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Exercise haemodynamics and maximal exercise capacity during β-adrenoceptor blockade in normotensive and hypertensive subjects

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1 The effects of atenolol administration on maximal exercise capacity and exercise haemodynamics have been compared in eight normotensive and eight mildly hypertensive subjects, matched for sex, age, body weight, and maximal oxygen uptake, and familiar with maximal exercise testing.

2 Supine and exercise blood pressure, and exercise total peripheral resistance were significantly higher, and exercise cardiac output was significantly lower in the hypertensive than in the normotensive subjects.

3 Administration of atenolol (1×100 mg day^{-1}) for 3 days reduced supine and exercise systolic blood pressure, heart rate, and cardiac output, and increased exercise stroke volume. Supine and exercise diastolic blood pressure and exercise total peripheral resistance were unaffected by atenolol. The effects of atenolol did not differ in the normotensive and the hypertensive subjects.

4 Maximal work load, maximal oxygen uptake, and maximal heart rate were reduced to a similar extent in normotensive and hypertensive subjects during atenolol treatment.

5 It is concluded that there is no difference in the effects of short-term atenolol administration on exercise haemodynamics and maximal exercise capacity in normotensive and mildly hypertensive subjects.

Keywords β-adrenoceptor blockade exercise haemodynamics hypertension

Introduction

In many studies, acute as well as chronic administration of nonselective and β_1-selective β-adrenoceptor blocking agents has been shown to reduce maximal exercise capacity in normotensive subjects (Anderson *et al.*, 1979; Folgering & Van Bussel, 1980; Hughson & MacFarlane, 1981; Tesch & Kaiser, 1983; Smyth *et al.*, 1984; Van Baak *et al.*, 1985, 1986). On the other hand, the majority of studies in hypertensive subjects suggests that maximal exercise capacity is not affected during β-adrenoceptor blockade (Hansson *et al.*, 1977; Reybrouck *et al.*, 1977; Franz *et al.*, 1979, 1982, 1985; Lijnen *et al.*, 1979; Leenen *et al.*, 1980; Lösment *et al.*, 1986). It is likely that the reduction of maximal exercise cardiac output during β-adrenoceptor blockade (Epstein *et al.*, 1965; Ekblom *et al.*, 1972) is involved in the reduction of maximal exercise capacity in normotensive subjects. Therefore, we investigated the hypothesis that the effect of β-adrenoceptor blockade on exercise haemodynamics differs in normotensive and hyperten-

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sive subjects. In order to minimize bias due to differences in training status and familiarity with exercise testing, we selected normotensive and hypertensive subjects who had experience with maximal exercise testing and matched them for maximal oxygen uptake, body weight, age and sex. The β-adrenoceptor blocker studied was atenolol, a predominantly β_1-adrenoceptor selective blocker.

Methods

Subjects

Subjects were recruited from a group of recreational cyclists, whose physical condition had been tested regularly by means of maximal bicycle ergometer testing, and from subjects who had participated in previous exercise studies in our department.

Sixteen subjects (14 male, two female) between 23 and 53 years of age were included in the study. Half of the subjects had a history of hypertension with sitting blood pressures > 140/90 mm Hg for at least 1 year prior to the study. Only two of the hypertensive subjects used antihypertensive medication, which was withdrawn 2 weeks before the start of the study. Normotensive and hypertensive subjects were matched for age, sex, body weight and maximal oxygen uptake.

The protocol of the study was approved by the Ethics Committee of the University of Limburg and all subjects gave their written informed consent.

