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CARDIOVASCULAR DYNAMICS AFTER ACUTE AND LONG-TERM α- AND β-ADRENOCEPTOR BLOCKADE AT REST, SUPINE AND STANDING, AND DURING EXERCISE

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1 After acute intravenous administration labetalol reduced mean values for BP, total peripheral resistance, heart rate and cardiac output. All changes were more pronounced during bicycle exercise.

2 After a mean duration of 20 months' treatment with oral labetalol the haemodynamic findings were broadly similar except for a more marked reduction in the total peripheral resistance and cardiac output had returned to pretreatment level due to an increased stroke volume which had counter balanced the reduction in heart rate. These changes occurred at rest, in the erect position and during exercise but the reductions in BP and peripheral resistance were most marked during exercise.

3 Left ventricular filling pressures and stroke volume/filling pressure ratios were not significantly altered after intravenous labetalol compared with pretreatment values.

4 Systolic BP × heart rate product was lowered particularly during exercise after both intravenous and oral labetalol.

5 After long-term oral labetalol, the most striking haemodynamic change was in the elevated resting stroke volume supine and standing.

Introduction

STUDIES in the experimental animal and in man have shown that hypertension rapidly induces structural changes in the precapillary resistance vessels consisting of a reduction of the internal vessel radius and an increase of the wall lumen ratio. These changes not only tend to increase vascular resistance during conditions of basal vasomoter tone but they also result in a hyperreactivity of these vessels with an exaggerated constrictor response to a given smooth muscle activation (Folkow, 1975). Recent studies have also suggested that these structural changes may be reversible in certain conditions, both in the experimental animal (Weiss, 1974) and in man (Silvertsson, 1977).

Constriction of the peripheral resistance vessels is predominantly mediated through α-adrenoceptors. Thus, α-adrenoceptor blockade would on theoretical grounds seem to be the most logical and efficient way to lower precapillary resistance and to counteract the vicious circle developing from the interaction of intravascular pressure increase and morphological changes.

Agents with α-adrenoceptor-blocking or other vasodilator properties, such as phentolamine, prazosin, hydrallazine and minoxidil, have been shown to reduce systemic vascular resistance and thereby BP in man. As labetalol combines α-adrenoceptor- with β-adrenoceptor-blocking properties it has the advantage over pure vasodilators of counteracting the baroreceptor reflex increase of heart rate and cardiac output elicited by the BP decrease. These unique pharmacological properties make labetalol seem to be a particularly attractive as an antihypertensive agent. In a series of haemodynamic studies it has been shown that labetalol, during both acute and long-term administration, produces effects which could be predicted from its pharmacological profile (Koch, 1977; Koch, 1979). This paper deals mainly with the effect of labetalol on circulatory dynamics with particular respect to conditions during erect posture and during exercise.

Methods

Thirteen patients (mean age 52 yr) in whom grade 1–2 essential hypertension was diagnosed, were studied, before and 30 min after intravenous administration of labetalol 50 mg, at rest both in the supine and upright positions and during ergometer bicycle steady-state exercise at two different loads corresponding to about 60 and 120 W. The latter load corresponded to an oxygen uptake of about 1.8 litres. Nine of these patients agreed to be re-examined in identical

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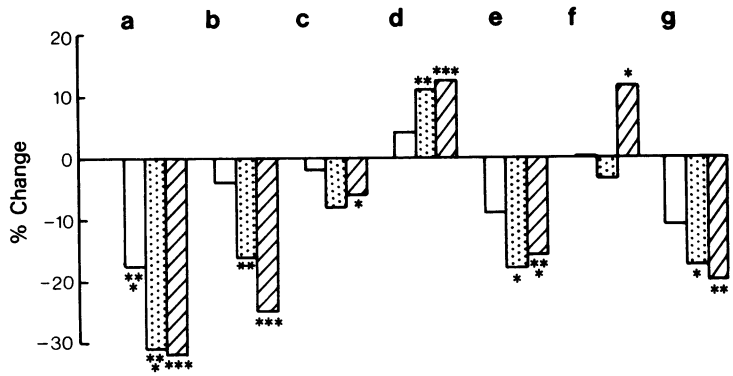

