Br. J. clin. Pharmac. (1984), **17**, 273–281

The effects of acute or chronic ingestion of propranolol or metoprolol on the physiological responses to prolonged, submaximal exercise in hypertensive men

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1 We have studied the physiological responses to 50 min of intermittent, moderate exercise in hypertensive men after the ingestion of a single dose of placebo, propranolol or metoprolol, and also after 28 days treatment. In addition, subjective assessments of mood were made during the last 7 days of each period of chronic treatment.

2 Heart rate and blood pressure, both at rest and during exercise, were significantly reduced by a single dose of propranolol or metoprolol; more marked effects were observed after chronic treatment.

3 Ventilation and gas exchange during exercise were only slightly disturbed by single doses of propranolol or metoprolol, whereas chronic treatment had no effect.

4 Perceived exertion scores were increased after a single dose of either drug, compared to placebo, and the effect of propranolol was greater than that of metoprolol. With chronic treatment there were fewer differences between the perceived exertion scores during exercise, although 'leg' fatigue remained greater after propranolol than after placebo.

5 Sweating from the forehead during exercise was enhanced by a single dose of either β-adrenoceptor antagonist, with propranolol having the greater effect. After chronic treatment the effect of propranolol was diminished, whereas the effect of metoprolol was maintained.

6 Very few disturbances of mood were found after chronic ingestion of the β-adrenoceptor antagonists.

Keywords propranolol metoprolol exercise β-adrenoceptor blockade hypertension

Introduction

Although β-adrenoceptor antagonists are widely used in the treatment of hypertension and angina pectoris, these drugs sometimes cause complaints of muscle fatigue (Zacharias, 1976); the reasons for this are unclear. In acute (intravenous or oral) single-dose studies in healthy volunteers this effect is seen as a reduced exercise endurance and an increased perception of the severity of a given exercise load (Epstein *et al.*, 1965; Anderson *et al.*, 1979; Pearson *et al.*, 1979). In one study, metoprolol, a β_1-selective antagonist, had less of an effect on endurance than propranolol, a non-selective antagonist (Pearson *et al.*, 1979). In chronic studies in hypertensive patients, however, neither the endurance of exercise nor its perceived severity have been adversely affected (Reybrouck *et al.*, 1977; Leenan *et al.*, 1980; Wilcox & Hampton, 1981). It is possible, therefore, that in the long-term some adaptive changes occur which ameliorate either the physiological and biochemical effects of β-adrenoceptor antagonists

or the perception of their effects by the patient.

Against this background we have investigated some physiological and biochemical responses to intermittent submaximal exercise in 10 hypertensive men after acute and chronic dosing with placebo, propranolol or metoprolol. The present paper reports the physiological results.

Methods

Ten men (age 31–65 years) with uncomplicated, sustained, mild to moderate essential hypertension (standing diastolic pressure (untreated) between 100–125 mm Hg, phase 5) took part in the study. None of them had any other known past or current medical problems and only two had previously been treated for hypertension; in these patients treatment was discontinued at least 8 weeks before the study. All the patients then attended for a preliminary exercise test before giving their final written consent to the study (which was approved by the Ethical Committee of University Hospital, Nottingham). All the exercise tests were performed in a temperature-controlled exercise laboratory (set at 18°C), after a fast of at least 8 h, during which alcohol, coffee and cigarettes were forbidden. The treatments comprised tablets of placebo, propranolol 80 mg, or metoprolol 100 mg, identical in colour, shape and consistency.

For the acute study the patients attended the laboratory 1.5 h after single oral doses of the treatments, each treatment separated by at least 1 week. For the chronic study the patients attended the laboratory 1.5 h after the last dose of twice daily treatment of 4 weeks duration. In both phases of the study the order of treatments was randomised for the β-adrenoceptor antagonists with placebo in between. The experimental procedure was common to each visit.