Study protocol

The study was performed according to a double-blind randomized crossover design. Each subject was tested after 3 days of oral treatment with placebo and atenolol (1×100 mg day^{-1}). Treatment periods were separated by a wash-out period of 1 week. The exercise test was performed approximately 2 h after the last dose had been taken. After 10 min supine rest, blood pressure was measured by sphygmomanometry (Korotkoff V for diastolic blood pressure). Thereafter, the subjects were seated on a chair and performed three CO_2 rebreathing manoeuvres in order to familiarize with the equipment and breathing technique. Subsequently, the exercise test on the electromagnetically braked bicycle ergometer (Lode, Groningen, The Netherlands) was started. Subjects exercised 6 min at 100 W, 6 min at 130 W and 6 min at 160 W. At each work load, blood pressure was measured by sphygmomanometry (Korotkoff IV for diastolic blood pressure) and two estimations of cardiac output ($\dot{Q}$) were made using the CO_2 rebreathing technique (Collier, 1956; Defares, 1958; Jones *et al.*, 1967) in conjunction with the MMC Horizon system (Sensormedics). The mean of the two determinations was used for statistical analysis. After completion of the rebreathing manoeuvres at 160 W, the rebreathing apparatus was removed. The exercise test was continued, increasing the work load by 30 W/3 min until exhaustion of the subject. During this part of the test, subjects breathed through a low-resistance valve (Hans Rudolph, Inc.) and minute ventilation and gas exchange variables were determined with the MMC Horizon system and registered per 15 s. Gas exchange data and heart rate (HR) (electrocardiogram) during the last 30 s of each work load were used for statistical analysis.

Between 2 and 5 min after the end of the exercise test, blood was obtained by venepuncture for determination of plasma lactate concentration (Roche lactate analyzer 640).

Data analysis

Results are presented as means ± s.d. The following calculations were made: stroke volume (SV) = $\dot{Q}$/HR; mean arterial pressure (MAP) = diastolic blood pressure (DBP) + 1/3 (systolic blood pressure (SBP)–DBP); total peripheral resistance (TPR) = MAP/$\dot{Q}$. Statistical analysis of the variables at rest and during maximal exercise was performed by two-way analysis of variance with repeated measures (BMDP2V). The data during submaximal exercise at 100, 130 and 160 W were also analyzed by two-way analysis of variance with repeated measures, using two treatment factors (drug and work load). The significance level of the analysis of variance was set at 0.05.

Results

Characteristics of the normotensive and hypertensive subjects participating in the study are shown in Table 1. Except for systolic and diastolic blood pressure, there were no statistically significant differences between the two groups.

Rest

Supine systolic and diastolic blood pressure was significantly higher in hypertensive than in normotensive subjects (Table 2). Systolic blood pressure was significantly reduced during atenolol treatment. No statistically significant interaction between treatment and subject group was found,

Table 1 Characteristics (mean ± s.d.) of the normotensive (NT) and hypertensive (HT) subjects

	Normotensive (n = 8)	*Hypertensive* (n = 8)	*NT* vs *HT*
Age (years)	37.0 ± 8.0	41.2 ± 11.5	NS
Sex	7 M, 1 F	7 M, 1 F	
Body weight (kg)	71.7 ± 12.3	77.7 ± 12.0	NS
Height (cm)	173.9 ± 8.8	175.6 ± 5.7	NS
$\dot{V}O_{2max}$ (ml min^{-1} kg^{-1})	52.1 ± 6.2	51.0 ± 10.4	NS
Sitting systolic blood pressure (mm Hg)	119.1 ± 10.6	148.1 ± 8.0	$P < 0.001$
Sitting diastolic blood pressure (mm Hg)	78.1 ± 8.4	95.0 ± 4.4	$P < 0.001$

Table 2 Supine blood pressure (BP) and heart rate (mean ± s.d.) of normotensive (NT) and hypertensive (HT) subjects during placebo (P) and atenolol (A) treatment

	Normotensives (n = 8)		*Hypertensives* (n = 8)			
	P	*A*	*P*	*A*	*P* vs *A*	*NT* vs *HT*
Systolic BP (mm Hg)	118.5 ± 12.2	112.8 ± 10.8	143.6 ± 9.9	133.1 ± 11.6	< 0.01	< 0.001
Diastolic BP (mm Hg)	71.2 ± 8.3	69.0 ± 8.4	88.4 ± 7.2	84.8 ± 2.2	NS	< 0.001
Heart rate (beats min^{-1})	66.1 ± 12.1	49.2 ± 7.3	68.1 ± 7.5	52.2 ± 8.4	< 0.001	NS

indicating that the systolic blood pressure reduction did not differ in normotensive and hypertensive subjects. Supine diastolic blood pressure was not affected during atenolol treatment (Table 2).

Resting heart rate was similar in normotensive and hypertensive subjects and the heart rate reduction during atenolol treatment was also similar in the two groups (Table 2).

