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ATP-Sensitive Potassium Channel Modulators: Both Pinacidil and Glibenclamide Produce Antiarrhythmic Activity During Acute Myocardial Infarction in Conscious Rats[1]

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ABSTRACT

We investigated the effects of pinacidil, an ATP-sensitive potassium channel opener, and of glibenclamide, an ATP-sensitive potassium channel inhibitor, on the incidence of arrhythmias and sudden cardiac death after coronary artery ligation in conscious rats. Occlusion of the left main coronary artery was produced by tightening a previously placed loose silk ligature. In the control group (n = 25) only 40% and 24% of the animals survived for 15 min and 16 hr after coronary artery ligation, respectively. Intravenous pretreatment with 0.1, 0.3 or 1 mg/kg pinacidil increased the survival rate to 67% (n = 15), 70% (n = 20) and 67% (n = 12) in the first 15 min and to 60%, 55% and 67% in the first 16 hr, respectively. Glibenclamide pretreatment (5.0 mg/kg i.p.) improved the survival rate at both time-points to 87% (n = 16). Both types of pretreatment significantly decreased the incidence of life-threatening arrhythmias and increased the number of animals that survived without developing any arrhythmia. In conclusion, the present findings demonstrate that in conscious rats, pretreatment with pinacidil and pretreatment with glibenclamide, although they obviously have different mechanisms of action, may result in a very similar final outcome with respect to arrhythmias and sudden cardiac death during the acute phase of experimental myocardial infarction.

The major goal of therapeutic intervention during myocardial infarction is to prevent lethal ventricular arrhythmias and to preserve myocardial tissue from irreversible damage. The former is a major problem during the acute phase of myocardial infarction; the latter assumes great importance when the patient has survived the first hours after infarction.

Since the discovery of K_{ATP} by Noma (1983), extensive work has been devoted to elucidating its role in physiological and pathological conditions. In the heart during normoxia, this channel is found mainly in a closed, inactive form. However, as the intracellular ATP concentration falls as a result of ischemia, the probability of the channel being open increases, thereby increasing the significance of potassium current during repolarization (Gasser and Vaughan-Jones, 1990). As a consequence, the myocardial action potential duration is shortened, the voltage-dependent calcium influx is decreased and cardiac work and oxygen consumption of the myocardium are reduced, which leads to preservation of ATP during ischemia. These changes may have a natural protective role in preserving the function of the heart for a longer time during ischemia (Escande and Cavero, 1992).

Several studies have suggested that administration of specific openers of K_{ATP} channels during the early phase of myocardial infarction can preserve myocardial function and decrease infarct size (Lamping *et al.*, 1984; Grover *et al.*, 1990; Toombs *et al.*, 1992; Yao and Gross, 1994; Auchampach and Gross, 1994). Other studies have yielded contradictory results, suggesting either that such agents do not influence the development of infarct size (Imai *et al.*, 1988; Sakamoto *et al.*, 1989; Smallwood *et al.*, 1993) or that they may even increase it (Kitzen *et al.*, 1992).

Theoretically, on the basis of the cellular electrophysiological effects, K_{ATP} openers, as a result of their action potential duration shortening effect, may inhibit the abnormal impulse generation that frequently occurs several hours or days after the onset of myocardial infarction (Lathrop *et al.*, 1990; Bril and Man, 1990; Spinelli *et al.*, 1991). Accordingly, K_{ATP} activators have been demonstrated to suppress arrhythmias that are present 22 to 24 hr after coronary artery ligation (Kerr *et al.*, 1985). On the other hand, further shortening of the action potential duration during the acute phase of myocardial infarction may contribute to the aggravation of reentry type arrhythmias (Chi *et al.*, 1990; Smallwood *et al.*, 1993). A similar proarrhythmic effect has been demonstrated in isolated, perfused heart preparations *in vitro* (Wolleben *et al.*, 1989; Fagbemi *et al.*, 1993; Di Diego and Antzelevitch,

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ABBREVIATIONS: K_{ATP}, ATP-sensitive potassium channel; VF, ventricular fibrillation; VT, ventricular tachycardia; VEB, ventricular extrasystole.

