Short-term diabetes decreases ischemia reperfusion-induced arrhythmia: the effect of alpha-2 blocker yohimbine and glibenclamide

Ömer BOZDOĞAN[1,*], Salih Tunç KAYA[2], Selçuk YAŞAR[1], Erçin Çağdas BAŞ[1],
Oğulcan Talat ÖZARSLAN[1], Didem EKŞİOGLU[1], Firdevs ERİM[1]
[1]Department of Biology, Faculty of Science and Arts, Abant İzzet Baysal University, Gölköy, Bolu, Turkey
[2]Department of Biology, Faculty of Science and Arts, Düzce University, Konuralp, Düzce, Turkey

Abstract: This study examined the effect of yohimbine alone and in combination with glibenclamide on ischemia and reperfusion-induced arrhythmias in diabetes. Six minutes of ischemia were produced in 1-week diabetic rats by ligation of the left coronary artery, and 6 min of reperfusion were produced by releasing the artery. A dose of 5 mg/kg of yohimbine and glibenclamide was administered for 7 days prior to the coronary ligation. The blood pressure, heart rate, and arrhythmia were determined from the recorded ECG during the 6 min of ischemia and reperfusion and then compared using a one-way ANOVA statistical program and the chi-square test. The score of arrhythmia calculated from the type and duration of arrhythmia decreased in the diabetic rats (3.5 ± 1.69 in control, 1.7 ± 0.81 in diabetes group). The arrhythmia score returned to the control value in the rats that were given a combination of yohimbine and glibenclamide (3 ± 1.73). Yohimbine is used in the treatment of erectile dysfunction; glibenclamide is used as an antidiabetic drug in diabetic patients and may be a risk factor in the increase of ischemia reperfusion-induced arrhythmias.

Key words: Ischemia, reperfusion, arrhythmia, diabetes, glibenclamide, yohimbine

1. Introduction

Ischemia that occurs following the occlusion of coronaries and reperfusion by reopening of the vessel induces lethal arrhythmia that is observed both in humans and experimentally in animals. In various studies (Balakumar et al., 2012; Nakau et al., 2012) it has been found that arrhythmias observed following myocardial ischemia and reperfusion decrease in the early stages of diabetes, whereas they increase in the later stages. However, the reason for this different response in diabetic rats is still a subject of ongoing research. Diabetic patients are susceptible to various diseases as well as to the effect of yohimbine and glibenclamide, which might be candidate drugs for the treatment of those diseases. Although the antiarrhythmic effect of yohimbine following ischemia and reperfusion and the antidiabetic effect of glibenclamide were shown experimentally in rats, their effects alone or in combination in diabetic rats are not yet known. Yohimbine decreases reperfusion-induced arrhythmias in nondiabetic rats (Roegel et al., 1996; Bozdoğan et al., 2004; Bozdoğan et al., 2013) and it has both an antidiabetic (Arrajab and Ahren, 1991; Sandberg et al., 2013) and a cardiovascular protective effect (Yiyang et al., 2013). Glibenclamide is

commonly used as an antidiabetic drug, although its effect on ischemia reperfusion-induced arrhythmia in nondiabetic rats is controversial (El-Reyani et al., 1999; Bozdoğan et al., 2000). Glibenclamide has been found to increase ventricular tachycardia and fibrillation in 2-week diabetes (Tosaki et al., 1995). Glibenclamide and yohimbine, which are used to treat diabetes and erectile dysfunction, respectively, can be used in combination. However, no studies have been conducted related to the combined effect of yohimbine and glibenclamide on ischemia reperfusion-induced arrhythmias in diabetes. This research aimed to investigate the effects of yohimbine alone and yohimbine in combination with glibenclamide treatments on ischemia reperfusion-induced arrhythmias in 1-week diabetic rats.

