EFFECTS OF COMBINED α - AND β -BLOCKADE BY LABETALOL IN PATIENTS WITH CORONARY ARTERY DISEASE

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- 1 The effect of labetalol 100 mg orally twice daily on exercise tolerance has been compared with placebo in 19 normotensive subjects with angiographic evidence of coronary artery disease.
- 2 Labetalol, at the same work load as during placebo exercise, significantly reduced systolic and diastolic blood pressures, as well as heart rate and rate-pressure product.
- 3 Similarly, ST segment depression was reduced by labetalol from 2.0 ± 0.4 to 1.36 ± 0.6 mm ($P < 0.001$), thus enabling an increase in exercise tolerance from a control value of 83.7 ± 18 to 95.3 ± 19 W ($P < 0.005$).
- 4 In seven other patients, also with coronary artery disease, the haemodynamic effects of a single 0.6 mg/kg intravenous dose of the drug was evaluated during exercise.
- 5 Compared with conditions during control exercise, labetalol induced a significant reduction in rate-pressure product from 17228 ± 2375 to 13445 ± 2404 mmHg/min ($P < 0.005$) and in peripheral vascular resistance from 612.0 ± 61.2 to 512.7 ± 36.2 dyn cm⁻⁵ m⁻² ($P < 0.0025$). These events were not accompanied by any change in cardiac index and in dP/dT left ventricular end-diastolic pressure (LVEDP) ratio.
- 6 These data suggest that labetalol may induce reduction in myocardial oxygen consumption, thereby increasing exercise tolerance in patients with coronary artery disease, without impairment of left ventricular performance.

Introduction

It has been suggested that a potentially beneficial combination may be obtained from the simultaneous use of two agents which exert their effects by two different pharmacological mechanisms. As an example a combination of α and β -adrenoceptor blockade could represent an interesting approach to the treatment of coronary artery disease. A decrease in heart rate and myocardial contractility mediated by way of β -adrenoceptor blockade and a decrease in ventricular afterload obtained by way of α -adrenoceptor blockade, both result in a reduction in myocardial oxygen consumption, the most important goal in the medical treatment of ischaemic heart disease.

Labetalol is the only drug having the characteristic of blocking both α - and β -adrenoceptors (Collier, 1972; Farmer, 1972). In animal and human studies this drug has been found to decrease systemic vascular resistance and, thus, arterial blood pressure, only moderately slowing down heart rate (Brittain & Levy, 1976; Richards, 1976; Koch, 1977; Mehta & Cohn, 1977). Labetalol has been

successfully used in the treatment of hypertension (Mehta & Cohn, 1977; Frick & Porsti, 1976; Prichard & Boakes, 1976); however, for the reasons mentioned above, it is conceivable that this drug could be beneficial also in coronary artery disease, independent of its anti-hypertensive action.

Accordingly, this study was designed to investigate by non-invasive methods the effects of oral therapy with labetalol on exercise tolerance in normotensive patients with coronary artery disease; and to evaluate the haemodynamic effects of a single intravenous dose of the drug during exercise.

Methods

Patients

The entire study population consists of 28 normotensive patients (22 male, 6 female; age range 36-67 yr). All patients presented arteriographic evidence of coronary artery disease; none of them was

affected by unstable or severe angina. Written consent was obtained from each patient after the nature and the goals of the study had been fully explained.

Criteria for inclusion in the protocol were: (a) presence of ST segment depression >1.5 mm, 80 ms after the J point, during exercise stress test; (b) arteriographic evidence of greater than 50% obstruction of the lumen of at least two major coronary vessels; (c) systolic blood pressure <150 mmHg and diastolic blood pressure <95 mmHg; (d) no evidence of valvular heart disease, congestive heart failure or previous myocardial infarction; (e) absence of severe bradycardia or conduction disturbances; (f) no history of taking digitalis for at least 2 months before the study.

