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Celiprolol: a positive inotropic β-adrenoceptor blocking agent in conscious dogs

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1 β-Adrenoceptor blocking agents are used to manage various cardiovascular disorders. A limiting factor in their use is the suppression of the cardiac contractile state. In our study, we examined the cardiac effects of celiprolol, a new β-adrenoceptor blocking agent with reported positive inotropic effects.

2 Dogs were instrumented by use of sterile surgical techniques for the study of myocardial inotropic state, heart rate and internal left ventricular dimensions. Following complete recovery from surgery, experiments were conducted in the conscious state.

3 Intravenous injection of celiprolol ($3\,mg\,kg^{-1}$) in nine dogs, increased LV dP/dt by $13 \pm 2.6\%$, velocity of shortening (LV dD/dt) by $9.2 \pm 3.4\%$, and heart rate by $19 \pm 4.6\%$ and decreased LV end-diastolic diameter by $1.8 \pm 0.8\%$, all significantly ($P < 0.05$). Celiprolol blocked the inotropic actions of isoprenaline ($0.5\,\mu g\,kg^{-1}$) but only partially reduced its hypotensive effects. Propranolol, in contrast, reduced LV dP/dt by $17 \pm 3.3\%$ and heart rate by $8.1 \pm 2.7\%$ ($P < 0.05$) while totally abolishing the hypotension, tachycardia and increase in LV dP/dt caused by isoprenaline. Following β-adrenoceptor blockade with propranolol and with heart rate held constant by electrical pacing, celiprolol increased LV dP/dt by $16 \pm 4.0\%$, LV dD/dt by $12 \pm 3.0\%$ and reduced LV end-diastolic diameter by $3.5 \pm 0.5\%$ ($P < 0.05$).

4 Thus, in conscious dogs, celiprolol increases inotropic state and reduces preload independently of β_1-adrenoceptor mechanisms and the Bowditch phenomenon, while effectively blocking β_1-receptors in the heart. These properties would make celiprolol useful in patients where a conventional β-adrenoceptor blocking agent might lead to pump failure.

Introduction

β-Adrenoceptor blocking agents are used in the treatment of many cardiovascular disease states including rhythm disturbances, hypertension and myocardial ischaemia (Gerber & Nies, 1985). One of the major limitations in the use of these agents is their negative inotropic action, which may be detrimental in disease states where myocardial contractility is already compromised. These actions are characteristic for most β-adrenoceptor blocking agents, including propranolol, atenolol, and timolol (Frishman, 1981). It is also believed that β-adrenoceptor blockers with marked membrane stabilizing properties such as propranolol are more likely to cause greater cardiac depression (Opie, 1983). For this reason, agents like sotalol that lack membrane stabilizing effects (van Zwieten & Timmermans, 1983) have been developed. Recently, celiprolol, a new β-adrenoceptor antagonist which not only lacks the negative inotropic actions of most β-adrenoceptor blockers but has a positive inotropic effect as well as lacking membrane stabilizing properties, was synthesized (Smith & Wolf, 1984).

Most previous studies on the myocardial actions of celiprolol have been conducted *in vitro* or in anaesthetized animals (Wolf *et al.*, 1985) where circulating levels of catecholamines and heart rate may be markedly elevated and the actions of β-adrenoceptor blocking agents overestimated. Anaesthetic agents are also known to modify autonomic control of the cardiovascular system (Vatner & Braunwald, 1975) as well as vascular reactivity (Altura & Altura, 1975). The purpose of our study was to determine the inotropic effects of celiprolol and its mechanism of action in chronically instrumented conscious dogs. A second aim of our study was to contrast and compare the actions of celiprolol with a known β-

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adrenoceptor blocking agent, propranolol, and to compare the relative β_1- and β_2-adrenoceptor blocking effects of these two drugs. Finally, preliminary studies indicated that celiprolol may relax isolated venous segments and thereby serve to regulate myocardial preload. This last observation was the third major focus of our study.