2. Materials and methods

2.1. Animals

In this study, 28 male rats between 6 and 7 months old were used. Animals were raised in 12L/12D photoperiods in a room with 40% humidity. Food and water were given ad libitum. The rats were divided into 4 groups. The first group was designated as the nondiabetic control; isotonic

solution in the daily amount of 1 mL/kg was given intraperitoneally to rats in this group during the 7 days prior to operation. The second, third, and fourth groups of rats were made diabetic via a single-dose injection of 50 mg/kg streptozotocin (STZ). Twenty-four hours after the STZ application, 1 mL/kg isotonic solution, 5 mg/kg yohimbine + 1 mL/kg isotonic solution, and 5 mg/kg yohimbine and 5 mg/kg glibenclamide were given daily to the second, third, and fourth groups, respectively, for 7 days. All injections were given intraperitoneally. At the end of the 7 days animals in all groups were operated on in order to produce myocardial ischemia and reperfusion.

2.2. Surgical procedures
The animals were anesthetized with 1.2 g/kg urethane prior to the operation. A tracheotomy was then performed for artificial respiration, and the carotid artery was cannulated for blood pressure measurement. A thoracotomy from 4–5 intercostal spaces and a pericardiotomy were performed to expose the heart. The heart was extracted from the thorax by pressing it gently on either side. The left arteria ramus interventricularis was ligated with 5/0 silk in order to produce 6 min of ischemia, and then 6 min of reperfusion was created by the releasing of this artery. Artificial respiration during the operation was performed at a rate of 60 strokes/min and 0.9 mL room air/100 mg body weight. Animals that had blood pressure below 70 mmHg or arrhythmia before ligation were removed from the studies.

2.3. Determination of risk of infarct zone
At the end of the experiments, the hearts were excised out and the coronary artery was ligated again. The hearts were perfused first with an isotonic solution and then with ethanol for demarcation of the nonperfused area from the perfused one. The nonperfused area remained light pinkish in color, while the perfused one turned white in color after the ethanol perfusion. The nonperfused area was cut out and separated from the perfused one. The weight of the nonperfused area was measured alone and then together with the perfused area. The percentage of the nonperfused area was calculated in respect to the whole weight of the ventricle and designated as the risk of infarct zone (Lepran et al., 1983).

2.4. Biochemical analysis
Blood glucose was measured by a glucometer (Glucotrend2, Roche Group, UK) prior to the operation. Animals that had a blood glucose level higher than 300 mg/dL were accepted as diabetic (Pushparaj et al., 2007).

2.5. Recording
Electrocardiograms and the blood pressure were recorded during ischemia and reperfusion using a computerized recording system (Biopac System Inc., USA; Turkish representative: Commat, Ankara, Turkey) using BSL Pro

3.7 software. The duration and the type of arrhythmias were determined from the recorded ECG according to the Lambeth Convention (Curtis et al., 2013). An arrhythmia score was defined in respect to the duration and type of arrhythmia observed during the ischemia and reperfusion in all animals where 0 indicates no arrhythmia, 1 indicates an arrhythmia duration of less than 10 s (ventricular tachycardia, extra systole, bigeminy or salvo), 2 indicates an arrhythmia duration of 11–30 s, 3 indicates an arrhythmia duration of 31–90 s, 4 indicates an arrhythmia duration of 91–180 s or reversible ventricular fibrillation (VF), 5 indicates an arrhythmia duration longer than 180 s or reversible VF for more than 10 s, and 6 indicates irreversible VF or death of the animal (Yaşar et al., 2015). The arrhythmia recorded during ischemia and reperfusion in diabetic rats is shown in Figure 1.

2.6. Statistical analysis
All the mean values, including blood pressure, heart rate, duration of arrhythmia, and the incidences of every type of arrhythmia during the ischemia and reperfusion, were analyzed and compared using one-way ANOVA. The survival rate at the end of ischemia and reperfusion was analyzed with the chi-square method (Fisher exact test).

3. Results
No statistically significant differences were found in the heart rate and blood pressure before coronary ligation and during ischemia among the groups (Table 1). The heart rate during reperfusion in the diabetic rats decreased, but the blood pressure did not change when compared to the nondiabetic rats (Table 2).

The body weight measured at the end of 1 week decreased in the diabetic groups in contrast to the nondiabetic control (P < 0.05). Similarly, but not significantly, the total ventricular weight decreased in the diabetic rats (Table 3). The risk of the infarct zone after the coronary ligation was found to be similar in all groups. Blood glucose did not decrease in the diabetic rats after the yohimbine application, both alone and in combination with glibenclamide (Figure 2).