Submaximal exercise

Although exercise heart rate appeared to be somewhat lower in hypertensive subjects, the difference with the normotensive subjects was not statistically significant. The reduction of exercise heart rate during atenolol treatment was similar in both groups (Figure 1).

Exercise systolic and diastolic blood pressure were significantly higher in hypertensive than in normotensive subjects. Atenolol reduced exercise systolic blood pressure and the effect was similar in normotensive and hypertensive subjects. β-adrenoceptor blockade did not influence exercise diastolic blood pressure significantly (Figure 2). Mean arterial pressure was significantly reduced during atenolol treatment.

Cardiac output during exercise, estimated by the CO_2 rebreathing technique, was significantly higher in normotensive than in hypertensive subjects. Atenolol caused a reduction of $\dot{Q}$ that did not differ statistically significantly between normotensive and hypertensive subjects (Figure 3). Stroke volume, which did not differ statistically significantly between the two groups of subjects, increased during atenolol treatment (Figure 4). Calculated total peripheral resistance was significantly higher in hypertensive than in normotensive subjects, but there was no effect of atenolol on total peripheral resistance (Figure 5).

Oxygen consumption during the three submaximal work loads tended to be lower ($P = 0.08$) and respiratory exchange ratio was significantly higher during atenolol treatment than during placebo. There was no statistically significant difference between normotensive and hypertensive subjects (Table 3).

Maximal exercise

Maximal work load (W_{max}) (i.e. the highest work load that could be maintained at least 1 min), maximal oxygen uptake ($\dot{V}O_{2\ max}$), maximal heart rate (HR_{max}), and plasma lactate concentration after maximal exercise ($lactate_{max}$) did not differ between normotensive and hypertensive subjects (Table 4), nor did the changes in these variables during atenolol differ between the two groups. Atenolol reduced maximal work load, maximal oxygen uptake and maximal heart

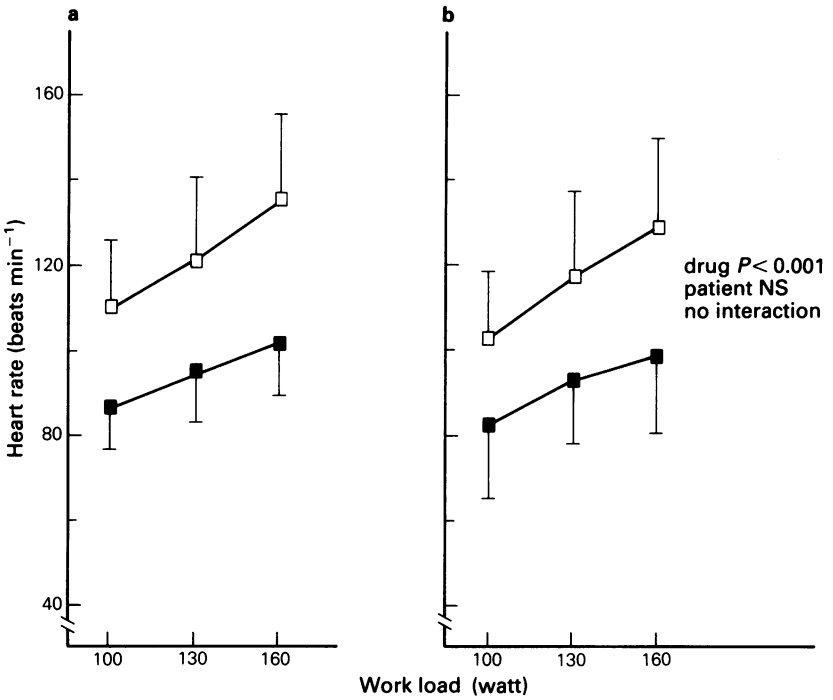

Figure 1 Heart rate (HR) (mean ± s.d.) during submaximal exercise in (a) normotensive and (b) hypertensive subjects during placebo (□) and atenolol (■) treatment.

rate significantly. Respiratory exchange ratio during maximal exercise was unaffected. Plasma lactate concentration after maximal exercise was significantly reduced during atenolol treatment (Table 4).

