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## **Effects of Different Preparations of Oxprenolol on Diurnal Variations of Non-steady-state Exercise Performance in Patients with Coronary Heart Disease Evaluated by Computer Assisted Ergospirometry**

By W. Reiterer

**Summary:** *The effect of two preparations of oxprenolol (80 mg twice a day; 160 mg slow-release once a day) on the diurnal non-steady-state exercise performance in patients with coronary heart disease (N = 11) has been studied after a treatment period of at least 7 days.*

*2 h after the intake of the standard preparation (80 mg oxprenolol) the symptom-limited exercise performance increased by 24%. The onset of symptoms of physical intolerance was postponed to work rates of heavier intensity (+18.8%). Despite a considerable fall in the exercise heart*

rate (—18.4%) the oxygen uptake per load was not affected suggesting that the adjustment of the cardio-pulmonary system to graded exercise was not impaired.

As the reduction of the exercise heart rate is regarded as a distinct sign of  $\beta$ -receptor blockade the standard regimen demonstrates a considerable long-term effect with respect to the heart rate regulation next morning (time interval 16 h). The slow-release preparation acts less powerfully in reducing the exercise heart rate in any test, but the beneficial effects on limiting symptoms of physical performance equal the standard regimen. The duration of the efficacy of slow-release oxprenolol is certainly limited: no effect on the exercise heart rate was demonstrable next morning (time interval 25 h).

To improve the efficacy in symptomatic treatment of coronary heart disease the duration of effects of the drug and the physical activities of the individual during every day life should be taken into account to adjust the timing for intake.

**Zusammenfassung:** Wirkungsprofil zweier galenischer Zubereitungsformen von Oxprenolol auf die tageszeitlichen Veränderungen der symptom-limitierten Leistungsfähigkeit von Koronarkranken

Nach einer jeweils 7tägigen Behandlungsphase wurden die Auswirkungen zweier galenischer Formen von Oxprenolol (2×1 Tabl. à 80 mg/d; 1×1 Tabl. à 160 mg Slow-release)

**Key words:**  $\beta$ -Blocker · Coronary heart disease · Oxprenolol · Trasicor®

## 1. Introduction

Coronary vascular disease leads to an imbalance between oxygen supply and demand of the heart under the conditions of physical and emotional stress. A critical increase of pressure and volume loading probably will induce symptoms of angina pectoris followed by ischemic alterations of the ECG. Consequently malfunction and damage of myocardial tissue will impair the functional capacity of the heart inducing congestive heart failure or sudden death as the extreme outcome.

The application of  $\beta$ -receptor blocking agents is well established in the treatment of coronary heart disease. The reduction of heart rate, elevated blood pressure values and contractility at rest and under physical or emotional stress is apt to improve the tolerance of coronary patients to every day life activities by approximately 20% [1, 7, 15, 21, 22, 25, 29].

This study has been designed to assess the efficacy of a standard regimen on exercise performance. Oxprenolol (Trasicor®\*) is a non-selective  $\beta$ -blocker with intrinsic sympathomimetic activity and less membrane stabilizing (or local-anaesthetic) activity than propranolol. The relative oral bioavailability is fair (70—95%) and the duration of the effect is considerably longer (more than 8 h) than indicated by the elimination half-life (2 h p.o.) [6, 13, 24, 32].

## 2. Patients and methods

11 male patients, aged 43 to 62, participated voluntarily after proper information. Symptoms of exercise induced angina pectoris and (or) ECG signs of myocardial ischemia limiting physi-

cal performance were stated as criteria for acceptance. The data of the individuals are given in Table 1. Not included were patients if apart from symptoms of cardiovascular disease they had other diseases which required special medication (antihypertensives, diuretics, digitalis) that might be expected to influence the result. All patients had a typical history of stable angina pectoris and had participated in several bicycle ergometer tests before they entered the study.

2 h nach Einnahme des Standardpräparates (80 mg Oxprenolol) nahm die symptom-limitierte Leistungsfähigkeit um 24% zu, der Beginn limitierender Symptome verschob sich in höhere Belastungsstufen (+18,8%). Trotz beträchtlicher Abnahme der Belastungsherzfrequenz (—18,4%) wurde die erreichbare Sauerstoffaufnahme unter ansteigender Belastung (non-steady-state) nicht beeinflusst, so daß die kardio-zirkulatorische Anpassung an den Belastungsimpuls nicht beeinträchtigt war.

Unter Beachtung der Belastungsherzfrequenz als Gradmesser der  $\beta$ -Rezeptorenblockade erwies sich die Standarddosierung von langer Wirkungsdauer (Test am darauffolgenden Morgen, Zeitintervall 16 h). Die Slow-release-Form wirkte zu jeglicher Testperiode geringer frequenzsenkend, der Beginn von Symptomen wurde jedoch gleichgerichtet zum Standardpräparat (Test am Abend, Zeitintervall 11 h) verzögert. Am darauffolgenden Morgen ist keine Auswirkung auf die Belastungsherzfrequenz zu erfassen (Zeitintervall 25 h).

Beide galenische Formen von Oxprenolol erwiesen sich in der medikamentösen Therapie der koronaren Herzkrankheit als ausreichend wirksam, wobei durch eine individuelle Dosierung unter Beachtung des Wirkungsprofils in der Zuordnung zu physischen Belastungsmaxima im Tagesgang die symptomatische Behandlung sich optimieren ließe.

