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A comparison of the chronic effects of oral xamoterol and enalapril on blood pressure and renal function in mild to moderate heart failure

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1 We compared the effects, after 3 weeks oral therapy, of xamoterol 200 mg twice daily and enalapril 2.5, 5 or 10 mg twice daily on home and clinic blood pressure, glomerular filtration rate (GFR) and renal plasma flow, stroke and minute distances, linear resistance and on plasma renin activity in 19 patients with mild to moderate heart failure in a single-blind randomised crossover study.

2 Enalapril reduced mean home blood pressure by 17/7 mm Hg compared with xamoterol ($P < 0.0001$) and by 19/7 mm Hg compared with placebo. Compared with placebo xamoterol had no effect. Enalapril reduced predose blood pressure, compared with xamoterol, on average by 15/5 mm Hg ($P = 0.02$ systolic, 0.09 diastolic) and by 20/7 mm Hg compared with placebo. At 4 h post-dose the mean differences were: xamoterol-enalapril 13/10 mm Hg ($P = 0.01$ systolic, 0.0007 diastolic) and placebo-enalapril 23/9 mm Hg.

3 Stroke and minute distances were marginally less 4 h following xamoterol than following enalapril: mean (s.e. mean) values were 9.4 (0.7) *vs* 10.4 (0.8) cm ($P = 0.23$) and 699 (51.7) *vs* 767 (62.1) cm ($P = 0.04$) respectively. Linear resistance was reduced by enalapril, from the placebo value of 13.2 (1.2) to 11.0 (0.9) mm Hg m^{-1} and marginally increased by xamoterol, to 14.2 (1.2) mm Hg m^{-1}, the difference between active treatments being statistically significant ($P = 0.03$).

4 Renal plasma flow, GFR and filtration fraction were not influenced by enalapril or xamoterol therapy. There were no significant correlations between glomerular filtration rate and either blood pressure or stroke distance. Neither xamoterol nor enalapril had any significant effect on these relationships. The changes in GFR seen in individual patients were not determined by age, baseline left ventricular ejection fraction, baseline renal function or diastolic blood pressure. There were weak, but statistically significant, negative correlations between baseline systolic blood pressure and enalapril- (but not xamoterol-) related change in GFR and between baseline 24 h urinary sodium excretion and xamoterol- (but not enalapril-) related change in GFR.

5 After 3 weeks enalapril increased pre-dose plasma renin activity (PRA) from 5.8 (placebo) to 13.4 ng AI ml^{-1} min^{-1} and 4 h post-dose PRA from 6.5 to 25.6 ng AI ml^{-1} min^{-1} ($P < 0.01$ in both cases). Xamoterol had no substantial effect on PRA.

6 One patient died during post-enalapril placebo washout. Symptoms probably or possibly related to drug therapy were more frequent with enalapril than with xamoterol.

7 Xamoterol 200 mg twice daily does not share the daytime hypotensive effect of enalapril. The effect of enalapril on blood pressure is mediated through a fall in vascular resistance, with no reduction in cardiac output, and is not reflected in altered renal haemodynamics. Xamoterol does not appear to compromise renal function in these patients.

Keywords enalapril xamoterol blood pressure renal function heart failure

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Introduction

'Functional renal insufficiency occurs during converting enzyme inhibition in up to one third of salt restricted patients with severe chronic heart failure treated with constant doses of diuretics' (Packer *et al.*, 1987).

