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THE HAEMODYNAMIC EFFECT OF INTRAVENOUS FLECAINIDE ACETATE IN PATIENTS WITH CORONARY ARTERY DISEASE

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1 Flecainide acetate has been shown to be a potent antiarrhythmic agent which is active for more than 8 h, whether given intravenously or orally. However, the negative inotropic effect demonstrated in animal studies could hamper the potential clinical utility of the drug.

2 Ten patients with coronary artery disease but without cardiac failure were given intravenous flecainide (2 mg/kg). Stroke index (SI), left ventricular systolic pressure (LVP), end diastolic pressure (EDP) and LV contractility indices (max dP/dt, VCE 40 mm Hg, peak VCE, V_{max} from total pressure (TP)) were measured immediately before and 10 min after flecainide, under resting conditions and during atrial pacing with heart rates up to 133 ± 4.2 beats/min (mean ± s.e. mean).

3 It is demonstrated that flecainide has a negative inotropic effect, not only under resting conditions, but also less apparently during pacing-induced tachycardia. The effect appears to be dose-related and may result in a reduction of cardiac performance.

Introduction

The clinical usefulness of any antiarrhythmic agent is often limited by its untoward effects on left ventricular performance. Most presently available antiarrhythmic agents have a negative inotropic effect when used in adequate doses to control severe ventricular arrhythmias. The potential clinical usefulness of any new antiarrhythmic agent would be significantly enhanced if it had a minimal or absent negative inotropic effect.

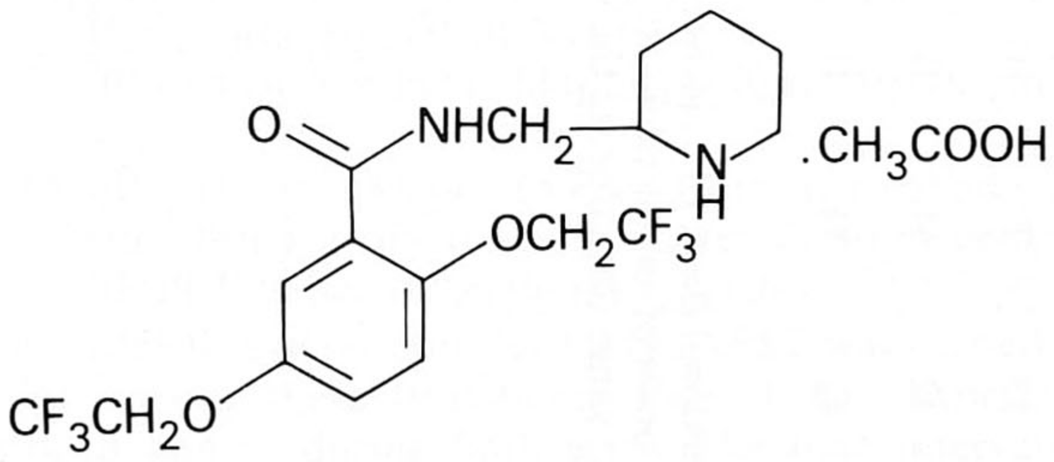

Figure 1 Molecular structure of flecainide acetate (R818).

Flecainide (R818): 2,5 bis (2,2,2-trifluoroethoxy)-*N*-(2-piperidylmethyl) benzamide acetate; Figure 1) is a new compound which has local anaesthetic properties similar to lignocaine. It effectively antagonises atrial and ventricular arrhythmias in dogs induced by aconitine, ouabain, and coronary artery ligation after both oral and intravenous administration (Schmid *et al.*, 1975). In man, preliminary reports indicate that the drug is effective for treating ventricular arrhythmias (Anderson *et al.*, 1981; Duff *et al.*, 1981; Gulker *et al.*, 1981; Hellestrand *et al.*, 1981a, b; Klempt *et al.*, 1980; Seipel *et al.*, 1981; Somani, 1980).

Electrophysiological studies in dogs have shown that flecainide depresses conduction in all myocardial tissues, most notably in the His–Purkinje system and in ventricular muscle (Hodess *et al.*, 1979). In man, flecainide predominantly depresses ventricular conduction (Breithardt & Seipel, 1976; Cowan & Williams, 1981; Olsson & Edvardsson, 1981; Seipel *et al.*, 1980).

The present study is designed to evaluate quantitatively the effects of intravenous flecainide on left ventricular function. Global and regional left ventricular function in patients with coronary artery disease is often normal at rest and only becomes impaired during loading when transient regional ischaemia can be provoked. The stress of atrial pacing is an ideal form of such loading, since catheter tip sensors in the left ventricle allow continuous measurement of contractility parameters (Brower *et al.*, 1977).

