Post-exercise hypotension: the effects of epanolol or atenolol on some hormonal and cardiovascular variables in hypertensive men

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1 Eight men with primary hypertension were treated for 3 weeks with placebo, epanolol (200 mg or 400 mg), or atenolol 100 mg in a randomised cross-over study. Each active treatment period was preceded by a 3 week placebo treatment period and both investigators and subjects were blind to the active drug sequence.

2 At the end of each period, measurements were made of resting cardiovascular (heart rate, blood pressure, forearm blood flow) and biochemical variables (plasma renin, angiotensin II, aldosterone, adrenaline, noradrenaline, vasopressin, sodium and potassium concentrations and osmolality). Responses to exercise (including gas exchange, sweat rate, and ratings of perceived exertion) and the reflex cardiovascular adjustments to distal body subatmospheric pressure were also assessed.

3 The reduction of exercise-induced tachycardia by epanolol 400 mg was comparable to that of atenolol. There was very little difference in the effects of atenolol or epanolol 400 mg on resting blood pressure, but in both cases blood pressures were usually significantly lower than with epanolol 200 mg.

4 Although each active treatment influenced the renin-angiotensin system and circulating levels of catecholamines, the exercise-induced reduction in blood pressure was unaffected. Thus, the hypotensive effects of pharmacological and non-pharmacological interventions were additive.

Keywords epanolol atenolol exercise baroreflexes hypotension

Introduction

The range of β -adrenoceptor antagonist drugs currently available encompasses a wide variety of additional pharmacological and physiochemical properties (Prichard & Tomlinson, 1986). Of these, hydrophilicity and cardioselectivity, perhaps, convey clinical advantages (Kendall, 1981; McDevitt, 1983). However, β -adrenoceptor antagonists with differing ratios of particular properties are continually being

developed in the expectation of their finding clinical niches. At present there is no widely available cardioselective β -adrenoceptor antagonist which also possesses selective β_2 -adrenoceptor agonism, although one compound, epanolol (Visacor, ICI 141292), is said to be a cardioselective β -adrenoceptor antagonist with β_1 -selective agonist activity (Smith *et al.*, 1983; Norris *et al.*, 1984; Pringle *et al.*, 1986). Although

unique, it is not yet clear whether this combination has specific clinical virtues in comparison with already established β -adrenoceptor antagonists.

In this study we have compared two different doses of epanolol with atenolol, a cardioselective β_1 -adrenoceptor antagonist without partial agonist activity, in men with primary hypertension. In particular, we have studied the comparative effects of these drugs on some cardiovascular and hormonal responses to dynamic treadmill exercise (Wilcox *et al.*, 1984; Macdonald *et al.*, 1984), and to distal body subatmospheric pressure before and after the exercise protocol (Bennett *et al.*, 1984).

Methods

We recruited eight men (aged 41–61 years) with newly diagnosed primary hypertension who, after a 3 month period of clinical observation without treatment, maintained a stable, standing, diastolic blood pressure in the range of 100–125 mm Hg (phase 5). None of them had any other known past or current medical problems and none had any contraindications to performing a treadmill exercise test or being treated with β -adrenoceptor antagonist drugs. All the patients attended the laboratory for preliminary exercise and distal body subatmospheric pressure (DBSP) tests before giving their final written consent to the study (which was approved by the Ethics Committee of University Hospital, Nottingham). All the study procedures were carried out in temperature controlled laboratories after a fast of at least 8 h, during which alcohol, coffee and cigarettes were forbidden.

Treatment schedules

Each treatment phase lasted 3 weeks and began with a run-in period during which the patients took placebo tablets once daily. The active treatment periods which followed were randomised and double-blind, comprising treatment with once daily atenolol (100 mg) or epanolol (200 mg or 400 mg). All the placebo and active tablets looked alike. The active treatment periods were separated by washout periods of 3 weeks, during which the patients again took placebo tablets once daily. We chose to incorporate these lengthy washout periods between treatments because of our uncertainty about the possible long-term carry-over of any metabolic changes induced by treatment with β -adrenoceptor antagonists. As it was, no carry-over effects were observed (see below). All the measurements were made start-

ing approximately 2 h after the last dose of active or placebo treatment.

Experimental procedure

Upon arrival in the laboratory (set at 24–25° C) the subject lay supine enclosed to the level of the iliac crests in an air-tight box in which the pressure was monitored using a pressure transducer. A plastic cannula was inserted into the left antecubital vein and kept patent with a slow infusion of isotonic saline. Using an industrial vacuum cleaner, subatmospheric pressures could be achieved in the box and this has the effect of pooling blood in the legs and abdomen and allowed assessment of baroreflex control of the blood pressure, forearm vascular resistance, and heart rate (Bennett *et al.*, 1984). Systemic arterial blood pressure was measured by auscultation over the left brachial artery, heart rate was derived electronically from a continuously displayed single channel electrocardiogram (Nielson rate meter) and forearm blood flow was assessed by venous occlusion plethysmography using a mercury-insilastic strain gauge around the right forearm. Forearm vascular resistance was derived by dividing mean arterial pressure [systolic + 2 (diastolic)/3] by forearm blood flow.