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### 2.1. Design of investigation

During a wash-out period of 10 days only nitroglycerin was permitted. Subsequently the patients were given oxprenolol (80 mg, 1 tablet twice a day: 7 a. m. and 4 p. m.) and oxprenolol slow-release (160 mg, 1 tablet once a day: 7 a. m.), each period lasting 8 to 10 days, wherein the sequence was chosen at random.

At the end of the wash-out period an exercise test was performed at 9.00 a. m. under standardized conditions and served as control. At the end of each treatment period the exercise tests were performed at 9 a. m. and at 6 p. m. as well as at 8 a. m. next morning, but without prior medication (8 a. m.). Referring to the treatment period with 80 mg oxprenolol (2×1 tabl./d, at 7 a. m. and 4 p. m., respectively) the interval between intake of the  $\beta$ -blocker and the stress test was 2 h in the morning and 2 h in the afternoon (some effect of the tablet taken in the morning should be considered even 11 h later), but 16 h on the next day. As oxprenolol slow-release was given once a day (1 tabl. at 7 a. m.) the time intervals between intake of the  $\beta$ -blocker and the stress tests were 2, 11 and 25 h.

### 2.2. Techniques, measurements, and statistical methods

The exercise performance of the patients was assessed quantitatively by computer assisted ergospirometry. The patients were familiar with the procedure of exercising in a sitting position on an electrically braked bicycle ergometer (Ergotest, Jäger, BRD). The test protocol was based on the rectangular-triangular

\*) Manufacturer: Ciba-Geigy GmbH, Wehr/Baden (FR Germany).

**Table 1:** Clinical data of patients.

Patient	Sex	Age (years)	Body weight (kg)	Diagnosis, limiting symptoms
1 A. A.	m	53	81	Two-vessel disease; ST-depression
2 K. K.	m	60	97	CHD; angina pectoris, ST-depression
3 F. E.	m	43	67	By-pass-op.; angina pectoris, ST-depression
4 K. H.	m	56	74	Myocardial infarction (1971); angina pectoris
5 P. V.	m	46	73	Small-vessel disease; angina pectoris
6 K. J.	m	56	95	CHD; angina pectoris, ST-depression
7 H. F.	m	62	69	CHD; angina pectoris, ST-depression
8 F. A.	m	54	91	CHD; angina pectoris, ST-depression
9 K. G.	m	56	75	CHD; angina pectoris, ST-depression
10 F. R.	m	54	76	Myocardial infarction (1975); angina pectoris
11 F. E.	m	54	64	Myocardial infarction (1975); angina pectoris
N = 11		54.0 5.5	78.3 ( $\bar{x}$ ) 11.3 (s)	

test procedure (2-min, increment test) following the principle of symptom-limited maximal stress-testing. The work load was incremented every 2 min by 25 W, unless the patient was physically exhausted or alarming signs of physical intolerance gave reason for prompt interruption: ECG signs of myocardial ischemia (horizontal or down-sloping ST-depression of more than 0.25 mV); rhythm and conduction disturbances; fall in systolic blood pressure, excessive increase in systolic blood pressure (exceeding 250/130 mm Hg in patients older than 50); sudden increase in the intensity of chest pain (rate score III-IV) and of subjective rating of perceived exertion (PER, Borg) and dyspnea. The ECG was taken from precordial leads (Wilson) and monitored continually. The heart rate was analyzed beat-to-beat to detect premature contractions from the tracing of the analog signal. The blood pressure was measured by cuff every second minute.

Ergospirometric parameters (oxygen uptake, carbon dioxide release, minute ventilation, tidal volume, respiratory ratio, oxygen pulse, and others) were evaluated by means of an open air circuit system, applying on-line computer technics for data processing. A print-out and a graphical display of the data was available every 30 s. At the end of each work load the anaerobic energy yield was calculated by subtracting the caloric equivalent of oxygen uptake during work exceeding the steady-state level during rest from the energy demand to sustain a given work load aerobically (Ergopneumotest, Jäger, BRD). During the recovery period (2nd to 3rd min) blood was taken from the hyperemic ear lobe. Data of blood gas analysis (pH, pCO<sub>2</sub>, pO<sub>2</sub>; Microbloodgas analyzer, AVL, Graz, Austria) were used to calculate the base excess (metabolic acidosis). The method of computer assisted ergospirometric stress testing has been fully described elsewhere [17, 19].

For statistical analysis maximal values and data from measurements during work loads, such as 50 and 75 W (1st and 2nd min per load) were selected. All the results in the tables are expressed as the means  $\pm$  SE of the mean. In the figures mean data and measurements of some individuals (number 1-5) are presented. The data were analyzed in comparison with the control and within the treatment periods by a Student paired t-test. A 2P value less than 0.10 was considered statistically significant.

### 3. Results

All patients accepted to the study completed the program of investigation. No undesirable side effects were reported.