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1993; Tosaki *et al.*, 1993). However, the proarrhythmic effect of K_{ATP} openers during the acute phase of experimental myocardial infarction is also subject to question, because the infarct size-limiting effect was also observed using smaller doses that did not produce shortening of the action potential duration in the normal myocardium (Grover *et al.*, 1990; D'Alonzo *et al.*, 1994; Yao and Gross, 1994; Grover *et al.*, 1995).

Because of their electrophysiologic effect in the heart, blockers of K_{ATP} channels, by inhibiting the shortening of the action potential duration selectively in the ischemic myocardium, would represent an antiarrhythmic treatment that is more specific to ischemic tissues. The antiarrhythmic effect has been demonstrated in *in vitro* experiments, using global or regional ischemia in perfused hearts (Kantor *et al.*, 1990; Wolleben *et al.*, 1989; Tosaki *et al.*, 1993; D'Alonzo *et al.*, 1994). Relatively few data are available, however, from *in vivo* experiments. These either demonstrate a protective effect against arrhythmias during the acute phase of experimental myocardial infarction in rats (Ballagi-Pordany *et al.*, 1990; Zhang *et al.*, 1991), or fail to show any beneficial effect on the incidence of ventricular fibrillation developing in response to a secondary ischemic insult in anesthetized dogs with recent myocardial infarction (Chi *et al.*, 1989).

Most of these *in vivo* experiments with K_{ATP} channel modulators involved only a few animals, which precluded any statistical analysis of the different types and occurrence of arrhythmias or of survival rate. Furthermore, these *in vivo* experiments were performed during anesthesia, where the anesthetic itself might interfere with the development of ischemic damage or arrhythmias. The aim of our present work was to study the effect of a well-known K_{ATP} channel opener, pinacidil (Arena and Kass, 1989a; Martin and Chinn, 1990), on the outcome of the acute phase of experimental myocardial infarction and to compare its effect to that of glibenclamide, a K_{ATP} channel blocker (Sturgess *et al.*, 1985; Fosset *et al.*, 1988) in a well-standardized model of arrhythmias in conscious rats.

Materials and Methods

Animals. Male Sprague-Dawley CFY rats weighing 300 to 350 g were used. Animals were fed commercial rat food pellet (Altromin, Gödöllö, Hungary) and were allowed to drink tap water *ad libitum*. Animals were handled according to a protocol reviewed and approved by the Ethical Committee of Research on Experimental Animals of the Albert Szent-Györgyi Medical University, Szeged, Hungary.

Myocardial infarction in conscious rats. In a preliminary surgery during ether anesthesia, after opening the thorax in the fourth intercostal space, we placed a loose loop of atraumatic silk (K 890 H, 5-0, Ethicon, England) around the left main coronary artery, about 2 mm from its origin (Leprán *et al.*, 1983). The silk was led through a cylinder-shaped polyethylene tubing, and the chest was closed with the tubing remaining inside the thoracic cavity. During its closure, the thorax was slightly compressed to stop pneumothorax and to regain spontaneous ventilation. The animals quickly recovered from this operation, and the mortality was negligible (less than 5%) because only a loose ligature was present around the coronary artery at this time.

After complete recovery from the preliminary surgery (about 7–10 days) and using a brief ether narcosis, s.c. electrodes were stitched under the skin to both sides of the chest wall, and the ends of the loose silk loop were made free from under the skin. The animals were taken into individual cages, and after about 2 hr of recovery from ether anesthesia and of accommodation to their new place, drug pretreatment was started and the loose silk ligature was tightened to achieve acute coronary artery ligation in conscious, freely moving animals.

The bipolar ECG was continuously recorded during the first 20 min after coronary artery ligation. The survival rate and the incidence and duration of arrhythmias were registered in accordance with the Lambeth Conventions (Walker *et al.*, 1988), *i.e.*, VF, VT, and other types of arrhythmias, including single VEBs, bigeminia, and salvos. When VF occurred, no attempt was made to defibrillate the animals.

