Peripheral vascular effects of β -adrenoceptor blockade: comparison of two agents

E. D. COOKE, M. B. MALTZ¹, R. E. SMITH, S. A. BOWCOCK, C. J. WATKINS & A. J. CAMM¹

Departments of Medical Electronics and Physics, and Cardiology¹, St Bartholomew's Hospital Medical College, London EC1A 7BE

- 1 The effects of atenolol (100 mg), a β_1 -adrenoceptor blocker, and bevantolol (200 mg) were compared on heart rate, blood pressure, lung function and on the peripheral circulation in normal volunteers before and after isoprenaline infusion. Recordings were obtained 2 and 24 h following a single dose and 24 h after continuous dosage for 7 days.
- 2 The effect of atenolol on the blockade of β -adrenergic stimuli, as measured by the ability to reduce isoprenaline-induced tachycardia, was greater than that of bevantolol. Though both drugs achieved a similar reduction in systolic pressure there was a significantly greater reduction in diastolic pressure with bevantolol. The lung function tests gave similar results to those with other β -adrenoceptor blockers.
- 3 Atenolol produced a fall in peripheral blood flow consistent with unopposed peripheral α -adrenoceptor stimulation. The effect of bevantolol differs from that of atenolol, an initial fall in peripheral blood flow being followed by a rapid recovery to baseline or greater. This effect may be due to partial α -adrenoceptor agonist activity.

Keywords atenolol bevantolol peripheral vascular resistance

Introduction

β -adrenoceptor blockade is presently established therapy in essential hypertension and angina. A reduction in peripheral blood flow has, however, been observed (Zacharias *et al.*, 1972; Marshall *et al.*, 1976; Vale *et al.*, 1977) and may be sufficiently severe for cessation of therapy (Gokal *et al.*, 1979). Since peripheral blood flow may already be impaired in these patients, for example, an increased peripheral vascular resistance is well-recognised in hypertension, (Conway, 1963; Folicow *et al.*, 1958; Sivertsson & Olander, 1968; Sivertsson *et al.*, 1976) and since the cardiac effects of the various drugs with this activity may be very similar, investigation of their peripheral effects may assume greater importance.

Bevantolol is a β_1 -adrenoceptor antagonist devoid of intrinsic β -sympathomimetic activity and with weak membrane stabilizing properties

(Hoelfe *et al.*, 1975). Following oral administration greater than 70% is absorbed; systemic availability is 60% due to the 'first pass' effect. Peak plasma concentrations are achieved after 1–2 h (plasma half-life: 1.5 h). Bevantolol exhibits linear pharmacokinetics within the therapeutic range (100–400 mg) with no change in half-life during chronic administration (Latts, 1986).

In a series of acute experiments Dukes & Vaughan Williams (1985) suggested that bevantolol may be an α -adrenoceptor agonist.

To elucidate further this 'novel' activity we have compared the acute and chronic effects of bevantolol on heart rate, blood pressure, respiratory function and peripheral vasculature with those of a well-established cardioselective β_1 -adrenoceptor antagonist, atenolol, in human volunteers.

Methods

In a double-blind randomised cross-over trial 10 healthy male volunteers, mean age 21.4 years, height 178 cm, weight, 67.1 kg, were treated with either bevantolol 200 mg daily or atenolol 100 mg daily for 7 days. All were non-smokers and none had a significant history of disease nor was taking any drug known to alter blood pressure or modify the activity of the autonomic nervous system prior to the commencement of the investigation. Exclusions included diabetes mellitus, conditions predisposing to hypoglycaemia, acute or chronic airways obstruction, second or third degree A-V block, previous or current heart failure, cardiac arrhythmias other than isolated, uncomplicated supraventricular or ventricular premature beats, and bradycardia below 56 beats min^{-1} .

The investigation was performed in a noise-free laboratory with temperature and humidity controlled at $24 \pm 1^\circ \text{C}$ and 40–50% relative humidity. Volunteers were recruited 4 weeks before the start of the study and asked to avoid all medicaments prior to the trial to avoid any effects which these might have on the peripheral vasculature. On the days of the trial the volunteers attended at 09.00 h having had a light meal (dry toast and fruit juice) 1 h previously. Resting heart rate, blood pressure, upper limb blood flow (fore-arm and right index finger), micro-circulatory flow (both middle fingers) and lung function tests were performed at baseline and following an infusion of isoprenaline given at the rate of $0.5 \mu\text{g min}^{-1}$ and increased by $0.5 \mu\text{g min}^{-1}$ increments up to a maximum of $2 \mu\text{g min}^{-1}$. Each dose was infused for 15 min or until an end-point of 160 beats min^{-1} was achieved as indicated by continuous ECG monitoring. Blood pressure was recorded every 15 min during the infusion and again at its termination. Limb blood flow and lung function tests were then again performed at the end of the infusion.

