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Effect of low dose β blockers on atrial and ventricular (B type) natriuretic factor in heart failure: a double blind, randomised comparison of metoprolol and a third generation vasodilating β blocker

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Abstract

***Objectives*—This study examines the acute effects of two differing β adrenergic blocking agents (metoprolol and a third generation vasodilating β blocker) on plasma concentrations of atrial natriuretic factor (ANF), brain (ventricular) natriuretic factor (BNF), and haemodynamic variables in patients with heart failure.**

***Setting*—University teaching hospital.**

***Methods*—20 patients with impaired left ventricular systolic function [ejection fraction 32 (SEM 2·3)%] were randomised in a double blind manner to receive either oral metoprolol 6·25 mg twice daily or celiprolol 25 mg daily. Haemodynamic variables were evaluated by Swan-Ganz pulmonary artery catheter over 24 hours. ANF and BNF concentrations were measured at baseline, 5 h, and 24 h by radioimmunoassay.**

***Results*—At baseline ANF and BNF concentrations were considerably raised compared to the normal range. Treatment with metoprolol caused ANF to rise further to 147% of the basal level at 5 h (P = 0·017) and 112% at 24 h (P = 0·029). This was associated with a small but non-significant rise in pulmonary capillary wedge pressure. Cardiac output and systemic vascular resistance were unchanged at 24 h. In contrast, after celiprolol ANF fell to 90% of basal levels at 5 h and to 74% of basal level at 24 h (P = 0·019), associated with a small but non-significant fall in pulmonary capillary wedge pressure [–3·3 (2·7) mm Hg] and systemic vascular resistance, and rise in cardiac output from 3·2 (0·2) to 4·0 (0·4) l/min (P = 0·04). BNF concentrations rose to 112% of baseline at 5 h (P = 0·09) after metoprolol but fell slightly, to 91% of baseline values, after celiprolol (NS).**

***Conclusions*—Metoprolol, even in very low doses (6·25 mg), produced a rise in ANF and BNF, although minimal haemodynamic changes were detected. In contrast, a vasodilating β blocker was associated with a significant fall in ANF and BNF and a small rise in cardiac output. This study confirms both the advantages of vasodilating β blockers over metoprolol for initial treatment of heart failure and the usefulness of ANF and BNF measurements for the assessment of drug effects in heart failure compared to traditional haemodynamic measurements.**

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Keywords: β blockers, natriuretic factor, heart failure

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Activation of the sympathetic nervous system is known to occur in heart failure and to be associated with a poor prognosis.[1 2] Acutely, sympathetic activation is compensatory, but prolonged excessive stimulation has many potential adverse effects including a direct cytotoxic action on myocardial cells,[3] promotion of arrhythmias,[4] decreased coronary blood flow, and excessive vasoconstriction reducing tissue perfusion.[5] Although β blockers were formerly considered inappropriate because of their negative inotropic action, several studies have now shown symptomatic benefit in patients with heart failure, although no reduction of mortality has yet been proved.[6] The most commonly used β blocker has been metoprolol, which was chosen by Waagstein and his colleagues in their initial studies in patients with idiopathic dilated cardiomyopathy.[7 8] However, intolerance to metoprolol has been reported in up to 15% of patients and this is directly related to the severity of heart failure.[9] Acute intravenous β blockade with metoprolol and propranolol have been shown to reduce left ventricular systolic function (end systolic elastance) to a similar extent.[10] β Blockers with vasodilator properties and reduced cardiodepressant effects such as carvedilol, bucindolol, or celiprolol might be more advantageous.[11] Although very low dose metoprolol is not usually associated with any gross changes in haemodynamics it may still have significant effects on the levels of natriuretic peptides, which are probably more sensitive and accurate indicators of the severity of heart failure.[12 13] There are no published reports of the effect of low dose β blockers on atrial (A type, ANF) or ventricular (brain, B type, BNF) natriuretic factor, or of the relative merits of the newer third generation β blockers over metoprolol when the doses used are very

small. We have therefore conducted a randomised double blind comparison of a vasodilator β blocker versus metoprolol in the initiation of β blocker treatment in heart failure patients to determine if the potential haemodynamic advantages of vasodilating β blockers are reflected in the levels of ANF and BNF over a 24 hour period.

