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Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol

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SUMMARY The effects on systemic and pulmonary haemodynamics of treatment with the alpha- and beta-adrenoceptor blocker labetalol for 20 months were studied in 9 hypertensive men aged 49 to 57 years, at rest in the supine and upright position and during exercise in the sitting position at 62 and 124 Watts. Pressures were recorded by means of catheters inserted percutaneously into the pulmonary and brachial artery, and cardiac output was determined by the Fick method.

Systemic systolic, diastolic, and mean pressures were considerably reduced by labetalol under all conditions. Pulmonary mean pressure was slightly higher during exercise, and left ventricular (pulmonary artery) diastolic pressure was virtually unchanged.

Systemic blood pressure was lowered by reduction of systemic vascular resistance alone. Though heart rate was significantly reduced under all conditions, cardiac output was unchanged because of a considerable rise in stroke volume which entirely counterbalanced the reduction in pulse rate. Compared with the haemodynamic pattern induced by intravenous labetalol, prolonged treatment resulted in a greater increase in stroke volume and a further decrease of heart rate, particularly at rest. Systemic vascular resistance showed a further tendency towards lower values. Postural hypotension which occurred frequently after intravenous labetalol was not observed after long-term treatment. Plasma renin activity and arterial lactate were consistently reduced. No serious side-effects were observed, nor were there any significant changes in haematological and biochemical variables.

Treatment of hypertension by combined alpha- and beta-receptor blockade using labetalol offers significant haemodynamic advantages compared with treatment by beta-receptor blockade alone.

Animal and human studies have shown that hypertension rapidly induces structural changes in the precapillary resistance vessels, including reduced internal vessel radius, increased wall to lumen ratio, and a consequent hyperactivity of these vessels with exaggerated luminal reductions for a given smooth muscle activation (Folkow, 1975). Recent studies also suggest that these structural changes may be reversible under certain conditions, both in the experimental animal (Weiss *et al.*, 1974) and in man (Sivertsson, 1977). Constriction of the peripheral resistance vessels is mediated through α-adrenoreceptors. Thus blockade of these receptors appears on theoretical grounds to be the most logical and efficient way to lower precapillary resistance and to damp the functional excitatory influences which, once the structural changes are established, enhance increases in the vascular pressure load and in turn serve to intensify the structural adaptation.

Agents with α-adrenoreceptor blocking properties such as phentolamine (Majid *et al.*, 1974) and labetalol (Koch, 1976b) have consistently been shown to reduce systemic vascular resistance and thereby blood pressure in man, at least in the acute experiment. As labetalol combines alpha-receptor with beta-receptor blocking properties it has an essential advantage over phentolamine and other peripheral vasodilators such as hydralazine and prazosin (Zacest, 1975), in that it counteracts the

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baroreceptor reflex increase of heart rate and cardiac output elicited by the pressure decrease.

Labetalol has been shown to have a considerable antihypertensive action (Richard and Turner, 1976; Brogden *et al.*, 1978). In the acute experiment it reduces blood pressure, at rest and during exercise, by lowering both the systemic vascular resistance and cardiac output but not stroke volume (Koch, 1976b, 1977). This pattern of haemodynamic effect distinguishes labetalol from most if not all other single antihypertensive drugs and offers a particularly attractive basis for treating hypertension from the physiological point of view.

Our knowledge of the haemodynamic effects of labetalol relates at present mainly to the acute intravenous administration of the drug. However it is well established that with many agents interfering with cardiovascular regulation, including antihypertensive drugs, the acute haemodynamic effects are attenuated or modified after prolonged treatment (Koch, 1976a). The purpose of the present study was, therefore, to define the long-term effects of oral labetalol with respect to circulatory dynamics. The haemodynamic effects on the systemic and pulmonary circulations in patients with essential hypertension have been investigated during rest in both supine and upright positions and during exercise.

Patients

Of the 13 patients who had participated in the initial investigation (Koch, 1977a), 9 men aged 49 to 57 years were restudied after an average of 20 months (range 16 to 24 months) treatment with oral labetalol as the sole antihypertensive agent in doses ranging from 600 to 2400 mg daily. Doses had to be repeatedly increased during the initial 6 months of oral treatment in order to maintain a similar blood pressure reduction as that obtained after the intravenous administration of labetalol; subsequently the dosage could be kept unchanged or slightly reduced.

