

Haemodynamic Effects of Intravenous Cibenzoline in Patients With Coronary Heart Disease

M. van den Brand, P. Serruys, Y. de Roon, M. F. Aymard¹, and A. Dufour¹

Catheterization Laboratory, Thoraxcentre, Erasmus University, Rotterdam, The Netherlands
and ¹UPSA Laboratories, Rueil – Malmaison Cedex, France

Summary. The effect of a single dose of cibenzoline ((diphenyl 2,2 cyclopropyl) – 2 imidazoline, Cipralan), a new compound with antiarrhythmic properties was studied in 14 patients undergoing routine heart catheterization for suspected coronary artery disease. The effect of the drug on dP/dt , V_{\max} TP, Vce, negative dP/dt , heart rate (HR), left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), cardiac index (CI) and systemic vascular resistance (SVR) was measured before and after drug administration. A significant decrease in left ventricular isometric contraction parameters was manifested immediately after injection, with its maximal effect 2 to 5 min after injection. An increase in HR, a decrease in LVSP, a decrease in CI and an increase in SVR were observed; LVEDP was not significantly altered, nor was negative dP/dt . The effect of the drug on V_{\max} TP and LVEDP was also examined during two atrial pacing stress tests (APST) done before and 10 to 20 min after drug administration. Although the negative inotropic action of the drug was apparent during the second APST, the effect was less pronounced at higher paced heart rates. No difference in the two tests was found between the maximal paced heart rate, nor was there a difference in the angina threshold. Finally the plasma level of the drug and the changes in certain parameters were compared. A positive correlation was found between the plasma level and dP/dt , V_{\max} TP and cardiac index.

Key words: cibenzoline, antiarrhythmic drug; coronary heart disease, cardiac performance, drug plasma level, cardiac catheter, inotropic action

Cibenzoline (Cipralan®; (diphenyl – 2,2 cyclopropyl) – 2 imidazoline); (Fig. 1) is an unusual imidazoline derivative as it appears to be the first such compound to possess antiarrhythmic properties. In vitro studies have revealed that cibenzoline belongs to three of the four main classes of antiarrhythmic agents (Millar and Vaughan, 1982; Williams 1982). Like quinidine it has no effect on the resting potential but it reduces the height of the action potential and the maximum rate of depolarization (Class 1). It also has been shown that cibenzoline, like amiodarone, prolongs the duration of the action potential and the absolute refractory period (Class 3). Finally it antagonizes the positive inotropic and chronotropic actions of calcium, although to a lesser extent than verapamil (Class 4). Verdouw et al. (1982) recently demonstrated that it caused a dose dependent decrease in myocardial contractility, an increase in systemic vascular resistance and a parallel decrease in epicardial and endocardial coronary blood flow in anaesthetized pigs.

The present study was undertaken to document the extent and duration of the negative inotropic action of cibenzoline in patients catheterized on suspicion of coronary heart disease.

