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Effect of vasopressin on electrocardiographic changes produced by ischemia-reperfusion in rats

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Abstract: The present study was conducted to identify the effect of vasopressin (AVP) on electrocardiographic changes produced by ischemia-reperfusion . Male rats were divided into seven groups (n=8-13) subjected to 30min ischemia and 120 min reperfusion. In protocol I (control group), saline was administered before ischemia. In protocol II, different doses of AVP (0.015, 0.03, 0.06 and 0.12µg/rat) were infused 10 min before ischemia. In protocol III SR49059 (1 mg/kg), was injected 20 min prior to ischemia with and without the effective dose of AVP (0.03 g/rat). Ischemia-induced arrhythmia and myocardial infarct size (IS) were measured. Different doses of vasopressin decreased IS. There were no significant differences in PR, QRS duration and ΔT/ΔST ratio between control and intervention groups in ischemia. ST elevation was significantly increased in control and AVP 0.015, 0.03, 0.06 groups during ischemia. In AVP 0.12 group there was no significant difference in ST deviation between the baseline and ischemia phase. JT interval was significantly increased in control and antagonist group during ischemia. AVP 0.12µg/rat prevented the increase of JT interval in ischemia compared to the baseline. In summary, AVP mediated preconditioning improved ST resolution, prevented prolongation of JT interval and decreased the likelihood of subsequently ventricular arrhythmia.

Keywords: Vasopressin, ischemia-reperfusion injury, electrocardiogram parameters.

INTRODUCTION

Ischemia-reperfusion injury (IRI) is a major damage which can result in cell necrosis and occur in myocardial infarction and another clinical setting such as coronary artery bypass graft (CABG) and cardiac transplantation (Murphy and Steenbergen 2008). The most important strategy to subside the side effect of this injury is ischemic preconditioning (IPC) described by Murry in 1986 that short episodes of ischemia/reperfusion can enhance myocardium cell tolerance against subsequently severe ischemia (Murry *et al.,* 1986). Preconditioning has two phases of cardioprotection: The first phase beginning in primary minutes and lasts for 4 hours and second phase beginning after 12 hours and lasts to several days (Bolli 2000). Preconditioning has a limitation in a clinical setting because we could not apply ischemia/reperfusion in patients. Hence in recent years most of the researchers wanted to found a therapeutic strategy to mimic ischemic preconditioning with pharmacological agents (Imani *et al.,* 2008). Preconditioning induced by many agents such as bradykinin، adenosine and opioid and also a lot of intracellular pathways (Baxter and Ebrahim 2002; Bolli 2001; Dana *et al.,* 2000; Gross and Peart 2003; Inagaki *et al.,* 2006; Kodani *et al.,* 2002; Vanden Hoek *et al.,* 1998). The new agent in inducing preconditioning that introduced in recent studies is vasopressin (AVP) (Nazari *et al.,* 2011) Vasopressin has four subtypes such as V1،V2،V3 and oxytocin receptor (OTR) in the body. Vasopressin has both antidiuretic and vasopressor effect. Vasopressin is secreted from magnocellular neurons in the hypothalamus. These vasopressor and antidiuretic effect mediate via V1 and V2 receptor (Holmes *et al.,* 2001). The receptor that found in myocardium cell and circulatory system is V1 and has a paradoxical effect on the vascular bed. It causes vasoconstriction in smooth muscle of vessels in the systemic circulation and leads to vasodilation in pulmonary circulation via secretion of nitric oxide (Andrew and 2008). As previously mentioned، vasopressin also induces preconditioning in experimental studies. Although exact mechanism poorly understood the activation of V1 receptor and release of NO has been proposed (Nazari *et al.,* 2011). There are several end points to determine the effect of preconditioning that used in many studies such as infarct size، Hemodynamic changes، Results of echocardiography، arrhythmia، release of cardiac biomarkers and ST segment elevation (Esmaili Dehaj *et al.,* 2009; Leesar *et al.,* 1997; Yogaratnam *et al.,* 2010) In most clinical studies the ST segment elevation is a single electrocardiographic sign that used to determine the effect of preconditioning and the other electrocardiographic changes of ECG were not assessed completely (Leesar *et al.,* 1997; Leesar *et al.,* 1999). Therefore, in the current

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study, we analyzed the all electrocardiographic sign (PR interval، QRS duration، ST elevation، JT interval) of ECG produced by ischemia-reperfusion in rats.