Renal impairment in congestive heart failure occurs through several mechanisms, the relative importance of which varies in individual patients. Systemic hypotension, with diminished renal perfusion may be accentuated by vasodilator or diuretic therapy. Activation of the renin-angiotensin system—on account of renal hypoperfusion, dietary salt restriction, sympathetic nervous activity, diuretic therapy and other mechanisms—may have dual, opposing effects in terms of renal function: angiotensin II may induce further direct renal vasoconstriction but tends to maintain glomerular filtration by virtue of its constrictor effect on the postglomerular arterioles (Ichikawa *et al.*, 1984; Packer *et al.*, 1986). The outcome of angiotensin converting enzyme (ACE) inhibition in individuals with congestive heart failure therefore reflects a complex interaction with many factors: the severity of underlying cardiac muscle disease, pre-existing renal impairment (including renovascular disease), the degree of systemic hypotension, extent of activation of the renin-angiotensin and sympathetic nervous systems and of interaction with kinin and prostanoid metabolism, the dietary sodium intake and the nature and doses of concomitant drug therapy. The dose and duration of action of the ACE inhibitor, the duration of therapy and the method of measurement of renal impairment may also be important factors.

Not surprisingly, therefore, individual studies of ACE inhibition in heart failure have reported both improvement (Creager *et al.*, 1981; Dzau *et al.*, 1980, 1984; Kubo *et al.*, 1984) and deterioration (Cleland *et al.*, 1985; Packer *et al.*, 1986; Pierpoint *et al.*, 1981; Powers *et al.*, 1982) in renal function, with large variations in the proportions of individual patients in whom renal function worsens. The undoubted potential for ACE inhibitors to compromise renal function in individual patients, and the difficulty of simply and reliably detecting early impairment, is a source of concern.

Xamoterol ('Corwin', ICI) is a β_1-adrenoceptor partial agonist, which has been shown to improve indices of left ventricular systolic and diastolic function, exercise capacity and symptoms in heart failure (Marlow, 1989). In contrast to enalapril it appears to have little (Virk & Davies, 1989) or no effect (The German and Austrian Xamoterol Study Group, 1988) on systemic blood pressure in mild to moderate heart failure. In healthy volunteers no effect is seen on glomerular filtration (Zech *et al.*, 1989) nor on plasma renin activity (Jennings *et al.*, 1984). These parameters have not been examined in controlled studies in heart failure.

The principal aim of the present study was to examine the effects of oral xamoterol and enalapril on blood pressure and renal haemodynamics, and the relationships between these, in patients with stable mild to moderate heart failure. Additionally we examined the effects of these drugs on plasma renin activity and on linear indices of cardiac output and vascular resistance as determined by transaortic velography.

Methods

Patients with mild to moderate heart failure (NYHA functional grades II–III), requiring regular diuretic therapy, were recruited. Demographic details of these patients are shown in Table 1. The study protocol was approved by the joint Grampian Health Board and Aberdeen University ethics committee and all patients gave informed, written, consent to participation.

Exclusion criteria were: severe heart failure (NYHA IV), females of childbearing potential, ages less than 20 or greater than 75 years, myocardial infarction within the preceding 8 weeks, hypertrophic obstructive cardiomyopathy, significant aortic stenosis, creatinine clearance less than 30 ml min^{-1}, insulin dependent diabetes mellitus or other serious medical or psychiatric disorder. Background diuretic with or without potassium replacement therapy was continued, as was concurrent therapy with nitrates, calcium antagonists, warfarin or digoxin. Patients requiring to continue therapy with angiotensin converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs were excluded.

Following a preliminary 2 week treatment stabilisation period subjects entered the single- (i.e. observer-) blind randomised, crossover study shown in Figure 1. Patients attended the research clinic on day 21 of placebo run-in and active treatment phases and on day 14 of placebo washout. Patients were observed for at least 4 h after the first dose of enalapril. All patients received enalapril 5 mg twice daily initially: after 1 week this was increased to 10 mg twice daily in those patients judged to have tolerated the lower dose.

Xamoterol 200 mg tablets and matching placebo were supplied by ICI Pharmaceuticals. Enalapril ('Innovace',

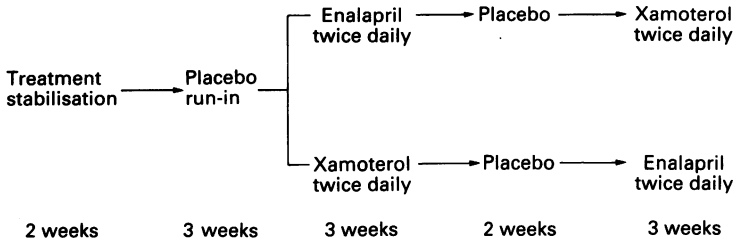

Figure 1 Study design. Patients attended on day 21 of placebo run-in and active treatment phases, and on day 14 of placebo washout. Home blood pressure measurements were undertaken on day 20 of placebo run-in and active treatment phases.

