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β-receptor blocker influences return of spontaneous circulation and chemical examination in rats during cardiopulmonary resuscitation*

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Abstract: Objective: We investigated the influence of β-receptor blocker metoprolol on return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation (CPR) in rats with induced myocardial infarction (MI). Methods: Male Sprague-Dawley rats were randomly divided into three groups: the sham-operated group, the MI group without metoprolol, which was fed the vehicle, and the MI+metoprolol group receiving intragastric metoprolol. Each group was further divided randomly into three subgroups, depending on the dosage of epinephrine administered during subsequent CPR applied after the induction of asphyxial cardiac arrest. Results: The ROSC rate was significantly decreased in the low dose subgroup of MI group, unchanged in the medium dose subgroup of MI group, and significantly decreased in the high dose subgroup of MI group, compared with the same dose subgroup of sham-operated group. MI+metoprolol group had a lower ROSC rate than MI group in the medium dose subgroup, and a higher ROSC rate than MI group in the high dose subgroup. There was no difference in blood K^+ values of successful rats between MI group and MI+metoprolol group. The rats with successful CPR had lower blood K^+ values than rats with unsuccessful CPR in each of the three treatment groups. Conclusions: Metoprolol administered to MI rats over a long period significantly improved ROSC rates under an appropriate dose of epinephrine during CPR. An increasing high blood K^+ value would attenuate the rate of a successful CPR.

Key words: β-receptor blocker, Cardiopulmonary resuscitation, Return of spontaneous circulation, Epinephrine, Chemical examination

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1 Introduction

It is well known that β agonists dramatically reduce survival from experimental cardiac arrest (Holmes *et al*., 1980). Experiments with normal animals showed that β-receptor blockers might improve survival (Huang *et al.*, 2004). Several large trials have also shown that long-term administration of β-receptor blockers to patients after myocardial infarction (MI) improves survival (Norwegian Multicenter Study Group, 1981). Data of the cooperative cardiovascular project disclosed that β-receptor blockers can reduce 40% mortality in patients with coronary artery disease and heart failure (Gottlieb *et al.*, 1998). Rats administered oral carvedilol for several days were more resistant to cardiac arrest induced by airway obstruction (Kurita *et al.*, 2010). Various guidelines for primary and secondary therapies are about β-receptor blockers, whose administration is one of the secondary prevention strategies employed for people with acute coronary syndrome or who have had an acute MI. β-receptor blockers reduce heart rate and improve left ventricular filling and coronary perfusion by prolonging diastolic time, reducing myocardial oxygen consumption, and elevating the threshold for

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ventricular fibrillation, thereby reducing the incidence of malignant arrhythmia (Lei *et al.*, 2004). However, a multinational survey at 134 sites in 19 countries discovered that 78% of patients with acute coronary syndrome used β-receptor blockers. All-cause mortality at 12 months was 7.3%, including deaths due to cardiac arrest, antithrombotic treatment, cardiogenic shock, and age>70 years (ACCESS Investigators, 2011). We are still not able to get successful cardiopulmonary resuscitation (CPR) to every post-infarct and heart failure patient. Metra *et al.* (2002) showed that when patients were administered a cardiotonic agent such as dobutamine, those who were also taking β-receptor blockers required more than the standard dosage to achieve the same therapeutic effect as those not taking β-receptor blockers. Epinephrine mainly acts by exciting α receptors, but its effects on β-receptors cause a strong contraction, accompanied by an accelerating heart beat, increasing myocardial oxygen demands, and damages of the myocardium (Attaran and Ewy, 2010). Therefore, an increased dose of epinephrine would increase myocardial oxygen demand and lead to malignant arrhythmia when it is intravenously injected to improve the return of spontaneous circulation (ROSC) during CPR (Berg *et al.*, 1996; Jeung *et al.*, 2011). In a domestic pig model, epinephrine proved to have adverse effects on cerebral microvascular blood flow via its α_1-agonist activity, increasing the severity of cerebral ischemia during CPR (Ristagno *et al.*, 2009).

