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Effect of labetalol on limb haemodynamics in patients following coronary artery bypass graft surgery

J. L. HALPERIN[1], B. P. MINDICH[2], ELIZABETH B. ROTHLAUF[1], R. F. REDER*, R. S. LITWAK[2] & J. KUPERSMITH[3]

[1]The Cardiothoracic Center, Mount Sinai Medical Center, the Divisions of Cardiology, [2]Cardiothoracic Surgery and Clinical Pharmacology, [3]Mount Sinai School of Medicine of the City University of New York, NY 10029, USA

Labetalol is a competitive inhibitor of α- and β-adrenergic receptors and has an antihypertensive action. To determine limb haemodynamic effects, we measured calf blood flow and venous capacitance by venous occlusion plethysmography before and after oral labetalol in 10 patients 3–7 days following coronary bypass surgery. Vascular resistance was calculated as the ratio of mean arterial pressure to arterial flow. The peak effect of labetalol was taken as the point of maximum blood pressure decline, and this interval was selected for evaluation of the limb haemodynamic response. Ninety to 120 min after administration of 100–200 mg of labetalol the mean blood pressure fell from 88 ± 3 to 79 ± 3 mm Hg; ($P < 0.005$). The mean arterial blood flow registered 5.1 ± 1.0 ml 100 ml^{-1} limb tissue min^{-1} which was not significantly different from the control value of 4.4 ± 0.8 ml 100 ml^{-1} limb tissue min^{-1}. The calculated index of limb vascular resistance was not affected by labetalol administration, averaging 37 ± 12 mm Hg 100^{-1} ml limb tissue min^{-1} before labetalol and 30 ± 11 mm Hg ml^{-1} 100 ml limb tissue min^{-1} at the time of peak hypotensive effect. There was a slight but statistically significant increment in limb venous volume to 1.9 ± 0.3 from 1.5 ± 0.3 ml 100 ml^{-1} limb tissue ($P < 0.025$). Placebo administration produced no consistent changes in blood pressure, arterial blood flow, vascular resistance or venous capacitance. The hypotensive action of labetalol involved no arteriolar vasoconstriction in the limbs of these patients, and mild venodilatation developed. The findings may be explained by balanced α- and β-adrenoceptor inhibitory effects on skeletal muscle arterioles and peripheral venous pooling. Unlike pure β-adrenoceptor antagonists, labetalol does not decrease perfusion of resting skeletal muscle in patients recovering from coronary surgery.

Keywords limb veins labetalol coronary bypass surgery

Introduction

Labetalol is an antihypertensive drug combining both α- and β-adrenoceptor blocking effects in a single molecule (Frishman & Halprin, 1979; Wollin & O'Neill, 1983; Michelson & Frishman, 1983). The drug has been shown regularly to decrease systemic arterial pressure in supine and upright subjects, both at rest and during exercise. It causes mild depression of cardiac output and the calculated systemic vascular resistance tends to remain unchanged or to fall slightly. Effects

*Present affiliation: Knoll Pharmaceuticals, Inc., Whippany, New Jersey, USA

Correspondence: Dr J. L. Halperin, Division of Cardiology, Mount Sinai Medical Center, Fifth Avenue at 100th Street, New York, NY 10029, USA

upon peripheral haemodynamics have been measured mainly in the exercising forearms of hypertensive patients where no changes in arterial blood flow have been identified (Hartling *et al.*, 1980a,b). Though the forearm is a highly reactive vascular bed, it frequently responds differently to pharmacological stimuli than the calf musculature, in which patients with atherosclerotic cardiovascular disease are more likely to develop ischaemic symptoms such as intermittent claudication. α-Adrenoceptor antagonist drugs produce more forearm than calf vasodilatation (Ahlquist, 1965). β-Adrenoceptor inhibitors constrict calf arterioles at rest but this action is attenuated during dynamic exercise (Smith & Warren, 1982a). The effects of combined α- and β-adrenoceptor blockade with labetalol on lower extremity haemodynamics in patients with atherosclerotic cardiovascular disease are therefore difficult to predict.

To examine the regional haemodynamic actions of oral labetalol on calf arteries and veins we performed plethysmographic studies in a group of patients recovering from coronary artery bypass surgery. Although these patients clearly had atherosclerosis there was no *clinical* evidence of obstructive arterial disease in the extremities so vascular effects of the drug at rest could be observed without confounding ischaemic factors.

