The effects of propranolol or atenolol on the cardiovascular responses to central hypovolaemia in Europeans and Bengalees

M. A. RAHMAN & T. BENNETT

Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH

1 The effects of single oral doses of propranolol (80 mg), or atenolol (100 mg) on resting heart rate, blood pressure, forearm blood flow and forearm vascular resistance and on responses to central hypovolaemia, were compared with those of placebo in nine healthy European and nine healthy Bengalee volunteers, in a double-blind, three-period, cross-over study.

2 Atenolol induced a significant reduction in resting systolic blood pressure (SBP) in Europeans but not in Bengalees, although the bradycardic effects of atenolol were similar in both groups. Atenolol did not have any significant effect on forearm blood flow (FBF) or forearm vascular resistance (FVR) in either group. In the presence of propranolol (80 mg) there were no statistically significant falls in BP but there were significant bradycardias, falls in FBF and rises in FVR that were similar in Europeans and Bengalees.

3 In the presence of placebo Europeans exhibited significant falls in diastolic blood pressure (DBP) during lower body negative pressure (LBNP) of 20 and 30 mm Hg. Bengalees did not show falls in DBP during LBNP. However, there were no significant differences between DBP responses in Europeans and Bengalee subjects. Both Bengalees and European subjects showed similar reductions in FBF and FVR during LBNP of 30 mm Hg.

4 In the presence of propranolol, significant changes in forearm blood flow and forearm vascular resistance were evident in Bengalee subjects during LBNP of 20 mm Hg and 30 mm Hg, whereas in the Europeans significant changes in those variables did not occur at any level. The changes in FBF and FVR during LBNP of 20 and 30 mm Hg in Bengalee and European subjects were significantly different.

5 In the presence of atenolol Europeans exhibited significant falls in diastolic blood pressure during lower body negative pressure of 20 mm Hg; no changes in DBP were observed in Bengalees during LBNP of 20 mm Hg. However, there were no significant differences between DBP responses in Europeans and Bengalee subjects. Reductions in FBF and FVR during LBNP of 30 mm Hg were similar in both Bengalees and European subjects.

6 Following release of LBNP at 20 or 30 mm Hg, in the presence of placebo Europeans exhibited significant falls in forearm vascular resistance and there was a significant overshoot in forearm blood flow. In Bengalee subjects an overshoot in forearm blood flow and a vasodilatation were seen only after release of LBNP at 30 mm Hg. No differences were observed between the groups in the response of FVR.

Correspondence: Dr M. A. Rahman, Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH

7 The fall in forearm vascular resistance and the overshoot in forearm blood flow following LBNP in European and Bengalee subjects was blocked by propranolol but was not affected by atenolol. The most likely explanation of this finding is that the fall in forearm vascular resistance following LBNP was due to β_2 -adrenoceptor stimulation.

Keywords lower body negative pressure cardiovascular responses propranolol atenolol ethnicity

Introduction

It has been known for a long time that different ethnic groups of people respond differently to certain drugs or chemicals. In the treatment of hypertension, people of Afrocaribbean origin respond better to diuretics (Grell *et al.*, 1984; Moser & Lunn, 1981; Seedat, 1980) but poorer to β -adrenoceptor antagonists like propranolol (Hollifield *et al.*, 1978; Humphreys & Delvin, 1968; Veterans Study, 1982), or atenolol (Abson *et al.*, 1981; Douglas-Jones, 1976; Seedat, 1980) than people of European origin. In a limited number of studies it has been reported that hypertensive patients of Indian origin tend to show an intermediate response (Seedat, 1971). Recently these differences in responses between different ethnic groups have become increasingly investigated and several possible explanations have been put forward including the ethnic difference in plasma renin activity (Buhler *et al.*, 1972; Laragh, 1973), differences in activity of the kallikrein-kinin system (Holland *et al.*, 1980) and differences in the renal handling of sodium and water (Ledingham, 1953; Borst & Borst 1961; Guyton *et al.*, 1972). Although some of the ethnic differences could be explained by such factors, others cannot and new approaches to understanding ethnic differences in drug effects are being sought.

Recently it has also been suggested that β -adrenoceptor sympathetic reactivity may differ in ethnic groups (Anderson *et al.*, 1988). However, most comparative studies have been carried out between subjects of Afrocaribbean and European origin. In the light of recently published reports of high morbidity and mortality in Bangladeshis from hypertensive-vascular disease (McKeigue *et al.*, 1988) an effort was made in the present study to assess any differences regarding relative adrenergic sympathetic reactivity in Bangladeshis and Europeans. Evidence of any such differences could help to define potential ethnic differences in the aetiology of hypertensive-vascular disease (Anderson *et al.*, 1988). Thus, the first aspect of this study was designed to investigate the comparative effect of propranolol

and atenolol on cardiovascular status in European and Bengalee subjects.