Discussion

In this study, we confirmed the finding of previous studies (Anderson *et al.*, 1979; Folgering & Van Bussel, 1980; Hughson & MacFarlane, 1981; Tesch & Kaiser, 1983; Smyth *et al.*, 1984; Van Baak *et al.*, 1985, 1986) that administration of β-adrenoceptor blockers reduces maximal exercise capacity in normotensive subjects. In addition, we showed that similar reductions of maximal work load and maximal oxygen uptake are found in hypertensive patients matched for age, sex, body weight and maximal oxygen uptake. This appears to be in contrast with a number of other studies in hypertensive patients showing no significant reduction of maximal exercise capacity after β-adrenoceptor blockade (Hansson *et al.*, 1977; Reybrouck *et al.*, 1977; Franz *et al.*, 1979, 1982, 1985; Lijnen *et al.*, 1979; Leenen *et al.*, 1980; Lösment *et al.*, 1986). One possible explanation for the discrepant findings is that most of the studies mentioned above may have suffered from methodological bias. In the majority of studies, placebo and β-adrenoceptor blocker treatment periods were not randomized (Hansson *et al.*, 1977; Reybrouck *et al.*, 1977; Franz *et al.*, 1979, 1982, 1985; Lijnen *et al.*, 1979; Lösment *et al.*, 1986) with the risk of bias due to habituation effects which is especially large in subjects unfamiliar with maximal exercise testing. In our study, we carefully selected normotensive and hypertensive subjects who exercised regularly and were familiar with maximal exercise testing in order to minimize habituation effects. In addition, treatment periods were randomized. Plasma lactate concentration after maximal exercise was 10.1 ± 3.6 mmol l^{-1} during placebo treatment. Only two subjects (one normotensive and one hypertensive) did not reach the 8 mmol l^{-1} level which is generally accepted as the minimum lactate level after maximal effort in progressive exercise testing (Löllgen & Ulmer, 1985). In one of these subjects, both heart rate

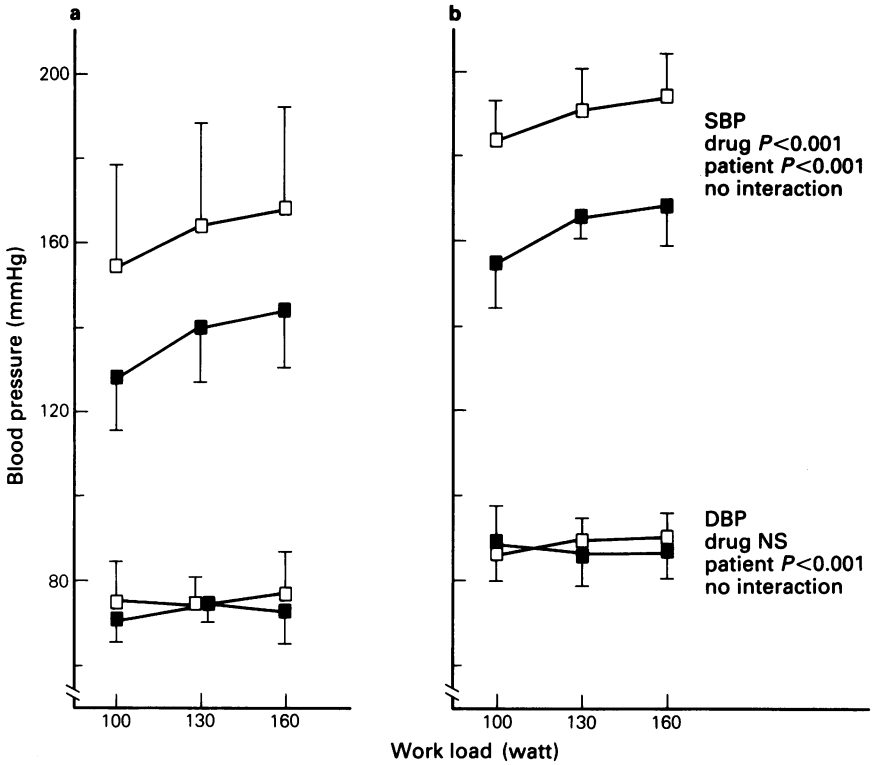

Figure 2 Blood pressure (BP) (mean ± s.d.) during submaximal exercise in (a) normotensive and (b) hypertensive subjects during placebo (□) and atenolol (■) treatment.