Table 1 Demographic details. Patients 2 and 8 withdrew; patient 17 died during the study; patient 18 died before run-in. 'Blood pressure' represents measurements on the final day (21) of placebo run-in

Patient	*Sex*	*Age (years)*	*Duration of CCF (months)*	*Cause*	*NYHA grade*	*LVEF (%)*	*Therapy discontinued*	*Concomitant therapy*	*Blood pressure (mm Hg)*	*CL_{cr} (ml min^{-1})*	*U_{Na+} (mmol 24 h^{-1})*
1	F	63	55	IHD MI×2	II	32	xamoterol	bumetanide 1 mg, KCl	124/81	105	187
3	M	64	48	IHD	II	20	ibuprofen, xamoterol	bumetanide 2 mg, KCl	168/93	42	—
4	F	67	36	cardiomyopathy	II	45		frusemide 80 mg, spironolactone, digoxin, GTN	125/77	—	—
5	M	60	36	cardiomyopathy	II	52	enalapril	frusemide 40 mg, KCl	117/58	97	151
6	F	62	66	IHD MI×1	II	21	xamoterol	bumetanide 0.5 mg, KCl	106/66	122	119
7	M	61	48	IHD	II	38	nicotinyl tartrate	bumetanide 1 mg, KCl, nifedipine	146/87	273	195
9	F	63	36	unknown	II	77		frusemide 40 mg, KCl	98/74	74	123
10	F	58	41	hypertensive	II	40		frusemide 40 mg, KCl, digoxin	138/90	66	81
11	M	61	38	IHD MI×2	II	34		frusemide 80 mg, KCl, GTN, ISMN	124/81	139	268
12	M	64	38	IHD	III	57	captopril	frusemide 80 mg, digoxin	137/88	163	140
13	M	64	6	IHD MI×1	II	28	warfarin, aspirin	frusemide 40 mg, GTN	206/107	—	99
14	M	60	48	IHD MI×1	II	22		frusemide 80 mg, KCl	121/80	75	95
15	M	68	92	IHD MI×1	II	76	captopril	frusemide 160 mg, nifedipine, allopurinol	218/111	44	—
16	M	64	4	IHD	II	41	aspirin	frusemide 40 mg, KCl	128/83	189	229
17	F	55	3	IHD MI×2	II	28		frusemide 80 mg, KCl, nifedipine, ISMN, GTN	120/73	185	269
19	M	73	12	IHD MI×1	III	12	aspirin	frusemide 80 mg, KCl, nifedipine, GTN	108/68	135	310
20	F	64	26	IHD MI×2	II	30	aspirin	frusemide 80 mg, spironolactone, GTN, thyroxine	135/73	70	83
21	M	69	12	IHD MI×1	II	24		frusemide 40 mg, digoxin, warfarin	121/68	78	166
22	F	60	41	MVD	II	50		frusemide 40 mg, amiloride, digoxin, warfarin	210/97	164	252
23	M	65	23	IHD MI×1	II	43	aspirin	frusemide 80 mg, KCl, trimeprazine	144/86	38	179

CCF = congestive cardiac failure; CL_{cr} = 24 h urinary creatinine clearance; U_{Na+} = 24 h urinary sodium excretion; IHD = ischaemic heart disease; MI = myocardial infarction; MVD = mitral valve disease; GTN = glyceryl trinitrate; ISMN = isosorbide mononitrate

MSD) 5 mg tablets were supplied from the Hospital Pharmacy.

Consecutive 24 h urinary collections for estimation of creatinine clearance and sodium excretion were made on the final 2 days of the treatment stabilisation phase.