Methods

PATIENTS

The study group included 20 patients (mean age = 60 (SD 11) years; 14 males, six females) with chronic heart failure resulting from idiopathic dilated cardiomyopathy (n = 11), or ischaemic heart disease (n = 9), with an estimated ejection fraction of less than 50% [32 (2·3)%] by echocardiography or MUGA scan. All patients were symptomatic (New York Heart Association (NHYA) Class III or IV) but were clinically stable. All patients had received standard treatment with diuretics and angiotensin converting enzyme (ACE) inhibitors if tolerated. The patients were excluded if they had asthma, significant obstructive airways disease, acute pulmonary oedema, significant obstructive valvar disease, renal disease with a serum creatinine > 215 μmol/litre, myocardial infarction within the previous six weeks, clinically significant hepatic or haematological disorders, cerebrovascular accident within the past six months, advanced heart block, or bradyarrhythmias.

The clinical features of the patients are shown in table 1. The two groups were reasonably well matched for age and left ventricular ejection fraction. The mean frusemide dose in subjects taking metoprolol was higher than in those taking celiprolol. This was mainly because one subject in the metoprolol group was taking 250 mg twice daily. If this patient is excluded the mean frusemide doses are similar (celiprolol group, 64 (8) mg; metoprolol group, 80 (9) mg). Similar numbers of subjects were taking ACE inhibitors. There were six men in the celiprolol group and eight in the metoprolol group. Each patient gave informed written consent before entry into the study. The study was approved by the ethics committee of the faculty of medicine, Chinese University of Hong Kong.

Table 1 Clinical characteristics of the two treatment groups. Values are means (SEM) or number of patients

	Metoprolol group (n = 10)	*Celiprolol group (n = 10)*
Age (years)	58 (3·5)	61 (3·5)
M/F	8/2	6/4
NYHA class		
III	6	5
IV	4	5
Diagnosis		
Idiopathic cardiomyopathy	7	4
Ischaemic cardiomyopathy	3	6
LVEF (%)	33 (3)	31 (3)
Concomitant treatment		
Frusemide dose (mg)	135 (45)	64 (8)
ACE inhibitors[a] (n)	6	7
Nitrates (n)	4	7

[a]Captopril or enalapril.
F, female; M, male; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotension converting enzyme.

PROTOCOL AND PROCEDURES

On the day before the study a triple lumen Swan-Ganz catheter was inserted percutaneously through the right internal jugular vein or the right subclavian vein and positioned in the pulmonary artery. Cardiac output was measured in triplicate using the thermodilution method and derived haemodynamic variables were calculated in the usual way according to standard formulae. The ECG was monitored throughout the study. All drug treatment was omitted from the day before the study, although intravenous frusemide was allowed after 12 hours on the study day if the patient complained of increasing breathlessness. Food was omitted in the morning and a light meal with 360 ml of fluid was allowed at 6 and 12 h. Patients were randomly allocated to receive either metoprolol 6·25 mg twice daily or celiprolol 25 mg once daily (with a placebo capsule at 12 h). Metoprolol, celiprolol, and placebo were placed in identical capsules and the study therefore was a double blind randomised comparison of the two treatments. Haemodynamic measurements were taken at baseline, 0·5, 1, 2, 3, 4, 5, 6, 10, 12, and 24 h after drug administration. Blood was taken for measurement of natriuretic peptides at baseline (0 h), 5 h, and 24 h. Venous blood samples (5 ml) were collected into chilled tubes containing EDTA as anticoagulant (100 KIU/ml) together with aprotinin (Trasylol, Bayer; 100 000 KIU/10 ml) and mixed thoroughly. Blood was centrifuged as soon as possible (about 3000 rpm for 10 min at 4°C) and the plasma was then stored at −70°C for later analysis.

ASSAY OF αhANF AND hBNF

This was carried out using a radioimmunoassay method as described previously.[14]

STATISTICAL ANALYSIS

The results are expressed as a mean (SEM). Comparison between the groups was performed by Student's *t* test. Correlation between variables was assessed by Pearson (parametric) and linear regression analysis (least square) using Graph Pad Instat and Prism package (version 1·0), with the F test used for statistical significance. The null hypothesis was rejected at $P < 0·05$.