Methods

Adult mongrel dogs, weighing between 20 and 30 kg, were instrumented by use of sterile surgical techniques under general anaesthesia. The dogs were sedated with acepromazine (Ayerst; 0.3 mg kg^{-1}) and anaesthetized with pentobarbitone sodium (Butler; 25 mg kg^{-1}). They were intubated and ventilated with room air. An incision was made in the left fifth intercostal space and Tygon catheters placed in the descending thoracic aorta and in the left atrial appendage. A solid state pressure gauge (Konigsberg Instruments Inc) was placed in the apex of the left ventricle through an apical puncture, which was sealed with a purse string suture. Ultrasonic crystals were placed on opposing endocardial surfaces of the left ventricle (LV) at the base for the measurement of LV internal diameter. Pacing electrodes were sutured to the right atrium and to the outflow tract of the right ventricle. All wires were run subcutaneously to the back of the neck, the incision closed in layers and the pneumothorax reduced. The dogs were given antibiotics (amoxicillin, Beecham; penicillin and dihydrostreptomycin, Pfizer) post-operatively.

Following surgery, the dogs were allowed 10 days to 3 weeks to recover fully before experiments were begun. Each dog was trained to lie quietly on the laboratory table. The laboratory was darkened and maintained quiet during experimentation. Experiments were initiated when the dogs were afebrile, had normal arterial pressures (about 100 mmHg) and low heart rates at rest, i.e., less than 100 beats per min, and were accustomed to the laboratory environment. On the day of the experiment an intracatheter was placed percutaneously in the femoral vein and attached via Tygon tubing to an extension such that all injections were given without disturbing the dog.

Arterial and left atrial pressures were measured by attaching the implanted catheters to strain gauge manometers (Statham P23ID). Left ventricular systolic and end diastolic pressure (EDP) were measured with a solid state pressure transducer. LV internal diameter was measured with the previously implanted sonomicrometers attached to a transit time ultrasonic dimension gauge (Patrick *et al.*, 1974). This instrument generates a voltage that is linearly proportional to the transit time of acoustic impulses travelling between the implanted crystals and, thus, gives an instantaneous and continuous measure of internal diameter. The first derivatives of LV pressure, LV dP/dt, and of changes in LV diameter, LV dD/dt, were derived by use of operational amplifiers (National Semiconductor LM324) set as differentiators having frequency responses of 700 and 400 Hz, respectively, and used as indices of LV contractility. Heart rate was derived from the LV pressure pulse interval by a cardiotachometer (Beckman). In some of the studies, heart rate was held constant by attaching the implanted pacing electrodes to a stimulator (Grass). Mean arterial and left atrial pressures were derived using 2s filters. All measurements were recorded on an 8-channel tape recorder (Bell & Howell, 3700B) and played back on a direct writing oscillograph (Gould Brush, 2800S). These techniques have been described in detail elsewhere (Hintze & Vatner, 1982).

Effects of celiprolol

In 9 dogs, celiprolol (Revlon, 3 mg kg^{-1}) was injected intravenously. The 3 mg kg^{-1} dose was chosen because it is at the top of the dose-response curve in studies done in anaesthetized dogs (Wolf *et al.*, 1985). Data were sampled before and 5, 10, 15, 20, 25 and 30 min after injection and then at 40, 50 and 60 min. In order to examine the β-adrenoceptor blocking effects of celiprolol, isoprenaline (0.5 μg kg^{-1}) was injected before and after the administration of celiprolol in all these dogs.

Effects of celiprolol after β-adrenoceptor blockade

In order to dissociate the positive inotropic actions of celiprolol from its possible partial β-adrenoceptor agonist activity, celiprolol (3 mg kg^{-1}) was administered after the injection of propranolol (1 mg kg^{-1}) in 6 dogs. The extent of β-adrenoceptor blockade with propranolol was assured by the elimination of the tachycardia and increase in LV dP/dt to isoprenaline (0.5 μg kg^{-1}). The maximum effects of isoprenaline after propranolol and celiprolol on mean arterial pressure, heart rate and LV dP/dt were compared.

