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Haemodynamic effects of encainide, flecainide, lorcainide and tocainide

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The haemodynamic effects of encainide, flecainide, lorcainide and tocainide in man are reviewed. Most of the investigations discussed are acute intervention studies after intravenous administration of the drugs. With all four drugs, haemodynamic changes, when present, were moderate. In most studies a decrease in left ventricular maximal dp/dt is demonstrated, suggesting a negative inotropic action. Left ventricular filling pressures are unchanged or slightly increased. A small decrease in cardiac performance, as determined by measurements of cardiac output and left ventricular ejection fraction, is usually observed, while systemic vascular resistance is increased or remains unchanged. Haemodynamic deterioration and/or hypotensive reactions after intravenous administration of any of the above drugs are uncommon in patients without severe cardiac dysfunction. Conclusions relative to drug safety in frank congestive failure are not warranted, in view of the small number of patients studied.

While comparative studies between the drugs discussed have not been performed, the data presented here indicate that, on the basis of haemodynamic action, no one drug can be preferred above the other.

Introduction

Most presently available antiarrhythmic agents have a negative inotropic effect when used in doses adequate to control ventricular arrhythmias. The potential clinical usefulness of new antiarrhythmic agents would be significantly enhanced if they depressed ventricular function only minimally, so that patients with impaired cardiac function, who often present with severe ventricular arrhythmias, could also benefit from their administration.

In the past few years the number of antiarrhythmic agents available for the treatment of arrhythmias has markedly increased. Encainide, flecainide, lorcainide and tocainide have all proved to be very effective in suppressing premature ventricular beats and more severe ventricular arrhythmias. All these newly developed drugs, classified as class I 'membrane depressant' agents according to Vaughan-Williams[1], have negative inotropic properties as demonstrated by animal studies[2–5]. We reviewed their haemodynamic effects in man during acute intravenous administration and during chronic oral treatment[6–23].

Haemodynamic effects of encainide

Following routine diagnostic cardiac catheterization Tucker *et al.*[6] administered 0·9 mg kg^{-1} encainide over a 15 min period. Baseline values were measured minimally 30 min after the last injection of contrast medium. Systemic vascular resistance and cardiac index were unchanged at the end of the infusion, but increased by 9% and decreased by 8%, respectively, after 30 min. A decrease in left ventricular end-diastolic pressure (LVEDP) by 15% was noted and heart rate augmented by 4%. Systemic arterial pressures and LV dp/dt remained unchanged throughout the study period. Interpretation of the data was complicated by the observation that the differences noted in cardiac index, LVEDP and systemic vascular resistance were not evident when post-encainide data were compared with the pre-angiography baseline data. Indeed, a residual effect of the contrast material was likely to be still present at the start of the encainide infusion, while a broad trend towards a return to pre-angiography values was noted during and after drug infusion. When subdividing patients according to cardiac index, this value in the low output group ($CI < 2{\cdot}4$ l min^{-1} m^{-2}), was significantly lower after encainide than before or after angiography. This modest decrease in cardiac output might also be a result of a decreased left ventricular filling pressure.

Di Bianco *et al.*[7] evaluated the effects of oral encainide on ventricular arrhythmia and left ventricular function in 21 patients with high-grade ventricular arrhythmias during a prospective 3-month single-blind

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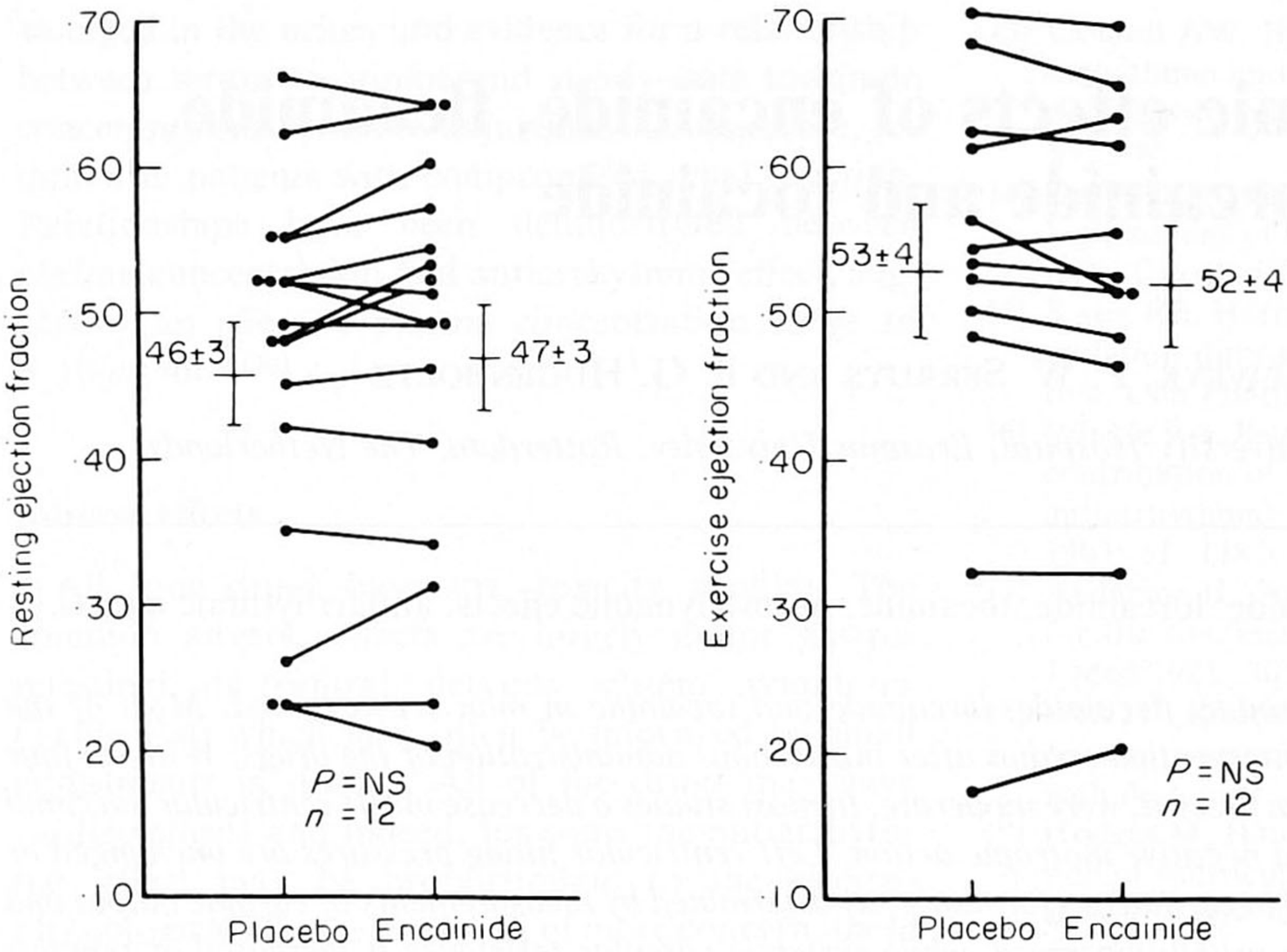