Figure 1 Percentage changes from pretreatment values of some haemodynamic variables after intravenous administration of labetalol 50 mg. *a*, Mean systemic BP; *b*, heart rate; *c*, oxygen uptake; *d*, arterio-mixed venous oxygen difference; *e*, cardiac output; *f*, stroke volume; *g*, total peripheral resistance. Asterisks denote level of statistical significance: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Open, Rest supine; stopped, rest upright; hatched, exercise 121 ± 27 W.

conditions after a nearly 2 yr treatment with oral labetalol in doses varying between 300 and 2400 mg daily.

Systemic and pulmonary arterial BPs were directly recorded through polyethylene catheters percutaneously introduced into the left brachial artery and the main pulmonary artery, respectively. The tip of the pulmonary artery catheter was placed into the main stem under fluoroscopy using a guide wire. Cardiac output was determined according to the Fick principle. Details of the procedure and of the analytical methods used and evidence of their reproductibility are reported elsewhere (Koch, 1977).

Table 1 Means and standard deviations (s.d.) of systemic arterial BPs and their mean ($\bar{D}$) and percentage ($\bar{D}$%) changes after intravenous administration of 50 mg labetalol, at rest in the supine (R) and upright (0) positions, and during exercise at two different work loads (W_1 = 60 W, W_2 = 120 W)

	Mean	*s.d.*	$\bar{D}$*	$\bar{D}$ %*
Brachial artery:				
Systolic BP				
R	174	32	−33	−19.0
O	179	35	−60	−33.5
W_1	202	34	−61	−30.2
W_2	241	34	−85	−35.3
Diastolic BP				
R	97	15	−14	−14.4
O	108	19	−35	−32.4
W_1	101	16	−24	−23.8
W_2	113	24	−36	−31.9
Mean BP				
R	126	18	−22	−17.5
O	136	23	−42	−30.9
W_1	143	20	−40	−28.0
W_2	163	28	−52	−31.9

*$P < 0.007$[1].

Results

Labetalol 50 mg intravenously resulted within 10 min in an average reduction in mean systemic BP of 22 mmHg in the supine position, and 42 and 52 mmHg in the erect position and during 120 W exercise, respectively (Table 1). The haemodynamic changes induced (Fig 1)—namely, reduction in heart rate and cardiac output with a parallel increase in arterio-mixed venous oxygen difference—are those usually observed with agents that solely block β-adrenoceptors. In addition, however, a decrease in peripheral vascular resistance was noted.

After a mean duration of 20 months of oral treatment the hypotensive effect was of a similar order but was now exclusively due to a reduction in peripheral vascular resistance, which tended to be still lower than after intravenous administration (Fig. 2). Cardiac output had returned to pretreatment levels due to an increase in stroke volume (Fig. 3) which completely counterbalanced the fall in heart rate.

Intrapulmonary pressures, including left ventricular filling pressures, showed slight but not significant changes, whereas pulmonary vascular resistance tended to be lower. Left ventricular performance characteristics in terms of stroke volume/filling pressure ratio was not significantly altered (Fig. 4), suggesting that labetalol lacks significant negative inotropic effects. Left ventricular load in terms of systolic BP × heart rate product was lowered, in particular, during exercise (Fig. 5), suggesting a significant reduction in myocardial oxygen demand.

The changes in the haemodynamic pattern induced by prolonged treatment with labetalol compared with acute administration of the drug are summarized in Fig. 6. The most important change is a considerable

