Arrhythmia Protection in Hypokalemia:
A Novel Role of Ca\textsuperscript{2+}-Activated K\textsuperscript{+} Currents in the Ventricle

Running title: Faggioni et al.; IKAS protects against hypokalemic arrhythmias

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Journal Subject Term: Ventricular Fibrillation

Key words: hypokalemia; calcium; Editorial
Whereas myocardial depolarization is a fast event mediated almost exclusively by rapid Na currents, myocardial repolarization is a much slower and more complex affair for the heart. It is regulated by a carefully orchestrated interplay of many different inward and outward currents that allows for a precise regulation of action potential (AP) shape and duration (Figure 1). Intact repolarization is essential for excitation-contraction coupling and helps protect the myocardium against spontaneous ectopic activity and reentrant arrhythmias. During hypokalemia, the fine balance of ion currents across the cell membrane is disrupted, resulting in action potential prolongation (Figure 2). This phenomenon, known as loss of repolarization reserve, has been also implicated in the cell pathophysiology of heart failure even during normokalemia.¹ Recent reports indicate that a small-conductance Ca-activated outward K (SK) current is upregulated in failing ventricular myocytes, which partially restores repolarization reserve and AP duration.² Since the Ca-activated K⁺ current is blocked by neurotoxin apamin, it is also known as apamin sensitive K current (I_{KAS}). The molecular correlate is likely the type 2 SK channel. However, previous studies had indicated that in healthy hearts, I_{KAS} plays a role only in atrial, but not ventricular electrophysiology.³

In this issue of Circulation, the Chen laboratory reports a new role for I_{KAS} during hypokalemia that is relevant even in the healthy ventricle:³ the authors discovered that, unlike in normokalemic conditions, during hypokalemia I_{KAS} is increased and appears to have two main functions: 1) I_{KAS} provides additional repolarization reserve and reduces the AP duration (APD) in particular at long pacing cycle lengths; and 2), I_{KAS} is important for short-term cardiac memory. Using isolated rabbit hearts as a model system, the authors found that in normokalemia I_{KAS} does not appear to be relevant because selective blockade of I_{KAS} with apamin does not prolong ADP significantly in intact hearts. In contrast, in hypokalemia, I_{KAS} is upregulated due to
the increase in cytosolic Ca (Figure 2), and I\textsubscript{KAS} block with apamin causes significant APD prolongation, activation wavebreak and spatially discordant APD alternans. This results in increased susceptibility to pacing induced ventricular fibrillation in hypokalemic hearts after apamin treatment. The authors suggest that I\textsubscript{KAS} is an “emergency” K current that acts as a defense mechanism against ventricular arrhythmias in a setting of reduced repolarization reserve and myocyte Ca overload due to hypokalemia.

**Effects of Hypokalemia on cardiac electrophysiology**

Hypokalemia is widely recognized as being associated with increased risk for ventricular arrhythmias, in particular in the setting of preexisting heart disease such as cardiac ischemia, bundle branch block, ventricular pacing or heart failure. The main effect of low extracellular [K] appears to be the reduction of repolarization reserve due to inhibition of outward K currents (Figure 2). Particularly affected are the rapid component of the delayed rectifier (IKr) and the inward rectifier (IK1) that together determine the fast downslope of the repolarization phase of the AP (Fig. 1). In addition, chronic hypokalemia causes an internalization of channels that leads to reduced IKr density. Conductance of the delayed rectifier K current (IKs) and the transient outward K current (Ito) are also regulated by extracellular K concentrations. In addition, hypokalemia inhibits the cell membrane Na/K ATPase pump, which further decreases the repolarization reserve due to the reduced outward Na/K pump current. As a result of the altered repolarization process, AP duration is prolonged which can trigger early afterdepolarizations (EAD). However, Weiss et al\textsuperscript{5} recently reported in an elegant combination of experimental studies and computer simulation that reduction of repolarization reserve by hypokalemia was not, by itself, sufficient to induce EADs, unless Na and Ca homeostasis were also altered. The underlying mechanism is illustrated in Figure 2: The hypokalemia-induced
Na/K pump inhibition not only reduces repolarization reserve but also leads to accumulation of intracellular Na ([Figure 2](#)), which in turn reduces Ca extrusion via the Na/Ca exchanger thereby causing intracellular Ca overload and delayed afterdepolarizations (DADs). The increased intracellular [Ca] activates the Ca/calmodulin-dependent protein kinase II (CaMKII), which seems to be another key component in Ca-induced arrhythmia risk. Activated CaMKII phosphorylates L-type Ca channels and Na channels thus generating a positive feedback that further raises intracellular Ca and late Na current, both involved in afterdepolarization and arrhythmia triggering. Inhibition of CaMKII prevents EAD and arrhythmias in rabbit hearts. In addition, the inhomogeneous distribution of APD changes and conduction slowing promote an arrhythmogenic substrate for reentrant circuits that sustain ventricular arrhythmias. As a result, hypokalemia produces significant arrhythmia risk even in structurally normal hearts, and Ca overload appears necessary to increase the risk of ventricular arrhythmias in the setting of hypokalemia.

