

## نقش گیرنده‌های بتا در آریتمی‌های ناشی از پروفوزیون مجدد

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### چکیده:

پروفوزیون مجدد شریان کرونر که یکی از مهمترین مداخلات درمانی شده‌است همراه با بروز آریتمی‌های قلبی است. مطالعه حاضر جهت بررسی نقش داروهای مسدود گیرنده‌های بتا آدرنرژیک، پروپرانولول (غیرانتخابی)، متوپرولول (انتخابی قلب) و پیندولول (با فعالیت سمپاتومیتیک ذاتی) روی آریتمی‌های ناشی از پروفوزیون مجدد در قلب خرگوش سالم انجام گرفت. از خرگوشهای آلبیتو از هر دو جنس با وزن ۲-۱/۵ کیلوگرم استفاده شد. حیوانات با پنتوباریتون داخل وریدی ۳۰ میلی‌گرم بازای هر کیلوگرم، بیهوش شدند. بعد از لوله‌گذاری داخل نایی، عمل بازکردن قفسه سینه جهت دسترسی به قلب انجام شد. به شاخه قدامی پائین رو چپ (LAD) شریان کرونر به مدت ۳۰ دقیقه بست زده شد و بعد پروفوزیون مجدد صورت گرفت. ECG در فواصل منظم به مدت یک ساعت گرفته و بررسی گردید. پروپرانولول در ۳ دوز (۰/۳، ۱، ۳ میلی‌گرم به ازای هر کیلوگرم) حفاظتی معادل ۶۶/۶-۳۳/۳ درصد را نشان داد. حفاظت با متوپرولول (۰/۵، ۰/۷۵ و ۱ میلی‌گرم بازای کیلوگرم) نیز در همان محدوده بود یعنی ۶۶/۶-۳۳/۳ درصد، در حالی که پیندولول حفاظتی در محدوده ۵۰-۲۵٪ را نشان داد. بنابراین داروهای مسدود گیرنده‌های بتا، قلب را در برابر بروز آریتمی‌های پروفوزیون مجدد مقداری حفاظت کردند. با وجود این فواصل اختصاصی مانند انتخابی بودن برای قلب و داشتن فعالیت سمپاتومیتیک ذاتی به نظر می‌رسد اثر مفید اضافی ندارد.

کلید واژه‌ها: ۱- پروفوزیون مجدد کرونر

۲- مسدودهای گیرنده‌های بتا آدرنرژیک

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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 rep

erfusion 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)

c. 3.0 mg/kg (n=6)

Group III: i) Metoprolol pretreatment group

a. 0.5 mg/kg (n=6)

b. 0.75 mg/kg (n=6)

c. 1.0 mg/kg (n=6)

ii) Metoprolol treatment group

a. 0.5 mg/kg (n==5)

b. 0.75 mg/kg (n=5)

c. 1.0 mg/kg (n=5)

Group IV i) Pindolol pretreatment group

a. 25 ug/kg (n==5)

b. 50 ug/kg (n=5)

c. 100 ug/kg (n==5)

ii) Pindolol treatment group

a. 25 ug/kg (n==6)

b. 50 ug/kg (n==6)

c. 100 ug/kg (n==6)

### DATA ANALYSIS

All data are expressed as mean  $\pm$  SEM values. Unpaired and paired "t" test were used to draw the intergroup and intragroup comparisons respectively. Fisher's exact test was applied in order to find the exact probability (p) and significance of difference between severity of arrhythmias and their overall incidence. The term "marginal protection" was used in the analysis of severity of arrhythmias refers to probability range of 0.1 to 0.4 according to Fisher's exact test.

## RESULTS

### EFFECT OF CORONARY ARTERY LIGATION AND REPERFUSION

A significant decrease in heart rate was

observed immediately after coronary artery ligation. Heart rate decreased to  $70.23 \pm 11.37\%$  of maximal and during reperfusion it further declined to  $52.14 \pm 8.14\%$  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

reperfusion arrhythmias at this time<sup>(18)</sup>.

It has been suggested that there is a large release of endogenous catecholamines during early reperfusion<sup>(15)</sup> and reducing myocardial catecholamine reserve either by 6 hydroxy-dopamine or with reserpine pretreatment, has been shown to decrease reperfusion arrhythmias<sup>(16,17,19)</sup>. These observations therefore suggest that stimulation of adrenergic receptors may be involved in the genesis of reperfusion arrhythmias and as such beta blocking agents might be expected to be potentially protective.

In the present study propranolol (treatment group) and metoprolol (pretreatment group) have shown equipotent results and the percent inhibition of arrhythmias was 33.3 to 66.6%. The animals in other groups showed less protection and with pindolol in pretreatment group with increasing dose protection was reduced (50 to 25%). This could be related to intrinsic sympathomimetic activity since it is analogous to stimulation of  $\beta_1$  receptors.

The anti-arrhythmic effects of beta adrenergic antagonists can be explained by their selective blockade of  $\beta$ -receptors. Propranolol is known to have two other direct actions that may be relevant to its antiarrhythmic activity. It increases background outward current and in high doses produced membrane stabilizing

action. 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<sup>(1)</sup>. Low amplitude premature responses are abolished by propranolol. This effect is probably due to and increase in background outward current.

Our results are in accordance with most investigators who demonstrated that adrenoceptor blocking drugs reduce lethal arrhythmias in experimental animals during coronary artery occlusion<sup>(5,8,13,14)</sup> and in man with coronary artery disease<sup>(2)</sup>. However, many drugs can exert potent anti-ischaemic effects, thereby showing the rate of development of ischaemic injury so that, at the time of reperfusion, hearts in the treated group are less severely injured<sup>(7)</sup>.

In the present study, maximum protection offered against reperfusion arrhythmias in rabbits was 66.6%. Though it was significant but apart from the mechanisms involving  $\beta$  receptors, some other mechanisms are certainly playing role in reperfusion arrhythmias and further studies with combination of  $\beta$ -blockers with other drugs are in progress.

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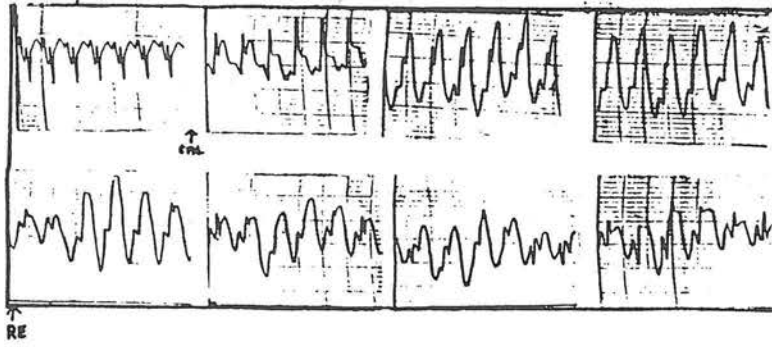


Fig. 1: Illustrates electrocardiographic changes in intact rabbit heart subjected to coronary artery ligation and reperfusion in control group.