Non-invasive study protocol

Twenty-one hospitalized patients fitting these criteria were selected for the study. Clinical details of each patient are shown in Table 1. The protocol of the study was as follows. After a wash-out period of 2 weeks during which any pharmacological treatment was discontinued, a bicycle exercise stress test was performed, and placebo twice daily was then administered for 1 week followed by a further week of labetalol therapy (100 mg twice daily). At the end of the placebo and labetalol treatment periods, bicycle ergometer stress tests were performed in the morning, in a quiet room at constant temperature 21°C. Tests were performed approximately 2 h after the last administration of placebo or labetalol. During the 12 h before the exercise tests, the patients were not allowed to consume any alcohol, tea, coffee or tobacco. The exercise test was performed in the sitting position on a bicycle ergometer. Radiotelemetry with the electrodes in CM lead position was used to record the electrocardiogram at rest and continuously during exercise. The initial work load of 50 W was gradually increased by 20 W every 2 min and the endpoint was established by the usual criteria. Heart rate and ST segment depression were recorded every 2 min as well as arterial blood pressure, measured using a cuff sphygmomanometer. The heart rate-systolic blood pressure product was calculated.

Haemodynamic study protocol

Studies were carried out in seven patients with history and electrocardiographic evidence of coronary artery disease, undergoing routine diagnostic cardiac catheterization and coronary arteriography. Clinical, haemodynamic and angiographic details of these patients are reported in Table 2.

All medications were withdrawn 2 d before the

procedure. Under local anaesthesia right heart catheterization was performed by way of a medial antecubital vein, and left heart catheterization, ventriculography and coronary arteriography were performed by way of the brachial artery. The protocol of the study was as follows. Observations were made under control conditions, followed by a supine exercise test at 70 W for 5 min on a bicycle ergometer. During the last minute of exercise, while the patient was still pedalling, haemodynamic indices were measured.

Approximately 20 min later, when the heart rate and arterial blood pressure returned to control levels, haemodynamic measurements at rest were obtained. Labetalol 0.6 mg/kg was administered intravenously and 5 min later, haemodynamics were re-assessed and the exercise test was repeated as before. At the end of the investigation, diagnostic selective coronary arteriography and left ventriculography were performed.

Haemodynamic measurements

Aortic and left ventricular end-diastolic pressure (LVEDP) were measured using a fluid-filled manometer and Statham P23Db pressure transducers, and recorded on an OTE Biomedica pre-amplifier. Systolic and diastolic blood pressures were calculated by averaging individual systolic and diastolic points for at least five heart beats. The mean pressure in the aorta was derived electronically. Cardiac output was determined by the thermodilution technique using a Swan-Ganz Edwards catheter for thermodilution placed into the main pulmonary artery, and a Cardiac Output Computer 9500 Edwards. The Lehman catheter placed into the aorta for pressure measurements was introduced in the left ventricle at various stages of the investigation to measure LVEDP and first derivative of left ventricular pressure (dP/dT max). This latter index was recorded through a modular pre-amplifier for differential operations. Heart rate was derived from the electrocardiogram (Lead II) continuously monitored during the study. From the haemodynamic data, systemic vascular resistance was calculated according to the formula:

$$\frac{(\text{MAP} - \text{right arterial pressure})}{\text{CO}} \times 80$$

where MAP indicates mean arterial pressure and CO cardiac output. Cardiac output, stroke volume and vascular resistance have been expressed as an index by dividing these values per body surface area.

Table 1 Clinical and angiographic data

Patient number	Age (yr)	Sex	Arterial pressure		Heart rate (beats/min)	Coronary artery obstruction (%)		Left ventricular asynergy
			Systolic (mmHg)	Diastolic (mmHg)		LAD system	Circumflex system	
1	49	M	150	80	50	80	-	-
2	53	F	120	80	68	90	-	-
3	39	M	150	90	62	90	70	+
4	48	M	140	80	62	60	-	-
5	61	M	140	90	62	-	70	-
6	59	F	150	80	68	30	90	-
7	63	F	140	90	88	-	90	-
8	67	M	150	95	75	60	95	-
9	53	M	145	90	100	90	-	+
10	48	F	145	95	78	75	60	-
11	51	M	150	90	60	90	-	+
12	36	M	150	90	70	-	90	-
13	43	M	150	90	75	75	75	-
14	56	F	140	90	88	95	-	+
15	67	M	150	85	80	70	-	-
16	59	M	150	90	65	80	-	-
17	62	M	140	90	80	-	70	-
18	58	M	140	90	75	75	75	-
19	56	F	130	80	84	-	80	-
20	62	M	130	70	78	90	75	+
21	64	M	130	80	78	75	80	-