MATERIALS AND METHODS

Male Wistar rats (weighing 280-310 g) were obtained from Tehran University of medical sciences and were housed under standardized conditions12-h light/dark cycle, 21-23◦C temperature and 40–50% humidity with free access to fed standard rat chow and tap water. All experiments were carried in accordance with the institutional guidelines of Tehran University of Medical Sciences (Tehran, Iran). The rats were anesthetized with sodium pentobarbital (60 mg/kg body weight, i.p.) and kept with supplementary doses (~30 mg/kg) every 60-70 min, as required. Body temperature was maintained at 37±1 ◦C.

All rats were ventilated with air- and oxygen mixture by Parvalux rodent respirator (15 ml/kg stroke volume and 60-70 Breaths/min) after a tracheotomy in the middle of the neck and tracheal intubation. A standard limb lead-II electrocardiogram (ECG) and arterial hemodynamic parameters were recorded during the experiment, using a computerized data acquisition system (ML750 Power Lab/4sp, AD Instruments). Rats were administered heparin (200 IU/kg, i.v.), and the left thoracotomy in the fourth rip approximately 3 mm from the sternum was done to expose the heart. The pericardium was incised and a 6-0 silk suture was placed around the left anterior descending coronary artery (LAD) close to its origin immediately the left atrial appendage to the right part of the LV. Both ends of the silk thread were passed through coronary ligature (Nazari *et al.,* 2011). Heart rate and blood pressure were allowed to stabilize for 15 min before the intervention protocols. Applying tension to the suture by ligature caused regional ischemia following coronary artery occlusion, and reperfusion was achieved by releasing the tension on the ligature. Ischemia was confirmed by ST elevation and increase in R-wave amplitude in ECG, or cardiac cyanosis subsequent decrease in blood pressure and reperfusion was confirmed by epicardial hyperemia. Any rat with a constant fall in blood pressure to less than 70 mmHg was discarded from the study.

Experimental protocol

This study included three protocols. Rats were randomly divided into seven groups (n = 8-13) and all of them subjected to 30 min ischemia and 120 min reperfusion (fig. 1). After a stabilization period following the surgical preparation, basal hemodynamic parameters were measured for 15 min before drug administration. In protocol I (control group), saline was administered intravenously before ischemia. In protocol II, different doses of AVP (0.015, 0.03, 0.06 and 0.12 _µg/rat) were given 10 min before ischemia. In protocol III, SR49059 (1 mg/kg), as an AVP-selective V1 receptor antagonist, was injected 20 min prior to ischemia with and without the effective dose of AVP (0.03 µg/rat) into two different groups. At the end of protocol study, the limb leads were dislodged and the ECG changes such as (QRS duration، RR duration، JT interval ،ST elevation ،PR interval) were analyzed by ECG analyzer (company).

Cardiac area at risk and infarct size determination

At the end of reperfusion, 2 ml of Evans blue (2%) was administered intravenously into the femoral vein for the area at risk (AAR) measurement. The hearts were iced overnight and then cut into slices of 2-mm-thick. The slices were incubated with a 1% solution of 2,3,5-triphenyltetrazolium chloride (TTC, in 0.1M phosphate buffer, pH 7.4) stain for 15 min at 37 ◦C, to visualize the infarct area. Then they were fixed in 10% formalin. Both outsides of each section were scanned using PhotoShop program (Adobe Systems, version 7.0). Total area at risk was stated as a percentage of the left ventricles (AAR/LV). Infarct size was expressed as a percentage of the area at risk (IS/AAR).

STATISTICAL ANALYSES

Statistical analysis was carried out in SPSS 20 (IBM; U SA). All data were expressed as mean ± SEM. Statistical significance was defined as $P<0.05$. All electro-cardiographic data are shown in related tables and the median has also been presented. Data were analyzed by Freidman test and between groups changes were examined by kruskal Wallis test. $p<0.05$ was regarded statistically significant.