The total durations of the arrhythmias, the ventricular arrhythmias, and the arrhythmia score determined during the 6 min of ischemia were not found to be significantly different in diabetic rats when compared with the nondiabetic rats. The incidence of ventricular arrhythmia and the survival rate determined at the end of the ischemia were also similar among the groups. However, the arrhythmia score calculated by examining the duration and type of the arrhythmia recorded during reperfusion was found to decrease significantly in the diabetic rats both with and without the yohimbine treatment in respect to the control (Table 4). The combination of glibenclamide with yohimbine increased the arrhythmia score back to
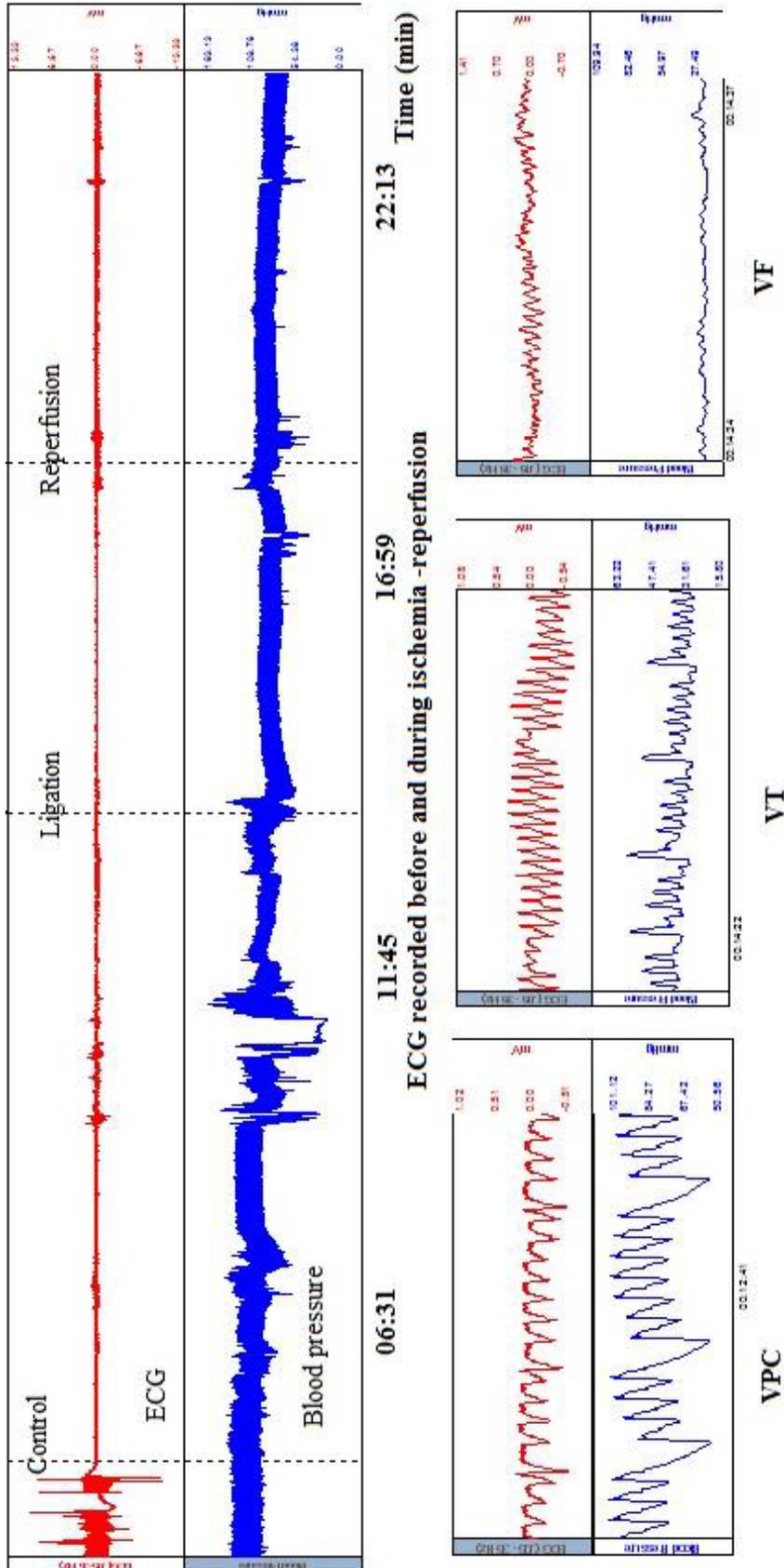
Figure 1. Ventricular arrhythmias observed during ischemia and reperfusion. Record was taken from diabetic animals that were administered yohimbine and glibenclamide. VPC: Ventricular premature contraction, VT: ventricular tachycardia, VF: ventricular fibrillation.

