Editorial

Altered expression of cardiac K⁺ channel genes during sub-acute and healing phases of myocardial infarction

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Received 24 June 1999; accepted 1 July 2001


1. Remodeling of the heart after myocardial infarction

In animal models of myocardial infarction (MI), in which the coronary artery is occluded permanently, the incidence of ventricular arrhythmias is classified into three categories according to when they occur after the onset of MI: acute, sub-acute and chronic phase arrhythmias [1]. In men who suffered from MI, ventricular tachyarrhythmias frequently occur in essentially the same manner as that encountered in the animal models. In the acute phase (within several hours from the onset of MI), the occurrence of life-threatening arrhythmias (ventricular tachycardia and ventricular fibrillation) is common. Reentry and triggered activities are the major causes of such fatal arrhythmias seen during the early phase of MI [1].

The hearts that survive acute MI undergo dynamic remodeling to cope with metabolic and mechanical de-rangements caused by the MI. Most of the myocytes in the ischaemic region die and are replaced by fibrous tissue. Myocytes surrounding the ischaemic region become hypertrophied. This restructuring phase (the sub-acute phase) starts several hours after the event and lasts for several days [1]. Recently, sufficient evidence has appeared to indicate that transcription and expression of sarcolemmal ion-channel genes are modified in this period.

Prominent changes occur in potassium (K⁺) channel currents. In the study appearing in this issue of Cardiovascular Research, Yao et al. [2] report the alteration in K⁺ currents in rat ventricular myocytes that survived 3 days after experimental MI (sub-acute phase). In cells probably isolated from the border zone, the transient outward (Iₒ), delayed rectifier (I_K) and inward rectifier (I_K1) currents were found to be depressed. Reduction of both Iₒ and I_K was greater in epicardial than in endocardial myocytes, while I_K was reduced equally in the two populations. Reduction in the current density of Iₒ, I_K and I_K1 was also reported for canine Purkinje fibers that survived 2 days after MI [3,4]. Similar changes in Iₒ were observed in failing human hearts [5]. Such findings indicate either that K⁺ channels are vulnerable to the insult of MI or that the process of K⁺ channel protein synthesis is vulnerable to such derangements. Most reports thus far support the latter possibility. There is a good correlation among the values for the reduction in the current density of a given channel (measured with patch-clamp techniques), for the decrease in the expressed channel protein (Western blotting) and for the decrease in mRNA (Northern blotting or RNAse protection assay) after MI. In this article, alterations in the three cardiac K⁺ channel families (I_K1, I_K and Iₒ) during the sub-acute phase to the chronic phase of MI will be discussed.

2. Inward rectifier K⁺ channels after MI

In addition to voltage-gated K⁺ (Kv) channels (among others I_K and Iₒ channels), which are characterized by six membrane-spanning regions including a voltage sensor, cardiac myocytes express a family of inwardly rectifying K⁺ (Kir) channels. The latter family includes classic inward rectifiers (I_K1, Kir 2.x), muscarinic M2 receptor-coupled ACh-activated K⁺ channels (K_ACh, Kir 3.x), and ATP-sensitive K⁺ channels (K_ATP, Kir 6.x+SURs). Kir channels have only two membrane spanning regions and lack voltage sensors. Their inwardly rectifying property is
determined by the channel block caused by intracellular polyamines and/or Mg$^{2+}$.

Akao et al. [6] reported that the expression of $K_{\text{ATP}}$ channel subunits in rats was differentially modified after MI. The $K_{\text{ATP}}$ channel in pancreatic cells is composed of an inward rectifier (Kir 6.2) and a sulfonylurea receptor (SUR1) protein [7]. In rat hearts, mRNAs for SUR1 are not expressed, but SUR2 (a cardiac-type sulfonylurea receptor) and both Kir 6.1 and Kir 6.2 subunits are abundantly expressed [6]. Thus, $K_{\text{ATP}}$ channels in rat heart are thought to be a complex of Kir 6.1 and/or Kir 6.2, and SUR2. After 60 min of regional ischaemia followed by 24–72 h of reperfusion, a two- to three-fold increases in Kir 6.1 mRNA and in protein levels was recognized in ischaemic as well as in non-ischaemic regions in the ventricle. In contrast, mRNAs for Kir 6.2 and SUR2 remained unchanged [6]. Thus, it is likely that increased wall stress in ischaemic as well as in non-ischaemic myocardium is a trigger for the induction of Kir 6.1 mRNA expression in the infarcted hearts.

Reduced $I_{k1}$-channel expression during the sub-acute phase of MI, which was reported in Purkinje myocytes by Pinto and Boyden [4], may have a particular pathophysiological significance. These authors showed that $I_{k1}$ conductance was markedly reduced in sub-endocardial canine Purkinje myocytes that survived 48 h after infarction. Delayed ventricular arrhythmias during the sub-acute phase with a single focus or multiple foci are thought to be caused by enhanced automaticity of subendocardial Purkinje fibers [8] (also see [1]). To recall the importance of $I_{k1}$ in determining firing frequency in this tissue, the latter was simulated using the Oxsoft Heart program (OXSOFT ver.4.0, Oxsoft Ltd.). As shown in Fig. 1(A and B), a 50% reduction of the $I_{k1}$ conductance markedly increased the frequency of automatic firing in the Purkinje fiber model. In contrast, a 50% reduction of $I_K$ or $I_{to}$ conductance modifies the action potential configuration (particularly in the case of $I_K$), while the effects of reduction of these currents on spontaneous activity were minimal (Fig. 1C and D).

