

# Electrophysiological effects of labetalol on canine atrial, cardiac Purkinje fibres and ventricular muscle

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- 1 Using conventional microelectrode techniques for the intracellular recordings of the membrane potential, the effects of labetalol were studied on cardiac Purkinje, atrial and ventricular muscle fibres of the dog.
- 2 Labetalol (1–10  $\mu\text{M}$ ) reduced, in a concentration-dependent manner, the action potential amplitude (APA) and the maximum rate of rise of the action potential ( $V_{\text{max}}$ ) in Purkinje fibres.
- 3 The action potential duration (APD) was decreased in Purkinje fibres but significantly increased in ventricular fibres after small concentrations of labetalol (1–3  $\mu\text{M}$ ). The atrial fibres were not very sensitive to labetalol.
- 4 Depolarization of the cardiac Purkinje fibres by increasing the external potassium concentration (8–12 mM), potentiated the labetalol effects on APA and  $V_{\text{max}}$  but blocked its effects on the APD.
- 5 The effects of labetalol on  $V_{\text{max}}$  of Purkinje fibres were dependent on the frequency of stimulation.
- 6 The ratio of the effective refractory period to the APD was increased both in normally polarized and depolarized Purkinje fibres after treatment with labetalol (10  $\mu\text{M}$ ).
- 7 Labetalol (10  $\mu\text{M}$ ) shifted the membrane responsiveness curve of Purkinje fibres by about 10 mV in the hyperpolarizing direction.
- 8 The slow response obtained in K-depolarized, Ba-treated Purkinje fibres was not significantly affected by labetalol (10–100  $\mu\text{M}$ ).
- 9 It is suggested that labetalol can exert Class I and Class III antiarrhythmic actions in cardiac muscle of the dog *in vitro*.

## Introduction

There is an increasing amount of interest in the use of  $\beta$ -blocking drugs in the control and treatment of cardiac arrhythmias following myocardial infarction (Sleight, 1986). Although the mechanisms responsible for the antiarrhythmic action of this group of drugs are not completely understood, studies have indicated that direct membrane effects may also play a role in the termination of some arrhythmias (Seth, 1980; Daugherty *et al.*, 1986).

Labetalol is a combined  $\alpha$ - and  $\beta$ -adrenoceptor blocking drug having approximately 0.3 of the potency of propranolol ( $\beta$ -adrenoceptor blocker) and 0.2 of the potency of phentolamine ( $\alpha$ -adrenoceptor blocker) (Brittain & Levy, 1976). The association of  $\alpha$ - and  $\beta$ -antagonistic properties makes labetalol a useful drug for the clinical management of hypertension (Kanto, 1985). Moreover, its antiadrenergic profile indicates a potentially important antiarrhythmic

action, since it has been suggested that  $\beta$ -adrenoceptors are involved in the genesis of arrhythmias associated with coronary occlusion, while  $\alpha$ -adrenoceptors are associated with those arrhythmias appearing during reperfusion (Penkoske *et al.* 1978; Pogwizd *et al.* 1982; Manning & Hearse, 1984).

In the present investigation the electropharmacological effects of labetalol were studied on fibres of dog myocardium using normal and depolarized preparations. Previous investigations on rabbit cardiac muscle showed that labetalol has Class I antiarrhythmic activity, which is potentiated by hypoxia (Vaughan Williams *et al.*, 1982).

## Methods

Adult mongrel dogs (12–18 kg) were anaesthetized with sodium pentobarbitone (30 mg kg<sup>-1</sup>, i.v.). Their hearts were exposed through a lateral thoracotomy

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and rapidly removed. Various pieces of heart muscle (right ventricular papillary muscle) and false tendons were obtained and studied as described previously (Riccioppo Neto, 1983). In some experiments, strips of the right atrial appendage were also excised for study. The preparations were mounted in a Sylgard-lined bottom of a 10 ml chamber perfused with Tyrode solution aerated with 95% O<sub>2</sub> and 5% CO<sub>2</sub> (pH 7.4). The solution flowed at a rate of 6–7 ml min<sup>-1</sup> and was kept at a temperature of 36 ± 0.5°C.