After a period of 15–30 min rest, observations on heart rate, blood pressure and forearm blood flow were made during exposure to subatmospheric pressure of 10, 30 and 50 mm Hg, each maintained for 1 min with intervening 1 min periods at atmospheric pressure.

The patient was then taken to another temperature controlled laboratory (set at 18–20° C) and after a 5 min period of sitting and then 5 min standing at rest, walked on a treadmill (10% slope) for three 15 min periods separated by periods of 3 min rest, sitting. Each patient walked at a treadmill speed determined during the placebo run-in period to maintain his heart rate at approximately 125 beats min^{-1} . This speed was constant for each patient and varied from 2.8 km h^{-1} to 4.4 km h^{-1} between patients. During the last 3 min of each exercise period, heart rate, blood pressure, respiratory gas exchange and sweat rates were measured and subjective ratings of perceived exercise exertion recorded. Following exercise the patient sat resting for the next 15 min before returning to the other laboratory for repeat haemodynamic measurements during DBSP.

Biochemical measurements

Venous blood was withdrawn from the left antecubital vein before treadmill exercise both sitting

and standing, towards the end of the last 15 min exercise period, and at the end of the post-exercise rest period sitting.

From each sample 12 ml of whole blood were placed in tubes containing lithium heparin and 9.5 ml of whole blood were placed in tubes containing 0.5 ml of a solution of 12.5 mM phenanthroline and 62.5 mM EDTA. The contents of the tubes were mixed and then centrifuged at 4° C for 10 min.

The plasma from the lithium heparin tubes was divided into aliquots and either kept on ice for the measurements of osmolality (Advanced Digimatic Osmometer 3DII), and sodium and potassium (IL 943 flame photometer) or frozen at -80° C for the subsequent measurement of vasopressin by radioimmunoassay (Rooke & Bayliss, 1982), aldosterone by radioimmunoassay (Symonds & Craven, 1977), and noradrenaline and adrenaline by high-performance liquid chromatography with electrochemical detection (Macdonald & Lake, 1985). The samples for catecholamine assay were stored with EGTA/glutathione as preservatives.

Three 1 ml samples of plasma from the EDTA/phenanthroline tubes had their angiotensin II extracted onto a cation exchange resin (BioRad AG 50W-XZ). The remaining plasma was stored at -80° C. Plasma angiotensin II (AII) and renin concentrations (PRC) were subsequently measured by radioimmunoassay (Broughton Pipkin & Symonds, 1977). In the non-pregnant adult, the generation of angiotensin I is dependent on PRC and is believed to be substrate independent. Since we could measure both PRC and AII, the primary effector agent of the renin-angiotensin system, we chose to do so rather than to use the scientifically less satisfactory measurement of plasma renin activity (PRA), which does not give direct information about enzyme release.

Statistical analysis

As there were no significant differences between any values obtained at the end of the placebo run-in and wash-out periods the means were compared with the results of the three drug periods by analysis of variance. Where *F*-ratios revealed significant differences between treatments ($P < 0.05$) paired comparisons were performed using *t*-tests, with the error mean square from the analysis of variance used as the estimate of the error variance in the *t*-test. Results are expressed as mean $\pm$ s.e. mean. Because this was an in-depth study of a small group of hypertensive patients the 95% confidence intervals are given for the key differences between atenolol and epanolol 400 mg.

Results

All eight men completed the protocol uneventfully. None had to be withdrawn from any treatment phase and no extra-trial medication was prescribed. Five men reported side-effects on a total of nine occasions: atenolol (3)—cold extremities, muscular fatigue, unhappiness; epanolol 200 mg (2)—muscular tiredness; epanolol 400 mg (2)—muscular fatigue and cold extremities, wheeze; placebo (2)—headache, paraesthesiae.

Effects of treatment on heart rate and blood pressure (Table 1)

At rest most of the drug effects were significantly different from placebo. Atenolol resulted in a significantly greater resting bradycardia than either dose of epanolol ($P < 0.001$). There was very little difference in the effects of atenolol or epanolol 400 mg on resting blood pressure, but in both cases blood pressures were usually significantly lower than with epanolol 200 mg (P varied < 0.05 – 0.001).

During the third exercise period, heart rate on placebo had increased significantly by an average of 45 beats min^{-1} . All active drugs reduced the magnitude of the increase in heart rate to between 30 and 35 beats min^{-1} and the peak heart rate to between 89 and 100 beats min^{-1} . The peak heart rate on atenolol was significantly different from that on either dose of epanolol ($P < 0.001$, 200 mg; $P < 0.01$, 400 mg).