The article by the Chen group clearly documents the hypokalemia-induced increase in intracellular Ca. The authors suggest that high cytosolic Ca is responsible for the activation of SK channels that likely generate the potentially antiarrhythmic outward $I_{KAS}$. Consistent with this mechanism, apamin had a greater effect on the AP duration in sites remote to the pacer where [Ca], and supposedly repolarizing $I_{KAS}$ activity, are higher. The authors also report that $I_{KAS}$ activation flattens the AP restitution curve and prevents discordant alternans, both of which are considered to reduce the likelihood of ventricular fibrillation, as confirmed experimentally by Chan et al. on intact perfused rabbit hearts. Taken together, the article by Chan et al. provides compelling evidence that $I_{KAS}$ activation protects the heart against ventricular fibrillation in the setting of hypokalemia.
IKAS as a pro arrhythmic current in diseased hearts?

IKAS has been studied not only in failing ventricular myocytes but also in other conditions such as tachycardia/ventricular pacing and myocardial infarction.\textsuperscript{10} IKAS is upregulated after an infarction, although potential regional differences in current expression between border zone and remote zone have not been thoroughly investigated.\textsuperscript{11} Besides its seemingly antiarrhythmic role in reducing APD, a proarrhythmic effect of IKAS has been hypothesized related to its heterogeneous expression in the human heart. Patch clamp studies show a higher IKAS density in the endocardial and epicardial layers in failing hearts. This transmural dispersion might generate different APD across the ventricular tissue and cause conduction blocks. In addition, excessive IKAS activation was associated with transient shortening of APD following defibrillation shocks in failing rabbit hearts. After a DC shock, cells displayed persistent cytosolic Ca accumulation that might activate IKAS and excessively reduce AP, thereby increasing the likelihood of post-shock reentry. Consistent with this mechanism, failing rabbit hearts developed spontaneous after-shock ventricular tachycardia attributed to ectopic ventricular activity during phase 3 of the AP. Interestingly, apamin administration prevented transient AP shortening and recurrent ventricular fibrillation after DC shock.\textsuperscript{12} Hence, IKAS activation and therefore IKAS blockers might be both proarrhythmic and antiarrhythmic depending on the underlying heart disease.\textsuperscript{13}

IKAS and short-term cardiac memory

The other main observation of the Chen article is that IKAS seems to be important for short-term cardiac memory.\textsuperscript{3} Cardiac memory refers to the phenomenon that a change in the direction of cardiac activation and/or the pacing rate can transiently modify the AP duration and the T-wave morphology on the EKG. It is called “memory” because the T wave maintains the same vector even after the altered activation has ceased. Cardiac memory has also been implicated as risk
factor for ventricular fibrillation. The mechanisms underlying short-term cardiac memory are poorly understood and multifactorial. Suppression of Ito current seems to be one of the changes responsible for the phenomenon of cardiac memory. Angiotensin, through its AT1 receptor, might promote Kv4.3 internalization with consequent loss of Ito. Interestingly, pacing frequency appears to be not as important in determining short-term memory as the pacing site and dyssynchrony. This suggests a role of mechanical stretch in mediating the electrical effects observed during ventricular pacing. However, the link between mechanical strain and altered electrical activity is not clear. In their article, the authors hypothesize a role of $I_{\text{KAS}}$ in cardiac memory based on the observation that apamin prolonged the AP more at late activated sites compared to sites close to the pacer. The time needed for an AP to reach a stable and constant morphology after an altered activation sequence, as during cardiac pacing, is an expression of cardiac memory. Since $I_{\text{KAS}}$ reduces AP duration and $I_{\text{KAS}}$ block with apamin affects the AP restitution curve, the prolonged AP shows a positive correlation with the AT, suggesting a role of $I_{\text{KAS}}$ in cardiac memory modulation. However, all studies on cardiac memory were done in hypokalemic hearts, where $I_{\text{KAS}}$ plays a prominent role in regulating AP duration, and $I_{\text{KAS}}$ may be upregulated because of increased intracellular Ca concentration regardless of the pacing condition (Figure 2). In normokalemic paced hearts, $I_{\text{KAS}}$ essentially has no effect on AP duration. Therefore, a role of $I_{\text{KAS}}$ on cardiac memory in normokalemic setting cannot be definitively inferred from the data presented. Clearly, multiple factors play a role in electrical memory such as strain induced intracellular signal activation, altered Ca handling and abnormal connexin distribution. Further experiments are required to interpret the complex changes associated with electrical remodeling and cardiac memory.