Table 1. Heart rate and mean arterial blood pressure recorded before and during 6 min of ischemia.

Groups	N	Heart rate (beats/minute)				Blood pressure (mmHg)			
		Before ligation	Following ligation			Before ligation	Following ligation		
			1 min	3 min	5 min		1 min	3 min	5 min
Control	8	358 ± 20	348 ± 28	347 ± 28	339 ± 35	111 ± 5	80 ± 9	83 ± 10	78 ± 10
STZ	6	317 ± 14	341.9 ± 24.18	314 ± 21	308 ± 23	114 ± 6	83 ± 11	92 ± 7	86 ± 6
STZ + YH	7	358 ± 16	351.6 ± 13.35	358 ± 12	347 ± 14	115 ± 2	83 ± 6	89 ± 9	90 ± 6
STZ + YH + GL	7	337 ± 22	364.9 ± 41.56	340 ± 25	328 ± 27	113 ± 5	84 ± 8	89 ± 6	78 ± 4

Control: Nondiabetic rats, STZ: diabetic rats, STZ + YH: diabetic rats treated with yohimbine, STZ + YH + GL: diabetic rats treated with combination of yohimbine and glibenclamide. N: Number of surviving animals at the end of 6 min of ischemia. Values represent mean ± standard error.

Table 2. Heart rate and mean arterial blood pressure recorded during 6 min of reperfusion.

Groups	N	Heart rate (beats/minute)			Arterial blood pressure (mmHg)		
		1 min	3 min	5 min	1 min	3 min	5 min
Control	8	453 ± 88	379 ± 23,	381 ± 22	58 ± 5	72 ± 12	67 ± 11
STZ	6	304 ± 18*	303 ± 23*	300 ± 23*	76 ± 10	85 ± 11	83 ± 10
STZ + YH	7	355 ± 13	351 ± 8	343 ± 15	89 ± 7	77 ± 8	89 ± 9
STZ + YH + GL	7	324 ± 25*	319 ± 29	324 ± 30	85 ± 11	99 ± 9	90 ± 9

N: Number of surviving animals at the end of 6 min of reperfusion. Values represent mean ± standard error. *P < 0.05; different from control.

Table 3. Weight of body and ventricle at the end of reperfusion and risk of infarct zone.

Groups	N	Body weight (g)		Ventricle weight (g)	Risk of infarct zone (%)
		Before STZ	After STZ		
Control	8	391 ± 11	388 ± 8	1.15 ± 0.09	47.4 ± 2.25
STZ	6	344 ± 14	325 ± 18*	0.85 ± 0.06*	48.3 ± 3.57
STZ + YH	7	325 ± 21	275 ± 22*	0.75 ± 0.04*	47.2 ± 1.83
ST + YH + GL	7	374 ± 8	325 ± 10*	0.91 ± 0.06*	50.8 ± 1.11

N: Number of surviving animals at the end of 6 min of reperfusion. Values represent mean ± standard error. *P < 0.05; different from control.