RESULTS

PR interval

Fig 2 shows the difference between PR duration baseline, ischemia and reperfusion phase in all groups. There were no significant differences among groups at baseline before treatment. There were no significant differences in PR duration between control and intervention groups in ischemia and reperfusion phase.

Complex QRS

Fig. 3 shows the difference between QRS duration of baseline، ischemia and reperfusion phase in all groups. There were no significant differences among groups at baseline before treatment. There were no significant differences in QRS duration between control and intervention group in ischemia and reperfusion phase.

ST Deviation

Fig 4 shows the difference between ST Deviation of baseline، ischemia and reperfusion phase in all groups. There were no significant differences among groups at

baseline before treatment. ST Deviation was significantly increased in control group and AVP 0.015, 0.03 and 0.06 during ischemia phase. In AVP 0.12 group there was no difference between base line and ischemia phase. There was a significant difference between the resolution of ST elevation of reperfusion phase of control and AVP (0.015،0.06، 0.03) groups.

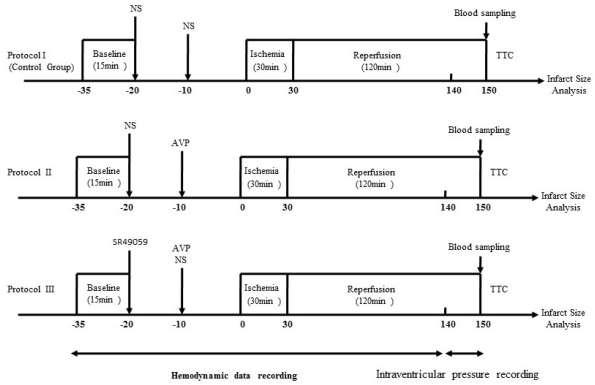

Fig. 1: Illustration of experimental groups. Animals in control group were subjected to 30 min ischemia followed by120 min reperfusion and saline was administered intravenously before ischemia, (protocol II) 0.015, 0.03, 0.06 and 0.12 µg/rat; doses of AVP was infused within 10 min prior to ischemia, (protocol III) SR49059 (1 mg/kg), as an AVP antagonist, was injected 20 min prior to ischemia with and without the effective dose of AVP (0.03µg/rat). NS, normal saline; AVP, vasopressin; TTC, triphenyltetrazolium chloride (n=8-13).

Table 1: The value of ΔT/ΔST among experimental groups at the end of ischemia phase.

Groups	ΔT/ ΔST
Control	0.67±12
AVP 0.12	-0.38±20
AVP 0.06	0.49±1.6
AVP0.03	-2.8±8.1
AVP 0.015	-40±10
SR	-1.3 ±1.4
SR+AVP	0.43±1.3

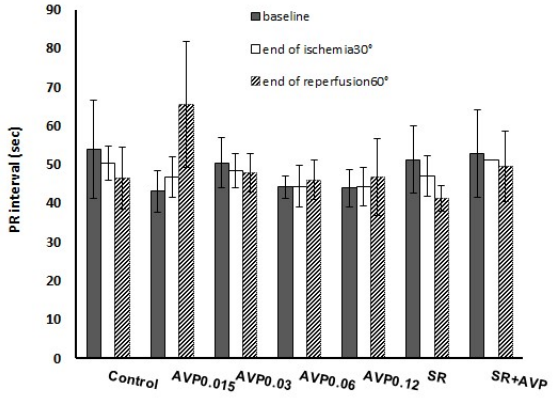

Fig. 2: The value of PR interval among experimental groups at base line, end of ischemia and end of reperfusion phase. Control, AVP (0.015, 0.03, 0.06, 0.12), SR + AVP (0.03 _g/rat) and SR groups. Data are presented as mean±SEM. AVP = arginine vasopressin, SR = SR49059.

