نقش گیرنده‌های بتا در آرتمی‌های ناشی از پروفوزیون مجدد

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چکیده:
بروز پروفوزیون مجدد شریان کرونر که یکی از مهم‌ترین مداخلات درمانی شدیدان شرایط همراه با بروز آرتمی‌های قلبی است، مطالعه حاصل جهت بررسی نقش داروهای مساد گیرنده‌های بتا آدنرزنیک، پروپرپانولول (نارگلین‌هایی)، متیوپراپانولول (انتخابی قلب) و پینپرپانولول (با فعالیت سمتیومیتیک ذاتی) روی آرتمی‌های ناشی از پروفوزیون مجدد در قلب خرگوش سالم انجام گرفت. از خرگوش‌های آلپنتو آزاد از هر دو جنس با وزن ۲/۵ کیلوگرم استفاده شدند. حیوانات با پنتوباراتیون داخل وریو ۳ میلی گرم بازی آرتمی کروما گرفته شدند. بعد از لوله‌گذاری داخل ناشی از شریان کرونر، به مدت ۳۰ دقیقه یک میلی‌گرم بازی آرتمی، یک میلی‌گرم بازی کروما یا کروما هر کیلوگرم حفاظتی معادل ۲۳/۱۲ درصد را نشان دادند.

کلید واژها: ۱- پروفوزیون مجدد شریان کرونر
۲- مساده‌های گیرنده‌های بتا آدرزنیک

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ROLE OF BETA RECEPTORS IN REPERFUSION INDUCED ARRHYTHMIAS IN INTACT RABBIT HEART

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ABSTRACT

Coronary artery reperfusion which has become one of the important therapeutic interventions is associated with development of cardiac arrhythmias. The present investigation was carried out to study the role of beta receptor blocking agents with different properties on reperfusion induced ventricular arrhythmias in intact rabbit heart. After anaesthesia the rabbit hearts were subjected to 30 minutes coronary artery ligation followed by reperfusion for one hour. Three doses of propranolol (0.3, 1 and 3 mg/kg), metoprolol (0.5, 0.75 and 1 mg/kg) and pindolol (25, 50 and 100 μg/kg) were given 5 minutes before (pretreatment group) and at the time of reperfusion (treatment group).

Propranolol exhibited 20-40% protection in pretreatment group and 33.3 to 66.6% protection in treatment group, with metoprolol, the protection was 33.3 to 66.6% (pretreatment) and 0 to 16.6% (treatment group). Pindolol offered 25 to 50% (pretreatment) and 16.6 to 33.3% (treatment group) protection. These results suggest a definite role of beta receptors in the pathophysiology of reperfusion induced arrhythmias.

Key Words: 1) Cardiac arrhythmias 2) Beta-blockers 3) Coronary reperfusion

INTRODUCTION

Timely restoration of coronary blood flow salvages jeopardized ischaemic heart muscle and constitutes the fundamental treatment of acute myocardial infarction. Despite the unequivocal utility of reperfusion in limiting cell death in the presence of severe ischaemia, reperfusion can elicit

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several biochemical, mechanical and electrophysiological adverse consequences which are collectively known as "reperfusion injury" (6,11). Reperfusion induced arrhythmias are the electrophysiological manifestation of reperfusion injury (4). Frequently encountered reperfusion arrhythmias are transient sinus bradycardia, premature ventricular contractions, accelerated idioventricular rhythm, ventricular tachycardia, bigeminy and ventricular fibrillation. Established antiarrhythmic agents are generally less effective in treating reperfusion arrhythmias (9,12,17).

Amongst the many factors responsible for the mechanism of reperfusion induced arrhythmias release of endogenous catecholamines plays an important role. Experimental and clinical studies have shown that beta adrenergic blockade limits myocardial necrosis (3) after coronary occlusion and therefore constitutes a valuable adjunct to reperfusion therapy (20). However, paucity of dose response studies of beta blockers and variable drug administration schedules render the valid comparison difficult. Therefore, the present work was undertaken to study the comparative antiarrhythmic effect of non-selective beta blocker (propranolol), cardioselective beta blocker (metoprolol) and beta blocker with intrinsic sympathomimetic activity (Pindolol) on reperfusion induced arrhythmias in intact rabbit heart.