Exposure to low levels of lower body negative pressure (LBNP) causes reductions in central venous pressure with little or no change in systemic arterial pressure (Zoller *et al.*, 1972). Under these conditions, there may be pronounced forearm vasoconstriction without significant change in heart rate. On this basis it has been suggested that the increase in forearm vascular resistance is due to selective unloading of the cardiopulmonary baroreceptors (Abboud *et al.*, 1979; Zoller *et al.*, 1972). When systemic arterial pressure is reduced during LBNP there is recruitment of arterial baroreflex mechanisms, in concert with cardiopulmonary baroreflexes, thereby enhancing α -adrenoceptor-mediated forearm vasoconstriction (Zoller *et al.*, 1972). Since there is some evidence for ethnic differences in cardiovascular reflexes (Anderson *et al.*, 1988) the second aspect of this study was devised to compare the effect of LBNP in European and Bengalee subjects in the presence or absence of β -adrenoceptor antagonists.

Following exposure of a subject to higher levels of LBNP, the blood pooled in the lower half of the body returns rapidly to the central circulation. This can result in an overshoot of blood pressure and in bradycardia but there have been very few systematic studies of the peripheral haemodynamic events accompanying the offset of LBNP. Moreover, since the first observations on the cardiovascular effects of release of LBNP (Greenfield *et al.*, 1963) there have been several conflicting reports in the literature. Some investigators observed overshoots in blood pressures and in forearm blood flow similar to Greenfield *et al.* (1963) (Ardill *et al.*, 1965; Brown *et al.*, 1966; Bennett *et al.*, 1979), but others found the variables returned to the baseline only (Abboud *et al.*, 1975; Duprez *et al.*, 1985). While previous investigators have made suggestions that forearm vasodilatation following LBNP was not likely to be due to carotid sinus reflexes (Greenfield *et al.*, 1963),

none considered that the event directly responsible for the fall in forearm vascular resistance following LBNP might be β_2 -adrenoceptor stimulation.

Against this background the third aspect of this study was to compare the cardiovascular changes following LBNP in European and Bengalee subjects in the placebo treated state and in the presence of atenolol (a β_1 -adrenoceptor antagonist) or of propranolol (a β_1 - and β_2 -(nonselective) adrenoceptor antagonist). Comparison of the results should make it possible to dissect out any β_2 -adrenoceptor mediated effects. This approach was necessary because selective β_2 -adrenoceptor antagonists are no longer acceptable for use in man.

Methods

Subjects

Nine Bangladeshi Asian and nine European healthy male volunteers aged between 20–29 years (mean 22 ± 3 and 26 ± 2 years, respectively) were recruited from within the University. The subjects were fully informed about the nature and objectives of the study, and the more common side-effects of the drugs to be used. Research protocols were reviewed and approved by the Medical School ethics committee.

Exclusion

Subjects were screened to exclude anybody with a known history of diabetes, any cardiovascular disease, or those taking medications which might affect the autonomic nervous system. They were given a questionnaire to fill in and signed an informed written consent form after being made familiar with the experimental procedure to be employed. Subjects were asked not to take vigorous exercise for 12 h following ingestion of the drug.

Procedure

The study was carried out using a double-blind crossover design (i.e. each subject studied on placebo, single standard oral dose of propranolol (80 mg) or atenolol (100 mg)). Cardiosensitivity of atenolol at doses at or below 100 mg in man has been reported before (Frishman, 1981; see also Frishman & Sonnenblick, 1986; Klausner *et al.*, 1988). Each subject had a trial run to familiarize them with the investigational procedure. Blood pressures were measured by the

'Accutorr 1A' automatic, noninvasive blood pressure machine (Datascope Corporation) preset at a 30 s measuring interval. Heart rate was monitored continuously with a heart rate-meter (Instantaneous ratemeter, type 2751) and the ECG signal was amplified and monitored on an electrocardiograph (Lifetrace-18, Albury Instruments Ltd, London) and recorded (see below). Flow to the forearm was measured every 15 s by strain gauge plethysmography (Whitney, 1953) during and following LBNP. The duration of each exposure to LBNP was 1 min (Ardill *et al.*, 1965) followed by a rest period of 1 min as full recovery between bouts of LBNP 0–40 mm Hg is complete within 45 s (Ardill *et al.*, 1969).

Subjects were given a capsule coded 1, 2 or 3 (the drugs were randomised by the Pharmacist), 2 h before the experiment. (Although plasma levels of atenolol and propranolol were not measured, maximum bradycardic effects were observed 2 h after dosing). The subjects evacuated their bladder before entering the LBNP box. The experiment was carried out in a temperature-controlled room set at 23° C. Subjects removed their clothes above the waist but kept their trousers on. Once in the box, the subject rested in a supine position until the experiment ended. The appropriate forearm strain gauge was chosen for each subject and the same strain gauge was used for the same subject throughout the experiment.

To correlate the timing of the blood pressure measurement with all the other measurements a microphone was placed under the cuff over the left brachial artery. Signals from the forearm strain gauge, the ECG, heart rate meter, and from the microphone were recorded on a multi-channel ultraviolet recorder (Oscillograph 2112) via a six channel amplifier (EMMA Medical d.c. amplifier Type E 4910).

