Response of the Systemic and Pulmonary Circulation to Alpha- and Beta-receptor Blockade (Labetalol) at Rest and During Exercise in Hypertensive Patients

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SUMMARY Labetalol (L), a drug with both α- and β-adrenoceptor blocking properties, was administered to 18 hypertensive patients for an average duration of 2.44 weeks, with an average final daily dose of 1.65 g. L decreased resting heart rate (HR) by 16% and maximal exercise HR by 21%; the phenylephrine-induced rise of brachial artery pressure (BAP) was reduced by 30–40%, and the rise of systemic vascular resistance (SVR) by 50%. L lowered BAP by 29/15 mm Hg in the recumbent position (RR), by 41/23 mm Hg at rest sitting (RS), and by 53/23 mm Hg at maximal exercise; SVR was not significantly affected at RR but was reduced at RS and at exercise; cardiac output (CO) decreased in all conditions. L reduced mean pulmonary artery and capillary wedge pressures only at RS. These hemodynamic observations suggest that the antihypertensive action of L is based mainly on its β-receptor blocking properties at RR, and on both its α- and β-receptor blocking effects sitting and at exercise. Finally pulmonary vascular resistance (PVR) was not influenced by L, and the phenylephrine-induced increase of PVR was unaffected; the pulmonary arterioles thus seem to react differently to L than the systemic arterioles.

ALPHA-ADRENERGIC receptor blocking agents lower blood pressure by inhibiting sympathetic vasoconstriction. However, these drugs have not been used frequently to treat hypertension, mainly because of postural hypotension; indeed, efferent adrenergic pathways operating through α-receptors play an important role in the cardiovascular adaptation to upright posture. Beta-adrenoceptor blocking agents are being used more frequently because of their effectiveness and relative freedom from side effects. Whereas α-adrenergic receptor blockers primarily decrease vascular resistance, β-blockers, regardless of their cardiospecific properties, lower cardiac output (CO) with, on average, unchanged systemic vascular resistance (SVR). Attempts to treat hypertensive patients with combined administration of an α- and a β-receptor blocking drug have had differing results. The results were encouraging in one study. In a second study, blood pressure decreased slightly when phentolamine was added to oxprenolol. In a third study, the combination resulted in severe side effects, including postural hypotension. However, research efforts have continued in this area and a drug with α-, β₁- and β₂-adrenoceptor blocking properties (labetalol, AH 5158) has been produced. The drug is six to 10 times less potent than phentolamine in blocking α receptors and one and one-half to three times less potent than propranolol in blocking β-adrenoceptors.

In this study we report the short-term hemodynamic effects of oral labetalol on the systemic and the pulmonary circulation in patients with hypertension, at rest and during exercise. In addition, its α-blocking properties were assessed by studying the inhibition of phenylephrine-induced rises in pressures and resistances in the systemic and pulmonary circulation, and its β-blocking properties by blockade of exercise tachycardia.

Patients and Methods

Eighteen patients, 10 males and eight females, with an average age of 43.7 ± 2.9 years (SEM) who weighed 72.3 ± 2.7 kg, were studied; 14 had essential and four renal hypertension (renal parenchymal disease in three and renovascular hypertension in one). Their casual recumbent blood pressure averaged 207 ± 7/123 ± 4 mm Hg. The severity of hypertension was assessed by the criteria of the World Health Organization. Ten had stage I, six stage II, and two stage III because of an eye fundus grade 3. Inclusion and exclusion criteria have been reported for similar studies; all patients were admitted to the hospital and had not taken antihypertensive drugs for at least 3 weeks.

Throughout the study patients received two tablets three times daily. During an initial period of 5–10 days each patient received placebo tablets, and then entered a single-blind study, where labetalol was given at weekly doubling doses until control of blood pressure (diastolic blood pressure ≤ 90 mm Hg) was obtained or maximal daily dose (2.4 g) reached; the starting dose was 0.3 g/day in five patients and 0.6 g in the others.