3. Delayed rectifier $K^+$ channels after MI

Yao et al. [2] reported that the current density of ‘$I_K$’ was decreased in rat ventricular myocytes that survived 3 days after MI. However, there is some confusion in the terminology of the delayed rectifier $K^+$ channel in rats, since ‘$I_K$’ in this species denotes a slowly inactivating $K^+$ channel current [9]. The ‘$I_K$’ in rat is neither the E-4031-sensitive $I_{Kr}$ (ERG, ether-a-go-go related gene) nor the chromanol 293B-sensitive $I_Ks$ current (KvLQT1+minK). As noted by Yao et al. [2], the ‘$I_K$’ is a TEA-sensitive, slowly decaying current, which is activated by depolarizations from deep negative holding potentials. The cDNA that encodes the rat ventricular ‘$I_K$’ channel is not known at this time.

In canine Purkinje myocytes, an E-4031-sensitive plateau current increased after MI [4]. However, because the current lacks an inward going rectification property at

![Simulation of the effects of reduced (by 50%) conductance of $I_{k1}$, $I_K$ and $I_{to}$ on automaticity and action potential configuration of a Purkinje fiber, using the Oxsoft Heart program (version 4.0, OXSOFT Ltd.). Decreased $K^+$ conductance during remodeling of the heart after myocardial infarction may be arrhythmogenic either by enhancing the automaticity of subendocardial Purkinje fibers (panel B) or by modifying the time course of repolarization of the action potentials (panels C and D).](https://academic.oup.com/cardiovascres/article-abstract/44/1/13/274491)
positive potentials, it is not the authentic $I_{K_1}$. In the canine model of MI, the mRNAs of ERG, KvLQT1, and minK are all reduced after MI [10]. In human explanted failing hearts (some are from patients with ischemic cardiomyopathy), however, the mRNA level of HERG (human ERG) was not changed [5]. Anyhow, at present, information on the current and the gene expression of the $I_{K_r}$ and $I_{K_s}$ channels after MI is very limited.

4. Transient outward current after MI

Qin et al. [11] have shown that hypertrophied post-MI rat ventricular myocytes (2 to 4 weeks after LAD ligation) had prolonged action potential duration, due to a decreased density of $I_{to,t}$ and $I_{to,t}$ (these two components were separated by the decaying time course). Gidh-Jain et al. [12] used the same model and reported that the mRNA and protein levels of Kv 2.1 and Kv 4.2 subunits were both decreased. These authors also suggested that the decreased $I_{to}$ current density is secondary to the hypertrophy of the cells. Namely, the density of $I_{to}$ decreased due to an increased membrane surface area, since the amplitude of $I_{to}$ in a cell that survived MI was not different from the control. Using similar MI model of rat at much a earlier stage of MI (3 days after the coronary ligation) in which hypertrophy of the myocytes was not detectable, Yao et al. [2] demonstrated that both the $I_{to}$ current and the expression of Kv 4 series channel proteins were significantly reduced.

In rat hearts, $I_{to}$ plays a major role in action potential repolarization. It is widely accepted that shal-type voltage-gated $K^+$ channels (Kv 4.2 and/or Kv 4.3) are the pore-forming subunits of the $I_{to}$ channel in adult rat, dog and human hearts [13,14]. Recently, it was shown that the Kv 1.4 subunit functions to form rabbit $I_{to}$ channels [14]. The $I_{to}$ density was reduced in many pathological conditions, including acute or chronic diabetes mellitus [15,16], hypertrophy induced by pressure or volume overload (see [17]), and failing hearts isolated from patients with dilated or ischaemic cardiomyopathy [5]. Unidentified common pathway(s) may underlie a down-regulation of the expression of $I_{to}$ channels in these pathological conditions. Possible candidates for triggering such channel remodeling could be altered levels of intracellular Ca$^{2+}$, cAMP, cytokines (interleukins, interferons, tumor necrosis factor and so on) as well as oxygen-free radicals [18].

5. Conclusion

During the sub-acute phase of myocardial infarction, the expression of potassium channels, e. g., the channels of inward rectifiers, delayed rectifiers and transient outward $K^+$ currents is modified. The changes in expression may be, at least in part, responsible for the occurrence of ectopic automaticities reported to occur in the subendocardial region of the ventricle [1]. Among these $K^+$ channel families, $I_{K_1}$ may have particular importance, since it acts to maintain the diastolic membrane potential of ventricular and Purkinje myocytes close to the $K^+$ equilibrium potential ($-90$ mV). Thus, the reduction in the $I_{K_1}$ conductance seen after MI may cause the membrane potential to become less negative and approach the threshold potential of action potential firing, thereby providing a basis for abnormal automaticity. On the other hand, a concomitant reduction in $I_{K_r}$ and $I_{to}$ should delay action potential repolarization and provide electrical substrates for the initiation of early after-depolarization (EAD) or delayed after-depolarization (DAD), in otherwise quiescent ventricular myocardium.

References