The Tyrode solution had the following composition (mM): NaCl 137, CaCl<sub>2</sub> 1.8, KCl 4, MgCl<sub>2</sub> 0.45, NaHCO<sub>3</sub> 12, NaH<sub>2</sub>PO<sub>4</sub> 0.32 and glucose 5.5. In order to obtain the slow response an equimolar concentration of NaCl was substituted by KCl (20 mM), BaCl<sub>2</sub> (1.0 mM) was added to the Tyrode solution and the preparations were driven at a rate of 0.8 Hz.

Transmembrane potentials were recorded by use of conventional glass microelectrodes filled with 3 M KCl (tip resistance of 20–40 MΩ) and displayed, via an input capacity neutralization preamplifier, on an oscilloscope (Tektronix 5112). The maximum rate of rise of the action potential was determined electronically using an OP-AMP (Analog 118 A). Oscilloscope traces were photographed on 35 mm film with a camera (Nihon-Konden PC-32).

Square wave pulses were obtained either from a Grass stimulator (S4-SIU4) or from a specially built stimulator so that an extra-stimulus (S<sub>2</sub>) could be delivered, with variable delay and amplitude, after the eight basis pulse (S<sub>1</sub>). S<sub>1</sub> pulses (1.5 × threshold, 1 ms duration) and S<sub>2</sub> pulses (3 × threshold, 1 ms duration)

were delivered to the preparation using the same pair of Teflon coated silver wire electrodes. For studies of membrane refractoriness two recording microelectrodes were used. The effective refractory period (ERP) was measured as the shortest interval between S<sub>1</sub> and S<sub>2</sub> pulses needed to produce an extrasystole that propagated to the distal microelectrode (Hoffman *et al.*, 1957). The normal frequency of stimulation was 1.5 Hz.

Action potential characteristics were analysed by hand after enlargement of the film (7 ×) and the following parameters were measured: maximum diastolic potential (MDP), action potential amplitude (APA), maximum rate of rise of action potential ( $V_{max}$ ), duration of the action potential from its peak to 50% (APD<sub>50</sub>) and 90% (APD<sub>90</sub>) repolarization. Frequency-dependent blockade of  $V_{max}$  was studied in Purkinje fibres showing no automaticity. The driving frequency was reduced from 1.5 to 0.3 Hz for 1 min and then abruptly increased to 3 Hz until  $V_{max}$  attained a new steady-state amplitude.

Data are shown as mean values ± s.e.mean. Comparisons between two means were made by Student's paired *t* test. Analysis of variance (F-test) was applied to compare simultaneously more than two means. The minimum significant difference was calculated by test of Tukey and *P* values less than 0.05 were considered to indicate significant differences.

Labetalol hydrochloride (Sigma) was directly dissolved in Tyrode solution. Unless otherwise stated, the results describe effects of drug applied at cumulative concentrations during a single stable impalement.

