HAEMODYNAMIC EFFECTS OF METOPROLOL AND PINDOLOL: A COMPARISON IN HYPERTENSIVE PATIENTS

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1   In a double-blind study, 36 patients with essential hypertension were randomly allocated to treatment with either metoprolol, 100–300 mg/day, or pindolol, 5–15 mg/day for 6 months. Haemodynamic investigations were made on three separate occasions. Blood flow in the calves and in the forearm was determined by venous occlusion plethysmography after 6 weeks of placebo, after 6 weeks and again after 6 months of active therapy.

2   Both drugs reduced blood pressure significantly, by 17.1/11.8 mm Hg with metoprolol and 21.9/10.9 mm Hg with pindolol after 6 weeks ($P<0.005$). No further changes were seen after 6 months.

3   Heart rate after 6 weeks was significantly reduced by metoprolol (10.7 ± 2.4 beats/min, $P<0.001$) but not by pindolol (4.4 ± 2.3 beats/min, NS). After 6 months a significant reduction was seen also in the pindolol group (5.2 ± 2.1 beats/min, $P<0.05$).

4   The vascular resistance in the calves at rest was reduced by pindolol ($P<0.05$), whereas resistance tended to increase with metoprolol.

5   Resting vascular resistance in the forearm after 6 months was significantly reduced in the metoprolol group ($P<0.001$) as well as in the pindolol group ($P<0.02$). The increase in forearm vascular resistance seen during leg exercise was not influenced by either drug.

6   Vascular resistance at maximal vasodilatation was unchanged in the calves, but a significant reduction ($-17.4\pm5.7\%$, $P<0.01$) in the forearm vascular bed was seen after 6 months of pindolol. No change was observed with metoprolol.

7   It is concluded that pindolol reduces elevated blood pressure partly through peripheral vascular mechanisms. Metoprolol, on the other hand, probably acts mainly via central cardiac mechanisms.

Introduction

Since the antihypertensive effect of propranolol was first described by Prichard & Gillam (1964), a large number of β-adrenoceptor blocking drugs have come into general use in the treatment of hypertension. These drugs are equally effective in reducing blood pressure in patients with essential hypertension (Morgan *et al.*, 1974), regardless of differences in bioavailability, affinity for β_1- and β_2-adrenoceptors, lipid solubility, metabolism and intrinsic sympathomimetic activity (ISA) (Imhof, 1976). However, all β-adrenoceptor blocking drugs share the ability to block β_1-adrenoceptors and consequently the mechanisms whereby blood pressure is reduced, are thought to be linked to this property. After nearly two decades of β-adrenoceptor blocker use these mechanisms are not yet fully understood, even if several theories have been advanced (Fitzgerald, 1975). Indeed, it is by no means certain that all

β-adrenoceptor blocking drugs lower blood pressure by the same mechanisms. In particular, drugs with pronounced ISA seem to induce a different haemodynamic response than drugs lacking this quality, causing only minor reductions of heart rate and cardiac output (Lysbo-Svendsen *et al.*, 1980). In general, a rather marked reduction of cardiac output and heart rate is seen in acute trials as well as during chronic treatment with β-adrenoceptor blocking drugs (Tarazi & Dustan, 1972; Hansson *et al.*, 1974; Lund-Johansen, 1980). In this context, the findings of Atterhög *et al.* (1977) are of interest, since they showed unchanged cardiac output after 16 months of treatment with pindolol, but reduced vascular resistance. This indicated that the haemodynamic effects of pindolol might differ from that of β-adrenoceptor blocking drugs in general.

Adrenaline infusion in man will increase systolic

blood pressure and heart rate, while diastolic and mean blood pressure will decrease. During non-selective β-adrenoceptor blockade with propranolol, a pronounced increase in diastolic and mean blood pressure is seen during adrenaline infusion, as well as reduced forearm blood flow (Johnsson, 1975). This effect is due to blockade of vasodilating β_2-adrenoceptors in the blood vessels, concomitant with unmasking of the α-adrenoceptor mediated vasoconstriction. Observations such as these have been used as arguments against non-selective β-adrenoceptor blockade (van Herwaarden *et al.*, 1977) since 'stress' of different kinds could cause haemodynamic alterations similar to those observed during adrenaline infusion.

