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MODULATION OF THE SEVERITY OF REPERFUSION-INDUCED ARRHYTHMIAS BY DIGOXIN IN THE ISOLATED RAT HEART

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ABSTRACT

In the present investigation, the effects of different concentrations of digoxin (5×10^{-8} - 5×10^{-6} M) on the number of premature ventricular contractions (PVCs), incidence, onset and duration of ventricular tachycardia (VT) and fibrillation (VF) have been studied on the isolated rat heart.

Digoxin (5×10^{-8} - 5×10^{-6} M) had no effect on the number of premature ventricular contractions, the incidence and the duration of ventricular tachycardia. Digoxin at the high concentration (5×10^{-6} M) has significantly reduced the onset of reperfusion induced ventricular tachycardia. It also increased the incidence and duration of reperfusion induced ventricular fibrillation.

The present investigation suggests that administration of high doses of digoxin may modulate the severity of arrhythmias resulting from reperfusion of ischaemic myocardium. This effect may be mediated through the effect of digoxin on the distribution of potassium and calcium ions.

INTRODUCTION

Relaxation of coronary artery spasm, leading to reperfusion-induced ventricular fibrillation has been suggested as a major cause of sudden death in man[1,2]. The mechanisms of reperfusion arrhythmias are no fully understood. Potassium, calcium and magnesium ions are known to affect the vulnerability of the heart to develop arrhythmias[3-8]. However, the effects of these ions on reperfusion arrhythmias have not been examined in detail. The current interest of reperfusion-induced arrhythmias made it seem worthwhile to examine the effects of agents which affect the distribution of these ions on the severity of reperfusion arrhythmias. One of these agents which cause changes in electrolyte levels is digoxin.

Digoxin is used most frequently to improve circulation in patients with congestive heart failure and to slow the venticular rate in the presence of atrial fibrillation and flutter. Digoxin was documented to have a positive inotropic responses which are accompanied by a net loss of K^+ and a net uptake of Na^+ leading to a net uptake of cellular Ca^{2+} [9]. Correlation between digoxin and severity of reperfusion arrhythmias has not been examined, therefore, it seemed interesting to investigate the effect of digoxin on reperfusion arrhythmias in the isolated rat heart. The isolated rat heart model is used in the present study to devoid the extracardiac reflex mechanisms which may modulate the effect of digoxin on reperfusion arrhythmias.

MATERIAL AND METHODS

Hearts from male wistar rats (about 200-250 g) were perfused retrogradly via the aorta at a constant flow rate of 10 ml/min at 37°C with Kreb's Henselit solution of the following composition (mM): NaCl 118; $CaCl_2$ 1.23; KCl 4.7; $MgSO_4$ 1.2; KH_2PO4 1.2; $NaHCO_3$ 25.0 and glucose 11.0 gassed with 95% O_2 and 5% CO_2. A loose ligature was immediately placed around the main left coronary artery. Both ends of the ligature were passed through a short piece of polythene tubing (1 mm i.d.) to form snare. Follwing a 15 min equilibration period, digoxin was added to the perfusate and five minutes later, the snare around the coronary artery was tightened and held in place with a small clip.

Successful ligation was indicated by an increase in perfusion pressure. Ten minutes after ligation of the coronary artery, the clip holding the ligature was removed and successful reperfusion was indicated by a sudden decrease in perfusion pressure. Epicardial ECGs were recorded by placing electrodes on the right atrium and left ventricle for 3 minutes following reperfusion as reperfusion-induced arrhythmias are very rapid in onset.

The developed tension was recorded at a diastolic tension of 2 g via a devices UF1 isometric transducer attached to the tip of the ventricle. The developed tension recording was used to trigger a devices rate meter (4521)

to monitor heart rate. A Bell Howell pressure transducer (4-442) was used for recording the perfusion pressure.

Criteria for Arrhythmias:

Premature ventricular contractions (PVCs) were counted from the ECG and developed tension tracing. Isolated PVCs were followed by a compensatory pause while runs of PVCs which constituted ventricular tachycardia (VT) always had smaller contraction amplitude than normal.

Ventricular fibrillation (VF) was diagnosed when the ECG recording showed chaotic activity with an amplitude less than that of normal ECG while ventricular tachycardia (VT) was diagnosed as five or more consecutive PVCs. The total number of PVCs and the incidence, onset and duration of VT and VF were recorded.