An arrhythmia score was used to evaluate the incidence and duration of different arrhythmias by giving a grade to the animals as follows: 0 = no arrhythmia; 1 = <10 sec VT or other arrhythmias, no VF; 2 = 11 to 30 sec VT or other arrhythmias, no VF; 3 = 31 to 90 sec VT or other arrhythmias, no VF; 4 = 91 to 180 sec VT or other arrhythmias and/or <10 sec reversible VF; 5 = >180 sec VT or other arrhythmias and/or >10 sec reversible VF; 6 = irreversible VF.

In the rats surviving for 16 hr, the mass of the infarcted area was measured by macroscopic staining (Nachlas and Shnitka, 1963). The animals were anesthetized by pentobarbitone (60 mg/kg i.p.), and the heart was excised and washed in isotonic saline solution. After being sliced with razor into transversal slices approximately 1 mm thick, the heart was stained in 0.1% nitroblue-tetrazolium dye (Fluka AG, Switzerland). The wet weight of the infarcted, unstained myocardium was expressed as a percentage of the total weight of the ventricles.

Drug treatment. Pinacidil (0.03, 0.1, 0.3 or 1.0 mg/kg) was dissolved in isotonic saline solution (1 ml/kg) and was applied during 1 min i.v. into the tail vein in conscious animals 10 min before coronary artery ligation. Glibenclamide (5.0 mg/kg) was dissolved in a 1:1 mixture of dimethylsulfoxide and ethanol and was applied i.p. in a volume of 100 μl/kg 30 min before coronary artery ligation. Half of the control animals (n = 13) were given i.v. 1 ml/kg isotonic saline solution as a vehicle; the others (n = 12) were given the solvent for glibenclamide (100 μg/kg i.p.). No differences were found in survival rate or occurrence of arrhythmias in the vehicle-treated groups, so they were combined for the final statistical calculations.

Statistical analysis. For the statistical analysis of the survival rate and the incidence of arrhythmias, the chi-square test was applied. The arrhythmia score was compared using Gehan's generalized Wilcoxon test (Knapp and Wise, 1985). The other parameters were expressed as mean ± S.E. and, after analysis of variance (one-way ANOVA), were compared by using the modified t statistic of Wallenstein *et al.* (1980).

Results

Pinacidil, given i.v. 10 min before coronary artery ligation in conscious rats, dose-dependently increased the HR, measured just before ligation (fig. 1). In the control group, the first 15 min of coronary occlusion was characterized by a moderate tachycardia (fig. 1). Pinacidil pretreatment did not influence the HR response during the acute phase of myocardial infarction. Glibenclamide, in the dose applied 30 min before coronary artery ligation, did not influence the basal HR or its response during the first 15 min of myocardial ischemia (fig. 1).

Coronary artery ligation in conscious rats resulted in severe arrhythmias that appeared around the fourth or fifth minute, but if the animal survived the acute phase of infarction, arrhythmias were rarely seen after the twelfth min. In all of the control rats, some kind of dysrhythmia developed during the first 15 min of coronary occlusion (table 1). Out of the 25 animals, VF failed to develop in only 6 rats, and in 15 cases the VF was irreversible. Out of the 10 animals that

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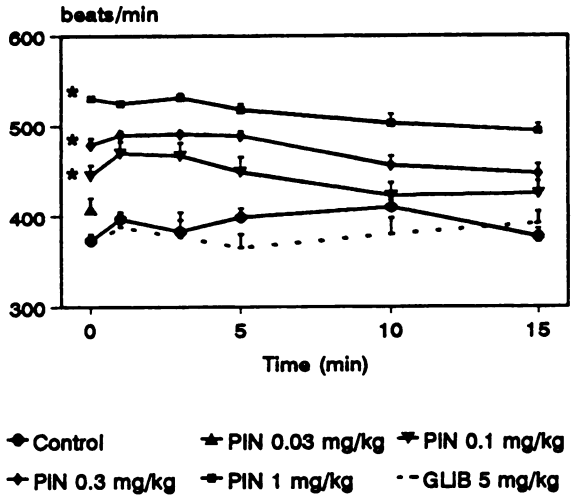

Fig. 1. Effect of pinacidil (PIN) and glibenclamide (GLIB) on the basal HR and its alteration during the acute phase of myocardial infarction in conscious rats. Pinacidil was applied i.v. 10 min, and Glibenclamide was given i.p. 30 min, before the start of coronary artery ligation. * indicates a statistically significant difference from the control group.

survived the first 15 min of coronary occlusion, 4 died during the next 16 hr (table 1).