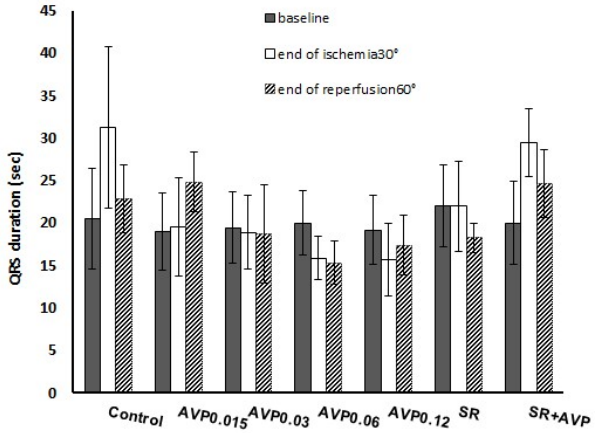

Fig. 3: the value of QRS duration among experimental groups at base line،ischemia and reperfusion phase. Control, AVP (0.015, 0.03, 0.06, 0.12), SR + AVP (0.03 g/rat) and SR groups. Data are presented as mean±SEM. AVP = arginine vasopressin, SR = SR49059.

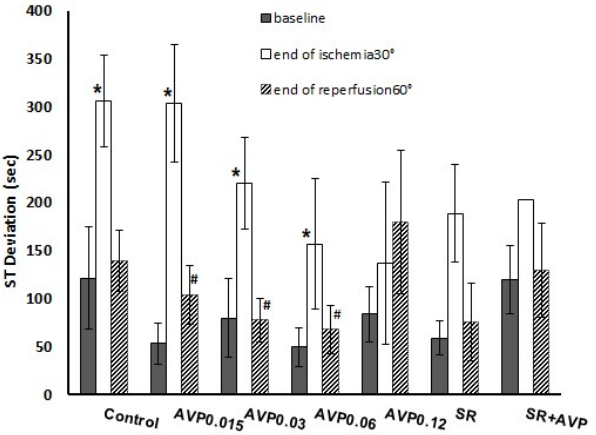

Fig. 4: the value of ST Deviation among experimental groups at base line،ischemia and reperfusion phase. Control, AVP (0.015, 0.03, 0.06, 0.12), SR + AVP (0.03 _g/rat) and SR groups. Data are presented as mean ± SEM. *P<0.05 vs its baseline within group. # P<0.05 vs control group. AVP = arginine vasopressin, SR = SR49059.

JT interval

Fig 5 shows the difference between JT interval baseline, ischemia and reperfusion phase in all groups. There were no significant differences among groups at baseline before treatment. JT interval was significantly increased in control and antagonist group during ischemia phase. AVP0.12 significantly prevented the increase in JT interval in ischemia phase compared to their baseline. The JT interval was decreased in reperfusion phase in all groups.

ΔT/ΔST

Table 1 demonstrates the difference between ΔT/ΔST at baseline and end of ischemia phase in all groups. There were no significant differences among groups at baseline before therapy. There was no significant difference of ΔT/ΔST in base line and ischemia phase in all groups.

Area at risk and infarct size measurements

There were no significant differences in AAR/LV among groups. Infarct size was 37.6±1.7% in control group, whereas administration of different doses of vasopressin AVP 0.015,06, 0.03 and 0.12µg/ rat significantly reduced infarct size (fig. 6). The decrease in infarct size by AVP was eliminated by SR49059 infusion while compared to AVP0.03 (28.8±2.4% vs.18.6±1.7%).

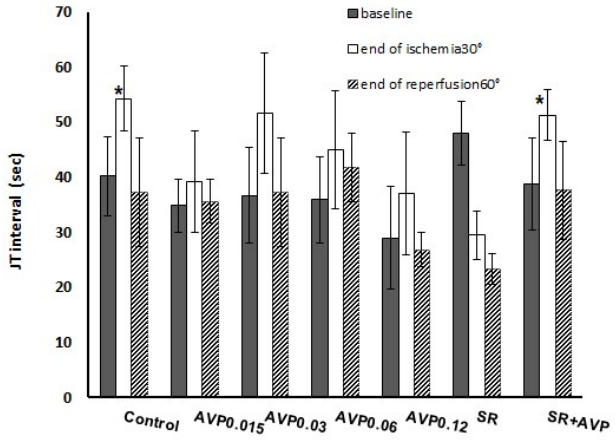

Fig. 5: the value of JT interval among experimental groups at base line‹ischemia and reperfusion phase. Control, AVP (0.015, 0.03, 0.06, 0.12), SR + AVP (0.03 _g/rat) and SR groups. Data are presented as mean ± SEM..*P<0.05 vs its baseline within group. AVP = arginine vasopressin, SR = SR49059.