and respiratory exchange ratio, however, were within the range expected during maximal exercise. These data suggest that the great majority of our subjects exercised maximally. In the other studies this is often not clear, either because plasma lactate concentrations were low (Franz *et al.*, 1979; Lösment *et al.*, 1986) or improbably high (Leenen *et al.*, 1980) or data on lactate concentrations and/or respiratory exchange ratio are lacking (Hansson *et al.*, 1977; Franz *et al.*, 1979, 1982; Lijnen *et al.*, 1979). During atenolol treatment plasma lactate concentrations were reduced, which is in agreement with findings in several other studies (Kindermann *et al.*, 1983; Kaiser *et al.*, 1986; Verstappen & Van Baak, 1987). Because muscle lactate concentrations after maximal exercise have been shown to be unaffected by β-adrenoceptor blocker administration (Kaiser *et al.*, 1986), the lower plasma concentrations may be due to a decreased washout from the active muscle, or an increased utilization of lactate in active or non-active tissues (Frisk-Holmberg *et al.*, 1981, 1985; Stanley *et al.*, 1986).

Other possible explanations for the fact that we found a similar reduction in maximal exercise capacity in normotensive and hypertensive subjects while other studies did not find an effect of β-adrenoceptor blocker treatment in hypertensive patients, could be a difference in population studied or a difference in the duration of treatment. The subjects in our study were mildly hypertensive similar to those in the study by Leenen *et al.* (1980). However, especially the studies by Reybrouck *et al.* (1977) and Lijnen *et al.* (1979) include subjects with more severe hypertension. We cannot be sure that our results are also valid for patients with higher levels of blood pressure. Although in most studies, treatment periods were longer than in our study, we do not consider this a very likely explanation for the discrepancies, since in normotensive subjects it has been shown that there is no difference in effect between a single dose and a chronic

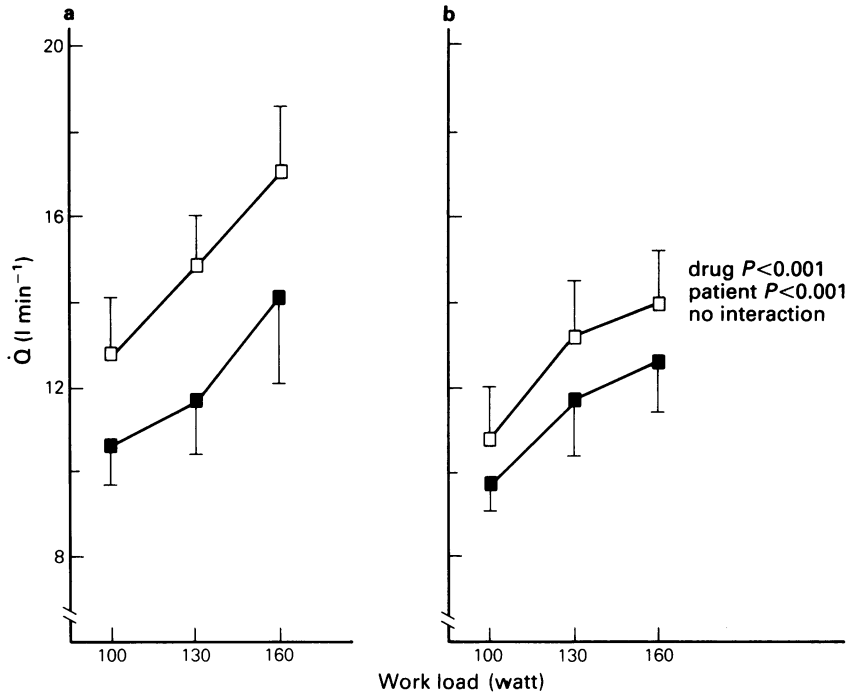

Figure 3 Cardiac output ($\dot{Q}$) (mean ± s.d.) during submaximal exercise in (a) normotensive and (b) hypertensive subjects during placebo (□) and atenolol (■) treatment.