$I_{\text{KAS}}$ has generated a lot of interest in recent years because it is upregulated in various
condition of altered electrical activity. However, two or more of these conditions often coexist as hypokalemia and heart failure or dyssynchrony and heart failure and it is difficult to discern what determines \( I_{KAS} \) activation and its relative contribution to arrhythmia risk. Moreover, amiodarone, possibly the most effective anti-arrhythmic drug on the market, blocks \( I_{KAS} \). Finally, we still do not know if other antiarrhythmic drugs affect \( I_{KAS} \) as part of their therapeutic effect. Nevertheless, the article by Chan et al has provided us with a new understanding of the physiological role of \( I_{KAS} \) in the hypokalemic heart.

**Conflict of Interest Disclosures:** None.

**References:**


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Figure Legends:

**Figure 1.** Major ionic currents that shape the ventricular action potential (AP). Inward currents (black ↓) depolarize the cell membrane and prolong the action potential; outward currents (grey ↑) repolarize the cell membrane and shorten the action potential. INa, Na+ current, ICa, L-type Ca$^{2+}$ current, Ito, transient outward K+ current, IKs, slowly-activating delayed rectifier K+ current, IKr rapidly activating delayed rectifier K+ current, IK1, inward rectifier K+ current, IKAS, apamin-sensitive Ca-activated K+ current, INaK, Na/K-ATPase pump current

**Figure 2.** Cardiomyocyte electrophysiology during hypokalemia. 1) Hypokalemia inhibits outward potassium currents (Ito, IKr, IKs and IK1) and the Na/K ATPase pump current (INaK) with consequent loss of repolarization reserve and increased intracellular Na. 2) High intracellular [Na+] inhibits Ca$^{2+}$ removal via the Na/Ca exchanger (NCX) and Ca$^{2+}$ accumulates in the cytosol. 3) High [Ca$^{2+}$]$_{cytosol}$ activates CaMKII which increases ICa and late INa inward currents. 4) Together with the hypokalemia-induced block of K+ currents, these changes in ionic currents cause AP prolongation and promote EAD and DAD triggered arrhythmias. 5) During hypokalemia, the increased [Ca$^{2+}$]$_{cytosol}$ activates apamin-sensitive I$_{Kas}$ currents, which shorten the AP. When I$_{Kas}$ is inhibited by apamin, AP is not restored and ventricular arrhythmogenesis ensues.
Figure 1

Diagram showing various ion currents and potentials involved in the Ventricular Action Potential:
- $I_{Na}$ (sodium current)
- $I_{Ca}$ (calcium current)
- $I_{to}$ (slow component of the T wave)
- $I_{NaK}$ (sodium-potassium pump)
- $(I_{KAS})$ (potassium current)
- $I_{Ks}$ (slow potassium current)
- $I_{Kr}$ (rapid potassium current)
- $I_{K1}$ (slow component of the action potential)

The diagram illustrates the flow and interaction of these currents throughout the cardiac cycle.
Figure 2

Hypokalemia

1. Loss of Repolarization Reserve
2. Na+ Accumulation
3. Ventricular Cardiomyocyte
4. DAD
5. HypoK

Ca2+ ATP
K+ Ito IK1IKs
Na+

CaMKII
PP
Na+

INa
IKAS
Apamin

Ca2+
K+

INaK
IKAS
EAD
HypoK
Apamin

NCX

Na+ Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+

Ventricular Cardiomyocyte

Figure 2
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Circulation, published online September 11, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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