#### 3.1. Work output (W min)

Compared to the control (394.5  $\pm$  52.6 W min) the symptom-limited maximal exercise performance significantly improved only under treatment with oxprenolol 80 mg at 9.00 a. m. (490  $\pm$  57 W min; + 24.4%; 2 P  $\leq$  0.05). Although no statistically significant difference was found between oxprenolol 80 mg and slow-release oxprenolol at any time of

testing, the improvement of exercise performance by the slow-release preparation became less evident (at 9.00 a. m.: + 13.5%, n. sig.) and at 6.00 p. m. the work output even equalled the control (see Table 2 and Fig. 1 a).

#### 3.2. Maximal work load (W)

The increase of the maximal work load tolerated during unsteady-state exercise was clearly demonstrated by oxprenolol 80 mg at 9.00 a. m. (+ 14.6%; 2 P  $\leq$  0.05). In the afternoon (6.00 p. m.) the second application of oxprenolol 80 mg did not cause further improvement. In contrast oxprenolol 160 mg slow-release was not able to improve the maximal load beyond the control value (93.2  $\pm$  5.9 W).

#### 3.3. Duration of exercise (t<sub>tot</sub>, min)

2 h after intake of oxprenolol 80 mg the duration of total work period increased by 0.9 min (+ 13.0%; 2 P  $\leq$  0.05); at any other time of testing (oxprenolol 80 mg and 160 mg slow-release, respectively) we observed no meaningful deviation from the control (6.9  $\pm$  0.5 min). 2 h after intake of oxprenolol 160 mg slow release the increase in duration of the work period was less pronounced (+ 8.0%; n. sig.).

#### 3.4. Onset of symptoms of physical intolerance (Angina pectoris, alteration of the ST-segment) related to work load (W)

The onset of symptoms was delayed significantly by both preparations of oxprenolol 2 h after intake (+ 18.8%; 2 P  $\leq$  0.05; control: 72.7  $\pm$  4.1 W; threshold after  $\beta$ -blockade: 86.4 W as the mean). In contrast to different effects on work output and heart rate (see 3.5.) both preparations delayed the onset of symptoms to exactly the same level of work intensity at 6.00 p. m. (+ 9.4%; n. sig.; 79.5  $\pm$  6.6 W).

#### 3.5. Heart rate

The heart rate represents a well established and practical parameter to observe the intensity and duration of  $\beta$ -receptor blocking activity.

The resting heart rate (control: 78.6  $\pm$  2.6 beats/min) declined by 10 beats/min as the mean (-13.5%; 2 P  $\leq$  0.01; oxprenolol 80 mg and 160 mg slow-release at 9.00 a. m.). A gradual increase of the resting heart rate was seen throughout the period of observation, less distinctly under treatment with oxprenolol 80 mg twice a day, which reduced the resting heart rate significantly at any time of testing. Compared to oxprenolol slow-release (79.9  $\pm$  2.6 beats/min) oxprenolol 80 mg reduced the heart rate at 8.00 p. m. next morning (72.1  $\pm$  2.0 beats/min; 2 P  $\leq$  0.10).