In this paper, we report the results of a randomized, double-blind 6 month trial with metoprolol and pindolol. Effects on blood pressure and peripheral haemodynamics at rest, during and after physical exercise and ischaemia were studied. Metoprolol is a β_1-selective adrenoceptor blocking drug devoid of ISA (Åblad *et al.*, 1975). Pindolol, in contrast, is a non-selective β-adrenoceptor blocker with a high degree of ISA, reported to be about 50% of the agonist effect of isoprenaline in the reserpinized rat (Barrett & Carter, 1970).

Methods

Material and design

Forty-three patients with mild to moderate hypertension were initially recruited for study. Thirty-six patients completed the first 12 weeks of the study, and some of their characteristics are summarized in Table 1. Patients with asthma, heart block, cardiac failure, recent myocardial infarction, peripheral vascular disease or abnormal renal function were excluded. Previous therapy, mainly diuretics or β-adrenoceptor blocking drugs, was withdrawn and substituted with placebo. After 6 weeks the first haemodynamic investigation was made, and then active treatment was instituted. The patients had been randomly allocated to double-blind treatment with either metoprolol, 100 mg once daily, or pin-

dolol 5 mg once daily as single antihypertensive drug. After 2 – 3 weeks the patients were seen at the Hypertension Clinic, and if the blood pressure reduction was considered inadequate (diastolic blood pressure above 90 mm Hg) the dose was doubled. After 6 weeks the haemodynamic investigation was repeated and if necessary the dose was increased to a maximim of 300 mg once daily (metoprolol) or 15 mg once daily (pindolol). After 6 months the mean dose was 179 mg of metoprolol and 11.8 mg of pindolol respectively. After 6 months of active therapy, the haemodynamic investigations were again repeated.

Investigative procedure and calculations

Rest After taking their medication in the morning, the patients came to the laboratory and completed the studies before noon. First the patients rested for 30 min in the recumbent position, the blood pressure was measured indirectly in one arm. The disappearance of the Korotkoff sounds (phase V) was taken as the diastolic pressure. The mean of three separate measurements was used in the analysis. Blood flow was then measured in both calves with the patient lying, using a Whitney mercury-in-rubber strain gauge technique (Whitney, 1953) as modified by Sivertsson (1970). One blood pressure cuff was applied around the ankle and another just above the knee, with pressure kept at about 55 mm Hg in both cuffs during flow registrations. Blood pressure was measured in the arm simultaneously with flow registrations. Mean blood pressure was approximated to diastolic pressure plus one third of the pulse pressure. Vascular resistance was the calculated by dividing mean blood pressure (mm Hg) by blood flow (ml $\times$ min^{-1} $\times$ 100 ml^{-1}) and expressed in resistance units (Conway, 1963). Five registrations in each leg were made after 30 min of rest in the supine position. The average of these was used in the statistical analysis.

Similar measurements were then made in one forearm, while blood pressure was measured in the other. One blood pressure cuff was applied around the wrist, the other just proximally to the elbow and cuff-pressure was kept at 55 mm Hg during flow registrations.

Table 1 Some characteristics of the study population

	Males/Females n	Smokers n	Previously treated n	Age, mean range (years)	Body weight (kg)	Pretreatment supine blood pressure
Metoprolol	13/6	5	9	45.1 ± 2.7 27–67	76.1 ± 3.1	162.2 ± 1.8/103.8 ± 1.8
Pindolol	12/5	6	11	44.8 ± 2.9 25–63	80.3 ± 3.5	163.3 ± 2.6/106.3 ± 1.5

No differences between groups were statistically significant.

