Antiarrhythmic efficacy of labetalol as assessed by programmed electrical stimulation

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1 The purpose of the present study was to investigate the haemodynamic, electrophysiological and antiarrhythmic effects of labetalol in the late reperfusion phase after myocardial infarction in conscious dogs.

2 Labetalol was administered in cumulative doses (0.5, 1 and 3 mg kg⁻¹ 90 min⁻¹, i.v.). Compared to control the systolic blood pressure was significantly decreased 20 min after 0.5, 1 and 3 mg kg⁻¹ and up to 30 min after 3 mg kg⁻¹ labetalol. The diastolic blood pressure was significantly decreased 20 and 30 min after 0.5 and 3 mg kg⁻¹ but was not significantly altered after 1 mg kg⁻¹ labetalol.

3 Labetalol significantly increased the PQ, QRS, QT and QTc intervals, the 2:1 AV-conduction point, the ventricular effective refractory periods and the intraventricular conduction time from the apex of the right ventricle to the infarcted LAD-area. With the exception of the alterations in the PQ interval and 2:1 AV-conduction point the effects described above were dose-dependent.

4 Labetalol was active against arrhythmias induced by programmed electrical stimulation. This effect was already present after the lowest dose (0.5 mg kg⁻¹).

5 The good antiarrhythmic activity of labetalol in this study can be explained by the adrenoceptor blocking properties and both the class I and III activity of this drug. Labetalol may be of potential benefit in controlling arrhythmias arising following myocardial infarction.

Introduction

Labetalol was first described in 1972 as an α - and β -adrenoceptor blocking agent (Farmer *et al.*, 1972). It contains two optical centres and is thus composed of 4 optical isomers each exhibiting different affinity for α - and β -adrenoceptors (Brittain *et al.*, 1982). Selective α_1 -adrenoceptor blocking qualities (Jarrot *et al.*, 1982), intrinsic β -adrenoceptor activity (Tadepalli & Novak, 1986) which is possibly selective for the β_2 -subtype (Baum & Sybertz, 1983) and direct vasodilator effects (Dage & Hsieh, 1980) have been ascribed to labetalol.

Clinically labetalol is used in patients suffering from hypertension (Kanto, 1985), coronary artery disease (Kanto, 1987; Nelson *et al.*, 1982) and phaeochromocytoma (Kanto, 1985).

Experimentally, labetalol has been shown to have local anaesthetic properties (Vaughan Williams *et al.*, 1982) with class I and III antiarrhythmic activity (Vaughan Williams, 1970) in rabbit isolated Purkinje fibres (Vaughan Williams *et al.*, 1982) and dog ventricular muscle cells (Mill & Neto, 1987). Furthermore the drug exhibited activity against electrically-induced ventricular fibrillation in anaesthetized dogs (Anderson *et al.*, 1983), ouabain- and noradrenaline-induced arrhythmias in anaesthetized dogs (Farmer *et al.*, 1972) and coronary occlusion- and reperfusion-induced arrhythmias in anaesthetized cats (Pogwizd *et al.*, 1982). However, no evaluation has so far been carried out in the conscious animal with respect to the efficacy of labetalol in counteracting arrhythmias induced by programmed electrical stimulation after myocardial infarction.

We have recently proposed a clinically relevant model to investigate experimentally-induced arrhythmias in the conscious dog (Krumpl *et al.*, 1989a,b,c). Within the framework of this approach programmed electrical stimulation (PES) is used to study arrhythmias in the late myocardial infarction period of dogs which had previously been subjected to a 4 h coronary occlusion-reperfusion procedure in the conscious state. In this model, lignocaine was shown to have a good,

although strongly dose-dependent activity against PES-induced arrhythmias (Krumpl *et al.*, 1989d; Todt *et al.*, 1989a). The purpose of this study was to evaluate the antiarrhythmic efficacy of labetalol in a similar experimental set up. Some of the results have been presented at the 10th meeting of the International Society for Heart Research (Krumpl *et al.*, 1989e).

Methods

The animals used in this study were handled in accordance with the animal welfare regulations of the University of Vienna. The method and the experimental protocol were approved by the Animal Subjects Committee of the University of Vienna and by the Austrian Ministry of Science.