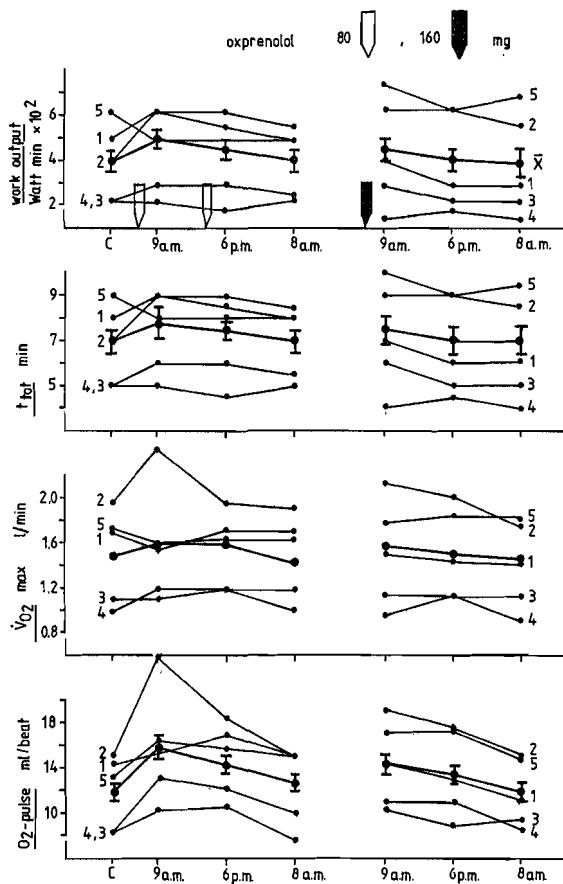


Fig. 1 a

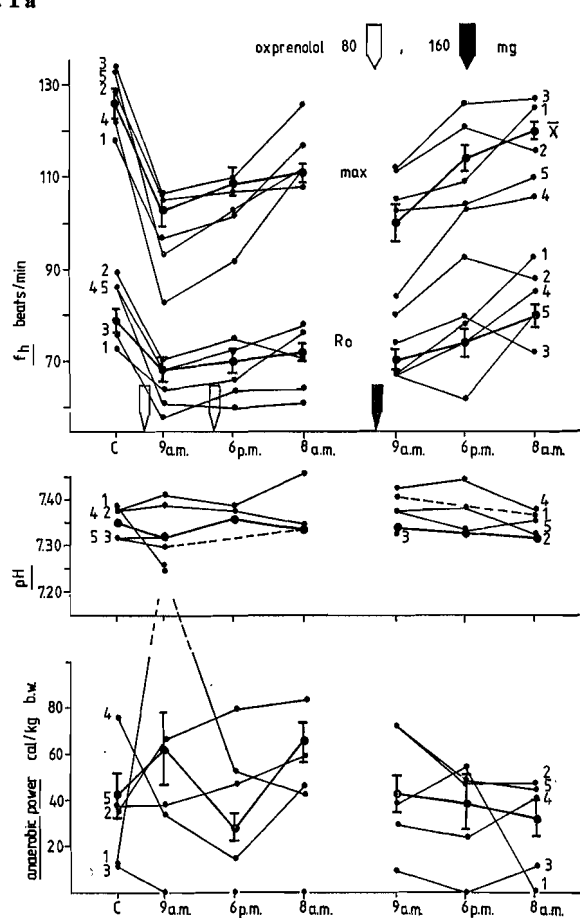


Fig. 1 b

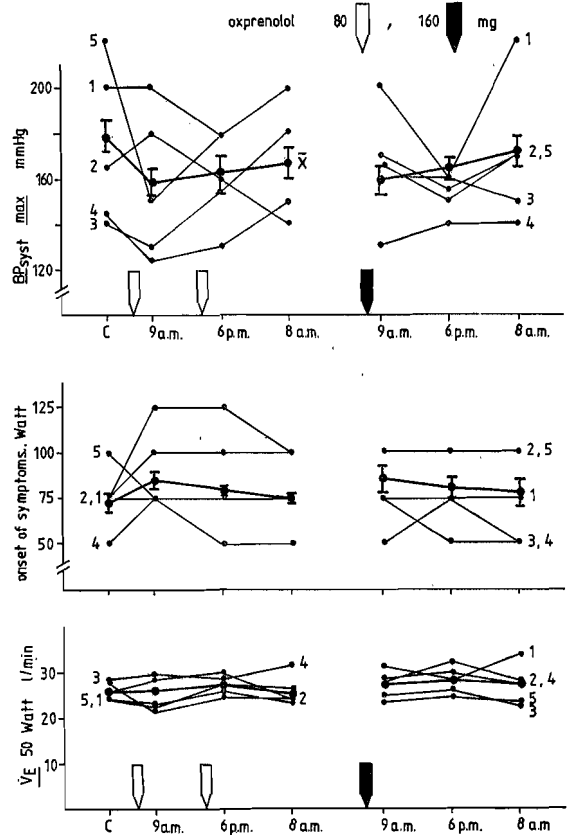


Fig. 1 c

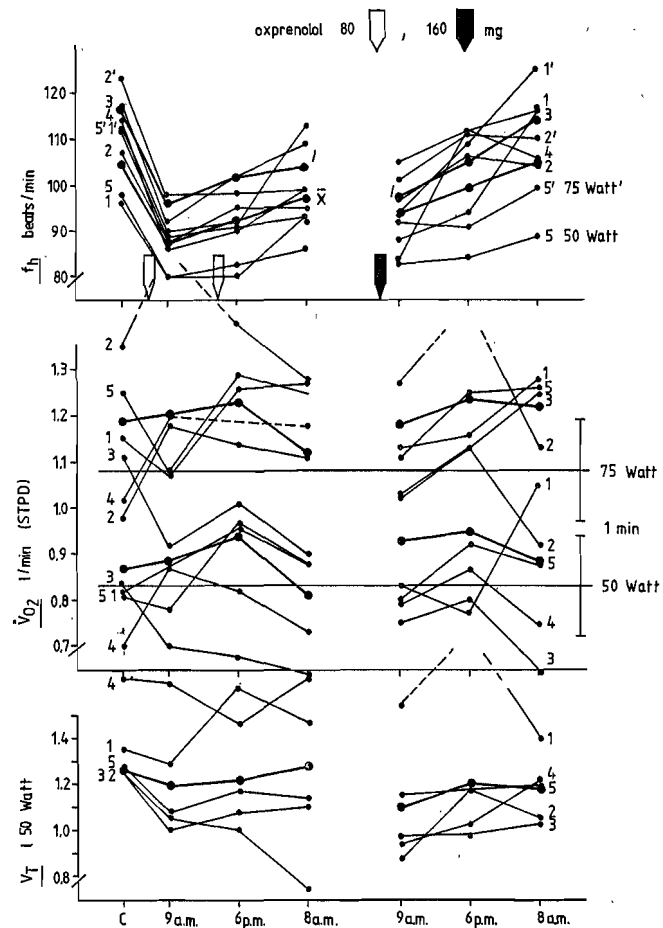


Fig. 1 d

Fig. 1 a-d: Effects of oxprenolol 80 min twice a day and oxprenolol 160 mg slow-release once a day on cardio-respiratory and metabolic parameters: diurnal variation of physical performance in symptom-limited stress-testing (mean values and data of some individuals, number 1-5; for abbreviations see Table 2).