Statistical analysis

All values are expressed as mean $\pm$ s.d. Statistical analysis have been performed using Student's *t* test for paired samples.

Results

Non-invasive study

Two out of 21 patients included in this study did not complete the trial, one because of the appearance of a cutaneous rash, the other for urinary retention developed within 48 h of starting labetalol treatment, which promptly recovered on cessation of the drug. In the remaining 19 patients, labetalol induced at rest a significant reduction in heart rate and heart rate-systolic blood pressure product, whereas systolic and diastolic blood pressures did not differ from values obtained at the end of the placebo period (Table 3). All patients performed three exercise stress tests, one at the end of the washout period, the other after the placebo period, the third 1 week following labetalol treatment. To evaluate the effects of the drug on exercise tolerance, we compared data obtained at the same work load. Results of the washout and of the placebo stress tests were comparable (Table 4); in contrast, labetalol significantly influenced all parameters:

Blood pressure and heart rate. After placebo, at the maximal level of exercise, systolic blood pressure reached a value as high as 210.0 ± 2 mmHg, whereas after labetalol, at the same work load as before, it was 196.3 ± 22 mmHg, a value significantly ($P < 0.05$) lower than that recorded during placebo exercise (Figure 1). Similarly, diastolic blood pressure was reduced by labetalol from a control value of 116.3 ± 13 to 109 ± 9 mmHg ($P < 0.05$) and heart rate from 132.0 ± 19 to 121.0 ± 23 beats/min ($P < 0.005$) (Figure 1).

Heart rate—systolic blood pressure product. Compared with placebo, there was a significant reduction in rate-pressure product during labetalol exercise. Actually, at the maximal level of placebo exercise it reached a value as high as 27516 ± 4294 mmHg/min, whereas after labetalol it was 23512 ± 4625 mmHg/min ($P < 0.001$) (Figure 2).

ST segment depression. The increase in exercise tolerance induced by labetalol was confirmed by the reduction in ST segment depression observed in all but two patients during labetalol exercise, as compared with that observed after placebo. Therefore, at the same work load, mean ST segment depression

Figure 1 Changes in heart rate (HR) and in systolic (SBP) and diastolic blood pressures (DBP) induced by oral labetalol during exercise. Solid columns represent placebo values, striped columns values after labetalol. All numbers are expressed as mean $\pm$ s.d. *Different from placebo ($P < 0.05$); **different from placebo ($P < 0.005$).

Figure 2 Effect of labetalol on rate-pressure product for individual patients. **Different from placebo ($P < 0.005$).

was reduced from a control value of 2.0 ± 0.4 to 1.36 ± 0.6 mm ($P < 0.001$) (Figure 3).

Exercise tolerance. The beneficial effect of the drug allowed that in most instances, during labetalol exercise, patients were able to prolong their effort beyond the levels reached during placebo exercise. Therefore, exercise tolerance was increased by labetalol from a control value of 83.7 ± 18 to 95.3 ± 19 W ($P < 0.005$).

Table 2 Clinical, haemodynamic and angiographic data

Patient number	Age (yr)	Sex	Aortic pressure		Heart rate (beats/min)	CI (l/min ⁻¹ m ⁻²)	LVEDP (mmHg)	Coronary artery obstruction (%)			Left ventricular asinergy
			Systolic (mmHg)	Diastolic (mmHg)				LAD system	Circumflex system	RCA	
1	39	M	120	80	108	3.3	23	75	80	60	+
2	48	M	150	80	80	4.4	18	80	60	80	+
3	48	M	130	76	78	3.6	10	-	80	80	-
4	55	M	140	70	86	3.2	23	90	-	80	-
5	47	M	120	60	100	2.6	12	80	-	90	-
6	55	M	145	80	94	4.2	15	80	80	70	+
7	54	M	130	80	80	5.2	20	90	-	60	-

CI, Cardiac index; LVEDP, left ventricular end-diastolic pressure.