Statistical Methods:

Results are presented as mean ± S.E.M. The X^2-test was used to compare the incidence of VT and VF in treated groups with that in control group. The Wilcoxon Rank Sum test was used to compare PVC numbers as well as the onset and duration of VT and V.F. $P < 0.05$ was considered to be significantly different from control values. (n = 9 - 12 rats).

Materials Used:

Digoxin (Wellcome, England) was added to the perfusate 5 min before coronary artery ligation and maintained throughout the remainder of the experiment.

RESULTS

(A) Effect of digoxin on the number of premature ventricular contractions (PVCs):

Addition of digoxin at the concentrations 5 x 10-8 - 5 x 10-6 M to the perfusate did not significantly change the number of reperfusion-induced premature ventricular contractions (Fig. 1).

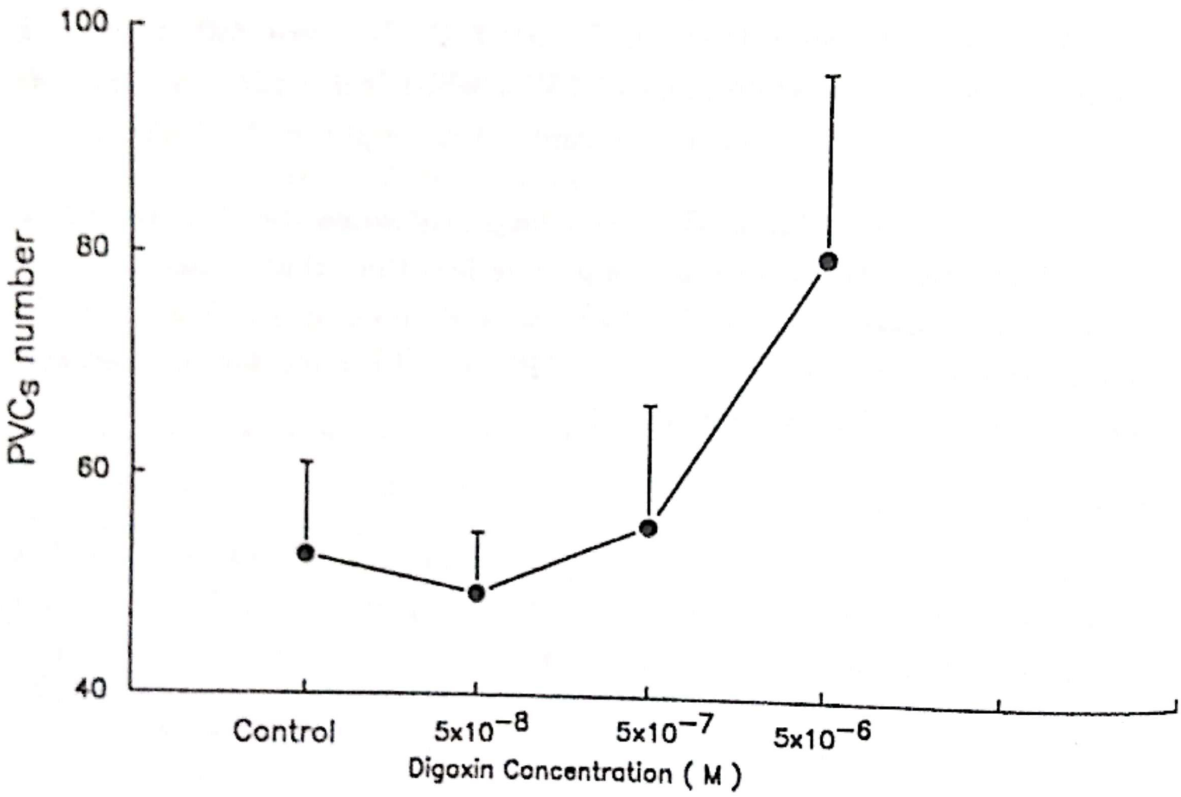

Fig. (1): Effect of different concentrations of digoxin (5×10^{-8} - 5×10^{-6} M) on the number of reperfusion induced premature ventricular contractions (PVCs).

(B) Effect of digoxin on ventricular tachycardia (VT):

As shown in Fig. (2), digoxin at the three concentrations used did not affect neither the incidence nor the duration of ventricular tachycardia. Digoxin in the two concentrations 5×10^{-8} & 5×10^{-7} M had no effect on the onset of VT while the higher concentration of digoxin (5×10^{-6} M) significantly reduced the onset of reperfusion-induced ventricular tachycardia (Fig. 2 b).