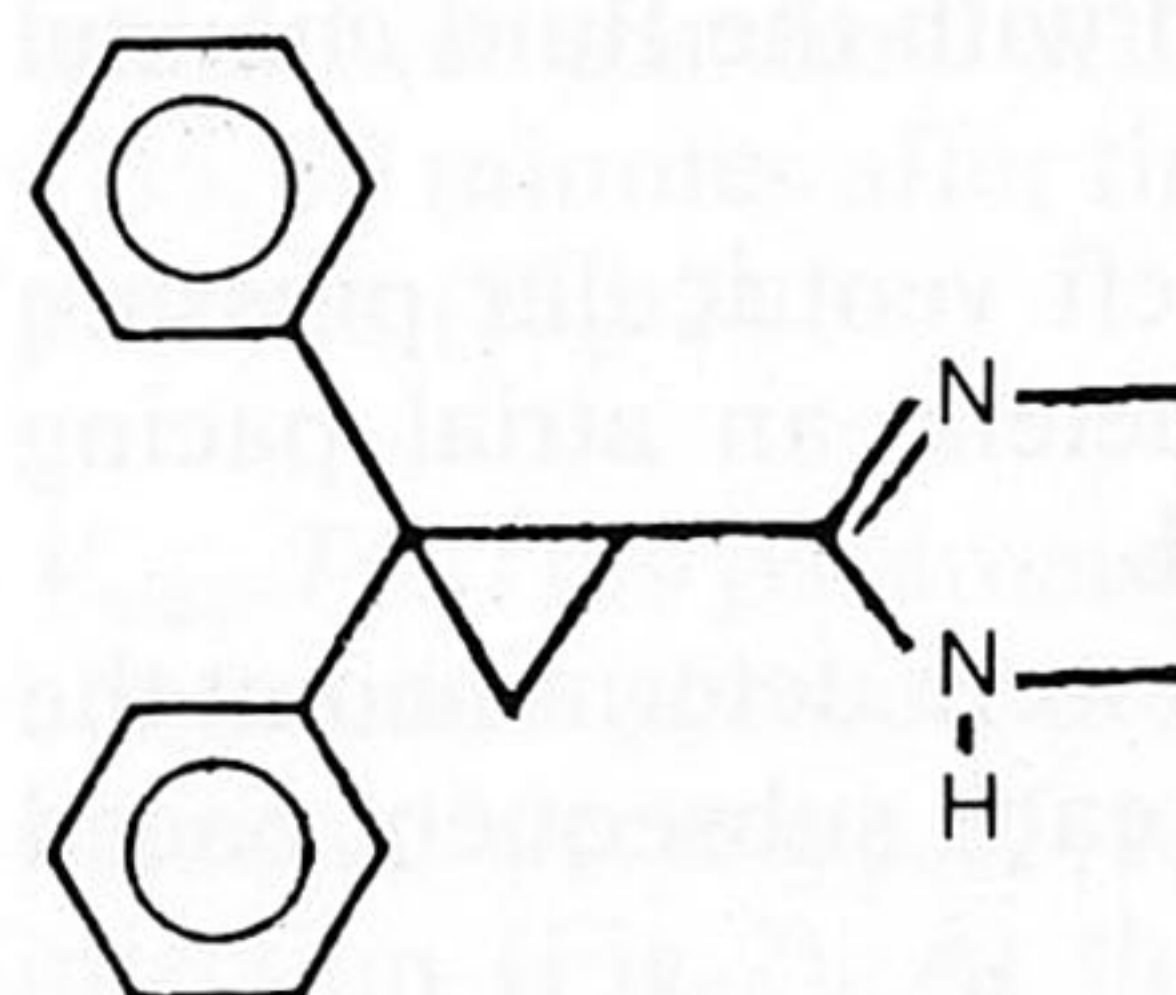


Fig. 1. Molecular structure of cibenzoline: (Diphenyl – 2,2 cyclopropyl) – 2 imidazoline

Table 1. Details of patients in the study

Patient	Age [years]	Sex	NYHA	EF [%]	EDV [ml/m ²]	APST I	APST II	Coronary angiography
A. 1. MF	51	M	II	63	74	180	180	minimal disease
2. CB	66	M	III	42	130	110 AVB	120 AVB	1 vessel disease
3. LE	46	M	II	67	90	110 AVB	–	1 vessel disease
4. BS	48	M	II	50	102	170 AP	150 AVB	1 vessel disease
5. LN	56	M	II	68	76	170 AVB	180 AVB	2 vessel disease
6. AP	57	M	II	67	84	140 AP	150 AP	1 vessel disease
7. JB	57	M	III	49	89	140 AP	160 AP	2 vessel disease
8. CC	52	M	II	53	77	150 AVB	150 AVB	minimal disease
9. RB	34	M	III	42	120	140 AVB	130 AVB	2 vessel disease
10. SK	39	M	III	63	104	160 AVB	160 AVB	1 vessel disease
B.11. MG	61	M	II	59	56	170 AP	150 AVB	1 vessel disease
12. KS	65	F	II	61	57	140 AVB	140 AVB	3 vessel disease
13. JB	55	M	III	39	78	150 AP	160 AP	2 vessel disease
14. LV	46	M	III	40	101	120 AP	120 AP	2 vessel disease

NYHA: functional class; EF: ejection fraction (normal $\geq 56\%$); EDV: end-diastolic volume (normal ≤ 90 ml/m²); APST I: atrial pacing stress test before and APST II: atrial pacing stress test after drug administration; AP: angina pectoris; AVB: atrioventricular block; Minimal disease: coronary obstruction not exceeding 50% narrowing of diameter. One/ two/ three vessel disease: respectively 1, 2 or 3 coronary arteries with more than 50% narrowing

Material and Methods

Patients and Procedures

14 patients catheterized because of suspected coronary heart disease were studied. Patients with unstable angina, impending infarction or severely compromised left ventricular function were excluded from the study.

The clinical details of the patients are summarized in Table 1. Patients were studied without pre-medication after an overnight fast. Beta-receptor blocking medication, cardiac glycosides and nitrates were withdrawn 24 hours before catheterization if the patients were able to tolerate this change in treatment.

Following right heart catheterization and measurement of cardiac output in duplicate by the thermodilution method, a bipolar pacing electrode catheter was positioned high in the right atrium. The left ventricle was catheterized via a right brachial artery cut down, with a Millar Instruments 7 or 8 F tip-manometer catheter. The reference level was set at mid-chest and was compared with the fluid channel for base line correction.

After recording control left ventricular pressure and pressure derived parameters, an atrial pacing stress test (APST) was started.