**Table 1** Dose-related effects of labetalol on the action potentials of normally polarized dog myocardium

	Labetalol (μM)					
	0	1	3	10	30	100
<i>Purkinje fibres</i>						
APA (mV)	130 ± 1	129 ± 1	128 ± 1	123 ± 2 <sup>‡</sup>	114 ± 2*	93 ± 4*
MDP (mV)	93 ± 1	94 ± 1	93 ± 1	93 ± 1	91 ± 2	88 ± 1*
$V_{max}$ (Vs <sup>-1</sup> )	759 ± 19	756 ± 14	745 ± 15	710 ± 19 <sup>‡</sup>	630 ± 18*	403 ± 37*
APD <sub>50</sub> (ms)	237 ± 15	222 ± 14	206 ± 8*	158 ± 8*	117 ± 16*	114 ± 16*
APD <sub>90</sub> (ms)	301 ± 16	289 ± 16 <sup>‡</sup>	280 ± 14*	265 ± 10*	239 ± 10*	250 ± 8*
<i>Ventricular muscle</i>						
APA (mV)	109 ± 1	106 ± 2	105 ± 1	104 ± 2	101 ± 2*	101 ± 2*
MDP (mV)	85 ± 1	83 ± 1	84 ± 1	84 ± 1	86 ± 1	87 ± 1
$V_{max}$ (Vs <sup>-1</sup> )	435 ± 19	456 ± 20	420 ± 16	367 ± 21*	308 ± 18*	276 ± 18*
APD <sub>50</sub> (ms)	128 ± 5	141 ± 4*	149 ± 3*	175 ± 4*	176 ± 4*	184 ± 5*
APD <sub>90</sub> (ms)	171 ± 4	187 ± 4*	198 ± 3*	221 ± 6*	227 ± 4*	239 ± 6*
<i>Atrial muscle</i>						
APA (mV)	105 ± 1	108 ± 2	108 ± 2	106 ± 2	101 ± 3*	85 ± 4*
MDP (mV)	85 ± 1	86 ± 1	86 ± 1	85 ± 1	85 ± 1	80 ± 3 <sup>‡</sup>
$V_{max}$ (Vs <sup>-1</sup> )	524 ± 21	516 ± 14	499 ± 22	472 ± 26*	411 ± 37*	315 ± 24*
APD <sub>50</sub> (ms)	70 ± 4	79 ± 5	72 ± 4	78 ± 4	75 ± 4	84 ± 6
APD <sub>90</sub> (ms)	148 ± 5	150 ± 4	148 ± 3	158 ± 4	171 ± 5*	189 ± 4*

The data are presented as mean ± s.e.mean of six preparations.

<sup>‡</sup> *P* < 0.05; \* *P* < 0.01.

## Results

### Effects on transmembrane action potentials of Purkinje, atrial and ventricular muscle fibres

Labetalol at low concentrations (1–3  $\mu\text{M}$ ) affected the action potential duration of Purkinje and ventricular fibres in opposite directions. Whereas the repolarization phase of the action potential was accelerated in Purkinje, it was delayed in ventricular fibres (Table 1). Higher concentrations (10–100  $\mu\text{M}$ ) further accentuated these effects and also decreased  $V_{\text{max}}$  and APA with a minor reduction in the MDP. Fibres from atrial muscle were less sensitive to labetalol and showed only some depression of  $V_{\text{max}}$  and APA at higher concentrations (Table 1).

These effects stabilized at 30–40 min after the beginning of the perfusion with labetalol and were not completely reversed upon washing for about 90 min.

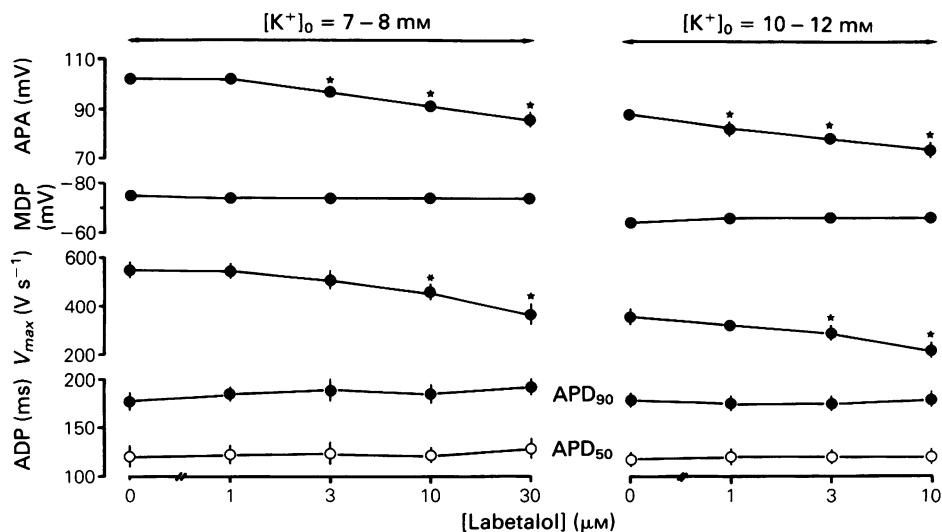
### Effects of depolarized Purkinje fibres