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 Rat = 240 beats/min.

Chart Speed = 25 mm/sec.

Recording lead = Bipolar limb lead II

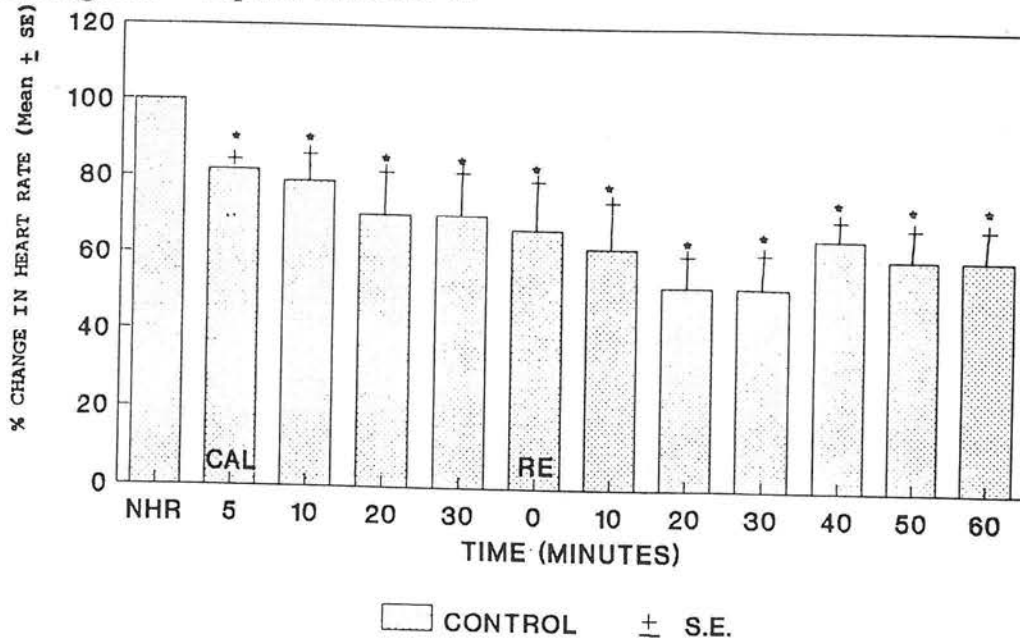


Fig. 2 : Effect of coronary artery ligation and reperfusion on heart rate in intact rabbit heart

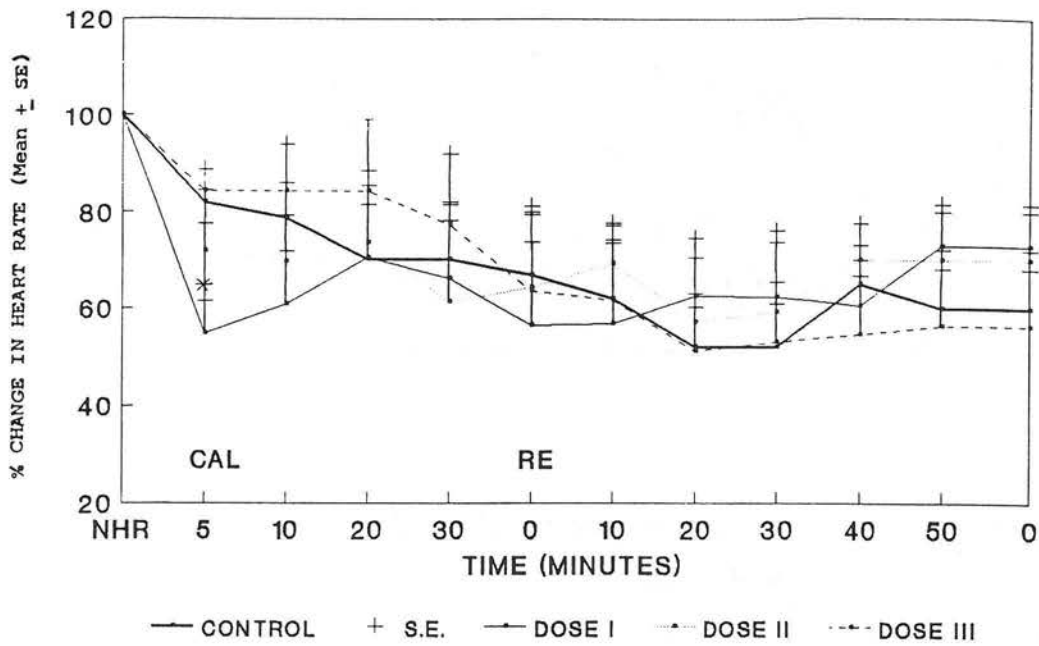


Fig. 3: Effect of propranolol (pretreatment) on heart rate in intact rabbit heart