The reduction of the exercise heart rate (maximal values and data during a load of 50 and 75 W) corresponded to the variation seen in the resting heart rate. At 9.00 a. m. the maximal heart rate (control:  $125.9 \pm 3.4$  beats/min) was reduced by oxprenolol 80 mg to 102.9 beats/min as the mean ( $-18.3\%$ ;  $2 P \leq 0.01$ ), the heart rate at 75 W to 95.5 beats/min as the mean ( $-18.4\%$ ;  $2 P \leq 0.01$ ) and at 50 W to 87.9 beats/min as the mean ( $-16.1\%$ ;  $2 P \leq 0.01$ ). At submaximal work rates (50 and 75 W) 2 h after intake the exercise heart rate was more reduced by oxprenolol 80 mg ( $\Delta$ : 5.6 beats/min as the mean during 50 W;  $2 P \leq 0.05$ ). In the afternoon (6.00 p. m.), 11 h after intake of oxprenolol 160 mg slow-release the exercise heart rate (fh-max, fh-75 W) declined much less ( $-9.5\%$  and  $-10.8\%$ , respectively).

Next morning no effects on the exercise heart rate could be referred to slow-release oxprenolol (25 h after intake), but oxprenolol 80 mg (16 h after intake) significantly suppressed the heart rate at work.

### 3.6. Oxygen uptake

The maximal oxygen uptake was significantly increased by oxprenolol 80 mg (2 h after intake). Despite a marked decrease of the exercise heart rate no influence on the kinetics of oxygen uptake ( $VO_2$ —50 W;  $VO_2$ —75 W) during graded exercise was observed. As the oxygen uptake at the first minute per load (50 W:  $0.83 \pm 0.107$  l/min STPD (standard temperature and pressure, dry gas); 75 W:  $1.083 \pm 0.107$ ; standard values [17]) lay within normal ranges; any impair-

**Table 2:** Cardio-respiratory and metabolic data. Diurnal variation in patients with coronary heart disease (N = 11) at work. a) time of intake of drug; b) time of exercise testing; fh = heart rate,  $VO_2$  = oxygen uptake, BE = base excess, BP = blood pressure, VE = respiratory minute ventilation, VT = tidal volume. Student paired t-test versus control (\*), within treatment periods (x; oxprenolol 80 versus 160)  $2P = 0.10$  (\*);  $2P = 0.05$  (\*\*);  $2P = 0.01$  (\*\*+).

Parameter $\bar{x} \pm s\bar{x}$	Control		Oxprenolol 80 mg $2 \times 1$ tbl.			Oxprenolol 160 mg SR $1 \times 1$ tbl.		
	a)		7.00 a.m.		4.00 p.m.	7.00 a.m.		
	b)	9.00 a.m.	9.00 a.m.	6.00 p.m.	8.00 a.m.	9.00 a.m.	6.00 p.m.	8.00 a.m.
Work output (W/min)		394.5 52.6	490 <sup>++</sup> 57	444.5 40.5	394.5 47.7	447.9 67.4	396.8 57	379.1 60.9
Workload max (W)		93.2 5.9	106.8 <sup>++</sup> 6.8	102.3 5.3	90.9 6.9	97.7 8.6	93.2 6.8	93.2 6.8
Work period (min)		6.9 0.5	7.8 <sup>++</sup> 0.5	7.5 0.4	6.95 0.5	7.45 0.6	6.9 0.6	6.8 0.6
Onset of symptoms (. . . W)		72.7 4.1	86.4 <sup>+</sup> 5.2	79.5 6.6	75.0 3.4	86.4 <sup>+</sup> 8.5	79.5 6.6	72.7 7.1
fh resting (beats/min)		78.6 2.6	68.0 <sup>+++</sup> 2.5	70.4 <sup>++</sup> 2.4	72.1 <sup>+</sup> 2.0	69.9 <sup>+++</sup> 2.1	74.6 2.9	79.9 <sup>xxx</sup> 2.6
fh max.		125.9 3.4	102.9 <sup>+++</sup> 2.8	108.7 <sup>+++</sup> 3.4	110.7 <sup>+++</sup> 2.4	101.1 <sup>+++</sup> 4.1	113.9 <sup>x++</sup> 3.3	119.5 <sup>xxx</sup> 2.4
fh 50 W (2. min)		104.7 2.3	87.9 <sup>+++</sup> 1.8	93.5 <sup>+++</sup> 3.0	97.1 <sup>++</sup> 2.1	93.5 <sup>+++</sup> 2.1 <sup>++</sup>	99.5 <sup>x</sup> 2.7	105 <sup>xxx</sup> 2.3
fh 75 W (2. min)		117.1 3.1	95.5 <sup>+++</sup> 1.96	101.6 <sup>+++</sup> 2.6	103.9 <sup>+++</sup> 2.3	97.4 <sup>x+++</sup> 1.2	104.5 <sup>++</sup> 2.7	114.1 <sup>xxx</sup> 3.4
$VO_2$ max. (l/min STPD)		1.49 0.13	1.63 <sup>+</sup> 0.13	1.59 0.13	1.44 0.12	1.57 0.15	1.52 0.11	1.47 0.11
$VO_2$ — 50 W (l. min)		0.87 0.04	0.89 0.04	0.94 0.05	0.81 0.06	0.93 0.05	0.95 0.04	0.88 0.03
$VO_2$ — 75 W (l. min)		1.19 0.06	1.20 0.06	1.23 0.06	1.12 0.07	1.18 0.04	1.24 0.04	1.22 0.03
$O_2$ -pulse max. (ml/beat)		11.9 0.8	15.8 <sup>+++</sup> 1.1	14.4 <sup>+</sup> 0.8	12.7 0.9	14.5 <sup>x+++</sup> 1.1	13.5 0.9	12.1 0.8
Anaerobic power (cal/kg b.w.)		41.6 11.9	63.3 13.7	28.5 7.5	63.2 11.7	43.0 8.1	39.2 13.1	31.9 <sup>xxx</sup> 7.8
(J/kg b.w.)		174.2 49.8	265.0 57.4	119.3 31.4	264.6 49.0	180.0 33.9	164.1 54.8	133.6 32.7
% of energy demand		14.5 4.2	15.5 2.8	14.4 3.2	20.6 4.1	14.0 2.6	12.2 3.4	11.8 <sup>xx</sup> 3.2
pH min.		7.35 0.01	7.32 <sup>+</sup> 0.01	7.36 0.02	7.34 0.02	7.34 0.02	7.33 0.04	7.32 0.02
BE max. (mmol/l)		-3.8 0.6	-5.6 <sup>+</sup> 0.6	-2.6 0.8	-4.9 0.8	-6.6 1.3	-3.8 0.8	-5.5 1.1
BP syst. max. (mm Hg)		179.1 8.1	159.5 <sup>++</sup> 6.4	162.7 8.0	167.3 7.0	158.6 <sup>++</sup> 5.7	164.1 4.8	171.8 6.6
VE 50 W 2. min (l/min BTPS)		26.1 1.2	26.1 1.2	27.6 1.1	25.6 1.1	27.1 0.9	28.1 0.9	27.5 1.3
VT 50 W (2. min l)		1.37 0.09	1.20 <sup>++</sup> 0.07	1.23 0.07	1.18 0.08	1.12 <sup>++</sup> 0.07	1.21 0.08	1.19 <sup>+</sup> 0.05