Exercise A certain degree of physical exercise was performed, by cycling on an ergometer bicycle in the supine position. The load was adjusted so that a heart rate of about 125 beats/min was attained during the placebo period. The same load was then used in the investigations during active therapy. With the right arm supported in a slightly elevated position, just as at rest, forearm blood flow was registered during leg exercise. Measurements were made each minute during the first 6 min of exercise. After 10 min the leg exercise was interrupted and a new series of measurements was begun. Registrations were made each of the first 5 min after exercise. Heart rate was determined by means of electrocardiogram during all measurements at rest, during and after physical exercise.

Maximal vasodilatation To evaluate 'minimal vascular resistance' ischaemia was used to induce 'maximal vasodilatation'. The proximal cuff, above the knee and elbow in the calf and forearm measurements respectively, was inflated to well above the systolic blood pressure. The patients then worked with their muscles until exhaustion and ischaemic pain prevented further exercise. During the reactive hyperaemia, 'maximal' blood flow values were re-

corded and vascular resistance calculated. These determinations were made in each leg and in the right arm. The mean of the altogether six registrations in the leg and the three measurements in the arm respectively was used in the statistical analysis.

The study was approved by the Ethical Committee of the University of Göteborg, and the patients' informed consent was obtained.

Conventional statistical methods were used for calculations. Student's two tailed *t*-test for paired observations or for observed groups were used where appropriate. Differences were considered significant with $P < 0.05$. All values are given as mean ± s.e.mean.

Results

Drop-outs

Forty-three patients entered the study. Of these, 36 could be investigated after 6 weeks of placebo and again after 6 weeks of active therapy. There were four drop-outs during the placebo period. One was due to a fatal accident, one patient failed to keep his appointments and two patients experienced such gas-
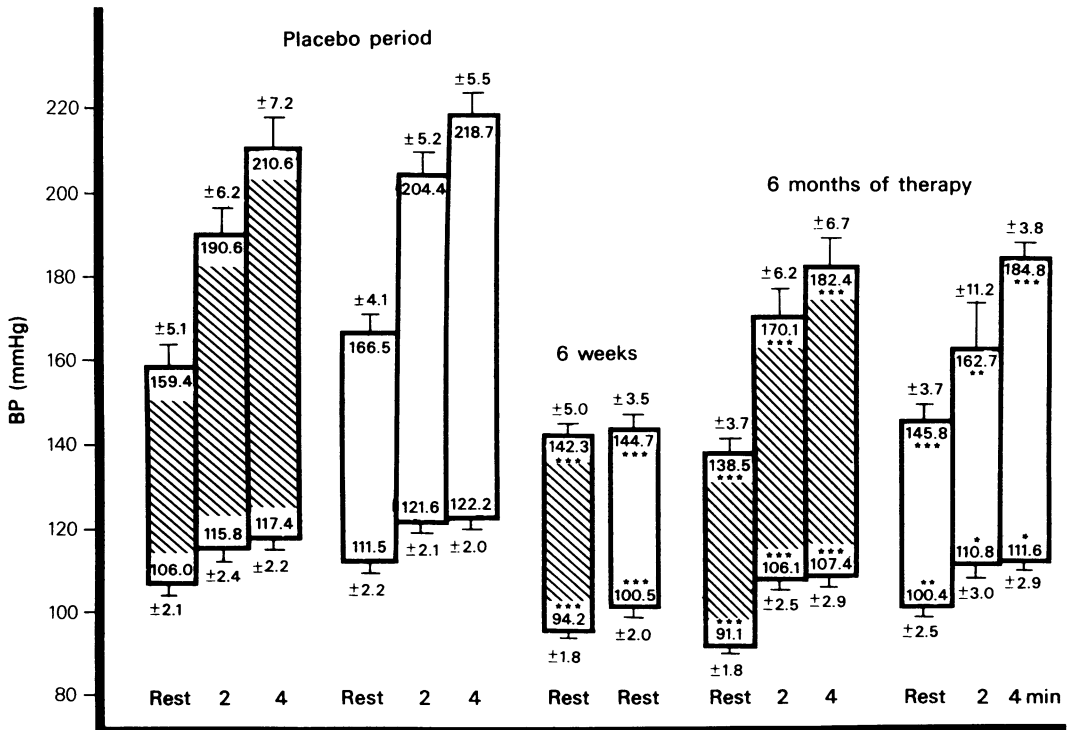