In the presence of atenolol systolic blood pressure during exercise was significantly lower than that with either dose of epanolol ($P < 0.001$, 200 mg; $P < 0.05$, 400 mg) but for diastolic blood pressure only the difference between the atenolol treatment and the lower (200 mg) dose of epanolol was significant ($P < 0.001$). The systolic and diastolic blood pressures during exercise in the presence of high and low doses of epanolol were significantly different ($P < 0.001$ systolic; $P < 0.05$ diastolic).

After exercise blood pressure fell significantly in all treatment groups such that the pre- to post-exercise changes in blood pressure were the same.

Effects of treatment on hormonal and biochemical changes during exercise

Renin concentration (Table 2) Atenolol and both doses of epanolol significantly reduced resting plasma renin concentrations to similar extents compared with placebo. Renin concentration increased during exercise significantly on placebo

Table 1 Effects of placebo, epanolol or atenolol on pre-exercise, peak exercise and post-exercise heart rate (HR beats min⁻¹) and blood pressure

		Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
<i>Pre-exercise</i>					
Sitting	HR	70 ± 2	64 ± 2*	63 ± 2*	52 ± 2***
	SBP	168 ± 3	159 ± 3*	152 ± ***	149 ± 3***
	DBP	104 ± 2	96 ± 2**	92 ± 2***	89 ± 2***
Standing	HR	76 ± 2	66 ± 2***	67 ± 2***	54 ± 2***
	SBP	169 ± 3	162 ± 3	150 ± 3***	153 ± 3**
	DBP	111 ± 2	105 ± 2*	101 ± 2**	95 ± 3***
<i>Peak exercise</i>					
	HR	121 ± 2	100 ± 2***	97 ± 2***	89 ± 2***
	SDP	184 ± 2	167 ± 2***	156 ± 2***	149 ± 2***
	DBP	89 ± 2	87 ± 3	83 ± 2**	80 ± ***
<i>Post-exercise</i>					
15 min sitting	HR	80 ± 1	69 ± 1***	70 ± 1***	59 ± 1***
	SBP	139 ± 3	129 ± 3*	120 ± 3***	120 ± 3***
	DBP	91 ± 2	85 ± 2*	80 ± 2***	78 ± 2***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with placebo.

SBP = systolic blood pressure, DBP = diastolic blood pressure mm Hg.

Table 2 Effect of placebo, epanolol or atenolol on renin, angiotensin II and aldosterone response to exercise

	Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
<i>Renin (ng angiotensin I ml⁻¹ h⁻¹)</i>				
Pre-exercise				
-sitting	4.1 ± 0.4	1.8 ± 0.4***	1.7 ± 0.4***	2.0 ± 0.4***
-standing	4.1 ± 0.5	2.3 ± 0.5*	2.1 ± 0.5**	2.4 ± 0.5*
Peak-exercise	6.1 ± 0.7	3.2 ± 0.7**	3.7 ± 0.7*	3.0 ± 0.7**
Post-exercise	5.0 ± 0.4	2.4 ± 0.4***	2.7 ± 0.4**	2.2 ± 0.4***
<i>Angiotensin II (pg ml⁻¹)</i>				
Pre-exercise				
-sitting	6.0 ± 1.4	4.7 ± 1.5	3.9 ± 1.9	4.9 ± 1.4
-standing	7.8 ± 1.2	3.7 ± 1.4	5.4 ± 1.5	4.4 ± 1.2
Peak-exercise	11.7 ± 1.6	6.2 ± 1.8	7.2 ± 2.0	5.4 ± 1.8
Post-exercise	9.4 ± 1.8	4.7 ± 2.0	5.4 ± 2.2	6.2 ± 1.8
<i>Aldosterone (ng dl⁻¹)</i>				
Pre-exercise				
-sitting	7.0 ± 0.6	6.1 ± 0.6	5.1 ± 0.6	4.9 ± 0.6
-standing	7.3 ± 0.6	6.4 ± 0.6	4.9 ± 0.6*	5.1 ± 0.6*
Peak-exercise	18.0 ± 2.0	15.5 ± 2.0	12.3 ± 2.0	8.2 ± 2.2**
Post-exercise	14.3 ± 1.8	11.1 ± 1.8	10.8 ± 1.8	7.4 ± 2.0

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with placebo.

($P < 0.01$); some increases in renin concentrations occurred during exercise on all three active treatments but the levels were significantly lower than on placebo. At 15 min post-exercise renin concentrations had fallen almost to pre-exercise values.

Angiotensin II (Table 2) There were no significant differences in plasma angiotensin II levels at rest under any condition. There was a significant increase during exercise only for placebo ($P < 0.05$). By 15 min post-exercise the angiotensin II levels on placebo remained significantly higher

than the pre-exercise sitting value ($P < 0.001$). The changes in angiotensin II were not obviously related to the changes in plasma renin concentration in individuals according to inspection of scatter plots of the individuals data.