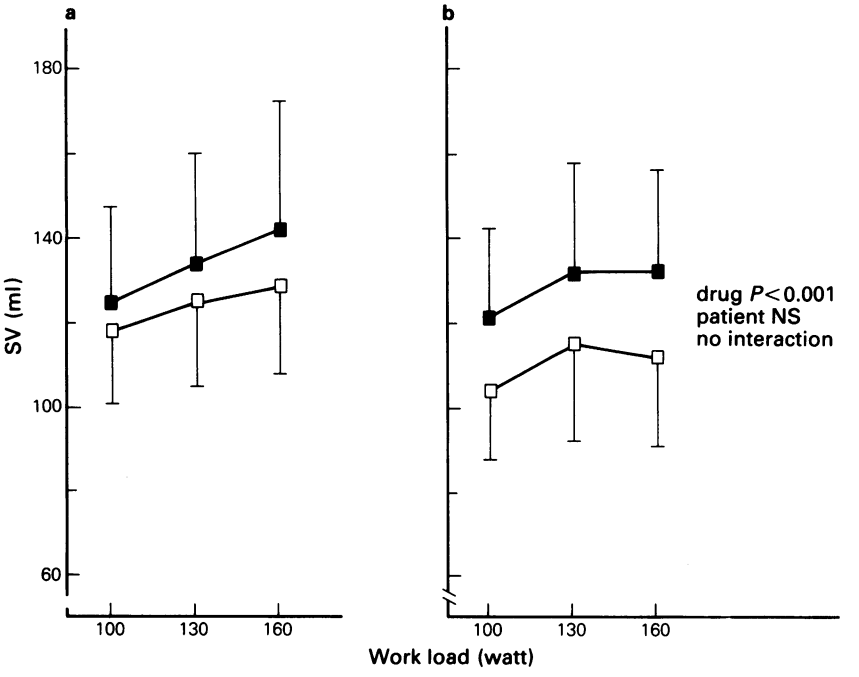

Figure 4 Stroke volume (SV) (mean ± s.d.) during submaximal exercise in (a) normotensive and (b) hypertensive subjects during placebo (□) and atenolol (■) treatment.

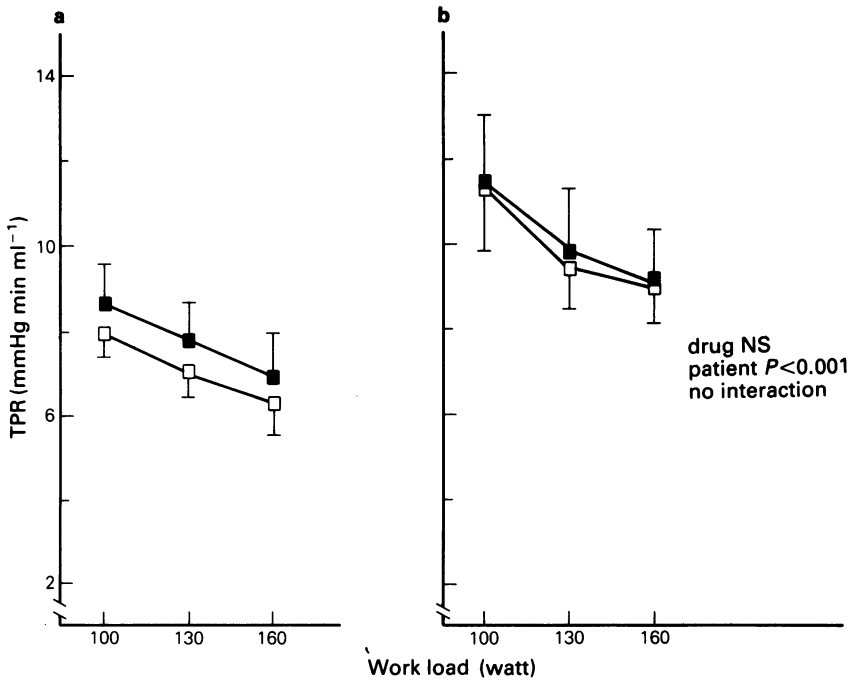

Figure 5 Total peripheral resistance (TPR) (mean ± s.d.) during submaximal exercise in (a) normotensive and (b) hypertensive subjects during placebo (□) and atenolol (■) treatment.