Methods

The first part of the study was aimed at proving the reproducibility of the atrial pacing stress test. Data

Table 1 Patient data—Group studies for assessment of the reproducibility of the atrial pacing stress test (APST)

Patient	*Age (years)*	*Sex*	*NYHA*	*EF*	*EDV (ml/m^2)*	*$APST_1$*	*$APST_2$*	*Coronary angiography*
1	47	M	III	0.26	118	160-AP	160-AP	3-vessel disease
2	46	M	I	0.66	71	170-AVB	170-AVB	1-vessel disease; postoperative 1 patent graft
3	46	M	II	0.55	96	180-AP	180-AP	1-vessel disease
4	60	M	III	0.56	92	120-AP-LBBB	120-AP-LBBB	3-vessel disease; proximal narrowing (75%) jump graft
5	50	M	II	0.68	69	120-AP	120-AP	3-vessel disease
6	53	M	II	0.44	113	120-AVB	120-AVB	3-vessel disease
7	62	M	II	0.65	79	170-AVB	170-AVB	1-vessel disease; postoperative 1 occluded graft
8	55	F	III	0.56	77	120-AP 150-AVB	120-AP 150-AVB	3-vessel disease
9	42	M	II	0.73	68	150-AVB	150-AVB	normal coronary arteries; LV biopsy: incipient cardiomyopathy
10	42	M	II	0.68	57	150-AVB	150-AVB	3-vessel disease; postoperative 1 occluded graft and 1 open graft

NYHA: functional class; EF: ejection fraction; EDV: end diastolic volumes; $APST_1$: maximum paced heart rate (BPM) and reason for arrest (AP: onset of angina pectoris; AVB: atrioventricular block; LBBB: left bundle branch block) during the first atrial pacing stress test. $APST_2$: same data during the second atrial pacing stress test.

were collected in duplicate from 10 patients who were catheterised because of suspected coronary artery disease. All but one proved to have abnormal coronary arteries. The clinical data from these patients are summarised in Table 1. Patients were studied after an overnight fast without pre-medication. β-adrenoceptor blockade and cardiac glycosides were withdrawn at least 24 h prior to catheterisation. Following right heart catheterisation and measurements of cardiac output by the thermodilution method, a bipolar pacing electrode catheter was positioned high in the right atrium. The left ventricle was catheterised via a right brachial arteriotomy and pressures were recorded by a Millar Instruments 7F dual tip manometer catheter. The reference level was set at midchest and compared with the fluid channel for baseline correction.

After control determinations of left ventricular pressures, the atrial pacing stress test (APST) was started at a level just above control heart rate (HR). One to two minutes was allowed for stabilisation followed by a 20 s data acquisition period where at least 12 heart beats were processed and averaged on-line by means of the representative beat method in a dedicated computer system (Meester *et al.*, 1974, 1975; Stenson *et al.*, 1968). The pacing rate was then increased in steps of 10–20 beats/min and the measurements repeated. Pacing was continued until any of the following endpoints was reached: (1) a rate of 180 beats/min (2) the onset of chest pain or (3) A-V dissociation. During the APST the following left ventricular pressure (LVP) derived variables were determined:

(1) Peak LV systolic pressure (LVSP) in mm Hg.
(2) LV end diastolic pressure (LVEDP) in mm Hg.
(3) Peak positive first derivative of LV pressure (peak dP/dt) in mm Hg/s.
(4) Peak LV dP/dt/P from total pressure, providing $P > 20$ mm Hg, (Peak Vce) in s^{-1}.
(5) dP/dt/P at 40 mm Hg of total pressure (Vce 40) in s^{-1}.
(6) dP/dt/P extrapolated to P = O mm Hg total pressure using a linear least squares fit from peak dP/dt/P to begin ejection, (V_{max}) in s^{-1}.

In order to assess reproducibility, APST was carried out twice in these 10 patients. Five of them experienced angina during both tests. The time interval between the tests was 20 min, during which time the patient's status was allowed to return to baseline.