A detailed description of the instrumentation procedure is given in Krumpl *et al.* (1989a). For the chronic instrumentation the animals were fasted overnight with free access to water. Morphine (1 mg kg⁻¹, s.c.) was given as premedication 1 h before the induction of anaesthesia with pentobarbitone (30 mg kg⁻¹, i.v.). After endotracheal intubation with a cuffed Magill tube, the animals were ventilated with a N₂O/O₂ mixture (2:1) in a rebreathing system using an Engstroem respirator. A sterile thoracotomy was performed in 7 trained mongrel dogs of either sex (weight 19–32 kg). A hydraulic occluder was placed around the descending branch of the left coronary artery (LAD) distal to the first diagonal branch. Two pairs of piezoelectric crystals (Triton Technology Inc., California, U.S.A.) were implanted subendocardially in the perfusion areas of the LAD and the circumflex branch of the left coronary artery (LCX). The crystals served for measurement of regional endocardial shortening (Brugge-Asperheim *et al.*, 1969; Gilly *et al.*, 1983; Krumpl *et al.*, 1986a,b; Raberger *et al.*, 1986), as ECG leads for determination of the respective regional refractory periods of the LAD- and LCX area (Krumpl *et al.*, 1989c) and, furthermore, for the induction of arrhythmias by the extrastimulus technique (Krumpl *et al.*,

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1989c). Pairs of stainless steel electrodes (Ing. Osypka Inc., Grenzach Whylen, F.R.G.) were sewn on to the left and right atrial appendage and the anterior wall of the right ventricle. A catheter (Tygon) was advanced into the descending aorta via the left carotid artery and served for measurement of arterial blood pressure. Another catheter was advanced from the left jugular vein into the right atrium and served for drug infusion and for withdrawal of blood samples. All catheters and wires were exteriorized between the scapulae. A pair of stainless steel electrodes was implanted subcutaneously after closure of the thorax. The instrumentation procedure took about 3 to 4 h. To provide long-lasting analgesia buprenorphine was given postoperatively. Antibiotics (procaine-penicillin, streptomycin) were administered for 4 days. The dogs recovered completely within a couple of days, but the investigations were started 1 week after surgery.

ECG signals from subcutis, right and left atrium, right ventricle, anterior and posterior left ventricular wall (or the contractile function of the anterior and posterior left ventricular wall) and the arterial blood pressure signal were recorded by a 14 channel video-data tape (TEAC, Japan) and continuously monitored on an 8-channel oscilloscope (Knott Electronic, F.R.G.) with Gould amplifiers. Later on the signals were replayed on to a Gould TA 2000 thermal paper recorder (filter setting: 50 Hz low pass) and the ECG parameters were measured at a paper speed of 100 mm s^{-1} . The R-R interval was expressed as the mean value of 4 consecutive R-R intervals. The QT interval was corrected for heart rate according to the following formula: $QT_c(\text{ms}) = QT \text{ in ms divided by } \sqrt{RR \text{ in s}}$ (Bazett, 1920). Results are expressed as mean values $\pm$ s.e.mean unless otherwise stated. Student's *t* test for paired data was used for statistical evaluation.

Experimental protocol

Details concerning the coronary artery occlusion (CAO) and reperfusion procedure were given in Krüml *et al.* (1989a,b). In brief, LAD occlusion lasting 4 h and subsequent reperfusion was performed in the same conscious, chronically instrumented dogs one week after the instrumentation procedure.

The method of programmed electrical stimulation (Wellens *et al.*, 1972; Ehrreich, 1986) was used to study the effects of labetalol against electrically-induced arrhythmias in the late reperfusion phase after myocardial infarction. The experiments were undertaken on one day in the period between days 6 and 12 of the late reperfusion phase after CAO when spontaneous arrhythmic activity had subsided (Krüml *et al.*, 1989b,c). Control experiments carried out with saline administration on days before and after the study with labetalol exhibited an induced arrhythmia to be reproducible another 3 times with a time schedule which was identical to that described below.

Labetalol was administered intravenously at intervals of 90 min; cumulative doses of 0.5, 1 and 3 mg kg^{-1} , respectively were used. The time course of this study is shown in Figure 1.

There was a 30 min period between each dose and the start of the stimulation procedure (PES = programmed electrical stimulation). According to the described protocol (for a detailed description see below) the determination of the refractory periods and, immediately thereafter, the attempts to induce ventricular arrhythmias (Figure 1: induction of arrhythmia, see legend) were carried out during a drug-free control phase (min -60 to 0: PES 1) and 30 min after the administration of the respective dosage of labetalol: min 30 to 90: PES 2: 0.5 mg kg^{-1} , min 120 to 180: PES 3: 1 mg kg^{-1} , min 210 to 270: PES 4: 3 mg kg^{-1} .