Steady depolarization of Purkinje fibres was achieved by the hypertonic addition of KCl to the Tyrode solution. Maximum diastolic potentials of –74 to –78 mV and of –66 to –70 mV were measured in final KCl concentrations of 7–8 mM and 10–12 mM, respectively. The effects of labetalol on APA and  $V_{\text{max}}$  were increased in depolarized preparations in comparison with preparations normally polarized (Figures 1

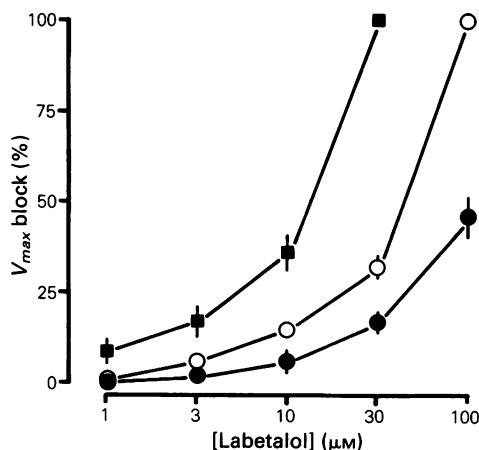
and 2). Calculations showed that the concentration of labetalol needed to induce a 25% reduction of  $V_{\text{max}}$  ( $\text{EC}_{25}$ ) decreased from 50  $\mu\text{M}$  in  $[\text{K}^+]_o = 4 \text{ mM}$  ( $n = 6$ ) to 23  $\mu\text{M}$  in  $[\text{K}^+]_o = 7\text{--}8 \text{ mM}$  ( $n = 5$ ) to 5  $\mu\text{M}$  in  $[\text{K}^+]_o = 12 \text{ mM}$ , ( $n = 5$ ). Preparations with MDP around –70 mV became completely inexcitable in labetalol 30  $\mu\text{M}$ . It is also interesting to note that the effects of labetalol on APD were blocked in depolarized preparations (Figure 1).

### Frequency-dependent blockade of $V_{\text{max}}$

The influence of the stimulation frequency on the depressant effects of labetalol on  $V_{\text{max}}$  was investigated in normal and depolarized Purkinje fibres. In untreated preparations there was no significant effect on  $V_{\text{max}}$  when the stimulation frequency was abruptly changed from 0.3 to 3 Hz, neither in control or in depolarized Purkinje fibres. For the three different extracellular concentrations of potassium, the values of  $\Delta V_{\text{max}}$  were calculated according to the formula:  $\Delta V_{\text{max}} = 1 - [(V_{\text{max}} \text{ at } 3 \text{ Hz}) / (V_{\text{max}} \text{ at } 0.3 \text{ Hz})]$  and plotted in Figure 3. In the presence of labetalol,  $\Delta V_{\text{max}}$  increased, in a concentration-dependent manner, as the frequency increased in both normally polarized and depolarized fibres. At a frequency of stimulation equal to 3 Hz, the  $\text{EC}_{25}$  for the increase of  $\Delta V_{\text{max}}$  decreased from 40  $\mu\text{M}$  in  $[\text{K}^+]_o = 4 \text{ mM}$ , to 14  $\mu\text{M}$  in  $[\text{K}^+]_o = 7\text{--}8 \text{ mM}$  and to 4  $\mu\text{M}$  in  $[\text{K}^+]_o = 10\text{--}12 \text{ mM}$ .