Figure 1 Blood pressure (mean ± s.e.mean) at rest and after 2 and 4 min of exercise. ▨ metoprolol, ☐ pindolol. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, treatment compared with placebo.

trointestinal disturbances, that they would not continue in the study. During active therapy one patient suffered a non-fatal myocardial infarction and was therefore excluded, one was excluded due to noncompliance and one patient changed himself back to his previous therapy, due to problems with diarrhoea. In the final haemodynamic investigation, 34 patients were included, since one patient taking metoprolol felt that his vision was disturbed and stopped taking his medication. The other drop-out was a patient whose medication, pindolol, was withdrawn in association with a gall bladder operation and not instituted again after the operation. Only data from the 36 patients that were investigated twice were used, in whom meaningful comparisons between placebo and active therapy could consequently be made.

Blood pressure Effects on blood pressure at rest and during physical exercise can be seen in Figure 1. Both drugs reduced blood pressure significantly and to the same extent at rest as well as during exercise. There was a tendency towards slightly higher blood pressure levels in the pindolol group, but this difference did not achieve statistical difference.

Heart rate

Resting heart rate was significantly reduced by metoprolol after 6 weeks by $14.8 \pm 3.1\%$ ($P < 0.001$) and by $12.9 \pm 3.9\%$ ($P < 0.005$) after 6 months, as shown in Figure 2. After 6 weeks of pindolol, however, only a slight reduction by $4.7 \pm 3.6\%$ (ns) was seen. After 6 months, the reduction was slightly larger, $6.4 \pm 3.0\%$ ($P = 0.052$). During physical exercise both metoprolol and pindolol reduced heart rate to the same extent (Figure 3). After exercise, however, there was a marked difference between meto-
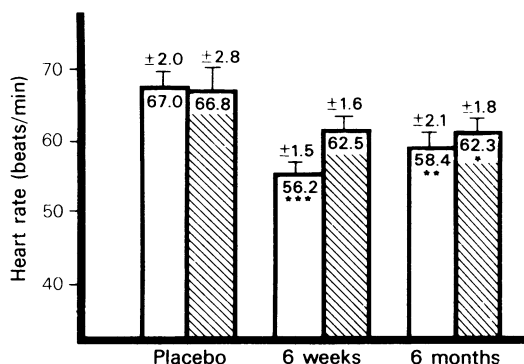
Figure 2 Heart rate (mean ± s.e.mean) at rest during placebo period and 6 weeks and 6 months after treatment with metoprolol (□) or pindolol (▧)
*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, treatment compared with placebo.

prolol, that reduced heart rate significantly, and pindolol, that did not affect heart rate at all. This difference in effect between the drugs was statistically significant as shown in Figure 3.
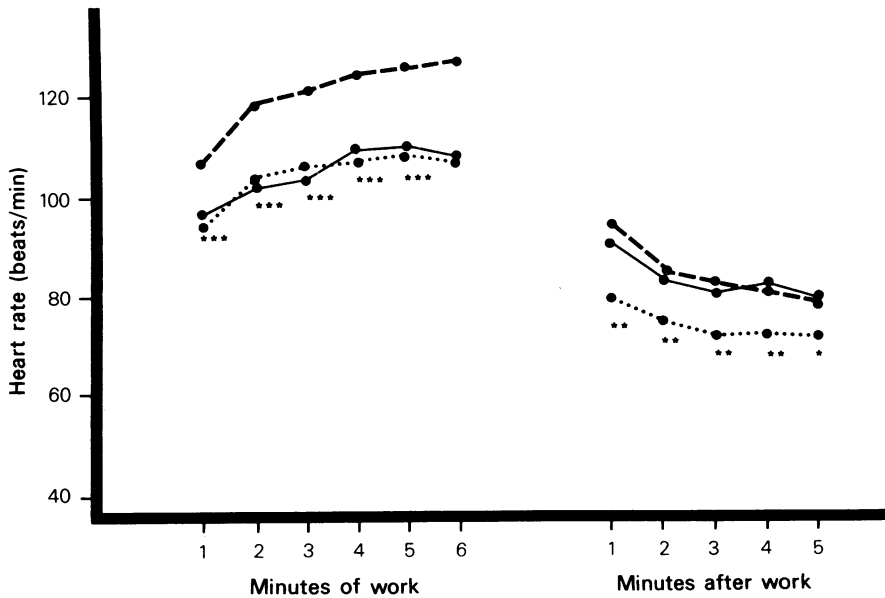
Blood flow and vascular resistance