β-receptor blockers have been reported to improve ROSC and myocardial function when administered immediately during cardiac arrest (Huang *et al.*, 2006). However, until now it has not been reported whether chronic β-receptor blocker use has any effect on ROSC during CPR upon cardiac arrest. In the present study rats with induced MI were treated with an oral β-receptor blocker (metoprolol) for four weeks to find whether metoprolol influences ROSC during CPR in cardiac arrest.

2 Materials and methods

2.1 Model preparation and grouping

We used ten-week old male Sprague-Dawley rats weighing between 250 and 300 g. The necessary tools were provided by the Laboratory and Animal Center in the Medicine College of Xi'an Jiaotong University. To establish a model of MI, permanent occlusion of the left anterior descending (LAD) coronary artery was performed in accordance with the extensively described method (Wang *et al.*, 2008). Rats were anesthetized with an intraperitoneal (i.p.) injection of 10% chloral hydrate (0.3 ml/100 g). They were placed supine with electrocardiograph (ECG) electrodes attached to the limbs, intubated, and artificially ventilated (room air) with a rodent ventilator (DH-150, Zhejiang University Medical Apparatus, China). Tidal volumes were 0.6 ml/100 g, positive end-expiratory pressure 3 cmH_2O (1 cmH_2O=98.0638 Pa), and ventilation rate 80 breathes/min. The heart was exposed through a left lateral thoracotomy of the fifth inter-rib space. After the pericardial incision, the proximal part of the LAD was ligated with a sterile 6.0 silk suture (Ethicon) 1–2 mm from the left atrium tip. Finally, the chest was closed in layers, and the endotracheal tube was removed when spontaneous breathing resumed. Sham-operated rats were subjected to the same protocol, except that the LAD was not ligated. During the surgical procedure, 47 of 182 animals died. An evaluation was performed to ensure that MI model had been established, whereby the R-wave amplitude is significantly increased in limb leads of the ECG, and the ST segment is elevated. In addition, one week after the surgical procedure during our preliminary experiments, the infarct area was observed ex vivo in the isolated heart of MI model (via blanching in the ischemic area) upon infusion of blue dye into the aortic root.

After recovery, rats were apportioned into treatment groups. The sham-operated (sham control) rats made up one group (n=45), and the other rats were randomly allocated either to a group that received 20 mg/(kg·d) metoprolol (MI+metoprolol) by intragastric administration 7 d after surgery (Sun *et al*., 2008) for four weeks, or a group that was not administered metoprolol (MI), with 45 rats in each group. The same volume of physiological saline was fed to both the sham control and MI groups. Each of the three groups was also randomly divided into low-dose (LD), medium-dose (MD), and high-dose (HD) subgroups depending on the amount of epinephrine (0.02, 0.04, or 0.06 mg/kg, respectively) to be administered each time during CPR. Thus, there

were nine subgroups in all. Five weeks post-surgery, the following experiments were conducted.

2.2 Experimental protocol

The CPR model was established via suffocation (Hendrickx *et al.*, 1984). Rats were anesthetized, intubated, and ventilated as for the MI procedure. Arterial pressure was monitored through the femoral artery using a PowerLab/4ST (a multiplying channel signal collection and handling apparatus, AD Instruments, Sydney, Australia). After allowing 10 min of stabilization, we induced asphyxia by stopping and disconnecting the ventilator, and clamping the tracheal tube at the end of exhalation. The standard index for cardiac arrest was either femoral systolic blood pressure <15 mmHg (1 mmHg=0.133 kPa) or QRS wave <40 times/min, lasting for more than 1 min. CPR was initiated once the standard indices of cardiac arrest were confirmed. CPR was performed by unclamping the tracheal tube, restarting mechanical ventilation with 100% O_2, administering epinephrine, and applying sternal compressions (with two fingers) at a frequency of 180 to 220 times/min (pressing 10 times and ventilating 4 times) at a depth of 1/3 the posterior-anterior diameter. If the rat failed to respond within 2 min, epinephrine was given repeatedly, three times at most. Meanwhile, ECG, left ventricular pressure, and femoral artery blood pressure were continuously monitored and recorded. Resuscitation was given for 15 min, and then we drew blood from the femoral artery. ROSC was defined as a systolic blood pressure ≥15 mmHg lasting for more than 1 min.