**Figure 1** Changes induced by increasing concentrations of labetalol on the membrane potential parameters of Purkinje fibres with different external potassium concentrations  $[\text{K}^+]_o$ . Each point corresponds to the mean of five preparations; vertical lines indicate s.e.mean. APA: action potential amplitude; MDP: maximum diastolic potential;  $V_{\text{max}}$ : maximum rate of rise of the action potential; APD<sub>50</sub> and APD<sub>90</sub>: action potential duration at 50% and 90% repolarization, respectively. In  $[\text{K}^+]_o$  of 10–12 mM labetalol 30  $\mu\text{M}$  blocked propagation completely. \* $P < 0.01$ .



**Figure 2** Decrease in the maximum rate of rise (expressed as %) of the action potential ( $V_{max}$ ) produced by labetalol in (●) normally polarized ( $[K^+]_o = 4$  mM) and (○, ■) depolarized ( $[K^+]_o = 7-8$  (○) and  $10-12$  (■) mM) cardiac Purkinje fibres at a constant rate of stimulation (1.5 Hz). Each point corresponds to the mean of five preparations; vertical lines indicate s.e.mean. Data from Figure 1 and Table 1.

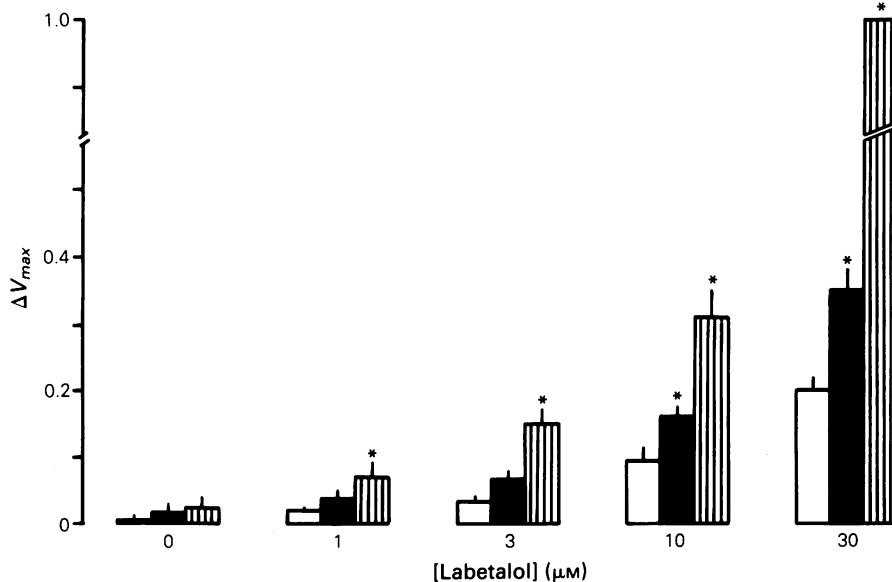
#### Effects on membrane responsiveness and refractoriness

Labetalol (10 μM) shifted the membrane responsiveness curve to more negative potentials by  $10 \pm 12$  mV ( $n = 4$ ; Figure 4).