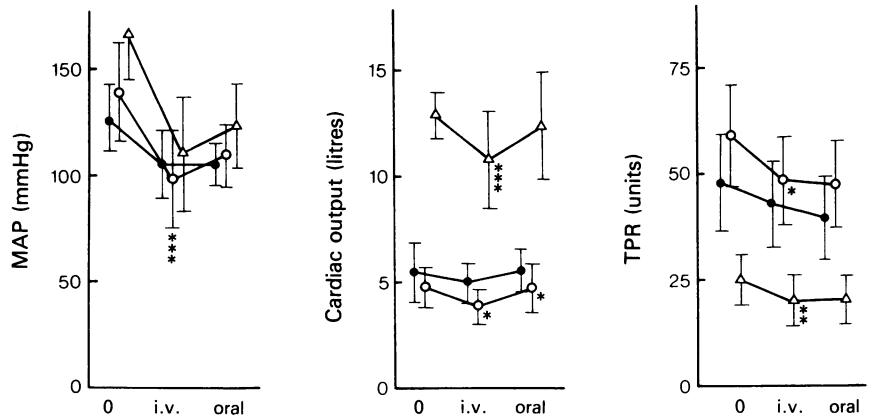

Figure 2 Means and standard deviations of mean systemic arterial BPs, cardiac output and total peripheral vascular resistance (TPR) in the supine (●) and upright (○) resting positions, and during exercise 121 ± 27 W (△) before (0) and after acute intravenous administration of labetalol 50 mg and after long-term oral treatment.

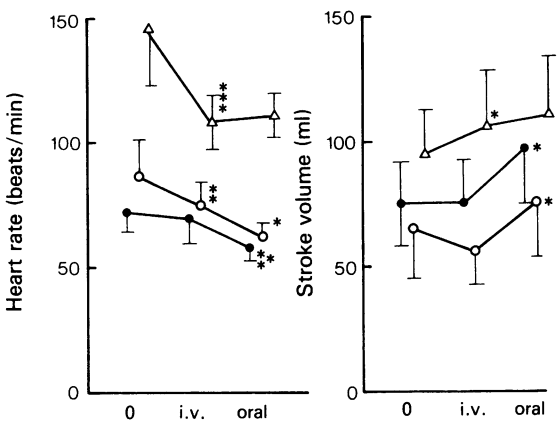

Figure 3 Means and standard deviations of heart rate and stroke volume before (0) and after acute intravenous and long-term oral treatment with labetalol. Symbols as in Figure 2.

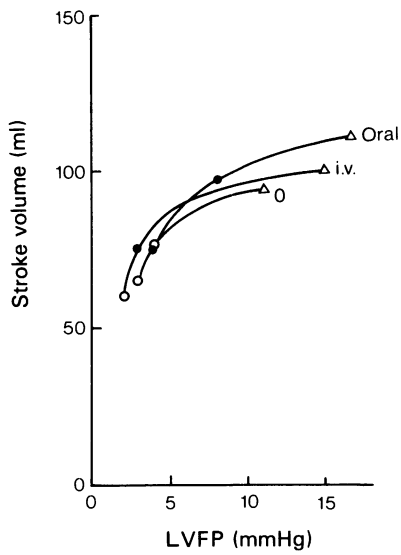

Figure 4 Relationship between stroke volume and left ventricular filling pressure (LVFP) before (0) and after intravenous and long-term oral treatment. Symbols as in Figure 2.

increase in stroke volume which actually over-compensates for the further decrease in resting heart rate thus leading to a higher cardiac output particularly in the erect posture. After long-term oral treatment, however, stroke volume is not only considerably increased in particular during resting conditions, but it is also considerably less reduced after change from the supine to the erect posture (Fig. 3).

Discussion

After acute intravenous administration of labetalol BP is reduced as is peripheral vascular resistance. This latter effect is presumably due to the α-adrenoceptor-blocking effect of labetalol which not only explains its acute antihypertensive effect but differentiates it from agents which only block β-adrenoceptors. The tendency of labetalol to modify stroke volume in the erect posture after acute intravenous administration may account for the symptoms associated with hypotension in some of the patients when changing from the supine to the

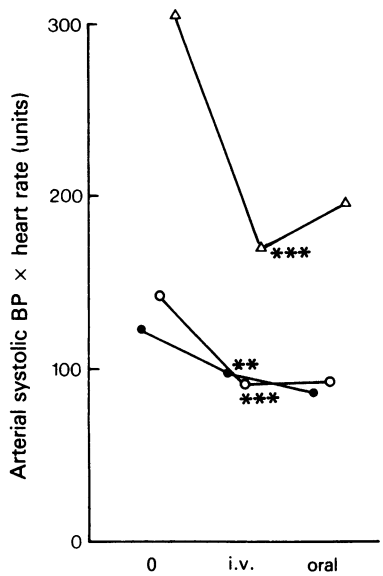

Figure 5 Arterial systolic BP × heart rate product before and after treatment with labetalol. Symbols as in Figure 2.

standing position. This suggests that labetalol's α-adrenoceptor-blocking effect is not confined to precapillary resistance vessels but may act also at the post capillary level, which in the erect position would allow a shift of blood volume from the intrathoracic to the extrathoracic compartment of the capacitance system.