For the second part of the study to assess the effect of Flecainide acetate (Tambocor®, Riker Laboratories) on left ventricular function, data were collected from 10 other patients also catheterised for suspected coronary artery disease. In these patients, a second atrial pacing stress test was carried out following administration of flecainide. Their clinical and haemodynamic data are summarised in Table 2. All patients were in sinus rhythm. Patients with a history

Table 2 Patient material for the flecainide study

Patient	*Age (years)*	*Sex*	*NYHA*	*EF*	*EDV (ml/m^2)*	*$APST_1$*	*$APST_2$*	*Coronary angiography*
1	55	M	II	0.52	88	160-AP	140-AVB	3-vessel disease
2	45	M	II	0.61	82	150-AVB	120-AVB	3-vessel disease
3	52	M	III	0.54	71	140-AP	120-AP	3-vessel disease
4	52	M	II	0.61	58	140-AVB	130-AVB	2-vessel disease
5	52	M	III	0.56	75	120-AP	120-AP	3-vessel disease
6	58	M	II	0.63	43	130-AVB	120-AVB	3-vessel disease; postoperative 1 patent and 1 occluded graft
7	52	M	III	0.62	72	140-AP	140-AVB	3-vessel disease
8	60	M	II	0.37	94	140-AP	140-LBBB	1-vessel disease
9	58	F	II	0.62	47	140-AP	140-VT+AP	2-vessel disease
10	36	F	II	—	81	180-AVB	160-AVB	normal coronary angiogram
				Mean ± s.e. mean		144 ± 5.2	133 ± 4.2	
						P value < 0.02		
						Student's paired *t*-test		

Same abbreviations as in Table 1. VT: ventricular tachycardia. $APST_1$: maximum paced heart rate (beats/min) and reason for arrest during the control atrial pacing stress test. $APST_2$: same data during the second atrial pacing stress test carried out following administration of flecainide.

of myocardial infarction or unstable angina within 6 weeks prior to the study, or with clinical evidence of heart failure were excluded. No significant conduction disturbances were present. Investigational drugs, other antiarrhythmic agents or agents that effect myocardial contractility (β-adrenoceptor blockers, cardiac glycosides) were not administered within four half-lives prior to this study. Also, patients with significant non-cardiac disease were excluded.

The procedure was explained to the patient who signed a formal consent before entering the study.

To assess the effect of flecainide acetate, the following protocol sequence was carried out. After baseline measurements, the control pacing stress test was performed. Post-pacing pressure derived variables were monitored every minute until they returned to basal values. A recovery period of 20 min was observed. The drug was then administered in the right atrium at a dosage of 2 mg/kg over a 10 min period. The pressure derived variables were monitored every minute. One minute after the end of infusion, blood was sampled from the coronary sinus in order to determine plasma levels of the drug. The samples were centrifuged immediately for at least 15 min (500–600 *g*) and the supernatant transferred to glass vials and frozen until determination of flecainide levels with a sensitive and specific gas–liquid chromatographic method (Johnson *et al.*, 1982). Cardiac output and haemodynamic measurements were then repeated at the basal HR and at a paced HR of 90 beats/min. Thereafter a second atrial pacing stress test was performed with drug plasma level sampling of the coronary sinus one minute after this second test had been completed.

Results

Reproducibility of haemodynamic parameters during pacing stress test

From the duplicate measurements at each level of heart rate, the s.d. of the random error component (e) in the measurement was estimated using the formula shown in Figure 2.

where: n = number of patients, i.e. 10.
ni = number of measurements made during the APSTs of the i-th patient
dij = the j-th difference between the first and the second APST-measurement at a given heart rate for the i-th patient

Sd(e) is a parameter which describes the spread of the measurements if they were to be repeated while the actual value remained constant. It is the 'yardstick' of the reproducibility of a measurement. The equation is a weighted average of a well known estimator of

$$sd(e) = \sqrt{\frac{\sum_{i=1}^{n}\left(n_i \sum_{j=i}^{ni} \frac{dij^2}{2n_i}\right)}{\sum_{i=1}^{n} ni}}$$

Figure 2 Equation expressing the random error component.

s.d.(e) when duplicate measurements are available (Barnett, 1971).

The duplicate measurements obtained during two consecutive APSTs are presented in Figure 3. S.d.(e) was estimated as 6.0 mm Hg for LVP, 2.9 mm Hg for EDP and 3.0 s^{-1} for V_{max}. For none of these parameters does the random error appear to depend on HR.

The differences observed in left ventricular pressure, end diastolic pressure and V_{max} during the two consecutive measurements were not affected by the increase in heart rate, so that the average difference between the two measurements remained close to zero over the entire pacing range. As the mesurements obtained during the APST showed good reproducibility, the test was employed to evaluate the action of flecainide in the same individual before and after drug administration.

Evaluation of flecainide acetate

Under resting conditions The cardiovascular effects of 2 mg/kg flecainide, administered at a rate of 0.2 mg kg^{-1} min^{-1} are summarised in Tables 3 and 4.