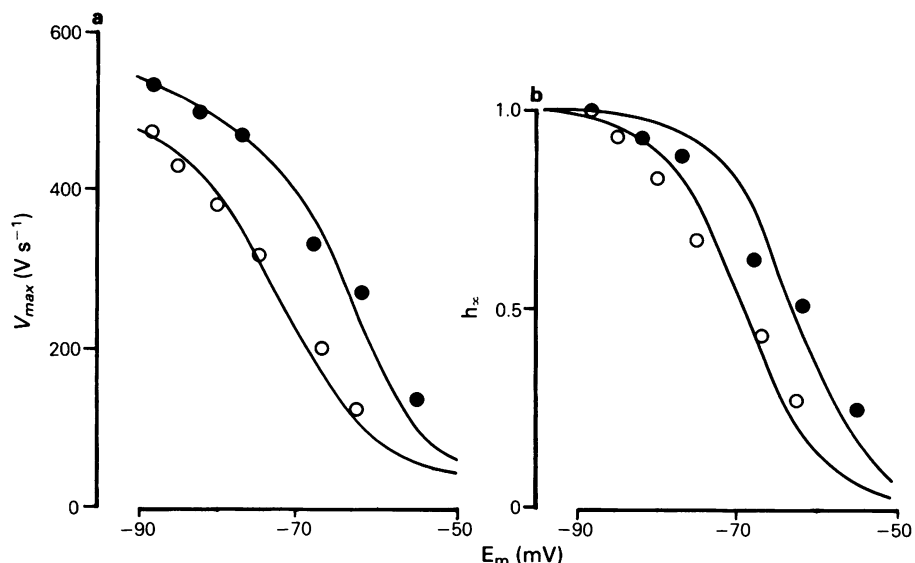
The effects on membrane refractoriness were studied in normally polarized ( $[K^+]_o = 4$  mM) and depolarized ( $[K^+]_o = 10$  mM) Purkinje fibres. Labetalol (10 μM) increased significantly the ratio ERP/APD from  $0.88 \pm 0.33$  (control conditions) to  $0.99 \pm 0.01$  ( $P < 0.01$ ;  $n = 8$ ) in normally polarized preparations and from  $1.11 \pm 0.01$  to  $1.20 \pm 0.03$  ( $P < 0.01$ ;  $n = 9$ ) in depolarized fibres.

#### Effects on the slow response

Labetalol in concentrations up to 100 μM, with the exception of some increase in the latency of response at high concentrations, did not significantly affect the slow response in the four preparations studied.



**Figure 3** Relative decrease in the maximum rate of rise of the action potential ( $\Delta V_{max}$ ) induced by labetalol in cardiac Purkinje fibres, after a sudden increase in the frequency of stimulation (0.3 to 3 Hz). Labetalol was added to Tyrode solutions containing different extracellular potassium concentrations  $[K^+]_o = 4$  mM (open columns,  $n = 6$ ),  $[K^+]_o = 7-8$  mM (solid columns,  $n = 5$ ) and  $[K^+]_o = 10-12$  mM (hatched columns,  $n = 5$ ). Each column represents the mean of  $n$  preparations; vertical lines indicate s.e.mean. \* $P < 0.05$ .



**Figure 4** (a) Membrane responsiveness curves (drawn by eye) of a dog cardiac Purkinje fibre before (●) and after (○) labetalol 10  $\mu$ M. (b) ' $h_{\infty}$  curves' calculated, from the data shown in (a), by the formula  $h_{\infty} = 1.1 + \exp [(E_m - E_h)/5]$ , where  $E_m$  is the membrane potential and  $E_h$  the value of  $E_m$  at which  $h_{\infty}$  is 0.5 (Weidmann, 1955).

## Discussion

It is generally accepted that the main antiarrhythmic action of  $\beta$ -blockers is exerted through a competitive occupation of the adrenoceptors in the heart (see Vaughan Williams, 1981; Pratt & Lichstein, 1982 for reviews). Despite some exceptions, in those  $\beta$ -blockers that have direct membrane-depressant effects, such as propranolol, an additional mechanism, found in Class I agents, would probably be present (Lucchesi & Patterson, 1984; Daugherty *et al.*, 1986).

Labetalol, a combined  $\alpha$ - and  $\beta$ -adrenoceptor blocking agent possessing local anaesthetic activity twice that of procaine (Vaughan Williams *et al.*, 1982), exhibited many electropharmacological properties when applied to dog cardiac fibres *in vitro*. In normally polarized Purkinje and ventricular fibres, the effects produced by small concentrations (1–3  $\mu$ M) were restricted to alterations of the action potential duration. Depression of  $V_{max}$  and/or APA were, however, found in depolarized Purkinje fibres treated with labetalol (1–3  $\mu$ M).