Results

EFFECT OF METOPROLOL AND CELIPROLOL ON HAEMODYNAMICS (table 2 and fig 1)

Treatment with metoprolol was associated with a small but not significant increase in pulmonary capillary wedge pressure maximal at 5 h after the dose (+ 3·3 (2·6) mm Hg; $P = 0·24$). By contrast in the celiprolol group

Table 2 Main results. Values are means (SEM); values in square brackets are percentage change in ANF and BNF from baseline values

	Time (h)										
	0	*0·5*	*1*	*2*	*3*	*4*	*5*	*6*	*10*	*12*	*24*
HR (beats/min)											
M	85 (6)	83 (6)	81 (6)	80 (6)	79 (6)	79 (6)	79 (6)	79 (6)	78 (6)	78 (6)	77 (7)
C	83 (5)	84 (5)	76 (5)	80 (5)	75 (5)	78 (6)	81 (5)	78 (5)	82 (5)	84 (6)	82 (6)
MAP (mm Hg)											
M	91 (7)	92 (7)	89 (6)	88 (6)	89 (6)	90 (7)	91 (6)	93 (6)	92 (7)	91 (7)	92 (7)
C	87 (4)	90 (4)	87 (5)	84 (5)	85 (5)	85 (5)	86 (5)	90 (3)	82 (2)	87 (4)	86 (3)
PAP (mm Hg)											
M	25 (3)	28 (3)	27 (3)	27 (3)	27 (3)	29 (4)	29 (3)	29 (3)	25 (2)	25 (3)	25 (3)
C	26 (3)	24 (2)	25 (3)	27 (3)	23 (2)	22 (2)	24 (3)	19 (3)	21 (2)	23 (2)	20 (2)
PCWP (mm Hg)											
M	16 (3)	16 (3)	17 (3)	16 (3)	16 (2)	18 (3)	19 (2)	18 (2)	15 (2)	16 (3)	17 (3)
C	16 (3)	17 (2)	17 (3)	17 (3)	16 (3)	14 (3)	15 (3)	13 (3)	13 (3)	14 (3)	13 (2)
CO (litre/min)											
M	3·8 (0·4)	3·6 (0·3)	3·4 (0·4)	3·3 (0·3)	3·4 (0·4)	3·3 (0·3)	3·4 (0·4)	3·6 (0·4)	3·3 (0·4)	3·5 (0·5)	3·7 (0·5)
C	3·2 (0·2)	3·3 (0·3)	3·3 (0·3)	3·0 (0·3)	3·1 (0·3)	3·6 (0·3)	3·7 (0·5)	3·7 (0·4)	3·5 (0·4)	3·7 (0·4)	4·0 (0·4)*
SVR (dyn·s·cm^{-5})											
M	2032 (263)	2084 (246)	2222 (250)	2117 (170)	2107 (231)	2088 (218)	2168 (205)	2055 (188)	2235 (172)	2204 (269)	2060 (201)
C	2240 (238)	2193 (213)	2105 (233)	2239 (213)	2229 (232)	1914 (187)	2109 (311)	2103 (230)	2074 (288)	2037 (245)	1787 (194)
ANF (pg/ml)											
M	311 (87)						462 (137)* [147 (23)%]				352 (104)* [112 (6)%]†
C	454 (88)						365 (42) [91 (11)%]				281 (47)* [74 (13)%]†
BNF (pg/ml)											
M	273 (66)						315 (77) [112 (9)%]				289 (72) [108 (6·4)%]
C	362 (62)						294 (42) [91 (11)%]				380 (62) [115 (20)%]

ANF, atrial natriuretic factor; BNF, ventricular (brain) natriuretic factor; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; M, metoprolol group; C, celiprolol group.
*P < 0·05 *v* basal level; †P < 0·01 M *v* C at 24 h (paired *t* test)

the wedge pressure was unchanged in the first 3 h and then fell 1 (3) mm Hg after 5 h, with a further reduction of 3·3 (2·7) mm Hg at 24 h (baseline to 24 h change, P = 0·27). In the metoprolol group cardiac output fell slightly from 3·8 (4) litre/min at baseline to 3·3 (0·3) litre/min at 4 h, but was largely unchanged at 24 h. In the celiprolol group cardiac output was slightly lower at baseline and there was a small increase in cardiac output from 4 h onwards, rising from 3·2 (0·2) litre/min at baseline to 4·0 (0·4) at 24 h (P = 0·04). There was a trend for systemic vascular resistance to fall in the celiprolol group from 2240 (238) to 1787 (194) dyne.s.cm^{-5} (P = 0·06). Heart rate was largely unchanged in the celiprolol group but there was a small fall between 3 and 5 h. In the metoprolol group heart rate fell from 85 (6) beats/min at baseline to 77 (7) at 24 h (P = 0·054). There was no significant change in the mean arterial pressure with either metoprolol or celiprolol. Thus the only