The clinical evaluation indicated that all patients had essential hypertension; plasma volume, blood counts, serum electrolytes, serum creatinine, liver and renal function tests were normal and virtually unchanged during the entire period of observation. In particular, there was no case of positive antinuclear factor during a total observation time exceeding 3 years. Fundoscopic examination before and after the 20-month period did not reveal any significant alteration: one patient had no abnormalities at all, the remainder had non-exudative grade 1 to 2 hypertensive changes. None had evidence of ischaemic heart disease as evaluated by repeated exercise electrocardiograms (maximal work load ranging between 150 and 200 Watts) or of significant cardiac enlargement. Some relevant patient data including blood volume, heart volume, total amount of haemoglobin, and plasma renin activity before, and their changes after, the 20-month period, are given in Table 1.

Table 1 *Means and standard deviations (SD) of some anthropometric data and of plasma renin activity (PRA) before and mean ($\bar{D}$) and percentage ($\bar{D}$%) changes after 20 months of antihypertensive treatment*

	Mean	*SD*	$\bar{D}$	$\bar{D}$%
Age (y)	53·8	2·6	1·8	3·2
Weight (kg)	83·4	8·1	− 1·5	− 1·8
Height (cm)	176·3	6·0	0	0
Blood volume (l)	6·49	1·24	− 0·45	− 6·9
Total Hb (g)	859	202	− 92	− 10·7
PRA (ng/ml per h)	2·10	1·96	− 1·3**	− 63·0**

** $P < 0.01$.

Methods

Haemodynamics were restudied after the 20-month period of oral treatment in precisely the same way and under conditions identical to the initial haemodynamic investigation. The haemodynamic measurements were made both in the supine and the upright positions and during steady state exercise at two different work loads (W_1: 62 ± 8, mean ± standard deviation, range 50 to 75 W; W_2: 124 ± 16, range 100 to 150 W) in the sitting position on a bicycle ergometer.

Both the orthostatic test and exercise at each work load lasted for 6 minutes. Systemic and pulmonary arterial pressures were directly recorded through polyvinyl catheters percutaneously introduced into the left brachial artery and the main pulmonary artery. Cardiac output was determined according to the Fick principle. Details concerning the general investigation procedure, analyses, calculations, including the reproducibility of the methods used and the statistical evaluation, are given elsewhere (Koch, 1976a, 1977).

Results

HAEMODYNAMICS AFTER LONG-TERM ORAL TREATMENT

Mean values and standard deviations of some relevant haemodynamic indices as measured before, as well as the changes observed after treatment, are given in Tables 2 and 3 and in Fig. 1.

Table 2 *Means and standard deviations (SD) of blood pressures and vascular resistances before and their mean changes ($\bar{D}$) after 20 months of antihypertensive treatment at rest in supine (R) and upright (O) position and during exercise at two different work loads*

		Mean	SD	$\bar{D}$
Brachial artery				
Systolic pressure (mmHg)	R	167	24	−18*
	O	174	31	−27**
	W_1	198	31	−42**
	W_2	235	23	−57**
Diastolic pressure (mmHg)	R	98	13	−17**
	O	104	17	−19**
	W_1	100	16	−20*
	W_2	111	17	−26**
Mean pressure (mmHg)	R	124	15	−18**
	O	133	22	−23**
	W_1	143	18	−32**
	W_2	162	20	−37**
Pulmonary artery				
Systolic pressure (mmHg)	R	22	6	3
	O	19	6	− 2
	W_1	30	6	5*
	W_2	36	9	5
Diastolic pressure (mmHg)	R	4	3	4
	O	3	3	1
	W_1	7	2	5
	W_2	11	4	4
Mean pressure (mmHg)	R	11	4	3
	O	8	4	1
	W_1	16	5	6*
	W_2	21	7	8*
Systemic vascular resistance index	R	48·8	12·1	− 9·3*
	O	57·4	14·7	−13·6*
	W_2	25·7	5·8	− 4·4*
Pulmonary vascular resistance index	R	3·0	1·3	− 0·7
	O	2·4	1·2	0
	W_2	1·6	0·6	0·8*

* $P < 0.05$;
** $P < 0.01$.
W_1 = 62 Watts;
W_2 = 124 Watts.