Experimental procedure

After being weighed the patients performed simple tests of lung function (vitalography and peak flow measurements) and then lay on a couch. Electrodes were applied to the chest for continuous ECG display and a venous cannula with a three-way tap was inserted into the left antecubital vein and kept patent with a slow infusion (0.3 ml/min) of normal saline (154 mmol NaCl/l). Ten and 20 min later venous blood was withdrawn for biochemical analysis and the blood pressure measured twice in the other arm using the Hawksley random zero sphygmomanometer. The patients stood for 5 min on the treadmill and then heart rate and blood pressure were measured and a blood sample taken before the start of the exercise test; this was approximately 2 h after having taken a tablet.

The exercise protocol involved walking on the treadmill set at a slope of 10% for five 10 min periods, each separated by 3 min rest sitting on a chair. The treadmill speed (determined during the patient's preliminary visit) was that required to produce a heart rate of approximately 120 beats/min in the untreated state. After the last 10 min exercise period the patients sat quietly for the next 30 min.

Measurements made during exercise

The following procedures were performed at the times indicated during each 10 min exercise period:

4–5 min: the rate of evaporation of sweat from the forehead was measured using a continuous air-flow technique (Lamke, 1970), with the water content of the air entering and leaving the capsule determined with dew-point sensors (Michell Instr., Cambridge, UK).

6–7 min: a timed sample of expired gas was collected in a Douglas Bag and analysed using a Morgan 901 Mk 2 CO_2 meter, a Servomex OA 137 O_2 meter and a Parkinson-Cowan industrial gas meter; volumes were corrected to STPD.

7.5–8.5 min: blood pressure was measured by sphygmomanometry and heart rate from the continuous ECG recordings; ratings of perceived exertion for 'total exertion', 'leg exertion', and 'breathing exertion' were recorded using the Borg scale (Borg, 1970).

9 min: blood was withdrawn for immediate estimation of glucose (Reflomat, Boehringer) to ensure subjects were not hypoglycaemic, and for later biochemical analysis (Macdonald *et al.*, 1984).

During the 30 min post-exercise recovery period blood samples were withdrawn at 15 and 30 min, and heart rate and blood pressure measured frequently. The total volume of saline infused (approx. 40 ml) and blood withdrawn (approx. 200 ml) were noted. The patients' haematocrits were checked before the first, third and fifth exercise test.

Subjective assessment of mood

During the last 7 days of each treatment period in the chronic phase of the study, the patients were asked to complete a daily mood inventory to describe their feelings over the previous 24 h. The inventory contained bipolar visual analogue scales representing a number of different dimensions of mood. The scales were based upon those used by Herbert *et al.* (1976) with the addition of

one scale reflecting the degree of tiredness during exercise. Patients indicated their assessments by placing a mark on each of the scales.

Statistical analysis

Treatment and exercise effects were assessed using standard analysis-of-variance methods. Variability in the data due to differences between subjects was controlled by including subject identity as a blocking factor in the analysis. Where *F*-tests revealed differential treatment or exercise/rest effects, the precise nature of these differences was identified using *t*-tests on contrasts in the group means. The bulk of the calculations were carried out using the facilities for the analysis of designed experiments provided by the statistical package GENSTAT (1980). For the subjects' mood assessments, for each patient the mean weekly score on each of the 18 visual analogue scales was calculated for each of the drug conditions. Comparisons of mood changes were made between the two active drugs and placebo and between the two drugs, using the nonparametric Wilcoxon test.

Results

All 10 patients completed the study but the results from one patient have been omitted since no metoprolol was detected in his blood after chronic treatment. The patients' body weights and simple tests of lung function were similar for all visits (Table 1). One man fainted whilst sitting, 30 min into the post-exercise period following the ingestion of metoprolol in the acute phase of the study. At that time his systolic pressure had fallen to 105 mm Hg (from a pre-exercise level of 162 mm Hg) and his heart rate was 91 beats/min (compared with 76 before exercise); his blood glucose was 4.4 mmol/l. He made an uneventful recovery and had no further problems. There were no other untoward events and on no occasion did blood glucose fall below 3 mmol/l.

