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The Acute Combined Effect of Pinacidil and Glimepiride on Ischemia and Reperfusion Induced Arrhythmia, "The Role of ATP-dependent Potassium Channel"

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ABSTRACT

Aim: The aim of the present study is to evaluate the effect of pinacidil and glimepiride combination on arrhythmias induced early phase of ischemia and reperfusion.

Main Method: 26 Anesthetized male Sprague-Dawley rats aged 6-7 months-old have been used in this study. Ischemia was performed for 6 min. by the ligation of left main coronary artery and reperfusion for 6 min.by releasing the silk thread on the artery.

Results: Pinacidil alone was anti-arrhythmic in reperfusion period, while glimepiride was pro-arrhythmic. The protective effect of pinacidil was abolished by glimepiride in combination group, and the expected protective results against I/R induced arrhythmia were not observed.

Conclusion: The result of this study showed that combination of KATP channel opener and blocker given in different time during ischemia and reperfusion period do not have synergic effect to decrease the arrhythmia. This might be increasing heterogeneity in action potential duration in ischemic or normal myocardium.

Key Words: Myocardial ischemia, reperfusion, arrhythmia, combination, pinacidil, glimepiride.

1. INTRODUCTION

In recent and past decades, ATP-potassium channels and their modulators have attracted the attention of many researchers through their protective role against Ischemia-Reperfusion myocardial injuries. In several studies, KATP channel modulators showed both pro-arrhythmic and anti-arrhythmic effects in both ischemia and reperfusion periods (1–6). Most animal studies have studied and evaluated the influence of drugs on I/R injury induced arrhythmia. In earlier studies, it was suggested that combinations between two channel modulators may have synergic effect (7).

Most earlier studies have demonstrated that the ionic currents in the ischemic cells determine what happens during ischemia and reperfusion; variations in Na^+, K^+, and Ca^{2+} ions affect cell excitability through action potential lengths and generate arrhythmia (8–12). The new intervention has been researched using drug therapy to decrease ischemic injury, and ischemia-reperfusion induced ventricular arrhythmia. (13). Perfusion and increased coronary blood flow are required to restore oxygen delivery to ischemic cells.

This may be provided by using a drug that works as a vasodilator like pinacidil (14). Pinacidil as a KATP channel opener, causes membrane hyperpolarization and vasodilation (15–17). The protective effect of channel opening by pinacidil infusion, unluckily had been appeared to cause ventricular tachycardia, by shortening the action potential duration mentioned before (18).

The molecular structure of ATP-sensitive potassium channel in myocardial cells had been studied in detail, and it was found that it is formed (Kir6x) subunits and sulfonylurea receptors (18–20). Sulphonylurea receptors are the main target of hypoglycemic drugs like glimepiride, which is also shown to have an antiarrhythmic effect (1). The channel blockers like glimepiride, decrease K+ efflux from ischemic cells and induce depolarization and vasoconstriction. It works oppositely to channel openers (21, 22). It should be mentioned that the density of receptors in myocardium is less than that in pancreatic and other tissue cells, even though there is a slight difference in the type of subunits, which affects the affinity of sulfonylurea drugs (18).

Vasodilation caused by pinacidil during ischemia, as well as prolonged action potential length in ischemic cells caused by glimepiride during reperfusion, were considered to be more effective at reducing arrhythmia (23). In very few previous studies, the protection of openers against ischemic injury was shown to be inhibited by ATP-dependent potassium channel blockers (24). However, no study has been found related to their combined effect on ischemia or reperfusion induced arrhythmia. Since the drug application to decrease the severe arrhythmia in patients having heart attacks admitted to the hospital is required in the acute stage, it is crucial to find a drug or drug combination that is effective in the acute period of myocardial ischemia and reperfusion. That is why in this study, the combined acute effect of the KATP channel opener pinacidil, and blocker glimepiride on the ischemia reperfusion induced arrhythmia was aimed at being researched.