One tablet of the β -adrenoceptor blocker was then taken and the same procedure performed 2 and 24 h afterwards. The subjects continued to take one tablet daily and the procedure was performed again 24 h following the seventh dose, i.e. on day 8. After a wash-out period of 4 weeks, the whole procedure was repeated using the alternative drug.

The instrumentation used for these various measurements comprised: a Hawksley random zero sphygmomanometer; strain gauge plethysmographs (Vasculab Model SPG 16), to determine finger and fore-arm blood-flow in absolute units; and an AC coupled infra-red photoplethysmograph (Medasonics model PA 13) to determine

flow features in the microcirculation – in particular the time to maximum filling of the micro-circulation (TF2), the time to the appearance of the dicrotic notch (TF3), and the dicrotic notch proportion of amplitude (DNP)—which all provide information on small vessel compliance (Cooke *et al.*, 1985a). Peripheral vascular resistance (PVR) was calculated from both finger and fore-arm blood flow (Bennett *et al.*, 1979). Total skin blood flow may be equated with finger blood flow (measured by strain gauge plethysmography) if the distribution of the blood supply to the digital tissues is considered. Similarly the terms fore-arm blood flow and muscle blood flow can be used interchangeably.

This methodology has been fully described elsewhere (Cooke *et al.*, 1985a). In brief, strain gauge plethysmography (SPG) and photoplethysmography (PPG) were carried out with the subjects seated and with their arms supported at 45 degrees so that their hands were at heart level. The SPG and PPG signals were recorded on each occasion for 15 min and stored on a minicomputer (Nova 3D) for subsequent analysis. Variation in the recordings was minimised by careful placement of the probes. The SPG was calibrated by using the 1%-extension auto-calibrate facility available on the Vasculab model SPG 16. The PPG amplitude deflection was standardised by moving a test surface towards and away from the probe at a frequency similar to that of cardiac activity (1 Hz or 60 beats min^{-1}). The last 5 min of each recording were analysed by the minicomputer and the results averaged for each parameter obtained.

Lung function parameters were measured immediately after the vascular measurements. Peak expiratory flow rate (PEFR) was determined with a Wright Peak Flow Meter (Airmed, UK), vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were measured using a Vitalograph spirometer (Vitalograph Ltd, UK). The best of three measurements was taken for each parameter. The same equipment and operator were used throughout the study. The spirometer traces were analysed under double-blind conditions by an independent expert.

A full laboratory screening was performed prior to admission of subjects to the investigation. All adverse effects volunteered or observed during the trial were recorded.

Statistical analysis was performed using analysis of variance and differences between means were identified using Duncan's Multiple Range Test (Duncan 1951, 1952; Miller, 1981). This method was used to provide some protection against the risk of spurious significant results to which a

large number of pairwise statistical tests can give rise. The analysis was carried out by an independent statistician who was previously unaware of the protocol. Significance was set at the 5% level. The Duncan's Multiple Range Test does not allow a confidence interval to be estimated (Miller, 1981), but for completeness the mean values presented graphically in the results section are each accompanied by their standard errors.

The drugs were supplied prepacked and were identical in outward appearance in order to maintain double-blind methodology.

The study was undertaken with the approval of the Hospital Ethical Committee and conducted in accordance with the Declaration of Helsinki on medical experimentation.

Results

All 10 volunteers completed the trial without adverse effects. All received the complete isoprenaline infusion regime without reaching the end-point ($160 \text{ beats min}^{-1}$). There was no significant difference in baseline measurements at the start of each epoch of active treatment.

The parameters shown in Figures 1, 2, 3 and 4 are plotted as the differences between the mean value at a given time and the mean value at baseline.