Figure 1 Individual patient responses for left ventricular ejection fraction determined by radionuclide cineangiography at rest and at maximal exercise during placebo and encainide treatment. (DiBianco *et al.*[7]) Reproduced with permission.

placebo-controlled study. Sixteen of the 21 patients underwent radionuclide angiographic studies on placebo and on a dose of encainide that effectively suppressed premature ventricular beats. The average ejection fraction, heart rate, systolic blood pressure and rate-pressure product at rest were not significantly different from the average values on placebo treatment (Fig. 1). Furthermore, no change in these parameters was present in 12 of these patients, during exercise when compared with placebo data. No deterioration in cardiac function was observed in six patients with pre-existing left ventricular functional impairment (EF $< 45\%$). Fifteen patients underwent symptom-limited treadmill exercise tests on placebo and during encainide treatment. Average exercise duration was not different on encainide compared with placebo. It was of interest to note, however, that maximum ST-segment depression was significantly increased on encainide, compared with placebo. It was concluded that oral encainide did not reduce exercise capacity or left ventricular ejection fraction at rest or during supine exercise.

In contrast, a recent study by Metcalfe *et al.*[8] demonstrated the cardiac depressant effects of intravenous encainide. They infused cumulative doses of 1·0 and 2·0 mg kg^{-1} over 15 min periods in 14 coronary artery disease patients. Measurements were repeated before infusion, after completion of the 1·0 and 2·0 mg kg^{-1} infusions of encainide and 30 min later. LV dp/dt_{max} declined by 11·9% after 1·0 mg kg^{-1} encainide and by 20% after 2·0 mg kg^{-1}. Cardiac index decreased by 18·5% and vascular peripheral resistance increased by 26·2% after 2·0 mg kg^{-1} encainide. The fall in LV dp/dt_{max} persisted for 30 min after infusion. The same authors observed a decrease in coronary vascular resistance after encainide. We agree with them that caution should be exercised when intravenous doses above 1·0 mg kg^{-1} are used in the presence of left ventricular dysfunction.

Haemodynamic effects of flecainide

Hodges *et al.*[9] studied the effects of flecainide on cardiac function in 10 normal subjects and in 20 patients with cardiac disease. Echocardiographic measurements and determinations of systolic time intervals were performed. Small increases in pre-ejection period, pre-ejection period/left ventricular ejection time ratio and left ventricular end-systolic volume were observed in both normal subjects and patients. There were also significant decreases in velocity of contractile shortening (Vcf) and ejection fraction. Calculated cardiac output remained unchanged as well as left ventricular end-diastolic volume. Although flecainide depressed cardiac performance, changes in overall pump function were minimal.