No significant effects of flecainide on LVP (Figure 4) and peak negative dP/dt were observed. LEVEDP and HR increased slightly, but significantly. All parameters related to contractility, such as peak positive dP/dt,. Vce 40, Vce, V_{max} both from total pressure and from developed pressure, decreased significantly (Figure 4). Administration of flecainide however had no effect on the decrease in ventricular pressure during early diastole (negative LV dP/dt).

Control values of cardiac index (CI) were 3.44 ± 0.63 l/min. One minute after flecainide was administered, this had decreased to 3.21 ± 0.63 l/min ($P < 0.05$). The small, but statistically significant decreases in cardiac index (CI) (− 7%) and stroke volume index (SI) (− 7%) observed after administration of flecainide were probably caused by the reduction of the contractile state of the left ventricle. Due to this reduction in cardiac output, the systemic vascular resistance was found slightly elevated (1100 ± 222 *vs* 1198 ± 259; $P < 0.05$). At a paced heart rate of 90 beats/min, CI and SI were also both reduced to a statistically significant extent after the administration of flecainide. (CI from 3.94 ± 0.87 to 3.59 ± 0.90; SI from 46 ± 9 to 42 ± 13). The mean plasma concentra-

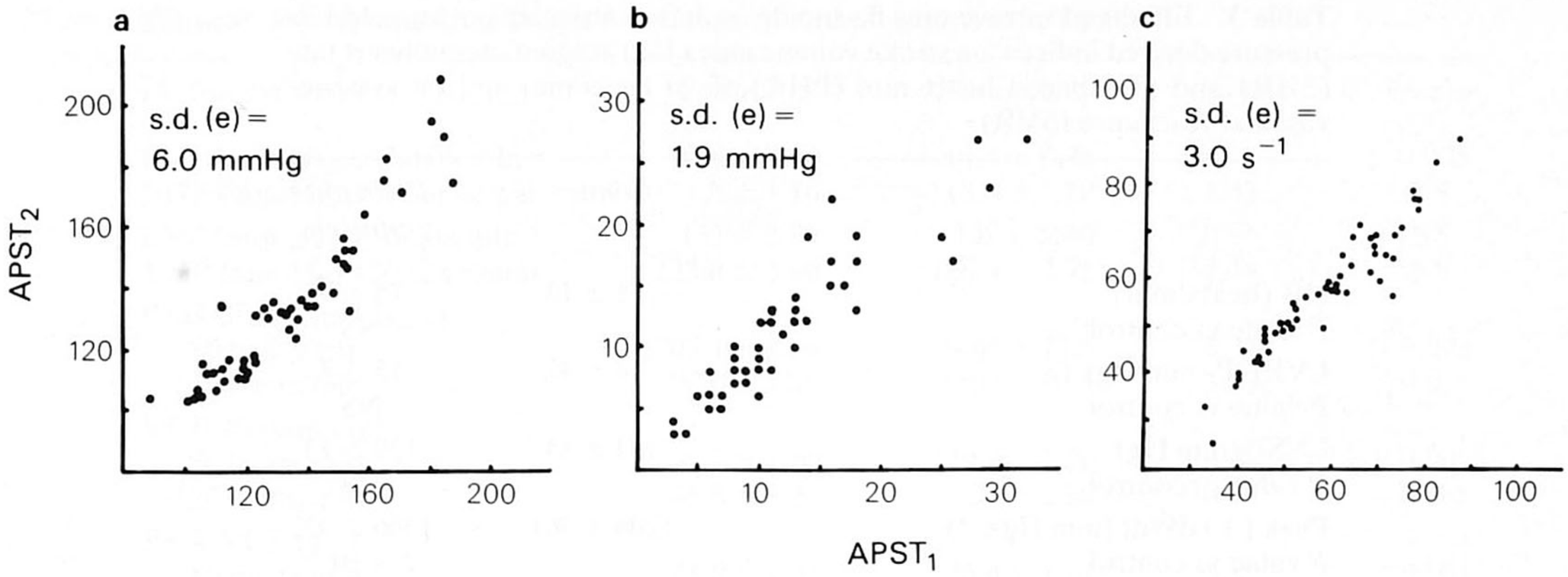

Figure 3 Individual data for a) LVSP, b) LVEDP and c) V_{max} during two consecutive atrial pacing stress tests in 10 patients with coronary artery disease.

tion of unchanged flecainide 1 min after the end of the intravenous administration was found to be 655 ± 70 ng/ml.

During the atrial pacing stress test After flecainide, the atrial pacing stress test had to be terminated in six patients at a lower paced heart rate than during the control stress test. In five because of an atrioventricular block and in one patient because of the occurrence of angina pectoris (Table 2). In addition, in two patients (Nos 8 and 9) the second atrial pacing (post-flecainide) stress test was discontinued at the same paced heart rate as during the first stress test because of the appearance of left bundle branch block in one patient and angina pectoris associated with a ventricular tachycardia (which reverted to sinus rhythm upon stopping the pacing) in the other.