ment of aerobic adjustment to increasing work rates can be denied.

### 3.7. Oxygen pulse (ml/beat)

The oxygen pulse is a useful index of stroke volume and arterio-venous oxygen saturation difference because

$$\text{oxygen pulse} = \text{VO}_2/\text{fh} = \text{SV} \times \text{avDO}_2.$$

After  $\beta$ -receptor blockade by oxprenolol 80 mg and 160 mg slow-release (2 h after intake) there was a marked increase of the oxygen pulse by 32.8% ( $2 P \leq 0.01$ ) and 21.8% ( $2 P \leq 0.01$ ), respectively. These data suggest a considerable augmentation of the stroke volume if any increase of the  $\text{avDO}_2$  is absent.

### 3.8. Anaerobic power and metabolic acidosis

Concerning the control values of the on-line calculated index of anaerobic power — the work output of the patients ranged between 45 and 75% of a predicted maximal load — the mean values ( $41.6 \pm 11.9$  cal/kg b. w. =  $174.2 \pm 49.8$  J/kg b.w.) seem to be rather low compared to findings in sedentary men of the same age but less overnight ( $83 \pm 27$  cal/kg b.w.; [17]). As overnight is contributing to a elevated oxygen uptake per load the on-line calculated index of anaerobic power resulted in a smaller anaerobic compartment in relationship with the work output.

After  $\beta$ -receptor blockade with oxprenolol the upstroke in oxygen uptake at non-steady-state work was not delayed at all, although the heart rate decreased considerably. Consequently an increase of anaerobic energy release should not be expected: the calculated index of anaerobic power varied insignificantly among the treatment periods.

As the work output was increased (control 394.5 W min as the mean) by oxprenolol 80 mg to 490.0 W min as the mean, it was likely to observe some increase of the parameter of metabolic acidosis, as the maximal oxygen uptake (1.63 l/min STPD) exceeded the anaerobic threshold, which was to be expected at a range of about 1.2 l/min oxygen uptake in patients with coronary heart disease [19]. Indeed, the variation of the base excess (BE) paralleled the increase in work output, which taxed the anaerobic energy sources in the working muscles (oxprenolol 80 mg, 9.00 a. m.: BE:  $-5.6 \pm 0.6$  mmol/l; control BE:  $-3.8 \pm 0.6$  mmol/l;  $2 P \leq 0.10$ ).

### 3.9. Systolic blood pressure

Despite an increase in the work output the maximal systolic blood pressure decreased significantly by 19.6 mm Hg as the mean ( $-10.9\%$ ;  $2 P \leq 0.05$ ) 2 h after intake of oxprenolol 80 mg and 160 mg slow-release. Compared to the control ( $179.1 \pm 8.1$  mm Hg) the systolic blood pressure still remained somewhat lower (n. sig.) at 6.00 p. m. and at 8.00 a. m. next morning.

### 3.10. Minute ventilation and tidal volume

Subjective complaints of dyspnea and symptoms of exercise induced asthma were not observed. The minute ventilation volume at a work load of 50 W (2nd min) was not changed anyway (26.1 l/min BTPS (body temperature and pressure, saturated with vapour) as the mean). The minor decline of the tidal volume after  $\beta$ -receptor blockade seems to be without relevancy.