Heart rate and blood pressure (Figure 1)

(i) *Acute phase* Following ingestion of placebo, the level of exercise employed resulted in a significant increase in heart rate (pre-exercise 74, exercise 124 beats/min, $P < 0.001$) and systolic blood pressure (SBP, pre-exercise 164, exercise 176 mm Hg, $P < 0.001$, Figure 1) and a significant fall in diastolic pressure (DBP, pre-exercise 107, exercise 90 mm Hg, $P < 0.001$).

Following single oral doses of propranolol or metoprolol there was a similar and significant decrease in resting and exercising heart rates compared with placebo ($P < 0.001$). Both the absolute and relative increases in heart rates during exercise in the presence of the drugs were lower than with placebo (35 *vs* 50 beats/min, i.e. 54% *vs* 73% of the resting value). The rate of fall of heart rate after exercise was similar on all three occasions, but the heart rates throughout the 30 min post-exercise recovery periods were approximately 10 beats/min higher than in the pre-exercise periods ($P < 0.001$, Figure 1).

Following the ingestion of metoprolol, SBP in the pre-exercise period (both supine and standing) was significantly lower than after placebo ($P < 0.01$). There was no significant difference in DBP after metoprolol or placebo when the sub-

Table 1 Body weight and lung function tests with acute and chronic administration of propranolol or metoprolol (Values are mean ± 1 s.e. mean, $n = 9$)

		Body weight (kg)	*FVC (l)*	*FEV_1 (l)*	*PEFR (l/min)*
Acute phase					
Placebo	mean	80.3	4.51	3.50	510
	s.e. mean	3.9	0.41	0.27	25
Propranolol	mean	80.7	4.61	3.37	510
	s.e. mean	4.1	0.37	0.24	24
Metoprolol	mean	80.5	4.56	3.45	520
	s.e. mean	4.1	0.45	0.33	24
Chronic phase					
Placebo	mean	80.7	4.74	3.51	521
	s.e. mean	4.1	0.39	0.29	25
Propranolol	mean	81.0	4.68	3.43	504
	s.e. mean	4.2	0.38	0.26	20
Metoprolol	mean	80.8	4.70	3.42	514
	s.e. mean	4.2	0.42	0.31	21