METHODS AND MATERIALS

Animals

A total of 26 male Sprague-Dawley rats 6-7 months old, weighing between 320 and 500g were used in our experiments. Animals were allowed to feed with pellet (commercial rat food) and drink water Ad libitum. All animals were treated with commitment to the instruction principles in the use and care of animals, together with the statement of the ethical principle of Helsinki. All study protocols were approved by The Animal Research Ethics Committee of Abant Izzet Baysal University (protocol number; 2021/28).

Surgical Procedures and Hemodynamic Measurements

The surgical protocols in this study were performed as reported in detail in the previous study (25).

Animals were anesthetized intraperitoneally with urethane (2g/kg) at a dose appropriate to body weight. After ensuring that anesthesia was complete, the animal was taken to the operation table, and the airway was opened with a simple incision through the trachea to connect the animal to the artificial respirator.

To record the mean arterial blood pressure, the femoral artery was cannulated and connected to a blood pressure monitor (Biopac Systems Inc., Goleta, CA; Turkey Distributor Commat, Ankara, Turkey). The artery was separated from the nerve and tied, then the cannula was inserted, and heparin was injected to prevent blood clots.

The chest cavity was opened at 3-4 intercostal ribs. When the heart was still in the thorax, the pericardium on the heart was removed. The respirator was turned off, and the heart was gently exposed by pressing the thorax on either side from right to left. Following heart exposure, the left coronary artery was clearly visualized, and the needle 6/0 in size passed under the left branch of the coronary artery at 2mm away from its origin in the aorta, and then the heart was returned to the thorax. The opening of the thorax was closed by using a piece of gauze, and the respirator was turned

on again. Electrocardiogram electrodes were placed under the skin to record electrical activities by using a data monitoring system (pro3.7, Biopac Systems Inc.). Following this operation, 5 minutes have been waited for stabilization of heart rate and blood pressure, and during this period, the silk from the coronaries was passed through a plastic tube and the needle was cut and out.

At the end of 5 minutes, as a fourth step, the left coronary artery was clamped by pressing the silk and left it for 6 minutes to produce ischemia. At the end of 6 minutes of ischemia, the silk was released by removing the clamp, and the reperfusion was produced for 6 minutes. Following the end of reperfusion, the ventilator was stopped, and 1ml/100 mg of heparin was given through a catheter into the carotid arteries to prevent blood clotting in coronaries. The heart was then getting out of the thorax for perfusion of the coronaries from the aorta.

A perfusion needle was inserted into the open end of the aorta, then firstly, saline solutions, followed by ethanol in 2ml, were given into the aorta. After injection of ethanol, unperfused area was seen in a pinkish color, and the perfused area with ethanol was seen in a white color. All other parts of the heart except the ventricle were removed, and the pale pink and white areas were separated from each other and weighted separately. The percentage of the area seen in pinkish color (ischemic area) was calculated according to the whole ventricle, that was the risk of an infarct zone.

RECORDING AND EVALUATION

The recording electrodes of the ECG device were connected to measure the heart rate, blood pressure, and other variables related to that, and it was read through the Pro 3.7 version of Biopac computerized recording system. Readings were taken in the first, third, and fifth minutes of both the 6 minutes of ischemia and reperfusion periods.

According to the scoring system used in our laboratory, the arrhythmia score was determined depending on the duration and incidence of different types of arrhythmia. Almost all types of arrhythmias have been noted, like ventricular tachycardia (VT), ventricular fibrillation (VF), and other types of arrhythmias including VPC, AV block, and ventricular escape rhythm. The identification of arrhythmia was performed by examining the heart rate and blood pressure according to Lambeth conventions (26).

The arrhythmia duration and the incidence were determined, and the scoring of arrhythmia was done as follows: 0 = No arrhythmia, 1 = < 10 sec VT or other arrhythmia, 2 = < 11-30 sec VT or other arrhythmia, 3 = < 31- 90 sec VT or other arrhythmia, 4 = < 91- 180 sec other arrhythmia, VT or reversible VF for less than 10 s, while 5 indicates arrhythmia duration longer than 180 s or reversible VF for more than 10 sec, and 6 indicates irreversible VF or death of the animal.