Effects of celiprolol after β-adrenoceptor blockade and with heart rate held constant

In order to evaluate the effects of celiprolol on preload, i.e. LV end-diastolic diameter and LV dP/dt, in the absence of changes in heart rate, celiprolol was administered to 8 dogs following β-adrenoceptor blockade (propranolol, 1 mg kg^{-1}) and with heart

rate held constant by right atrial pacing to eliminate the possible influence of increases in heart rate on contractility. Data were collected as described above.

Statistical analysis

Data were collected before and after the intravenous injection of celiprolol at 5 min intervals for the first 30 min and at 10 min intervals for an additional 30 min (i.e. a total of 1 h). Following the injection of isoprenaline, data were collected before and at the peak effects of isoprenaline on arterial pressure, heart rate and LV *dP/dt* both before and after the administration of propranolol or celiprolol. Statistical analysis was performed by a one-way analysis of variance for changes from control and a two-way analysis of variance for differences between groups i.e. β-blocked and β-blocked with pacing, in order to avoid multiple *t* tests (Armitage, 1973).

Results

Data are expressed as the mean ± the standard error of the mean (s.e. mean) in the text, table and figures. The effects of celiprolol in one of the dogs is shown in Figure 1. Although data were collected periodically, only the changes which occurred 30 min after the administration of celiprolol will be discussed in the text. However the data for 20, 40 and 60 min after celiprolol administration are shown in the Table 1.

Effects of celiprolol (Table 1)