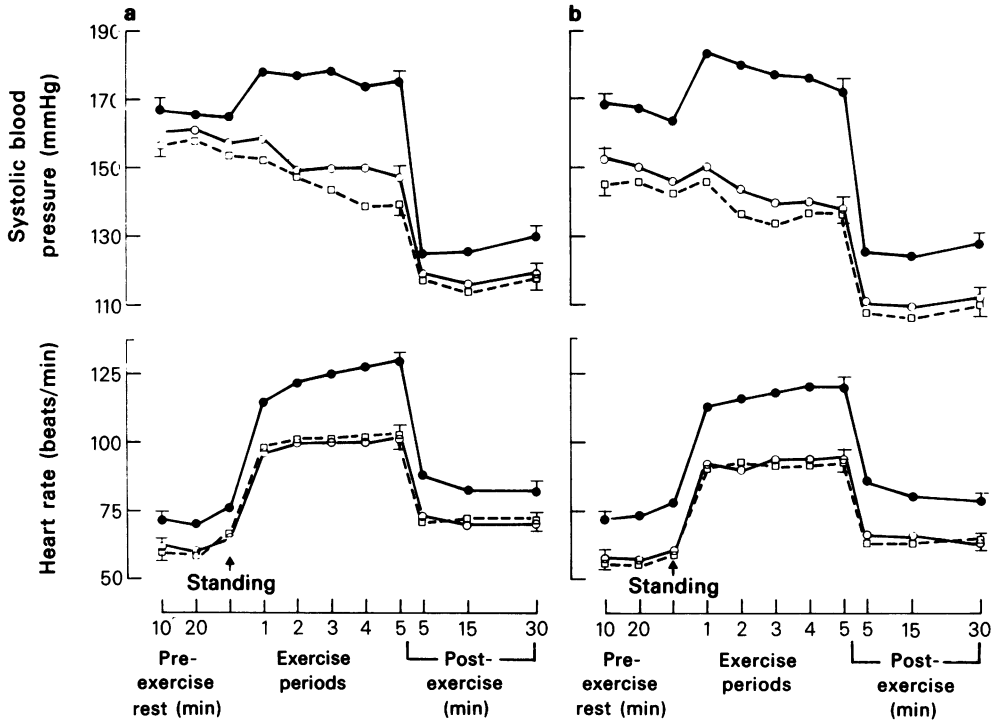

Figure 1 Systolic blood pressure (SBP) and heart rate before, during and after exercise following ingestion of placebo (●), propranolol (○) or metoprolol (□) in both the acute (**a**) and chronic (**b**) phases of the study. Values are mean ± 1 s.e. mean, $n = 9$.

jects were supine, but in the upright posture DBP was significantly lower after metoprolol (mean 98 mm Hg) than after placebo (108 mm Hg, $P < 0.01$). The ingestion of propranolol had a smaller effect on resting blood pressure pre-exercise; SBP was significantly lower than after placebo for the first supine measurement and after 5 min standing ($P < 0.05$), whereas there was no effect on DBP.

The rise in SBP during exercise after placebo (mean 12 mm Hg) was abolished both by propranolol and by metoprolol (Figure 1). In exercise periods 4 and 5, SBP was significantly lower after the ingestion of metoprolol than after propranolol ingestion ($P < 0.01$). After exercise on all occasions there were significant falls in SBP and DBP that persisted throughout the post-exercise period. In the presence of the β-adrenoceptor antagonists, blood pressure was lower than with placebo in the post-exercise recovery period; however, even after placebo, eight of the nine patients had a DBP of less than 95 mm Hg (sitting, phase 5, 30 min post-exercise), and SBP ranged from 114–154 mm Hg (mean 128 mm Hg).

(ii) *Chronic phase* After chronic ingestion of placebo, heart rate and blood pressure values before, during and after exercise were similar to those recorded after the acute ingestion of placebo except that heart rate during exercise was slightly lower in the chronic phase of the study ($P < 0.01$).

Compared to the acute administration of either drug, chronic ingestion of propranolol or metoprolol had only a minor effect on resting heart rate when supine, but produced a significant reduction (5 beats/min) in heart rate whilst standing ($P < 0.05$). Chronic ingestion of either drug was associated with a lower heart rate during exercise than after a single dose ($P < 0.01$), but the difference in heart rate during exercise with either propranolol or metoprolol and placebo was similar in the two phases of the study. Heart rates during the post-exercise recovery periods were significantly lower after chronic than after acute ingestion of either drug ($P < 0.05$).

Chronic ingestion of propranolol or metoprolol was associated with larger reductions in resting blood pressure, both pre- and post-exercise, than were seen after a single dose of either drug ($P < 0.01$). SBP during each exercise period was significantly lower after chronic ingestion of propranolol than after a single dose

of the drug ($P < 0.01$). After chronic ingestion of metoprolol, SBP during exercise was lower than after a single dose of metoprolol only in the first three exercise periods ($P < 0.05$). Thus, in exercise periods 4 and 5, SBP was similar after either acute or chronic ingestion of metoprolol.