STATISTCAL ANALYSES

The blood pressure, heart rate and arrhythmia duration were analyzed by both One- way ANOVA with LSD post hoc. tests, and double comparison between control and drug treated group by independent t-test. The mean and standard error were calculated for all data. The survival rate and the incidence of arrhythmia was compared by Chi-square test.

DRUGS

The drug solutions were prepared daily before the start of operation. Pinacidil and glimepiride as a pure powder (Sigma) were always stored and preserved in closed, dark, cool, and dry place.

PREPERATION OF DRUGS

In this work, two different drugs were prepared with their own solvent. The stock solution of pinacidil included 0.1 mg of drug powder dissolved in only 1 ml of isotonic solution. In a similar way, 1 mg of glimepiride powder was dissolved in 0.25 ml dimethyl sulfoxide (DMSO) mixed with the same ratio of ethanol, then added to 0.5 ml of isotonic solution to make 1 ml of stock solution. The doses were given to each animal based on its weight.

DRUG ADMINISTRATION PROTOCOL AND EXPERIMENTAL GROUPS

In this study 4 groups have been formed with 5-8 animals in each group:

Group I, Drug control:

Only the solvents of the drugs were given, pinacidil solvent (isotonic solution) at the second minute of ischemia, and glimepiride solvent (DMSO + ethanol + isotonic solution) at the start of reperfusion.

Group II, Pinacidil:

0.1mg/kg of pinacidil was given at the second minute of ischemia, and glimepiride solvent (DMSO + ethanol + isotonic solution) was given at the start of reperfusion.

Group III, Glimepiride:

Pinacidil solvent (isotonic solution) was given at the second minute of ischemia, and 1mg/kg of glimepiride drug was given at the start of reperfusion.

Group IV, Combination group:

In the combination group, 0.1mg/kg of pinacidil at the second min. of ischemia, and 1mg/kg of glimepiride at the start of reperfusion were given intravenously.

RESULTS

In this experiment, 58 animals were used. Various results have been observed in all successful rats. The criteria for accepting successful and unsuccessful animals were listed as follows: the observation of the QRS amplitude, ST-segment elevations just following coronary ligation, body weights between 320-500 gr, and a clear reading of both the ECG and blood pressure during the operation. In some cases, failures occurred in the recording system or equipment set-up, such as catheter displacement. Some animals at the end of the operation had no spontaneous respiration, so the arrhythmia data were not evaluated.

From those 58 rats, a total of 26 rats and were used in data analyses and considered successful based on these criteria (27).

The risk of infarct zone was not significantly different among groups. This was evidence for the right point of coronary ligation, (Table 1).

Table 2. Arrhythmias incidence during 6 min. of Ischemia and surviving number after 6 min. of Ischemia. (*P<0.05, **P<0.01)

Groups	N	Survival animals	Incidence of Arrhythmias (N/%)				Arr. Score
			VPC	VT	VF	BRAR	
Control (a)	6	6	4/66	0	0	0	0.66 ± 0.2
Pinacidil (b)	5	5	5/100	0	0	0	1.20 ± 0.2
Glimepiride (c)	7	7	7/100	1/14	0	0	1.42 ± 0.2
Combination (d)	8	7	7/87	0	0	1/14	1.62 ± 0.6

Table 1. Body weight and the risk of infarct zone in rats within 6 min. ischemia and 6 min. reperfusion. (Mean ± standard error), *P<0.05, **P<0.01

Groups	N	Body wight (gr)	Heart wight (gr)	Risk of Infarct zone size (gr)	Risk of Infarct zone size (%) / HW
Control (a)	6	417.50 ± 19.8	1.18 ± 0.03	0.46 ± 0.05	38
Pinacidil(b)	5	374.00 ± 13.8	1.05 ± 0.05	0.48 ± 0.05	45
Glimepiride(c)	7	408.71 ± 15.9	1.06 ± 0.06	0.49 ± 0.04	46
Combination(d)	8	418.78 ± 13.5	1.15 ± 0.04	0.49 ± 0.06	42