Aldosterone (Table 2) Aldosterone levels were significantly lower on atenolol and epanolol 400 mg compared with placebo standing at rest and during exercise. Exercise resulted in a significant increase for all treatments except atenolol ($P < 0.05 - 0.001$). At 15 min post-exercise after placebo and epanolol treatments the aldosterone levels were significantly different from pre-exercise values.

Although active treatment suppressed the renin-angiotensin II aldosterone axis in individual subjects there was no clear relationship between the magnitude of the suppression of each component, as judged by inspection of scatter plots of the data points.

Adrenaline (Table 3) Standing resulted in a small but significant increase in plasma adrenaline level only for placebo ($P < 0.05$). Exercise resulted in significant increments in adrenaline in the presence of epanolol 200 mg ($P < 0.05$), epanolol 400 mg ($P < 0.01$) and atenolol ($P < 0.01$). Only in the presence of atenolol did the post-exercise level of adrenaline remain significantly higher than the pre-exercise level ($P < 0.001$).

Noradrenaline (Table 3) Standing significantly increased plasma noradrenaline levels after each treatment ($P < 0.05$ to < 0.001). Exercise resulted in a further increment in the presence of epanolol

200 mg ($P < 0.01$), epanolol 400 mg ($P < 0.001$) and atenolol ($P < 0.001$). By 15 min post-exercise there were no significant differences from the pre-exercise levels.

Vasopressin (Table 4) There were no significant differences between treatments. Vasopressin levels increased slightly during exercise and were still significantly higher post-exercise compared with pre-exercise values for placebo and both doses of epanolol. Scatter plots did not suggest that these elevations correlated with the degree of fall in blood pressure after exercise.

Potassium (Table 4) Resting levels were slightly higher on epanolol 200 mg and 400 mg and significantly so for atenolol. Under all treatment conditions there were significant increases in plasma potassium levels during and after exercise ($P < 0.001$), the absolute levels on epanolol and atenolol being significantly higher than on placebo ($P < 0.01$).

Sodium There was little or no change in plasma sodium during any treatment, the levels remaining virtually constant between 139–142 mmol l⁻¹.

Osmolality There was little change throughout in plasma osmolality. Basal levels ranged from 282–286 mosm kg⁻¹ and increased to 285–288 mosm kg⁻¹ at peak exercise.

Summary of hormonal changes In general, epanolol and atenolol attenuated the renin-angiotensin-aldosterone responses to exercise with increasing effect from the lower dose of epanolol through to atenolol. The changes in

Table 3 Effect of placebo, epanolol or atenolol on the adrenaline and noradrenaline responses to exercise

	Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
Adrenaline (nmol l⁻¹)				
Pre-exercise				
-sitting	0.27 ± 0.03	0.24 ± 0.03	0.25 ± 0.03	0.22 ± 0.03
-standing	0.38 ± 0.04	0.30 ± 0.05	0.30 ± 0.04	0.31 ± 0.04
Peak-exercise	0.50 ± 0.14	0.72 ± 0.15	0.83 ± 0.14	1.03 ± 0.14
Post-exercise	0.29 ± 0.05	0.32 ± 0.06	0.32 ± 0.05	0.40 ± 0.05
Noradrenaline (nmol l⁻¹)				
Pre-exercise				
-sitting	3.12 ± 0.33	2.73 ± 0.36	2.82 ± 0.33	3.40 ± 0.33
-standing	4.09 ± 0.38	3.73 ± 0.41	3.61 ± 0.38	3.79 ± 0.38
Peak-exercise	4.21 ± 0.34	5.50 ± 0.37*	5.25 ± 0.34*	5.77 ± 0.34**
Post-exercise	3.07 ± 0.21	3.19 ± 0.23	3.16 ± 0.21	3.16 ± 0.21

* $P < 0.05$, ** $P < 0.01$ compared with placebo.

Table 4 Effect of placebo, epanolol or atenolol on the vasopressin and potassium responses to exercise

	Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
<i>Vasopressin ($\mu\text{mol l}^{-1}$)</i>				
Pre-exercise				
-sitting	1.42 $\pm$ 0.31	1.57 $\pm$ 0.34	1.03 $\pm$ 0.31	1.29 $\pm$ 0.31
-standing	1.72 $\pm$ 0.48	2.34 $\pm$ 0.48	1.33 $\pm$ 0.48	1.27 $\pm$ 0.48
Peak-exercise	2.03 $\pm$ 0.43	2.67 $\pm$ 0.44	1.84 $\pm$ 0.44	1.70 $\pm$ 0.44
Post-exercise	2.83 $\pm$ 0.51	2.74 $\pm$ 0.51	1.87 $\pm$ 0.51	1.92 $\pm$ 0.51
<i>Potassium (mmol l^{-1})</i>				
Pre-exercise				
-sitting	3.88 $\pm$ 0.07	4.04 $\pm$ 0.07	4.01 $\pm$ 0.07	4.19 $\pm$ 0.07**
-standing	3.86 $\pm$ 0.05	4.01 $\pm$ 0.06	4.00 $\pm$ 0.05	4.11 $\pm$ 0.05**
Peak-exercise	4.44 $\pm$ 0.05	4.92 $\pm$ 0.05***	4.76 $\pm$ 0.05***	4.86 $\pm$ 0.05***
Post-exercise	4.17 $\pm$ 0.07	4.60 $\pm$ 0.07***	4.49 $\pm$ 0.07**	4.61 $\pm$ 0.07***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with placebo.