Stimulation protocol

The protocol used for the PES experiments was as follows: Pacing was performed by use of a Medtronic programmable

Figure 1 Time protocol of a single experiment. PES = programmed electrical stimulation; (■) arrhythmia induction.

constant-current stimulator (SP 0503 MK IV) with rectangular impulses of 2 ms duration at twice diastolic threshold.

The effective atrial refractory period (Table 2, ERP-A₃₀₀) was determined by premature stimulation with a single extra-stimulus after 8 paced beats at a basic cycle length of 300 ms delivered to the right atrium.

The 2:1 AV-conduction point (Table 2, 2:1) was defined as the maximal cycle length leading to a stable 2:1 atrioventricular conduction pattern following continuous atrial stimulation of 30 s duration.

The respective effective ventricular refractory period (Table 2, ERP-LCX, -LAD, -RV) was determined by premature stimulation with a single extra-stimulus after 8 paced beats first at a basic cycle length of 330 ms and then at 250 ms.

Intraventricular conduction was assessed during right ventricular stimulation at a cycle length of 250 ms. Conduction time was measured from the stimulus artefact to the maximum negative dV/dt in the LAD lead.

After the individual refractory periods had been determined induction of ventricular arrhythmias was attempted by ventricular stimulation at a basic cycle length (BCL) of 330 ms with single, double and triple extrastimuli delivered after 8 paced beats. If unsuccessful the procedure was repeated at 250 ms BCL.

Induction of tachycardia was first attempted by stimulation via the right ventricular electrodes then by stimulating the LCX area and finally the infarcted area (LAD). If, in response to control stimulation (PES 1) the arrhythmia was inducible from one site, no further induction-attempt was performed from the other locations. All subsequent induction-trials during drug testing remained confined to this area. The endpoint of a stimulation-cycle was the induction of sustained ventricular tachycardia (SVT) or ventricular fibrillation (VFIB) or completion of the full pacing protocol.

Classification of PES-induced arrhythmias

Non-inducible (NI) was defined as any self terminating response of less than 6 non-driven beats. *Non-sustained ventricular tachycardia* (NSVT) was defined as any self terminating response of at least 6 or more non-driven beats lasting less than 15 s. *Sustained ventricular tachycardia* (SVT) was defined as a stable arrhythmia with uniform QRS complexes lasting longer than 15 s. Termination of tachycardia was achieved by overdrive stimulation or d.c. cardioversion. When, in the case of haemodynamic collapse, earlier termination was necessary, a stable ventricular tachycardia of less than 15 s duration was also considered sustained. *Ventricular fibrillation* (VFIB) was defined as a fast, pleomorphic tachycardia which lasted longer than 15 s and had to be treated by defibrillation. Antiarrhythmic efficacy was defined as conversion of the respective control tachycardia (SVT or VFIB) into NSVT or NI.

Determinations of plasma concentrations of labetalol

Blood was sampled and centrifuged 30, 60 and 90 min after the administration of the respective labetalol doses; $20\text{ }\mu\text{l}$ of a

10% EDTA in distilled water solution was used as anticoagulant. Plasma was then frozen until determination by high performance liquid chromatography. Fifty μl of a 2 M ammonium sulphate-buffer (pH = 9.0) and 1500 μl chloroform were added to 100 μl plasma in an Eppendorf 2 ml micro test tube. The mixture was shaken for 10 min and then centrifuged. A 1000 μl aliquot of the organic phase was transferred to a second tube and taken to dryness at 45°C. The residue was then redissolved in 300 μl mobile phase and 100 μl of this solution was injected into the chromatograph. The chemicals used were of analytical grade and obtained from Loba Feinchemie (Austria). The apparatus used included a Beckman programmable solvent module 116, a Kontron MSI T-660 sampler equipped with a 100 μl loop, a Nucleosil C8 5 μm 50 $\times$ 4 mm precolumn and an analytical Supelco LC C8 DB 5 μm 50 $\times$ 4.6 mm column and a Beckman programmable detector 166 operated at 207 nm. Chromatograms were registered on a Shimadzu C-R5A Chromatopac recorder. The mobile phase was a 25% acetonitrile in 50 mM sodium phosphate-buffer (pH = 3.0). Standards were prepared of Trandate 100 mg i.v. injection solution (Glaxo, GB) containing 5 mg ml⁻¹ labetalol hydrochloride. Linear calibration curves with labetalol concentrations in the range 0.2–8.0 $\mu\text{g ml}^{-1}$ plasma were obtained by addition of 20 μl standard solution to 1 ml blank dog-plasma.