Increased venous distensibility after acute intravenous administration of labetalol has already been described (Brod, 1979). These effects may therefore explain why acute intravenous administration of labetalol may lead to postural hypotension. However, the findings after long-term oral administration in the same patients were somewhat different. In particular, compensatory increases occurred in stroke volume and the observations suggest that the α-adrenoceptor-blocking effect of labetalol in the capacitance vessels is attenuated by long-term oral treatment. In addition, the more marked effect on resting heart rate suggests an increased dominance of the β-adrenoceptor-blocking effect of labetalol.

It is now known that after acute and chronic β-adrenoceptor blockade both at rest and during exercise, circulatory catecholamines levels tend to be increased. Increased levels of circulatory noradrenaline may be a factor contributing to the increased vascular resistance observed during acute and long-term β-adrenoceptor blockade in patients. In addition, this may explain why peripheral vascular resistance after long-term β-adrenoceptor blockade does not decrease significantly below pretreatment values. This, in relation to the findings after combined α- and β-adrenoceptor blockade with labetalol, may explain why α-adrenoceptor-blockade is an important determinant of reduced vascular resistance. In turn this may also be important in the development of structural damage associated with increased vascular resistance. In this regard, therefore, labetalol may offer advantages in the long-term treatment of hypertension compared with simple β-adrenoceptor-blocking drugs.

It is evident, therefore, that antihypertensive treatment should not only aim at lowering systemic BP at any price (though this is the primary and most important goal) but should attempt to reverse the pathophysiological changes induced by the disease process. That implies, of course, that in choosing an

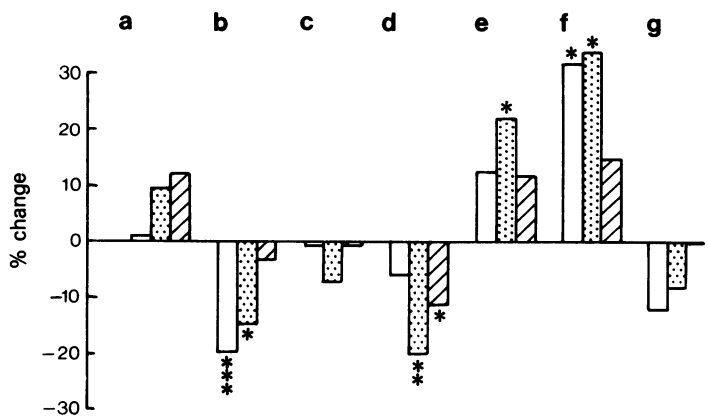

Figure 6 Percentage changes of some haemodynamic variables after 20 months' oral treatment compared with values measured after acute intravenous administration of labetalol. Abbreviations and symbols as in Figure 1.

antihypertensive agent factors such as stage and specific haemodynamic pattern of the disease and the pharmacological and haemodynamic profile of the drug should be taken into account. As early structural changes at the level of the resistance vessels is one of the most prominent and decisive features in hypertension, it seems that the principle of combined α- and β-adrenoceptor blockade is more logical and rational than β-adrenoceptor blockade alone, at least in most instances. In addition, the considerable reduction of myocardial oxygen demand after labetalol suggests that the drug might also have considerable potential in the management of patients with ischaemic heart disease in particular when associated with hypertension.

Finally, detailed blood and urine analysis including the determination of plasma volume and of the antinuclear factor did not reveal any change after 3 yr treatment. Over this time plasma renin activity was decreased (as expected) due to the β-adrenoceptor-blocking component. No significant ocular or funduscopic alterations attributable to labetalol occurred during a continuous 3-yr assessment period.

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