The average of the first three systolic blood pressure values was taken as the baseline systolic blood pressure and the Accutorr 'low limit alarm' was set 20 mm Hg below that, so if systolic blood pressure fell by more than 20 mm Hg during LBNP the procedure could be stopped immediately.

Statistical analysis

The baseline values for each parameter given in the text and tables represent the mean over the 1 min steady state just before exposure to LBNP. Those during LBNP represent the mean during 1 min exposure to LBNP at each level. The values quoted for the post-LBNP changes refer to the means over the 45 s following LBNP. Analysis

of variance was performed for each of the variables separately using a three-factor repeated measurement approach with the help of the P2V programme of the BMDP statistical package. Ethnicity was used as a grouping factor, and treatment and pressure as within-subject factors. Where the analysis of variance showed differences these were assessed using the P3D programme of the BMDP statistical package for *t*-test. Between-group comparisons were not considered in the analysis where no statistically significant differences were observed from the baseline value. A *P* value < 0.05 was taken to indicate a significant difference.

Results

Resting variables

Resting data for Bengalees and Europeans are summarised in Table 1. There were no significant differences in resting cardiovascular variables in the presence of placebo in Europeans and Bengalees.

Bengalees Propranolol: In Bengalee subjects propranolol reduced heart rate and forearm blood flow and increased the calculated forearm vascular resistance significantly.

Atenolol: In the presence of atenolol heart rate was reduced significantly, but forearm blood flow was unaffected. Thus, there was a significant difference in the action of atenolol and propranolol on forearm blood flow.

Europeans Propranolol caused significant falls in heart rate and forearm blood flow, and a rise in calculated forearm vascular resistance.

Atenolol reduced the systolic blood pressure and heart rate but did not affect forearm blood flow. Thus, there was a significant difference in the action of propranolol and atenolol on forearm blood flow and forearm vascular resistance.

Bengalees vs Europeans The clearest difference between the two groups was that atenolol reduced systolic blood pressure in Europeans but not in Bengalees. The between-group difference in the response of systolic blood pressure to atenolol was also significant statistically.

Effect of exposure to LBNP

Analysis of the haemodynamic responses to LBNP in Bengalee and European subjects is presented in Table 2.

Bengalees Placebo: No statistically significant alteration was recorded in any of the variables during LBNP of 10 mm Hg or 20 mm Hg. However, there was a significant fall in forearm blood flow accompanied by an increase in forearm vascular resistance with LBNP of 30 mm Hg (Table 2).

Propranolol: There were falls in forearm blood flow with LBNP of 20 and 30 mm Hg. The calculated forearm vascular resistances during LBNP of 20 and 30 mm Hg, were different from the resting value as well as from that during LBNP of 10 mm Hg (Table 2).

Atenolol: No significant changes in any variable were seen during LBNP of 10 or 20 mm Hg, but during LBNP of 30 mm Hg diastolic blood pressure and forearm blood flow were reduced significantly. Forearm blood flow during LBNP of 30 mm Hg was also different from that during LBNP of 10 mm Hg (Table 2). Forearm vascular resistance increased concomitantly during LBNP of 30 mm Hg (Table 2).

Europeans Placebo: There were significant reductions in diastolic blood pressure during LBNP of 20 mm Hg, and 30 mm Hg. Significant reductions in systolic blood pressure and forearm blood flow and an increase in forearm vascular resistance were recorded during LBNP of 30 mm Hg (Table 2).

Propranolol: In the presence of propranolol

Table 1 Comparison of the resting haemodynamic data for Bengalees (*n* = 9) and Europeans (*n* = 9). All values are mean $\pm$ s.d.

		Bengalees			Europeans		
		Placebo	Propranolol	Atenolol	Placebo	Propranolol	Atenolol
SBP	(mm Hg)	112(9)	109(8)	110(7)	119(8)	112(9)	109(9)*
DBP	(mm Hg)	61(8)	59(7)	62(6)	60(5)	55(6)	55(7)
HR	(beats min ⁻¹)	73(5)	64(9)*	63(9)*	68(8)	56(4)*	58(4)*
FBF	(ml min ⁻¹ 100 ml ⁻¹)	4.0(1.1)	2.6(0.7)*	3.4(0.8)†	4.2(0.9)	2.5(0.6)*	3.5(0.8)†
FVR	(units)	24(9)	35(12)*	26(7)	22(4)	35(8)*	25(6)†

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, FBF = forearm blood flow, FVR = forearm vascular resistance (in arbitrary units). Statistical significance: **P* < 0.05 compared with placebo, †*P* < 0.05 compared with propranolol.

Table 2 Data for different cardiovascular variables in Bengalees (BENG) and Europeans (EURO) during 1 min of lower body negative pressure (LBNP) in presence of placebo (PLA), propranolol (PRO) or atenolol (ATE). All values are mean $\pm$ s.d.