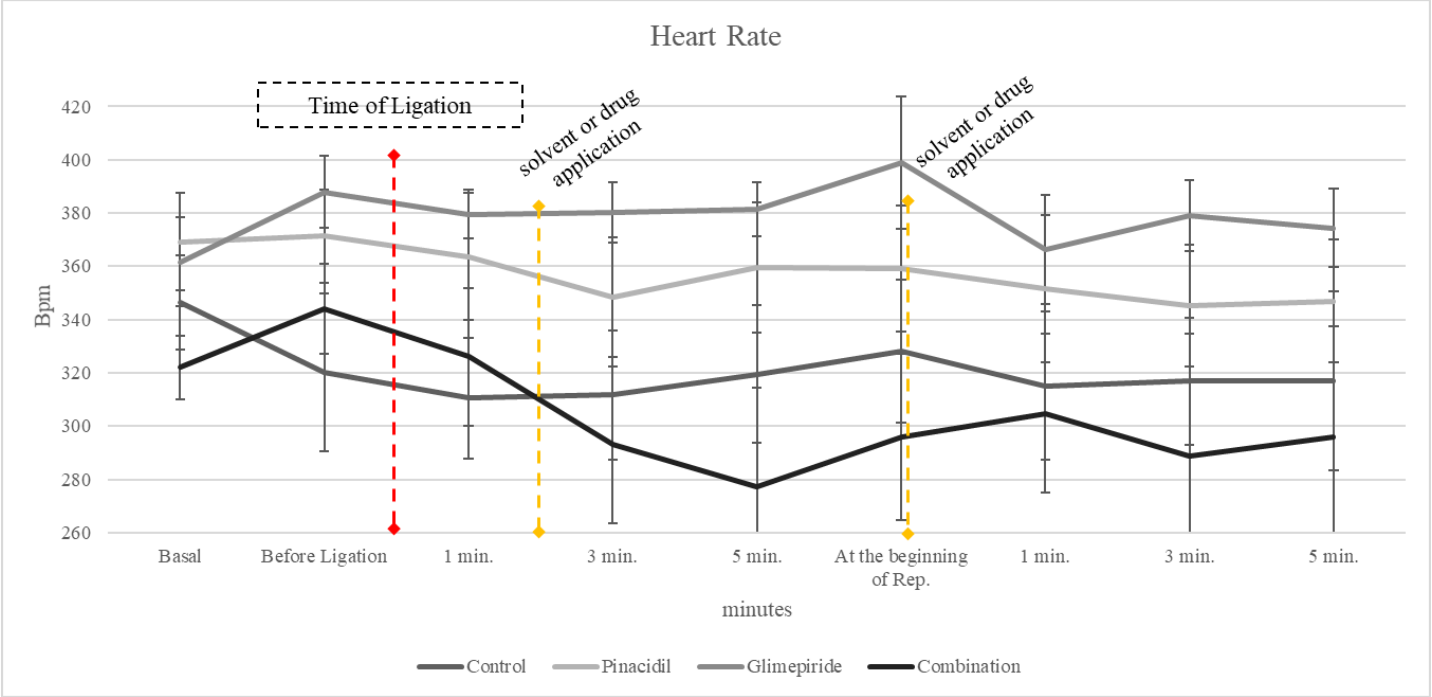


Figure 1. Heart Rate during ischemic and reperfusion periods.