Celiprolol increased LV systolic pressure (7.7 ± 2.7%), LV *dP/dt* (13 ± 2.6%), LV *dD/dt* (9.2 ± 3.4%) and heart rate (19 ± 4.6%). Mean arterial pressure did not change (0.2 ± 2.7%) while LV end-diastolic diameter, LV systolic diameter and

Table 1 Cardiovascular effects of celiprolol in conscious dogs

	Control	Change from control 20 min	40 min	60 min
LV systolic pressure (mmHg)				
Unblocked	120 ± 4.2	8.7 ± 3.4*	8.5 ± 2.4*	7.9 ± 3.2*
β-Blocked	121 ± 4.8	10 ± 3.3*	10 ± 3.4*	5.7 ± 1.9*
β-Blocked/paced	124 ± 2.9	9.4 ± 2.1*	5.5 ± 1.1*	7.0 ± 1.4*
LV end-diastolic pressure (mmHg)				
Unblocked	7.4 ± 0.8	−0.7 ± 0.4	−0.9 ± 0.2*	−0.9 ± 0.3*
β-Blocked	9.0 ± 0.5	−0.4 ± 0.2	−0.6 ± 0.2*	−0.8 ± 0.1*
β-Blocked/paced	4.6 ± 0.4	−1.2 ± 0.2*	−1.0 ± 0.2*	−1.0 ± 0.2*
LVdP dt ($mmHg\,s^{-1}$)				
Unblocked	2750 ± 184	334 ± 94*	398 ± 81*	280 ± 55*
β-Blocked	2401 ± 104	408 ± 77*	359 ± 76*	397 ± 75*
β-Blocked/paced	2191 ± 74	350 ± 85*	344 ± 97*	308 ± 82*
LV end-diastolic diameter (mm)				
Unblocked	38 ± 3.4	−0.7 ± 0.2*	−0.9 ± 0.3*	−0.6 ± 0.2*
β-Blocked	40 ± 2.6	−1.8 ± 0.3*	−0.7 ± 0.1*	−1.6 ± 0.2*
β-Blocked/paced	33 ± 2.3	−1.1 ± 0.3*	−1.3 ± 0.3*	−1.4 ± 0.3*
LV end-systolic diameter (mm)				
Unblocked	28 ± 2.4	−0.6 ± 0.2*	−0.5 ± 0.2*	−0.6 ± 0.2*
β-Blocked	30 ± 2.3	−0.8 ± 0.2*	−1.3 ± 0.3*	−0.8 ± 0.3*
β-Blocked/paced	27 ± 2.5	−1.0 ± 0.2*	−1.4 ± 0.2*	−1.5 ± 0.2*
LV dD/dt ($mm\,s^{-1}$)				
Unblocked	85 ± 3.0	8.6 ± 4.0*	6.2 ± 1.7*	7.1 ± 1.9*
β-Blocked	82 ± 3.2	8.6 ± 2.2*	11 ± 1.7*	9.2 ± 1.7*
β-Blocked/paced	82 ± 6.6	6.2 ± 1.9*	9.6 ± 3.1*	10 ± 2.7*
Mean arterial pressure (mmHg)				
Unblocked	101 ± 2.6	−0.2 ± 1.6	−0.6 ± 1.4	−1.3 ± 1.9
β-Blocked	99 ± 1.4	3.7 ± 3.7	1.1 ± 3.6	2.3 ± 3.1
β-Blocked/paced	104 ± 2.5	0.3 ± 2.0	−0.1 ± 2.4	1.9 ± 1.6
Heart rate ($beats\,min^{-1}$)				
Unblocked	85 ± 4.0	9.5 ± 2.9*	11 ± 2.6*	9.4 ± 2.5*
β-Blocked	78 ± 3.3	6.0 ± 2.0*	6.0 ± 3.5*	7.0 ± 2.6*
β-Blocked/paced	128 ± 5.0	0.0	0.0	0.0