Results

Haemodynamic and ECG parameters

Haemodynamic and ECG parameters at control and the labetalol-induced changes 20 min after bolus administration (the time when maximal changes were registered) and 30 min after bolus administration (the time when PES was started) are given in Table 1.

The time course of the drug-induced changes reveals a fall in systolic and diastolic blood pressure values after 0.5 mg kg⁻¹ labetalol, no further change after the consecutive intermediate dose (1 mg kg⁻¹) and a further fall after the final 3 mg kg⁻¹ dose. Compared to control the systolic blood pressure was significantly decreased 20 min after 0.5, 1 and 3 mg kg⁻¹ and up to 30 min after 3 mg kg⁻¹ labetalol. The diastolic blood pressure was significantly decreased 20 and 30 min after 0.5 and 3 mg kg⁻¹ labetalol but insignificantly altered after 1 mg kg⁻¹.

The drug did not influence the heart rate (R-R interval) in any dose studied. Labetalol increased the PQ, QRS, QT and QTc intervals whereby QRS, QT and QTc were altered in a dose-dependent fashion. With the exception of the influence on the QRS complex these changes were significant even after the lowest dose and persisted for the entire observation period (i.e. up to 30 min) after bolus administration. A significant increase in the duration of the QRS complex was only registered after the highest dose (3 mg kg⁻¹) of labetalol.

Electrophysiological parameters

The electrophysiological parameters as assessed by programmed electrical stimulation are given in Table 2. Labetalol did not change the atrial stimulation threshold and the atrial refractory period. The 2:1 AV-conduction point was significantly increased. In the presence of unchanged ventricular stimulation thresholds a marked, significant and dose-dependent increase in the effective ventricular refractory periods of the left and right ventricle at either 330 or 250 ms basic stimulation rate was found. A dose-dependent and significant increase of the intraventricular conduction time was registered.

Antiarrhythmic effects

A comparison between the type of arrhythmia induced during control and after labetalol (antiarrhythmic efficacy) is given in Figure 2. Ventricular fibrillation (VFIB) could be induced in 2 dogs and sustained ventricular tachycardia (SVT) could be induced in 5 dogs in response to control stimulation (PES 1). Labetalol prevented the induction of the control arrhythmia in 71% of all induction attempts ($n = 21$). The highest degree of efficacy was registered with 1 mg kg⁻¹ following 0.5 mg kg⁻¹ when non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia or ventricular fibrillation were non-inducible (NI) in 5 of 7 animals by PES. Two animals did not respond to any of the doses studied. The labetalol-induced haemodynamic and electrophysiological effects in these 2 dogs were comparable to those observed in the 5 responding dogs.

After intravenous administration of labetalol, 0.5, 1 and 3 mg kg⁻¹ in cumulative doses, the plasma levels (Figure 3) during the PES-procedures were in the range of 0.25 (PES 2), 0.9 (PES 3) and 3 $\mu\text{g ml}^{-1}$ (PES 4), respectively. The plasma concentrations did not change significantly during the time