**MATERIALS AND METHODS**

Young healthy rabbits (1.5 - 2.0 kg) were maintained on standard feed and water ad lib. The animal was anaesthetised with pentobarbitone sodium (30 mg/kg i.v.) via ear vein.

Trachea was cannulated after mid cervical incision and animal was maintained on positive pressure respirator through the study. Left thoracotomy was performed and the left anterior descending branch (LAD) of the coronary artery was carefully exposed and ligated about 2 mm from its origin to produce regional ischaemia for a period of 30 minutes. Ligature was then released to achieve reperfusion for a period of 60 minutes. Limb lead II ECG was monitored regularly throughout the study. The drugs were administered by intravenous route 5 minutes before reperfusion (pretreatment group) and at the time of reperfusion (treatment group). The study groups were as follows:

- **Group I**: Control group (n=8)
- **Group II**: i) Propranolol pretreatment group
  - a. 0.3 mg/kg (n=5)
  - b. 1.0 mg/kg (n=5)
  - c. 3.0 mg/kg (n=5)
  - ii) Propranolol treatment group
    - a. 0.3 mg/kg (n=6)
    - b. 1.0 mg/kg (n=6)
observed immediately after coronary artery ligation. Heart rate decreased to 70.23 ± 11.37% of maximal and during reperfusion it further declined to 52.14 ± 8.14% signifying the reperfusion induced damage (Fig.1 & 2).

On reperfusion, arrhythmias ranging from accelerated idioventricular rhythm to ventricular fibrillation was observed. The type of arrhythmias observed were ventricular fibrillation VF (25%), ventricular bigeminy BG, and trigeminy TG (37.5%) accelerated idioventricular rhythm AIVR (50%), premature ventricular contractions PVC (62.5%), atrioventricular block AVB (37.5%) and atrioventricular dissociations AVD (12.5%). The mortality due to reperfusion arrhythmias was 50% and AVB was the major cause of death.

**Effect of propranolol**

Propranolol in the three doses used did not produce any significant change in heart rate in both pretreatment as well as treatment groups (Fig 3 & 4).

In the pretreatment group, all the three doses of propranolol showed marginal protection against VT/VF, BG/TG, AVD and AVB. PVCs were significantly protected by all three doses (Fig 5). The percent protection offered against arrhythmias was dose dependent and ranged from 20-40% (Fig.6).

In the treatment group there was...
marginal reduction in PVC and VF with second and third dose but the incidence of AVB was not reduced significantly (Fig 7). The percent protection from arrhythmias was 33.3 to 66.6% in a dose related manner (Fig 8).

**Effect of metoprolol**

Metoprolol in the three doses used produced a nonsignificant decrease in heart rate (Fig 9 & 10).

In the pretreatment group, it has marginally reduced VT/VF, BG/TG and AVD with first dose, AIVR with the second dose and mostly all types of arrhythmias with the third dose whereas a significant reduction in PVC with second and third dose was observed (Fig 11). The total percent protection against arrhythmias ranged from 33.3 to 66.6% (Fig 12).

In the treatment group, the first dose exhibited marginal protection in VT/VF, BG/TG and significant reduction in PVCs. The second and the third dose (marginally protected against VT/VF and BG/TG). The third dose produced appreciable protection against AIVR also (Fig 13). Overall, a maximum of 0-16.6% protection against arrhythmias was observed in this group (Fig 14).

**Effect of pindolol**

No significant change in heart rate was observed in pindolol pretreatment groups whereas bradycardia which was not significant was observed with all the dose groups in pindolol pretreated animals (Fig 15 & 16).

In the pretreatment group first dose completely abolished VT/VF, BG/TG, AVB & AVD. AIVR was marginally reduced. The second dose had abolished VT/VF, BG/TG, AIVR and AVDs. The third dose provided marginal protection against all arrhythmias except PVCs which were completely abolished (Fig 17). The percent protection was 50 to 25% i.e. with higher dose there was less protection against arrhythmias (Fig 18).