Methods

Ten patients with atherosclerotic coronary artery disease were studied on the third to seventh day following uncomplicated myocardial revascularization surgery involving autologous saphenous vein grafts. Eight patients were male and two were female; ages ranged from 51 to 68 years (mean 58 ± 2 years). In all cases, vasodilator and β-adrenoceptor inhibitor antianginal medications were withdrawn at the time of surgery, though all patients were maintained on oral digoxin in the postoperative period. All medications were withheld for a period of 10 h before study. Written informed consent was obtained from each subject in accord with a protocol approved by the institutional review board governing research involving human subjects.

Four patients reported hypertension prior to the surgical procedure but all were normotensive at rest at the time of haemodynamic evaluation. All patients were free of intermittent claudication and showed no clinical signs of obstructive arterial disease in the extremities. Systolic blood pressures at the ankles were determined in all cases by Doppler sphygmomanometry and were normal both at rest and following leg exercise. None had evidence of congestive heart failure. The limb selected for study was contralateral to the one used for saphenous vein harvesting. Oedema was absent in the studied limb in all cases. We performed venous occlusion plethysmography with a Parks Electronics Laboratories model 291 plethysmograph in conjunction with Whitney mercury/Silastic strain gauges stretched 10% beyond their relaxed lengths. Each patient was positioned with the leg bearing the plethysmographic apparatus elevated above the level of the heart. A sphygmomanometric cuff was placed around the ankle and inflated to at least 50 mm Hg above systolic blood pressure during measurement of limb haemodynamics to exclude the foot vasculature. We produced venous occlusion by sudden inflation of a 20 cm cuff placed about the thigh. The lowest venous occlusion pressure sufficient to elicit a maximum rate of circumferential calf enlargement was determined at the outset for each patient and averaged 53 ± 2 mm Hg. Limb arterial blood flow was derived from the rate of increase in calf circumference during venous occlusion and was expressed in ml 100 ml^{-1} of limb tissue min^{-1}. Limb vascular resistance was calculated as the ratio of mean arterial pressure to blood flow and expressed in resistance units (mm Hg ml^{-1} 100 ml^{-1} limb tissue min^{-1}). We measured limb venous capacitance during inflation of the thigh cuff to 30 mm Hg above the effective venous filling pressure (which averaged 9 ± 2 mm Hg). Pressure was maintained at this level until graphic evidence of equilibration was achieved. The resultant value was expressed in ml 100 ml^{-1} of limb tissue. Blood pressure was measured by sphygmomanometry over the brachial artery.

After a suitable baseline period for equilibration which lasted 30–60 min in each case, patients ingested a placebo tablet, identical in appearance to labetalol, and measurements of blood pressure, arterial blood flow and venous capacitance were made at 15 min and 45 min after administration. Labetalol, 100–200 mg was then administered orally (see Table 1) and plethysmographic measurements repeated at 15, 45, 75, 105, 135, 165, 195 and 225 min thereafter.

Results were evaluated by means of the paired Student's *t*-test with comparison to control and placebo values. The peak effect of labetalol was taken as the point of maximum blood pressure decline, and this interval was selected for evaluation of the limb haemodynamic response. Data are expressed as the mean ± s.e. mean for the 10 subjects. Statistical significance was accepted at the 95% confidence level.

Table 1 Limb haemodynamic responses to labetalol

Patient	*Labetalol*		*Mean arterial pressure (mmHg)*	*Blood flow (ml 100 ml^{-1} min^{-1})*	*Vascular resistance (mmHg ml^{-1} 100 ml^{-1} (limb tissue min^{-1})*	*Venous capacitance (ml 100 ml^{-1})*
	Before		73	4.5	17	1.7
1	After	200 mg	72	5.4	14	1.9
	Before		83	9.3	9	2.4
2	After	100 mg	82	2.5	33	2.9
	Before		96	0.9	113	1.9
3	After	100 mg	87	2.2	40	1.7
	Before		83	6.5	13	3.1
4	After	100 mg	69	4.7	15	3.7
	Before		103	5.7	18	1.2
5	After	200 mg	81	11.7	7	1.5
	Before		94	2.8	34	0.9
6	After	200 mg	85	3.2	26	1.6
	Before		83	4.3	19	1.6
7	After	200 mg	70	5.9	12	1.9
	Before		87	6.3	14	1.6
8	After	200 mg	81	4.2	19	1.2
	Before		75	3.0	27	0.4
9	After	200 mg	66	10.4	6	1.6
	Before		101	0.9	109	0.3
10	After	200 mg	94	0.7	126	0.6
Mean	Before		88 ± 3	4.4 ± 0.8	37 ± 12	1.5 ± 0.3
± s.e. mean	After		79 ± 3	5.1 ± 1.0	30 ± 11	1.9 ± 0.3
P			< 0.005	NS	NS	< 0.025