		LBNP 0		LBNP10		LBNP20		LBNP30	
		BENG	EURO	BENG	EURO	BENG	EURO	BENG	EURO
SBP	PLA	112 (9)	119 (8)	110 (9)	117 (8)	107 (10)	114 (7)	106 (9)	111* (6)
	PRO	109 (8)	112 (9)	107 (7)	108 (7)	105 (7)	106 (6)	102 (6)	102* (9)
	ATE	110 (7)	109 (8)	109 (8)	108 (8)	107 (8)	106 (8)	104 (8)	103 (8)
DBP	PLA	61 (8)	60 (5)	58 (8)	57 (5)	56 (7)	53* (4)	54 (8)	53* (4)
	PRO	59 (7)	55 (6)	57 (8)	51 (6)	55 (7)	48* (4)	54 (7)	48* (4)
	ATE	62 (6)	55 (7)	59 (6)	50 (6)	55 (6)	48* (4)	53* (8)	46* (5)
HR	PLA	73 (5)	68 (8)	72 (4)	68 (8)	70 (6)	69 (8)	72 (7)	71 (9)
	PRO	64 (9)	56 (4)	64 (8)	57 (4)	65 (9)	57 (6)	62 (8)	59 (4)
	ATE	63 (9)	58 (4)	63 (9)	59 (4)	62 (10)	58 (4)	61 (9)	60 (4)
FBF	PLA	4.0 (1.1)	4.2 (.9)	3.5 (1.0)	3.9 (.8)	3.0 (1)	3.5 (.8)	2.6* (.8)	3.1* (.8)
	PRO	2.6 (.7)	2.5 (.6)	2.2 (.5)	2.4 (.6)	1.9* (.5)	2.2* (.6)	1.6* (.3)	2.0 (.6)
	ATE	3.4 (.8)	3.5 (.8)	3.0 (.6)	3.2 (.8)	2.7 (.6)	3.0 (.7)	2.3* (.6)	2.6* (.6)
FVR	PLA	24 (9)	24 (4)	26 (9)	23 (4)	30 (13)	25 (5)	35* (12)	28* (6)
	PRO	35 (12)	35 (8)	39 (11)	36 (8)	44* (13)	38 (8)	50* (10)	43 (12)
	ATE	26 (7)	25 (6)	28 (6)	26 (6)	31 (6)	28 (6)	36* (7)	33* (7)

SBP = systolic blood pressure (mm Hg), DBP = diastolic blood pressure (mm Hg), HR = heart rate (beats min^{-1}), FBF = forearm blood flow ($\text{ml min}^{-1} 100 \text{ ml}^{-1}$ tissue), FVR = forearm vascular resistance (in arbitrary units). * $P < 0.05$ for difference vs baseline (LBNP 0).

there were significant drops in diastolic blood pressure during LBNP of 20 and 30 mm Hg. A significant reduction in systolic blood pressure was recorded only during LBNP of 30 mm Hg. There were no significant changes in forearm blood flow (Table 2) or in forearm vascular resistance at any level of LBNP (Table 2).

Atenolol: Diastolic blood pressure fell during LBNP of 20 and 30 mm Hg. There was a significant decrease in forearm blood flow during LBNP of 30 mm Hg, and calculated forearm vascular resistance was significantly different during LBNP of 30 mm Hg from that at rest and during LBNP of 10 mm Hg (Table 2).

Comparison of Bengalees and Europeans Falls in forearm blood flow and concomitant rises in forearm vascular resistance were observed during LBNP of 30 mm Hg in both the groups, both in the presence of placebo and of atenolol. In the presence of propranolol, significant changes in forearm blood flow and forearm vascular resistance were evident in Bengalee subjects during LBNP of 20 mm Hg and 30 mm Hg, whereas in the Europeans significant changes in those variables did not occur at any level. In the presence of propranolol the magnitude of fall in FBF and simultaneous rise in FVR during LBNP of 20 and 30 mm Hg were also more in Bengalees than in European subjects at all levels of LBNP. This occurred despite no significant differences in responses of arterial blood pressure during the manoeuvre between the two groups.

No differences were observed in the responses of any variables to LBNP in the presence of placebo or atenolol.

Effect of release of LBNP

Analysis of the cardiovascular responses following LBNP is presented in Table 3.

Bengalees Placebo: No significant overshoot in forearm blood flow was observed during the 1 min following release of LBNP at 10 or 20 mm Hg. However, a significant overshoot was observed in forearm blood flow after release of LBNP at 30 mm Hg. This was associated with a significant fall in forearm vascular resistance.

Propranolol: In the presence of propranolol no overshoot in forearm blood flow or fall in forearm vascular resistance was seen following the release of LBNP at any level.

Atenolol: Diastolic blood pressure remained reduced after release of LBNP at 20 and 30 mm Hg. Forearm blood flow showed a significant overshoot after the release of LBNP at 30 mm Hg, but the fall in forearm vascular resistance was not statistically significant.

Europeans Placebo: Overshoots in forearm blood flow were recorded after release of LBNP at 20 and 30 mm Hg. These changes were accompanied by significant reductions in forearm vascular resistance. The fall in forearm vascular resistance after release of LBNP at 30

Table 3 Cardiovascular variables in Bengalees (BENG) and Europeans (EURO) over the 45 s following lower body negative pressure (LBNP) in the presence of placebo (PLA), propranolol (PRO) or atenolol (ATE). All values are mean $\pm$ s.d.