Other authors[10–12] have evaluated echocardiographic parameters of left ventricular function. No

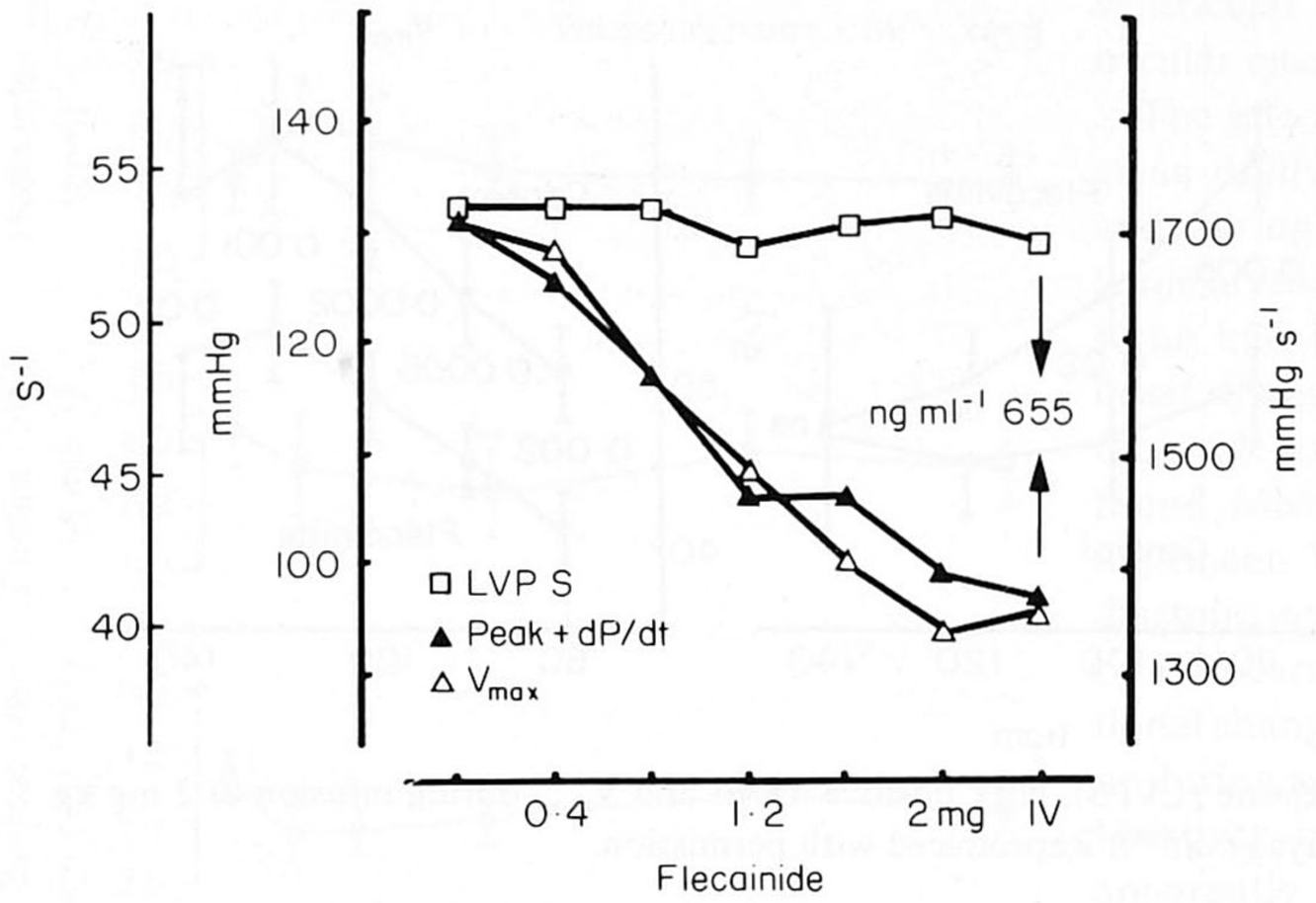

Figure 2 Change in left ventricular systolic pressure (LPV), left ventricular end-diastolic pressure (EDP) and V_{max} during two atrial pacing stress tests, one during a control period and one after 2 mg kg^{-1} intravenous flecainide administration. (Surruys *et al.*[14]) Reproduced with permission.

statistically significant change in blood pressure, heart rate, ejection fraction or fractional shortening was noted. During exercise testing, patients taking flecainide had normal blood pressure responses, and no change was seen in exercise performance.

Legrand *et al.*[13] studied invasively the effect of 2 mg kg^{-1} flecainide over 30 min in 10 patients with a recent acute myocardial infarction and ventricular arrhythmias. At the time of haemodynamic measurements, 15 min after drug infusion, plasma levels were between 329 and 470 ng ml^{-1}. An increase of 27% in pulmonary wedge pressure was observed. In four patients the increase in pulmonary wedge pressure equalled or exceeded 50%. Diastolic volume after flecainide was unchanged, but systolic volume increased in all patients, causing a significant decrease in stroke index (−10%) and ejection fraction (−9%). No significant increase in systemic and pulmonary vascular resistance was noted. In six patients the contractility parameter dp/dt was measured, which exhibited a progressive decrease during flecainide infusion and returned to near basal values within 15 min after infusion. The authors concluded that flecainide exerts a negative inotropic effect on the myocardium. It is important to stress that the plasma levels of flecainide reached at the time of haemodynamic evaluation were relatively low.