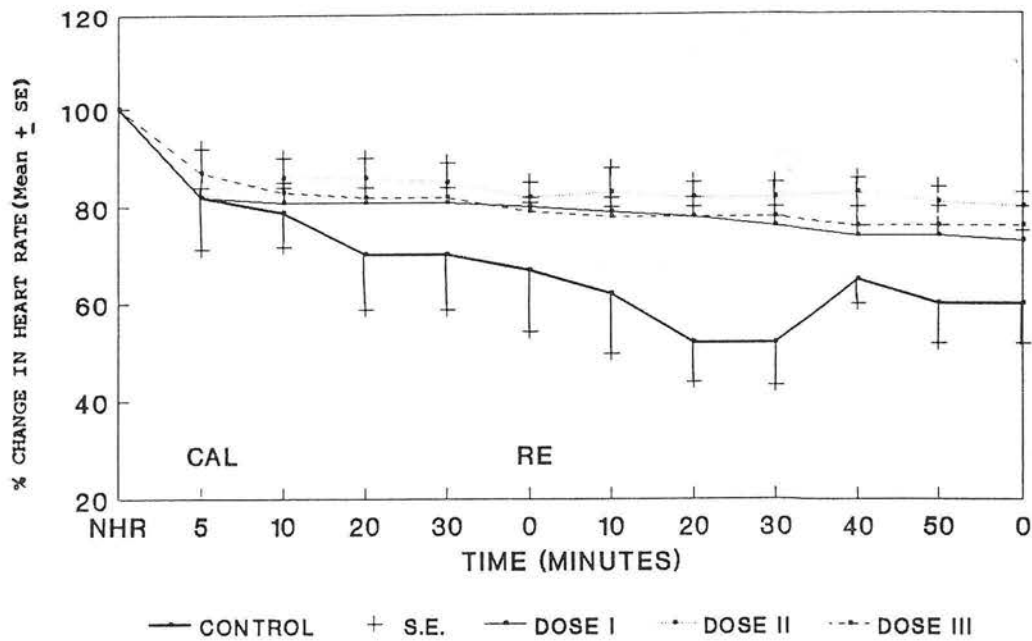


Fig. 4: Effect of propranolol on heart rate in intact rabbit heart



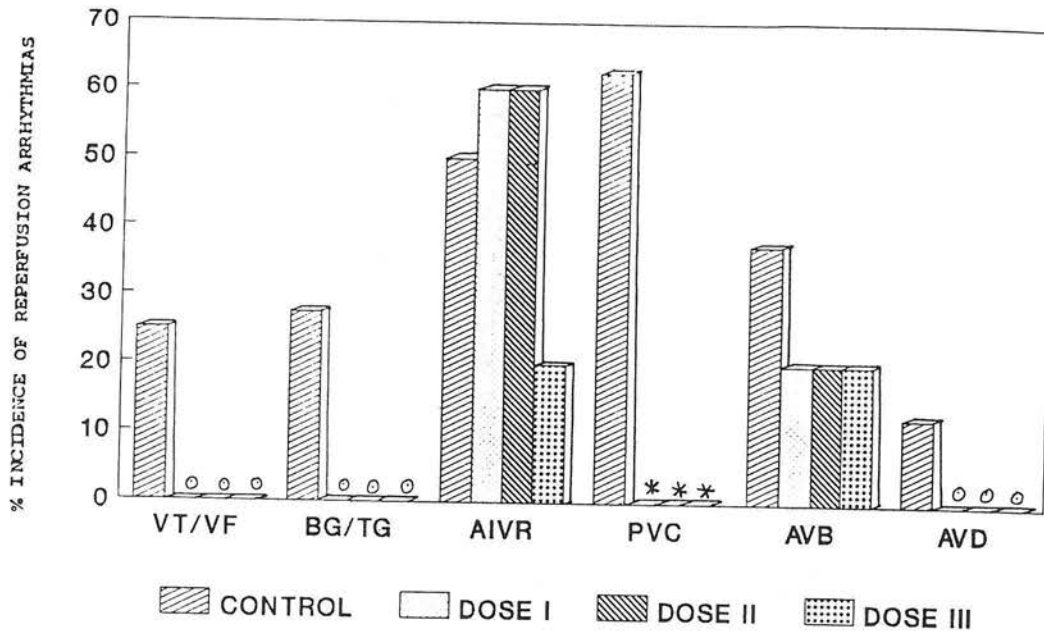


Fig.5: Effect of propranolol (pretreatment) on the severity of reperfusion arrhythmias in intact rabbit heart