DISCUSSION

We investigate the effects of AVP and its antagonism on preconditioning in rats undergoing LAD ligation. The findings of this study conclude that AVP mediated preconditioning improves ST resolution, significantly decreased infarct size and administration of SR49059, decreased the cardioprotective effects of AVP. AVP reduces ST elevation and JT interval duration during ischemia phase. The ischemia has a lot of adverse effect on the electrocardiogram in animal and human studies. PR interval is a first component that affected and prolonged during ischemia. It has been shown that the conduction of electrical impulse can be delayed (Crisel *et al*., 2011; Packard *et al*., 1954). QRS duration also increases during ischemia and is a sign of intraventricular conduction defect on surface ECG (Almer *et al.,* 2016; Barnhill *et al.,* 1985). Furthermore, ST segment deviation (depression and elevation) is a most important change of ECG during ischemia and infarction. ST elevation is a clinical guide in a determination of acute myocardial infarction in a clinical setting and reflected the infract size. The other components of ECG that change during ischemia is QT and JT interval. QT interval shows depolarization and repolarization of ventricular and is a marker of prolonged repolarization but in patients who have ventricular conduction defect (VCD) QT interval could not reflect the repolarization duration exactly therefore in this situation (VCD and ischemia) the JT interval that is an independent of QRS duration can be an appropriate index of repolarization (Berul *et al.,* 1994). Many investigators used of JT interval to assess the repolarization of ventricular that prolonged during ischemia (Jarusevicius *et al.,* 2004). T wave has a various change during ischemia. The T wave is a sign of repolarization of ischemia zone and normal tissue around it. Early repolarization leads to tall T wave and delayed repolarization lead to negative T wave (Kleber *et al.,* 1978). PR prolongation is also a sign of ischemia and in clinical studies in patients who have coronary artery disease is associated with adverse prognosis (Crisel *et al.,* 2011).

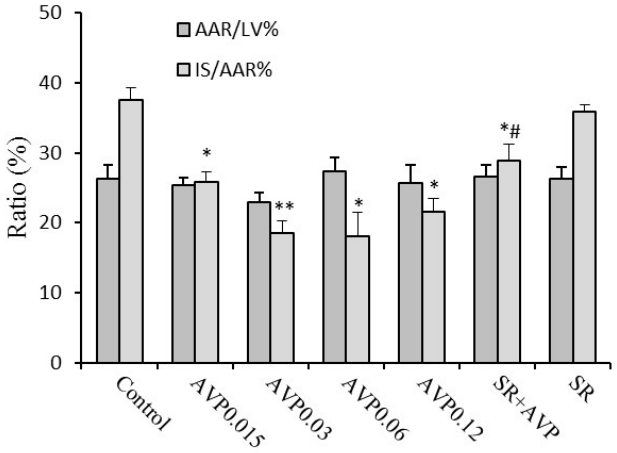

Fig. 6: Myocardial area at risk (AAR/LV %) and infarct size (IS/AAR %) in Control, AVP (0.015, 0.03, 0.06 and 0.12µg/rat), SR49059 (1mg/kg) with and without the effective dose of AVP (0.03µg/rat) groups. Data are presented as mean ±S.E.M. AVP, arginine vasopressin; SR = SR49059, as an AVP antagonist *P<0.05 vs. Control group. **P<0.01vs. Control group # P<0.05 vs. AVP0.03 group (n=13).