Table 1 Haemodynamic and ECG-data before and after labetalol

	Control	Labetalol (0.5 mg kg ⁻¹)		Labetalol (1 mg kg ⁻¹)		Labetalol (3 mg kg ⁻¹)	
		20 min	30 min	20 min	30 min	20 min	30 min
SAP kPa	17.5 $\pm$ 0.6	15.6 $\pm$ 0.5*	15.9 $\pm$ 0.5	15.7 $\pm$ 0.4**	15.5 $\pm$ 0.5	14.0 $\pm$ 0.4**	14.4 $\pm$ 0.5**
DAP kPa	12.3 $\pm$ 0.5	10.5 $\pm$ 0.6*	10.7 $\pm$ 0.5*	11.0 $\pm$ 0.5	10.9 $\pm$ 0.4	9.6 $\pm$ 0.6*	9.9 $\pm$ 0.6*
RR ms	553 $\pm$ 45	528 $\pm$ 20	549 $\pm$ 29	541 $\pm$ 29	522 $\pm$ 23	539 $\pm$ 26	525 $\pm$ 18
PQ ms	96 $\pm$ 3	104 $\pm$ 4*	103 $\pm$ 4*	104 $\pm$ 4*	104 $\pm$ 4*	106 $\pm$ 5*	105 $\pm$ 5*
QRS ms	55 $\pm$ 2	55 $\pm$ 2	55 $\pm$ 2	55 $\pm$ 2	56 $\pm$ 2	58 $\pm$ 2*	58 $\pm$ 2*
QT ms	188 $\pm$ 7	197 $\pm$ 4*	199 $\pm$ 3*	206 $\pm$ 5*	205 $\pm$ 5*	211 $\pm$ 6**	210 $\pm$ 5**
QTc ms	254 $\pm$ 8	272 $\pm$ 6**	271 $\pm$ 9**	282 $\pm$ 11**	285 $\pm$ 10**	288 $\pm$ 7**	290 $\pm$ 7**

Values are mean $\pm$ s.e.mean ($n = 7$); 20 min: maximal changes, 30 min: start of programmed electrical stimulation. The Student's *t* test for paired data; significance symbols (values after labetalol compared to control): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Conversion factor 1 kPa = 7.5 mmHg. Formula for QTc: see text.

Table 2 Electrophysiological parameters before and after labetalol

	Control	Labetalol (0.5 mg kg ⁻¹)	Labetalol (1 mg kg ⁻¹)	Labetalol (3 mg kg ⁻¹)
Th-A mA	2.4 ± 0.6	2.2 ± 0.6	2.1 ± 0.5	2.0 ± 0.5
ERP-A ₃₀₀ ms	125 ± 10	120 ± 6	124 ± 7	120 ± 5
2:1 ms	147 ± 7	167 ± 5*	171 ± 5*	173 ± 7*
Th-LAD mA	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	1.1 ± 0.5
ERP-LAD ₃₃₀ ms	122 ± 3	131 ± 4*	133 ± 4*	139 ± 4**
ERP-LAD ₂₅₀ ms	120 ± 2	126 ± 8*	129 ± 4*	134 ± 4**
Th-LCX mA	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
ERP-LCX ₃₃₀ ms	116 ± 4	127 ± 9***	129 ± 9***	133 ± 7***
ERP-LCX ₂₅₀ ms	112 ± 5	123 ± 5***	125 ± 4***	129 ± 3***
Th-RV mA	3.7 ± 0.7	3.8 ± 0.7	3.8 ± 0.7	3.7 ± 0.6
ERP-RV ₃₃₀ ms	116 ± 4	121 ± 5*	124 ± 5*	129 ± 5**
ERP-RV ₂₅₀ ms	113 ± 5	119 ± 5*	121 ± 5*	124 ± 5**
Conduction time ms	51.3 ± 3	55.9 ± 3**	56.5 ± 3**	57.6 ± 3***

ERP-A 300: effective refractory period of the atrium as assessed by the extrastimulus technique. Basic rhythm: 8 beats with a coupling interval of 300 ms. 2:1 = 2:1 AV-conduction point, the maximal cycle length leading to a stable 2:1 atrioventricular conduction pattern following atrial stimulation of 30 s duration; ERP-LAD, LCX and RV 330 and 250: effective refractory period of the LAD, LCX and RV area be assessed by the extrastimulus technique. Basic rhythm: 8 beats with a coupling interval of 330 or 250 ms; Conduction time: intraventricular conduction time from the right ventricle to the LAD area. For further details see text.

Values are mean ± s.e.mean (*n* = 7); Student's *t* test for paired data; significance symbols (values after labetalol compared to control):

P* < 0.05, *P* < 0.01, ****P* < 0.001.

course of PES 2 (min 30–90), PES 3 (min 120–180) and PES 4 (min 210–270). The absolute plasma levels of labetalol and the decrease in the elimination phase were in accordance with the kinetic data reported for dogs (Martin *et al.*, 1976). The drug

levels determined for the 2 non-responding dogs did not differ from those measured for the 5 responding animals.

Figure 2 Plasma levels of labetalol in dogs. Values are mean (*n* = 7) with s.e.mean shown by vertical bars.