Hemodynamic measurements at rest while recumbent (RR), at rest while sitting (RS) and during exercise were performed at the end of the placebo period and during the final treatment step, always in the

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morning, in the laboratory where room temperature was 18–22°C and humidity 40–60%. The brachial artery was punctured (Vygon, 115.09) to measure intra-arterial pressure and to sample arterial blood. A venous catheter (Swan-Ganz, 93.110.5F) was introduced in the antecubital vein and positioned in the pulmonary artery to sample mixed venous blood. The venous catheter was positioned so that pulmonary capillary wedge pressure (PCWP) was measured when the balloon near its tip was inflated, and pulmonary artery pressure when the balloon was deflated. Pressures were registered on a recorder (Mingograph 81) using Eletma-Schönander EMT 34 pressure transducers. Uptake of oxygen (VO₂) was measured continuously by the open-circuit method; minute-volume and oxygen were determined by a pneumotachograph and a paramagnetic gas analyzer (Siregnost Siemens). CO was determined by the direct-oxygen Fick method. SVR was calculated from MAP, obtained by electrical damping, and CO, and pulmonary vascular resistance (PVR) from mean pulmonary artery (MPAP) and capillary wedge pressures (MPCWP) and CO. HR was recorded from the ECG. Stroke volume (SV) was calculated from CO and HR.

A first set of measurements was obtained during RR 30 minutes after the technical procedures. Then a phenylephrine infusion test was started in 13 of the 18 patients, whose systolic pressure was ≤ 200 mm Hg. The drug was infused intravenously at 50, 100 and 200 µg/min (4 minutes at each rate); the 200 µg/min infusion rate was not given in five patients because the increase of systolic arterial pressure had reached ≥ 50 mm Hg at the 100 µg/min level. After interruption of the drug infusion, 30 minutes were allowed for its effects to dissipate. All patients were seated on the bicycle and the RS measurements were obtained 10 minutes later. A graded, uninterrupted exercise test was then started at a work load of 20 W for 4 minutes and the load was increased by 30 W every 4 minutes until exhaustion; pressures and HR were recorded at every step, but CO was determined every other step and at the final work load.

A similar but noninvasive exercise test was also performed at the end of each treatment period for assessment of exercise tachycardia. With this exercise protocol there was no significant difference between VO₂ at the third and fourth minute at each work load, and VO₂ taken at the fourth minute increased in a linear fashion with advancing work load.

Statistical analysis was performed using regression analysis and the two-tailed t test for paired comparison. The dispersion of the data is mean ± SEM.

Results

The average duration of treatment with labetalol was 2.44 weeks (range 1–4 weeks) and the final daily dose of the drug averaged 1.65 g (0.3–2.4 g).

Assessment of the α-blocking Properties of Labetalol

The effects of the α-receptor agonist phenylephrine on systolic brachial artery pressure and HR during placebo and during labetalol treatment are shown in figure 1. On the final dose of the drug the increase of systolic arterial pressure was reduced by 30–40% at the various infusion rates of phenylephrine; there was no significant relationship between percent reduction of pressure and the final dose of the drug for the individual patients. HR dropped during phenylephrine, but the reduction was significantly less when the patients were on labetalol.

In six patients systemic and pulmonary hemodynamics were measured before the phenylephrine infusion and at the end of the 100 µg/min infusion rate. Table 1 shows that the phenylephrine-induced increase of MAP was reduced by 27% by labetalol and the rise of SVR by 52%; the significant increase of PVR in response to the α-agonist, however, was not affected by labetalol.

Assessment of the β-blocking Properties of Labetalol

The β-blocking properties of the drug were assessed by inhibition of exercise tachycardia. At exercise, maximal work load averaged 125 ± 11 W during placebo and was similar during labetalol (122 ± 10 W). Figure 2 shows the HR response at rest and during exercise on placebo and at the final labetalol dose;
resting HR was reduced by 16% and maximal HR by 21%.

Maximal exercise HR was also assessed at several dose levels of labetalol. At 0.3 g (n = 4) it was reduced by 11.2 ± 1.2%, at 0.6 g (n = 14) by 16.0 ± 2.1%, at 1.2 g (n = 13) by 21.8 ± 1.9% and at the highest dose level of 2.4 g (n = 9) by 24.7 ± 2.9% (p < 0.01 for all); the percent reduction of HR (y) was significantly related to the log of the daily dose of labetalol in g (x) (y = 19.5 + 15.3 log x; r = 0.99).