plasma catecholamines, however, were slightly enhanced by the β -adrenoceptor antagonists, again with increasing effect, as above. Increments in plasma potassium levels were also enhanced during active treatment, but here no particular drug pattern was obvious.

Effects of treatment on gas exchange, sweat rate and ratings of perceived exertion during exercise

Although these variables all increased during exercise there were no significant differences under the different treatment regimes.

Effects of treatment on cardiovascular responses to DBSP

Pre-exercise (Table 5) Active treatment caused reductions in supine resting heart rate; in the presence of atenolol, heart rate was significantly lower than in the presence of epanolol at either dose ($P < 0.01$). With epanolol 400 mg and atenolol, systolic blood pressure was lower than in the presence of placebo or epanolol 200 mg ($P < 0.01$ vs epanolol 400 mg; $P < 0.001$ vs atenolol). Diastolic blood pressure was significantly lower in the presence of epanolol 400 mg or atenolol than in the presence of placebo, and there was a significant difference between diastolic blood pressures with epanolol (200 mg) and atenolol ($P < 0.01$). Resting forearm blood flows were similar in all groups.

Exposure to DBSP had no differential effects on heart rate except at 50 mm Hg where there was a significantly ($P < 0.001$) greater tachycardia in the presence of placebo than with the active treatments; the tachycardias seen in the latter

conditions were not different from each other. Under no circumstances were the changes in systolic blood pressures evoked by exposure to DBSP significantly different. There were no differences in the changes in diastolic blood pressure with DBSP of 10 or 30 mm Hg under any treatment condition. However, with DBSP at 50 mm Hg, the increase in diastolic blood pressure in the presence of epanolol 400 mg was significantly greater than with atenolol or placebo ($P < 0.05$). Furthermore, the increase in diastolic blood pressure in the presence of epanolol 200 mg was significantly greater than that seen with atenolol ($P < 0.05$). The reductions in forearm blood flow during DBSP were similar in all groups. Thus, active treatment shifted the relation between forearm blood flow and mean arterial pressure, but did not influence its character.

Post-exercise (Table 6) Exposure to DBSP was begun about 30 min post-exercise; at that time heart rates were not significantly different from the pre-exercise values, but systolic and diastolic blood pressures and forearm blood flows were all significantly (< 0.001) lower. As in the pre-exercise condition, heart rates in the presence of active treatment were significantly lower than with placebo. Furthermore, heart rate was significantly lower in the presence of atenolol than either of the other two active treatments ($P < 0.001$). Systolic blood pressure was lower ($P < 0.05$) in the presence of atenolol than epanolol 200 mg while diastolic blood pressure was less with atenolol than with either dose of epanolol (200 mg $P < 0.01$, 400 mg $P < 0.01$). Forearm blood flows were similar under all conditions.

Table 5 Effect of placebo, epanolol or atenolol on cardiovascular responses to application of distal body subatmospheric pressure (DBSP) of 10, 30 and 50 mm Hg before exercise

	Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
<i>Rest (supine)</i>				
HR	68 ± 2	61 ± 2*	59 ± 2**	51 ± 2***
SBP	170 ± 2	166 ± 2	156 ± 2***	151 ± 2***
DBP	105 ± 2	100 ± 2	97 ± 2**	92 ± 2***
FBF	6.1 ± 0.8	5.5 ± 0.8	5.9 ± 0.8	5.0 ± 0.8
<i>DBSP (10 mm Hg)</i>				
HR	69 ± 2	60 ± 2*	60 ± 2*	50 ± 2***
SBP	169 ± 3	166 ± 3	156 ± 3**	151 ± 3***
DBP	105 ± 2	102 ± 2	98 ± 2**	92 ± 2***
FBF	5.4 ± 0.6	3.9 ± 0.6	5.1 ± 0.6	4.0 ± 0.6
<i>DBSP (30 mm Hg)</i>				
HR	71 ± 2	61 ± 2**	62 ± 2**	52 ± 2***
SBP	163 ± 3	161 ± 3	151 ± 3**	147 ± 3***
DBP	106 ± 2	103 ± 2	99 ± 2*	93 ± 2***
FBF	4.2 ± 0.5	3.5 ± 0.5	3.8 ± 0.5	3.4 ± 0.5
<i>DBSP (50 mm Hg)</i>				
HR	76 ± 2	65 ± 2**	63 ± 2***	52 ± 2***
SBP	156 ± 3	154 ± 3	145 ± 3*	141 ± 3**
DBP	106 ± 2	105 ± 2	102 ± 2	94 ± 2***
FBF	3.3 ± 0.4	2.8 ± 0.4	2.9 ± 0.4	2.8 ± 0.4

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with placebo.