The haemodynamic effect of flecainide was studied at rest and during an atrial pacing stress test by our group[14]. Ten patients with coronary artery disease but without cardiac failure were given 2 mg kg^{-1} intravenous flecainide over a 10 min period. Under resting conditions during the infusion period parameters related to contractility, such as peak positive dp/dt and V_{max}, decreased gradually in a dose-related manner (Fig. 2). No significant effect on left ventricular systolic pressure or on the parameter of left ventricular relaxation, peak negative dp/dt, was observed. LVEDP and heart rate increased towards the end of the infusion, but these changes became insignificant 1 min after stopping flecainide. Control values of cardiac index were $3{\cdot}44 \pm 0{\cdot}63$ l min^{-1} m^{-2}. One minute after flecainide was administered, this had decreased to $3{\cdot}21 \pm 0{\cdot}63$ l min^{-1} m^{-2}. The small, but statistically significant decrease in CI (−7%) and also in stroke volume index (SI) (−7%) were probably caused by the reduction of the contractile state of the left ventricle. Systemic vascular resistance was found to be slightly elevated after flecainide (+9%). At a paced heart rate of 90 beats min^{-1}, CI and SI were also both reduced by 9%. During the control pacing and after flecainide, left ventricular systolic pressure showed the same slight decrease from basal rates to the highest paced rate.

On the other hand, at paced heart rates of 80 and 100 beats min^{-1}, LVEDP was significantly increased by 4 mmHg and 2 mmHg when flecainide was given (Fig. 3). Nevertheless the curves converge at the highest paced heart rate. The curve of V_{max} versus heart rate is shifted downward, but remains parallel to the control over the entire pacing range. These data indicate that flecainide has a negative inotropic effect, not only during resting conditions but also during pacing-induced tachycardia. It therefore appears advis-

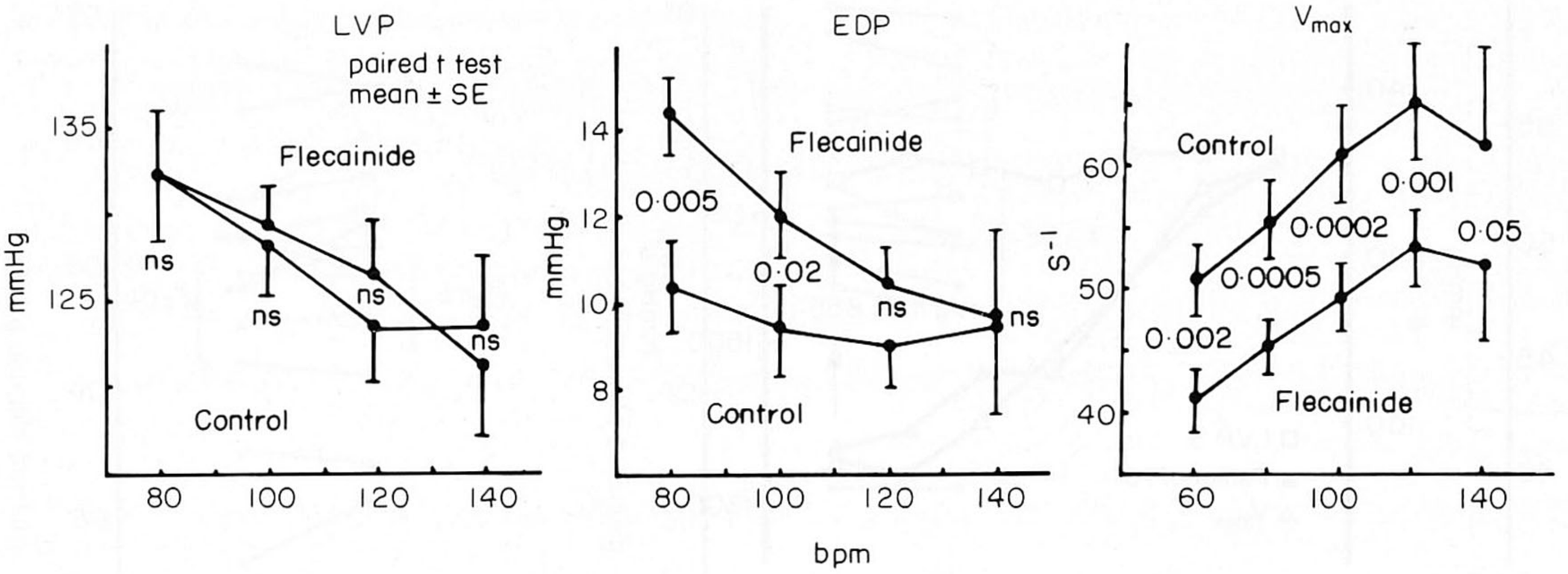

Figure 3 Change in left ventricular systolic pressure (LVPS), peak positive dp/dt and V_{max} during infusion of 2 mg kg^{-1} flecainide at a rate of 0·2 mg kg^{-1} min^{-1}. (Serruys *et al.*[14]) Reproduced with permission.