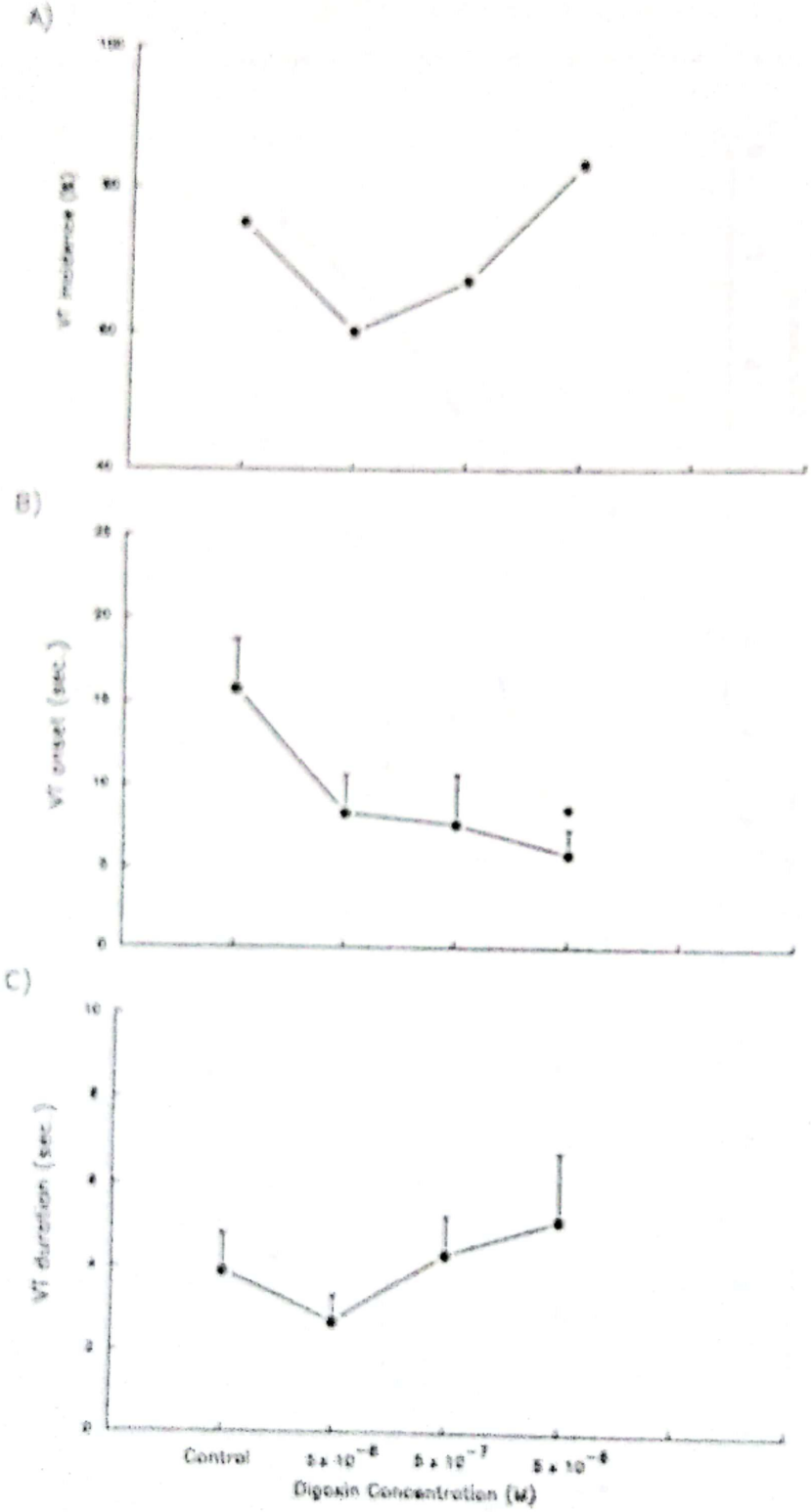

Fig. (2): Effect of different concentrations of digoxin (5×10^{-8} - 5×10^{-6} M) on: A. incidence, B. onset and C. duration of reperfusion-induced ventricular tachycardia (VT) in the isolated rat heart.