Figure 3 Antiarrhythmic efficacy of labetalol as assessed by PES. Abbreviations: NI = non-inducible, NSVT = non-sustained ventricular tachycardia, SVT = sustained ventricular tachycardia, VFIB = ventricular fibrillation, for further definitions see text.

Discussion

Recently we have proposed a model in which arrhythmias induced by ischaemia, reperfusion and by programmed electrical stimulation (PES) can be studied in one and the same conscious, chronically instrumented dog (Krumpl *et al.*, 1989a,b,c). In the late reperfusion phase PES-induced arrhythmias had been shown to be reproducible (Krumpl *et al.*, 1989c) thus allowing the performance of multiple drug tests. The purpose of the present study was to investigate the haemodynamic, electrophysiological and antiarrhythmic effects of labetalol when studied with PES in the late reperfusion phase after coronary occlusion.

Labetalol demonstrated good antiarrhythmic activity against electrically-induced arrhythmias provoked in the conscious dog with reperfused anterior myocardial infarction. The proposed electrophysiological concept for these arrhythmias is a circus movement of the excitation wavefront (El-Sherif *et al.*, 1977a,b; Josephson *et al.*, 1978; Karageuzian *et al.*, 1979; Michelson *et al.*, 1980). Inhibition of arrhythmia-induction might thus be expected from an increase in ventricular refractoriness (Wellens *et al.*, 1984). El-Sherif *et al.* (1977b) have provided evidence that depression of conduction within the reentry circuit might also lead to suppression of reentry movements. Labetalol increased both ventricular refractoriness and the intraventricular conduction time. The latter effect was measured in the presence of an unchanged QRS morphology which suggests a decrease in conduction velocity to the infarcted and reperfused LAD-supplied area.

The influence of labetalol on refractory periods and conduction time exhibited dose-dependency. The greatest percentage increase was observed after the first dose of 0.5 mg kg⁻¹ labetalol which led to plasma levels well within the proposed β -adrenoceptor-blocking range (Richards *et al.*, 1977; Frishman *et al.*, 1988). The PQ prolongation and the increase in the 2:1 AV conduction point after labetalol were not altered dose-dependently. Such a constant influence on AV-conduction and AV-refractoriness might be explained by achievement of maximal β -adrenoceptor blockade even at the lowest dose level. If this holds true a further dose-increase should thus have no effect in presence of a constant sympathetic drive during the experiment. Constancy in β -adrenoceptor blockade might also explain the lack of dose-dependent antiarrhythmic

effects in this study. However, there is some evidence against the assumption that β -adrenoceptor blockade is the only quality that is responsible for the antiarrhythmic effect of labetalol.

β -Adrenoceptor blocking agents with low membrane stabilizing activity do not affect ventricular conduction velocity and, at least acutely and in the presence of normal sympathetic tone, do not increase ventricular refractoriness (Seides *et al.*, 1974; Wit *et al.*, 1975a,b; Rizzon *et al.*, 1978; Robinson *et al.*, 1978; Marchlinski *et al.*, 1984; Venditti *et al.*, 1987).

Flestolol, an ultra-short acting β -adrenoceptor blocker without membrane stabilizing effects (Gorczynski & Vuong, 1984) showed comparable effects on atrio-ventricular conduction and refractoriness but smaller influence on ventricular refractoriness along with less antiarrhythmic efficacy in the same experimental set up (Todt *et al.*, 1989b,c). From this comparison one might speculate that in our model β -adrenoceptor blockade induces a certain antiarrhythmic effect which, as shown in the present study with labetalol, might be enhanced by direct membrane stabilizing qualities. In the case of labetalol such qualities are reported to be present in the therapeutic range (Vaughan Williams *et al.*, 1982; Mill & Neto, 1987; Venditti *et al.*, 1987).

Labetalol has α -adrenoceptor blocking qualities which, it has been proposed, may play a role in counteracting arrhythmias, at least experimentally (Stewart *et al.*, 1980; Corr & Witowski, 1983; Manning & Hearse, 1984; Aubry *et al.*, 1985). There is evidence that the number of α -adrenoceptors is increased by ischaemia (Corr *et al.*, 1981) and that this receptor can mediate reperfusion-induced calcium accumulation (Sharma *et al.*, 1983). However, the basic electrophysiological effects mediated via stimulation of this receptor are the subject of controversy (Quadbeck & Reiter, 1975). Yet most of the experimental studies have come to the conclusion that α -adrenoceptor agonists increase (Govier *et al.*, 1966; Pappano, 1971) and respective antagonists decrease (Gould *et al.*, 1977; Vaughan Williams *et al.*, 1982) the refractory periods of myocardial cells. So far the effect of α -adrenoceptors on myocardial conduction velocity has not been studied extensively. Hence, more basic electrophysiological studies are needed to clarify to which particular extent the adrenoceptor blocking qualities and the direct membrane activity of α - and β -adrenoceptor blocking drugs such as labetalol contribute to the observed electrophysiological and antiarrhythmic effects of these agents.