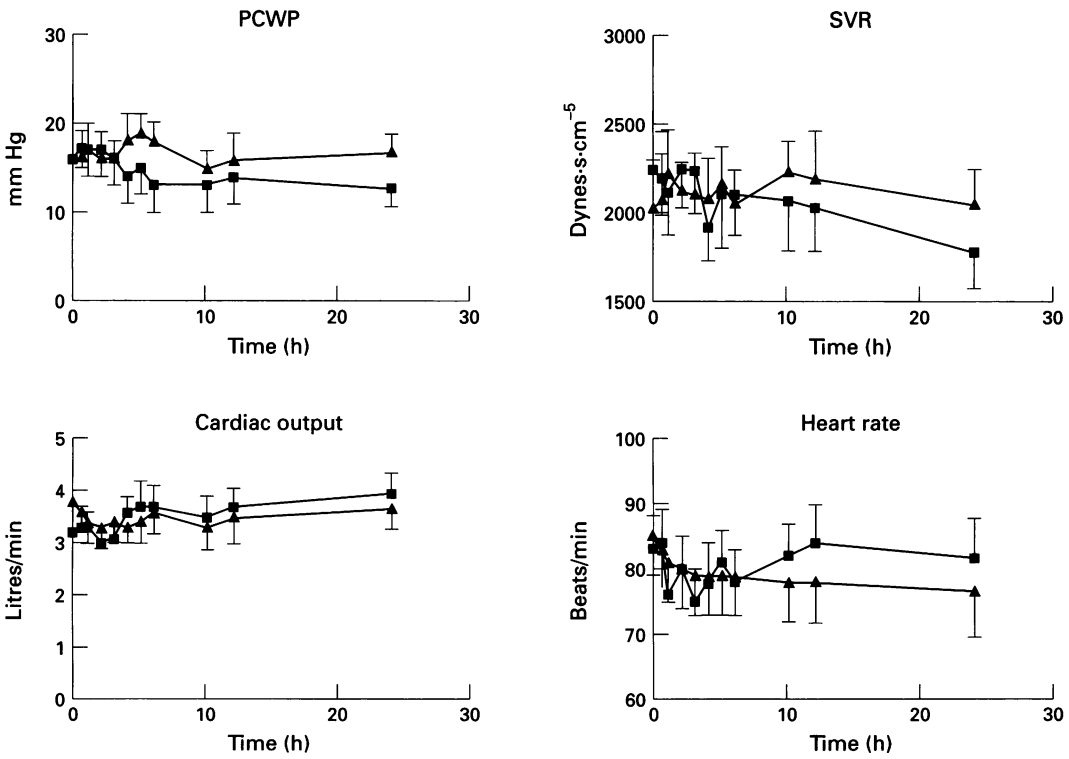

Figure 1 Main haemodynamic changes; ■ celiprolol; ▲ metoprolol. PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

haemodynamic change to reach statistical significance was the small increase in cardiac output with celiprolol treatment.

EFFECT OF METOPROLOL AND CELIPROLOL ON PLASMA ANF AND BNF (table 2)

At baseline plasma ANF and BNF concentrations were higher in all patients than in our normal population, in whom mean ANF was 23·0 (5·8) pg/ml and BNF was 12·2 (7·6) pg/ml. Values were slightly higher at baseline in the celiprolol group than in the metoprolol group, compatible with lower cardiac output and higher SVR in the celiprolol group. At 5 h, however, there was a significant fall in plasma ANF concentration in the celiprolol group to 91% of basal values at 5 h and 74% of basal values at 24 h (P = 0·019). In contrast, in the patients given metoprolol ANF rose to 147% of the basal values at 5 h (P = 0·017) and was still increased compared to basal levels at 24 h, with a 112% rise (P = 0·029). The difference between percentage change in ANF concentrations between the metoprolol and the celiprolol groups at 24 h was highly significant (P = 0·009). Plasma BNF was also lower at baseline in the metoprolol group compared to the celiprolol group. However, after the drug was given plasma BNF fell to 91% of basal levels at 5 h and was largely unchanged at 24 h in the celiprolol group; in the metoprolol group plasma BNF rose to 112% of the baseline value (P = 0·09) but was largely unchanged at 24 h, at 108% of the baseline value (P = 0·12). Although the difference in the percentage changes of BNF at 5 h between metoprolol and celiprolol was not statistically significant (P = 0·07), a trend was apparent. ANF concentrations were weakly but significantly correlated with pulmonary capillary wedge pressure (correlation coefficient r = 0·39, 95% confidence interval = 0·104 to 0·62; r^2 = 0·154; P = 0·0092; fig 2). However there is no correlation between wedge pressure and BNF (fig 2).