The following parameters were determined at the resting heart rate and during each subsequent paced heart rate.

1. Peak left ventricular systolic pressure in mmHg (LVSP).

2. Left ventricular end-diastolic pressure in mmHg (LVEDP).

3. Peak positive first derivative of LV pressure (pk LV dP/dt) in mmHg/sec.

4. Peak LV dP/dt/P from total pressure (pk Vce) in sec⁻¹.

5. dP/dt/P extrapolated to P = 0 mmHg pressure using a linear least squares fit from peak dP/dt/P to commencement of ejection (V_{max} TP) in sec⁻¹.

Right atrial pacing was begun after recording control values at a heart rate just above the resting level. After 1 min of pacing, left ventricular function was assessed during 12 consecutive beats and was averaged on line in a dedicated computer system by the representative beat method (Brower 1977; Meester 1975; Stenson 1968). The pacing rate was increased in steps of 20 beats/min and the measurements were repeated after 1 min at each pacing rate. The endpoint of the APST was any of the following events: 1. A paced heart rate of 180 beats/min, 2. the onset of chest pain, or 3. atrio-ventricular block.

Drug Administration

After baseline measurements, including an atrial pacing stress test, cibenzoline 1.0 mg/kg was administered over 2 min to 10 patients (A), whilst 4 others received the same dose in 10 s. (B)

From the start of the injection the following parameters were measured or calculated every 15 s during a one minute period, using the representative beat method mentioned above: LVSP, LVEDP, pk dP/dt, V_{max} TP and heartrate. 2, 5, 10, 20 and 30 min

after termination of the injection, the same parameters were recorded, as well as peak Vce, cardiac output, right atrial pressure and aortic pressure, and the systemic vascular resistance (SVR) was also calculated from the formula:

$$\text{SVR} = \frac{\text{mean aortic pressure [mmHg]} - \text{mean right atrial pressure [mmHg]}}{\text{cardiac output [l/min]}} \times 80$$

Between 10 and 20 minutes after administration of the drug, the atrial pacing stress test was repeated, and the maximal paced heart rate and left ventricular pressure-derived parameters were compared with the values found in the baseline atrial pacing stress test.

Plasma Assay

Before the injection of cibenzoline, a control 10 ml blood sample was collected during catheterization and was mixed with 0.1 ml sodium heparin solution, 1000 i.u./ml.

1, 2, 5, 10, 20, 30 and 60 min after termination of drug administration, further 5 ml blood samples were collected and mixed with 0.05 ml of the heparin solution. Samples were collected through a catheter not used for injection of the drug. Blood was centrifuged for 10 min at 3000 r.p.m. and the plasma separated and stored frozen at -17°C . Plasma cibenzoline was determined by UPSA laboratories, using a specific method (Canal 1983) with a three step extraction procedure in the presence of an internal standard (UP 339-03); ditrifluoro acetylated derivatives were analyzed in a gas liquid chromatograph using electron capture detection.

Pharmacokinetic Analysis

The pharmacokinetic pattern of cibenzoline after intravenous injection has previously been determined in healthy volunteers (Canal 1983) and in patients (Desoutter 1983). The distribution of the drug is in two rapid phases; the half life of elimination from plasma is 4.5 h in healthy volunteers and 7.3 h in patients.

The decline in the plasma concentration of cibenzoline after injection was analyzed by the equation of Wagner (1976). This equation was adjusted for each subject by modifying the constants of distribution, to obtain the best agreement between the observed and calculated concentrations for every sampling time in the first 60 min.