The pretreatment average systemic blood pressure was 167/98 (mean 124) mmHg at rest in the supine and 174/104 (mean 133) mmHg in the upright position. It rose to 235/111 (mean 162) mmHg during exercise (W_2). Treatment with oral labetalol resulted in a significant reduction (by 11 to 25%) under all conditions, the effect being most pronounced during exercise. At rest, both in the supine and upright posture, mean and diastolic pressures were affected more than systolic pressures.

Blood pressures in the pulmonary circulation were within normal limits both before and after treatment. Except for upright conditions there was a general tendency towards slightly higher values after treatment, in particular as regards systolic ($P < 0.05$, W_1) and mean pressures ($P < 0.05$, W_1 and W_2) during exercise. However, the absolute changes in pressure were minimal.

Heart rates were significantly reduced during all conditions (by 13 beats in the supine position and 28 beats during W_2); oxygen uptake ($\dot{V}O_2$) and ventilation ($\dot{V}E$) were unaffected.

Because of a significant increase in stroke volume which fully counterbalanced the reduction in heart rate, cardiac output was virtually unchanged. The arteriovenous oxygen difference was slightly reduced in the supine position only.

Pretreatment systemic vascular resistances were greatly increased at rest, both in the supine and especially in the upright positions. They were considerably reduced during all conditions after treatment (by 19 to 27%). Pulmonary vascular resistances were low before and after treament, and did not show any consistent change during the 20-month period.

Plasma renin activity (Table 1) and arterial blood lactate levels were significantly reduced (by 35 to 65%) under all conditions.

Table 3 *Means and standard deviations (SD) of some circulatory and respiratory variables before and their mean changes ($\bar{D}$) after 20 months of antihypertensive treatment at rest in supine (R) and upright (O) position, and during exercise at two different work loads*

		Mean	*SD*	$\bar{D}$
Heart rate	R	72	8	− 13***
	O	81	14	− 18**
	W_2	139	20	− 28**
Ventilation $\dot{V}_E$ (l/min BTPS)	R	11·6	4·6	− 1·4
	O	15·5	5·0	− 2·6
	W_2	56·6	10·5	− 2·3
Oxygen uptake, $\dot{V}o_2$ (l/min STPD)	R	262	42	− 3
	O	351	66	− 43
	W_2	1805	184	−115
AVo_2 difference (ml/l)	R	51·0	11	− 3
	O	76·0	12	− 13**
	W_2	139·6	12	− 2
Cardiac output (l/min)	R	5·42	1·57	0·13
	O	4·81	1·21	0·21
	W_2	13·06	1·87	− 0·71
Stroke volume (ml)	R	75	20	22*
	O	65	21	16
	W_2	94	11	17
Lactate (mmol/l)	R	0·97	0·39	− 0·57**
	O	1·01	0·47	− 0·66**
	W_2	3·93	0·71	− 1·39***
	4′ after work	4·39	1·05	− 1·56***

W_1 = 62 W; W_2 = 124 W.
* P < 0·05;
** P < 0·01;
*** P < 0·001.

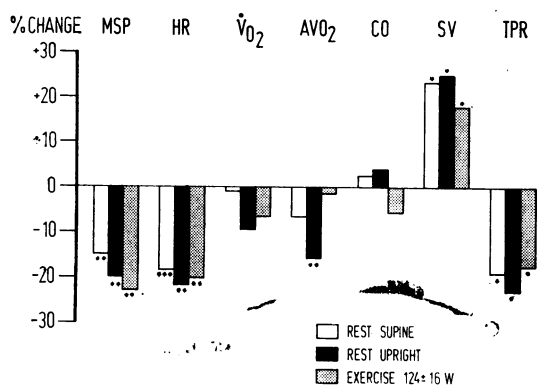

Fig. 1 *Percentage changes from pretreatment values of some haemodynamic variables after 20 months of antihypertensive treatment. MSP, mean systemic blood pressure; HR, heart rate; $\dot{V}o_2$, oxygen uptake; AVo_2, arterio-mixed venous oxygen difference; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance. Asterisks denote level of statistical significance: * P < 0·05, * * P < 0·01, * * * P < 0·001.*