Table 3 Response to oral labetalol at rest in 19 patients

	Arterial pressure		Heart rate (beats/min)	Heart rate $\times$ systolic pressure (mmHg/min)
	Systolic (mmHg)	Diastolic (mmHg)		
Placebo	Mean	87.1	74.9	10461
	$\pm$ s.d.	6.3	12.4	1881
Labetalol	Mean	86.8	68.7	9936
	$\pm$ s.d.	6.7	11.4	1841
P	NS	NS	<0.01	NS

NS, Not significant.

Table 4 Effect of exercise stress test during wash-out and placebo periods

	Arterial pressure		Heart rate (beats/min)	Heart rate $\times$ systolic pressure (mmHg/min)	ST segment depression (mm)	Exercise tolerance (W)
	Systolic (mmHg)	Diastolic (mmHg)				
Wash-out	Mean	115.3	127.7	26783	2.0	83.7
	$\pm$ s.d.	11	19	3587	0.2	19
Placebo	Mean	116.3	132.0	27516	2.0	83.7
	$\pm$ s.d.	13	19	4254	0.4	18
	NS	NS	NS	NS	NS	NS

NS, Not significant.

Haemodynamic study. None of the seven patients included in the study suffered any side-effect as a consequence of intravenous administration of labetalol.

Blood pressure and heart rate. Intravenous administration of labetalol induced at rest a slight but

significant reduction in heart rate and in systolic aortic pressure. Diastolic aortic pressure remained unchanged (Table 5). During exercise, systolic blood pressure was reduced by the drug from a control value of 164.6 ± 25 to 138.6 ± 19 mmHg ($P < 0.001$) and diastolic blood pressure from 94.7 ± 12 to 88.4 ± 10 mmHg ($P < 0.005$) (Figure 4). Similarly, heart rate was reduced from 104.6 ± 10 to 96.4 ± 10 beats/min ($P < 0.005$) (Figure 4).

Product of heart rate and systolic blood pressure. The decrease in systolic blood pressure and heart rate induced by labetalol, reflected a reduction in the double product both at rest and during exercise. In the first condition the rate-pressure product was reduced from 1188 ± 1256 to 10047 ± 1461 mmHg/min ($P < 0.001$) (Table 5); and during exercise it fell from a control value of 17228 ± 2375 to 13445 ± 2404 mmHg/min ($P < 0.005$) (Figure 4). In addition, the rate-pressure product increased by 45% during exercise after placebo but only by 28% during labetalol exercise.

Cardiac index. Cardiac index at rest and during exercise was not modified by labetalol (Table 5). After exercise the cardiac index was 5.4 ± 0.6 l min⁻¹ m⁻² following placebo and 5.4 ± 0.9 l min⁻¹ m⁻² after labetalol (Figure 5).

Left ventricular end-diastolic pressure. Labetalol had no significant effect on LVEDP at rest (Table 5) or during exercise (Figure 5). During exercise conditions, LVEDP was slightly reduced after labetalol

Figure 3 Reduction in ST segment depression (ST ↓) induced by labetalol during exercise. **Different from placebo ($P < 0.005$).

Figure 4 Mean values ($\pm$ s.d.) for systolic (SBP) and diastolic blood pressures (DBP), heart rate (HR) and rate-pressure product (RPP) during exercise before (solid columns) and after (striped columns) labetalol given intravenously. **Different from control ($P < 0.005$).

from the control value of 21.4 ± 2.3 to 19.5 ± 2.0 mmHg (Figure 5).

dP/dT/LVEDP ratio. This index was not modified by labetalol. At rest it was $109.7 \pm 19.8/s$ in control condition and $116.1 \pm 31.1/s$ after labetalol (Table 5); during exercise it was $92.0 \pm 43.0/s$ before labetalol and $102.9 \pm 38.3/s$ after the drug was administered (Figure 5).