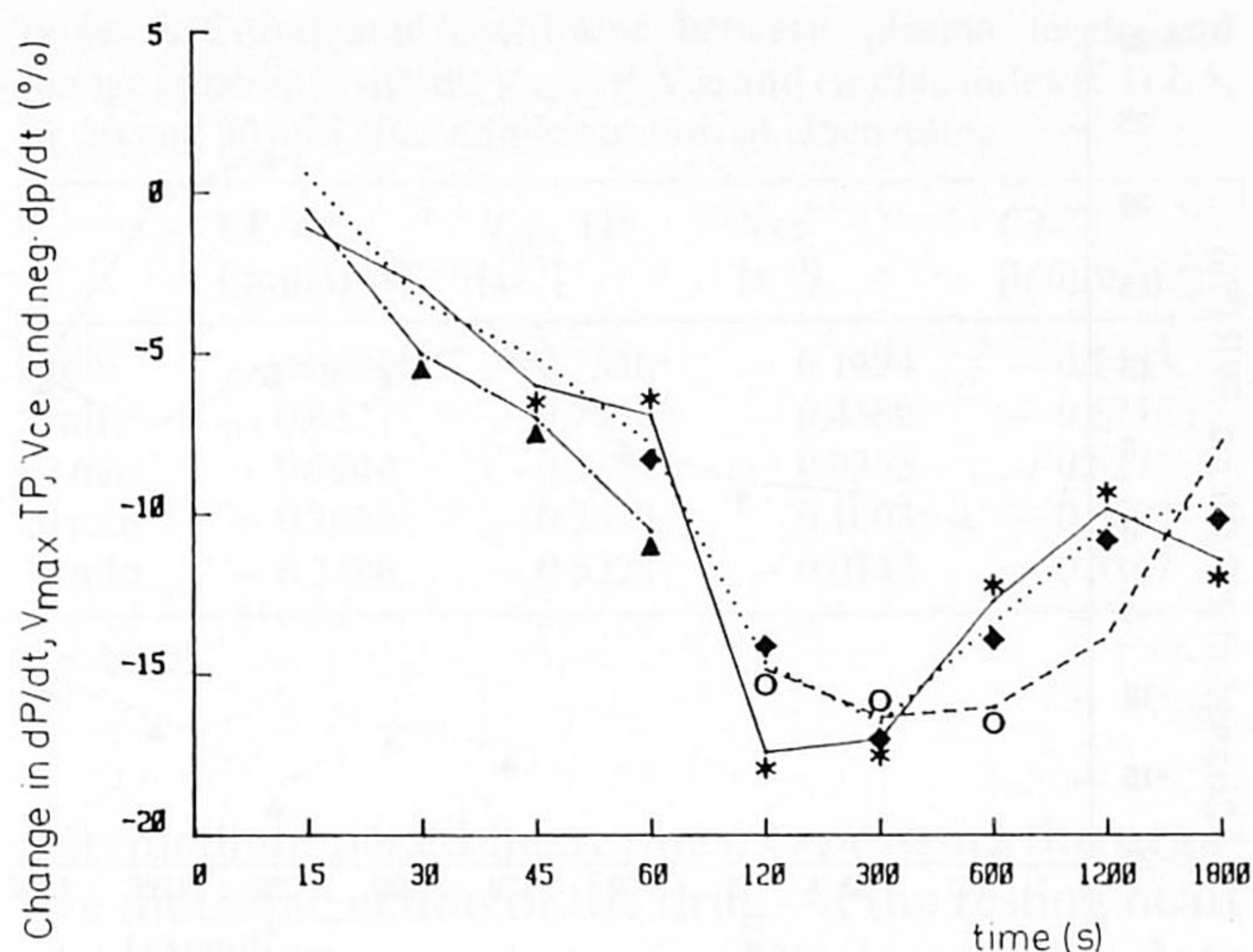


Fig. 2. Percent change in dP/dt , V_{\max} TP, Vce and negative dP/dt , after cibenzoline

dP/dt after cibenzoline	—	$p < 0.05$	★
V_{\max} TP after cibenzoline	$p < 0.05$	◆
Vce after cibenzoline	----	$p < 0.05$	○
Negative dP/dt after cibenzoline	-.-.-	$p < 0.05$	▲

Statistical Analysis

The effects of cibenzoline 1.0 mg/kg administered in 2 min to 10 patients are presented as percentage change from baseline values. Student's paired t -test (Snedecor and Cochran 1967) was used to determine the significance of the changes ($p < 0.05$, two tailed).

The relationship between certain effects and the plasma concentration of cibenzoline in all 14 patients was determined by linear regression.

Results

(Clinical details of the patients are given in Table 1)

Haemodynamic Parameters at Rest After Cibenzoline

Peak Positive dP/dt . A significant decrease in the first derivative of left ventricular pressure was found, which was maximal after 2 min when it amounted to 17%. 30 minutes after the injection the effect was still present. (Fig. 2)

V_{\max} TP. This parameter of isometric left ventricular contraction showed the same course as dP/dt . The maximal decrease of 16% was observed 5 min after injection (Fig. 2). At the end of the experiment all values were still significantly below the control level, although there had been some recovery.