Rest Changes in calf blood flow and vascular resistance are shown in Table 2. The response to the two drugs was of two different kinds. The blood flow was slightly but not significantly reduced with metoprolol, whereas a tendency toward increased blood flow was seen with pindolol. When the vascular resistance was calculated, this difference in effect was more clearly demonstrated. Thus, resting vascular resistance in the calf was slightly elevated by metoprolol, $+7.1 \pm 7.5\%$ at 6 weeks and $+8.1 \pm 8.2\%$ at 6 months respectively. In the pindolol group, on the other hand, a clear reduction of resting vascular resistance in the calf was seen, $-13.7 \pm 6.0\%$ ($P < 0.05$) and $-13.5 \pm 6.8\%$ ($P < 0.05$) was seen after 6 weeks and 6 months respectively. The difference in effect between the two drugs was quite marked ($P < 0.005$ at 6 weeks and 6 months).

In the forearm, changes in resting blood flow was also seen, but they did not coincide with the findings in the calves (Table 2). With metoprolol, blood flow increased by $18.7 \pm 14.3\%$ (NS) at 6 weeks and $33.9 \pm 9.7\%$ ($P < 0.005$) at 6 months. The same tendency was noted with pindolol, but increases of $7.6 \pm 9.4\%$ and 36.7 ± 17.8 after 6 weeks and 6 months did not quite achieve statistical significance. When vascular resistance in the forearm was calculated neither the reduction with metoprolol ($-5.2 \pm 10.7\%$) or pindolol ($-8.3 \pm 8.0\%$) at 6 weeks was significant. After 6 months, however, the reduction with metoprolol, $-30.2 \pm 4.7\%$, was significant ($P < 0.001$) as well as the reduction seen with pindolol, $-22.0 \pm 8.2\%$ ($P < 0.02$).

Exercise During placebo, leg exercise increased the vascular resistance in the forearm by approximately 65%, from 31 units to 51 units. Resistance was calculated as the mean of the values at 1, 2, 3 and 4 min of exercise. There were some difficulties with artefacts during exercise, and some registrations could not be used. To get reliable figures, the mean of all these measurements was used. After 4 min, vascular resistance would begin to decrease due to cutaneous vasodilatation in association with sweating, and therefore further registrations were not used. After 6 months of therapy, identical increases to 50 units during exercise were seen in the two treatment groups, i.e. not different from the placebo period.

After exercise During placebo treatment, the forearm blood flow was slightly elevated, compared

Figure 3   Heart rate during physical exercise and after work. --- placebo, ... metoprolol and —— pindolol.
*$P<0.05$, **$P<0.01$ and ***$P<0.001$ treatment compared with placebo.

with the resting values. During active therapy blood flow and vascular resistance were largely unchanged compared to placebo. The changes that were seen were inconsistent with regard to duration of therapy and elapsed time after interruption of exercise.

Maximal vasodilatation   Vascular resistance at 'maximal vasodilatation' in the calf vascular bed was not influenced by 6 months of treatment with either metoprolol or pindolol. In the forearm, however, a reduction of 'minimal' vascular resistance was seen after 6 months of pindolol $(-17.4 \pm 5.7\%, P<0.01)$. No such change was seen with metoprolol.