Several studies have found that QRS duration was prolonged during ischemia and can be a suitable marker of decreased collateral flow during coronary artery disease (Almer *et al.,* 2016; Barnhill *et al.,* 1985). Besides QRS duration significantly prolonged in occlusion of left artery descending or circumflex artery during coronary angioplasty (Nowinski *et al.,* 2000). In this study similar PR duration, there were no significant differences in QRS duration between control and intervention groups in ischemia and reperfusion phase, so this result showed that the preconditioning has not electrophysiological effect on

these component [PR and QRS duration] of surface ECG. JT interval is increased during ischemia in control group and was normal in intervention groups. These results showed that the ventricular repolarization was not prolonged and will reduce the subsequent ventricular arrhythmia that was confirmed in our previous study (Nazari *et al.,* 2011). In similar study, the influence of ischemic preconditioning on ventricular repolarization (QT dispersion) was assessed and found that the preconditioning can prevent prolongation of QT dispersion and reduce subsequently cardiac arrhythmia during coronary angioplasty and in humans (Okishige *et al.,* 1996). The findings of our study confirmed the results of these studies. In our study, the beneficial preconditioning effect of AVP on ST segment elevation was demonstrated in (AVP 0.12) group. Several clinical studies also found that the ST segment elevation was less than control group by many pharmacologic agents (Leesar *et al.,* 1997; Leesar *et al.,* 1999). It was shown that decrease in ST elevation is a sign of preconditioning effect in coronary angioplasty in humans (Cohen *et al.,* 1997) that is associated with less myocardial damage that was confirmed also in the present study with smaller infarct size in preconditioning group (AVP group). In our previous studies, we observed that vasopressin significantly decreased CK and LDH levels, and improved rate pressure product (RPP) in the rat heart subjected to an ischemia-reperfusion period (Nazari *et al.,* 2011). The mechanism of vasopressin in inducing preconditioning was poorly understood but the activation of V1 receptor and release of NO has been proposed (Nazari *et al.,* 2011). In the earlier study, we showed that the use of L-NAME (antagonist of NO) lead to the death of all rats and this evidence support the mechanism of vasopressin mediated via NO. The other component that was assessed, is ΔT/ΔST ratio which introduced as a new indicator of preconditioning effect. Meijs *et al* showed that the reduction of ADP (adenosine diphosphate) is the earliest sign of ischemia that leads to increasing in T wave amplitude. Also, the increase of ΔT/ ΔST ratio (T wave amplitude increase relative to the amount of ST elevation) may be a good indicator of preconditioning effect. The preconditioning shortening increased APD (action potential duration) and lead to tall T wave without marked ST elevation so increase the ΔT/ ΔST ratio (Meijs *et al.,* 2014). Birnbaum *et al.,* showed that tall T waves without any ST elevation are an indicator of less severe ischemia suggested that may be associated with good collateral perfusion (Birnbaum *et al.,* 1993). Unlike Meijs *et al* study, there were no significant differences between ΔT/ΔST ratio in all groups in our study. The another important phase in the treatment of myocardial infarction is reperfusion phase (Birnbaum *et al.,* 2002). In a clinical study, Doevendans *et al* found that ST-segment normalization is the best important sign of successful reperfusion that occurs in the first hour of thrombolytic therapy (Doevendans *et al.,* 1995). In our study, we examined the resolution of ST-segment elevation as the best sign of reperfusion in all groups. Up to now the preconditioning effect on reperfusion phase was not determined. We hypothesized that the preconditioning has a good effect on reperfusion period and lead to better reocclusion in coronary artery but this theory was not confirmed in our study.

The present study also showed that different doses of vasopressin significantly decreased infarct size vs. control group that are in the line with previous our study, which showed that AVP was positively related with infarct size and biochemical levels (Nazari *et al.,* 2011).

Taken together, we provided evidence that the preconditioning effect of vasopressin decreased ST elevation during ischemia, prevented prolongation of JT interval and decreased the likelihood of subsequently ventricular arrhythmia.

CONCLUSION

The main finding from the results presented here is that the preconditioning effect of vasopressin decreased ST elevation during ischemia, prevented prolongation of JT interval and decreased the likelihood of subsequently ventricular arrhythmia.

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