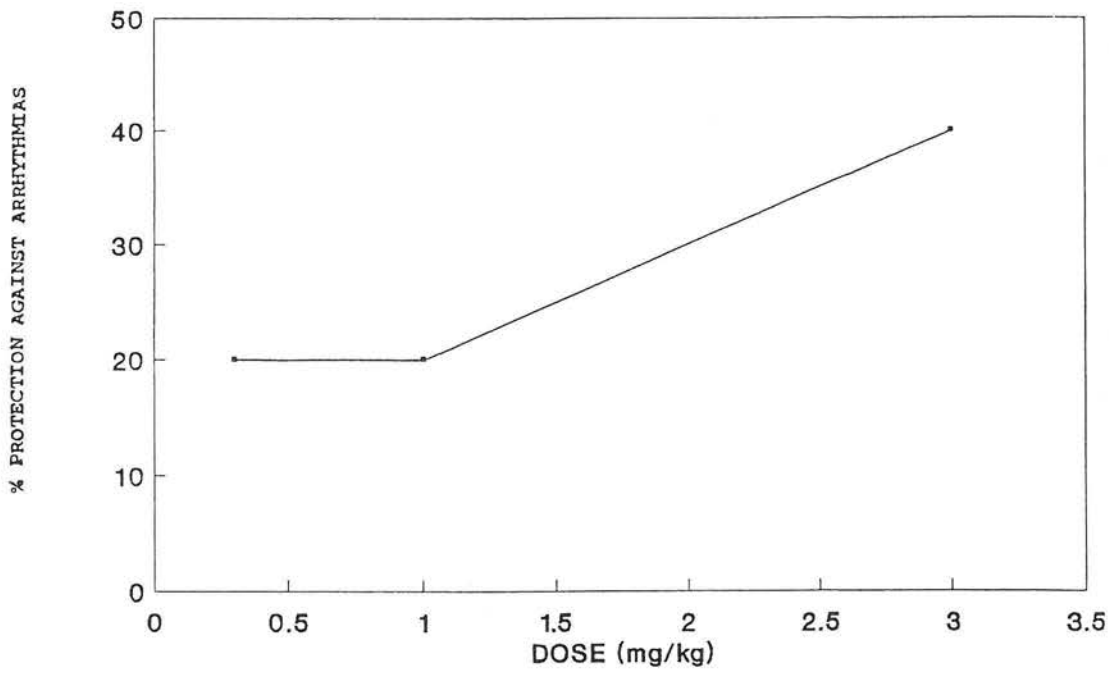


Fig.6 : Dose response curve of propranolol (pretreatment) in intact rabbit heart

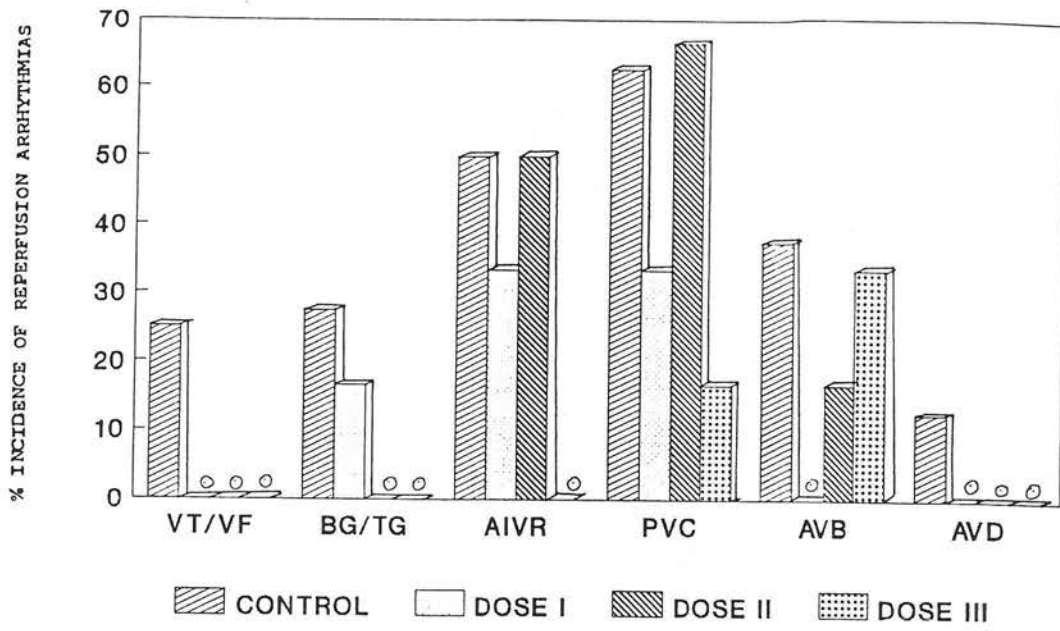


Fig 7: Effect of propranolol on the severity of reperfusion arrhythmias in intact rabbit heart

