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Editorial

ATP and the role of $I_{K,\text{ATP}}$ during acute myocardial ischemia: controversies revive

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Detailed insight into the electrophysiology of ischemia is of utmost importance in understanding the arrhythmogenic nature of myocardial ischemia. The players in the field—the ionic currents—are known, but their respective roles are disputed. Direct recordings of ionic currents are best obtained in isolated cells, but the impossibility of exposing isolated cells to ischemia seriously complicates this issue. Even elegant solutions like the mineral oil droplet technique [1] do not meet all criteria. Hitherto, recordings of ionic currents have usually been obtained from tissue or cells in simulated ‘ischemia’, that is exposure to a variable combination of ischemic factors including hypoxia or metabolic deprivation by metabolic inhibitors, high extracellular potassium ($[K^+]_o$), acidosis and catecholamines. In this respect, the theoretical studies by Shaw and Rudy [2,3] may offer a new dimension to the long-lasting discussion on the mechanism underlying the most essential events.

In the simulation study, published in this issue of *Cardiovascular Research* [3], the focus is on the three components of ischemia which are generally accepted as the most essential: i.e., anoxia, acidosis and elevated ($[K^+]_o$). The results are not very surprising: elevated ($[K^+]_o$) by depolarizing the resting membrane reduces Na⁺ channel availability and thus affects cell excitability, and anoxia underlies the action potential shortening by activating ATP-sensitive K⁺ current ($I_{K,\text{ATP}}$) [3]. The role of acidosis seems modifying in nature but of importance, in particular where it concerns the transition from the Na⁺-current-dominated to the Ca²⁺-current-dominated action potential upstroke.

Shaw and Rudy only studied these three elements of ischemia and one may argue that this study is similar to experiments in which isolated cells are exposed to (only) these ischemic factors. However, the detailed quantitative evaluation of the electrophysiological changes is unique and particularly helpful in the analysis of indirect changes in other currents by the changes in action potential configuration [3]. As indicated by the authors, pharmacological assessment of ischemic arrhythmias should take these significant indirect changes into account. In addition, by including more ischemia-related variables, this theoretical exercise has strong potential to resolve many controversial issues on the role of other potentially contributing currents and/or contributing ischemic conditions. Some of them are mentioned in the article, others include the potential role of chloride currents and of the transient outward current $I_{TO}$ which may also be involved in modulation of action potential duration [4,5]. Other issues which might be addressed are the electrophysiological background of the initial prolongation which is observed in many experimental models (for review, see Ref. [6]) and the secondary improvement in upstroke velocity (and transient lengthening of the action potential) observed after 10–15 min of ischemia. The absence of the initial prolongation in the present simulations is compatible with experimental data suggesting that inhibition of $I_{TO}$ underlies the initial increase in action potential duration [5]. Because the model used is based on guinea-pig ventricular cells, $I_{TO}$ is not included.

The role of $I_{K,\text{ATP}}$ in action potential shortening is disputed. In this theoretical study application of the theo-
retical presumptions for $I_{K-ATP}$ activation, which are based on sound experimental evidence, provides compelling evidence that $I_{K-ATP}$ is the main current involved in the shortening of action potential [3]. The experimental evidence, however, is less convincing and almost exclusively based on the observation that sulfonylureas inhibit or even abolish the shortening [6,7]. As indicated previously, sulfonylureas affect several other ionic currents and affect cell metabolism with potential consequences for the action potential duration. In addition, $I_{K-ATP}$ in isolated cells is activated with a fairly long time delay after exposure to hypoxia [8] or simulated ischemia [1]. The latter observations are particularly difficult to reconcile with a dominant role for $I_{K-ATP}$ in early action potential shortening. In the absence of more specific $I_{K-ATP}$ blockers, further theoretical studies with an even more extensive model (incorporating more ionic currents) can be very helpful. Shaw and Rudy argued that elimination of other factors that can explain action potential shortening “supports $I_{K-ATP}$ as the dominant factor in ischemic action potential shortening” [3]. This argument cannot be considered a very strong one since only those factors included can be eliminated. As indicated above, at least two potentially involved ionic currents have not been included. Nevertheless, I tend to agree with the outcome of the model with regard to the pivotal role of $I_{K-ATP}$. An eventual role for $I_{K-ATP}$ may have clinical impact because (inhomogeneous) action potential shortening determines, at least in part, the degree of ST-segment elevation. Indeed, in dogs glibenclamide has been shown to attenuate the ST segment changes in acute myocardial ischemia [9]. Extrapolation of these findings to diabetic patients on sulfonylureas potentially masks the early electrocardiographic signs of an acute myocardial infarct [10].