Effects on the peripheral vasculature before isoprenaline

Two and 24 h after the first dose of bevantolol mean finger blood flow was slightly reduced; a larger reduction was seen with atenolol. (Figure 1a). However, with continuous dosage of bevantolol mean finger blood flow increased above baseline whereas with atenolol mean finger blood flow remained below the baseline value. The between-treatment difference was significant ($P < 0.05$), at Day 8. These findings were reflected in an increase in mean finger PVR with atenolol. In contrast, mean finger PVR with bevantolol remained near baseline except for a short initial increase 2 h after the first dose (Figure 1b). Similarly, the time to maximum filling of the microcirculation (TF2) (Figure 2a), was persistently and significantly increased over baseline with atenolol ($P < 0.05$) but only 2 h after the first dose of bevantolol, this effect disappearing thereafter. There was a significant difference between the drugs 24 h after the first dose. The time to appearance of the dicrotic notch (TF3), (Figure 2b), and the dicrotic notch proportion of amplitude (DNP) (Figure 2c), were significantly increased from baseline throughout treatment

Figure 1 Changes in mean finger blood flow (a) and mean finger peripheral vascular resistance (b) before isoprenaline infusion. The fall in finger blood flow ($\text{ml min}^{-1} 100 \text{ ml}^{-1} \text{ tissue}$) and rise in PVR ($\text{mmHg min}^{-1} 100 \text{ ml tissue ml}^{-1}$) seen at 2 and 24 h after the first dose of atenolol ($\square$) persisted until day 8. In contrast, after bevantolol ($\blacksquare$) the slight fall in mean finger blood flow at 2 and 24 h and the rise in PVR at 2 h did not persist; on day 8 blood flow was slightly increased and PVR was reduced.

+, The difference in mean finger blood flow between the drugs was significant on day 8 ($P < 0.05$).

with atenolol. With bevantolol an effect was only seen with DNP, again 2 h following the first dose. Compared to bevantolol there was also a significant delay in TF3 with atenolol at 2 and 24 h (Figure 2b). Significant differences in DNP between the drugs were seen at 24 h and 8 days (Figure 2c). Mean muscle blood flow and vascular resistance (Figure 3a and b) showed a similar, but less marked, pattern as mean finger blood flow and PVR (see Figure 1) but the values did not reach statistical significance. In particular, a sharp increase in muscle PVR

Figure 2 Before isoprenaline infusion showing the effect of atenolol and bevantolol on: (a) the time to maximum filling of the microcirculation (TF2); (b) the time to the appearance of the dicrotic notch (TF3); (c) the dicrotic notch proportion of amplitude (DNP). There was a sharp increase in TF2 2 h after both drugs which persisted with atenolol ($\square$) at 24 h and on day 8. In contrast, with bevantolol ($\blacksquare$) TF2 fell to baseline at 24 h and was only slightly increased on day 8. Following atenolol TF3 was significantly increased at all times but TF3 did not change with bevantolol; DNP showed a similar pattern to TF2. *, significant difference from baseline ($P < 0.05$). +, significant difference between drugs ($P < 0.05$).

Figure 3 Before isoprenaline infusion demonstrating the changes in mean muscle blood flow (a) and mean muscle peripheral vascular resistance (b) with atenolol ($\square$) and bevantolol ($\blacksquare$). Mean muscle blood flow ($\text{ml min}^{-1} 100 \text{ ml}^{-1} \text{ tissue}$) and mean muscle PVR ($\text{mmHg min}^{-1} 100 \text{ ml tissue ml}^{-1}$) showed a similar pattern to finger blood flow (see Figure 1). However, the differences from baseline and between the drugs were not statistically significant.

followed by an equally sharp fall to below the mean baseline values was again seen with bevantolol while with atenolol mean muscle PVR was slightly increased at day 8, at which point the difference in mean muscle PVR was most apparent.

Effects on the peripheral vasculature after isoprenaline

Mean finger blood flow was significantly reduced and vascular resistance was increased after the infusion of isoprenaline. Following bevantolol there was no significant change in either from the post infusion baseline whereas with atenolol mean finger blood flow fell and PVR was persistently increased. The pattern of change was comparable to that seen before isoprenaline, (see

Figure 4 After isoprenaline infusion the time to maximum filling of the microcirculation (TF2) was significantly increased from baseline 2 h after the first doses of both drugs. With atenolol ($\square$) this effect persisted, remaining significant at 24 h, whereas with bevantolol ($\blacksquare$) the values fell to near baseline at 24 h and 8 days.

*, significant difference from baseline ($P < 0.05$).