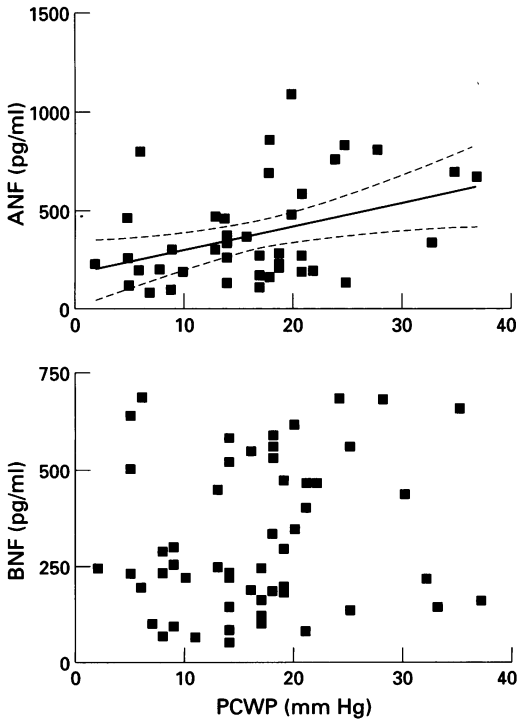

Figure 2 Relations of ANF and BNF to pulmonary capillary wedge pressure (PCWP). Dotted lines are 95% confidence intervals.

PREDICTION OF THE RESPONSE TO THERAPY

There were no obvious distinguishing features of those patients in whom ANF and BNF rose most significantly when they were given metoprolol. There was a slight trend for a higher ejection fraction to be associated with a smaller rise in ANF after drug administration but this was not significant. In addition there was no clear relation between heart rate reduction and rise in ANF concentration after metoprolol. The two subjects with the greatest rise in ANF at 5 h had no significant change in heart rate between baseline and 5 h.

Discussion

Congestive heart failure is an important cause of morbidity and mortality throughout the world. Angiotensin converting enzyme inhibitors have been shown to reduce morbidity and mortality in a broad spectrum of patients with heart failure or asymptomatic left ventricular dysfunction.[15 16] However, many patients are unable to take ACE inhibitors because of cough and other side effects (which appear to be more troublesome in Chinese subjects).[17] Thus there is a need for alternative treatments that will further improve the prognosis in patients with heart failure. Sympathetic nervous system activation is well documented to occur as a compensatory mechanism in heart failure but with deleterious effects over the long term, and serum noradrenaline levels are clearly related to prognosis.[1-5] There is increasing evidence that β adrenergic blocking drugs can produce haemodynamic and symptomatic improvement in patients with heart failure, whether due to idiopathic dilated cardiomyopathy or ischaemic heart disease, although to date there is no convincing evidence that mortality is reduced.[6] The larger randomised control trials of β adrenergic blocking agents in congestive heart failure have been mainly in patients with idiopathic dilated cardiomyopathy and have used metoprolol. Smaller trials have used the newer vasodilating β blockers, in particular carvedilol or bucindolol.[6 11] However, all these trials have compared β blockade with placebo. There are no published randomised blinded studies which have compared directly the newer β blockers against metoprolol. One small unblinded study compared the acute effects of carvedilol and metoprolol and showed that carvedilol, but not metoprolol, reduced systemic blood pressure, systemic vascular resistance, and left ventricular filling pressures, suggesting a direct vasodilator action.[18] The vasodilator properties of the newer β blockers may be particularly useful for the initiation of therapy. It is estimated that approximately 15% of cardiac patients are intolerant of β blockers (principally metoprolol) and this occurs more frequently in patients with severe heart failure who may have the most to gain from β blocker treatment. Therefore there is a need for β blockers which

could be used more easily and more safely for the initiation of treatment. However, it is not known whether the theoretical advantages of vasodilating β blockers are translated into real advantages, in particular on neurohormonal activation. All previous studies have examined haemodynamic variables, such as contractility indices, but it is increasingly apparent that measurements of neurohormonal activation are likely to provide more sensitive markers of the severity of heart failure.[12 13] There are no published reports on the acute effects of β blockers on ANF and BNF concentrations, both of which are known to be increased in heart failure.[12 13] We therefore conducted a blinded randomised comparison of the acute effects of very low dose metoprolol versus celiprolol, to assess their actions not only on haemodynamic variables but also on the natriuretic factors ANF and BNF. In this study we used celiprolol as a vasodilating β blocker, an agent widely used for the treatment of hypertension. The vasodilating action of celiprolol is complex and appears to result from a mixture of α_2 receptor blockade, partial β_2 receptor agonist activity, and an unexplained direct action.[19] Celiprolol also has an inhibitory effect on platelet aggregation, which may be a useful property in patients with ischaemic heart disease.[20]