* Significantly different from control value at $P < 0.05$.

increasing the concentration of digoxin up to 5 x 10^{-6} M, both the incidence and duration of VF were increased. The higher concentration of digoxin had no significant effect on the onset of reperfusion-induced ventricular fibrillation.

DISCUSSION

Over the years, digoxin has become the most important drug in the treatment of congestive heart failure. Many of the effects of digoxin on the heart result from glycoside-induced modification of both autonomic neural activity and the sensitivity of the heart to the vagal and sympathetic neurotransmitters[10]. The inotropic effects of digoxin are accompanied by a net loss of potasium and a net uptake of Na^+ leading to anet cellular uptake of Ca^{++}[9]. These effects of digoxin might be expected to modulate the severity of reperfusion induced arrhythmias.

In the present investigation, the high concentration of digoxin has increased the incidence and duration of reperfusion-induced ventricular fibrillation. This effect may be expected to be the result of the potassium loss produced by digoxin[9] especially when used at high concentrations. Potassium is known to reduce reperfusion-induced ventricular arrhythmias[11]. Digoxin via increasing loss of potassium from ischaemic myocardial cell may stimulate the automaticity of latent pacemakers[12].

Digoxin-induced potassium loss may also increase the steepness of the gradient of potassium from ischaemic to non-ischaemic zones[11 & 13] and thereby increases the reperfusion-induced dispersion of refractoriness between ischaemic and non-ischaemic zones[14 & 15] and nonhomogeneous recovery in conduction[16]. These effects were reported to be a possible cause of re-entry mechanisms which are documented to be one of the causes of reperfusion-induced arrhythmias[17].

The net uptake of Ca^{2+} induced by digoxin may contribute to the arrhythmogenic effect of digoxin as calcium overload was reported to initiate arrhythmias[18-20] and to occur during reperfusion[21].

It has been reported that local release of catecholamines plays an

important role in the generation of reperfusion arrhythmias[22] and the adrenergic effects are crucial in the chain of events leading to ventricular fibrillation[23]. On the other hand, many of the effects of digoxin are played on the electrical and modification of both autonomic neural activity and the sensitivity of the heart to the vegal and sympathetic neurotransmitters.

This may have partially attenuated the arrhythmogenic effects of the high concentration of digoxin and mask that of other concentrations used in the present investigation. This proposal is in agreement with previous studies which indicated that acute administration of therapeutic doses of digoxin reduces the sympathetic activity[10].

From the present investigation, it can be concluded that administration of high doses of digoxin may modulate the severity of reperfusion-induced arrhythmias. This effect may be mediated through the effect of digoxin on potassium and calcium ions

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تعديل فى شدة حدوث الخلل فى ضربات القلب المحدث نتيجة إعادة سريان المحلول الفسيولوجى إلى قلب الجرد المفصول بواسطة عقار الديجوكسين

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تم فى هذا البحث دراسة تأثيرات التركيزات المختلفة من الديجوكسين (٥ ط ١٠$^{-٨}$ - ٥ ط ١٠$^{-٦}$ مول) على عدد الانقباضات البطينية الغير كاملة النضج وكذلك معدل حدوث والزمن اللازم وطول مدة حدوث الخلل فى ضربات القلب الناتجة من إعادة سريان المحلول الفسيولوجى إلى قلب الجرذ المفصول .

لم يحدث الديجوكسين فى التركيزات الثلاثة المستخدمة فى هذا البحث أى تأثير على عدد الضربات البطينية غير كاملة النضج وكذلك على معدل حدوث ومدة زمن حدوث سرعة الضربات البطينية بينما أدى استعمال التركيز العالى من الديجوكسين (٥ ط ١٠$^{-٦}$ مول) إلى انخفاض ملحوظ فى الزمن اللازم لحدوث سرعة الضربات البطينية المحدثة بإعادة سريان المحلول الفسيولوجى إلى القلب . أدى هذا التركيز أيضاً إلى زيادة معدل حدوث وطول مدة حدوث الارتعاشات البطينية المحدثة بإعادة سريان المحلول الفسيولوجى إلى عضلة القلب .

تقترح هذه الدراسة أن إعطاء جرعات عالية من عقار الديجوكسين من الممكن أن يعدل فى شدة حدوث الخلل فى ضربات القلب الناتج من إعادة المحلول الفسيولوجى إلى عضلة القلب . هذا التأثير من الممكن أن يكون نتيجة لتأثير الديجوكسين على توزيع أيونات البوتاسيوم والكالسيوم .