Pinacidil pretreatment (except for the smallest dose) increased the survival rate during the first 15 min of occlusion; moreover, some animals did not develop arrhythmias at all (table 1). Although pinacidil did not decrease significantly the incidence of VF at each dose, the chance for spontaneous defibrillation was increased, and the occurrence of irreversible VF was smaller (*e.g.*, 54% after 0.3 mg/kg pinacidil *vs.* 79% in controls). Significant effects were even achieved by 0.1 mg/kg pinacidil, which did not produce maximal increases in HR (fig. 1; table 1).

Glibenclamide significantly increased the survival rate both during the first 15 min and during the subsequent 16 hr of myocardial infarction (table 1). The pretreatment decreased the incidence of VF and VT and increased the number of animals that did not develop any arrhythmia during the first 15 min after coronary artery ligation (table 1).

The arrhythmia score, which expressed the severity and duration of arrhythmias as well as the surviving rate in a single number, was also significantly decreased after both pinacidil and glibenclamide pretreatments (table 1).

There was no significant difference between the control and the drug-treated groups in the appearance of the first arrhythmia, determined in the animals that did show some kind of dysrhythmia (not presented in the tables). However, as a result of the increased number of animals that did not develop arrhythmias at all, the onset of the first arrhythmia was delayed and the duration of the arrhythmic period was shortened after both pinacidil and glibenclamide pretreatments (table 2). The length of different arrhythmic attacks in the surviving animals was decreased as well (table 2).

We lost the majority of the control animals within 15 min after coronary artery ligation. This time was too short for the animals to develop histologic change detectable by nitrobluetetrazolium staining, so we could not determine the infarct size in those animals that died during the acute phase of myocardial infarction. The infarct size in the control animals that survived for 16 hr was 32.4% ± 5.3% (n = 6), and infarcts extended to the anterior and lateral free wall of the left ventricle. There was a tendency of infarct size to decrease after pinacidil pretreatment. It was 34.5% ± 3.7% (n = 9), 24.0% ± 3.8% (n = 11), and 21.9% ± 8.0% (n = 8) after 0.1, 0.3 and 1 mg/kg pinacidil, respectively. Glibenclamide pretreatment resulted in an infarct size involving 24.5% ± 5.3% (n = 14) of the wet weight of the ventricles.

Discussion

Coronary artery ligation in rats is a widely used and widely accepted method for studying the pathophysiology of acute myocardial infarction and for investigating various antiarrhythmic and "anti-ischemic" interventions. Such a method is relatively simple, is quick, and makes it possible to include sufficient numbers of animals for the statistical analysis of parameters, such as the incidence of arrhythmias or sudden cardiac death. Using the modified method, *i.e.* ligation of the coronary artery by a previously placed loose silk loop, we were able to avoid the use of any anesthetic agent during coronary artery ligation. Therefore, the acute phase of myocardial infarction could be induced in conscious rats with intact autonomic reflexes.

The present results demonstrate that pretreatment with either pinacidil, a K_{ATP} channel opener, or glibenclamide, a K_{ATP} channel inhibitor, may offer significant protective effect during the acute phase of experimental myocardial infarction in conscious rats. Both drugs were highly effective in decreasing the incidence of life-threatening arrhythmias and increasing the number of animals that survived without developing any arrhythmia during the acute phase of myocardial infarction.