For all these reasons, the mean highest paced heart rate after flecainide administration was significantly lower than during the control atrial pacing stress test (133 ± 4.2 *vs* 144 ± 5.2 beats/min; $P < 0.02$) (Table 2). During the control pacing and after flecainide, left ventricular pressure (LVP) showed, as expected, the same slight decrease of pressure from basal to highest paced rate. Despite a cross-over of the two curves, no significant differences could be demonstrated. On the other hand, at the basal heart rate and at a common heart rate of 100 beats/min, LVEDP was significantly increased by 4 mm Hg and 2 mm Hg, the difference being significant at the 0.005 and 0.02 levels respectively when flecainide was given (Figure 5). Nevertheless both the curves converge at the highest paced heart rate. This is surprising, because it indicates that the effective slope of the two curves is different. The decrease in LVEDP during pacing is generally interpreted as being the result of reduced diastolic filling, since with the increase in heart rate the filling period is reduced.

The curve of V_{max} *vs* HR is shifted downward, but remain parallel to the control over the entire pacing range (Figure 5). V_{max} post-flecainide is significantly lower than V_{max} control and the two relationships

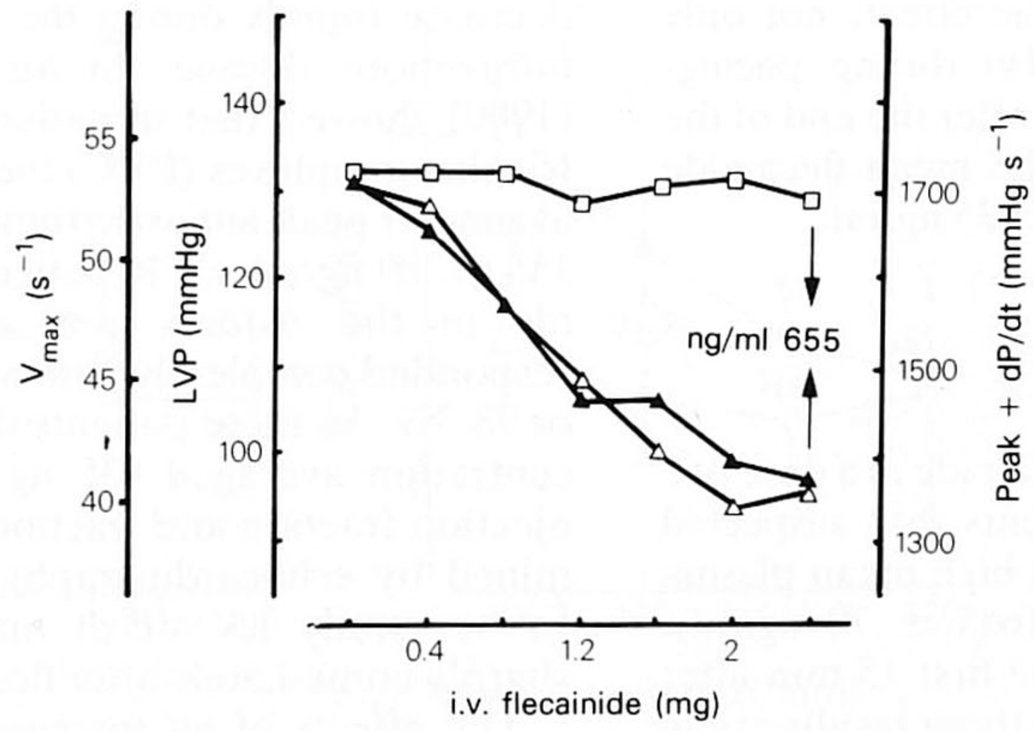

Figure 4 Change in LVP (□), peak positive dP/dt (▲) and V_{max} (△) during infusion of 2 mg/kg flecainide at a rate of 0.2 mg kg^{-1} min^{-1}.