Respiratory variables (Tables 1 and 2)

There were no significant differences on any of the six occasions in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) at rest (Table 1), or in oxygen consumption ($\dot{V}O_2$) during exercise (Table 2). Total ventilation ($\dot{V}_E$) during exercise was slightly higher after the acute dose of metoprolol than after either propranolol or placebo ($P < 0.05$), and carbon dioxide production ($\dot{V}CO_2$) was slightly lower after the acute dose of propranolol compared with metoprolol ($P < 0.05$) although neither differed significantly from placebo. There were no significant differences in $\dot{V}_E$ or $\dot{V}CO_2$ recorded for the three treatments in the chronic phase of the study.

Perceived exertion scores (Figure 2)

(i) *Acute phase* Perceived exertion scores ('total', 'leg', 'breathing') increased with each 10 min exercise period on all three occasions. When compared to the scores for leg exertion during exercise after placebo, the values obtained after ingestion of propranolol were significantly increased for all exercise periods ($P < 0.01$), whilst after the ingestion of metoprolol a significant increase in leg fatigue was recorded only for the first three exercise periods ($P < 0.05$). Only in the presence of propranolol was the total exertion score in each exercise period significantly higher than in the presence of placebo ($P < 0.01$), whereas, overall during exercise, total exertion was significantly higher after propranolol or metoprolol than after placebo ($P < 0.01$). There were no significant differences between the breathing scores recorded with the three treatments.

(ii) *Chronic phase* In the chronic phase of the study, there were fewer differences between the exertion scores for the three treatments than in the acute phase. This may, in part, have been contributed to by the tendency for the exertion scores after chronic ingestion of placebo to be higher than after acute treatment with placebo. When compared to the score for leg exertion after chronic ingestion of placebo, the chronic ingestion of either drug was associated with an increase in leg exertion during the first exercise period ($P < 0.05$), whereas only after propranolol was there a significant increase in the fourth and fifth exercise periods ($P < 0.05$).

Sweating (Figure 3)

(i) *Acute phase* Sweating from the forehead increased with each successive exercise period, the increase being greater after propranolol than after metoprolol or placebo ($P < 0.01$, Figure 3) and greater after metoprolol than after placebo ($P < 0.01$).

(ii) *Chronic phase* The sweating values ob-

Table 2 Respiratory variables during the first and fifth exercise periods with either acute or chronic administration of propranolol, metoprolol or placebo. (Values are mean ± 1 s.e. mean, $n = 9$)

		$\dot{V}_E$ (l/min)		$\dot{V}O_2$ (ml kg^{-1} min^{-1})		$\dot{V}CO_2$ (ml kg^{-1} min^{-1})	
		First	*Fifth*	*First*	*Fifth*	*First*	*Fifth*
Acute phase							
Placebo	mean	34.7	35.3	18.2	17.6	16.9	16.6
	s.e. mean	1.9	2.1	0.6	0.9	0.9	0.7
Propranolol	mean	31.1	36.5	17.0	18.6	15.1	16.7
	s.e. mean	2.2	1.8	0.8	0.5	0.8	0.4
Metoprolol	mean	35.4	37.9	18.3	18.6	16.9	17.1
	s.e. mean	2.1	2.9	0.7	0.7	0.6	0.8
Chronic phase							
Placebo	mean	34.0	36.8	18.6	18.4	17.6	16.8
	s.e. mean	2.5	2.4	0.7	0.4	0.6	0.5
Propranolol	mean	34.8	37.4	17.9	18.1	16.4	16.7
	s.e. mean	2.4	2.3	0.7	0.5	0.8	0.6
Metoprolol	mean	34.3	37.5	17.8	18.6	16.6	17.2
	s.e. mean	2.2	2.0	0.5	0.5	0.7	0.7