HR = heart rate beats min^{-1} ; SBP = systolic blood pressure, DBP = diastolic blood pressure, mm Hg; FBF = forearm blood flow, $\text{ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$.

Table 6 Effect of placebo, epanolol or atenolol on cardiovascular responses to application of distal body subatmospheric pressure (DBSP) of 10, 30 and 50 mm Hg after exercise

	Placebo	Epanolol (200 mg)	Epanolol (400 mg)	Atenolol (100 mg)
<i>Rest (supine)</i>				
HR	70 ± 2	61 ± 2***	62 ± 2**	52 ± 2***
SBP	147 ± 2	141 ± 2	135 ± 2**	133 ± 2***
DBP	96 ± 2	92 ± 2	89 ± 2**	82 ± 2***
FBF	3.0 ± 0.4	3.5 ± 0.4	2.6 ± 0.4	2.6 ± 0.4
<i>DBSP (10 mm Hg)</i>				
HR	71 ± 1	62 ± 1***	63 ± 1***	52 ± 1***
SBP	148 ± 2	141 ± 2*	133 ± 2***	128 ± 2***
DBP	97 ± 2	92 ± 2*	90 ± 2*	83 ± 2***
FBF	2.5 ± 0.3	2.4 ± 0.3	2.3 ± 0.3	2.4 ± 0.3
<i>DBSP (30 mm Hg)</i>				
HR	78 ± 2	68 ± 2***	68 ± 2***	55 ± 2***
SBP	140 ± 3	129 ± 3**	125 ± 3***	122 ± 3***
DBP	101 ± 2	94 ± 2*	92 ± 2**	85 ± 2***
FBF	1.9 ± 0.3	2.2 ± 0.3	1.8 ± 0.3	1.8 ± 0.3
<i>DBSP (50 mm Hg)</i>				
HR	82 ± 2	69 ± 2***	69 ± 2***	56 ± 2***
SBP	135 ± 3	128 ± 3	120 ± 3***	119 ± 3***
DBP	103 ± 2	97 ± 2	92 ± 2**	87 ± 2***
FBF	1.5 ± 0.3	2.0 ± 0.3	1.5 ± 0.3	1.2 ± 0.3

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with placebo.

Abbreviations as Table 5.

There was no significant change in heart rate with DBSP of 10 mm Hg in any group. With DBSP of 30 mm Hg, the increase in heart rate was significantly less with epanolol 400 mg ($P < 0.01$) or atenolol ($P < 0.001$) than with placebo. Furthermore, there was a significantly greater tachycardia in the presence of epanolol 200 mg than in the presence of atenolol ($P < 0.01$). With DBSP of 50 mm Hg, all active treatments were accompanied by a smaller tachycardia than was seen with placebo ($P < 0.01$ vs epanolol 200 mg; $P < 0.001$ vs epanolol 400 mg or atenolol). However, the changes in systolic blood pressure and diastolic blood pressure evoked by DBSP at any level were similar in all groups.

With DBSP of 10 mm Hg, the fall in forearm blood flow in the presence of epanolol 200 mg was significantly greater than that seen with epanolol 400 mg ($P < 0.05$) or atenolol ($P < 0.01$). At greater levels of DBSP there were no significant differences between the changes in forearm blood flow seen in any group. Therefore, as was seen in the pre-exercise tests, active treatment shifted the relation between mean arterial blood pressure and forearm blood flow.

Discussion

Apart from considering the general points mentioned in the introduction, our objectives in this study were to answer the following questions.

Do cardioselective β -adrenoceptor antagonists with and without β_1 -selective agonistic effects have differential influences on resting cardiovascular status and the responses to exercise in patients with primary hypertension?

Do the biochemical effects of such drugs correlate with their putative pharmacological profiles and their observed physiological actions?

Does treatment with such drugs influence the reduction in blood pressure seen following intermittent exercise in patients with primary hypertension?

The discussion centres around the following points.