In the treatment group the first dose VT/VF, and BG/TG were completely abolished. There was significant reduction in PVCs and AIVRs were marginally suppressed with second dose VT/VF and AIVR were completely abolished BG/TG, PVCs and AVB were completely suppressed. The third dose marginally suppressed AIVR and BG/TG, PVC and AVD (Fig 19). The percent protection was 16.6 to 33.3% (Fig 20).

**DISCUSSION**

In the present study, rabbit was selected as an animal model because of low incidence of mortality and generation of uniform ischaemic zones. Ischaemia was produced for a period of 30 minutes because of maximum vulnerability of the heart to
Propranolol is known to have two other actions that may be relevant to its antiarrhythmic activity. It decreases background outward current and in high doses produces membrane stabilizing effects. The antiarrhythmic effects of beta-adrenergic antagonists can be explained by the following mechanisms:

1. Inhibition of cardiac sympathetic activity, since it is analogous to stimulation of beta-1 receptors.
2. Reduction of the intrinsic sympathomimetic activity (ISA) which is related to the dosage level.
3. Protection against ischemia/reperfusion injury, which is related to the dose.
4. Protection against ischemia/reperfusion injury, which is related to the dose.
5. Protection against ischemia/reperfusion injury, which is related to the dose.
6. Protection against ischemia/reperfusion injury, which is related to the dose.

In the present study, propranolol (treatment group) and metoprolol (pretreatment group) have shown protection against ischemia/reperfusion injury, and such beta blocking agents might be expected to be potentially protective.

It has been suggested that there is a large release of endogenous catecholamines during early reperfusion and reducing 6-hydroxy-dopamine or with reserpine myocardial catecholamine reserve either by reducing the amplitude or decreasing catecholamines.

Beta-adrenergic blocking agents block the spontaneous firing rate of sinus node and have significant inhibitory effect on automaticity in cardiac Purkinje fibres when their firing rate has been increased by catecholamines.

Role of Beta Receptors in Repolarisation

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Fig. 1: Illustrates electrocardiographic changes in intact rabbit heart subjected to coronary artery ligation and reperfusion in control group.

A. Control ECG, heart rate = 300 beats/min.
B. C and D. ECG at 0, 10, 20 min of CAL respectively, showing ST segment elevation and hence successful production of ischaemia.

Heart Rate = 240 beats/min.

E, F, G and H. ECG at 0/15/30 and 60 min. of RE idioventricular rhythm was observed with ST segment elevation.

Heart Rate = 240 beats/min.

Chart Speed = 25 mm/sec.

Recording lead = Bipolar limb lead II

Fig. 2: Effect of coronary artery ligation and reperfusion on heart rate in intact rabbit heart
Fig. 3: Effect of propranolol (pretreatment) on heart rate in intact rabbit heart

Fig. 4: Effect of propranolol on heart rate in intact rabbit heart
Fig. 5: Effect of propranolol (pretreatment) on the severity of reperfusion arrhythmias in intact rabbit heart.

Fig. 6: Dose response curve of propranolol (pretreatment) in intact rabbit heart.
Fig 7: Effect of propranolol on the severity of reperfusion arrhythmias in intact rabbit heart

Fig 8: Dose Response curve of propranolol in intact rabbit heart
Fig. 9: Effect of metoprolol (Pretreatment) on heart rate in intact rabbit heart

Fig. 10: Effect of metoprolol on heart rate in intact rabbit heart
Fig. 11: Effect of metoprolol (pretreatment) on the severity of reperfusion arrhythmias in intact

Fig. 12: Dose response curve of metoprolol (pretreatment) in intact rabbit heart
Fig. 13: Effect of metoprolol on the severity of reperfusion arrhythmias in intact rabbit heart

Fig. 14: Dose response curve of metoprolol in intact rabbit heart
Fig. 15: Effect of pindolol (pretreatment) on heart rate in intact rabbit heart

Fig. 16: Effect of pindolol on heart rate in intact rabbit heart
Fig. 17: Effect of pindolol (pretreatment) on the severity of reperfusion arrhythmias in intact rabbit heart.

Fig. 18: Dose response curve of pindolol (pretreatment) in intact rabbit heart.
Fig. 19: Effect of pindolol on the severity of reperfusion arrhythmias in intact rabbit heart

Fig. 20: Dose response curve of pindolol in intact rabbit heart
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