Radionuclide ventriculography using the technique of Multiple Gated Acquisition (MUGA) was carried out to assess resting left ventricular ejection fraction at the end of placebo run-in. The MUGA scans were performed after labelling red blood cells *in vivo* with 700 MBq 99 m technetium pyrophosphate. Cardiac imaging was performed at rest in the left anterior oblique 45° position using a single crystal gamma camera (International General Electric 400A) and nuclear medicine software (Link Analytical). 16–24 frames were collected per R-R interval, collecting 200,000 counts per frame. Functional images were generated and the left ventricular ejection fraction calculated from the end-diastolic and end-systolic images.

Self-measurement of blood pressure was carried out on day 20 of placebo run-in and active treatment phases, using the Copal UA-251 semiautomated sphygmomanometer (A & D Company Ltd, Japan). This instrument has been shown to agree well with conventional mercury sphygmomanometry (Gallagher *et al.*, 1985; Malatino & Brown, 1988). Patients were instructed to sit for 5 min before each recording, with the forearm supported at heart level, and took recordings at hourly intervals from 08.00 to 20.00 h. Sitting blood pressure was measured on each study day before and 4 h after administration of medication on each study day, again by Copal UA-251.

On each study day, after a light breakfast, forearm venous cannulae were inserted for blood sampling and (in the opposite arm) administration of radioisotopes. After 20 min seated, blood was drawn into precooled potassium EDTA tubes, immediately centrifuged at 4° C and the supernatant plasma stored at −20° C until assayed for plasma renin activity. Plasma renin activity (generation of angiotensin I ml^{-1} min^{-1}) was measured by radioimmunoassay (Medgenix Diagnostic, High Wycombe, UK) according to the manufacturer's specifications.

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined following the administration of 1.8 MBq ^{51}Cr EDTA and 1.0 MBq ^{125}I sodium iodohippurate respectively. Heparinised samples were collected at 45 min, 2, 3, and 4 h and radioactivity measured in a gamma well counter. GFR and ERPF were calculated from these values using the conventional mathematical equations for these determinations (Smith & Gemmell, 1989). The GFR was corrected for height and weight relative to a body surface area of 1.73 m^2 using standard tables (Diem & Letner, 1970).

Stroke and minute distances were measured supine by Doppler ultrasound, using a Doptek Spectrum Analyser (Doptek Ltd, Chichester, West Sussex) as described by Metcalfe & Rawles (1989), at 4 h post-dosing. Linear resistance (Daniel *et al.*, 1986) was calculated as: mean arterial pressure/minute distance.

The individuals carrying out the radionuclide and Doppler studies were blind as to study medications.

Statistical analysis

Eighteen or more patients completing all study phases were required in order to detect an 18% difference between treatments in glomerular filtration rate (Cleland *et al.*, 1985) with greater than 90% power at the 5% significance level. The sample size was also sufficient to detect 5 mm Hg or greater differences in blood pressure with 90% power at the 5% level. The power of the study in respect of the remaining variables is limited in comparison. Analysis of variance was employed to evaluate treatment, subject, order and visit effects and statistically significant differences between xamoterol and enalapril determined by *F* test. The relationships between changes (active treatment *vs* placebo run-in) in glomerular filtration and in blood pressure and stroke distance were examined by linear regression, with calculation of Pearson correlation coefficients for each relationship. The possibilities that changes in glomerular filtration rate might be determined by age, LVEF, baseline renal function, blood pressure and 24 h urinary sodium excretion were likewise examined by regression analysis. Plasma renin activities were not normally distributed: differences between active treatments were examined by Wilcoxon rank sum test.