## 4. Discussion

The effects of  $\beta$ -blocking agents on the heart are characterized by removal of sympathetic support, reduced capacity of sarcoplasmic reticular  $\text{Ca}^{++}$  and depletion of membrane bound  $\text{Ca}^{++}$  store. Consequently by reduction of systolic tension, heart rate, left ventricular tension time and inotropism (determinants of external contractile element work) and despite an increase of left ventricular volume counteracting economizing myocardial oxygen consumption the functional capacity of the myocardium will benefit in coronary heart disease [5, 14, 29]. The frequency of anginal attacks and nitroglycerin consumption is reduced, the exercise performance and total work will increase [1, 4, 7, 25].

Referring to  $\beta$ -receptor blocking agents with intrinsic sympathomimetic activity studied in healthy individuals maximal heart rate ( $-25\%$ ), heart rate-systolic pressure product ( $-26\%$ ), maximal oxygen consumption ( $-9\%$ ), total work ( $-8\%$ ) and cardiac output are found reduced. Left ventricular filling pressure ( $+49\%$ ) and arterio-venous oxygen saturation difference ( $+11\%$ ) are augmented, whereas the increase of stroke volume and heart volume remains somewhat insignificant ( $+6\%$  as the mean). In long-term treatment vascular resistance and venous tone will fall by 21.5% and 31%, respectively [2, 3, 10, 16].

At submaximal work rates of steady-state pattern the oxygen uptake remains unchanged. The fall in cardiac output ( $-12\%$ ) is compensated by the increase in arterio-venous oxygen saturation difference, due to a fall of the mixed venous oxygen content [22, 31]. In contrast, the onset of production of lactic acid was found delayed. The fall in cardiac output has been interpreted as a reduction of luxury perfusion not affecting the aerobic metabolic processes in the working muscles [9, 12].

Our findings in non-steady-state exercise (2-min increment test, rectangular-triangular bicycle ergometry [17]) delineate the adequate adjustment of oxygen uptake to graded work intensities after  $\beta$ -receptor blockade by oxprenolol. As the oxygen uptake at the first minute per load is unaffected by oxprenolol it can be assumed, that the adaptational forces of the cardio-pulmonary system will meet the aerobic energy demands of the muscles despite a considerable decrease of the heart rate ( $-18\%$ ). There is no evidence of augmented metabolic acidosis per se.

The on-line computed index of anaerobic power reveals no alteration of the relationship between aerobic and anaerobic energy compartments in symptom-limited exercise testing in patients with coronary heart disease. This conclusion is supported by the findings of other investigators who observed even a reduction of lactic acid concentration in the working muscles [12]. Recent studies at our laboratory succeeded in demonstrating no shift of the anaerobic threshold (criterion of endurance performance) after acute administration and long-term treatment with pindolol [20].

Evaluating the efficacy of the two preparations of oxprenolol (80 mg twice a day; 160 mg slow-release once a day) the degree and duration of  $\beta$ -receptor blockade is best recognized by the reduction of the exercise heart rate. Compared to the control 11 h after the intake of oxprenolol slow-release (test at 6.00 p.m.) a significant suppression of the exercise heart rate is found, but of a lower degree compared to the standard regimen (80 mg twice a day). This small difference in reducing the exercise heart rate does not result in a different delay upon the onset of symptoms of physical intolerance. The sustained release preparation exhibits a satisfactory degree of  $\beta$ -receptor blockade during the day but fails in acting until next morning (test 25 h after intake). If some cardiac protective activity of the  $\beta$ -blocker regimen were to remain until the next morning, we should give preference to the standard regimen which significantly reduced the resting and exercise heart rate next morning (time interval between intake and test 16 h).

Discussing the data the duration of the treatment period should be taken into account: after a period of at least 7 days considerable hepatic (first-pass) elimination is unlikely to persist — in particular this phenomenon has been related to propranolol and alprenolol — and the bioavailability of oxprenolol even may improve in long-term treatment [24, 30]. Despite of a rather short half-life of oxprenolol  $\beta$ -receptor blockade can be expected to last for at least 16 h after intake of 80 mg oxprenolol.

Regarding the symptom-limited exercise performance in the afternoon the work output is reduced in comparison to the physical capacity in the morning 2 h after intake of the  $\beta$ -blocker.

This striking difference, especially under treatment with oxprenolol 80 mg twice a day, may be related to an auto-

mous diurnal variation of physical performance (—16% in the late afternoon [8]).

From this study we may conclude that in coronary heart disease the time schedule of application and the dosage of antianginal drugs with respect to the duration of efficacy should be adjusted to the main period of physical activity of the individual. The single application of a long-lasting preparation is likely to increase the patient's compliance, but to optimize symptomatic treatment in coronary heart disease the mode and duration of effects of the drug should be considered.