Figure 1). The differences between the drugs in mean finger PVR after isoprenaline were statistically significant at 24 h. Isoprenaline infusion did not affect the time to maximum filling of the microcirculation (TF2). Two hours after the first dose of both β -adrenoceptor blockers this time was significantly increased compared with the effect of isoprenaline alone (Figure 4). This effect was not apparent 24 h after the first or seventh dose of bevantolol, but persisted with atenolol. The time to the appearance of the dicrotic notch (TF3) was not significantly influenced by isoprenaline, nor by either β -adrenoceptor blocker following isoprenaline infusion; however, the pattern of response is similar to that seen before isoprenaline (see Figure 2b).

No significant effects were seen in DNP, muscle blood flow or muscle PVR following isoprenaline infusion.

Effect on heart rate

Both β -adrenoceptor blockers produced a significant fall in heart rate throughout the period of treatment. Atenolol was more effective than bevantolol in reducing isoprenaline-induced tachycardia (Table 1).

Effect on blood pressure

Before isoprenaline there were no significant differences between the drugs in either systolic or diastolic pressure (Table 1) although both

Table 1 The effect of bevantolol and atenolol (mean values, $n = 10$) on heart rate and blood pressure before and after isoprenaline infusion

Mean values	Day 1			Day 8			Day 2			Day 8			Day 2			Day 8		
	Pre-treatment	2 h post dose	24 h post dose	Pre-treatment	2 h post dose	24 h post dose	Pre-treatment	2 h post dose	24 h post dose	Pre-treatment	2 h post dose	24 h post dose	Pre-treatment	2 h post dose	24 h post dose	Pre-treatment	2 h post dose	24 h post dose
Before isoprenaline																		
Bevantolol	64.60	58.90*	58.80*	125.1	114.9*	123.5	79.8	73.2*	76.0	118.7	118.7	122.7	73.2*	76.0	73.4*	73.4*	73.4*	73.4*
Atenolol	62.45	58.15*	52.50*	125.9	115.6*	116.2*	77.5	74.4	74.8	122.7	122.7	122.7	74.4	74.8	75.7	75.7	75.7	75.7
Bevantolol vs Atenolol	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
After isoprenaline																		
Bevantolol	87.85	68.65*	75.95	157.4	130.2*	154.8	71.7	72.3	68.1	146.5*	146.5*	145.2*	72.3	68.1	70.0	70.0	70.0	70.0
Atenolol	90.10	64.00*	67.40*	159.7	126.7*	145.6*	67.8	69.0	72.2	145.2*	145.2*	145.2*	69.0	72.2	66.5	66.5	66.5	66.5
Bevantolol vs Atenolol	NS	*	*	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS $P > 0.05$, * $P < 0.05$ Duncan's multiple range test.

Both bevantolol and atenolol produced a significant fall in heart rate evident 2 and 24 h following initial dosage and 24 h following 1 week's treatment. Bevantolol, however, produced a significantly greater fall in diastolic pressure than atenolol.

drugs caused reductions in blood pressure. Significant decreases were obtained in systolic pressure 2 h after the first dose with both drugs and at 24 h after the first dose of atenolol, whereas significant decreases in diastolic pressure only occurred with bevantolol at 2 h after the first dose and on day 8. The increase in systolic blood pressure produced by the infusion was diminished by both drugs, atenolol having a

significantly greater effect than bevantolol at 24 h after the first dose. Neither β -adrenoceptor blocker had a significant effect on the reduction in diastolic pressure produced by isoprenaline.

Effect on lung function tests

The results of the lung function tests are shown in Figure 5. No statistically significant effects

Figure 5 The effect of bevantolol (●) and atenolol (○) on the mean values of peak expiratory flow rate (PEFR), vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) a) before and b) after isoprenaline. The differences between the drugs and the differences from baseline were not such as to suggest clinical importance.

*, Significant difference from baseline ($P < 0.05$).