Cardiovascular variables and responses to exercise

Atenolol and both doses of epanolol reduced resting heart rates and blood pressures. The effects of the higher dose of epanolol were greater than those of the lower dose, while the bradycardia with atenolol was greater than that with either dose of epanolol. However, the absolute exercise-induced increase in heart rate in the presence of epanolol or atenolol was similar,

indicating comparable degrees of β -adrenoceptor antagonism. These observations suggest that epanolol 400 mg has more marked hypotensive effects than previously found in patients with very mild hypertension (Dahlof *et al.*, 1984); that the β_1 -adrenoceptor actions of epanolol are more convincingly expressed following chronic treatment of patients with primary hypertension than after single dose treatment of normotensive subjects (Pringle *et al.*, 1986); and that the possession of modest β_1 -adrenoceptor agonism does not, necessarily, prevent the expression of the hypotensive action of β_1 -adrenoceptor antagonists (Leonetti *et al.*, 1984).

Biochemical effects

Renin, angiotensin II and aldosterone Both atenolol and epanolol evoked significant falls in basal plasma renin concentration with no difference related to drug type or dose. Proportionally smaller falls were observed in basal angiotensin II and aldosterone concentrations (Table 2). Several previous studies have shown an effect of atenolol on basal plasma renin activity in both normo- and hypertensive subjects (summarized in Keeton & Campbell, 1981). We chose in this study to measure plasma renin and angiotensin II concentrations, rather than the relatively less specific plasma renin activity. It appears that both epanolol and atenolol inhibited the release of renin and the consequent production of angiotensin II. The depression of basal plasma renin concentration was more than 50% in each treatment group, while that of angiotensin II was considerably less. Dissociation of plasma angiotensin II and renin activity has previously been noted in patients with essential hypertension (Walker *et al.*, 1976). Whether this was due to changes in the rate of enzyme:substrate reaction, converting enzyme activity or the metabolic clearance of angiotensin II in such patients is not known.

The greatest suppression of exercise-induced increases in plasma renin, angiotensin II and aldosterone concentrations occurred during treatment with atenolol. This is consistent with previous observations that β -adrenoceptor antagonists without partial agonist activity suppress stimulated plasma renin activity to a greater extent than do those with such activity (Buhler *et al.*, 1975). Epanolol has some β_1 -adrenoceptor agonist activity, which could account for the observed differences. This assumes that the evidence cited above for equally effective β_1 -adrenoceptor antagonism by epanolol and atenolol on the heart applies also to their effects on the kidney.

Interestingly, the effect of the drugs on the response of plasma aldosterone concentrations to exercise was considerably less marked than their effects on the response of renin and angiotension II. Indeed, the mean proportional increment above basal was the same for placebo and both epanolol-treated groups (157, 154 and 141% respectively); only in the atenolol-treated groups was the mean proportional response less (67%). A steepening of the dose-response curve to angiotension II has been reported for aldosterone in patients with essential hypertension (Fraser *et al.*, 1979). It might be that diminution of basal activity of the renin-angiotensin system by β -adrenoceptor blockade further enhanced the response, particularly in the presence of somewhat raised basal serum potassium concentrations (Table 4), another stimulus to aldosterone production.

Catecholamines Standing was accompanied by similar increases in plasma noradrenaline concentrations after each treatment. By contrast, exercise was associated with further increases in noradrenaline levels after treatment with epanolol or atenolol, but not after placebo. Although this difference could be due entirely to a reduction in noradrenaline clearance from the circulation (Cryer *et al.*, 1980) this seems unlikely for there was no difference in noradrenaline levels after standing. We have previously reported similar effects after treatment with propranolol or metoprolol (Macdonald *et al.*, 1984). Thus, it seems probable that noradrenaline levels are truly elevated during exercise after treatment with a wide variety of different β -adrenoceptor antagonist drugs.

Plasma adrenaline levels increased significantly during exercise with both epanolol and atenolol, with the greatest increase occurring after treatment with epanolol 400 mg. In contrast we observed no significant increase after placebo, a finding similar to that in young normotensive subjects after mild to moderate exercise (Kjaer *et al.*, 1985). Again the problem of enhanced release versus reduced clearance cannot easily be resolved. After exercise plasma adrenaline levels returned rapidly towards resting values. It is therefore unlikely that the post-exercise hypotension was mediated via peripheral β_2 -adrenoceptor activation causing a reduction in peripheral resistance (see below).

Vasopressin Although vasopressin levels increased during and after exercise, in no phase of the study was there a significant effect of active treatment. Against the background of suppression of the renin-angiotensin axis (see above)

this may appear surprising (Wade, 1984). However, it remains unclear what mechanisms underlie exercise-induced elevations in plasma vasopressin levels. There was no evidence in the present study of a relation between post-exercise changes in diastolic blood pressure and plasma vasopressin levels (see below).

Exercise-induced hypotension In this study we have confirmed our previous finding that, following intermittent exercise in patients with primary hypertension, there is a significant reduction in systolic and diastolic blood pressures unaccompanied by any tachycardia (Wilcox *et al.*, 1982; Bennett *et al.*, 1984). Several other groups also have confirmed our original observations in various experimental and clinical circumstances (Somers *et al.*, 1985; Floras *et al.*, 1986; Nelson *et al.*, 1986).