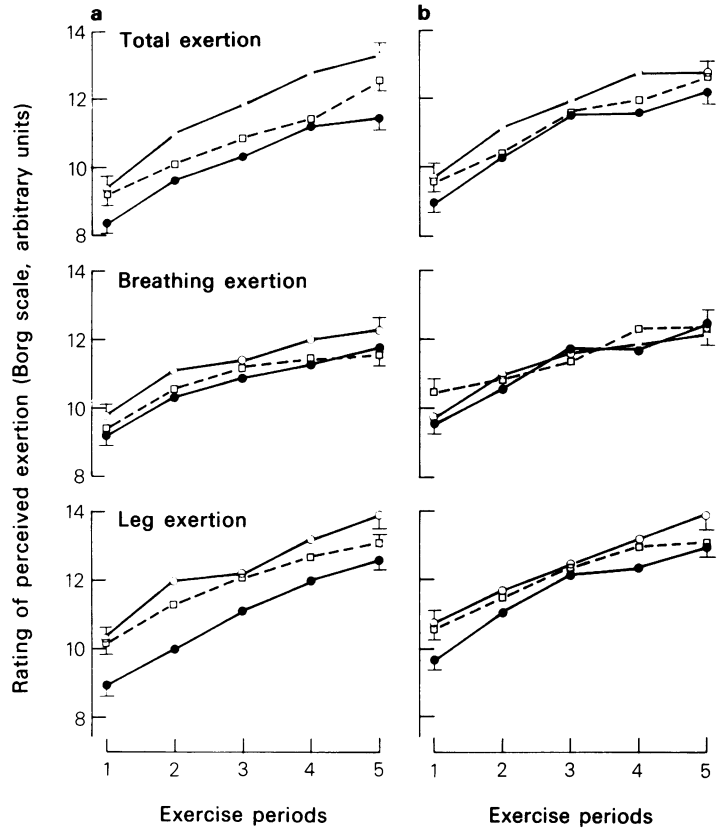

Figure 2 Perceived exertion scores (top: Total; middle: Breathing; bottom: Leg) during exercise following ingestion of placebo (●), propranolol (○) or metoprolol (□) in both the acute (**a**) and chronic (**b**) phases of the study. Values are mean ± 1 s.e. mean, $n = 9$.

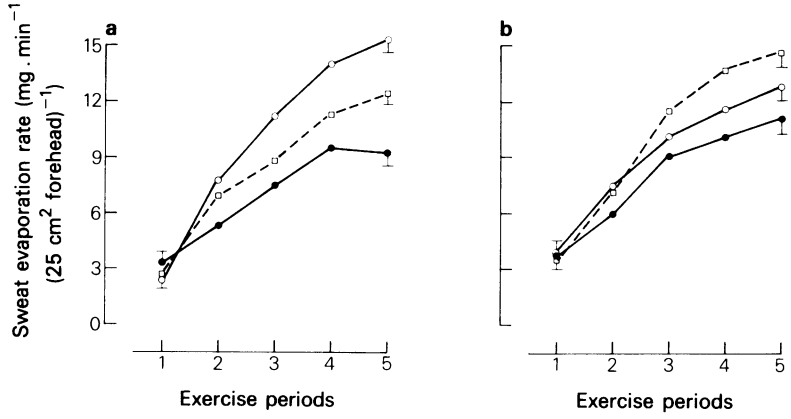

Figure 3 Sweating from the forehead during exercise following ingestion of placebo (●), propranolol (○) or metoprolol (□) in both the acute (**a**) and chronic (**b**) phases of the study. Values are mean ± 1 s.e. mean, $n = 9$).

tained after chronic ingestion of placebo were slightly higher than after acute ingestion of placebo, the difference, however, was significant only for the fifth exercise period ($P < 0.05$).

Following chronic ingestion of metoprolol, sweating from the forehead was significantly greater than after placebo in exercise periods 3, 4 and 5 ($P < 0.01$), and was greater than after propranolol in exercise periods 4 and 5 ($P < 0.05$). After chronic ingestion of propranolol sweating from the forehead was reduced compared with the acute phase and was only significantly greater than placebo during exercise period 5 ($P < 0.05$).

Drug levels

The plasma levels of propranolol and metoprolol were higher after chronic treatment than after acute dosing.