Results

Twenty-three Caucasian patients were recruited. Of these, two withdrew during placebo run-in for personal reasons unrelated to the study medications. Two patients died: one following recruitment but before placebo run-in, and one of myocardial infarction, during post-enalapril placebo washout. Reasons for discontinuation of therapy are shown in Table 2. The final dose of enalapril was 10 mg twice daily in thirteen patients and 5 mg twice daily in three. Three further patients

Table 2 Adverse experiences leading to discontinuation of study medication. Enalapril was reintroduced in patients 10 and 20

	Patient	*Stopped by*	*Relationship*	*Reason*
Enalapril	10	patient	possible	headache
	17	investigator	probable	chest pain
			probable	myocardial infarction
			probable	death
	20	patient	unlikely	epistaxis
			probable	chest pain
Xamoterol	nil			

were unable to tolerate 5 mg doses on account of postural dizziness, and in these the dose was reduced to 2.5 mg twice daily. Experiences judged to be *probably* related to enalapril therapy were: hypotension, cold extremities and dizziness in one patient, headaches and dizziness in a second and exacerbation of angina, dyspnoea and ankle swelling in a third. Adverse experiences judged to be *possibly* related to enalapril therapy were: emotional lability and headaches in one patient, myocardial infarction in a second and cold extremities in a third. Possible adverse effects of xamoterol were: left ventricular failure and chest pain in one patient and lightheadedness in a second. The dose of frusemide was increased from 80 to 160 mg day^{-1} in one patient and reduced from 80 to 40 mg day^{-1} in another following placebo run-in.

Blood pressure

Table 3 shows the absolute values, together with differences between each active treatment and placebo, for home and study-day (pre-dose, 4 h post-dose) blood pressures. Figure 2 shows the 12 h profiles (mean, s.e. mean) at the end of placebo run-in and active treatment periods. Figure 3 shows individual values for average and minimum blood pressures recorded at home on day 20 of placebo run-in, and each active treatment phase.

Renal haemodynamics

We found no differences, on average, between enalapril and xamoterol in renal plasma flow, glomerular filtration rate and filtration fraction (Table 4). Individual

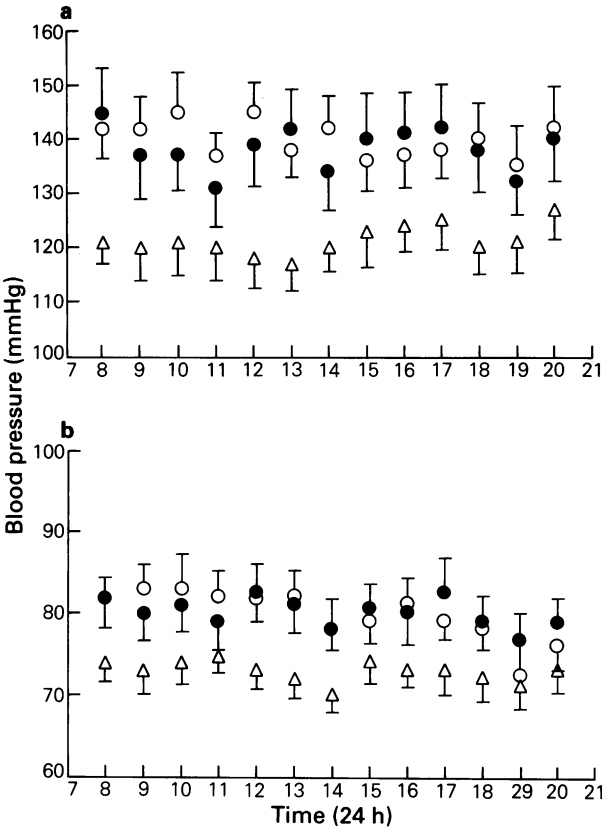

Figure 2 Hourly a) systolic and b) diastolic blood pressures (mean, s.e. mean). ○ = placebo, ● = xamoterol, △ = enalapril.