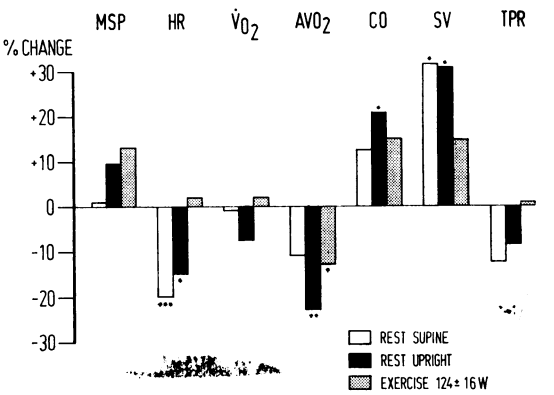

Fig. 2 *Percentage changes in some haemodynamic variables after 20 months of oral treatment compared with values measured after acute intravenous administration of 50 mg labetalol. Abbreviations and symbols as in Fig. 1.*

HAEMODYNAMICS AFTER LONG-TERM ORAL TREATMENT COMPARED WITH ACUTE INTRAVENOUS TREATMENT

Fig. 2 denotes the changes in the main haemodynamic indices that were observed after oral treatment compared with the haemodynamics as induced by acute intravenous administration of 50 mg labetalol (Koch, 1977a).

Mean systemic blood pressures were virtually unchanged at rest in the supine position; there was a weak yet statistically insignificant tendency towards slightly higher pressures in the upright position and during exercise. Heart rate showed a further decrease, at least during resting conditions, while stroke volume was significantly higher (23% in the

upright position, $P < 0.05$) resulting in slightly increased cardiac output. In accordance with the increased cardiac output the arteriovenous oxygen difference was significantly lower, particularly in the upright position. The systemic vascular resistance showed a further tendency towards lower values at rest.

Discussion

Treatment with oral labetalol for an average duration of 20 months resulted in considerably lower blood pressures under all conditions. Systemic mean pressures were reduced by 18 and 23 mmHg at rest in the supine and erect posture, and by 32 and 37 mmHg during exercise at loads W_1 (62 ± 8 W) and W_2 (124 ± 16 W corresponding to an oxygen uptake of approximately 1·8 l), respectively.

The mode of antihypertensive action was practically identical at rest, both in the supine and erect posture, and during exercise. Blood pressure was lowered by a reduction of peripheral vascular resistance alone; though heart rate was significantly lower under all conditions, cardiac output was virtually unchanged because of a considerable increase in stroke volume which entirely counterbalanced the reduction in pulse rate. It is particularly noteworthy that the increase in stroke volume which was consistently observed under all conditions was achieved without any significant rise in pulmonary artery diastolic pressure, that is in left ventricular filling pressure. Though the use of left ventricular filling pressure as a method of evaluating myocardial contractility is crude and insensitive, the absence of any significant pressure rise both at rest and particularly during exercise, in association with considerably increased stroke volumes, suggests that labetalol lacks significant negative inotropic effects.

A completely different pattern of haemodynamic adaptation is regularly seen with agents that exclusively block adrenergic beta-receptors. In the rare instances when left ventricular filling pressures were measured during long-term oral treatment with beta-blockers, left ventricular filling pressures were regularly found to be higher at corresponding exercise levels. This applies for oxprenolol and propranolol (Taylor *et al.*, 1970) as well as for the combination of oxprenolol and hydralazine (Koch, 1976a). Cardiac output was found to be consistently reduced, and the arteriovenous O_2 difference correspondingly increased, during both resting and exercise conditions, after long-term treatment with alprenolol, atenolol, metoprolol, and timolol, while the peripheral vascular resistance consistently showed a tendency towards slightly higher values (Lund-Johansen and Ohm, 1976). The same general pattern of haemodynamic adjustment was observed after a 13-month treatment with oxprenolol despite supplementary administration of the vasodilator hydralazine in a daily dose ranging between 150 and 225 mg during the last 6 months (Koch, 1976a). Data obtained during treatment with propanolol, though limited to resting conditions, suggest a similar haemodynamic response (Tarazi and Duston, 1972), even when combined with hydralazine (Trap-Jensen *et al.*, 1976a). A particular feature of Tarazi's study was the observation that systemic vascular resistance was greatly increased in the early stage of treatment, but approached pretreatment levels after a period of 20 months of treatment. Surprisingly enough, pindolol, a non-selective beta-receptor antagonist, has recently been reported to lack the cardiac output reducing effect on long-term treatment and to exert its antihypertensive action solely by reduction of the peripheral vascular resistance (Atterhög *et al.*, 1977). However, the mechanism behind this effect, unusual for a beta-receptor blocker, remains obscure.