Discussion

Many β-adrenoceptor blocking drugs have come into use in the treatment of hypertension during the last decade. This group of drugs is characterized by some differences with regard to pharmacological properties (Imhof, 1976) but the blood pressure lowering effect of the different drugs is the same (Opie, 1980). The ability to block β_1-adrenoceptors by competitive inhibition is, however, common to all these drugs. It is therefore obvious that the theories concerning the blood pressure lowering mechanisms of these drugs have been focused on β_1-adrenoceptor blockade. At various times suggestions have been made that the

Table 2   Resting blood flow and vascular resistance in the calf and forearm vascular beds (mean $\pm$ s.e.mean)

	Placebo	Metoprolol 6 weeks	6 months	Placebo	Pindolol 6 weeks	6 months
Calf blood flow (ml/min × 100 ml)	3.22±0.19	2.93±0.26	2.84±0.19	2.82±0.19	3.07±0.14	3.08±0.18
n	19	19	18	17	16	15
Calf vascular resistance (units)	41.4 ±2.5	43.0 ±3.2	43.0 ±3.4	50.8 ±3.5	41.2 ±2.3 *	41.5 ±2.20 *
Forearm blood flow (ml/min × 100 ml)	4.04±0.4	4.36±0.46	4.89±0.33**	4.07±0.31	4.22±0.35	5.01±0.31
n	19	19	18	17	16	15
Forearm vascular resistance (units)	36.1 ±3.4	31.3 ±3.7	23.5 ±1.7 ***	34.7 ±2.6	30.7 ±3.0	24.6 ±1.8 **

*$P<0.05$, **$P<0.02$, ***$P<0.001$ compared with placebo.

main mechanism is one of the following (Fitzgerald, 1975).

a) Blockade of sympathetic control of renin release from the kidney
b) Antagonism of cardiac β_1-adrenoceptors, with resulting reduction of cardiac output
c) A reduction of sympathetic nervous outflow from the central nervous system
d) Changes in baroreceptor activity, resulting in an altered balance of the control system of the circulation

None of these theories have been generally accepted as the key to the blood pressure reduction induced by β-adrenoceptor blocking drugs. It may well be that for different drugs one or another of these or other mechanisms is of primary importance.

It is generally accepted that the acute administration of a β-adrenoceptor blocking drug results in reduced cardiac output and increased total peripheral vascular resistance with little or no change in blood pressure (Tarazi & Dustan, 1972; Hansson *et al.*, 1973, Lund-Johansen, 1980). In contrast, non-selective (pindolol) and β_1-selective (ICI 89.406) adrenoceptor blocking drugs with pronounced ISA do not reduce cardiac output or heart rate at rest (Lysbo-Svendsen *et al.*, 1979), and vascular resistance is not affected. Other investigators comparing other drugs with less pronounced ISA to drugs without ISA, have failed to show this difference (Lund-Johansen & Ohm, 1976).

During long-term treatment with most β-adrenoceptor blockers, a gradual return of total peripheral resistance to pre-treatment levels concomitant with a reduction of blood pressure is seen. The findings by Atterhög *et al.* (1976), that cardiac output was unchanged and systemic vascular resistance decreased after 16 months of pindolol therapy implied that the haemodynamic pattern may differ between β-adrenoceptor blocking drugs. In a two month study by Velasco *et al.* (1980) similar results were reported, i.e. unchanged heart rate and cardiac output but reduced total peripheral resistance with pindolol. The lack or existence of ISA probably plays a role in this respect.

Design and methods

Treatment, measurements and calculations of blood pressure, heart rate, blood flow and vascular resistance were made double-blind. The random allocation of patients to one or the other of the two drugs tended to put patients with somewhat higher blood pressure in the pindolol group, but the difference during placebo did not achieve statistical significance ($P = 0.1$, diastolic blood pressure). This tendency probably explains why 8 out of 17 with pindolol compared to 4 out of 19 patients with metoprolol

needed the maximum dose. The once daily dosage used has been proved efficacious in the treatment of hypertension with metoprolol (Lyngstam & Rydén, 1979) as well as with pindolol (Frithz, 1978).