Table 3 Oxygen uptake ($\dot{V}O_2$) and respiratory exchange ratio (R) during submaximal exercise in normotensive (NT) and hypertensive (HT) subjects during placebo (P) and atenolol (A) treatment (mean ± s.d.)

Work load		$\dot{V}O_2$ (*l min*$^{-1}$)		*R*	
(watt)		*NT*	*HT*	*NT*	*HT*
100	P	1.651 ± 0.123	1.662 ± 0.170	0.806 ± 0.079	0.806 ± 0.062
	A	1.592 ± 0.133	1.627 ± 0.081	0.820 ± 0.052	0.820 ± 0.057
130	P	1.992 ± 0.131	1.978 ± 0.197	0.868 ± 0.064	0.860 ± 0.049
	A	1.926 ± 0.201	1.916 ± 0.118	0.907 ± 0.047	0.887 ± 0.017
160	P	2.356 ± 0.108	2.352 ± 0.143	0.884 ± 0.069	0.884 ± 0.046
	A	2.292 ± 0.159	2.251 ± 0.207	0.921 ± 0.042	0.921 ± 0.048
Two-way analysis of variance		drug: $P = 0.08$ patient: NS no interaction		drug: $P < 0.01$ patient: NS no interaction	

treatment of 4 weeks with a β-adrenoceptor blocker (Smyth *et al.*, 1984; Van Baak *et al.*, 1985).

Based on the results obtained we have to reject the hypothesis that the effect of β-adrenoceptor blocker administration on exercise haemodynamics differs between normotensive and hypertensive subjects. However, normotensive and hypertensive subjects had different haemodynamic profiles during exercise: higher blood pressure, lower cardiac output and higher total peripheral resistance in the hypertensives, a pattern which is similar to that described by Lund-Johansen (1967). In our study, the lower

Table 4 Variables at maximal exercise (mean ± s.d.) in normotensive (NT) and hypertensive (HT) subjects during placebo (P) and atenolol (A) treatment

	Normotensives (n = 8)		*Hypertensives* (n = 8)			
	P	*A*	*P*	*A*	*P* vs *A*	*NT* vs *HT*
W_{max} (watt)	291 ± 49	258 ± 45	296 ± 58	259 ± 48	< 0.001	NS
$\dot{V}O_{2max}$ (l min^{-1})	3.71 ± 0.56	3.32 ± 0.61	3.93 ± 0.77	3.25 ± 0.56	< 0.001	NS
HR_{max} (beats min^{-1})	178.5 ± 12.0	124.0 ± 14.5	172.4 ± 11.2	120.8 ± 16.4	< 0.001	NS
$Lactate_{max}$ (mmol l^{-1})	10.7 ± 3.9	7.4 ± 5.0	9.5 ± 3.6	8.5 ± 2.2	< 0.05	NS
R_{max}	1.00 ± 0.06	1.01 ± 0.07	0.99 ± 0.05	1.02 ± 0.06	NS	NS

cardiac output appeared to be due to a combination of a lower heart rate and a lower stroke volume in the hypertensives than in the normotensives, although both differences as such were not statistically significant.

Since the oxygen uptake during submaximal exercise did not differ between the normotensive and the hypertensive group, the lower cardiac output in the hypertensives suggests either a lower blood flow to the active muscle in combination with an increased capability for oxygen extraction or a different regional distribution of the lower cardiac output, so that blood flow to the active muscles is similar to that in normotensive subjects at the cost of blood flow to inactive tissues.

Atenolol tended to decrease the oxygen uptake during submaximal exercise, which is in agreement with a number of other studies (Pearson *et al.*, 1979; Tesch & Kaiser, 1983; Wilmore *et al.*, 1985; Van Baak *et al.*, 1987). This may be due to a shift from fat to carbohydrate metabolism, since β-adrenoceptor blockers have been shown to limit the supply of plasma free fatty acids to exercising muscle (Frisk-Holmberg *et al.*, 1985). The explanation is supported by the increase in respiratory exchange ratio during submaximal exercise found in this and other studies (Tesch & Kaiser, 1983; Wilmore *et al.*, 1985; Van Baak *et al.*, 1987).

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