* $P < 0.05$ from control by analysis of variance.
$n = 9$ for each group.

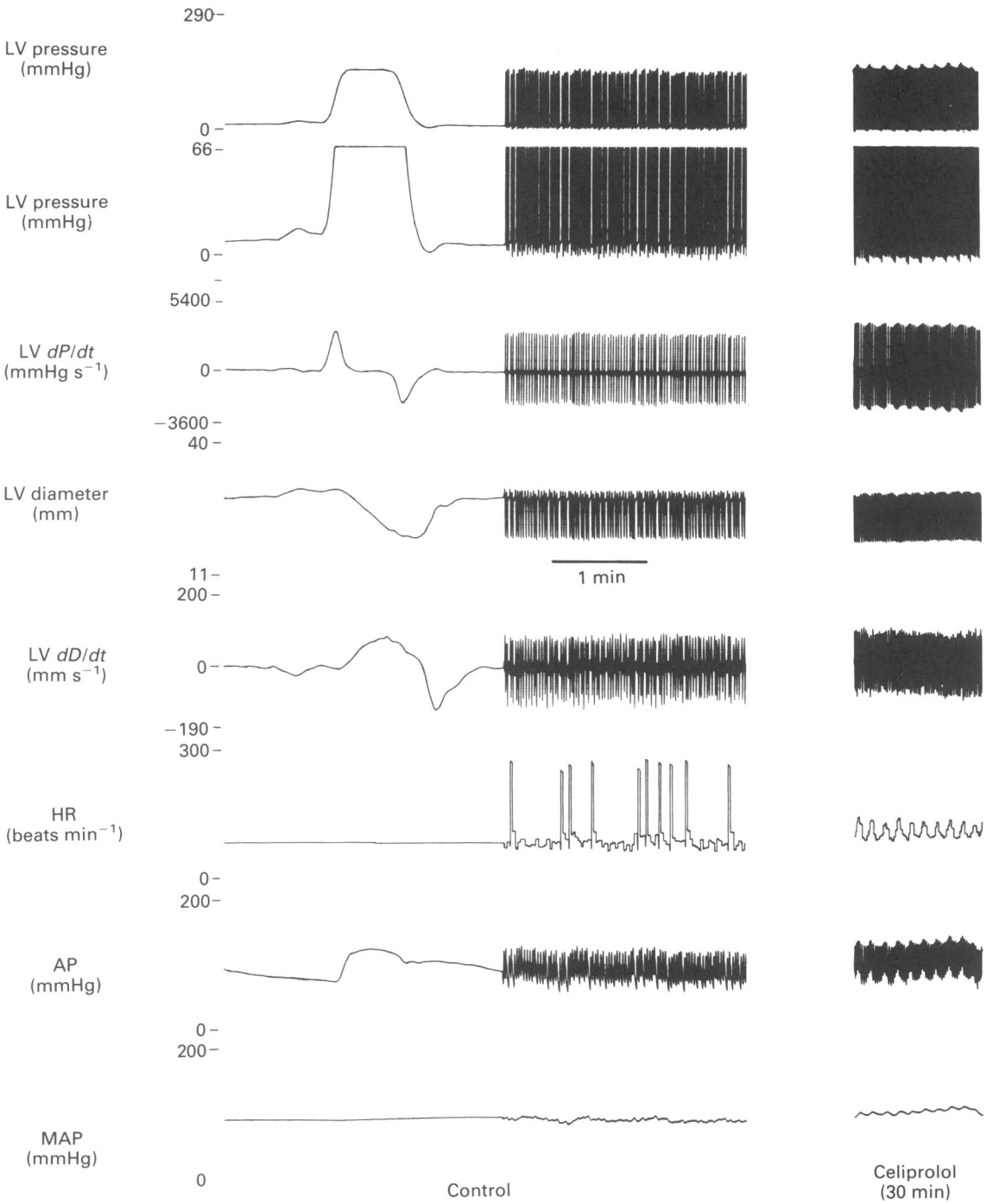

Figure 1 The effects of celiprolol (3 mg kg^{-1}, i.v.) on one of the dogs are shown on the right compared to control on the left. Celiprolol caused an increase in LV systolic pressure, LV *dP/dt*, LV *dD/dt* and heart rate (HR) while reducing LV diameter and having no effect on mean arterial pressure (MAP). The first part of each control trace is shown expanded such that the time bar represents 0.5 s not 1 min.

LV end-diastolic pressure were reduced 1.8 ± 0.8%, 2.3 ± 0.9%, and 16 ± 5.8% respectively ($P < 0.05$).

Effects of propranolol vs celiprolol

Propranolol caused a decrease in heart rate and LV *dP/dt* 8.1 ± 2.7% and 18 ± 3.3%, respectively, in contrast to celiprolol which increased heart rate and LV *dP/dt* by 19 ± 4.6% and 13 ± 2.6%, respectively ($P < 0.05$). Propranolol eliminated the tachycardia, reduction in mean arterial pressure and increase in LV *dP/dt* induced by injection of isoprenaline completely while after celiprolol, injection of isoprenaline caused mean arterial pressure to decrease and LV *dP/dt* and heart rate to increase (Figure 2) albeit to a much lesser degree.