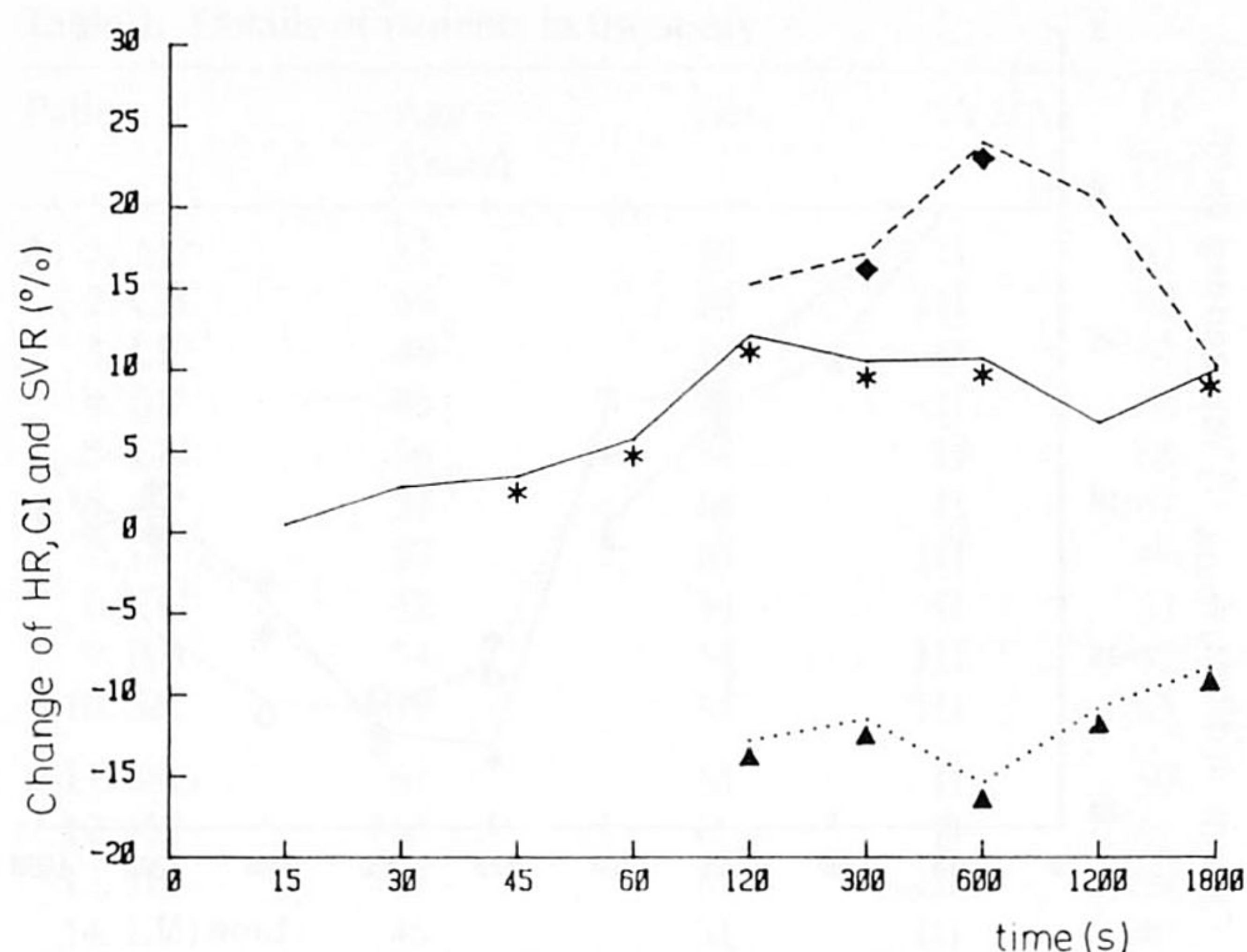


Fig. 3. Percent change of heart rate, cardiac index and peripheral resistance, after cibenzoline

Heart rate after cibenzoline ————— $p < 0.05$ ★
 Cardiac index after cibenzoline $p < 0.05$ ▲
 Systemic vascular resistance after cib. - - - - - $p < 0.05$ ◆