Table 3 Effects of intravenous flecainide on left ventricular pressure and its pressure derived indices, on stroke volume index (SI) at spontaneous heart rate (SHR) and at a paced heart rate (PHR) of 90 beats/min and on systemic vascular resistance (SVR)

	Control	*1 min after infusion*
HR (beats/min)	71 ± 13	75 ± 9
P value *vs* control		NS
LVEDP (mm Hg)	14 ± 4	15 ± 4
P value *vs* control		NS
LVSP (mm Hg)	133 ± 14	129 ± 13
P value *vs* control		NS
Peak (+) dP/dt (mm Hg s^{-1})	1706 ± 361	1366 ± 322
P value *vs* control		2×10^{-5}
VCE 40 (mm Hg s^{-1})	35 ± 9	27 ± 6
P value *vs* control		< 0.0002
Peak VCE (s^{-1})	42 ± 14	31 ± 8
P value *vs* control		< 0.001
V_{max} TP (s^{-1})	53 ± 13	40 ± 8
P value *vs* control		< 0.0005
V_{max} DP (s^{-1})	77 ± 17	63 ± 9
P value *vs* control		< 0.0005
Peak (−) dP/dt (mm Hg s^{-1})	1908 ± 374	2008 ± 496
P value *vs* control		NS
SI with SHR ml $syst^{-1}$ m^{-2}	49 ± 10	45 ± 11
P value *vs* control		< 0.005
SI with PHR (90 beats/min) ml $syst^{-1}$ m^{-2}	46 ± 9	42 ± 13
P value *vs* control		< 0.02
SVR (dynes s cm^{-5})	1100 ± 222	1198 ± 259
P value *vs* control		< 0.05

HR: heart rate; LVEDP: left ventricular enddiastolic pressure; LVSP: left ventricular systolic pressure; VCE 40 mm Hg s^{-1}: velocity of contractile elements at 40 mm Hg; TP: total pressure; DP: developed pressure (Student's paired *t*-test; mean ± s.d.).

maintain their concave downward curvature up to the highest paced heart rate. These data indicate that flecainide has a negative inotropic effect, not only under resting conditions but also during pacing-induced tachycardia. One minute after the end of the second atrial pacing stress test the mean flecainide plasma level was found to be 412 ± 35 ng/ml.

Discussion

Intravenous administration of flecainide in a dose of 2 mg/kg, at 0.2 mg/kg/min to patients with suspected coronary artery disease results in high mean plasma levels of unchanged flecainide (655 ± 70 ng/ml), which decrease rapidly during the first 15 min after administration (412 ± 35 ng/ml); these results are in good agreement with plasma level data in healthy male subjects following single intravenous doses of 0.5 to 2.0 mg/kg (Conard *et al.*, 1976, 1979) and further indicate that initial levels of flecainide decrease rapidly during the distribution phase after intravenous dosage. In his clinical study Somani (1980) showed that in patients with premature ventricular complexes (PVC) the effective concentration at time of peak antiarrhythmic response ranged from 155 to 389 ng/ml. Of 10 patients receiving oral flecainide in the Anderson *et al.* (1981) study, nine responded completely with a mean PVC suppression of 98.3%. In these patients the effective plasma concentration averaged 635 ng/ml. In the same study ejection fraction and fractional shortening, as determined by echocardiography, remained unchanged. In our study LV dP/dt max and V_{max} decreased sharply immediately after flecainide administration.

The effects of an increase in heart rate on V_{max} during two consecutive atrial pacing stress tests and before and after flecainide are summarised in Figure

Table 4 Pacing stress test (mean ± s.e. mean). Abbreviations as in Table 3

Pacing stress test	*Control*	*Flecainide*	t *value*	P *value*
EDP (mm Hg) 80 beats/min	10.4 ± 0.99	14.4 ± 0.38	4	< 0.005
EDP (mm Hg) 120 beats/min	9 ± 1.16	10.4 ± 1.22	1.53	NS
LVP (mm Hg) 80 beats/min	132 ± 3.89	132 ± 5.40	0	NS
LVP (mm Hg) 120 beats/min	123.4 ± 3.60	128.4 ± 2.72	2.18	NS
Peak dP/dt (mm Hg/s)				
80 beats/min	1705.1 ± 82.6	1466 ± 73.6	5.38	< 0.002
120 beats/min	1936 ± 130	1692 ± 90	3.53	< 0.01
VCE 40 (mm Hg)				
80 beats/min	36.3 ± 1.60	29.8 ± 1.26	6.68	< 0.0005
120 beats/min	43.8 ± 3.32	36 ± 2.20	4.74	< 0.002
Peak VCE (s^{-1})				
80 beats/min	45.8 ± 2.31	36.4 ± 1.61	5.52	< 0.001
120 beats/min	56.3 ± 4.96	45.7 ± 3.49	4.76	< 0.001
V_{max} TP (s^{-1})				
80 beats/min	55.5 ± 2.54	45.5 ± 1.93	6.59	< 0.0005
120 beats/min	65.5 ± 4.76	53.5 ± 3.32	5.25	< 0.001
V_{max} DP (s^{-1})				
80 beats/min	76.6 ± 4.44	67.8 ± 3.13	4.38	< 0.005
120 beats/min	90.2 ± 5.39	74.3 ± 3.61	6.11	< 0.0002
Peak (−) dP/dt (mm Hg s^{-1})				
80 beats/min	2034 ± 114	1908 ± 109	1.50	NS
120 beats/min	1990 ± 116	2008 ± 135	0.87	NS

5. Since no significant increase in difference between V_{max} (control) and V_{max} (flecainide) could be demonstrated at higher paced heart rate, it might be argued that the drug had no additional depressant effect on left ventricular performance at an increasing level of stress (Figure 6).