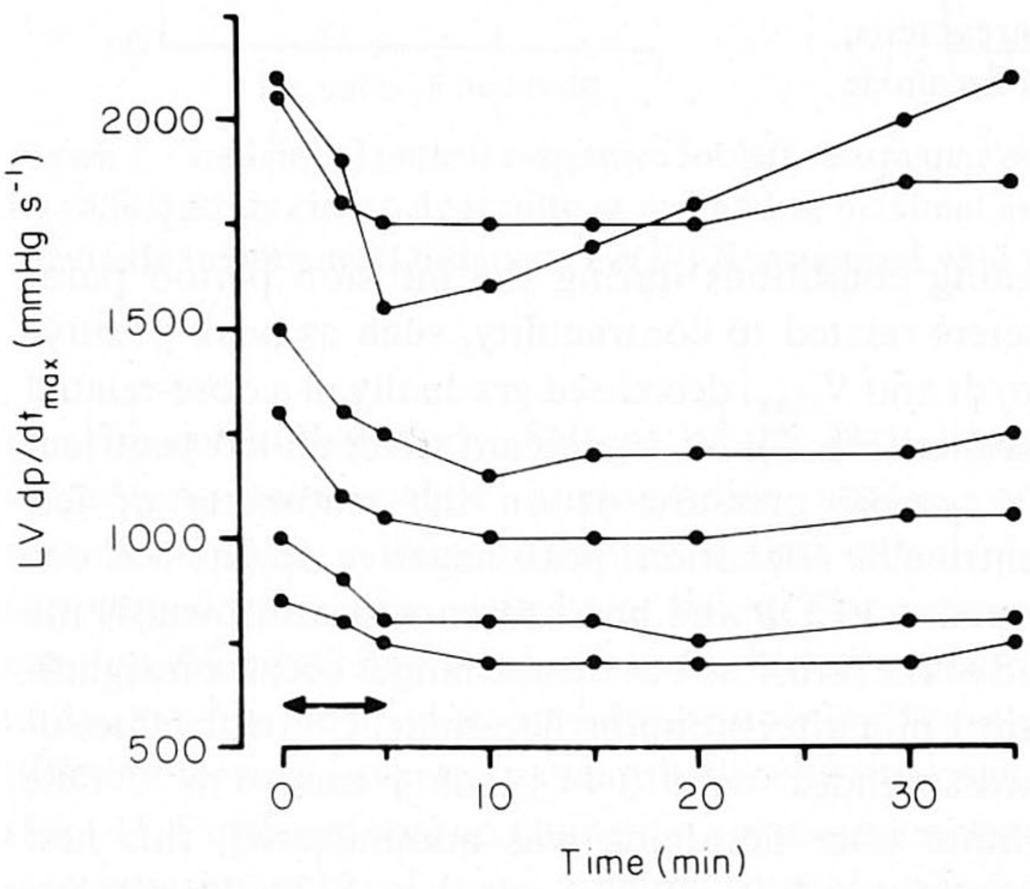

Figure 4 Left ventricular maximal positive dp/dt before and after administration of lorcainide (2 mg kg^{-1} intravenously in 5 min) in individual patients. A significant decrease in maximal +dp/dt is observed, reaching its maximum effect 5 to 15 min after beginning the infusion. (Meinertz *et al.*[15]) Reproduced with permission.

able to administer the drug at a slower rate in patients at risk in order to avoid the acute haemodynamic changes related to initial high plasma levels.

Haemodynamic effects of lorcainide

Meinertz *et al.* [15] studied the haemodynamic (6 patients) and the angiographic (8 patients) effect of intravenous lorcainide 2 mg kg^{-1} over 5 min. Lorcainide depressed dp/dt by 19% (Fig. 4). Cardiac output and systemic vascular resistance remained unchanged after lorcainide, while a slight and short-lasting decrease in systolic aortic and pulmonary pressure was produced. In seven out of eight patients, lorcainide decreased left ventricular ejection fraction (−10·4% of baseline values). Also VCF diminished in all patients. The decrease in ejection fraction was no more severe in the three patients with an ejection fraction below 30%. The authors concluded that the depressant effects of lorcainide reflect a direct action on the myocardium, since preload and afterload were not significantly altered.

In ten patients with an uncomplicated acute myocardial infarction, studied by Shita *et al.*[16], the haemodynamic changes observed after 150 mg lorcainide IV over 6 min also reflected some depression in myocardial function. During the first half hour after starting the drug infusion, stroke index decreased by 10%, as a slight increase in heart rate was noted together with an unchanged cardiac index (Fig. 5). The mean pulmonary wedge pressure increased transiently from 6·6 to 8·4 mmHg and no change in systemic arterial pressures or peripheral vascular resistance was found. One hour after lorcainide administration a 5% decrease in cardiac output and a minimal increase in peripheral resistance were still present. The use of intravenous lorcainide in patients with an uncomplicated acute myocardial infarction appears safe, as this drug causes only slight and transient myocardial depression.

Haemodynamic effects of tocainide

Winkle *et al.*[17] evaluated the haemodynamic effects of intravenously administered tocainide in 12 patients, 10 of whom had proven coronary artery disease. Doses were 0·5 mg kg^{-1} min^{-1} (4 patients) or 0·75 mg kg^{-1} min^{-1} (8 patients) over a 15 min period. At the end of the tocainide infusion, small but significant increases were present in pulmonary and