Regulation of $I_{K-ATP}$ during myocardial ischemia is another issue of controversy. At what level of intracellular ATP ([ATP]) is $I_{K-ATP}$ activated in myocardial ischemia? It is known that metabolic factors such as ADP, intracellular pH and lactate decrease $I_{K-ATP}$ sensitivity to [ATP]-based inactivation. By including this in their model Shaw and Rudy calculated that [ATP] = 3.0 mM led to 0.8% $I_{K-ATP}$ activation. At this level of $I_{K-ATP}$ activation the impact on the action potential duration is already significant and as such the “spare channel hypothesis” has been adopted by these authors. Alternatively, it has been suggested that ATP may be compartmentalized and that ATP produced by anaerobic glycolysis preferentially regulates the activity of the channel [11]. This seems to contrast the experimental fact that selective inhibition of oxidative phosphorylation (by 2,4-dinitrophenol [DNP] or cyanide) also activates $I_{K-ATP}$. Shigematsu and Arita addressed this controversy and designed experiments to answer the question whether $I_{K-ATP}$ is regulated primarily by ATP derived from glycolysis, oxidative phosphorylation or from a combination of the two [12]. Their conclusion that the major part of regulation of $I_{K-ATP}$ under conditions of quiescence and anoxia is by ATP produced by oxidative phosphorylation is of interest and contrasts with earlier findings [11]. There are at least two theoretical arguments which favor this conclusion. The first has been mentioned above and simply relates to the fact that selective inhibition of oxidative phosphorylation activates $I_{K-ATP}$. In this respect the use of DNP should, however, be re-evaluated since preliminary data suggest that DNP directly affects the gating characteristics of the channel [13]. Secondly, if glycolytically produced ATP were to control $I_{K-ATP}$, activation in early ischemia might be prevented because of the reported enhancement of anaerobic glycolysis in this phase.

Are the experimental data of Shigematsu and Arita sufficient to demonstrate that primarily ATP produced by oxidative phosphorylation regulates $I_{K-ATP}$ activity? Three arguments are given: (1) omission of glucose from the perfusate does not affect action potential duration (over 2 hours) and (2) the presence of glucose exerted only a limited effect on the anoxia-induced shortening. It may, however, be argued that utilization of intracellular glyco-
gen stores is sufficient to maintain adequate ATP levels and to prevent $I_{K-ATP}$ activation. Under anoxic conditions anaerobic glycolysis might become inhibited after pro-

longed anoxia and thus no longer contribute to ATP production. Hence, the presence of glucose would be of no significance. The third argument—the complete restoration of the action potential duration and complete inhibition of $I_{K-ATP}$ by oxygen alone—is addressed by the authors. Indeed, glycolytically produced ATP (by ‘aerobic’ glycol-
ysis) might be sufficient to inactivate $I_{K-ATP}$.

In my view the authors are to be complimented that they tried to resolve a controversy that has gone apparently unnoticed over so many years. However, it is questionable whether their data do permit the conclusion that glycolytically produced ATP can be excluded as important in the regulation of $I_{K-ATP}$ under anoxic (and ischemic) conditions. It seems that further investigation is needed to conclude that ATP produced by oxidative phosphorylation and not ATP produced by anaerobic glycolysis regulates K-ATP channels. It is highly conceivable that the gap between theory and experiment can similarly be bridged by computer model studies.

References