the control level. The incidence of ventricular tachycardia and VF during reperfusion decreased in the diabetic rats in respect to the control rats (Table 4) at P < 0.05. The decrease in the incidence of ventricular tachycardia and VF was also seen in the yohimbine-treated diabetic rats. However, the combination of glibenclamide with yohimbine nonsignificantly increased the incidences of these arrhythmias back to control levels (Table 4). The arrhythmia started earlier during reperfusion in the diabetic rats in contrast to the control animals (Table 5) at P < 0.05. On the other hand, the arrhythmic period during reperfusion measured between the start and the end of arrhythmia increased in all the diabetic groups compared to the nondiabetic control (Table 5) at P < 0.05. Bradycardia was observed in the control groups, but not in the diabetic rats.
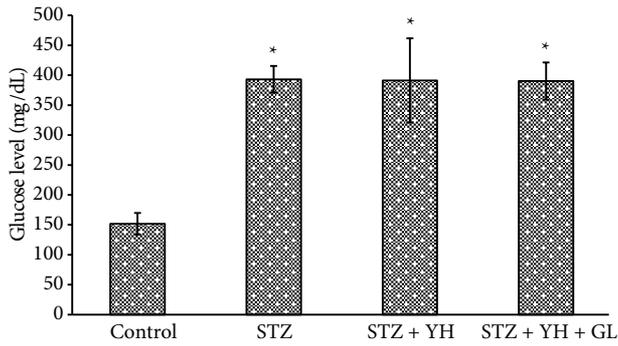
Figure 2. Blood glucose levels. Control: Nondiabetic rats, STZ: diabetic rats, STZ + YH: diabetic rats treated with yohimbine, STZ + YH + GL: diabetic rats treated with combination of yohimbine and glibenclamide. *P < 0.05; different from control.

4. Discussion

Previous studies (Tosaki et al., 1995; Zhang et al., 2002; Ravingerova et al., 2003) have shown that short-term diabetic duration decreases reperfusion-induced ventricular arrhythmias. This is consistent with the results of the present study. Yohimbine did not change

the incidences of these arrhythmias. The combination of glibenclamide and yohimbine increasing ventricular arrhythmias in diabetic rats compared to a nondiabetic control is being reported in this study for the first time. However, in a similar study, opposite results were reported (Tosaki et al., 1995). This difference may be due to two reasons: the effect of glibenclamide was examined in the later stage of diabetes, and a global ischemia and reperfusion model was performed in that study. The effect of yohimbine on ischemia and reperfusion-induced arrhythmia in the diabetic rats was first examined in this study. Yohimbine did not change the cardioprotection induced by the diabetes against arrhythmia. Several studies have shown that yohimbine decreases ischemia and reperfusion-induced arrhythmia in normal rats (Francis et al., 1983; Bozdoğan et al., 2004; Yiyang et al., 2013). In contrast to the protection against ischemia reperfusion arrhythmia generated in the early phase of diabetes, this protection disappeared in the late phase of diabetes, as has been previously shown (Balakamur et al., 2012). The protective effect of diabetes against ischemia reperfusion-induced arrhythmia was observed as variable, as it was examined in the early and late stages of diabetes (Goel and

Table 4. The incidence of arrhythmia and arrhythmia score determined at the end of 6 min of reperfusion.

Groups	N	Survival rate (%)	Incidence (N/%)				Arrhythmia score
			VF	VT	Others	Bradycardia	
Control	8	100	4 / 50	6 / 75	8 / 100	4 / 50	3.5 ± 1.69
STZ	6	100	0 / 0*	1 / 16*	6 / 100	0 / 0*	1.7 ± 0.81*
STZ + YH	7	100	1 / 14	1 / 14*	5 / 71	0 / 0*	1.6 ± 1.39*
STZ + YH + GL	7	100	2 / 28	5 / 71	6 / 85	0 / 0*	3 ± 1.73

N: Number of surviving animals at the end of 6 min of reperfusion. Values represent mean ± standard error. *P < 0.05; different from control. VF: Ventricular fibrillation, VT: ventricular tachycardia. Others: Ventricular extrasystole, bigeminal ventricular arrhythmia, salvo. N/%: Number of animals/percentage.

Table 5. Duration of arrhythmia determined during 6 min of reperfusion.

Groups	N	Start of arrhythmia (s)	Arrhythmic period (s)	Duration of arrhythmia (s)				
				VF	VT	Others	Total	Bradycardia
Control	8	85.1 ± 41.81	144.8 ± 31.78	49.4 ± 33.75	7.7 ± 2.67	17.9 ± 4.70	75.0 ± 34.79	68.3 ± 40.60
STZ	6	40.2 ± 14.95*	196.3 ± 47.25*	0.0	0.8 ± 0.81	15.5 ± 5.30	13.4 ± 5.45	0.0*
STZ + YH	7	21.4 ± 11.08*	69.0 ± 38.65	1.3 ± 1.28	10.7 ± 10.68	15.3 ± 5.30	40.7 ± 15.39	0.0*
STZ + YH + GL	7	7.7 ± 7.05*	118.0 ± 47.49	6.5 ± 4.28	15.1 ± 6.57	13.5 ± 3.53	21.0 ± 7.95	0.0*

N: Number of surviving animals at the end of 6 min of reperfusion. Values represent mean ± standard error. *P < 0.05; different from control.