After a single, oral dose the plasma propranolol concentrations were between 45 and 663 nmol/l (mean 224 ± 64 (s.e. mean) nmol/l), whilst after chronic treatment the concentration range was 304–2120 (mean 726 ± 210) nmol/l. Plasma levels of metoprolol were between 222–578 (mean 350 ± 38) nmol/l after a single dose, and between 156–1450 (mean 781 ± 142) nmol/l after chronic treatment. Thus, for both drugs there was marked inter-individual variation in plasma levels, but due to the small number of subjects we have not attempted to relate the individual drug levels to any of the other variables measured in this study.

Mood assessment

Of the 18 dimensions assessed with the visual analogue scales, only three revealed significant differences between placebo, propranolol or metoprolol. The three dimensions were: Tired during exercise – Energetic during exercise; Alert – Drowsy; Clearheaded – Muzzy.

Compared with placebo, metoprolol produced greater feelings of tiredness during exercise ($P < 0.05$) but, conversely, more general feelings of alertness during the week as a whole ($P < 0.02$). When compared with propranolol, the results suggested that metoprolol produced marginally more muzziness ($P < 0.05$; one-tailed test).

Discussion

We have confirmed, in a group of hypertensive men, that single oral doses of propranolol (80 mg) or metoprolol (100 mg—a dose considered to be β_1-selective, Ablad *et al.*, 1973), produce similar levels of β_1-adrenoceptor antagonism, as judged by the reduction in exercise heart rates and systolic blood pressures. The failure of propranolol or metoprolol to abolish exercise-induced tachycardia is well-known and is, in part, probably due to an inhibition of cardiac vagal tone contributing to the rise in heart rate.

The acute ingestion of either β-adrenoceptor antagonist caused a significant reduction in resting blood pressure, but the reduction after chronic ingestion was significantly greater. Other work suggests that the further reduction in blood pressure after chronic treatment with β-adrenoceptor antagonists occurs within a few days (Haglund & Collste, 1980; Leonetti *et al.*, 1975).

We have commented elsewhere on the moderate increase in systolic blood pressure, seen during exercise in the hypertensive patient when treated with placebo (Wilcox *et al.*, 1982); the abolition of this pressor response by either propranolol or metoprolol might have been due to these drugs reducing cardiac output, but this does not explain the progressive fall in systemic arterial blood pressure with each exercise period, especially since heart rate remained constant (and elevated). This fall in systemic arterial blood pressure could be explained by a progressive reduction in total peripheral resistance due to elevated venous levels of lactate and K^+ during exercise in the presence of propranolol or metoprolol (Macdonald *et al.*, 1984).

There was a persistent fall in both systolic and diastolic blood pressures during the post-exercise recovery period; it was notable that the post-exercise hypotension was not accompanied by a tachycardia. One possible explanation of these observations is that exercise leads to a change in baroreflex sensitivity; we are investigating this possibility presently.

While no effect of either drug on resting respiratory variables (FVC, FEV_1, PEFR), were detected, slight differences in ventilation and respiratory gas exchange during exercise, were observed. Other studies employing a shorter duration of exercise have shown differences in respiratory gas exchange (Twentyman *et al.*, 1982) but, as our study shows, if exercise is continued such initial differences disappear, both after acute and chronic treatment. A study of the kinetics of gas exchange at the onset of exercise has shown that the administration of propranolol lengthens the time constant relating to the increase in $\dot{V}O_2$, but has no effect on the eventual steady state value (Petersen *et al.*, 1983).