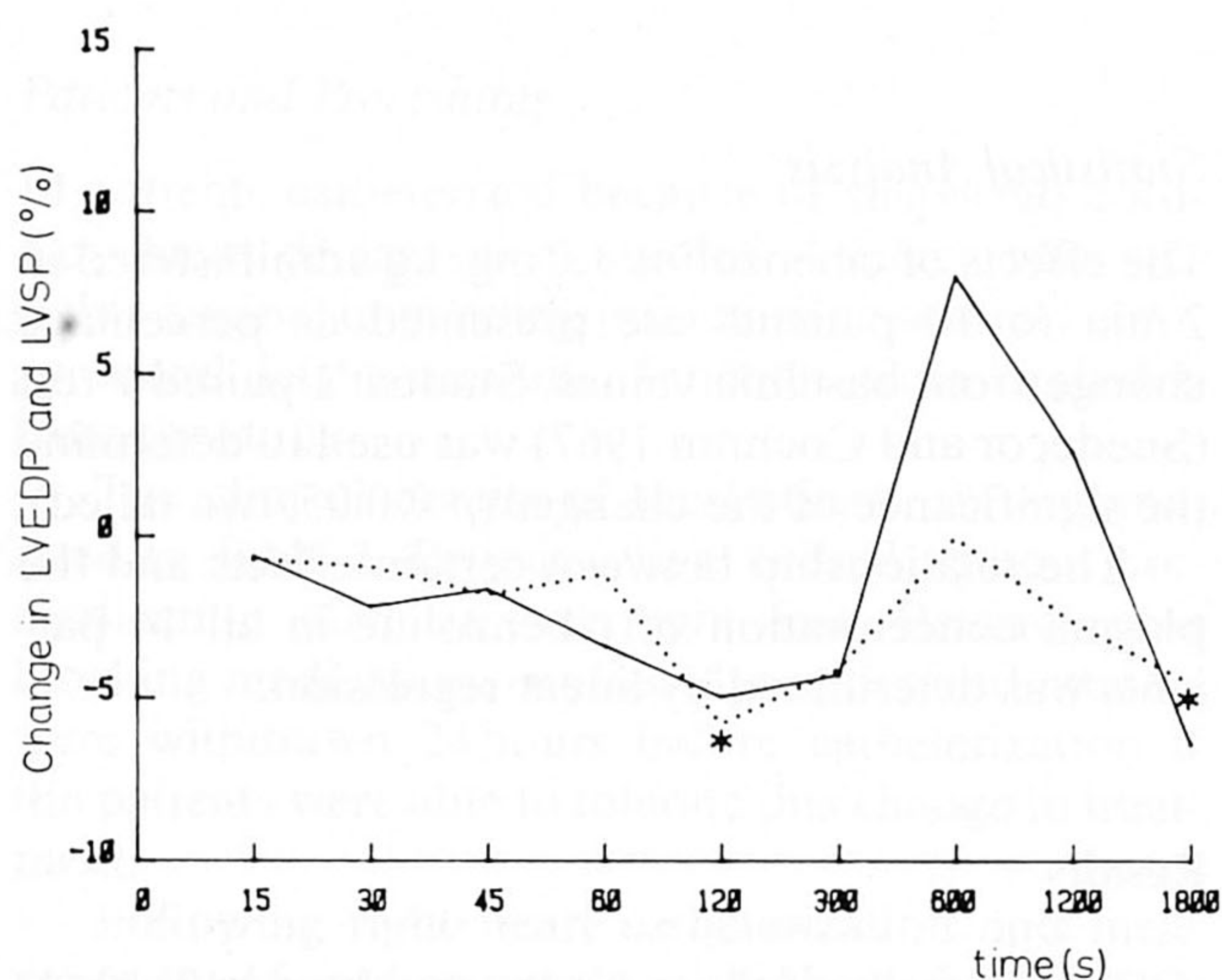


Fig. 4. Percent change of left ventricular systolic and end-diastolic pressure, after cibenzoline

Left ventricular enddiastolic pressure after cibenzoline —————
 Left ventricular systolic pressure after cibenzoline $p < 0.05$ ★

Peak Vce. This parameter also reflects the negative inotropism of cibenzoline. The maximal effect of a 16% reduction was observed between 2 and 10 min after the injection. After 30 min the effect was still apparent, although no longer statistically significant (Fig. 2).

Peak Negative dP/dt . This parameter of left ventricular relaxation was only measured during injection and during both atrial pacing stress tests. A decrease in negative dP/dt during injection was observed, the difference being significant 30, 45 and 60 s after beginning the injection of cibenzoline (Fig. 2). Between 10 and 20 min after the injection, during the second APST, negative dP/dt was not significantly different from the control value.

Heart Rate. Average resting heart rate was 68 bpm. During administration of the drug, the heart rate increased to a maximum rise of 12% two min after the drug was administered. 30 min after administration the effect was still present (Fig. 3).

Cardiac Index (CI). A maximal decrease in the mean cardiac index of 15% was found. The decrease was already present 2 min after injection and an effect was still detectable at the end of the experiment (Fig. 3).

Systemic Vascular Resistance. A maximal rise of 24% in systemic vascular resistance was calculated, the increase reaching statistical significance 5 and 10 min after the injection (Fig. 3).

Left Ventricular Systolic Pressure. A significant decrease in LVSP of 6% was observed 2 min after injection of cibenzoline. At the end of the experiment the effect was almost abolished (Fig. 4).

Left Ventricular End Diastolic Pressure. No significant changes in LVEDP were observed (Fig. 4).