Exposure to DBSP elicited competent baroreflex responses in the post-exercise hypotensive period (Bennett *et al.*, 1984). Neither epanolol nor atenolol prevented or enhanced the absolute change in blood pressure due to exercise and thus the hypotensive effects of pharmacological and non-pharmacological interventions were additive. Following exercise in the placebo treatment phase there were indications of persistent activation of the renin-angiotensin system and stimulation of vasopressin release. Such factors could be directly responsible for the increased forearm vascular resistance seen following intermittent treadmill exercise. It is also feasible that these hormones have indirect cardiovascular effects. For example, exogenous angiotensin II appears to have vagolytic actions in man (Mace *et al.*, 1985) but if this is true for endogenous angiotensin II we would expect a post-exercise tachycardia, which we did not observe.

The role of endogenous vasopressin in modulating baroreflexes in man is a very contentious area (Bennett & Gardiner, 1986), and the picture has not been clarified by recent findings (Simpson *et al.*, 1986; Ebert *et al.*, 1986; Williams *et al.*, 1986). Furthermore, current information indicates that an influence of endogenous vasopressin on the neural control of forearm vascular resistance should cause vasodilatation rather than vasoconstriction (Aylward *et al.*, 1986). While inhibition of sympathetic efferent outflow to other vascular beds might account for post-exercise hypotension (Floras *et al.*, 1986), it is clear that β -adrenoceptor antagonism with epanolol or atenolol did not interfere with the phenomenon. Indeed, the hypotensive effect of moderate exercise appears to be additive to that produced by these two β -adrenoceptor blocking drugs.

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Appendix

Table 1a Means and 95% confidence limits for the difference of epanolol 400 mg from atenolol 100 mg for exercise heart rate and blood pressures

		Mean	Lower limit	Upper limit
<i>Pre-exercise</i>				
Sitting	HR	11.4	5.5	17.3
	SBP	3.0	-4.8	10.8
	DBP	2.8	-1.8	7.3
Standing	HR	12.8	7.7	17.8
	SBP	-3.0	-11.8	5.8
	DBP	6.0	0.8	11.2
<i>Peak exercise</i>				
	HR	7.5	2.5	12.5
	SBP	6.8	0.8	12.7
	DBP	3.0	-0.7	6.7
<i>Post-exercise</i>				
15 min sitting	HR	10.9	7.0	14.8
	SBP	-0.4	-8.7	8.0
	DBP	2.3	-3.0	7.5

SBP = systolic blood pressure, DBP = diastolic blood pressure
mm Hg.

Table 5a Means and 95% confidence limits for the difference of epanolol 400 mg from atenolol 100 mg for cardiovascular reponses (DBSP)

<i>Pre-exercise</i>		<i>Mean</i>	<i>Lower limit</i>	<i>Upper limit</i>
<i>Rest (supine)</i>				
	HR	8.8	2.7	14.8
	SBP	5.5	-1.4	12.4
	DBP	5.3	-0.0	10.5
	FBF	0.9	-1.5	3.3
<i>DBSP (10 mm Hg)</i>				
	HR	9.9	3.6	16.1
	SBP	5.5	-2.4	13.4
	DBP	5.3	0.0	10.5
	FBF	1.2	-0.7	3.1
<i>DBSP (30 mm Hg)</i>				
	HR	9.9	3.0	3.1
	SBP	4.0	-3.3	11.3
	DBP	6.8	0.4	13.1
	FBF	0.5	-1.0	1.9
<i>DBSP (50 mm Hg)</i>				
	HR	10.6	3.7	17.5
	SBP	3.3	-6.2	12.7
	DBP	8.3	1.8	14.7
	FBF	0.0	-1.0	1.1

Abbreviations as Table 5:

Table 6a Means and 95% confidence limits for the difference of epanolol 400 mg from atenolol 100 mg for cardiovascular reponses (DBSP)

<i>Post-exercise</i>		<i>Mean</i>	<i>Lower limit</i>	<i>Upper limit</i>
<i>Rest (supine)</i>				
	HR	10.6	5.9	15.3
	SBP	2.0	-5.0	9.0
	DBP	7.0	2.7	11.3
	FBF	0.0	-1.3	1.3
<i>DBSP (10 mm Hg)</i>				
	HR	11.0	6.8	15.2
	SBP	4.8	-1.4	10.9
	DBP	7.3	2.2	12.3
	FBF	-0.1	-1.1	0.8
<i>DBSP (30 mm Hg)</i>				
	HR	12.9	7.7	18.0
	SBP	3.0	-4.7	10.7
	DBP	7.5	1.4	13.6
	FBF	0.0	-0.9	1.0
<i>DBSP (50 mm Hg)</i>				
	HR	13.4	8.1	18.7
	SBP	0.8	-6.7	8.2
	DBP	5.3	-1.6	12.1
	FBF	0.3	-0.7	1.3

Abbreviations as Table 5.