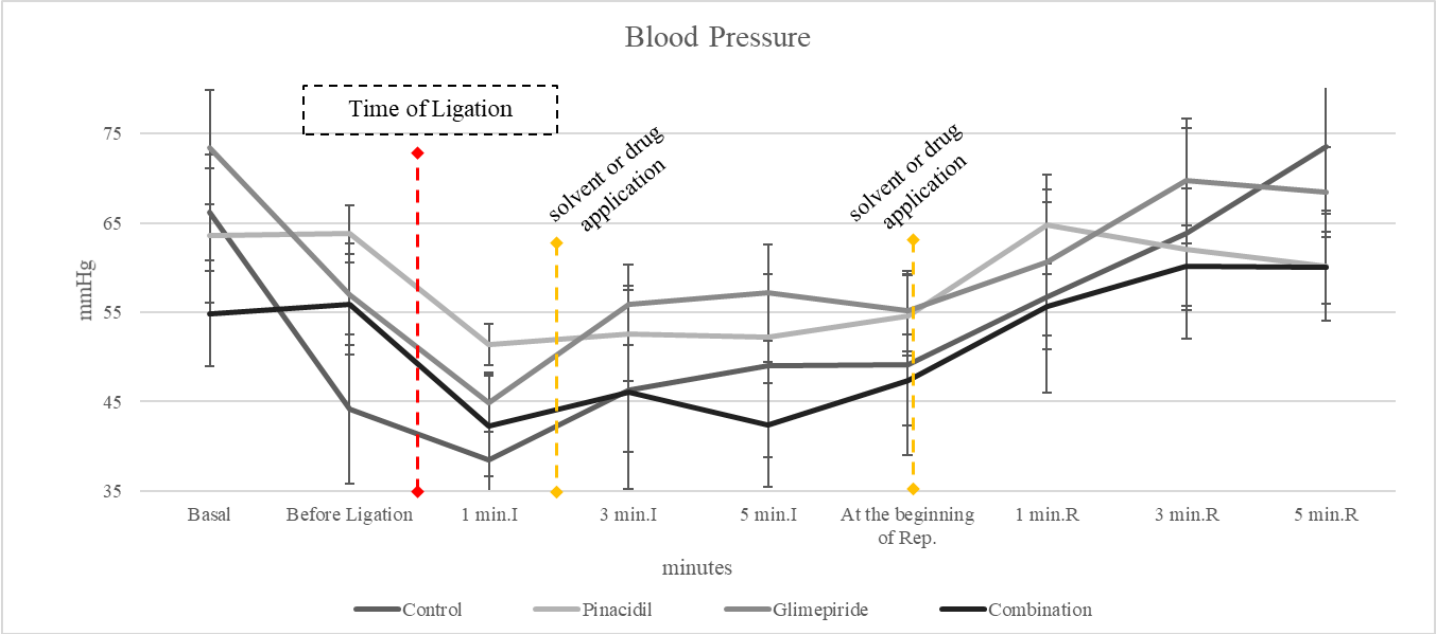
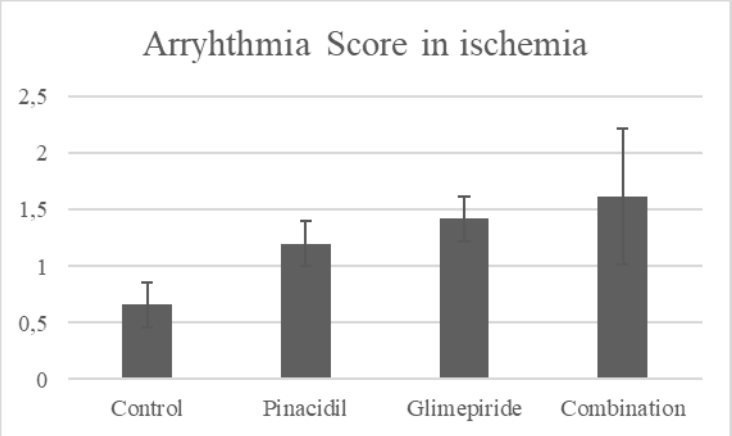


Figure .2 Blood Pressure during ischemic and reperfusion periods.