Comparisons among the treatment groups were based on the ROSC rate (the percentage of rats reaching ROSC within the treatment group), the total dose of epinephrine for each subgroup, blood pressure (BP) before CPR, heart rate (HR) before CPR, clamping time (from clamping the tracheal tube to the beginning of CPR), and time for ROSC (from the beginning of CPR to ROSC), as well as arterial pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), Na^+, K^+, blood urea nitrogen (BUN), and creatinine (Cr).

2.3 Statistical analyses

All values were expressed as mean±standard deviation (SD) except that ROSC rates were expressed by percentage. A chi-squared test was performed to test the differences in percentage between any two subgroups. One-way analysis of variance (ANOVA) and Student-Newman-Keuls test were used to compare other variables among the subgroups and between them, respectively. The difference was considered statistically significant at $P<0.05$.

3 Results

3.1 ROSC rates

The ROSC rate of LD subgroup in the MI group decreased when compared to LD subgroup in the sham control ($P<0.01$), but there was no difference between the two ROSC rates of MD subgroups in the sham control and MI groups ($P>0.05$), and the MD subgroup in MI group had an increased ROSC rate when compared with the LD subgroup in the same group. These results suggest that a little higher epinephrine dosage might be good to MI rat ROSC during CPR. However, the ROSC rate in HD subgroup of the MI group also decreased when compared with HD subgroup in the sham control ($P<0.05$), which demonstrates that a much higher epinephrine dosage might not be continuously good to MI rats ROSC during CPR (Table 1).

Both the MI and MI+metoprolol groups had low ROSC rates in LD subgroup without difference. The ROSC rate of MD subgroup in the MI+metoprolol group was significantly lower than that of the MD subgroup in the MI group ($P<0.05$), whereas the ROSC rate of the HD subgroup in the MI+metoprolol group was significantly higher than that of the HD subgroup in the MI group ($P<0.05$), and the ROSC rate of the HD subgroup in the MI+metoprolol group was significantly higher than that of the MD subgroup in the same group ($P<0.01$). All of the above results show that a much higher epinephrine dosage would be good to the ROSC rate of MI rats under long-term metoprolol.

Within any one of the main treatment groups (sham control, MI, and MI+metoprolol), the total amount of epinephrine administered was significantly different among the LD, MD, and HD subgroups ($P<0.05$, all). There were no significant differences in amount of epinephrine administered among any three subgroups with the same dose category ($P>0.05$).

Before CPR, there were no differences in BP, HR, or clamping time among the subgroups (Table 1). Within any one of the main treatment groups, there were no differences in the time for ROSC among the LD, MD, and HD subgroups ($P>0.05$).

3.2 Chemical examination

ROSC was considered the sign of successful CPR. For each of the treatment groups, we compared the results of standard chemical examination values between those rats for whom CPR was successful (i.e., ROSC was achieved) and those for whom CPR failed (Table 2). In the sham control, compared to rats with unsuccessful CPR, the rats who achieved ROSC during CPR had significantly lower pH, PCO_2, and K^+ values ($P<0.01$), and higher PO_2 ($P<0.01$). The chemical examination values were the same for the MI and MI+metoprolol groups, in which K^+ was lower and PO_2 was higher in those rats who achieved ROSC than in those who did not ($P<0.01$, both). There were no differences in blood K^+ value of successful rats between the MI group and the MI+metoprolol group. The mean K^+ values for all the rats for whom CPR was successful and unsuccessful were (6.0±0.8) and (7.0±0.7) mmol/L, respectively, which have an extremely significant difference ($P<0.01$). Our study showed that the blood K^+ value in rats with successful CPR in each treatment group was beyond 5.0 mmol/L, and the majority was over 5.5 mmol/L. There were no differences in Na^+, BUN, and Cr values between the successfully treated and unsuccessfully treated rats of each group.