The calf plethysmographic method has been evaluated (Sivertsson, 1970; Andersson, 1978) and found to be adequate. However, it is known that indirect measurement of blood pressure tends to overestimate diastolic blood pressure at rest (Raftery & Wand, 1968) as well as during post-ischaemic hyperaemia of the hand vascular bed (Gudbrandsson, 1981). In this respect, there would be no difference between the two treatment groups, and meaningful comparisons to placebo periods can also be made. The theoretical objection, that β-adrenoceptor blockade might change the form of the pulse curve has been discussed and refuted elsewhere (Sivertsson *et al.*, 1980). The difference in heart rate between placebo and propranolol treatment in the investigation by Sivertsson *et al.* (1980) did not affect the factor, 1/3, whereby pulse pressure should be multiplied before addition to diastolic pressure to obtain the mean blood pressure. Therefore, the slight difference in heart rate between the metoprolol and pindolol groups could hardly influence the mean blood pressure and calculated vascular resistance.

Calf vascular bed

Our study supports the earlier findings, where central haemodynamics were studied. We observed a significant reduction of calf vascular resistance at rest with pindolol at 6 weeks and 6 months. Such a reduction was not seen by Velasco *et al.* (1980), who also studied blood flow and vascular resistance in the calf with pindolol. With the method they used, venous occlusion pneumo-plethysmography, the resting blood flow seemed to be high, 6 ml/min × 100 ml. The blood flow of about 3 ml/min × 100 ml we found is more in accordance with figures given in text-books of circulatory physiology (Folkow & Neil, 1971). Blood flow during maximal vasodilatation, about 70 ml/min × 100 ml with placebo and 65 ml/min × 100 ml during β-adrenoceptor blockade, is also in accordance with maximal blood flow in muscle founded by others (Folkow & Neil, 1971). The fact that no changes in resistance at maximal vasodilatation was seen, implies that no change of vascular structure was caused by 6 months of treatment with either metoprolol or pindolol in this vascular bed.

The reduction of vascular resistance at rest cannot be explained by blood pressure reduction or β_1-adrenoceptor blockade, as metoprolol, if anything, tended to increase the vascular resistance despite significant blood pressure reduction. In a study with the same methodology, atenolol was shown to in-

crease calf vascular resistance after 6 months of treatment (Sivertsson *et al.*, 1979), but the doses used in that study were high compared to the ones in our study, which probably accounts for the discrepancy in findings. The fact that calf blood flow is not reduced by pindolol is probably explained by the pronounced ISA of this drug.

When the β_1-selective drugs H87/07 (Stenberg *et al.*, 1975) and ICI 89.406 (Lysbo-Svendsen *et al.*, 1979) with marked ISA were given intravenously, cardiac output and peripheral resistance remained unchanged. The same observation was made with pindolol, whereas non-selective and β_1-selective adrenoceptor blocking drugs without ISA induced a reduced cardiac output and increased peripheral resistance (Svendsen *et al.*, 1981). However, ISA acting on β_1-adrenoceptors hardly explains the *reduction* of calf vascular resistance seen in our pindolol treated patients. Instead it is probably a result of ISA-induced stimulation of β_2-adrenoceptors, as dilatation of peripheral vessels are mediated via β_2-adrenoceptors, according to the classification by Lands *et al.* (1967). The β_2-adrenoceptor agonist terbutaline, usually used in asthma, has recently been shown to produce peripheral vasodilatation in patients with congestive heart failure (Slutzky, 1981). As pindolol is non-selective with regard to β_1- and β_2-adrenoceptors and possesses a strong receptor-stimulating activity ISA) this seems to be a reasonable assumption, and in accordance with the finding that pindolol induces relaxation of isolated arterial and vein preparations (Thulesius *et al.*, 1982).