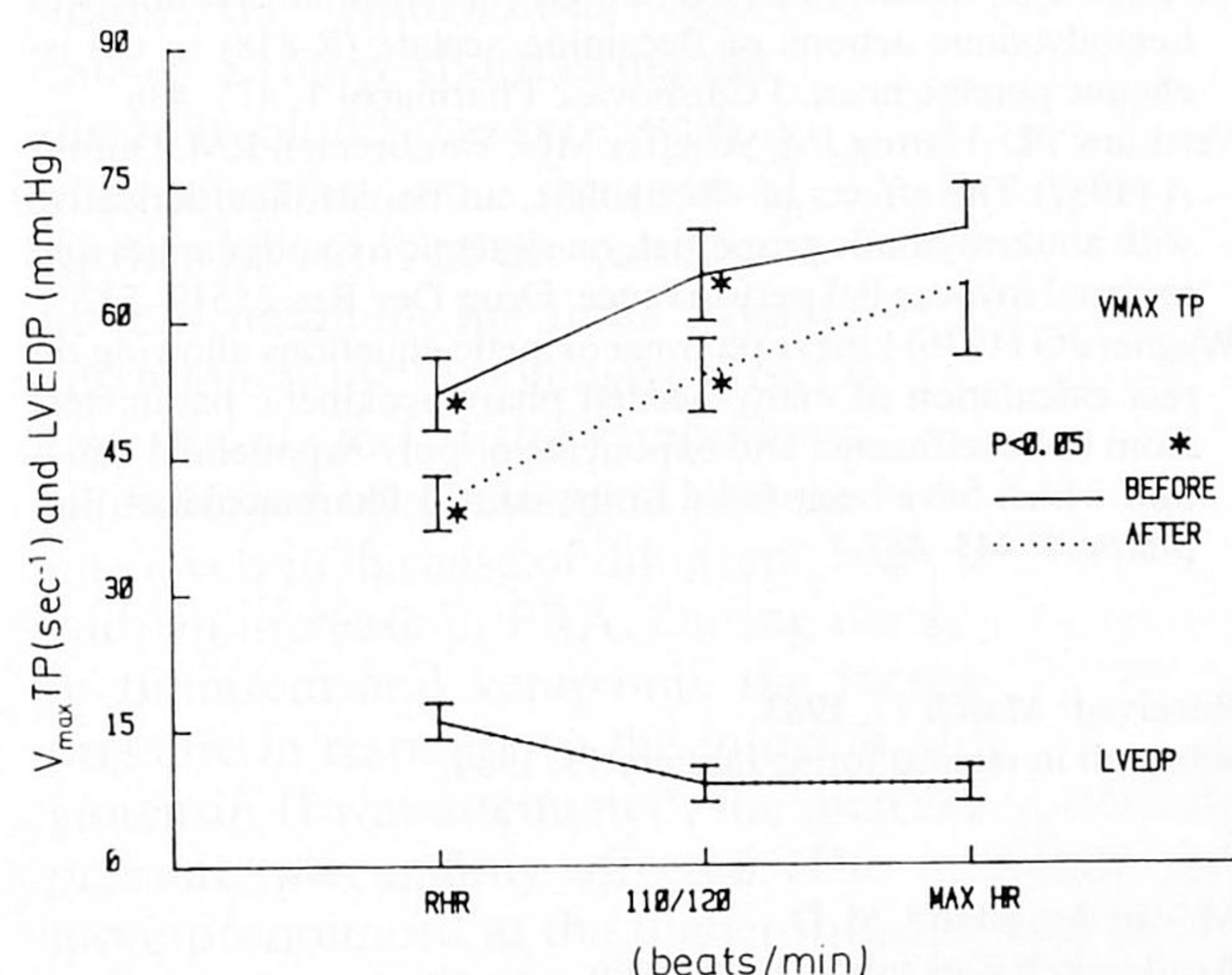
Atrial Pacing Stress Test

Resting Heart Rate and Maximal Paced Heart Rate. Resting heart rate and maximally paced heart rate did not differ significantly during either stress test (Table 2). One patient only had a stress test before drug administration, because he developed complete heart block 14 min after injection of cibenzoline. Before administration of the drug he had shown the same phenomenon intermittently. The reasons for stopping the test were no different before and after drug administration (Table 1). There was no indication that patients developed ischaemia at a lower heart rate after cibenzoline. Mean values for LVEDP, V_{max} and negative dP/dt at resting heart rate, at a paced heart rate of 110 to 120 beats/min, and at maximal paced heart-rate were also comparable (Table 2).

Table 2. Comparison of resting heart rate, maximal paced heart rate and the behaviour of V_{\max} TP, left ventricular end-diastolic pressure and peak negative dP/dt during atrial pacing stress tests before and after cibenzoline (CIB); mean \pm SEM

Dose CIB/kg bodyweight 1.0 mg in 2 min				
	before	after	$p < 0.05$	
No. of patients	10	9		
Resting heart rate [beats/min]	71 \pm 3	76 \pm 3	n.s.	
Max. paced heart rate [beats/min]	142 \pm 8	149 \pm 7	n.s.	
LVEDP [mmHg]	A	16 \pm 2	n.s.	
	B	9 \pm 2	n.s.	
	C	9 \pm 2	n.s.	
V_{\max} TP [s^{-1}]	A	52 \pm 4	s	
	B	65 \pm 5	s	
	C	70 \pm 5	n.s.	
Peak neg. dP/dt (mmHg/s)	A	1904 \pm 77	n.s.	
	B	2078 \pm 83	n.s.	
	C	2089 \pm 105	n.s.	