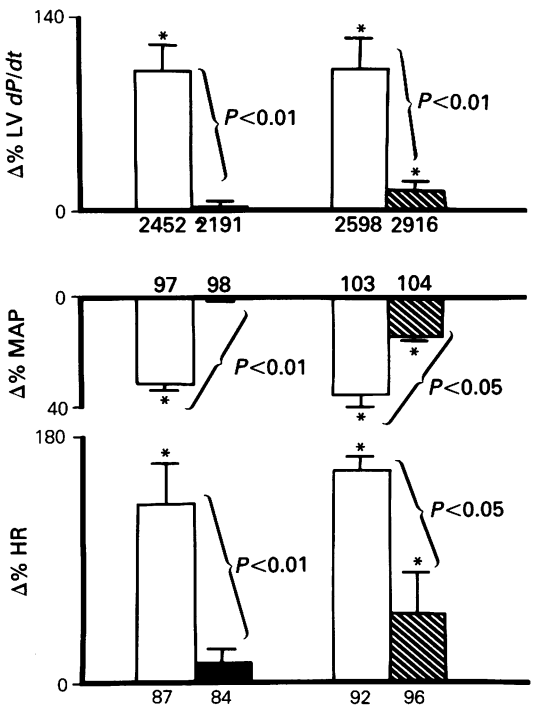

Figure 2 In order to test the β-adrenoceptor blocking effects of celiprolol, isoprenaline ($0.5\,\mu g\,kg^{-1}$) was injected before (open column) and after propranolol (solid columns) or celiprolol (hatched column). Propranolol totally eliminated the changes in LV *dP/dt*, mean arterial pressure (MAP) and heart rate (HR) following isoprenaline injection. In contrast, celiprolol only partially eliminated the hypotension caused by isoprenaline which resulted in a small but significant increase in LV *dP/dt* and heart rate, most probably due to withdrawal of vagal tone. *$P < 0.05$ compared to control. The values above or below the bars are control values. $n = 9$.

Effects of celiprolol after β-adrenoceptor blockade (Table 1)

Following combined β_1 and β_2-adrenoceptor blockade with propranolol, celiprolol still increased LV *dP/dt* (16 ± 4.3%), heart rate (6.5 ± 2.5%), LV *dD/dt* (10.0 ± 2.2%), LV systolic pressure (8.7 ± 1.4%) and reduced both LV end-diastolic diameter (1.7 ± 0.5%) and LV end-systolic diameter (3.6 ± 0.7%) significantly ($P < 0.05$). Mean arterial pressure did not change (3.4 ± 4.2%).

Effects of celiprolol following β-adrenoceptor blockade and with heart rate held constant (Table 1)

Celiprolol increased LV systolic pressure (4.7 ± 0.1%), LV *dP/dt* (16 ± 4.0%) and LV *dD/dt* (12 ± 3.0%). LV end-diastolic diameter was reduced by 3.5 ± 0.5% and LV end-systolic diameter was reduced by 5.5 ± 0.9%. Mean arterial pressure did not change significantly (− 1 ± 2.2%). Figure 3 shows the time course for the 60 min following the injection of celiprolol on LV *dP/dt*, LV *dD/dt*, (two indices of contractility) both of which were increased and sustained for the duration of recording. Figure 4 shows the time courses for three indices of LV preload, end-diastolic diameter, end-diastolic pressure and also mean left atrial pressure, all of which were reduced and sustained for the 1 h of recording. Mean left atrial pressures were assessed because at these high heart rates (128 ± 5 beats per min) LV end-diastolic pressure can be difficult to evaluate precisely.

Discussion

Unlike most β-adrenoceptor blocking agents, celiprolol has a positive inotropic effect in the conscious dog. In addition, it appears that celiprolol reduces cardiac size, i.e. preload, since LV end-diastolic diameter and LV end-diastolic pressure were reduced significantly. Celiprolol significantly reduced the inotropic actions of β_1-adrenoceptor stimulation with isoprenaline. In assessing myocardial contractility, LV *dP/dt* was used as an index. LV *dP/dt* is load-dependent, i.e. an increase in preload will cause an increase in LV *dP/dt* (Wallace *et al.*, 1963; Mahler *et al.*, 1975). Velocity of shortening, *dD/dt*, as an index of contractility is also sensitive to load changes (Mahler *et al.*, 1975), i.e. an increase in preload or a decrease in afterload will increase or reduce LV *dD/dt*, respectively. In our study, however, there were no changes in mean arterial pressure and a decrease in preload (LV end-diastolic diameter). LV *dP/dt* and LV *dD/dt* increased and, therefore, in this study represent accurate indices of enhanced myocardial