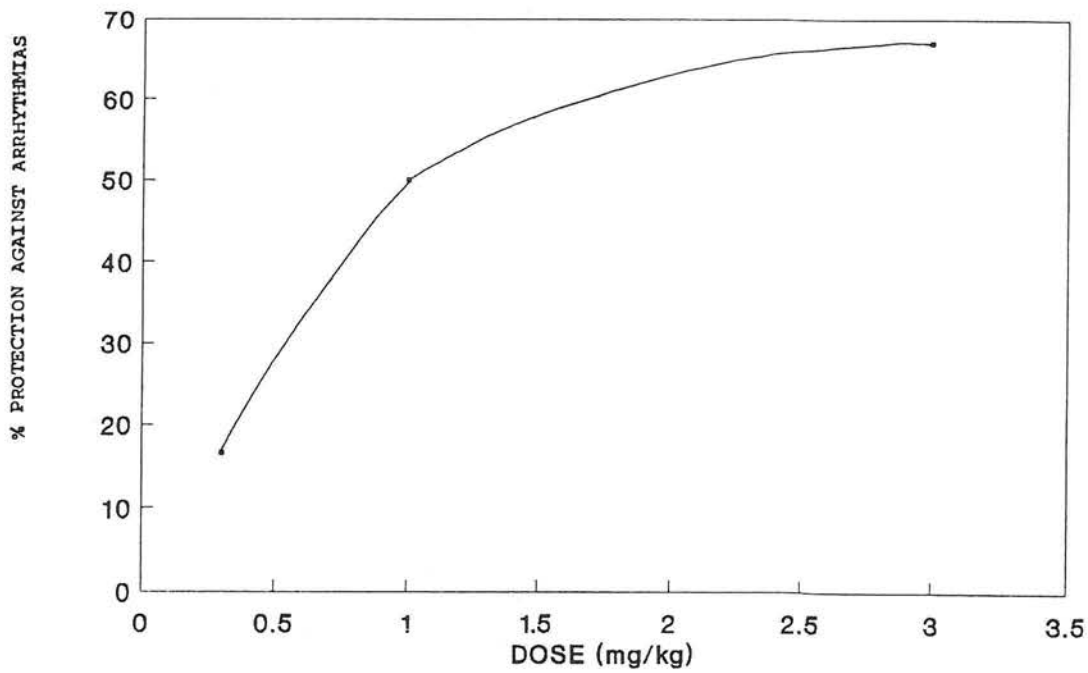


Fig. 8: Dose Response curve of propranolol in intact rabbit heart

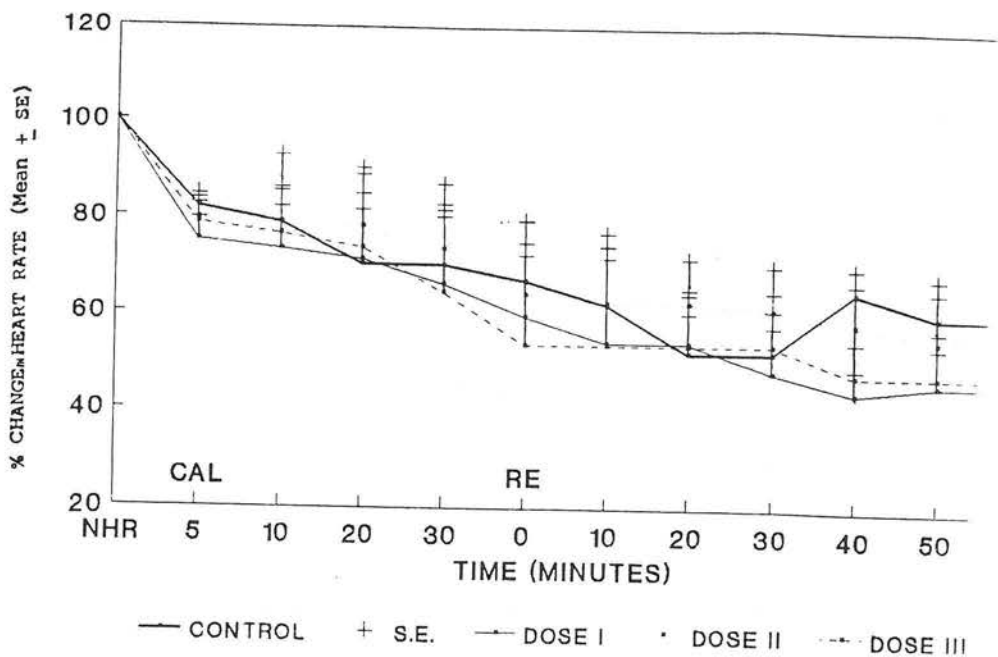


Fig. 9: Effect of metoprolol (Pretreatment) on heart rate in intact rabbit heart

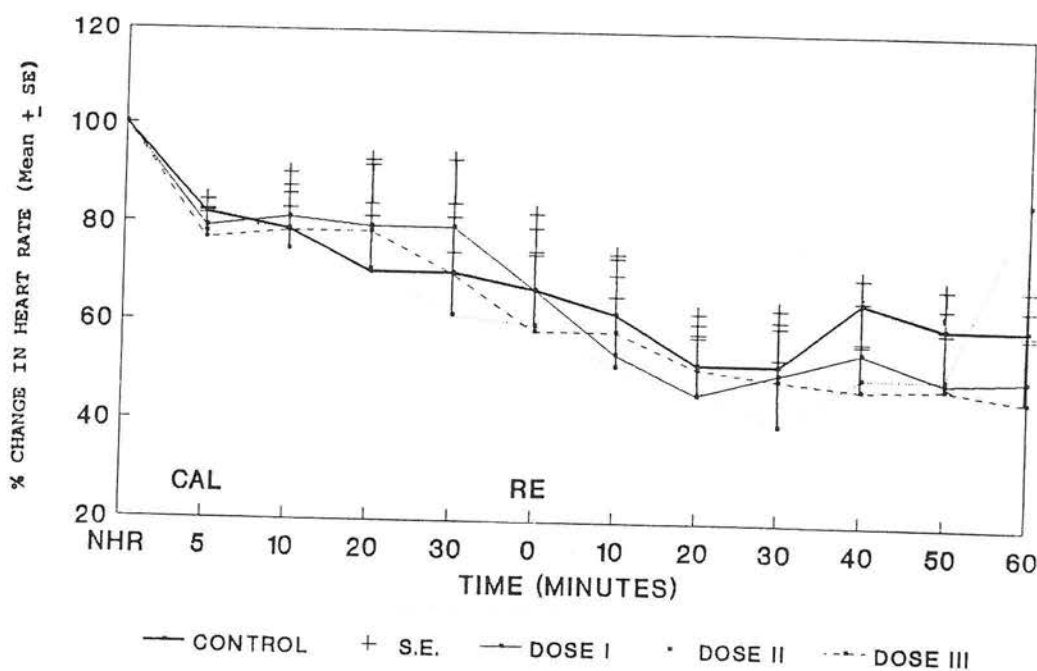


Fig. 10: Effect of metoprolol on heart rate in intact rabbit heart

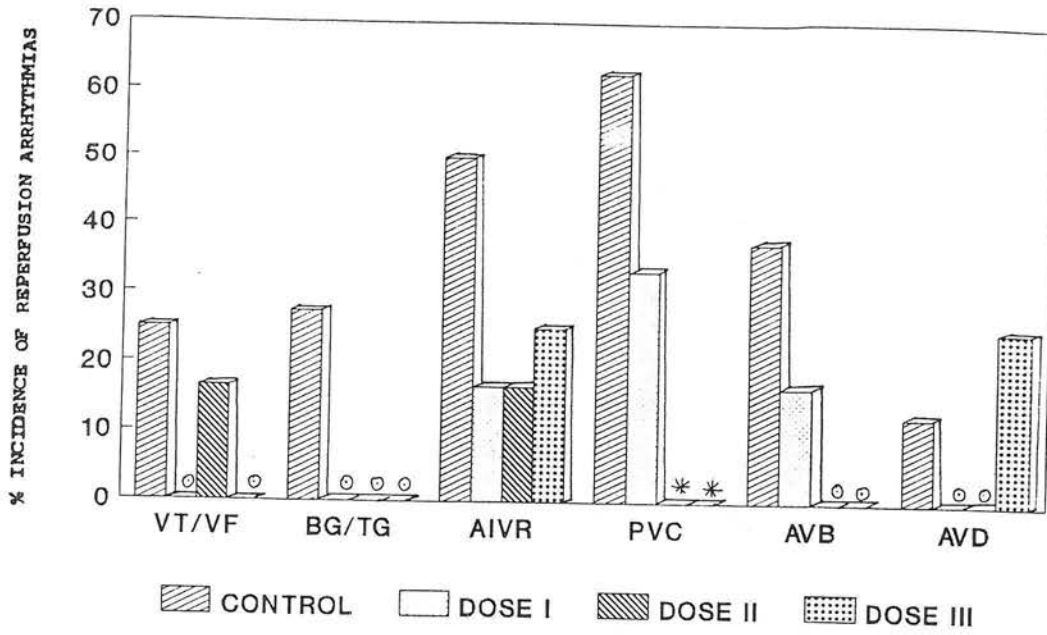


Fig. 11: Effect of metoprolol (pretreatment) on the severity of reperfusion arrhythmias in intact