Table 3. Arrhythmias incidence during 6 min. of Reperfusion and surviving number after 6 min. of Reperfusion. (*P<0.05, **P<0.01)

Groups	N	Survival animals	Incidence of Arrhythmias (N/%)				Arr. Score
			VPC	VT	VF	BRAR	
Control (a)	6	6	2/33	2/33	0	0	1.00 ± 0.3
Pinacidil (b)	5	5	1/20	1/20	0	0	0.20 ± 0.2 *a p-value=0.33
Glimepiride (c)	7	7	6/85	3/42	1/14	0	1.42 ± 0.3
Combination (d)	8	6	3/37	2/25	0	1/14	1.12 ± 0.8



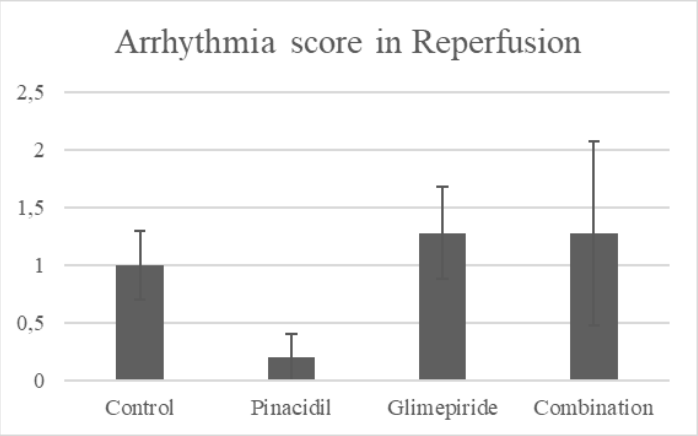


Table 4. The duration of arrhythmias during 6 min. of Ischemia. (*P<0.05, **P<0.01). *a: difference to control

Groups	N	Length of Arrhythmia (sec.)				
		VPC	VT	VF	Total arr.	Bradycardia
Control (a)	6	1.80 ± 0.9	0	0	1.80 ± 0.9	0
Pinacidil (b)	5	6.44 ± 3.2	0	0	6.44 ± 3.2	0
Glimepiride (c)	7	8.67 ± 2.9	0.80 ± 0.8	0	9.51 ± 2.7 *a p-value=0.029	0
Combination (d)	8	4.96 ± 1.7	0	0	4.70 ± 1.7	0.12 ± 0.1

HEMODYNAMIC PARAMETER

In all groups, blood pressure (BP) decreased instantly after ligation. The changes in BP were not significantly different among groups, but the blood pressure and heart rate (HR) were the highest in the glimepiride group compared to the control and the other two groups throughout the ischemic period. There was no significant difference between all groups in BP and HR during the reperfusion period; instead, the values were almost close to each other. (Figure 1,2)

ARRHYTHMIAS DURING CORONARY ARTERY LIGATION AND REPERFUSION.

The incidence of arrhythmia was not significantly different between groups. The ventricular premature contraction (VPC) and other type of arrhythmia was observed in all groups. Ventricular tachycardia (VT) was observed only in glimepiride group in 2 animals out of 7 animals. As like ischemic period, all type of arrhythmia were observed during reperfusion period. (Tables 2, 3).

Arrhythmia score was determined with evaluation of the type and duration of arrhythmia in each phase. There was no significant difference among groups in both ischemia and reperfusion periods. The arrhythmia score was nonsignificantly lower in pinacidil group (p= 0.33) in respect to control. figures (5) and tables (2, 3). The total duration of arrhythmia during ischemia was significantly higher in glimepiride treated group in respect to control.

Table .5 The duration of arrhythmias during 6 min. of Reperfusion. (*P<0.05, **P<0.01). *a: difference to control

Groups	N	Length of Arrhythmia (sec.)				
		VPC	VT	VF	Total arr.	Bradycardia
Control (a)	6	2.79 ± 2.5	3.58 ± 2.3	0	6.37 ± 2.8	0
Pinacidil (b)	5	0.03 ± 0.03	1.21 ± 1.2	0	1.25 ± 1.2 *a p-value=0.40	0
Glimepiride (c)	7	6.43 ± 5.3	4.52 ± 2.2	0.81 ± 0.8	11.6 ± 6.5	0
Combination (d)	8	1.49 ± 0.8	1.01 ± 0.7	0	2.73 ± 1.0	0.55 ± 0.5

However, throughout the reperfusion period, it was not significantly greater. Table (4, 5). In comparison to the control group, pinacidil had no significant effect on the overall duration of arrhythmia during reperfusion (P = 0.40).

