, constitute an endogenous myocardial protective mechanism. K\textsubscript{ATP} activation during ischemia postpones the onset of irreversible damage, and reduces the size of the area of myocardial infarction (reviewed by Schotborgh and Wilde 1997). Blockade of K\textsubscript{ATP} channels by sodium 5-hydroxydecanoate (5-HD) and sulfonylurea derivatives abolishes these cardioprotective effects. 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 (Garratt et al. 1999). However, over the years much attention has been focused on the pro-arrhythmic potential of K\textsubscript{ATP} 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 pro-arrhythmic and anti-arrhythmic effects of KCOs have been described (Chi et al. 1990, Kerr et al. 1985). 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\textsubscript{ATP} 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

Electrophysiological effects of 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 by Wilde and Aksnes 1995 and Janse and Wit 1989). Within minutes, the potassium concentration in the extracellular space rapidly rises, resulting from an increase in efflux of potassium ions from myocardial cells presumably compensating for an influx of cations such as sodium (Shivkumar et al. 1997). More importantly, inhomogeneity in [K\textsuperscript{+}]\textsubscript{o} develops during regional ischemia, both within the border zone between the ischemic and normal myocardium, and in the central ischemic...
**K\textsubscript{ATP} and arrhythmias**

Zone (see Janse and Wit 1989). 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\textsuperscript{+}]\textsubscript{o}) reaches a plateau-phase after about 8 minutes of ischemia, and a third phase (second rise in [K\textsuperscript{+}]\textsubscript{o}) is observed after about 16-18 minutes of ischemia, correlating with the onset of irreversible myocardial damage (Wilde and Aksnes 1995, Cascio et al. 1990). At this stage, anaerobic glycolysis is exhausted and the extracellular pH does not decrease further.

Electrically, cells in the ischemic area depolarise within minutes, i.e., the resting membrane potential decreases, at least partly due to the alterations in extracellular potassium concentrations (reviewed by Wilde and Aksnes 1995). Secondary to the depolarisation, 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 K\textsubscript{ATP} channels seems to be involved (Shaw and Rudy 1997). 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 (Wilde and Aksnes 1995). 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 re-entrant arrhythmias during early myocardial ischemia (Janse and Wit 1989).

**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 by Janse and Wit 1989). 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 re-entry, since they occur when slowing of conduction and delayed activation are most prominent (Kaplinsky et al. 1979). Mapping experiments, using simultaneous electrogram recordings from multiple
myocardial sites, have demonstrated that circus movement re-entry occurs during the 1a phase of ischemic arrhythmias (Janse and Wit 1989). 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 (Smith et al. 1995, Cinca et al. 1997). Uncoupling of cells may provide favourable conditions for (micro-) re-entry. In addition, the endogenous release of catecholamines in the myocardium, also occurring around this time (Wilde et al. 1988), may contribute to the occurrence of arrhythmias. Involvement of catecholamines may be pertinent to all electrophysiological mechanisms.

During the later, sub-acute stage of myocardial ischemia, delayed ventricular arrhythmias occur about 12-18 hours to days after the onset of ischemia. These so-called phase 2 arrhythmias are based on abnormal automaticity (Janse and Wit 1989). During the following weeks and years, surviving fibres within the infarct area may provide an anatomical substrate for re-entrant pathways, leading to degeneration into late ventricular tachycardia or fibrillation.

**K$_{ATP}$ channels and ischemia: electrophysiology and effects on arrhythmias**

**Electrophysiological effects of K$_{ATP}$ activation during ischemia**

When the intracellular ATP-concentration decreases, as occurs during ischemia and hypoxia, K$_{ATP}$ 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 by Wilde 1997). K$_{ATP}$ channel sensitivity to [ATP]$_i$ is altered during ischemia, and intracellular compartmentalisation of ATP may occur. It has been suggested that K$_{ATP}$ channel activation is regulated by ATP produced by oxidative phosphorylation and not by ATP produced by anaerobic glycolysis (Shigematsu and Arita 1997), but this issue has not been settled yet.

Pre-treatment with K$_{ATP}$ channel blockers such as glibenclamide reduces, but does not abolish potassium loss from ischemic myocardium (Wilde et al. 1990). Concomitant with a decrease in $[K^+]_o$, the decrease in conduction velocity is attenuated and conduction block is prevented (Bekheit et al. 1990). In contrast, K$_{ATP}$ 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 (Wilde et al. 1990). However, the rate of action potential shortening is enhanced in the presence of KCOs, and is decreased by K$_{ATP}$ blockers (see Schotborgh and Wilde 1997).
From the functional point of view, K\textsubscript{ATP} channel activation during ischemia is beneficial, and pre-treatment with KCOs postpones the onset of contracture and electrical uncoupling (i.e. the onset of irreversible myocardial damage) and may diminish infarct size (Auchampbach and Gross 1993). The concept of a cardioprotective effect of KCOs is further supported by the observation that the K\textsubscript{ATP} blocker glibenclamide reverses this effect, leading to an acceleration of onset of irreversible damage and an increase in eventual infarct size (Schotborgh and Wilde 1997, Auchampbach and Gross 1993). 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 (Yao and Gross 1994). One such mechanism may be activation of K\textsubscript{ATP} channel in the mitochondrial inner membrane (Liu et al. 1998). Alternatively, we recently reported that cromakalim reduces endogenous myocardial noradrenaline release during global ischemia in rabbits, which may also favourably affect the functional status of ischemic myocardium (Remme et al. 1998).