+, Significant difference between drugs ($P < 0.05$).

were seen in peak expiratory flow rate (PEFR). With both drugs vital capacity (VC) was reduced from baseline 2 h after the first dose; however, 24 h after the last dose the VC with atenolol was significantly greater than with bevantolol. Following isoprenaline infusion there were no significant differences in VC between the drugs and infusion baseline. Forced vital capacity (FVC) was significantly reduced from baseline 2 and 24 h after the first dose of atenolol but not after bevantolol. The between treatment difference was significant 24 h after the first dose. No significant changes from baseline occurred following isoprenaline infusion. A significant between treatment difference occurred 24 h after the last dose, the FVC being greater with atenolol. No significant between-treatment difference was observed in forced expiratory volume (FEV_1), either before or after isoprenaline infusion. Both β -adrenoceptor blockers significantly reduced the post-infusion value of FEV_1 2 h after the first dose. All the changes in these respiratory parameters are small and were not such as to suggest clinical importance.

Discussion

Though the β -adrenoceptor blockade effect of atenolol as measured by the ability to reduce isoprenaline-induced tachycardia was shown to be greater than that of bevantolol, both drugs reduced systolic blood pressure to a similar degree. Diastolic blood pressure was however reduced significantly more by bevantolol when compared with atenolol. This finding may be explained by the significant fall in peripheral blood flow and the increase in peripheral vascular resistance observed during atenolol therapy. With bevantolol, the blood flow and PVR showed little change from base-line and this suggestion of a between drug difference in vessel compliance was reflected in the other parameters measured, i.e. faster maximum microcirculatory filling, a reduction in the time to the appearance of the dicrotic notch and reduction in dicrotic notch proportion of amplitude on the PPG record. The peripheral vascular effect of bevantolol appears, however, to be more complex: a short-lived period of unopposed α -adrenoceptor agonism, characteristic of β -adrenoceptor blockade, followed by vasodilatory effects consistent with α -adrenoceptor antagonism which appears to be sustained. This action would be not entirely unexpected when current concepts of the action of agonists and antagonists at peripheral receptor sites are considered (Shepherd & Vanhoutte, 1980). This effect on the peripheral vasculature

has not previously been described in clinical studies for bevantolol, though it has been postulated that bevantolol may be a central and peripheral partial α -adrenoceptor agonist.

Equally, the changes, both before and after isoprenaline infusion, in skin peripheral vascular resistance and blood flow (measured from the finger) that occurred with atenolol, a selective β_1 -adrenoceptor antagonist, are consistent with unopposed peripheral α -adrenoceptor stimulation via the sympathetic nervous system.

The possibility that bevantolol has partial α -agonistic activity is interesting (Dukes & Vaughan Williams, 1985), since if centrally acting, this could explain the behaviour of muscle PVR which increased 2 h following the first dose of bevantolol but had fallen at 24 h and was much reduced after the seventh dose. Only receptors with β_2 -characteristics are represented on the blood vessels supplying muscle, which on stimulation produce vasodilation.

While it is recognised that affinity for a particular receptor site does not equate with intrinsic activity, bevantolol, *in vitro*, has been shown to have an affinity for α_1 and α_2 adrenoceptors in rat brain membranes while atenolol does not possess this property (Kaplan, 1986). However, indirect evidence of α -adrenoceptor blocking activity has been observed in several clinical trials. For example, the early morning rise in blood pressure, which is probably mediated via α -receptors in the peripheral arterioles, has been observed to be controlled with bevantolol (Al-Khawaja *et al.*, 1986). Also, there was a ten-fold higher incidence of diarrhoea in patients with hypertension treated with bevantolol compared to treatment with atenolol (Fairhurst, 1986), (it is well recognised that diarrhoea occurs with peripheral α -adrenoceptor blockade, e.g. prazosin) and, unlike atenolol, bevantolol was found to be associated with an increase in the HDL to LDL cholesterol ratio (Salonen *et al.*, 1986).

Though there were differences between the drugs on the various respiratory parameters measured these were similar to those reported for other cardioselective β -adrenoceptor blockers (Benson, 1977).

The principal difference between the drugs was the apparent beneficial effect of bevantolol on the peripheral vasculature. However it remains to be shown that this phenomenon would occur in patients with untreated essential hypertension in whom peripheral vascular resistance is known to be increased and whether the reduction in peripheral vascular resistance, if it occurs, would be sufficient to avoid the enhanced cold sensitivity which may be evident in these patients when

untreated or during treatment with other β -adrenoceptor blockers (Cooke *et al.*, 1985b). It would appear that a substance with β -adrenoceptor antagonism of the same order as

other β -adrenoceptor blockers and with partial α -adrenoceptor antagonistic action on the peripheral vasculature would have such therapeutic possibilities.