Table 1 Comparisons of ROSC rate and correlated parameters among three treatment groups during CPR

Group	Subgroup	Total number	ROSC rate	Epinephrine dose (μg)	BP before CPR (mmHg)	HR before CPR (bpm)*	Clamping time (min)	Time for ROSC (min)
Sham control	Low	15	14 (93%)	23.2±5.7	4±13	54±16	6.4±1.2	4.8±0.4
	Medium	15	14 (93%)	36.4±4.2	2±9	58±16	6.5±1.2	5.0±0.3
	High	15	13 (87%)	58.8±6.5	5±11	61±16	6.3±1.2	4.3±0.2
MI	Low	15	3 (20%)[a]	25.3±5.7	3±10	61±14	6.3±1.3	5.3±0.5
	Medium	14	9 (64%)[b]	38.9±6.6	9±18	61±16	6.7±1.3	5.7±0.9
	High	14	7 (50%)[c]	65.1±8.3	5±13	52±15	6.3±1.5	6.1±1.1
MI+ metoprolol	Low	15	2 (11%)	25.2±7.7	7±16	54±13	6.6±1.4	5.4±0.2
	Medium	14	3 (21%)[d]	41.7±7.8	3±11	60±14	6.4±1.3	6.0±0.9
	High	14	12 (86%)[e,f]	63.4±8.2	4±11	58±16	6.1±1.0	5.8±0.7

Values are expressed as mean±SD except that ROSC rates are expressed by percentage. * bpm: beats per min. [a] $P<0.01$, compared with the LD subgroup in the sham control group; [b] $P>0.05$, compared with the MD subgroup in the sham control group; [c] $P<0.05$, compared with the HD subgroup in the sham control group; [d] $P<0.05$, compared with the MD subgroup in the MI group; [e] $P<0.05$, compared with the HD subgroup in the MI group; [f] $P<0.01$, compared with the MD subgroup in the MI+metoprolol group

Table 2 Comparisons of chemical examination values between rats successfully and unsuccessfully resuscitated after cardiac arrest within each treatment group

Group	CPR	*n*	pH	PCO_2 (mmHg)	PO_2 (mmHg)	K^+ (mmol/L)	Na^+ (mmol/L)	BUN (mmol/L)	Cr (μmol/L)
Sham control	Failed	4	7.02±0.03	79±2	40±1	7.9±0.3	143.5±1.0	7.3±0.7	72.6±4.2
	Successful	41	6.89±0.07[a]	54±8[a]	72±8[a]	6.0±0.8[a]	141.5±2.2	7.5±0.7	76.2±7.1
MI	Failed	24	6.95±0.08	64±6	40±3	6.9±0.7	142.4±2.3	7.4±0.7	77.0±6.0
	Successful	19	6.90±0.07	62±7	69±8[b]	5.8±0.9[b]	141.7±2.0	7.6±0.9	77.3±5.6
MI+ metoprolol	Failed	26	6.92±0.08	62±7	40±2	6.9±0.7	142.2±1.9	7.6±0.9	76.9±0.9
	Successful	17	6.91±0.07	61±8	75±7[c]	6.1±0.8[c]	142.3±1.6	7.4±0.7	77.1±6.6
Total for three groups	Failed	54	6.94±0.08	64±8	40±2	7.0±0.7	142.4±2.0	7.5±0.7	76.6±6.4
	Successful	77	6.90±0.07	58±9[d]	72±8[d]	6.0±0.8[d]	141.7±2.0	7.5±0.8	76.7±6.6

Values are expressed as mean±SD. [a, b, c, d] $P<0.01$, comparisons between rats with successful and failed CPR in each treatment group