Similar depressant effects upon  $V_{max}$  and APA were described after application of labetalol (3–6  $\mu$ M) in rabbit muscle (Vaughan Williams *et al.*, 1982), these effects being increased by hypoxia. The present results are in agreement with the Class I actions described for labetalol by Vaughan Williams *et al.* (1982). This class of antiarrhythmic agent usually depresses  $V_{max}$  of the action potential upstroke (related to the fast inward

sodium current) in a manner modulated by the level of membrane potential and the rate of stimulation (Johnson & McKinnon, 1957; Chen & Gettes, 1976). The combination of these two factors is explained by the 'modulated receptor' (Hille, 1977; Hondeghem & Katzung, 1977; 1984) and the 'guarded receptor' (Grant *et al.*, 1984) hypotheses. Although not marked, labetalol showed a higher affinity for activated than inactivated channel states, since its inhibitory effects on  $V_{max}$  of Purkinje fibres were dependent on the frequency of stimulation and on the membrane potential. This was also confirmed by the finding that labetalol induced a shift of the membrane responsiveness curve. Accordingly, labetalol also increased significantly the ratio between the effective refractory period and the action potential duration in Purkinje fibres.

The present experiments showed that dog atrial muscle is less sensitive than ventricular fibres to labetalol and that this agent accelerates repolarization in Purkinje, but increases APD of ventricular fibres. A similar prolongation of the APD was recently found for labetalol and amosulalol (a new  $\alpha$ - and  $\beta$ -adrenoceptor blocking agent) (Tohse *et al.*, 1986), in rabbit papillary muscle. In contrast to what was found in the dog, the APD of rabbit cardiac Purkinje fibres is greatly increased by labetalol (Dukes & Vaughan Williams, 1984; Vaughan Williams *et al.*, 1982),

phenomena that must be related to species differences.

Labetalol, even at high concentrations, did not reduce the slow response obtained in Purkinje fibres. This possible lack of influence on the slow inward current would explain the observation that labetalol had no effect on the contraction of rabbit papillary or atrial muscle (Vaughan Williams *et al.*, 1982). The increase in the rate of repolarization caused by labetalol in Purkinje fibres cannot, therefore, be attributed to an effect on the slow current. A labetalol-induced increase in outward current during phase 3 of the action potential would cause a reduction in the APD. The blockade of this effect in preparations depolarized by high potassium and treated by labetalol (Figure 1) would argue in favour of this hypothesis. On the other hand, a decrease in the non-inactivating, plateau sodium current ('window current', Attwell *et al.*, 1979) could also occur after labetalol and accelerate repolarization. It has been suggested that tetrodotoxin (Coraboeuf *et al.*, 1979; Attwell *et al.*, 1979) and lidocaine (Carmeliet & Saikawa, 1982; Colatsky, 1982) at concentrations not affecting  $V_{max}$ , shorten the APD of Purkinje fibres by blocking window sodium currents. Any of these possibilities, or a combination of several, cannot be

excluded by the present experiments. On the other hand, the increase in APD observed in ventricular muscle fibres treated with labetalol might be explained by a drug-induced decrease in the potassium conductance during phase 3 of the action potential, an effect shared by sotalol, another  $\beta$ -blocker showing Class III antiarrhythmic activity (Carmeliet, 1985).

There is experimental evidence indicating that labetalol, due to its combination of  $\alpha$ - and  $\beta$ -adrenoceptor blocking properties, is effective in arrhythmias originating during both myocardial ischaemia and reperfusion (Pogwizd *et al.*, 1982). Given its characteristics of high liposolubility and low plasma protein binding (Kanto, 1985), the lower concentrations of labetalol used in the present study (1–5  $\mu$ M) might have clinical significance (see also Vaughan Williams *et al.*, 1982). Therefore, additional Class I and III antiarrhythmic actions would certainly increase the clinical usefulness of this drug.

We thank Ms Fátima Helena Ferreira for typing the manuscript. This investigation was supported in part by a grant from the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP 86/1395-0.

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(Received May 8, 1987.

Revised July 9, 1987.

Accepted July 16, 1987.)