Effects of Labetalol on Systemic Hemodynamics

At the time of the introduction of the Swan-Ganz catheter, mean right atrial pressure averaged 1.53 ± 0.50 mm Hg on placebo and 1.70 ± 0.70 mm Hg on labetalol (p > 0.8); right ventricular end-diastolic pressure did not change between treatment periods (3.90 ± 0.64 vs 3.60 ± 0.81 mm Hg; p > 0.7).

At RR (30 minutes after catherization) labetalol reduced brachial artery pressure by 29/15 mm Hg, but in the sitting position the hyptensive effect increased to 41/23 mm Hg, without producing postural hypotension. The hyptensive effect of the drug was maintained during exercise, and during maximal exercise the difference in pressure between both treatment periods attained 53/23 mm Hg (fig. 3). One patient had postexertion hypotension despite continued pedaling against 20 W; his pressure dropped to 80/50 mm Hg.

CO was significantly reduced, by 8–13% in the various experimental conditions (fig. 4), while labetalol decreased SVR at RS and during exercise, but not significantly (p > 0.4) in the supine patient (fig. 5). SVR was not significantly affected at rest and at 50 W, but was higher at the maximal exercise level when it attained 99 ml/beat with a control value of 84 ml/beat (p < 0.01).

Effects of Labetalol on Pulmonary Hemodynamics

Labetalol reduced MPAP and MPCWP only in the sitting position at rest; these pressures were not significantly affected at RR and during exercise (fig. 6). Control values of PVR were 1.04 ± 0.13 at RR,
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**Figure 3.** Systolic and diastolic brachial artery pressures at rest recumbent (RR), at rest sitting (RS), during graded exercise (20–80 W), and at final work load (125 ± 11 W) before and during labetalol treatment. Values are mean ± SEM. Numbers in parentheses are the number of observations.

**Figure 4.** Cardiac output at rest recumbent (RR), at rest sitting (RS), at 50 W and at final work load (125 ± 11 W) before and during labetalol treatment. Values are mean ± SEM. Numbers in parentheses are the number of observations.

**Figure 5.** Systemic vascular resistance at rest recumbent (RR), at rest sitting (RS), at 50 W and at final work load (125 ± 11 W) before and during labetalol treatment. Values are mean ± SEM. Numbers in parentheses are number of observations.

1.48 ± 0.13 at RS (p < 0.005 when compared with RR), and 1.08 ± 0.07 mm Hg/l/min at maximal exercise. PVR was not different from control during labetalol (p > 0.1): PVR then averaged 0.97 ± 0.10 at RR, 1.79 ± 0.12 at RS, and 1.18 ± 0.07 mm Hg/l/min at maximal exercise.

**Discussion**

Labetalol has been shown to be a competitive adrenergic blocking agent at both α- and β-receptor sites. In the present study both the α- and β-receptor blocking properties of labetalol were observed during short-term treatment of hypertensive patients. On the average final daily dose of 1.65 g, the increase of systolic brachial artery pressure by intravenous phenylephrine was antagonized by 30–40% (fig. 1), consistent with other observations in hypertensive patients, while the reduction of the rise in SVR attained 52% (table 1). This dose of the drug reduced maximal exercise HR by 21% (fig. 2). The reduction was dose-dependent and amounted to 25% in the nine patients in whom the daily dose could be increased to 2.4 g. This is less than the 35% reduction
observed with high doses of other \( \beta \)-adrenoceptor blocking agents such as propranolol, atenolol and metoprolol in similar experimental conditions.\(^{19, 20} \)

The apparent lower potency of labetalol in blocking exercise tachycardia in hypertensive patients is in agreement with the pharmacological observations in animals.\(^{14} \) However, the lower SVR during labetalol at exercise (fig. 5) may have provoked some baroreceptor reflex-induced increase in HR, thus limiting the reduction of exercise tachycardia. Therefore, blockade of exercise tachycardia is possibly not a reliable indicator for the \( \beta \)-blocking potency of an agent with combined \( \alpha \)- and \( \beta \)-blocking properties.