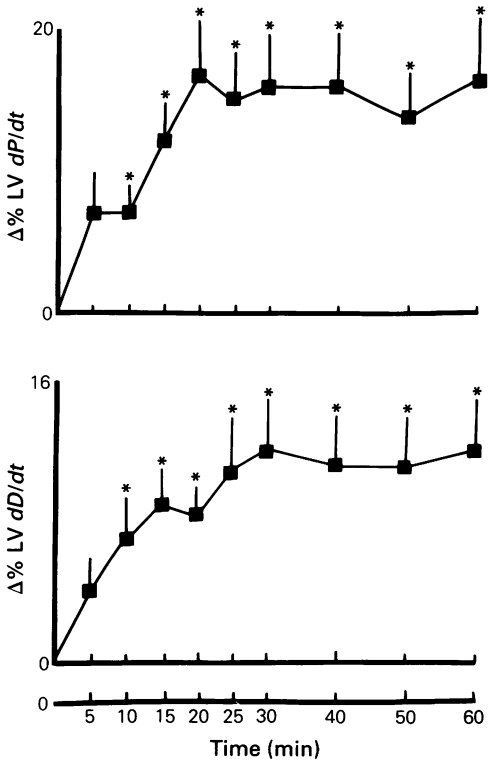

Figure 3 Celiprolol, in the presence of combined β_1- and β_2-adrenoceptor blockade with propranolol and with heart rate held constant by electrical pacing, increased LV *dP/dt* and LV *dD/dt* significantly. Data are shown as percentage change from control, for 5 min intervals for 30 min and then 10 min intervals for an additional 30 min. Asterisks indicate changes that are significantly different from control, ($P < 0.05$). $n = 9$.

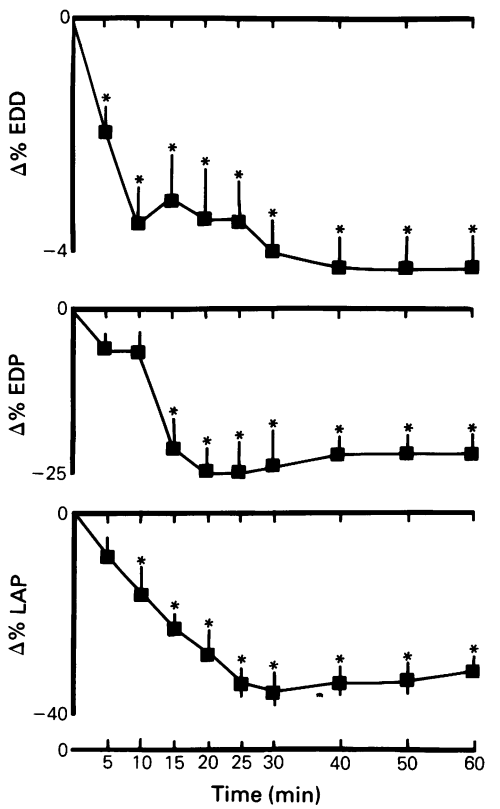

Figure 4 With the same protocol as in Figure 3, the effects of celiprolol on LV end-diastolic diameter (EDD), LV end-diastolic pressure (EDP) and mean left atrial pressures (LAP) are shown. These three indices of preload were reduced significantly for the period of recording (*$P < 0.05$ from control). $n = 9$.

contractile state. Celiprolol has been reported to have intrinsic sympathetic activity (Smith & Wolf, 1984). The increase in LV *dP/dt* by celiprolol in this study was not due to partial β-adrenoceptor agonist activity since complete β-adrenoceptor blockade with propranolol did not affect the increase in LV *dP/dt* by celiprolol. This failure of propranolol to inhibit the positive inotropic affect of celiprolol has also been observed with anaesthetized dog preparations (Wolf *et al.*, 1985).

Activation of the force-frequency relationship as a result of the tachycardia by celiprolol could cause an increase in myocardial contractility, the Treppe phenomenon, (Koch-Weser & Blinks, 1963; Mahler *et al.*, 1974). This is not the case in our study since, with heart rate held constant by electrical pacing, LV *dP/dt* still increased significantly. Celiprolol, therefore, increases LV *dP/dt* in conscious dogs by an as yet unknown mechanism.