Results

Resting mean blood pressure ranged from 73 to 103 mm Hg and averaged 88 ± 3 mm Hg in the 10 subjects. Calf arterial blood flow ranged from 0.9 to 9.3 ml 100 ml^{-1} limb tissue min^{-1} and averaged 4.4 ± 0.8 ml 100 ml^{-1} limb tissue min^{-1}. These results are within the range obtained in most normal subjects in our laboratory (2.5–5.0 ml 100 ml^{-1} limb tissue min^{-1}). As a result, the calculated index of limb vascular resistance ranged from 9 to 113 (average 37 ± 12) mm Hg ml^{-1} 100 ml^{-1} limb tissue min^{-1}. Limb venous capacitance was lower than the normal range of 2.0–4.0 ml 100 ml^{-1} limb tissue), averaging 1.5 ± 0.3 ml 100 ml^{-1} limb tissue (range 0.3–3.1 ml 100 ml^{-1} limb tissue).

Placebo administration produced no consistent changes in blood pressure, arterial blood flow, vascular resistance or venous capacitance. Labetalol resulted in a sustained decline in blood pressure in the 10 patients ($P < 0.005$; Figure 1) but no symptomatic side effects were observed while the patients were kept supine and at rest. Pressure fell an average of 9 ± 3 mm Hg. This 10% decline in blood pressure is roughly half as great as the fall generally reported in upright hypertensive patients treated with oral labetalol

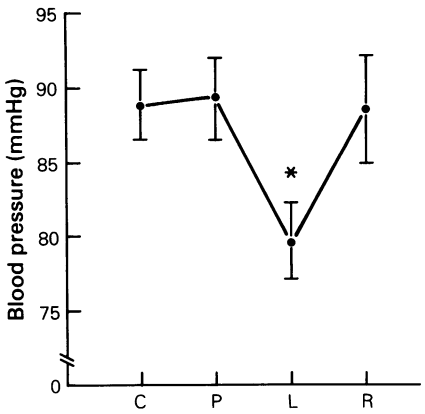

Figure 1 Mean blood pressure in 10 patients at baseline (C), after placebo administration (P), at the time of peak hypotensive effect after labetalol (L) and 4–5 h after dosing (R). Results are shown as the mean ± s.e. mean. *$P < 0.005$.

(Brogden *et al.*, 1978). Results in individual subjects are provided in Table 1. At the point of greatest blood pressure fall, mean arterial blood flow in the calf registered 5.1 ± 1.0 ml 100 ml^{-1} limb tissue min^{-1} (range 0.7–11.7 ml 100 ml^{-1} limb tissue min^{-1}). As depicted in Figure 2, this

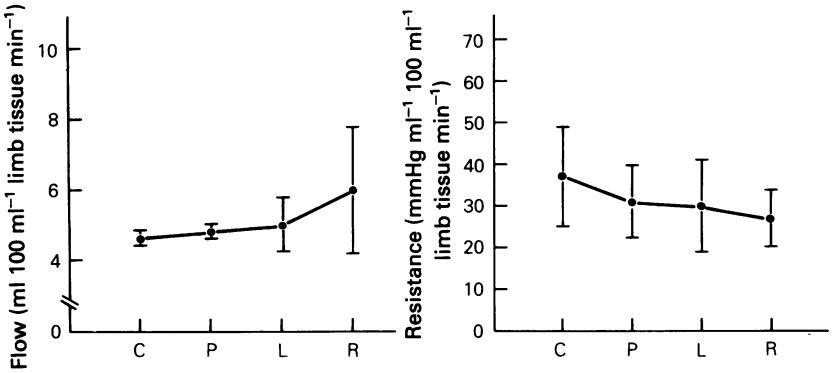

Figure 2 Calf arterial blood flow and calf vascular resistance in 10 patients before intervention, after placebo administration, at the time of peak hypotensive effect, after labetalol and during recovery (mean ± s.e. mean). Abbreviations as in Figure 1.

was not significantly different from the control or placebo values. Despite opposing directional changes in pressure and flow, the calculated index of limb vascular resistance was not significantly lower after labetalol administration, averaging 30 ± 11 mm Hg ml^{-1} 100 ml^{-1} limb tissue min^{-1} at the time of peak hypotensive effect. In contrast, as shown in Figure 3, there was a slight but statistically significant increment in limb venous volume to 1.9 ± 0.3 ml 100 ml^{-1} limb tissue (range 0.6–3.7 ml 100 ml^{-1} limb tissue; $P < 0.025$). Within 4–5 h after drug administration, blood pressure and venous volume were restored to pretreatment levels.