Pierce, 1999; Akula et al., 2003; Ravingerova et al., 2003). The underlying mechanism of this protection is not the focus and lies outside the scope of this research. However, it is clearly demonstrated that a 1-week diabetic duration results in the decrease of ischemia and reperfusion-induced arrhythmia. Myocardial injury following coronary ligation was shown to decrease in the initial stage, but it increased in the later one (Akula et al., 2003; Nakou et al., 2012). A period of 6 weeks of hyperglycemia was mentioned as the reason for increased myocardial injury (Akula et al., 2003). In another study it was shown that diabetes increases the sensitivity of the myocardium to ischemia and reperfusion injury, and also increases the infarct size while decreasing the superoxide dismutase activity in the early stage (Haobo et al., 2013).

Sulfonylurea drugs are commonly used to treat diabetes. However, these drugs also increase erectile dysfunction (Freitas et al., 2009). No epidemic research was found on whether the incidence of erectile dysfunction increases in patients using glibenclamide. In an experimental study it was shown that glibenclamide decreases arrhythmia following ischemia reperfusion in diabetes (Tosaki et al., 1995). There are various studies indicating that glibenclamide either decreases or increases the ischemia reperfusion-induced arrhythmia in nondiabetic rats (El-Reyani et al., 1999; Bozdoğan et al., 2000). Some drugs from the sulfonylurea group have been shown to decrease myocardial cell damage by increasing fibrinolysis and decreasing platelet activation and oxidative stress (Thisted et al., 2006). A combination of glibenclamide with yohimbine increased the arrhythmia observed in the early stage of diabetes; this may be due to the ischemic effects of glibenclamide (Bozdoğan et al., 2000). This suggestion is supported by clinical findings that higher mortality following acute myocardial infarction has been observed more frequently in patients using glibenclamide as an antidiabetic drug (Thisted et al., 2006). Glibenclamide and yohimbine have been shown to decrease blood glucose as well as arrhythmia in myocardial ischemia and reperfusion in nondiabetic rats (Bozdoğan et al., 2004). However, this type of synergic effect has not been demonstrated in diabetic rats. The ineffectiveness of glibenclamide and yohimbine on blood glucose may be due to the complete damage of pancreatic beta cells. In this study it was observed that glibenclamide has a proarrhythmic effect in early diabetes. However, the effect of glibenclamide in the later stages of diabetes requires clarification. Yohimbine alone was not found to be effective for decreasing arrhythmia in diabetic rats. This ineffectiveness of yohimbine might be due to the decreased sensitivity of yohimbine in binding the alpha-2 adrenergic receptor (Padayatti and Paulose, 1999).

Body weight and total ventricular weight are decreased in diabetic rats (Shiomi et al., 2003; Kim et al., 2012; Haobo et al., 2013). No differences were found in the blood pressure and heart rate before and during ischemia and reperfusion in diabetic and nondiabetic rats. These findings from the present study are consistent with previous studies (Shiomi et al., 2003; Kim et al., 2012).

In conclusion, 1 week of diabetes increases the resistance of the heart against ischemia and reperfusion injury, thereby decreasing ventricular arrhythmias. Protection against arrhythmia produced by diabetes did not change with yohimbine. However, glibenclamide potentiated these arrhythmias. Further investigation into the effects of yohimbine and glibenclamide on ischemia and reperfusion-induced arrhythmia in the late stages of diabetes can be crucial in order to evaluate the clinical usage of these drugs.

The effect of glibenclamide alone on ischemia and reperfusion-induced arrhythmia in diabetic rats was not researched in this study. That might be useful for understanding the mechanism of the effect of glibenclamide on arrhythmias in experimentally produced myocardial ischemia and reperfusion in nondiabetic rats. Another limitation of the study is the number of animals used in each group. The maximum number in each group was limited to 8 animals. Increasing the number might be useful to decrease statistical variation in the different arrhythmic responses of hearts to ischemia and reperfusion.

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