The protection afforded by pinacidil pretreatment occurred in spite of a very intense tachycardia. This effect was probably due to the intact baroreflex control in conscious animals and occurred as a consequence of the well-known blood pressure-lowering effect of pinacidil. Tachycardia itself could increase myocardial oxygen consumption and decrease the efficacy of cardiac work; it is considered undesirable during acute myocardial infarction (Bernier *et al.*, 1989). On the other hand, sinus tachycardia may work as an overdrive suppression during ventricular arrhythmias and may contribute significantly to the antiarrhythmic effect of pinacidil in conscious rats. Such a mechanism may play a role only in conscious animals, however, because in an anesthetized rat model, pinacidil afforded similar protective effects against reperfusion-induced arrhythmias while having no significant tachycardiac effects (Baczkó *et al.*, 1994).

The mechanism of the significant antiarrhythmic effect offered by pinacidil in our experiments is not known; both peripheral and cardiac effects may be involved. The peripheral vasodilation induced by pinacidil may decrease the total peripheral resistance and thereby reduce cardiac work. Such an unloading may help the ischemic myocardium to survive the most critical phase of myocardial infarction. However, this mechanism may be significant mainly in the later phase of myocardial infarction (days or weeks after coronary ligation), whereas decreasing the blood pressure during the acute phase of myocardial infarction would rather precipitate arrhythmias, because of the decrease in coronary perfusion pressure. This was demonstrated in our previous experiments in anesthetized rats during a short coronary artery

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TABLE 1

Effect of pinacidil and glibenclamide on the survival rate and the incidence of arrhythmias during the acute phase of myocardial infarction in conscious rats

Group	Dose (mg/kg)	n	Survived 15 min (No./%)	Survived 16 hrs (No./%)	Incidence of Arrhythmias (No./%)					Arrhythmia Score
					None	VF	VT	Other[a]	Brady[b]	
Control		25	10/40	6/24	0/0	19/76	24/96	15/60	6/24	5.1 ± 0.27
Pinacidil	0.03	9	2/22	1/11	0/0	8/89	9/100	3/33	1/11	5.3 ± 0.55
	0.10	15	10/67	9/60 *	3/20 *	6/40 *	9/60 **	7/47	1/7	3.0 ± 0.65 **
	0.30	20	14/70 *	11/55 *	4/20 *	11/55	13/65 *	11/55	7/35	3.6 ± 0.52 **
	1.00	12	8/67	8/67 **	4/33**	5/42 *	5/42 ***	3/25*	2/17	2.7 ± 0.81 **
Glibenclamide	5.00	16	14/87**	14/87***	5/31**	4/25**	9/56 **	9/56	1/6	2.4 ± 0.56***

[a] Arrhythmias, *e.g.* VEBs, salvos, and bigeminia.
[b] Bradycardia.
Asterisks denote statistically significant difference calculated by the chi-square method or by Gehan's generalized Wilcoxon test: *P < .05, **P < .01, ***P < .001.
n = total number of animals; No. = number of animals exhibiting the given response.

TABLE 2

Effect of pinacidil and glibenclamide on the appearance and length of arrhythmias in conscious rats that survived the acute phase of regional myocardial ischemia

Group	Dose (mg/kg)	n	Appearance of Arrhythmias (min)	Duration of Arrhythmias (min)	Length of arrhythmic attacks (sec)			
					VF	VT	Other	Total
Control		10	5.03 ± 0.49	4.87 ± 0.70	24 ± 12.6	44 ± 16.3	50 ± 12.2	118 ± 29.6
Pinacidil	0.03[a]	2	4.02 ± 0.36					
	0.10	10	9.17 ± 1.36*	1.97 ± 0.79*	5 ± 5.0	8 ± 3.9*	11 ± 4.6*	24 ± 9.6*
	0.30	14	8.39 ± 1.19	3.25 ± 0.83	21 ± 8.7	21 ± 10.9	34 ± 11.3	77 ± 27.1
	1.00	8	11.9 ± 1.50**	0.75 ± 0.38**	9 ± 8.8	1 ± 1.3*	10 ± 5.3*	20 ± 14.6*
Glibenclamide	5.00	14	8.17 ± 1.43	3.35 ± 1.01	4 ± 3.1	25 ± 8.6	31 ± 11.1	61 ± 20.5