Table 3 Blood pressures (mm Hg) measured at home, and on study days pre- and 4 h post-dosing (day 21 of placebo run-in and active treatment periods; day 14 of placebo washout). Figures represent mean (s.e. mean). Home BPs represent mean of 13 recordings taken hourly from 08.00–22.00 h. Δ represents difference between each active treatment and placebo (run-in). *P* refers to differences between active treatments

	Home blood pressure				*Study day blood pressure*							
					Systolic				*Diastolic*			
	Systolic	Δ	*Diastolic*	Δ	*pre-dose*	Δ	*4h post-*	Δ	*pre-dose*	Δ	*4 h post-*	Δ
Placebo run-in	141 (5.6)		80 (2.6)		140 (7.4)		135 (4.6)		82 (2.9)		74 (2.1)	
Placebo washout	—		—		130 (6.6)		128 (6.0)		79 (2.9)		75 (2.3)	
Xamoterol	139 (6.7)	2	80 (2.7)	0	135 (6.6)	5	125 (4.4)	10	80 (2.6)	2	75 (2.0)	−1
Enalapril	122 (4.8)	19	73 (1.9)	7	120 (3.5)	20	112 (3.9)	23	75 (1.6)	7	65 (1.6)	9
P	0.0001		0.0001		0.02		0.01		0.09		0.0007	
n	17		17		18		18		18		18	

Table 4 Comparison of the effects of xamoterol and enalapril on renal haemodynamics, linear indices of cardiac output, linear resistance and on plasma renin activity. Figures represent mean (s.e. mean): plasma renin activities represent median values. *P* refers to differences between active treatments

	Glomerular filtration rate ($ml\ min^{-1}$)	*Renal plasma flow* ($ml\ min^{-1}$)	*Filtration fraction* (%)	*Stroke distance* (*cm*)	*Minute distance* (*cm*)	*Linear resistance* ($mm\ Hg\ m^{-1}$)	*Plasma renin activity*	
							predose	*4 h post-dose*
							($ng\ AI\ ml^{-1}\ min^{-1}$)	
Placebo run-in	85 (4.7)	399 (38.1)	25 (2.9)	10.7 (0.9)	781 (67.6)	13.2 (1.2)	5.8	6.5
Xamoterol	79 (6.6)	384 (34.1)	22 (1.3)	9.4 (0.7)	699 (51.7)	14.2 (1.2)	4.2	4.9
Enalapril	79 (6.3)	408 (36.5)	22 (2.4)	10.4 (0.8)	767 (62.1)	11.0 (0.9)	13.4	25.6
P	0.59	0.70	0.66	0.23	0.04	0.03	< 0.01	< 0.01
n	18	15	15	15	15	15	18	18