Discussion

Labetalol has previously been shown to act as a competitive antagonist of both α- and β-adrenergic receptors (Frishman *et al.*, 1984; Farmer *et al.*, 1972). Responses to adrenoceptor-mediated sympathetic nerve stimulation are inhibited by labetalol as effectively as it blocks the exogenously administered catecholamines, phenylephrine and isoprenaline (Frishman *et al.*, 1984; Brittain & Levy, 1976). Like prazosin, labetalol appears to inhibit selectively α_1- (postsynaptic, vascular) adrenoceptors rather than α_2- (presynaptic) adrenoceptors, responsible for negative feedback control of neurotransmitter release (Levy & Richards, 1980; Hoffman & Lefkowitz, 1980). Though labetalol is a more potent inhibitor of β- than α-adrenergic receptors (Mehta & Cohen, 1977), the drug possesses partial β_2-adrenoceptor agonist properties and also displays direct vasodilator effects (Baum & Sybertz, 1983; Dage & Hsieh, 1980).

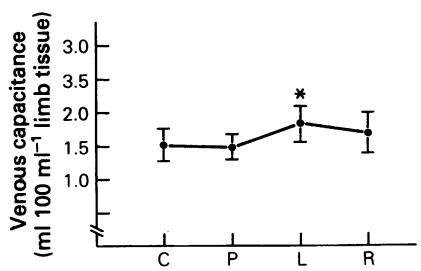

Figure 3 Effects of placebo and labetalol on calf venous capacitance in the 10 patients (mean ± s.e. mean). Abbreviations as in Figure 1. *$P < 0.025$.

Propranolol, by blocking both β_1- and β_2-adrenoceptors, lowers heart rate, blood pressure and cardiac output and exerts a constrictor effect upon peripheral arterioles and veins (Ahlquist, 1965; Smith & Warren, 1982a,b). Vasoconstriction is thought to be the basis for coldness of the extremities and occurrence of Raynaud's phenomenon which has been encountered during therapy with propranolol and several other β-adrenoceptor antagonists. Limb venoconstriction produced by noradrenaline is potentiated by propranolol (O'Grady *et al.*, 1978). This potentiation is blocked by oxprenolol, which possesses partial intrinsic sympathomimetic activity. Direct venodilator activity has not been shown for any β-adrenoceptor antagonist compound.

Although peripheral vasoconstriction is common shortly after heart surgery, (Fouad *et al.*, 1978; Wallach *et al.*, 1980; Estafanous & Tarazi, 1980), the pretreatment values for calf blood flow in our patients examined 3–7 days postoperatively were within the normal range. The fact that the fall in calf vascular resistance in our patients did not reach statistical significance

differs from results in resting forearms or total systemic circuits (Frishman *et al.*, 1984). The finding of no statistically significant arteriolar vasodilatation or vasoconstriction in calf musculature after oral labetalol might reflect a balance between opposing α- and β-adrenoceptor antagonistic effects, though a trend toward vasodilatation was evident. It is clear, nevertheless, that the blood pressure lowering effect of this drug at rest in patients recovering from coronary artery bypass graft surgery must depend partly on mechanisms unrelated to lower limb arterial vessels. In contrast, the pretreatment venous capacitance in these patients was below normal. After labetalol administration, a mild venodilator response was evident, amounting to a net 28% increase in limb venous capacitance. It seems feasible, therefore, that the hypotensive action of labetalol may depend partly upon peripheral venodilatation resulting in reduced systemic venous return and lower ventricular preload. Since the mechanism of baseline venoconstriction in these subjects was not determined, however, it cannot be confirmed that α-adrenergic receptor inhibition by labetalol was responsible for the venodilatation which developed.

Since the saphenous veins of the contralateral leg were excised and employed for aorto-coronary bypass, it is intriguing to speculate that labetalol-induced venodilatation might favourably affect graft diameter and flow. It is noteworthy, moreover, that in other studies of labetalol, vasodilator activity becomes augmented after vessel denervation (Baum & Sybertz, 1983; Gagnon *et al.*, 1982), and coronary sinus blood flow increases in patients with coronary artery disease after intravenous administration (Gagnon *et al.*, 1982). It is not realistic, however, to extrapolate our results in the intact limb to denervated venous segments recruited to provide myocardial perfusion without direct measurement of coronary haemodynamics. It is clear, nevertheless, that a lack of calf arteriolar constriction and slight but significant venodilatation distinguish labetalol from β-adrenoceptor blocking drugs like propranolol, and suggest that symptoms referable to impaired limb circulation would not complicate therapy with labetalol in the early period after coronary artery bypass graft surgery.

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