		LBNP 0		After LBNP10		After LBNP20		After LBNP30	
		BENG	EURO	BENG	EURO	BENG	EURO	BENG	EURO
SBP	PLA	112 (9)	119 (8)	109 (10)	116 (8)	108 (9)	113 (6)	109 (9)	114 (5)
	PRO	109 (8)	112 (9)	108 (7)	111 (7)	105 (8)	108 (8)	105 (9)	109 (7)
	ATE	110 (7)	109 (8)	107 (8)	109 (9)	107 (9)	108 (9)	106 (7)	108 (9)
DBP	PLA	61 (8)	60 (5)	56 (9)	56 (6)	54 (7)	53 (4)	55 (7)	54 (5)
	PRO	59 (7)	55 (6)	55 (8)	51 (5)	54 (8)	50 (4)	53 (7)	48* (5)
	ATE	62 (6)	55 (7)	57 (6)	49 (4)	54* (8)	49 (6)	53* (8)	49 (7)
HR	PLA	73 (5)	68 (8)	72 (5)	67 (8)	72 (6)	69 (8)	73 (7)	70 (8)
	PRO	64 (9)	56 (4)	64 (7)	58 (4)	65 (8)	59 (6)	66 (7)	61* (6)
	ATE	63 (9)	58 (4)	63 (10)	59 (4)	63 (10)	60 (4)	64 (9)	61 (4)
FBF	PLA	4.0 (1.1)	4.2 (.9)	4.0 (1.2)	4.6 (.8)	4.3 (1.3)	5.2* (.8)	4.9* (1.4)	5.8* (1)
	PRO	2.6 (.7)	2.5 (.6)	2.4 (.6)	2.7 (.6)	2.5* (.6)	2.8 (.6)	2.5 (.6)	2.8 (.6)
	ATE	3.4 (.8)	3.5 (.8)	3.5 (.9)	3.7 (.7)	3.7 (1.1)	3.9 (.8)	4.2* (1.6)	4.2* (.7)
FVR	PLA	24 (9)	24 (4)	23 (9)	20 (3)	21 (8)	17* (3)	19* (8)	15* (3)
	PRO	35 (12)	35 (8)	36 (10)	31 (6)	34 (10)	31 (6)	33 (10)	30 (6)
	ATE	26 (7)	25 (6)	24 (7)	23 (4)	23 (7)	22 (4)	21 (7)	20* (4)

SBP = systolic blood pressure (mm Hg), DBP = diastolic blood pressure (mm Hg), MBP = mean blood pressure (mm Hg), PP = pulse pressure (mm Hg), HR = heart rate (beats min⁻¹), FBF = forearm blood flow (ml min⁻¹ 100 ml⁻¹ tissue), FVR = forearm vascular resistance (arbitrary units). **P* < 0.05 for difference vs baseline (LBNP 0).

mm Hg, was significantly greater than that after release of LBNP at 10 mm Hg.

Propranolol: There were no significant overshoots in forearm blood flow or falls in forearm vascular resistance following release of LBNP at any level, but diastolic blood pressure remained reduced after release of LBNP at 30 mm Hg. A significant rise in heart rate was also observed after the release of LBNP at 30 mm Hg.

Atenolol: An overshoot in forearm blood flow and a fall in forearm vascular resistance were recorded after the release of LBNP at 30 mm Hg.

Comparison of Bengalees and Europeans Forearm vascular resistance fell significantly in both groups on withdrawal of LBNP at 30 mm Hg. In Europeans falls in FVR were also evident following LBNP at 20 mm Hg. However, there were no differences in responses of FVR between Bengalees and Europeans following LBNP of either 20 or 30 mm Hg.

Discussion

The present study had three objectives, namely:

- 1) to investigate the comparative effect of propranolol and atenolol on cardiovascular status in European and Bengalee subjects
- 2) to compare the cardiovascular responses to LBNP in European and Bengalee subjects
- 3) to analyse the influences of propranolol and

atenolol on cardiovascular changes during and after LBNP in European and Bengalee subjects.

The results will be discussed with regard to these objectives.

Comparative effects of propranolol and atenolol on cardiovascular status in European and Bengalee subjects

In the placebo-treated state, resting cardiovascular status was similar in European and Bengalee subjects in the present study. In both groups treatment with propranolol caused similar reductions in forearm blood flows and these changes were unaccompanied by significant changes in systemic arterial blood pressure. This finding differs from that reported in hypertensive patients of European and Indian origin (Seedat, 1971). This might indicate differences in variables such as plasma renin activity in normotensive and hypertensive groups.

It was notable that atenolol treatment caused a significant fall in systolic blood pressure in Europeans, but not in Bengalee subjects, and this differential effect is consistent with findings in European and Indian hypertensive patients (Seedat, 1980). Interestingly, the bradycardic effect of atenolol in both groups was similar, and in neither was there a significant reduction in forearm blood flow. Since a fall in systolic blood pressure would be expected to unload arterial baroreceptors, and hence elicit reflex vasoconstriction in the forearm, these results might

indicate some interference with baroreflexes by atenolol in European subjects (Wallin & Fagius, 1988). Robinson *et al.* (1983) reported significant reductions in resting forearm blood flow when patients with primary hypertension were treated with atenolol, a finding that differs from the results of the present study.