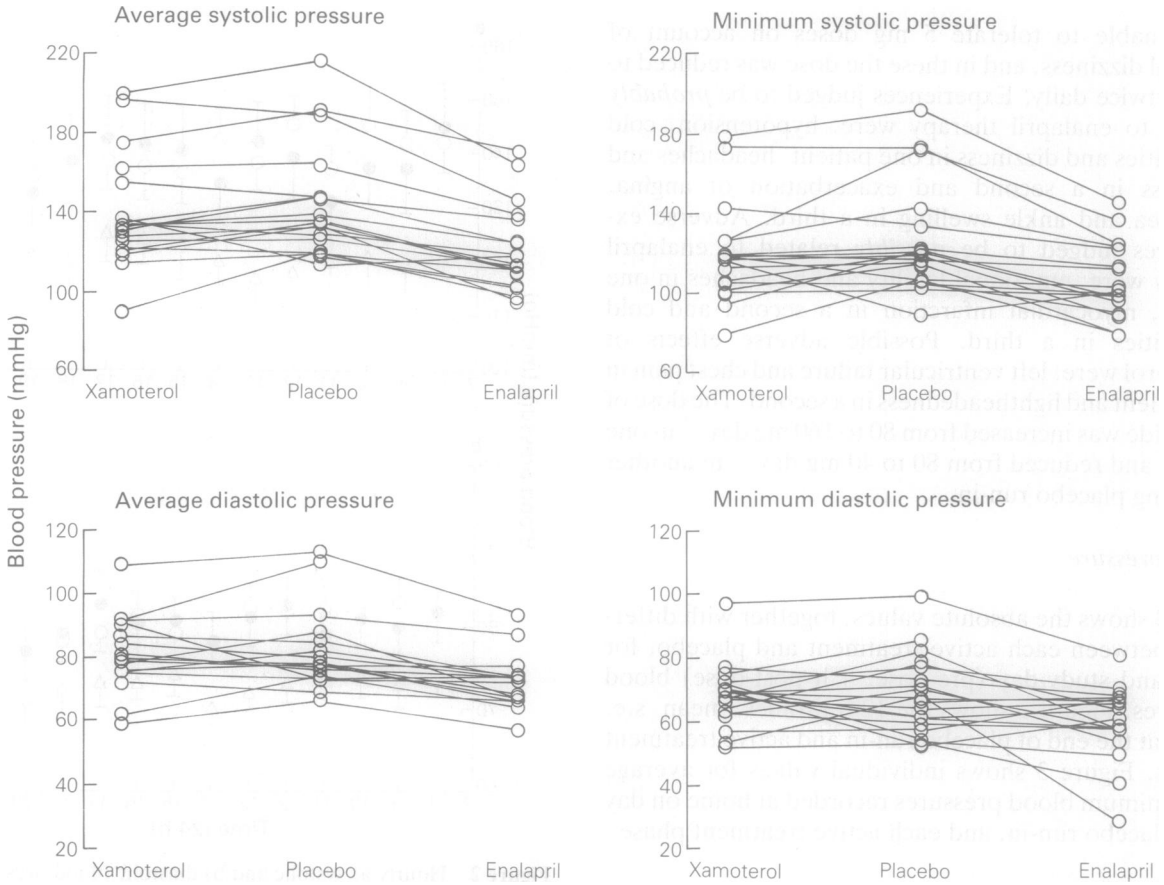

Figure 3 Individual variation in average and minimum blood pressures recorded at home (08.00–20.00 h) on day 20 of placebo run-in and each active treatment phase.

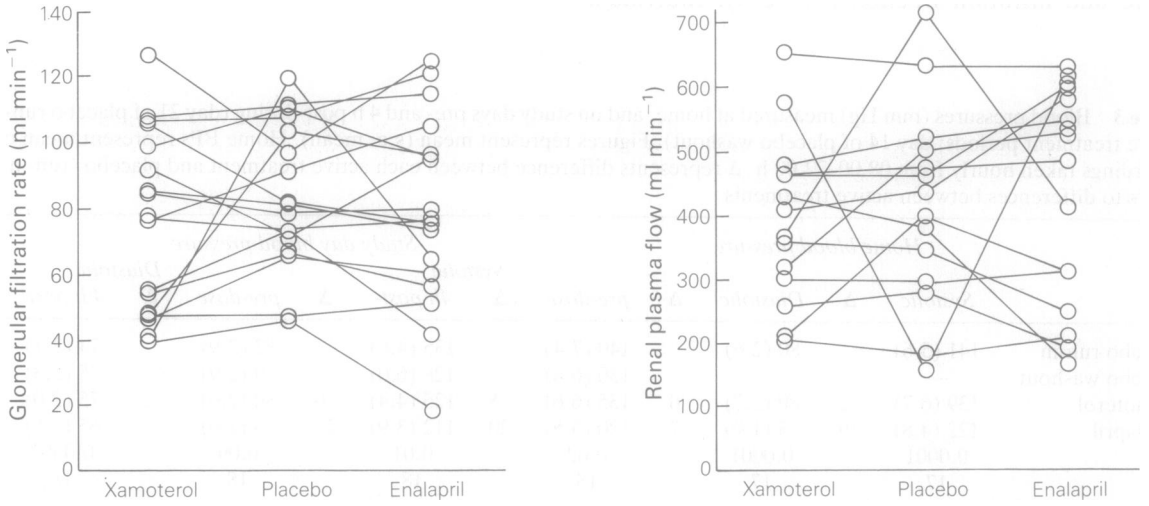

Figure 4 Individual variation in glomerular filtration rate and renal plasma flow at the end of placebo run-in and active treatment phases.

variation in glomerular filtration rate and in renal plasma flow at the end of placebo run-in and of active treatments is shown in Figure 4.