DISCUSSION

This competitive study found that there was no significant difference between pinacidil and glimepiride on ischemia reperfusion induced arrhythmia. In previous studies on the acute phase of ischemia and reperfusion, it was found that pinacidil administration decreased the arrhythmia in ischemic periods (28–32). ATP channel openers improve cardiac function during the reperfusion period (33).

The previously mentioned findings, which correlate with our results, confirm that the channel antagonist glimepiride is pro-arrhythmic (34–36). The results obtained from this study did not support our initial hypothesis. The synergy for decreasing arrhythmia was not observed when two drugs given in combination in different periods of ischemia and reperfusion. Conversely, decreased arrhythmia observed during reperfusion in the pinacidil treated group was abolished by the treatment of glimepiride.

The hypotensive effect of pinacidil was observed minimally during ischemia. This is mainly due to the low pinacidil dosage that was utilized in this study. Increased sympathetic reflex activity brought on by pinacidil-induced hypotension is another potential reason. The blood pressure and heart rate in the combination group were observed similarly to the control. Since there has been previous research in the field of molecular docking and competition between channel opener and blocker to bind to the same receptor (37), it was assumed that the combination group's blood pressure and heart rate results might be the average value obtained from the pinacidil and glimepiride groups. These data, however, were comparatively unexpected.

In that study, KATP channel blocker glibenclamide was found to have the predominant effect against the strong selective channel opener diazoxide and inhibit the K^+ efflux. It seems that the I/R preconditioning was inhibited by the influence of glibenclamide because of competition of both drugs for the binding site in the receptors (34). They explained that the disappearance of protective preconditioning effect of channel opener by the glibenclamide was due to the specific shape of glibenclamide molecule, which they have a specific portion named as Cyclohexyl group that considered to be the best target for receptors protein and not found in the channel opener (38).

Regarding the possible mechanism behind the anti-arrhythmic effect of the pinacidil group, it can be said that it may be due to the working of pinacidil as a mediator of NO release (39,40). MitoKATP channels in many studies were suggested as the most capable target or mediator of preconditioning, but because pinacidil is a nonselective channel opener and the dose used in the present study is small (30), it is likely that pinacidil through its vasorelaxant ability, stimulates NO release and consequently NO induces the opening of mitoKATP channels indirectly.

The pro-arrhythmic effect of glimepiride observed in the present study might be related to increased Ca^{2+} overload. At the beginning of reperfusion, mitochondrial dysfunction affects the cellular events, causing Ca^{2+} overload and membrane depolarization. Thus, by the opening of these channels may prevent Ca^{2+} overload, remove excess Ca^{2+} from the mitochondria inner membrane, and reduce Ca^{2+} entry through the sarcolemmal membrane by the voltage gated Ca^{2+} channel (24,41).

It is investigated that the bioavailability of pinacidil is more and it was rapidly absorbed, with a lesser amount of around 20% not absorbed and remaining in plasma (42). This may also be another explanation for why pinacidil showed an antiarrhythmic effect in the reperfusion period and why combination group arrhythmia score was close to that of the glimepiride treated group rather than the pinacidil group.

CONCLUSION

The protective effects of pinacidil against reperfusion induced arrhythmia disappear with the glimepiride

application. This result indicates that heterogeneity between ischemic and nonischemic myocardial cells increases, and more arrhythmias occur in combination of these two drugs. Since there is no relation found between blood pressure changes and the arrhythmia after pinacidil treatment, it can be said that the protection produced by pinacidil against arrhythmia may depend on changes in action potential duration not its hypotensive effect. Since this study does not have cellular recording, no further evaluation can be done about the mechanism of the anti-arrhythmic or pro-arrhythmic effect of pinacidil and glimepiride alone or in combination. These results may require further studies using different doses of drugs and the timing of drug application.

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CONFLICTS OF INTEREST

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

ETHICAL STATEMENT

Ethical permission for this study was obtained from the Animal Experiments Local Ethics Committee of Bolu Abant İzzet Baysal University Medical School with the 2021/28 number.

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