The differential effect of propranolol and atenolol on forearm blood flow and forearm vascular resistance in both groups in the present study could be taken to indicate that the increase in forearm vascular resistance in the presence of propranolol was due to antagonism of β_2 -adrenoceptors that were mediating a tonic vasodilator effect. This possibility is made more likely by the finding that the increase in forearm vascular resistance following treatment with propranolol in both groups was unaccompanied by any changes in systemic arterial blood pressure, whereas the lack of any effect of atenolol in the European subjects was in the face of a fall in systolic blood pressure (see above). The drugs in this study were given orally and as propranolol (but not atenolol) is lipophilic, a primary central effect of propranolol is a possibility. However, reports concerning the central effect of β -adrenoceptor antagonists are inconsistent and sometimes even contradictory (Levander & Gillner, 1982). Lader & Tyrer (1972) did not find any central effect at doses around 120 mg of propranolol and it is thought that the effect of propranolol on limb blood flow is mainly due to its effect on limb vascular β_2 -adrenoceptors (Oakley *et al.*, 1980).

Cardiovascular responses to LBNP in European and Bengalee subjects

In the presence of placebo or atenolol the responses of arterial blood pressure, forearm blood flow and forearm vascular resistance to LBNP were not different in the two groups studied. It is notable that in neither group during LBNP were there significant changes in heart rate, although there were increases in forearm vascular resistance. The relative contributions of so-called low (cardiopulmonary) and high (arterial and ventricular) pressure baroreceptor systems to the reflex responses elicited by LBNP have been widely debated. One view has been that the forearm vasoconstrictor response to LBNP is signalled from the cardiopulmonary receptors unloaded by falls in central venous pressure, whereas tachycardia and splanchnic vasoconstriction only occur when high pressure baroreceptors are unloaded (Abboud *et al.*, 1979). However, there are several anomalies in this scheme (see review by Mancina & Mark,

1983; Bennett, 1987), and it is now clear that factors such as flow through the carotid sinus can influence afferent discharge, even when pressure profiles change little (Hajduczkow *et al.*, 1988). Hence it is likely that cardiopulmonary and arterial baroreceptors act in concert under most normal conditions. The fact that in the present study no tachycardia was observed when systemic arterial blood pressure fell during LBNP might have been due to opposing effects between reflex tachycardic drive and bradycardic effects of reduced atrial stretch (Bennett, 1987).

Influence of propranolol and atenolol on cardiovascular responses to LBNP in European and Bengalee subjects

In Bengalee subjects in the presence of propranolol forearm vasoconstrictor responses to LBNP were enhanced; this effect was not seen in European subjects. Assuming the effects of propranolol on the control of forearm blood flow are not due to central effects (see above), it is feasible that antagonism of putative pre- and post-junctional β_1 - and β_2 -adrenoceptors in the forearm unmasks a possible ethnic difference in α -adrenoceptor-mediated vasoconstrictor responses to LBNP.

Although there have been few systematic studies of the cardiovascular events accompanying the offset of LBNP, early observations by Greenfield *et al.* (1963) showed that following LBNP at 70 mm Hg there was an overshoot in forearm blood flow and arterial blood pressure and a bradycardia. Some investigators mentioned similar changes in variables following release of high levels LBNP (Ardill *et al.*, 1965; Bennett *et al.*, 1979; Brown *et al.*, 1966) while others found the variables only returned to the baseline (Abboud *et al.*, 1975; Duprez *et al.*, 1985) following LBNP. Murray *et al.* (1968) carried out experiments with graded degrees of LBNP until syncope, but did not observe any significant overshoot in forearm blood flow on release of negative pressure.

Even less information is available about the changes that follow the release of LBNP at low levels (30 mm Hg or less). There is little evidence in the existing literature of an overshoot in any cardiovascular variables taking place following LBNP at 20 or 30 mm Hg. However, Bennett *et al.* (1979) reported that nine out of their 16 subjects showed an overshoot in forearm blood flow following LBNP at as low as 10 mm Hg, whereas McNamara *et al.* (1969) reported only a slow return of the variables to the baseline. In the present study a significant overshoot in fore-

arm blood flow was not seen until the release of LBNP at 30 mm Hg.

Although previous investigators have made suggestions that forearm vasodilatation following LBNP was not likely to be due to carotid sinus reflexes (Greenfield *et al.*, 1963), none considered that activation of β_2 -adrenoceptor-mediated mechanisms might be directly responsible for the fall in forearm vascular resistance following LBNP. In the present study the forearm vasodilatation following LBNP in European and Bengalee subjects was blocked by propranolol but not by atenolol. The most likely explanation of this finding is that the fall in forearm vascular resistance following LBNP was due to β_2 -adrenoceptor stimulation.