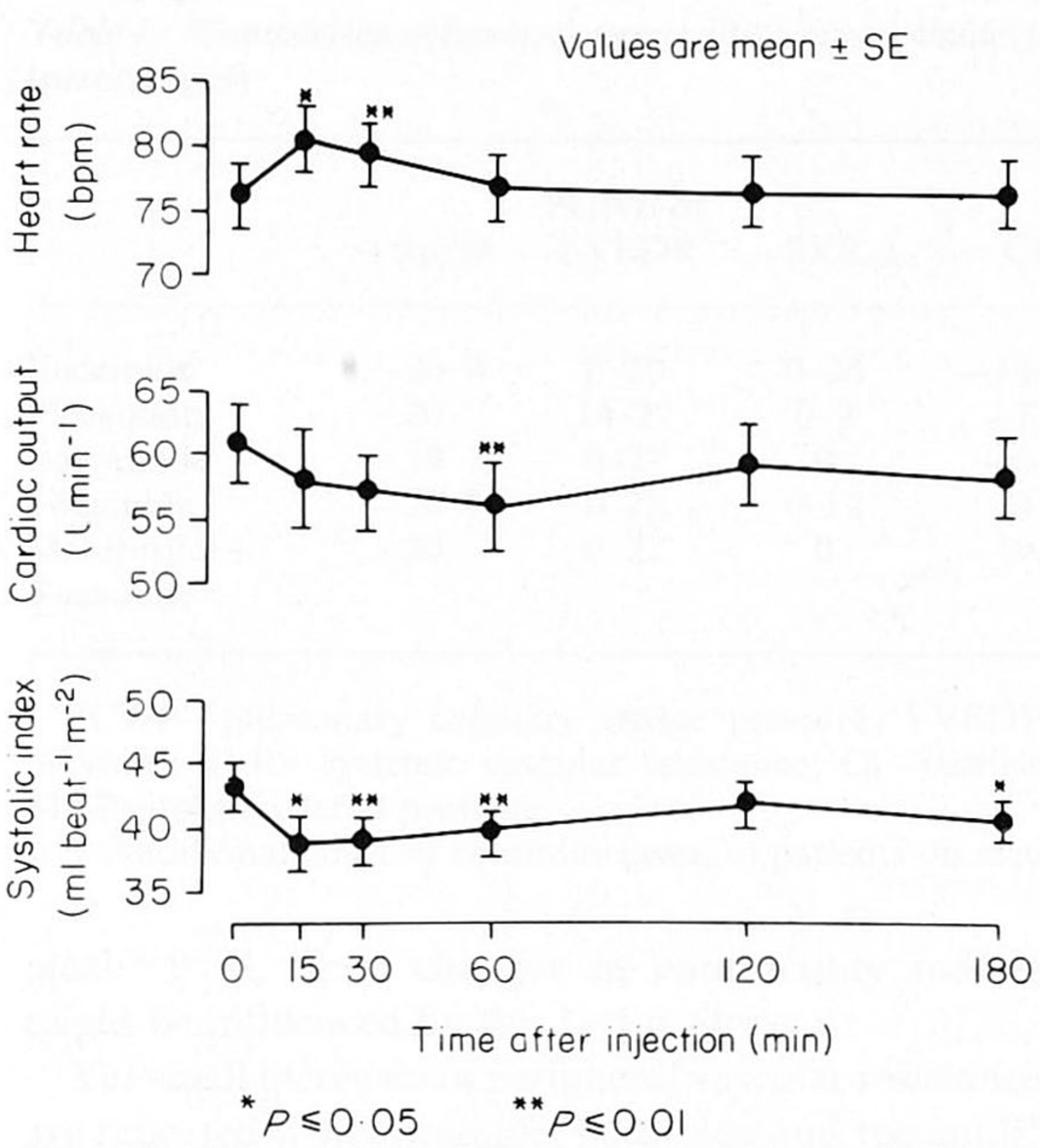

Figure 5 Heart rate, cardiac output and systolic index before (time 0) and after intravenous injection of 150 mg lorcainide in 6 min. (Shita *et al.*[16]) Reproduced with permission.

systemic vascular resistance (+12%), pulmonary and aortic arterial pressure (+7·3%) increase in mean aortic pressure) and in right and left ventricular (+28·2%) end-diastolic pressure. No significant change in left ventricular dp/dt, heart rate or cardiac index could be demonstrated. The transient rise in left ventricular end-diastolic pressure may have resulted from the small increase in vascular resistance or from a direct myocardial depressant effect, as suggested by the authors themselves.

Schwartz *et al.*[18] studied the haemodynamic actions of 0·50 mg kg^{-1} min^{-1} or 0·75 mg kg^{-1} min^{-1} intravenous tocainide over 15 min in 11 subjects undergoing diagnostic cardiac catheterization. Mean LV ejection fraction before tocainide was 45·6% and mean cardiac index measured 1·70 ± 0·12 l min^{-1} m^{-2}. The data of the two differing dosages were combined, since no statistically significant difference between the two rates of infusion was noted. Contrary to the results of Winkle *et al.* no change in systemic or pulmonary vascular resistance was present. The only changes present were a decrease in LV dp/dt by 19·7% at the end of infusion and 17·6% 15 min after infusion, while pulmonary artery diastolic and mean pressure increased temporarily.

It is of further interest to note that Klein *et al.*[19], in a study evaluating the antiarrhythmic efficacy of tocainide, did not observe clinical deterioration in left ventricular function in three patients with a left ventricular ejection fraction below 30%.

The effects of 400 mg tocainide, three times daily given orally, on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure were studied non-invasively by Ryan and Karliner[20] in ten patients with valvular heart disease. In this double-blind crossover trial of tocainide and placebo, no significant difference was found. Mean velocity of circumferential fibre shortening (mean VCF), mean posterior wall velocity, end-diastolic and end-systolic dimensions, all determined by echocardiography, demonstrated the same directional changes after increasing heart rate with atropine or during acute pressure loading with phenylephrine. However, mean plasma tocainide concentration was apparently lower than during the above-mentioned acute intervention studies.