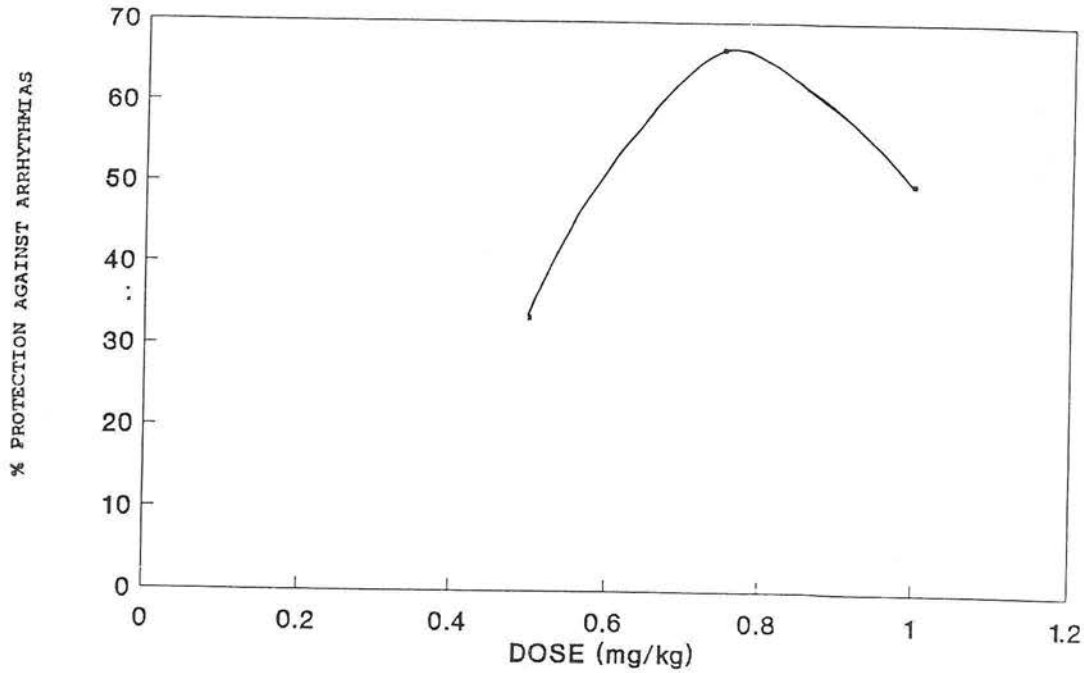


Fig. 12: Dose response curve of metoprolol (pretreatment) in intact rabbit heart

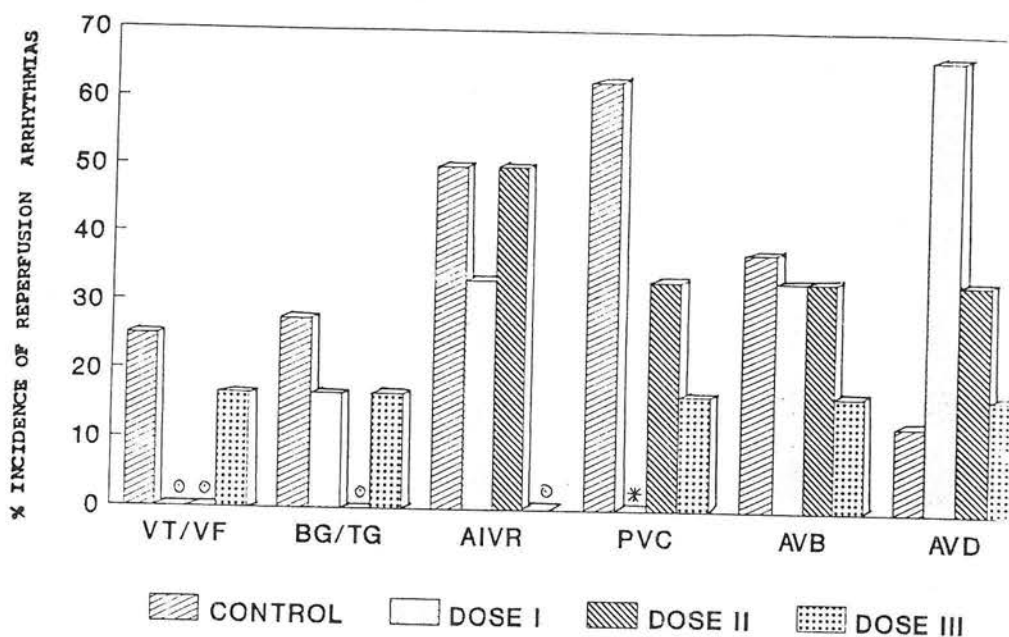


Fig. 13: Effect of metoprolol on the severity of reperfusion arrhythmias in intact rabbit heart