Labetalol effectively decreased systemic arterial pressure. At RR the drop in brachial artery pressure averaged 29/15 mm Hg and was characterized by a fall in CO without significant change in SVR (figs. 3–5). This hemodynamic pattern is similar to the one observed with only \( \beta \)-blocking drugs regardless of their cardioselectivity.\(^{3–9} \) In contrast to the observations with \( \beta \)-blockers\(^{21} \) labetalol became more effective at RS, and in addition to the fall in CO the decrease of SVR was significant. These observations are compatible with the fact that \( \alpha \)-receptor mediated vasoconstriction provides an important mechanism for the maintenance of blood pressure in the upright position, while sympathetic tone is low in the RR position. Assuming that \( \beta \)-receptor blockade primarily reduces CO and \( \alpha \)-receptor blockade decreases SVR, these results suggest that the antihypertensive effect of labetalol is based mainly on its \( \beta \)-receptor blocking properties at RR, and on both its \( \alpha \)- and \( \beta \)-receptor blocking effects in the sitting position. None of the patients experienced side effects in the sitting position, which confirms the favorable experience of several studies, with, on average, a 7% incidence of subjective complaints of postural hypotension.\(^{22} \)

The observations on PCWP are compatible with the interpretation that \( \alpha \)-blockade was mainly effective in the seated position. Indeed, the normally observed drop of wedge pressure on assumption of the sitting position, ascribed to pooling of blood in the lower part of the circulation, was accentuated by labetalol (fig. 6), suggesting effective blockade of the arteriolar and/or venous \( \alpha \)-receptors in this condition producing vasodilatation and decreased filling of the circulation. In the supine patient, however, mean right atrial pressure, right ventricular end-diastolic pressure and PCWP were unaltered by the drug, which is compatible with the interpretation that \( \alpha \)-receptor blockade was not operative in this position. Also, during short-term treatment with the \( \beta \)-blocker atenolol these pressures remained unchanged in the supine patient.\(^{3} \)

Although the whole hemodynamic picture of our observations suggests that the \( \beta \)-blocking part of labetalol was predominantly responsible for its hypotensive effect in the recumbent hypertensive patient, two other studies report an unchanged CO during short-term treatment with labetalol in the supine position\(^{18, 23} \) with either a significant decrease\(^{18} \) or no significant change\(^{23} \) of SVR; in these studies the drop in supine HR was 16–17%, which is exactly what we observed in the supine patient. Pulmonary hemodynamics were not studied. There is no final explanation for these discrepancies, but hemodynamics were performed on only six\(^{18} \) and eight\(^{23} \) patients. Dose and duration of treatment were comparable. In one study\(^{18} \) most of the patients had labile hypertension and it is possible that resting sympathetic tone is increased in such patients;\(^{24} \) however, it is still difficult to explain how \( \alpha \)- and \( \beta \)-blockade leave CO unchanged and HR and SVR decreased in labile hypertension. Our data should not be compared with acute studies in the supine position because labetalol does not change HR in this condition.\(^{25, 26} \) In the upright position acute and chronic studies consistently show decreases in HR and SVR, while CO either decreased\(^{25} \) or did not change.\(^{19} \)

The hypotensive effect of labetalol was maintained during exercise (fig. 3). Brachial artery pressure was reduced by 53/23 mm Hg at maximal exercise, due to reduction of both CO and of SVR (figs. 4 and 5), in agreement with other reports.\(^{23, 26} \) In contrast, \( \beta \)-blockers only reduce CO in similar experimental conditions.\(^{4, 8, 21} \) Therefore, \( \alpha \)-blockade probably contributed to the hypotensive effect of labetalol during exercise. This also seems to indicate that \( \alpha \)-receptor-mediated vasoconstriction opposes the powerful arteriolar dilatation that occurs in active muscles as a consequence of local metabolic processes during exercise and/or contributes to the vasoconstriction in the nonworking vascular beds.\(^{27} \)

Finally, the effects of labetalol on the pulmonary circulation deserve some comment. At the infusion rate of 100 \( \mu \)g/min the \( \alpha \)-receptor agonist pheno-
Phenylephrine increased both the SVR and the PVR by 30% (table 1), indicating that both the pulmonary and the systemic arterioles are sensitive to exogenous α-stimulation, provided that phenylephrine is a pure α-receptor agonist. On assumption of the sitting position, arteriolar resistances increased by 40% on both sides of the circulation, and it is likely that these increases are mediated by endogenous α-receptor stimulation. However, while labetalol reduced both the phenylephrine-induced (table 1) and the postural (fig. 5) increases of SVR, the rise of PVR that occurred in these experimental conditions was not affected by labetalol; also, PVR at exercise was not affected by labetalol. The pulmonary arterioles thus seem to react differently than the systemic arterioles to labetalol.

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