A At resting heart rate; B At an intermediate paced heart rate (110–120 beats/min); C At maximal paced heart rate; s = p value < 0.05 , significant; n.s. = non significant

**Fig. 5** Mean values for V_{\max} TP and LVEDP during atrial pacing before and after administration of cibenzoline

Mean values for V_{\max} TP and LVEDP during atrial pacing before and after administration of cibenzoline

LVEDP. No statistically significant difference in end-diastolic pressure at resting heart rate, a medium paced heart rate of 110 to 120 beats/min and at maximal paced heart rate were observed (Fig. 5).

V_{\max} TP. Values for V_{\max} TP were significantly lower after drug administration at resting heart rates and at

Table 3. Correlation coefficient between plasma levels and change in positive dP/dt, V_{\max} TP, Vce and cardiac index (CI) 2, 5, 10, 20 and 30 min after administration of cibenzoline

	dP/dt [mmHg/s]	V_{\max} TP [s^{-1}]	Vce [s^{-1}]	CI [l/min/m ²]
2 min	– 0.6697 ^a	– 0.7336 ^a	– 0.1494	– 0.1453
5 min	– 0.6527 ^a	– 0.7058 ^a	0.4389	– 0.1773
10 min	– 0.3944	– 0.3678	– 0.0365	– 0.5271
20 min	– 0.3939	– 0.3639	0.1003	– 0.8692 ^a
30 min	– 0.2496	– 0.5228	– 0.0742	– 0.3167

^a $p < 0.05$

intermediate paced heart rates, expressing the negative inotropic action of the drug. At the resting heart rate, V_{\max} TP on average was 23% lower after drug administration, 17% lower at an intermediate paced heart rate and 9% lower at maximal paced heart rate. Thus, the negative inotropic action of the drug appeared to be less during cardiac stress than under resting conditions (Fig. 5).

Peak Negative dP/dt. The value of this parameter was lower after drug administration at all paced heart rates, but the differences were never statistically significant.

Plasma Levels and Haemodynamic Effects

Plasma levels of cibenzoline 2, 5, 10, 20 and 30 min after administration in all experiments were compared with the corresponding changes in dP/dt, V_{\max} , peak Vce and cardiac index. A summary of the correlations is given in Table 3.

Discussion

Cibenzoline possesses antiarrhythmic properties in man after intravenous administration of 1.0 mg/kg (Thebaut 1980; Thizy 1981). It is the first known imidazoline derivative with this property. Recent reviews of the haemodynamic effects of a variety of antiarrhythmic drugs have shown a decreased cardiac output and, with the exception of digitalis, a negative inotropic action on the myocardium (Lucchesi 1977; Bigger and Hoffman 1980; Dreifus and Morganroth 1980). A similar effect of cibenzoline has been seen in animal experiments, with depressed myocardial contractility and diminished cardiac output.

A negative inotropic effect and diminished cardiac output has now been shown in patients catheterized for investigation of coronary artery disease. No difference in effect was found under the stress of atrial pacing in patients who became ischaemic dur-

ing the test and the patients who did not. Moreover, the negative inotropic action of the drug appeared to be less pronounced at higher heart rates on comparison of the values of the two atrial pacing stress tests before and after cibenzoline. This is in keeping with animal experiments, in which only a minor additional negative inotropic effect of the ischaemic myocardium was observed with other antiarrhythmic drugs (Verdouw 1977, 1979).

An increase in systemic vascular resistance was noted, as with most other antiarrhythmic drugs. This effect together with the diminished cardiac index prevented a marked fall in systolic blood pressure, the latter being at the most 5% below its control level. No rise in blood pressure was noted during injection of the drug, as has been seen in animal experiments (Verdouw 1982). The use of general anaesthesia in the animal experiments may account for this difference.

The increase in heart rate after drug administration could possibly represent a β -receptor mediated reflex mechanism to diminish the negative inotropic action of the drug and the fall in pressure.

For two parameters of left ventricular isometric contraction (dP/dt and V_{max} TP) and cardiac index a good correlation was found between the plasma level of cibenzoline and the decrease in these measurements. No correlation was found for the other measured or calculated parameters. No adverse reaction was noted after drug administration.

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M. van den Brand, M. D.
Academisch Ziekenhuis Rotterdam
Heartcatheterization
Laboratory, Thoraxcenter
Dr. Molewaterplein 40
NL-3015 GD Rotterdam
The Netherlands