Results are mean ± S.E.
Asterisks denote statistically significant difference calculated by the modified *t* statistic: *P < .05, **P < .01, ***P < .001.
[a] Because of the small number of surviving animals in this group, the duration and length of arrhythmias were not calculated.
For other details, see table 1.

ligation followed by reperfusion (Baczkó *et al.*, 1994), wherein a large dose of pinacidil that induced long-lasting hypotension did not offer any protective effect against reperfusion-induced arrhythmias.

Coronary collateral blood flow may significantly limit the extent of myocardial damage (Nienaber *et al.*, 1983). The vasodilating effect of pinacidil at the level of collaterals could limit the development of infarct size, and such a mechanism could result in a decreased incidence of arrhythmias. Although we did not measure collateral circulation in our experiments, the very limited collateral blood flow in this species (Maxwell *et al.*, 1987) makes it unlikely that such a mechanism is responsible. Even in dogs, where well-developed collaterals exist, pinacidil did not influence collateral blood flow during ischemia (Auchampach and Gross, 1994).

In spite of the fact that pinacidil pretreatment significantly increased the survival rate both during the acute phase (first 15 min) and in the second phase (until the 16th hour) of myocardial infarction, the infarct size was only slightly decreased. The present experiments, however, were devoted to investigating the acute phase arrhythmias, not the extent of infarct size in the rat. We suppose that having a control group with a low survival rate (as in the present experiments, where only 6 out of 25 animals survived), we may have underestimated the infarct size because of losing animals with large evolving myocardial infarction before the infarct size could be determined. On the other hand, if the drug treatment increased the chance to survive the first phase of myocardial infarction, we could measure infarct size in more animals, including those that had larger myocardial infarction. Therefore, we may have overestimated infarct size after an effective drug treatment (Leprán *et al.*, 1983). For the investigation of infarct size, it would be preferable to produce smaller myocardial infarction that results in a higher survival rate in the control group as well. Experimental findings in dogs suggest that K_{ATP} openers may actually decrease infarct size (Gross *et al.*, 1989; Grover *et al.*, 1990; Auchampach and Gross, 1994).

In theory the electrophysiological effects produced by K_{ATP} channel openers, *i.e.*, shortening of the action potential duration, may result in proarrhythmic effect and may precipitate arrhythmias during the acute phase of myocardial infarction. Indeed, Chi *et al.* (1990) demonstrated that pinacidil produced profibrillatory action in a subset of dogs unresponsive to programmed electrical stimulation during the subacute phase of anterior myocardial infarction and known to be at low risk of VF due to a second acute posterolateral ischemia. Others have shown that pinacidil, after intracoronary administration, may increase the incidence or the severity of ventricular arrhythmias (Smallwood *et al.*, 1993). In some *in vitro* experiments using global ischemia of perfused heart, an increased incidence of arrhythmias during ischemia or reperfusion was also reported (Wolleben *et al.*, 1989; Fagbemi *et al.*, 1993; Tosaki *et al.*, 1993; Kaiser *et al.*, 1994). In these experiments, however, relatively high concentrations of pinacidil or other K_{ATP} channel openers were applied—higher than those reached in patients after long-term treatment with a high dose of pinacidil (Friedel and Brogden, 1990).

Other investigations, using smaller doses of K_{ATP} channel openers, have demonstrated an antiarrhythmic effect in addition to limitation of the infarct size (Grover *et al.*, 1990;

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D'Alonzo *et al.*, 1994). In the present experiments in conscious rats, we also found a protective effect against arrhythmias during the acute phase of myocardial infarction.