α_1 - and β_2 -adrenoceptor influences counteract each other in the forearm muscle vasculature at rest. The vasoconstrictor effects of α_1 -adrenoceptors predominate because of the larger number of these receptors (Taylor *et al.*, 1980) and their close proximity to the sites of noradrenaline release from the postganglionic

sympathetic nerves. Peripheral pooling of blood during LBNP disinhibits sympathetic nervous activity and increased noradrenaline output at the postganglionic nerve terminals results. Since noradrenaline has such a marked effect on α_1 -adrenoceptors (Jai, 1986), any action on β_2 -adrenoceptors tends to be masked. However, from the present study it appears that following LBNP the vasodilator effects of β_2 -adrenoceptor stimulation persist longer than those of α_1 -adrenoceptor mediated vasoconstriction. This may be due to differences in the post receptor events and/or to involvement of circulating catecholamines in the β_2 -adrenoceptor mediated vasodilatation. While these questions will be resolved only by further experiments it is clear from the present results that European and Bengalee subjects do not seem to differ in these respects.

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References

- Abboud, F. M., Eckberg, D. L., Johannsen, V. J. & Mark, A. L. (1979). Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. *J. Physiol.*, **286**, 173–184.
- Abboud, F. M., Mark, A. L., Heistad, D. D., Eckberg, D. L. & Schmid, P. G. (1975). Selectivity of autonomic control of the peripheral circulation in man. *Trans. Am. clin. Climatol. Soc.*, **86**, 184–197.
- Abson, C. P., Levy, L. M. & Eyherabide, G. (1981). Once daily atenolol in hypertensive Zimbabwean blacks. *S. Afr. med. J.*, **60**, 47–48.
- Anderson, N. B., Lane, J. D., Muranaka, M., Williams, R. B. & Houseworth S. J. (1988). Racial differences in blood pressure and forearm vascular responses to cold face stimulus. *Psychosom. Med.*, **50**, 57–63.
- Ardill, B. L., Bannister, R. G., Fentem, P. H. & Greenfield, A. D. M. (1965). Some effects of simulated gravitational shift of blood on the circulation of horizontal subjects. *J. Physiol.*, **180**, 23–24.
- Ardill, B. L. & Fentem, P. H. (1965). Emptying of the capacity vessels in the forearm against pressure during simulated gravitational shift of blood. *J. Physiol.*, **181**, 46–47.
- Ardill, B. L., Fentem, P. H., Finlay, R. D. & Isaac, P. (1969). Some effects on the blood vessels of the human forearm of local exposure to pressures below atmospheric. *J. Physiol.*, **203**, 31–43.
- Bennett, T. (1987). Cardiovascular responses to central hypovolaemia in man: Physiology and pathophysiology. *Physiologist*, **30**, Suppl, S143–S146.
- Bennett, T., Hosking, D. J. & Hampton, J. R. (1979). Cardiovascular responses to lower body negative pressure in normal subjects and in patients with diabetes mellitus. *Cardiovasc. Res.*, **13**, 31–38.
- Borst, J. G. G. & Borst, De. G. A. (1961). Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet*, **i**, 677–680.
- Brown, E., Goei, J. S., Greenfield, A. D. M. & Plassaras, G. C. (1966). Circulatory responses to simulated gravitational shifts of blood in man induced by exposure of the body below the iliac crests to sub atmospheric pressure. *J. Physiol.*, **183**, 607–627.
- Buhler, F. R., Laragh, J. H., Baer, L., Vaughan, E. D. & Brunner, H. R. (1972). Propranolol inhibition of renin secretion. *New Engl. J. Med.*, **287**, 1209–1214.
- Douglas-Jones, A. P. & Cruickshank, J. M. (1976). Once daily dosing with atenolol in patients with mild or moderate hypertension. *Br. med. J.*, **1**, 990–991.
- Duprez, D., De Pue, N. & Clement, D. (1985). Peripheral vascular response during stimulation of the low pressure receptors in man. *J. Hypertension*, **3** (Suppl. 3), S135–S136.
- Frishman, W. H. (1981). β -adrenoceptor antagonists: New drugs and new indications. *New Engl. J. Med.*, **305**, 500–506.
- Frishman, W. H. & Sonnenblick, E. H. (1986). β -