When considering the data above, the question whether K\textsubscript{ATP} activation and blockade during ischemia is beneficial and deleterious, respectively, appears simple and straightforward. Unfortunately, the issue is considerably complicated by the effects of both openers and blockers on ischemia-related ventricular arrhythmias, as will be discussed below.

**K\textsubscript{ATP} channel modulation and arrhythmias during early ischemia**

The hypothetical background for the potential pro-arrhythmogenic effects of KCOs in the setting of myocardial ischemia relates to their ability to accentuate action potential shortening in the early stages of ischemia. This effect is intensified by the fact that the sensitivity of K\textsubscript{ATP} channels to KCOs is enhanced during ischemia, resulting in action potential duration changes at relatively low dosages of KCOs (reviewed by Wilde and Janse 1994). The enhancement of action potential shortening may be expected to increase the incidence of re-entrant arrhythmias, potentially resulting in an increased number of phase 1a arrhythmias during early ischemia. On the other hand, KCOs do not affect the initial changes in [K\textsuperscript{+}]o, and therefore do not seem to influence the second parameter critical for the development of re-entry, (inhomogeneous) slowing of conduction.

The experimental evidence for a pro-arrhythmic effect of KCOs is actually very limited. The observation that glibenclamide and other K\textsubscript{ATP} antagonists diminish arrhythmias during ischemia is often used as an argument but sulfonylurea derivatives in
particular affect several other cell functions and ionic channels, which may potentially contribute to their anti-arrhythmic efficacy (see Schotborgh and Wilde 1997). Several studies have investigated the pro-arrhythmic potential of KCOs in myocardial ischemia; the contradictory results observed may be explained by the large variety of experimental models used (see Wilde and Janse 1994). Some studies using models with a high incidence of arrhythmias in control animals, have shown an acceleration of the time of onset of ventricular arrhythmias due to KCOs (discussed by Wilde 1993 (Figure 1), which may reflect an increase in phase 1a arrhythmias. The study by Chi et al. (1990) showed a pro-arrhythmic effect of the KCO pinacidil in conscious dogs with coronary artery ligation, but heart rate was not controlled and infarct-size could not be determined in the pinacidil-treated animals. In addition, in this study and in most other studies showing a pro-arrhythmic effect of K<sub>ATP</sub> activation, pinacidil was used, and increased propensity to arrhythmias during ischemia occurred only at high doses which often produce hypotension and reflex tachycardia. Therefore, it remains unclear whether the observed pro-arrhythmic effects of pinacidil indeed result from myocardial K<sub>ATP</sub> modulation itself. When dosages with no additional effect on action potential duration

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**Figure 1.** The incidence of ventricular fibrillation (VF) and ventricular tachycardia (VT) (Y-axis) during global ischemia in the stimulated isolated rabbit heart. In control hearts, VT/VF occurred in 67% of hearts, after a mean interval of 11.4 minutes of ischemia. Cromakalim 3 μM but not 1 μM added 15 minutes before the onset of ischemia accelerated the time of onset of VT/VF to a mean interval of 5.2 minutes, without altering the incidence. Finally, glibenclamide (3 μM) markedly reduced the incidence of VT/VF (13%) (reproduced in modified form from ref. [23], with permission)
are used, no ventricular pro-arrhythmia is observed (Yao and Gross 1994). Consequently, it seems feasible to benefit from the cardioprotective potential of KCOs (see above), without necessarily creating more favourable conditions for arrhythmogenesis. Besides their effects on phase 1a arrhythmias, KCOs may decrease or postpone phase 1b arrhythmias, since activation of KATP channels postpones the onset of irreversible myocardial damage and reduces infarct size (Auchampbach and Gross 1993, Yao and Gross 1994). Our observation that cromakalim reduces endogenous noradrenaline release during ischemia (Remme et al. 1998), may also contribute to this anti-arrhythmic potential. However, to the best of our knowledge, there have been no studies in which the effects of KCOs on both phase 1a and 1b arrhythmias were evaluated simultaneously, since there are few experimental models in displaying only one distinct peak of early ischemia-related arrhythmias are unsuitable for such studies (discussed Janse and Wit 1989, and Wilde and Janse 1994). The question therefore remains, whether a reduction or delay of phase 1b arrhythmias due to potassium channel openers is possible without a simultaneous increase in phase 1a arrhythmias. With the use of selective mitochondrial KATP openers (Liu et al. 1998), one would expect such a differentiated effect on ischemia-related arrhythmias.