Different results have been reported by Wester and Mouselimis[21]. In a randomized study in 20 patients with coronary artery disease they evaluated the influence of different antiarrhythmic drugs on left ventricular function as determined by echocardiography. Propafenon, mexiletine, tocainide, disopyramide or placebo were given over seven-day periods. During the tocainide treatment period a decrease in mean arterial pressure by 11 mmHg was noted. End-diastolic and end-systolic diameters increased by 6 and 11%, respectively. Interventricular septum and left ventricular posterior wall motion both decreased by 24% and mean velocity of circumferential fibre shortening by 11%. It was of interest to observe that the changes induced by propafenon and mexiletine were very similar to those seen after tocainide, while the negative inotropic properties of disopyramide were more pronounced. Indeed, three patients developed pulmonary oedema, while receiving disopyramide.

Since it is possible that combinations of antiarrhythmics or combinations of an antiarrhythmic agent with a drug known to depress myocardial contractility might result in more pronounced haemodynamic changes, Ikram[22] examined the haemodynamic effects of 0·20 mg kg^{-1} intravenous metroprolol followed by a 15 min infusion of 0·75 mg kg^{-1} min^{-1} tocainide in six patients undergoing routine diagnostic catheterization. Left ventricular dp/dt_{max} decreased by 17·5% 15 minutes after metoprolol infusion and decreased further by 20·4% immediately after tocainide. Left ventricular end-diastolic pressure was unaltered after metoprolol and slightly increased by approximately 1 mmHg after adding tocainide. Cardiac index decreased from 3·49 ± 1·53 l min^{-1} m^{-2} to 2·80 ± 1·64 l min^{-1} m^{-2} after metoprolol. After adding tocainide a cardiac