The efficacy of labetalol against PES-induced arrhythmias can be attributed to its electrophysiological effects, i.e. an increase in ventricular refractory periods and in intraventricular conduction time. These alterations reflect, at least partially, the proposed class I and III activity of this drug (Vaughan Williams *et al.*, 1982; Mill & Neto, 1987). Class III activity is also indicated by the increase in the rate corrected QT interval (QTc) which cannot be expected to occur after β -adrenoceptor blockade (Edvardsson & Olsson, 1981). Class I activity (sodium channel blockade) might eventually lead to a decrease in conduction velocity, an effect that can explain the increase in QRS duration registered after the highest dose and the dose-dependent increase in intraventricular conduction time as measured from the right ventricular apex to the LAD related infarction area. Catecholamines may restore the resting membrane potential in depolarized cells (Antoni & Zerweck, 1967; Wit *et al.*, 1975a,b) and thus improve local conduction. Hence the observed increase in intraventricular conduction time might also be attributed to a labetalol-mediated β -adrenoceptor related antagonism of the catecholamine effect. However, in the light of the assumption that

β -blockade was completely established after the administration of 0.5 mg kg^{-1} , i.e. the first dose applied, the dose-dependent increase in intraventricular conduction time might favour an explanation via influence on the sodium-channels. Although no antiarrhythmic response was observed in two dogs, the labetalol plasma levels and the drug-induced changes in the electrophysiological and haemodynamic parameters of these two animals were comparable to those assessed in the group of responders. Such a discrepancy which is also observed in clinical antiarrhythmic drug-trials (Wellens *et al.*, 1986) cannot be explained sufficiently from the data assessed in this study. Anecdotally it is worth mentioning that in both non-responding dogs lignocaine was efficacious when tested under comparable conditions (Krumpl *et al.*, 1989d; Todt *et al.*, 1989). Total unresponsiveness to pharmacological interventions can thus be ruled out as an explanation for the lack of antiarrhythmic effects in these two animals.

In the clinical setting the applicability of an antiarrhythmic agent is considerably influenced by its effects on the AV-conduction system and on the arterial blood pressure. In this study the refractory periods of the AV-node have not been determined directly since bundle of HIS monitoring was not performed. However, studies in man have shown that the Wenckebach point (Bissett *et al.*, 1975) and thus the 2:1 AV-conduction point correlate with the refractoriness of the AV-node. Both, a labetalol-induced prolongation of atrioventricular conduction time (PQ interval) and an increase in refractoriness of the AV-conduction system have been found in a former study on anaesthetized dogs (Amelie *et al.*, 1978) and could also be shown in the present investigation with conscious dogs. Comparable effects of labetalol are reported in clinical trials (Harley *et al.*, 1981; Pozzoni *et al.*, 1983). Yet it is to be stated that a severe depression of AV-conduction such as 2:1 AV-blockade during spontaneous rhythm was not observed even with the highest dose of labetalol.

An immediate reduction in blood pressure was registered after bolus administration of labetalol. However, this effect was transient. A significant reduction in systolic and diastolic arterial blood pressure 30 min after bolus administration, i.e. the time point where stimulation was started, could only be registered after the highest dose (3 mg kg^{-1}), while antiarrhythmic efficacy was already observed in response to 0.5 and 1 mg kg^{-1} labetalol. The dose-dependency of the blood-pressure lowering quality of labetalol can easily be explained by the additional α -adrenoceptor blocking qualities of this substance which should gain relevance when higher plasma levels are reached (Farmer *et al.*, 1972).

In summary we conclude that, in this study, the good results achieved with labetalol can be explained by the adrenoceptor blocking properties and both, the class I and III activity of this drug. Labetalol may thus not only be of clinical value in the treatment of hypertension and coronary artery disease but may also be of potential benefit in controlling arrhythmias arising following myocardial infarction. These experimental findings await clinical confirmation.

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