## 5. References

[1] Arstila, M., Kallio, V., Wendelin, H., *Ann. Clin. Res.* **5**, 91–100 (1973) — [2] Atterhög, J. H., Dunér, H., Pernow, B., *Acta Med. Scand. Suppl.* **606**, 55–59 (1977) — [3] Bailey, I. K., Anderson, S. D., Rozea, P. J., Bernstein, L., Nyberg, G., Korner, P. I., *Am. Heart J.* **92**, 416–426 (1976) — [4] Bjerle, P., Jacobsson, K. A., *Curr. Therap. Res.* **16**, 101–116 (1974) — [5] Bretschneider, H., Die hämodynamischen Determinanten des myokardialen Sauerstoffverbrauches. In: Die therapeutische Anwendung beta-sympathikolytischer Stoffe. Ed. H. J. Dengler. F. K. Schattauer, Stuttgart (1972) — [6] Clark, B. J., Pharmacology of beta-adrenoceptor agents. In: Beta-adrenoceptor blocking agents. The pharmacological basis of clinical use. Ed. P. R. Saxena and R. P. Forsyth. North-Holland Publishing Company, Amsterdam (1976) — [7] Frithz, G., Nordgren, L., *Curr. Therap. Res.* **17**, 133–138 (1975) — [8] Graf, O., Die Tagesperiodik der Leistungsbereitschaft; zit. in: Leistungsphysiologie. Physiologische Grundlagen der Arbeit und des Sportes. J. Stegemann, Hrsg., G. Thieme, Stuttgart (1971) — [9] Hollmann, W., Friedmann, G., Heck, H., Bützler, H. O., Liesen, H., *Med. Welt* **23**, 1094–1095 (1972) — [10] Jeschke, D., Caesar, K., Hensel, G., Schubert, J., Kaufmann, W., *Herz/Kreisl.* **6**, 263–270 (1974) — [11] König, K., Gebhardt, W., Ullmann, H. W., Reindell, H., *Z. Kreislaufforsch.* **57**, 415–429 (1967) — [12] Liesen, H., Hollmann, W., *Verh. Dtsch. Ges. Kreislaufforsch.* **38**, 147–154 (1972) — [13] Meier, J., *Curr. med. Res. Op.* **4**, Supp. 5, 31–38 (1977) — [14] Naylor, G. W., Chang, A., Cellular pharmacology of beta-blocking drugs. In: New perspectives in beta-blockade. D. M. Burley, J. H. Frier, R. K. Rondel, S. H. Taylor, Hrsg. CIBA Lab., Horsham (1973) — [16] Reale, A., Motolese, M., Die Wirkung verschiedener Betablocker auf den Kreislauf bei

Patienten mit koronarer Herzkrankheit. In: Die kardioprotektive Wirkung der Betablocker. Tatsachen und Theorien. F. Gross, Hrsg. H. Huber, Bern (1977) — [15] Prichard, B. N. C., *Drugs* **7**, 55–84 (1974) — [17] Reiterer, W., *Basic Res. Cardiol.* **71**, 482–503 (1976) — [18] Reiterer, W., Vogt, R., Czitober, H., Einfluß der beta-Rezeptorenblockade auf Kriterien der körperlichen Leistungsfähigkeit. In: Tagungsbericht d. Arbeitsgemeinschaft f. klinische Atemphysiologie, Graz (1976) — [19] Reiterer, W., *Wien. med. Wschr.* **127**, Supp. 42 (1977) — [20] Reiterer, W., Effects of longterm treatment with a beta-receptor blocker (Prindolol) combined with a diuretic agent (Clopamid) on exercise performance in hypertension. In preparation — [21] Rivier, J. L., Die Behandlung der Angina pectoris mit Betablockern. In: Die Betablocker – Gegenwart und Zukunft. W. Schweizer, Hrsg., H. Huber, Bern (1976) — [22] Roskamm, H., Hämodynamik und Kontraktilität in Ruhe und während körperlicher Belastung bei Sympathikolyse. In: Die therapeutische Anwendung beta-sympathikolytischer Stoffe. H. J. Dengler, Hrsg., F. K. Schattauer, Stuttgart (1972) — [23] Schnellbacher, K., Roskamm, H., Reindell, H., *Herz/Kreisl.* **6**, 432–437 (1974) — [24] Shand, D. G., *Drugs* **7**, 39–47 (1974) — [25] Sharma, B., Taylor, S. H., A critical review of the symptomatic, electrocardiographic and circulatory effects of adrenergic beta-receptor antagonists in angina pectoris. In: New perspectives in beta-blockade. D. M. Burley, J. H. Frier, R. K. Rondel, S. H. Taylor, Hrsg., CIBA Lab., Horsham (1973) — [26] Sharma, B., Meeran, M. K., Galvin, M. C., Tulpule, A. T., Whitaker, W., Taylor, S. H., *Brit. Med. J.* **III**, 152–155 (1971) — [27] Simpson, F. O., *Drugs* **7**, 85–105 (1974) — [28] Strauer, B. E., *Internist* **18**, 294–302 (1977) — [29] Taylor, S. H., Mechanism of action of adrenergic beta-receptor antagonists in angina pectoris. In: New perspectives in beta-blockade. D. M. Burley, J. H. Frier, R. K. Rondel, S. H. Taylor, Hrsg., CIBA Lab., Horsham (1973) — [30] Taylor, S. H., Klinisch relevante Aspekte der Behandlung kardiovaskulärer Erkrankungen mit Betablockern. In: Die kardioprotektive Wirkung der Betablocker. Tatsachen und Theorien. H. Huber, Bern (1977) — [31] Tsukiyama, H., Otsuka, K., Miyamoto, K., Hashimoto, M., Yasutake, S., Horii, M., Matsui, Y., Ueda, A., Tanaka, T., Yamamoto, Y., *Jap. Circ. J.* **40**, 655–664 (1976) — [32] Waal-Manning, J. H., *Drugs* **12**, 412–441 (1976)

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