Perceived exertion

In most studies involving progressive exercise to maximum capacity, β-adrenoceptor antagonists

appear to reduce performance (Ekblom *et al.*, 1972; Anderson *et al.*, 1979; Pearson *et al.*, 1979) and increase the individual's subjective rating of the severity of the effort (perceived exertion) at submaximal workloads (Pearson *et al.*, 1979). In the present study employing steady-state submaximal exercise, we observed that the rating of perceived exertion was greater when patients had received single doses of β-adrenoceptor antagonists, and was highest in the presence of propranolol. It is of some interest that the greater perceived exertion was more attributable to leg fatigue, than to difficulty in breathing. It is feasible that the metabolic disturbances produced by administration of the β-adrenoceptor antagonists (Macdonald *et al.*, 1984) had specific effects on the exercising muscles and were responsible for the greater leg fatigue. However, it remains to be determined if the effects of the β-adrenoceptor antagonists on the sweating responses to exercise contribute to 'total' perceived exertion and whether the central nervous effects of these drugs influence perception of exertion.

In the chronic phase of the study there was very little difference between perceived exertion scores under any conditions, but this was due partly to an increase in the scores in the placebo-treated state.

Sweating

The effect of β-adrenoceptor antagonists on sweating during exercise has not been fully investigated. Davies *et al.* (1978) reported that intravenous practolol had no effect on weight loss (hence, by inference, evaporative water loss) during prolonged exercise. In the present study, a single oral dose of either metoprolol or propranolol potentiated sweating from the forehead during exercise, with propranolol having a greater effect than metoprolol. This effect is similar to that for sweating from the forehead (Macdonald *et al.*, 1982) and for insensible weight loss from the whole body (Molnar & Read, 1974) seen during insulin-induced hypoglycaemia in the presence of propranolol or metoprolol. The increased sweating in the present study may, in part, have been due to elevated plasma catecholamine levels (Macdonald *et al.*, 1984) leading to increased α-adrenoceptor-mediated sweating (Chalmers & Keele, 1951). In addition it has been suggested that there is a β-adrenoceptor-mediated inhibitory mechanism, the antagonism of which, by propranolol, leads to a potentiation of cholinergically-mediated sweating (Foster *et al.*, 1971). Finally, it is possible that the increased sweating was a thermoregulatory response to an increase in core temperature resulting from a reduced skin blood flow during exercise with systemic administration of β-adrenoceptor antagonists. Both the acute and chronic administration of propranolol, for instance, have been reported to cause a significant reduction in resting forearm blood flow compared with placebo or oxprenolol (Vandenberg, 1982).

Mood assessment

Both propranolol and metoprolol are lipophilic drugs (log partition coefficient in octanol/water 3.65 and 2.15 respectively) so one might expect that they would influence mood. In fact very little difference was found between these drugs and placebo. The strongest finding to emerge was that metoprolol resulted in greater levels of alertness during the week of its ingestion than did placebo. However, there was no difference between the effects of metoprolol and propranolol on this dimension. Furthermore, ingestion of metoprolol was associated with greater feelings of tiredness during everyday activities.

In the present study, chronic treatment with propranolol or metoprolol had a greater antihypertensive effect than a single dose of either drug. In contrast, the effects of the drugs on respiration, perceived exertion and sweating during exercise were less marked after chronic treatment. The extent to which the latter may be due to effects of the drugs on metabolism during exercise is considered in the subsequent paper (Macdonald *et al.*, 1984). This study has shown that although a single dose of propranolol disturbs the responses to exercise more than a single dose of metoprolol, this difference is not maintained after chronic treatment. Thus, there do not appear to be any differences of sufficient importance between the drugs to merit the selection of one, in preference to the other, for therapeutic uses. Furthermore, it is important to note that the patients were readily able to perform this type of exercise in the presence of either drug.

We are grateful to Professor John Wikstrand and Dr Eric Fellenius (AB Hässle, Mölndal, Sweden) for their advice and encouragement and for determining the plasma levels of propranolol and metoprolol, and Astra Pharmaceuticals, St Albans, UK for financial support. We thank Dawn Lake, Christine Lewis and Hilary Green for their excellent technical assistance and Rosemary Goodwin for typing the manuscript.

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(Received August 16, 1983, accepted November 18, 1983)