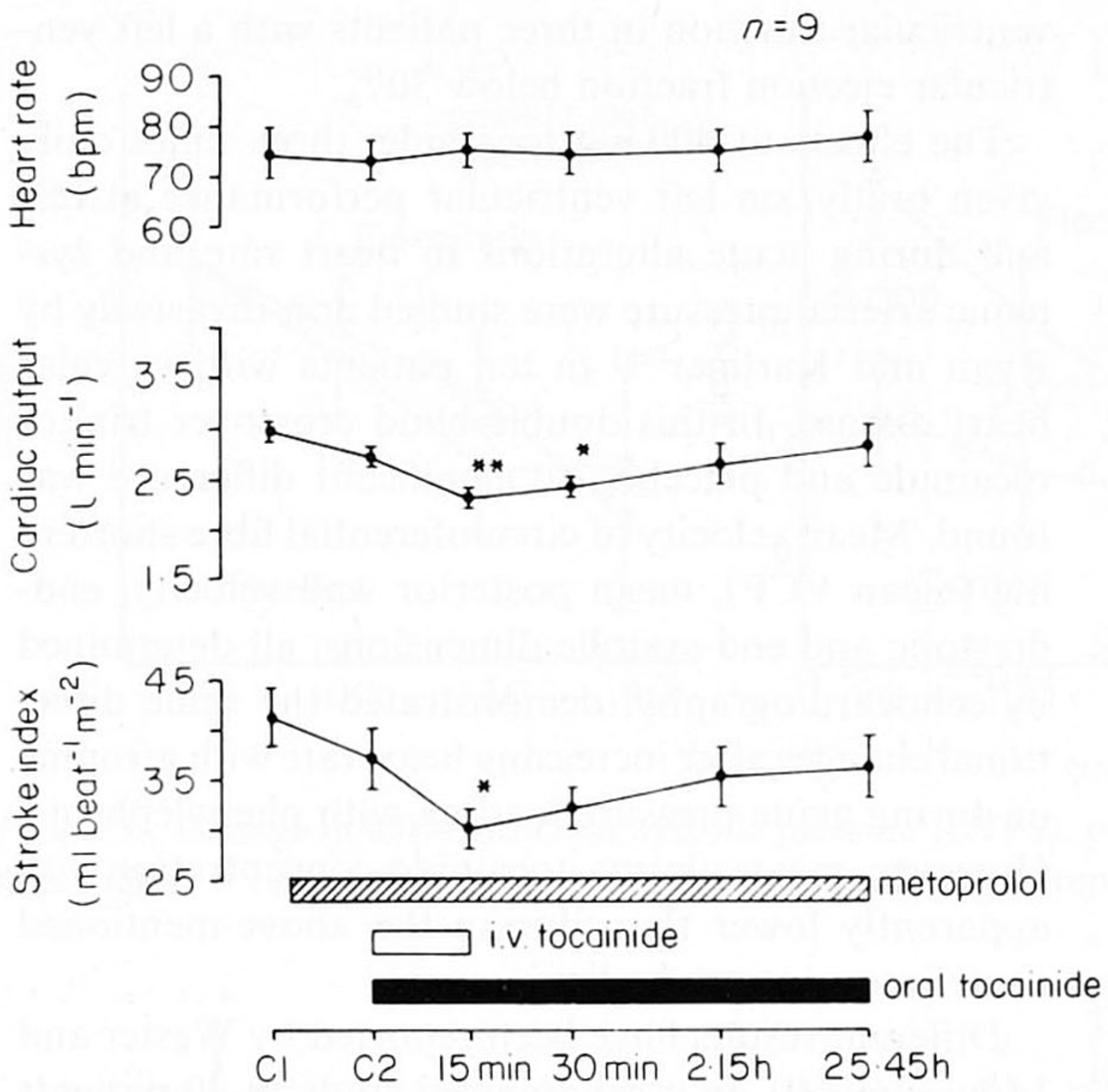

Figure 6 Heart rate, cardiac index and stroke index before (C_1, C_2) and 15 min, 30 min, 2 h 15 min and 2 h 45 min after injection of 750 mg tocainide over 15 min in patients pretreated with metroprolol. Values are mean ± S.E.M. $*P < 0{\cdot}05$; $**P < 0{\cdot}01$. (Renard *et al.*[23]) Reproduced with permission.

index of 2·27 l min^{-1} m^{-2} was measured. The latter change was statistically insignificant, but it is obviously of importance to evaluate combined administration of the various antiarrhythmic agents with beta-blocking agents in a larger group of patients.

The haemodynamic interaction of metoprolol and tocainide was further evaluated by Renard *et al.*[23] in nine patients hospitalized with an acute uncomplicated myocardial infarction. Patients were given metoprolol 50 mg orally three times daily during two days. Tocainide 750 mg intravenously over 15 min was added 25 h after the start of metoprolol, immediately followed by 800 mg tocainide orally and then by 400 mg tid. Except for moderate decreases in systolic and mean arterial pressures, the haemodynamic changes observed after oral metoprolol were minor, and difficult to assess because of possible spontaneous haemodynamic changes. Cardiac index and stroke index were significantly reduced by 15% and 19% at the end of the tocainide infusion (Fig. 6). Neither the systemic vascular resistance nor the pulmonary wedge pressure changed significantly after tocainide. The haemodynamic changes observed during and shortly after intravenous tocainide administration had all disappeared when measurements were repeated 2 h after stopping the infusion. The authors concluded that addition of intravenous tocainide to patients on metoprolol results in a transient depression of left ventricular function, and advised a slower rate of administration of tocainide in patients pretreated with metoprolol or other beta-blocking agents.

Concluding remarks

Haemodynamic changes due to a negative inotropic action must be anticipated as 'side-effects' of most current available antiarrhythmic agents. Data concerning the haemodynamic actions and their influence on myocardial ischaemia are rather limited, since most of the studies have concentrated, as can be expected, on their antiarrhythmic properties. Impairment of myocardial performance might be of clinical importance and can hamper the potential utility of an antiarrhythmic agent[24]. However, it should also be taken into account that suppression of frequent ventricular premature beats or more severe ventricular arrhythmias should ameliorate myocardial function.

From our review we conclude that most investigations are acute intervention studies after intravenous administration of the drugs.

Left ventricular contractility indices such as maximal dp/dt remain unchanged or demonstrate a tendency towards lower values. Since all drugs discussed, except for tocainide, can induce prolongation of intraventricular conduction with widening of the QRS-com-

Table 1 Comparison of haemodynamic effects of encainide, flecainide, lorcainide and tocainide (percentages)

	+dp/dt	PCWP or LVEDP	SVR	CI	EF	MAP
Encainide	−20–0	0–20	0–26	−19–0	0	0
Flecainide	−20	14–27	0–9	−7	−9	0
Lorcainide	−19	0–27	0	−6–0	−10	0
Tocainide	−20–0	0–28	0–12	0	—	0–7
Metoprolol + Tocainide*	−20	0–22	0	−19–15	—	0

PCWP—pulmonary capillary wedge pressure; LVEDP—left ventricular end-diastolic pressure; SVR—systemic vascular resistance; CI—cardiac index; EF—ejection fraction; MAP—mean arterial pressure.

* Additional effect of tocainide given to patients on metoprolol.

plex[13, 25–27], these changes in contractility indices might be influenced by this factor alone.

Yet small increases in peripheral vascular resistance are reported with encainide, flecainide and tocainide. Changes in myocardial performance, as determined by measurements of cardiac output and left ventricular ejection fraction, are moderate and should be tolerable even in patients with some cardiac dysfunction. Conclusions relative to drug safety in frank congestive heart failure are not warranted in view of the small number of patients studied. Indeed, haemodynamic deterioration after encainide[6, 7] in compromised patients has been described. Slower infusion rates than usual may be advised in this subgroup of patients. When haemodynamic changes become evident after acute intravenous injection they are most pronounced at the time of initial high plasma drug levels. The data of Renard *et al.*, albeit in beta-blocked patients, seem to indicate that haemodynamic changes observed during acute intravenous tocainide administration are short-lasting. In fact, at similar plasma drug levels after an oral tocainide loading dose, no haemodynamic change is observed. The lack of haemodynamic effects observed during chronic oral treatment in most (non-invasive) studies suggests that changes after oral treatment will be less pronounced than after intravenous administration.

Since comparative haemodynamic studies between the drugs discussed have to the best of our knowledge not been performed, the data presented here indicate that, on the basis of haemodynamic action, no one drug can be preferred above the other as is evident from Table 1.

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