4 Discussion

During CPR, epinephrine is an effective treatment for cardiac arrest. In the 1970s, surgeons found that 1 mg of epinephrine administered via intracardiac injection could revive a patient's heartbeat, and they assumed that this effect could also be achieved if epinephrine was administered at the same dose by intravenous injection. Thus, a 1-mg dose of epinephrine became the standard delivered during CPR (Emergency Cardiac Care Committee and Subcommittees, American Heart Association, 1992). When more than 1 mg of epinephrine was administered, the β-receptors of the heart were over-stimulated, which would not be good to ROSC during CPR. In the present study, the ROSC rate in MI model rats (who had not been given prior treatment with metoprolol), who had been given low-dose epinephrine during CPR, was lower than that in the sham-operated rats in the same dose subgroup. This is probably because myocardial tissue is injured after MI, leading to myocardial contractile dysfunction. When the epinephrine was increased to the moderate level, the ROSC rate in the MI model was higher than that in the sham-operated group, given the same moderate-level dose. We conclude that an increase in epinephrine may enhance the excitability of the α-receptors and improve circulation. However, with a further increase in epinephrine to the high-dose level, the ROSC rate in the MI model was again lower than that in the sham-operated group, given the same dose, indicating that the higher dose could not have improved spontaneous circulation. We attribute these phenomena to a greater consumption of myocardial oxygen. We then observed that when comparing the MI rats that had been given prior treatment with oral metoprolol with the MI rats who had not, at the moderate dose of epinephrine the ROSC rate in the metoprolol-treated rats was lower, but at the high dose the ROSC rate was higher. The higher epinephrine dose obviously improved the ROSC rate in the MI+metoprolol group, which may present a concern regarding the decrease in myocardial oxygen consumption due to the application of β-receptor blockers resulting in the improvement in myocardial blood and oxygen supply.

Until now, most of us working in the hospital performed CPR in accordance with 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (American Heart Association) for every patient undergoing cardiac arrest (Neumar *et al*., 2010), and there was no difference in the dose of epinephrine or other medicines except between adults and children. No clinical or experimental studies have dealt with a possible association between the effect of chronic use of β-receptor blockers and the epinephrine dose during CPR. Our study showed for the first time that to improve survival the standard epinephrine dose to be administered during CPR should be changed when a cardiac arrest patient has previously used β-receptor blockers over a long period. Prior treatment with oral β-receptor blockers may reduce resuscitation success in the presence of MI in a way that might be remedied by increasing the dose of epinephrine during resuscitation.

There has been much research conducted regarding arterial values during CPR, but until recently, no consensus has been reached. Our study shows that high PO_2 and low blood K^+ values are related to the successful CPR rate of rats, whereas blood Na^+, BUN, and Cr values are not different between the successful and unsuccessful CPR rates of rats. We found that the blood K^+ value in rats with successful CPR in each treatment group was at least in an upper limit of normal. Previous studies found that the blood K^+ value was elevated upon heart arrest and the initiation of CPR. Geddes *et al.* (2006) induced ventricular fibrillation in a porcine model using a right ventricular catheter electrode, and the biochemical parameters were detected at different time. They found that the blood K^+ value would elevate ~50% within the beginning 6 min of CPR. However, Lisachenko and Ivanova (1999) performed experiments on 25 dogs, and showed that the blood K^+ value decreased in the prophase (5 min to 9 h). Although high blood K^+ was thought to be associated with the development of pulseless electrical activity (Tran, 2005), high K^+ injection could end ventricular fibrillation, resulting in a higher ROSC rate (Liakopoulos *et al.*, 2010). Elevated blood K^+ during CPR may be attributed to the accumulation of K^+ from intracellular and damaged cells of the pressed tissue, and has nothing to do with the amount of epinephrine (Lindner *et al.*, 1988).

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Compliance with ethics guidelines

Xiao-jing ZHAO, Zhuo PEN, Ping LI, Er-xiu CHEN, Jian LIU, Yan-xia GAO, Yun-xia REN, and Li-jun LI declare that they have no conflict of interest.

All institutional and national guidelines for the care and use of laboratory animals were followed.

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