Cardiac output

Stroke and minute distances were marginally lower during xamoterol than during enalapril therapy (Table 4). The difference in minute distance was statistically significant. Linear resistance was reduced by 17% by enalapril compared with placebo and by 22% compared with xamoterol ($P < 0.05$ in both cases). The small (8%) increase in linear resistance seen with xamoterol compared with placebo was not statistically significant.

Plasma renin activity

Plasma renin activities (Table 4) pre- and 4 h post-dose were higher on enalapril than on xamoterol or placebo. Xamoterol marginally reduced plasma renin activity compared with placebo.

Relationships between GFR and other variables

We found no significant correlation between glomerular filtration rate and either blood pressure or stroke distance at 4 h post-dose (systolic BP: correlation coefficient (r) = 0.06, P = 0.75; diastolic BP r = 0.25, P = 0.17; stroke distance r = −0.17, P = 0.39). Neither xamoterol nor enalapril therapy had any effect on these relationships.

There was no significant correlation between the percentage change in GFR (expressed as: (GFR on active therapy − GFR on placebo)/GFR on placebo) and: age, left ventricular ejection fraction, diastolic blood pressure, nor initial (end placebo run-in) GFR. There were, however, weak, but statistically significant, negative correlations between changes in GFR and i) baseline (end placebo run-in) systolic blood pressure, for enalapril but not xamoterol (r = −0.47, P = 0.05) and ii) baseline 24 h urinary sodium excretion, for xamoterol but not enalapril (r = −0.67, P = 0.009).

Discussion

Oral therapy with xamoterol 200 mg twice daily in patients with mild–moderate heart failure taking background diuretic therapy but without restriction of dietary sodium intake is not associated with the same degree of daytime hypotension as is seen with enalapril 5–10 mg twice daily. The differing effects of these drugs on systemic blood pressure are not, however, reflected in differences in glomerular filtration rate and do not appear to influence renal plasma flow and filtration fraction.

Enalapril, predictably, achieved its hypotensive effect by means of a reduction in systemic vascular resistance as evidenced by the reduction seen in linear resistance and by the lack of change in stroke and minute distances. True differences in linear cardiac indices and in renal plasma flow may have been obscured in view of the relatively limited power of the study in respect of these variables. That renal plasma flow was maintained, in the face of an approximately 17% fall in mean arterial pressure with enalapril implies, however, an average reduction in renal vascular resistance of the same order.

The changes in glomerular filtration rate seen in individuals were not determined by age, baseline left ventricular ejection fraction or renal function. The inverse relationship between baseline systolic blood pressure and enalapril-associated change in GFR should not be overinterpreted, but suggests that pre-existing systemic hypotension may, in individual patients, predispose to converting enzyme inhibitor-induced renal impairment. Alternatively, inadequate renal perfusion in those with initially low arterial pressure may disguise a potentially beneficial effect of ACE inhibition.

Xamoterol appears to be better tolerated than enalapril at these doses, judging from the number of subjects unable to tolerate 10 or 5 mg doses of enalapril and by the relatively greater proportion of minor adverse effects attributed to enalapril.

The possible importance of therapy-induced alteration in blood pressure profile (including truly ambulatory and nocturnal pressures) in determining individual outcome in patients with heart failure has yet to be established. Unloading the failing myocardium by peripheral vasodilation is an established therapeutic approach. Whether any benefits of this on left ventricular function may be offset by detrimental effects of systemic hypotension is uncertain. A 'J' shaped relationship between blood pressure and mortality in essential hypertension has been suggested (Cruickshank *et al.*, 1988). It is not unreasonable to propose that a similar relationship may exist in heart failure, particularly in patients with ischaemic cardiomyopathy. Drugs, such as xamoterol, which do not affect pre-existing blood pressure may prove to be useful alternatives to converting enzyme inhibition or other vasodilator therapy in mild heart failure and merit further study.

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