**KATP channels and arrhythmias during the sub-acute phase of ischemia**

As mentioned before, arrhythmias occurring during the sub-acute phase of ischemia (12-18 hours after onset), are due to abnormal automaticity, i.e. spontaneous impulse formation occurring at a less negative diastolic membrane potential. Theoretically, opening of KATP channels, by increasing K\(^+\) conductance, hyperpolarises the resting membrane potential (reviewed by Wilde and Janse 1994), potentially reducing abnormal pacemaker activity. Indeed, abnormal automaticity during normoxic conditions as well as ventricular arrhythmias present 22-24 hours after the onset of coronary artery ligation, are suppressed by potassium channel openers (Kerr et al. 1985, Wilde and Janse 1994).

**Ischemic preconditioning and arrhythmias**

Several studies of preconditioning (PC) have shown a reduction of the incidence and severity of arrhythmias during the period of ischemia following the PC stimulus, although the results are controversial (reviewed by Dekker 1998). Since infarct size is also decreased in the preconditioned myocardium, it seems likely that this may influence the incidence of arrhythmias. In addition, the onset of irreversible myocardial damage is postponed, which may delay the onset of phase 1b arrhythmias. Indeed, Cinca et al. (1997) showed that PC postpones electrical uncoupling as well as the 1b phase of arrhythmias during sustained ischemia in pigs. However, an anti-arrhythmic effect
without concomitant decrease in contractile dysfunction has also been described (Botsford and Lukas 1998), suggesting that different mechanisms underlie the various effects of PC. In the latter study, a marked reduction in dispersion in APD between epicardium and endocardium was observed in preconditioned hearts, which may decrease the substrate for re-entrant arrhythmias. So far, there have been no reports concerning the specific effects of PC on 1a arrhythmias; obviously, the degree of action potential shortening may be of importance. KATP channels seem critically involved in the preconditioning process (see Dekker 1998). Hence, pharmacological KATP modulation will affect the extent and timecourse of PC and will impact on its (electrophysiological) consequences.

Clinical observations

Most clinical studies concerning KATP modulation in the heart have focused on the effects of the KATP blocker glibenclamide, a sulfonylurea derivative commonly used by diabetic patients. Many of these patients also suffer from cardiovascular disease, and the use of glibenclamide may theoretically have deleterious effects during ischemic episodes or myocardial infarction (discussed by Schotborgh and Wilde 1997). Indeed, in a recent retrospective study, Garratt et al. (1999) found an increased risk of early in-hospital mortality after coronary angioplasty for acute myocardial infarction among diabetic patients taking sulfonylurea drugs compared to diabetic patients not using these drugs. Since an increase in ventricular arrhythmias could not explain the observed effect, the authors suggested a deleterious effect of sulfonylurea drug use on myocardial tolerance for ischemia and reperfusion. In addition, oral administration of glibenclamide may abolish ischemic preconditioning in the setting of coronary angioplasty, as shown by the lack of improvement of ECG changes normally observed after the second balloon inflation during coronary angioplasty (Tomai et al. 1994). Two studies have shown a marked decrease in ventricular arrhythmias in the setting of myocardial infarction in patients using glibenclamide (Davis et al. 1998, Lomuscio et al. 1994). In a randomised cross-over study, glibenclamide compared favourably with metformin in diabetic patients in terms of incidence of ventricular premature beats and ventricular tachycardia during transient myocardial ischemia (Cacciapuoti et al. 1991).

Potassium channel openers (KCOs) were first advocated as antihypertensive agents. In small clinical studies with KCOs no pro-arrhythmic effects have been reported (Friedel and Brogden 1990, Krumenacker and Roland 1992). Potassium channel openers as anti-anginal agents (nicorandil) have only recently been studied by Patel et al. (1999). In this randomised study, either nicorandil or placebo was administered to 188 patients.
with unstable angina and already on a full anti-anginal drug regimen. Nicorandil significantly reduced the number of episodes of non-sustained ventricular tachycardia compared to placebo (Figure 2). Since nicorandil also reduced the number of episodes of transient myocardial ischemia, it is likely that the anti-arrhythmic effect of nicorandil is secondary to its anti-ischemic effect. So far, in none of the available reports an increase in the occurrence of arrhythmias due to KCOs has been observed, although transient T wave inversion or T wave flattening may be seen on the electrocardiogram (Goldberg 1988).

From the available clinical data so far, it may be concluded that the pro-arrhythmic potential of potassium channel openers during ischemia is overestimated. We believe that pro-arrhythmia will only be observed in the presence of significant hemodynamic and electrophysiological effects. Hence, the observed pro-arrhythmia due to KCOs in experimental models is most likely due to the high doses used, and may not reflect the clinical situation.

Conclusions

During ischemia, the potential cardioprotective effect of pharmacological opening of $K_{ATP}$ channels may be abolished by the pro-arrhythmic potential of potassium channel
openers. Although there is a solid theoretical background to this issue, there is actually little experimental or clinical evidence. The few available clinical studies with potassium channel openers do not show any pro-arrhythmic effects; if any, a decrease in arrhythmias concomitant with a reduction in ischemic events has been described. It is very well possible that the pro-arrhythmic potential of KCOs is overestimated, since the available data suggest that this side-effect only occurs with high dosages, while the cardioprotective effect is already available at low dosages. Future experimental and clinical studies should be focused on these issues, in order to clearly establish both favourable and unfavourable effects of these promising drugs during ischemia.

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