The considerable reduction in total peripheral vascular resistance in association with unchanged cardiac output (Fig. 1) suggests that labetalol, because of its alpha-receptor antagonism, might lack the flow reducing effect exerted by propranolol in different vascular beds such as the splanchnic-hepatic circulation and the skeletal muscle (Trap-Jensen *et al.*, 1976b). The significant reduction in arterial blood lactate during and after exercise while on prolonged treatment (Table 3) might indicate a different action of labetalol with respect to microcirculation and/or metabolism, since lower lactate levels probably reflect a lesser degree of anaerobic metabolism in the working muscles. A decline of lactate was not seen after the acute administration of labetalol (Koch, 1977) and clonidine (Koch, 1971), or after long-term treatment with propranolol (Trap-Jensen *et al.*, 1976b) and with oxprenolol in combination with hydralazine (Koch, 1976a), that is conditions where cardiac output was consistently reduced. Recent studies on renal haemodynamics have also shown a reduction in renal vascular resistance after the administration of labetalol (Koch, 1978).

During the acute experiment, signs and symptoms of conspicuous postural hypotension were frequent (Koch, 1976b), but were not observed after long-term oral treatment. Neither did any of the patients complain of signs attributable to decreased orthostatic tolerance in daily life activities during a total

observation period of 3 years. The acute effects of labetalol consist mainly in a negative chronotropic action via beta-receptors in the myocardium and in an alpha-receptor mediated dilatation of the resistance vessels inducing a reduction of cardiac output and predominantly of vascular resistance; but intravenous labetalol also results in lower pulmonary artery pressures and tends to decrease left ventricular filling pressures (Koch, 1977). These latter effects suggest that the acute administration of the drug also induces, particularly in the supine and upright position, a blood volume shift from the intrathoracic to the peripheral compartments of the low pressure capacitance system. This peripheral blood pooling is probably the result of a vasodilatory effect on the venules and small veins as well. Attenuation of this particular effect appears to be the main alteration occurring during long-term treatment since the peripheral vascular resistance tends to decrease further. This would explain both the considerable increase in stroke volume and cardiac output, again most pronounced during resting conditions, and the presence of postural hypotension during the acute experiment but not after long-term treatment. On the other hand, the additional decrease in resting (supine and upright) heart rates suggests a greater influence of the beta-receptor blocking action after long-term therapy.

As previously mentioned, adaptive structural changes appear early in the course of hypertension in the precapillary section of the vascular system and the left heart (Folkow, 1975). The precapillary structural adjustment taking the form of an increased wall lumen ratio implies a mutual reinforcement between functional and structural factors, resulting in exaggerated increases of resistance and arterial pressure, for given increases of vascular smooth muscle activity. Furthermore, evidence has recently been provided that both acute and prolonged adrenoceptor blockade results in increased blood levels of adrenaline and noradrenaline. This has been shown to apply not only to non-selective beta-receptor blockers such as propranolol (Trap-Jensen *et al.*, 1976b) and cardioselective agents such as metoprolol (Koch, unpublished data), respectively, but also to labetalol (Koch, 1978). Raised levels of circulating noradrenaline may be an important factor contributing to the increased vascular resistance regularly observed during acute and short-term beta-receptor blockade, particularly with non-selective antagonists, and to the failure of the vascular resistance to decrease significantly below pretreatment levels during long-term therapy. This implies that additional alpha-receptor blockade is a prerequisite for peripheral vascular resistance to be distinctly lowered and a definite advantage with respect to the interaction between structural changes and functional excitatory influences.

The comparison of intravenous and oral labetalol in this series shows that considerably higher oral doses are required to achieve a blood pressure reduction similar to that obtained with 50 mg intravenous labetalol. This is obviously mainly caused by a considerable first-pass metabolism that reduces bioavailability to about 40 per cent (Brogden *et al.*, 1978). This explains also the need for frequent dose readjustment in the initial stage of treatment if therapy is started with relatively low doses as was the case in this series (Koch, 1976c). However, the fairly high doses (2400 mg daily) that had to be used in some of these patients who had not satisfactorily responded to previous treatment with different antihypertensive regimens, were in all cases well tolerated. The complete lack of troublesome side-effects attributable to the drug after a 3-year continuous treatment in this series is noteworthy.

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