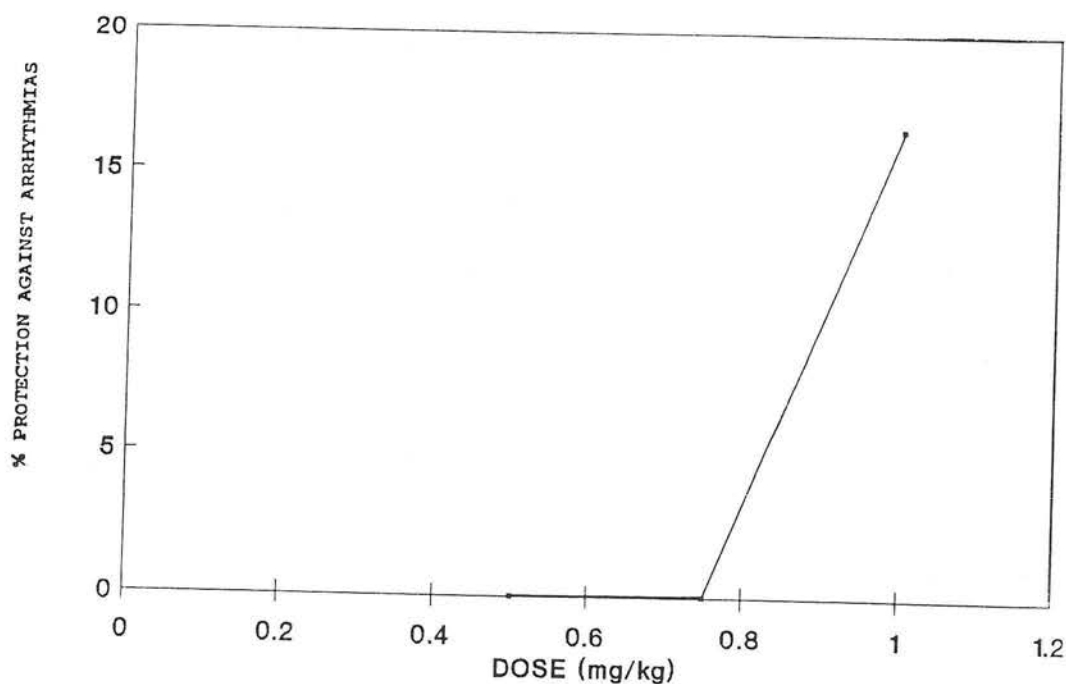


Fig. 14: Dose response curve of metoprolol in intact rabbit heart

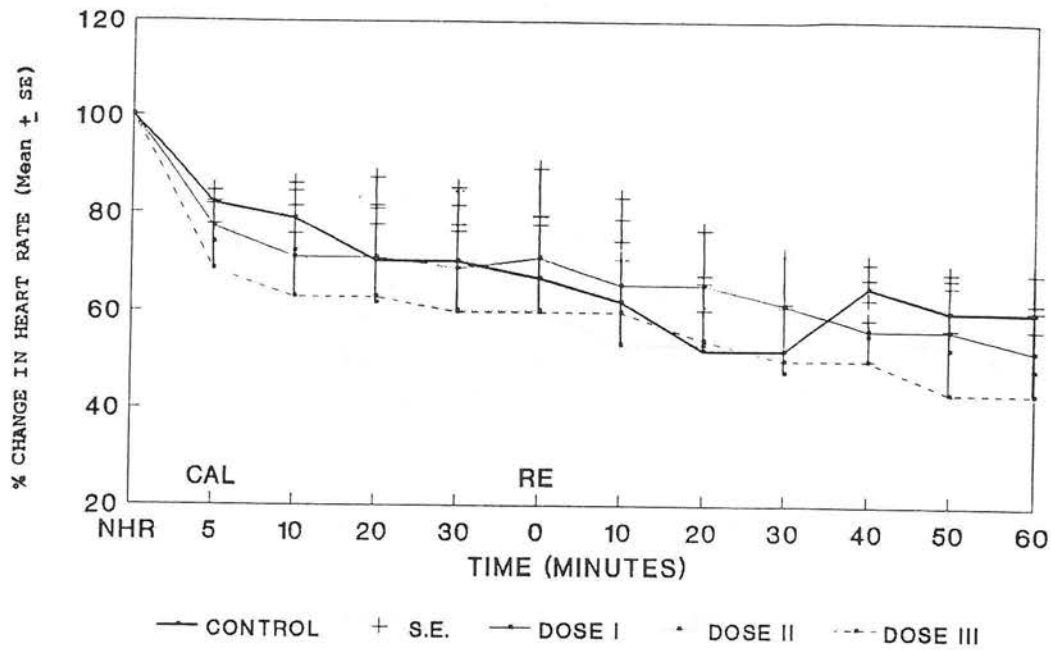


Fig. 15: Effect of pindolol (pretreatment) on heart rate in intact rabbit heart

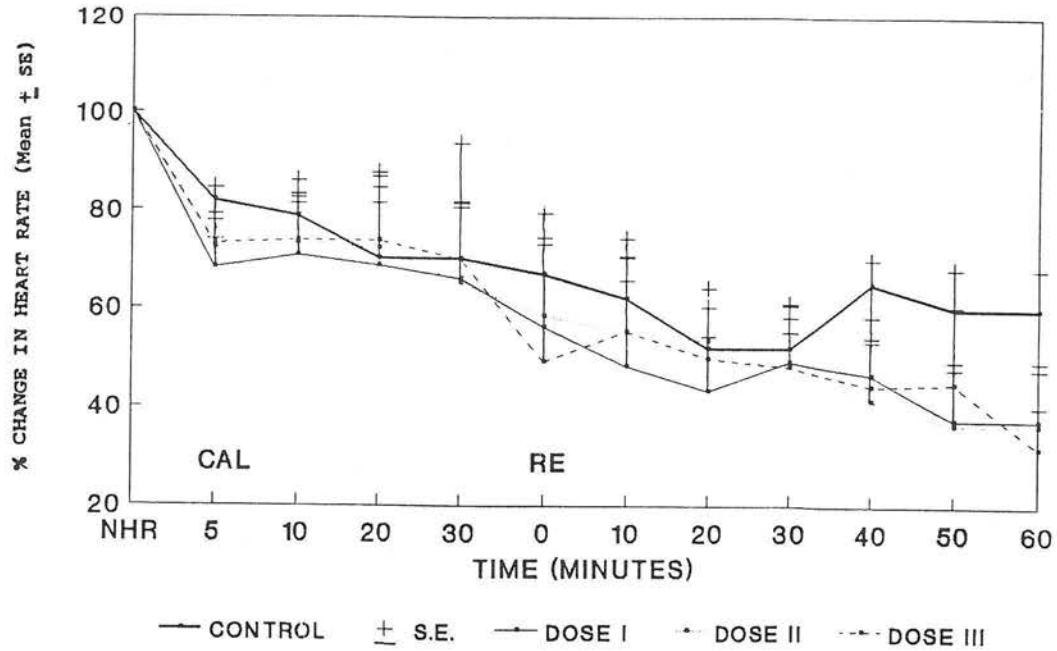


Fig. 16: Effect of pindolol on heart rate in intact rabbit heart

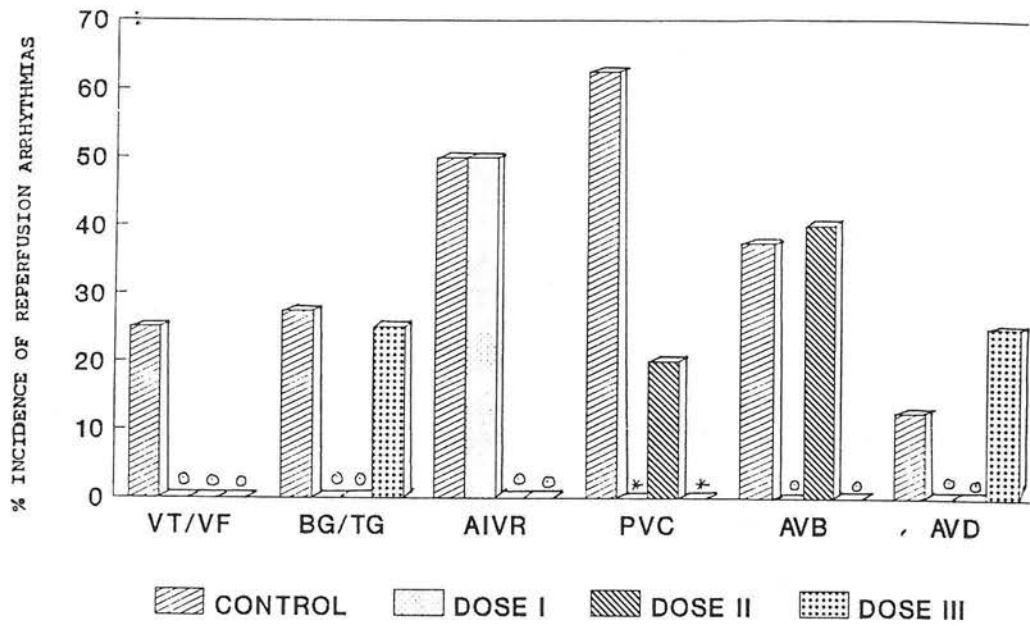


Fig.17 : Effect of pindolol (pretreatment) on the severity of reperfusion arrhythmias in intact rabbit heart