References

- Al-Khawaja, I. M., Caruana, M. P., Prince, H., Whittington, J. & Raftery, E. B. (1986). Once- and twice-daily bevantolol for systemic hypertension using 24-hour ambulatory intra-arterial blood pressure recording. *Am. J. Cardiol.*, **58**, 17E–20E.
- Benson, M. K. (1977). Cardiosensitivity studies. *Proc. Roy. Soc. Med.*, **70** (Suppl 5), 48–49.
- 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.
- Conway, J. (1963). A vascular abnormality in hypertension. *Circulation*, **29**, 520–529.
- Cooke, E. D., Bowcock, S. A. & Smith, A. T. (1985a). Photoplethysmography of the distal pulp in the assessment of the vasospastic hand. *Angiology*, **36**, 33–39.
- Cooke, E. D., Bowcock, S. A. & Smith, A. T. (1985b). Cold sensitivity in essential hypertension: the effect of beta- and combined alpha- and beta-blockade. *Eur. J. clin. Pharmac.*, **29**, 33–36.
- Duncan, D. B. (1951). A significance test for differences between ranked treatments in an analysis of variance. *Virginia J. Sci.*, **2**, 171–189.
- Duncan, D. B. (1952). On the properties of the multiple comparisons test. *Virginia J. Sci.*, **3**, 49–67.
- Dukes, I. T. & Vaughan Williams, E. M. (1985). Cardiovascular effects of bevantolol, a selective beta₁ adrenoceptor antagonist with a novel pharmacological profile. *Br. J. Pharmac.*, **84**, 365–380.
- Fairhurst, G. J. (1986). Comparison of bevantolol and atenolol for systemic hypertension. *Am. J. Cardiol.*, **58**, 25E–27E.
- Folicow, B., Grimby, G. & Thulesins, O. (1958). Adoptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance. *Acta Physiol. Scand.*, **44**, 225–272.
- Gokal, R., Dorman, T. L. & Ledingham, J. G. G. (1979). Peripheral skin necrosis complicating beta-blockade. *Br. med. J.*, **1**, 721–722.
- Hoelfe, M. L., Hastings, S. G., Meyer, R. F., Corey, R. M., Holmes, A. & Stratton, C. D. (1975). Cardiosensitive β -adrenoceptor blocking agents. 1-[(3,4-dimethoxyphenylethyl)-amino]-3-aryloxy-2-propanols. *J. med. Chem.*, **18**, 211–213.
- Kaplan, H. R. (1986). Pharmacology of bevantolol hydrochloride. *Am. J. Cardiol.*, **58**, 3E–7E.
- Latts, J. R. (1986). Clinical pharmacokinetics and metabolism of bevantolol. *Angiology*, **37**, 221–225.
- Marshall, A. J., Roberts, C. J. C. & Barritt, D. W. (1976). Raynaud's phenomenon as side-effect of beta-blockers in hypertension. *Br. med. J.*, **1**, 1948–1949.
- Miller, R. G. (1981). *Simultaneous statistical inference* (2nd ed.). New York: Springer-Verlag.
- Salonen, J. T., Taskinen, E., Salonen, R., Seppänen, K., Venäläinen, J. & Rauramaa, R. (1986). Effects of bevantolol and atenolol on symptoms, exercise tolerance and metabolic risk factors in angina pectoris. *Am. J. Cardiol.*, **58**, 35E–40E.
- Shepherd, J. T. & Vanhoutte, P. M. (1980). *The human cardiovascular system*. New York: Raven Press.
- Sivertsson, R. & Olander, R. (1968). Aspects of the nature of the increased vascular resistance and increased 'reactivity' to noradrenaline in hypertensive subjects. *Life Sci.*, **7**, 1291–1297.
- Sivertsson, R., Sannerstedt, T. & Lundgren, S. (1976). Evidence for peripheral vascular involvement in mild deviation of blood pressure in man. *Clin. Sci. mol. Med.*, **51** (Suppl 111), 65–68.
- Vale, J. A., Van de Pette, S. J. & Price, T. M. L. (1977). Peripheral gangrene complicating beta-blockade. *Lancet*, **ii**, 412.
- Zacharias, F. J., Cowen, K. J., Prestt, J., Vickers, J. & Wall, B. G. (1972). Propranolol in hypertension. A study of long-term therapy, 1964–70. *Am. Heart J.*, **83**, 755–761.

(Received 16 July 1986,
accepted 1 May 1987)