ANF and BNF concentrations were both considerably raised in the metoprolol and celiprolol groups compared to our normal reference range, confirming numerous previous reports that ANF rises with worsening left ventricular dysfunction.[12 21 22] However, metoprolol, even in very low doses of 6·25 mg twice daily, had detectable deleterious effects with a further rise in ANF in all but one patient at five hours and 24 hours. BNF concentrations also rose in six out of 10 of the patients receiving metoprolol at four hours and in seven out of 10 at 24 hours. There was a highly significant difference between the effect of metoprolol and celiprolol on ANF. This effect of metoprolol at such low doses is rather surprising but clearly explains why administration of even very low doses of metoprolol can be hazardous in patients with severe heart failure. In contrast, celiprolol produced more favourable effects and was associated with a significant fall in both ANF and BNF, coupled with a small fall in pulmonary capillary wedge pressure and a rise in cardiac output. Presumably this difference is a result of the additional vasodilating properties of celiprolol, which occur without a reflex tachycardia. There is no evidence that the drugs have different actions on the metabolic clearance of ANF and BNF. The deleterious effects of metoprolol on ANF and BNF were not associated with any significant changes in pulmonary capillary wedge pressure, cardiac output, or systemic vascular resistance, confirming the superiority of measurements of natriuretic peptides for the assessment of drug effects in heart failure in comparison with traditional haemodynamic measurements.

Although the acute effects of celiprolol appear to be more favourable than metoprolol, its chronic effects are unknown and are presently under study. Concern has been raised that by using a selective β_1 receptor blocker an increase in β_2 receptor density may occur, and it has been suggested that this may be one reason why mortality is not reduced with metoprolol treatment.[23] However, early trials with non-selective β blockers such as propranol were discouraging and it was poorly tolerated.[11 24] A recent study has shown that there is not always an increase in β_2 receptor activity after β_1 selective blockade.[25] It seems unclear therefore at present whether or not β_1 selective blockade leads to increased sensitisation of the myocardium to β_2 stimulation. However, stimulation of β_2 receptors may produce a useful enhancement of cardiac contractibility.[26]

LIMITATIONS OF THIS STUDY

Although the two groups of patients receiving metoprolol or celiprolol were well matched in terms of ejection fractions (31 (3·4)% and 33 (3·4)% respectively) there were differences that may be of some significance. In the group receiving celiprolol there were rather more patients with ischaemic cardiomyopathy—six compared to three patients in the group receiving metoprolol. The NYHA classes were similar in both groups, but the dose of frusemide was higher in patients who received metoprolol. This may be the reason why the baseline ANF concentrations were lower in the metoprolol group than in the celiprolol group (310 (87) compared to 453 (89) pg/ml), although the pulmonary capillary wedge pressures were similar in the two groups at baseline. The number of subjects taking ACE inhibitors was approximately the same (seven and six respectively in the two groups) but rather more patients (seven versus four) were taking nitrates in the celiprolol group than in the metoprolol group. This study does not contain a placebo group but since the purpose of the study was to compare a newer third generation β blocker with what may be considered to be the standard β blocker for heart failure (metoprolol) it was not felt that a placebo group was necessary. Many studies have already compared the effects of metoprolol against placebo.[6] Haemodynamic changes may occur during and immediately after cardiac catheterisation[27] and therefore we placed the Swan-Ganz thermodilution catheter the day before the study. Eating is known to have a vasodilator effect and therefore all patients were studied fasting and allowed one light meal with 360 ml of fluid at six and 12 hours.

CONCLUSION

In summary this study has shown that celiprolol, a third generation vasodilating β blocker, has effects which contrast with those of metoprolol, lowering ANF and BNF and inducing small but largely favourable haemodynamic changes. This study emphasises first, the need for larger comparative studies between the new vasodilating third generation β blockers and metoprolol to determine whether the

acute beneficial neurohormonal effects are associated with a long term benefit and reduction in mortality, and second, the value of measuring indices of neurohormonal activation, such as ANF and BNF instead of haemodynamic indices for the assessment of drug treatments in heart failure.

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