In the anaesthetized pig a negative inotropic action on the myocardium was observed following 2 mg/kg flecainide intravenously as stroke volume decreased, while pre- and afterload were not affected and max LV dP/dt decreased by 20% (Verdouw *et al.*, 1979). In the present study in humans, similar changes in stroke index and max LV dP/dt were observed. It is thus reasonable to assume that the decrease in the stroke index in this study is at least partly due to a slight negative inotropic effect of flecainide, although one must also take into account that the systemic vascular resistance was elevated. In the forementioned experimental study (Verdouw *et al.*, 1979) a high correlation existed between the widening of the QRS-complex, plasma levels of flecainide, and the depression of max LV dP/dt. Although from this type of investigation it cannot be concluded whether there is a direct relationship between these two variables, it

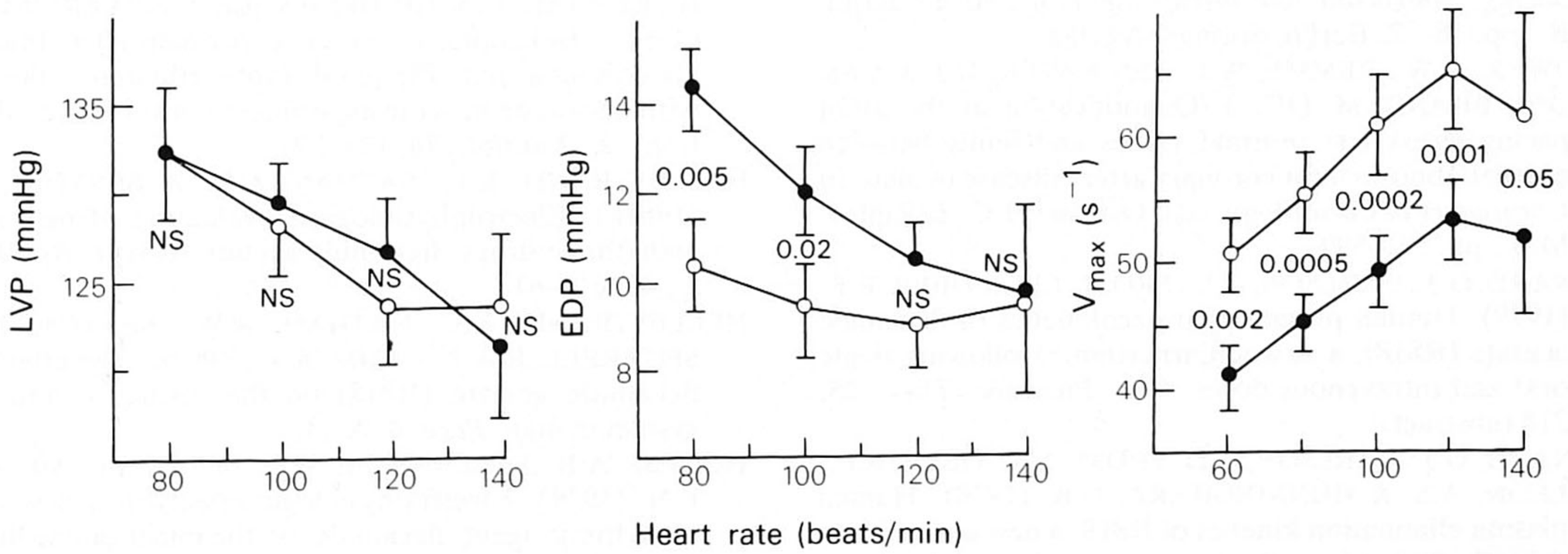

Figure 5 Mean ± s.e. mean effect of flecainide (●) on left ventricular pressures and V_{max} during the atrial pacing stress test. (○) control. Statistical analysis—Student's paired *t*-test.