The depression of cardiac function, i.e. LV *dP/dt* and heart rate by propranolol, can render it contraindicated in patients whose level of cardiac performance is already compromised as in heart failure (Lucchesi & Whitsitt, 1969; Frishman, 1981; Opie, 1983; Gerber & Nies, 1985). Celiprolol, on the other hand, caused a significant increase in LV *dP/dt* and heart rate in our study. Unlike propranolol which effectively blocks both β_1- and β_2-receptors, celiprolol is 100 times more effective in blocking β_1- than β_2-receptors (Smith & Wolf, 1984). Stimulation of β_1- and β_2-adrenoceptors with isoprenaline, after celiprolol, still caused a β_2-mediated hypotension resulting in increases in heart rate and LV *dP/dt* that were due most probably to a baroreflex-induced withdrawal of vagal tone, since these increases in heart rate and LV *dP/dt* can be elicited by β_2-adrenoceptor receptor stimulation and a major part of the response eliminated by pretreatment with

reserpine and atropine to eliminate reflex effects (Vatner *et al.*, 1982). In this study however, the effects of β_2-adrenoceptor stimulation after celiprolol were not investigated. The effects of isoprenaline after celiprolol could also reflect an incomplete β-adrenoceptor blockade of celiprolol at this dose.

β-Adrenoceptor blockade is known to increase preload, i.e. heart size, by decreasing both heart rate and myocardial contractility (Chamberlain, 1966). Unconventionally, in our study, β-receptor blockade by celiprolol caused a decrease in preload. The decrease in preload could be due to venodilatation resulting in a decrease in venous return or an increase in emptying of the heart as a result of the increased inotropic state. The decrease in preload was not due to the increase in heart rate since the decrease in preload was observed even with heart rate held constant.

It has been suggested that the beneficial effects of propranolol in angina may be due to a reduction in myocardial oxygen requirement (Wolfson *et al.*, 1966). Oxygen consumption by the left ventricle is related to heart rate, contractility and wall tension (Bing, 1965) of which preload and afterload are the major determinants (Levine & Wagman, 1962). The decrease in heart rate and contractility by propranolol would tend to decrease myocardial oxygen consumption, while the ability of propranolol to increase preload, i.e. LV filling pressure (Parker *et al.*, 1968), will tend to increase oxygen consumption. The net effect, therefore, is a balance between these actions variably to decrease or to increase myocardial oxygen consumption. Lewis & Brink (1968) in a clinical study with propranolol, found conflicting results; a decrease in myocardial oxygen consumption in 4 patients and an increase in 4 other patients.

The actions of celiprolol are manifested by offsetting effects on myocardial oxygen demand; i.e. its ability to increase heart rate and contractility would tend to increase oxygen consumption while its preload reducing effect would tend to decrease oxygen consumption. Because celiprolol is being tested successfully clinically in alleviating angina (Smith & Wolf, 1984), it seems that the decrease in preload is large enough to offset the expected increase in myocardial oxygen consumption secondary to the increase in heart rate and LV dP/dt.

β-Adrenoceptor blockade by propranolol has been reported to exacerbate coronary artery spasm (Robertson *et al.*, 1982). One possible explanation for this phenomenon is that blockade of β_2-receptors by propranolol would leave an unopposed vasoconstrictor α-adrenoceptor tone that could cause coronary artery spasm (Parratt, 1980). β_2-Adrenoceptor stimulation of the coronary circulation causes significant arterial dilatation (Vatner *et al.*, 1982). Celiprolol, by increasing heart rate and contractility, would have a metabolically-mediated vasodilator effect (Berne & Rubio, 1979) while having a weak β_2-receptor antagonism. Recent reports have also shown that celiprolol blocks α_2-adrenoceptors (Rodenberg *et al.*, 1986). Post-synaptic α_2-receptors may be involved in coronary constriction more so than α_1-receptors (Holtz *et al.*, 1982). Due to the α_2-adrenoceptor blocking activity of celiprolol it might be less prone to promote coronary artery spasm.

Celiprolol, therefore, would be suited for use in states where β-adrenoceptor blockade is indicated and cardiac depression is to be avoided. Its weak β_2-blocking effects would also make it suitable for use in asthmatic patients where β_2-blockade can cause bronchoconstriction (van Herwaarden, 1983). Furthermore, this weak β_2-blocking effect and the reported α_2-adrenoceptor blocking action, may make this drug useful in patients susceptible to coronary vasospasm.

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