Forearm The finding that resting blood flow was increased and vascular resistance reduced by both drugs (Table 2) is rather puzzling. The observation that pindolol reduced vascular resistance at rest is in accordance with our results in the calf and the findings of Atterhög *et al.* (1977), who noted a reduction of forearm vascular resistance at rest after 16 months of treatment with pindolol. Forearm blood flow and vascular resistance seem not to have been investigated during long-term treatment with other β-adrenoceptor blocking drugs. It is conceivable that the successive reduction of the initially elevated peripheral resistance during β-adrenoceptor blockade is more or less pronounced in different tissues. The reduced cardiac output during β-adrenoceptor blockade seems to be redistributed, so that blood flow to vital organs is preserved at the expense of skeletal muscle (Nishiyama *et al.*, 1975) and the splanchnic-hepatic region (Trap-Jensen *et al.*, 1976). Regional differences within the skeletal muscle system seem not to have been investigated, but our results indicate the possibility that the calf and forearm vascular beds may behave differently during chronic β-adrenoceptor blockade. The possibility

that the 'stress' of the investigative procedure could induce vasoconstriction, which would diminish in the later investigations as the patients got accustomed to the situation, cannot be ruled out. Variations in ambient temperature were not of such magnitude that they would cause variations in skin blood flow, which only contributes a smaller part of total forearm blood flow.

The reduction of vascular resistance at 'maximal' vasodilatation implies regression of hypertensive vascular changes. This finding will be discussed further elsewhere.

Physical exercise

The increase in heart rate during physical exercise (Figure 3) was attenuated to the same degree with both drugs, indicating a similar degree of β-adrenoceptor blockade (Carruthers *et al.*, 1976). The reduction of exercise-induced blood pressure elevation was also of the same magnitude with both drugs (Figure 1). Blood flow and vascular resistance in the forearm was not influenced by either drug during leg exercise. The reduction of blood flow and increase in vascular resistance, that takes place in resting tissue during physical exercise, has been shown to be accentuated by propranolol (Trap-Jensen *et al.*, 1976). This was probably due to α-adrenoceptor stimulation in association with increased arterial catecholamine concentrations. In the presence of β_2-adrenoceptor blockade, the unopposed alpha-adrenoceptor stimulation would lead to vasoconstriction, as has been demonstrated during adrenaline infusion (Johnsson, 1975). We could not find any difference in forearm vascular resistance during leg exercise. This indicates that the unopposed α-adrenoceptor mediated vasoconstriction seen during propranolol but not metoprolol (Johnsson, 1975) is not seen with pindolol. ISA acting on the vasodilating β_2-adrenoceptors probably explains this difference compared to propranolol.

Heart rate

Heart rate at rest was significantly reduced by metoprolol at 6 weeks and 6 months (Figure 2). With pindolol, on the other hand, the heart rate was barely lowered at 6 weeks, the reduction not being significant. At 6 months, the reduction achieved statistical significance. Different investigators have at various times noted unchanged (Velasco *et al.*, 1980; Svendsen *et al.*, 1981) or reduced heart rate (Atterhög *et al.*, 1977) during pindolol administration. The unchanged or reduced heart rate has been paralleled by unchanged or reduced cardiac output in these investigations. The explanation of the differences may be the initial heart rate, as a reduction was seen in those

studies where initial heart rate was above 70 beats/min, but not when heart rate was below 65 beats/min. With a higher sympathetic activity, the β_1-adrenoceptor blocking property of pindolol would dominate, whereas the ISA mediated β_1-receptor stimulation would dominate during low adrenergic drive (Man in't Veld & Schalekamp, 1981). In the middle range, the effect on heart rate would be nil. The dose may also be of importance as shown by Andrén & Hansson (1982), who found a significant reduction of heart rate with 10 and 20 mg pindolol/day, but not with 30 mg/day whereas there was a clear relation between dose level and antihypertensive effect.

In conclusion, there was a clear difference in effect on heart rate, demonstrated most clearly after physical exercise, where metoprolol reduced heart rate significantly, but pindolol did not affect heart rate at all (Figure 3).

Conclusion

The β-adrenoceptor blocking drugs metoprolol and pindolol are equally effective in reducing blood pressure at rest, during and after physical exercise, in hypertensive patients. They do, however, affect the heart and the peripheral resistance vessels differently. Metoprolol seems to lower blood pressure mainly through cardiac mechanisms (as exemplified by reduced heart rate) while pindolol seems to act partly through peripheral vascular mechanisms, probably as a result of its pronounced ISA.

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