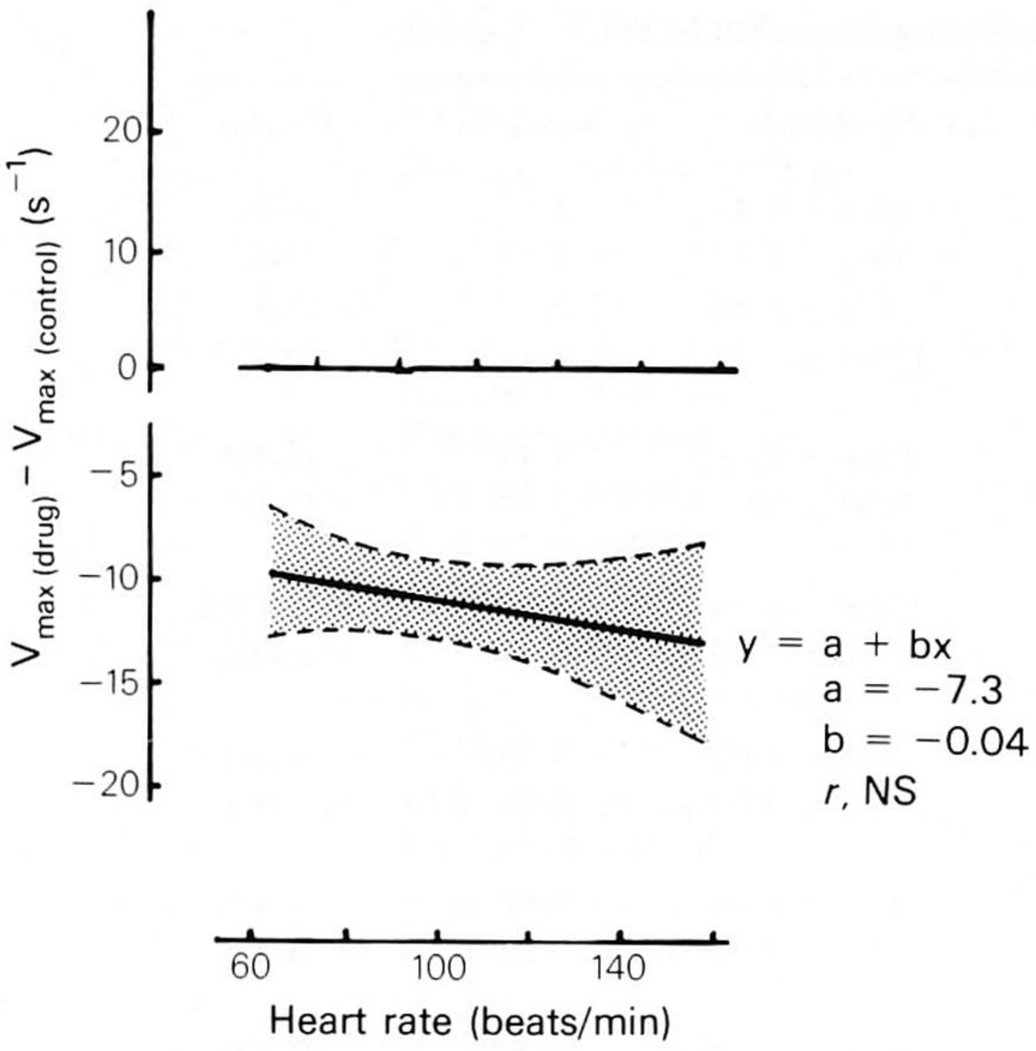

Figure 6 Difference between V_{max} control and V_{max} after flecainide at different heart rates during the atrial pacing stress test. The shaded portion represents the 95% confidence interval.

may be of interest to monitor QRS-width as an indicator of plasma concentrations of flecainide and depression of cardiac function.

The negative inotropic effect and the slight increase in peripheral vascular resistance may be undesired in patients with severe ischaemic heart disease or those suffering from a myocardial infarction and a failing heart. It therefore appears advisable to administer the drug at a rate much slower than 0.2 mg/kg/min in patients at risk in order to avoid these acute haemodynamic changes related to the initial high plasma levels.

Relatively little attention has been paid to the effects of antiarrhythmic drugs on the ischaemic myocardium. In their experimental study in pigs, Verdouw *et al.* (1979) demonstrated that flecainide did not modify the degree of ischaemia and that the ischaemic heart could tolerate the administration of a dose of 2 mg/kg without additional depression of overall left ventricular function. However in the present study, one patient on flecainide experienced angina at a lower paced heart rate than during the control APST. Another, with pacing-induced angina at the same heart rate as during the control test, developed ventricular tachycardia that spontaneously reverted to sinus rhythm after stopping the pacing.

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