K_{ATP} channel openers in therapeutic concentrations that evoke hypotension do not produce significant electrophysiologic effects in the normally oxygenated myocardium (Arena and Kass, 1989b; Nakayama *et al.*, 1990). On the other hand, their effect is enhanced during myocardial ischemia when intracellular ATP concentration falls (Arena and Kass, 1989b; Nakayama *et al.*, 1990; Martin and Chinn, 1990). Channel opening would result in improved repolarization and the inhibition of voltage-dependent calcium influx into myocardial cells, thereby decreasing contractile activity within the ischemic zone (Cole *et al.*, 1991). This effect may preserve energy and improve tolerance to the ischemic insult. In this respect, what we have measured as an "antiarrhythmic" effect probably is not only a direct effect, mediated by ionic currents through the membrane, but can also be attributed to an increase in tolerance to ischemia.

The progression of myocardial ischemia is not homogeneous, not even in the occluded area, and may lead to a nonhomogeneous shortening of the action potential duration. This increased electrical inhomogeneity may be involved as an electrophysiologic substrate to develop ventricular arrhythmias and VF during the acute phase of myocardial infarction (Janse and Wit, 1989). K_{ATP} openers may decrease electric inhomogeneity within the ischemic area, possibly by further shortening the action potential duration in "less ischemic" fibers. The electrophysiologic difference between severely ischemic and less severely damaged fibers could be diminished by this means. Such a mechanism might contribute to the antiarrhythmic effect observed in our experiments during the acute phase of infarction, when the electrophysiology of the myocardium is most unstable.

K_{ATP} inhibitors, on the other hand, may inhibit K^+ loss from jeopardized cells and inhibit nonuniform shortening of the action potential duration during the progression of myocardial ischemia (Tweedie *et al.*, 1993; MacKenzie *et al.*, 1993). Such an effect produced by glibenclamide, in the way opposite that described above for pinacidil, could alleviate the increase in electric inhomogeneity between the ischemic and normally oxygenated tissues and might inhibit the substrate for reentrant pathways, resulting in antiarrhythmic, antifibrillatory action during the acute phase of myocardial infarction. Although we did not perform dose-response evaluation for the antiarrhythmic effects of glibenclamide, the present data are in good agreement with the results of Ballagi-Pordany *et al.* (1990). They found a decreased incidence of arrhythmias in anesthetized rats after applying 3 to 10 μmol/kg of glibenclamide i.p.. It should be emphasized that the protective effect by glibenclamide occurred in spite of its hypoglycemic action, which may exacerbate the antiarrhythmic effect.

The present results in conscious rats are in good correlation with that described by D'Alonzo *et al.* (1994), showing both potassium channel openers and glibenclamide to have potential antiarrhythmic activity during coronary artery ligation and reperfusion in an isolated, perfused rat heart model. Their suggestion is that these compounds may influence different types of arrhythmias that are linked with myocardial ischemia. Accordingly, K_{ATP} channel openers may abolish triggered activity, whereas glibenclamide may reduce reentry. This explanation may also be in accordance with our *in vivo* experiments and may account for the marked antiarrhythmic and antifibrillatory action.

It should be noted that many investigators have described K_{ATP} openers as proarrhythmic during the acute phase of myocardial infarction (Wolleben *et al.*, 1989; Fagbemi *et al.*, 1993; Tosaki *et al.*, 1993; Chi *et al.*, 1990; Smallwood *et al.*, 1993), whereas glibenclamide has been found to increase infarct size (Cole *et al.*, 1991; Thornton *et al.*, 1993). The conflicting effects on arrhythmias and on the development of myocardial damage may be related to different models of myocardial infarction, *e.g.*, global or regional ischemia, *in vitro* or *in vivo* experiments, and so on.

The present results demonstrate that both opening and closing K_{ATP} channels by pinacidil and glibenclamide pretreatments, respectively, may offer a protective effect against life-threatening arrhythmias and increase the chance to survive the acute phase of myocardial infarction in conscious rats. The mechanism of these actions needs further investigations, but inhibition of the increase in electric inhomogeneity during acute myocardial ischemia may be involved in both cases. An increased tolerance to the development of myocardial ischemia after pinacidil treatment may also be responsible. Further investigation of more selective compounds—compounds that have less significant vascular or hypoglycemic effects and more specific action on myocardial cells—may help to elucidate this question.

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