Systemic peripheral vascular resistance index. Labetalol reduced this parameter in both conditions. Actually, it was reduced from 651.9 ± 123.8 to $596.4 \pm 109.9 \text{ dyn}^{-1} \text{ s}^{-1} \text{ cm}^{-5} \text{ m}^{-2}$ ($P < 0.05$) (Table 5) at rest and from 612.0 ± 61.2 to $512.7 \pm 36.2 \text{ dyn}^{-1} \text{ s}^{-1} \text{ cm}^{-5} \text{ m}^{-2}$ ($P < 0.025$) during exercise (Figure 5).

Discussion

The most important goal in the treatment of coronary artery disease is to restore the normal balance between myocardial oxygen consumption and supply.

Medical therapy has primarily focused on the reduction of myocardial oxygen demand and, in this regard, β -adrenoceptor blockers have a well established role (Miller, 1975; Turner, 1978). However, these drugs have the disadvantage of depressing both the myocardial contractility and conduction tissue (Stephen, 1966). Thus, congestive heart failure and conduction disturbances are among the complications and represent the contraindications of therapy with β -adrenoceptor blockers. It is for these reasons that the search continues for agents capable of reducing myocardial oxygen consumption with a more favourable therapeutic index and with less depression of the myocardium.

α -adrenoceptor blockers, which do not have a depressant action on the myocardium, could be used in the management of coronary patients, for their ability to reduce after-load and, thus, myocardial oxygen consumption. However, their unpleasant side-effects, mainly reflex tachycardia and orthostatic hypotension, limit their usefulness in the clinical practice.

It has already been demonstrated that the simultaneous blockade of α - and β -adrenoceptors shows no apparent side-effects, leading to a significant reduction in rate-pressure product (Majid, 1974), an index that is highly correlated to myocardial oxygen consumption (Gobel, 1978). Labetalol is the only drug having β_1 and β_2 as well as α -adrenoceptor-blocking properties (Collier, 1972; Farmer, 1972).

The results of our study demonstrate that this

Table 5 Response to intravenous labetalol at rest in seven patients

	SAP (mmHg)	DAP (mmHg)	HR (beats/min)	RPP (mmHg/min)	CI (l/min) ²	LVEDP (mmHg)	dP/dT/LVEDP (s ⁻¹)	SVRI (dyn ⁻¹ s ⁻¹ cm ⁻⁵ m ⁻²)
Before labetalol	Mean 133.6	75.1	89.4	11881	3.8	17.3	109.7	651.9
	$\pm$ s.d. 18.8	7.6	11.5	1256	0.8	5.1	19.8	124
After labetalol	Mean 120.6	70.3	83.6	10047	3.9	15.8	116.1	596.4
	$\pm$ s.d. 14.9	8.6	9.6	1461	0.8	4.2	31.1	110
<i>P</i>	<0.05	NS	<0.01	<0.001	NS	NS	NS	<0.05

SAP, Systolic aortic pressure; DAP, diastolic aortic pressure; HR, heart rate; RPP, rate-pressure product; CI, cardiac index; LVEDP, left ventricular end-diastolic pressure; dP/dT, first derivative of left ventricular pressure; SVRI, systemic vascular resistance index.

Figure 5 Mean values ($\pm$ s.d.) for cardiac index (CI), (LVEDP), $dp/dt/LVEDP$ and systemic vascular resistance index (SVRI) recorded during exercise under control conditions (solid columns) and following labetalol 0.6 mg/kg intravenously (striped columns). *Different from control ($P < 0.05$).

drug is able to reduce this index also in normotensive patients affected by coronary artery disease. This reduction was achieved by a decrease in heart rate and in arterial pressure, which were both significantly decreased from control during labetalol exercise. The labetalol-induced reduction in myocardial oxygen consumption was accompanied by a significant reduction in ST segment depression. ST segment, in fact, was depressed to a lesser extent in all but two patients during labetalol exercise compared with the control stress test, when the comparison was made for the same work load. Therefore, exercise tolerance in these coronary patients increased significantly.