- adrenergic blocking drugs. In *The Heart*, ed. Hurst, W. 6th ed., pp. 1606–1624. New York: McGraw-Hill.
- Greenfield, A. D. M., Brown, E., Goei, J. S. & Plassaras, G. C. (1963). Circulatory responses to abrupt release of blood accumulated in the legs. *Physiologist*, **6**, 191.
- Grell, G. A. C., Forrester, T. E. & Alleyne, A. O. (1984). Comparison of the effectiveness of a beta blocker (atenolol) and a diuretic (chlorthalidone) in black hypertensive patients. *South. med. J.*, **77**, 1524–1529.
- Guyton, A. C., Coleman, T. G. & Granger, H. J. (1972). Circulation: Overall regulation. *Ann. Rev. Physiol.*, **34**, 13.
- Hajduczuk, G., Chappleau, M. W. & Abboud, F. M. (1988). Rheoreceptors in the carotid sinus of dog. *Proc. Natl. Acad. Sci. USA*, **85**, 7399–7403.
- Holland, O. B., Chud, F. M. & Braunstein, H. (1980). Urinary kallikrein excretion in essential and mineralocorticoid hypertension. *J. clin. Invest.*, **65**, 347–356.
- Hollifield, O. B., Chud, F. M. & Braunstein, H. (1978). Age, race and sex as a determinant of successful antihypertensive therapy. *Prev. Med.*, **7**, 112.
- Humphreys, G. S. & Delvin, D. G. (1968). Ineffectiveness of propranolol in hypertensive Jamaicans. *Br. med. J.*, **2**, 601–603.
- Jai, K. (1986). *Characterization and (patho-)physiology of vascular alpha-adrenoceptors: studies in the forearm*. Ph.D. Thesis. University Hospital Leiden, Netherlands.
- Klausner, M. A., Ventura, D. F., Coelho, J., Mullane, J. F., Irwin, C., Hitzemberger, G., Magometschnigg, D., Kaik, G., Garg, D. C. & Weidler, D. J. (1988). Cardiosensitivity of cetamolol compared with atenolol and nadolol. *J. clin. Pharmacol.*, **28**, 495–504.
- Lader, M. H., & Tyrer, P. J., (1972). Central and peripheral effects of propranolol and sotalol in normal human subjects. *Br. J. Pharmacol.*, **45**, 557–560.
- Laragh, J. H. (1973). Vasoconstriction-volume analysis for understanding and treating hypertension. The use of renin and aldosterone profiles. *Am. J. Med.*, **55**, 261–274.
- Ledingham, J. M. (1953). Distribution of water, sodium and potassium in heart and skeletal muscle in experimental renal hypertension in rats. *Clin. Sci.*, **12**, 337–345.
- Levander, S. & Gillner, A. (1982). Metoprolol and propranolol: No CNS effects of a single oral dose. *Psychopharmacology*, **60**, 211–215.
- Mancia, G. & Mark, A. L. (1983). Arterial baroreflex in humans. In *Handbook of Physiology*. The cardiovascular system. Peripheral circulation and organ blood flow, eds Shepherd J. T. & Abboud F. M. Bethesda, MD: *Am. Physiol. Soc.*; sect 2, vol III(2), 755–793.
- McKeigue, P. M., Marmot, M. G., Court, S. Y. D., Cottier, D. E., Rahman, S. & Riemersma, R. A. (1988). Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in East London. *Br. Heart J.*, **60**, 390–396.
- McNamara, H. I., Sikorski, J. M. & Calvin, H. (1969). The effect of lower body negative pressure on hand blood flow. *Cardiovasc. Res.*, **3**, 284–291.
- Moser, M. & Lunn, J. (1981). Comparative effects of pindolol and hydrochlorothiazide in black hypertensive patients. *Angiology*, **32**, 561–566.
- Murray, R. H., Thompson, L. J., Bowers, J. A. & Albright, C. P. (1968). Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *Am. Heart J.*, **76**, 799–811.
- Oakley, N. W., Dormandy, J. A. & Berent, A. (1980). Preliminary studies on the interaction of propranolol and hydralazine on lower limb blood flow. In *Proceedings of an international symposium, Berlin*. England: CIBA Laboratories.
- Robinson, B. F., Bayley, S., Chiodini, P., Dobbs, R. J., Philips, R. J. & Wilson, P. (1983). A functional abnormality of forearm resistance vessels in men with primary hypertension. *Gen. Pharmacol.*, **14**, 181.
- Roddie, I. C., Shepherd, J. T. & Whelan, R. F. (1958). Reflex changes in human skeletal muscle blood flow associated with intrathoracic pressure changes. *Circ. Res.*, **6**, 232–238.
- Seedat, Y. K. (1971). Propranolol in the South African non-white hypertensive patient. *S. Afr. med. J.*, **45**, 284–285.
- Seedat, Y. K. (1980). Trial of atenolol and chlorthalidone for hypertension in black South Africans. *Br. med. J.*, **281**, 1241–1243.
- Taylor, S. H., Silke, B. & Nelson, G. I. C. (1980). Peripheral circulatory effects of β -blocking drugs. In *Proceedings of an international symposium, Berlin*, pp. 277–286. England: CIBA Laboratories.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982). Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. *J. Am. med. Ass.*, **248**, 1996–2003.
- Wallin, B. G. & Fagius, J. (1988). Peripheral sympathetic neural activity in conscious humans. *Ann. Rev. Physiol.*, **50**, 565–576.
- Whitney, R. J. (1953). The measurement of volume changes in human limbs. *J. Physiol.*, **121**, 1–5.
- Zoller, R. P., Mark, A. L., Abboud, F. M., Schmid, P. G. & Heistad, D. D. (1972). The role of low pressure baroreceptors in reflex vasoconstrictor responses in man. *J. clin. Invest.*, **51**, 2967–2972.

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