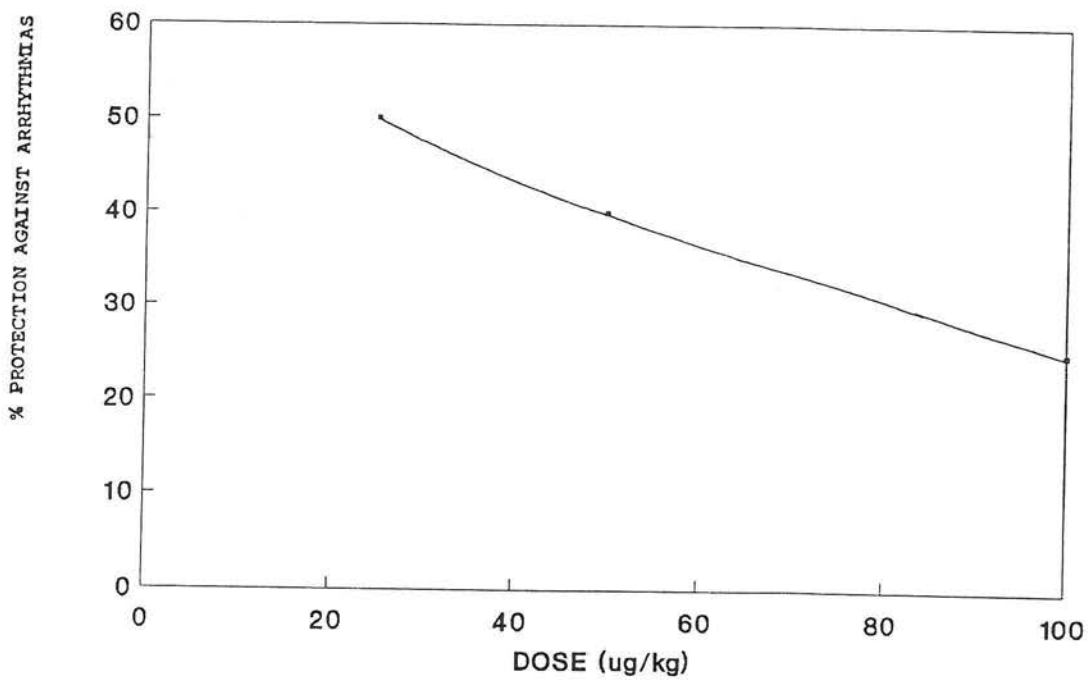


Fig. 18: Dose response curve of pindolol (pretreatment) in intact rabbit heart

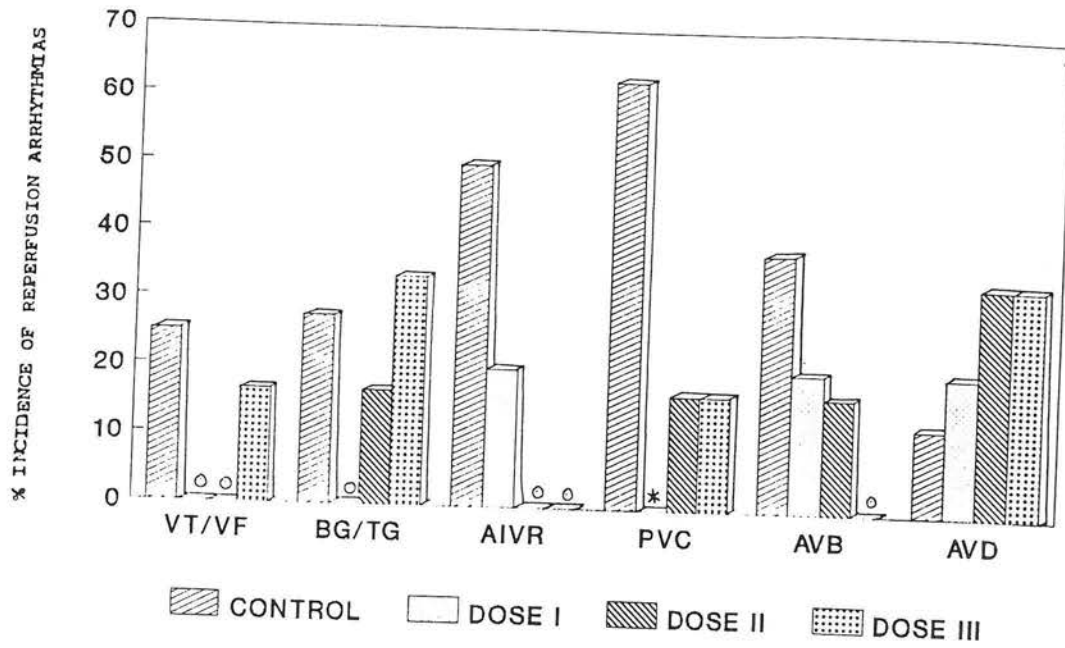


Fig. 19: Effect of pindolol on the severity of reperfusion arrhythmias in intact rabbit heart

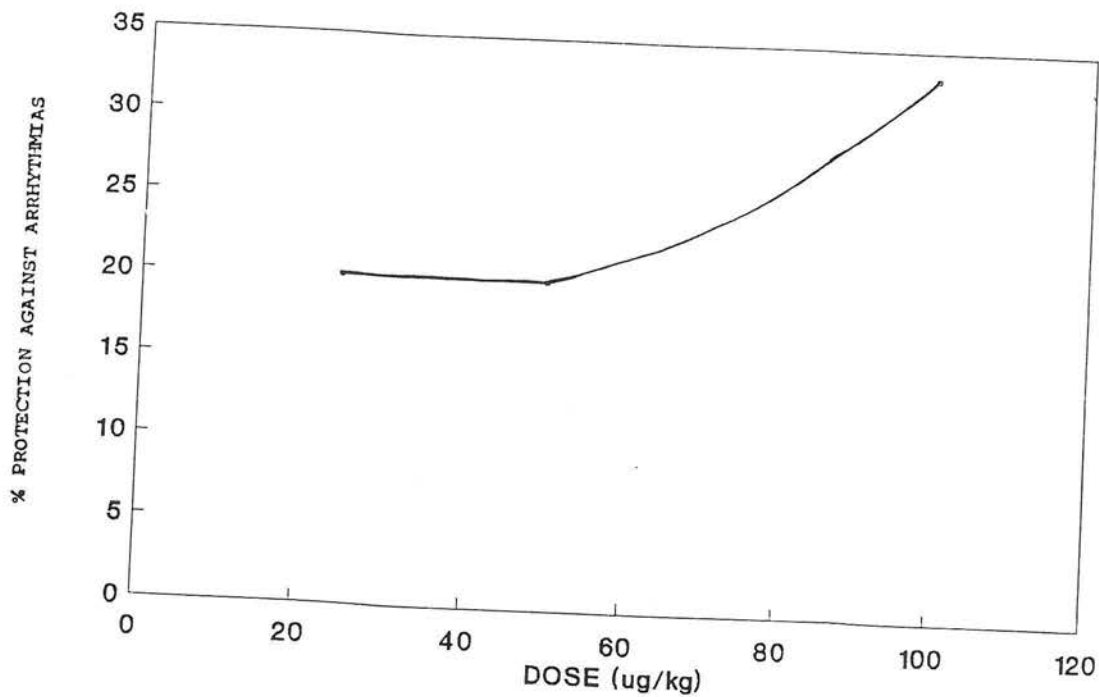


Fig. 20: Dose response curve of pindolol in intact rabbit heart

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