Despite the α -adrenoceptor-blocking action of the drug, none of the patients had either tachycardia or orthostatic hypotension during labetalol therapy. This is attributable to the simultaneous blockade of the β -adrenoceptors, since the β_1 adrenoceptor would counteract the baroreceptor homeostatic mechanism activated by the peripheral vasodilation, leading to a reflex increase in heart rate. In addition, the β -adrenoceptor blockade, may help restore the normal receptor balance in the peripheral nervous system, which may then prevent the orthostatic hypotension usually induced by α -adrenoceptor blockade.

At rest at an oral dose of 100 mg twice daily labetalol did not induce any change in systolic or diastolic blood pressures. Labetalol given intravenously, however, did induce a slight but signifi-

cant reduction in blood pressure at rest, due to the significant decrease in systemic vascular resistance, as cardiac output remained unchanged. LVEDP and $dp/dt/LVEDP$ ratio did not change after intravenous administration of the drug, whereas heart rate decreased moderately.

These responses are quite different from that usually observed following intravenous β -adrenoceptor blockers, which do not have any hypotensive effect but induce a greater slowing of heart rate, a decrease in cardiac output in $dp/dt/LVEDP$ ratio, and an increase or no change in vascular resistance.

The maintenance of cardiac output despite the β -adrenoceptor-blocking action of labetalol is probably due to the simultaneous blockade of α -adrenoceptors and the consequent peripheral vasodilation, which triggers off a positive inotropic effect counterbalancing the depressant effect of the β -adrenoceptor-blocking effect on cardiac output. The reflex positive inotropic mechanism is probably also responsible for the lack of modification in $dp/dt/LVEDP$ ratio. The administration of β -adrenoceptor blockers generally increases left ventricular filling pressure (Helfant, 1971; Harrison, 1978). In contrast, our results show that labetalol, at least in acute administration and at the dose used in this study, does not produce any change in LVEDP. These beneficial results, that is, decrease in myocardial oxygen consumption without impairment of ventricular performance, have been obtained after labetalol both at rest and during exercise.

It is not surprising that in some situations it is possible to reduce myocardial oxygen consumption without depression in myocardial performance. This is well illustrated by the current use of vasodilator therapy in patients with power failure following acute myocardial infarction. Recent studies with intravenous vasodilators, such as nitroprusside, phentolamine and nitroglycerin, indicate that cardiac performance can be improved while at the same time myocardial oxygen needs are reduced (Franciosa, 1972; Majid, 1971; Gold, 1972). This therapeutic intervention should serve to emphasize the fact that cardiac performance and myocardial oxygen consumption are not always directly linked. In particular in patients with coronary artery disease it is important to appreciate that performance under certain circumstances can be maintained with a simultaneous reduction in myocardial oxygen consumption.

Labetalol seems to satisfy these requirements and reduced the demand of the heart for oxygen without

negative inotropic effect. Moreover, the α -adrenoceptor-blocking effect of labetalol may also provide additional benefit. α -adrenoceptors are present in the coronary arteries and by blocking the adrenergic tone this may increase blood supply to the myocardium. A previous study has already shown that labetalol increases the coronary blood flow (Maxwell, 1973). The beneficial action of labetalol in ischaemic heart disease was also confirmed by a previous experimental study performed in our laboratory showing the protective effect of the drug on ischaemic necrosis (Chiariello, 1980).

In conclusion, this study shows that labetalol improves exercise tolerance in patients with ischaemic heart disease and that this effect is not accompanied by negative effects upon myocardial performance. Therefore, the simultaneous α - and β -adrenoceptor blockade may represent a progress in the treatment of patients with coronary artery disease as compared to the use of β -blocker.

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