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Treatment of hypertension in acute stage of myocardial infarction
Haemodynamic effects of labetalol

M RENARD, A RIVIÈRE, P JACOBS, R BERNARD

From the Department of Cardiology and the Coronary Care Unit, Saint-Pierre University Hospital, Brussels, Belgium

SUMMARY Labetalol was used to treat systemic hypertension (systolic blood pressure above 150 mmHg) in 11 patients with acute myocardial infarction; its haemodynamic effects and tolerance were studied.

Increasing doses of labetalol were infused to lower systolic blood pressure to less than 130 mmHg; the optimal rate was then maintained for one hour (mean rate: 2·3 mg/min). Haemodynamic variables were measured before, during, and after labetalol infusion. Labetalol lowered blood pressure in all patients; this effect was related to a decrease both in total systemic resistance (17·7 to 14 IU) and in cardiac index (3·1 to 2·7 l/min per m^2); the stroke index remained unchanged and the heart rate was reduced (94 to 81 beats/min). There was no significant change in the mean pulmonary wedge pressure; it was decreased, however, in the six patients with an initial pressure greater than 15 mmHg. The double product was greatly decreased (16 497 to 8598 mmHg × beats per min), which is favourable in acute myocardial infarction.

We conclude that labetalol is a drug of choice to treat hypertension in acute myocardial infarction because it is very effective; its haemodynamic effects are likely to reduce myocardial oxygen requirements and suggest that labetalol administration does not worsen moderate left sided heart failure. The drug, however, may reduce the cardiac output.

Systemic hypertension is frequent in the acute stage of myocardial infarction[1] and is associated with a higher incidence of complications.[2–4] Labetalol which combines alpha and beta adrenoceptor blockade seems to be an effective drug in managing this type of hypertension.[5 6]

This study was designed to evaluate the haemodynamic changes and the clinical response after intravenous administration of labetalol to such patients.

Patients and methods

Eleven patients were studied (10 men and one woman), all of whom were less than 70 years of age.

Criteria for inclusion were: (1) acute (less than 48 hours) infarction (that is severe chest pain, appearance of new Q waves and/or abnormal levels of MB creatinine kinase); (2) systemic hypertension (systolic value greater than 150 mmHg) persisting over six hours in spite of adequate sedation and control of chest pain; (3) normal sinus rhythm; and (4) cardiac index greater than 2·4 l/min per m^2.

Patients with clinical signs of severe heart failure or with second or third degree atrioventricular block were excluded, as were patients previously treated with digitalis, beta blockers, or vasodilators.

RHYTHM AND CONDUCTION CHANGES

The standard electrocardiogram was recorded before and during each haemodynamic measurement. In addition, continuous bedside monitoring was carried out through the period of observation.

HAEMODYNAMIC MEASUREMENTS

A Swan-Ganz flow directed catheter was inserted into the pulmonary artery for the measurement of right

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atrial pressure, pulmonary artery pressure, and pulmonary wedge pressure. The thermodilution technique was used for determination of cardiac output (Edwards Laboratory Inc.). Each cardiac output was expressed as the mean value of at least four measurements. A radial intra-arterial catheter was introduced for measurement of systemic blood pressure.

The following variables were calculated according to the usual formulae: cardiac index, stroke index, left ventricular stroke work index, total systemic resistance, and total pulmonary resistance.

LABETALOL ADMINISTRATION

Before the administration of labetalol, two series of stable haemodynamic measurements were obtained at five minute intervals; the mean of the two control observations was used as steady state value.

Labetalol was administered intravenously by constant infusion. The infusion solution consisted of 200 mg labetalol in 150 ml 5% glucose in water. The infusion was initiated with a dose of 0·5 mg/min; at intervals of five minutes, labetalol dosage was increased by increments of 0·3 mg/min until the optimal dose for each individual patient was obtained. The dose was considered optimal when the systolic blood pressure was reduced below 130 mmHg. The infusion of labetalol was then given at this optimal dose over a period of 60 minutes. Complete sets of haemodynamic measurements were repeated at intervals 15, 30, and 60 minutes from the beginning of infusion at the optimal rate. The labetalol infusion was then stopped and haemodynamic measurements were obtained after a period of 60 minutes in all the patients. In addition, in nine patients, haemodynamic measurements were obtained at four hours after completion of the labetalol infusion, though cardiac output was only obtained in six of these patients.

STATISTICAL ANALYSIS

The statistical analysis was performed by using the analysis of variance—two sided anova—followed by a modified t test.[7]

Results

CLINICAL CHARACTERISTICS OF POPULATION

The clinical characteristics of the 11 patients are summarised in Table 1. This table shows the age range (41 to 68 years), the site of infarction, delay from onset of infarction when measurements were started (16 to 47 hours), and patients with known prior hypertension.

OPTIMAL INFUSION RATE OF LABETALOL

The optimal infusion rate of labetalol determined from the haemodynamic response was within the range of 0·8 to 4·8 mg/min (mean 2·3 mg/min); the drug was generally effective within the first minutes of the infusion.

HAEMODYNAMIC RESULTS

Mean values are given in Table 2 and illustrated in Fig. 1 to 5.

COMPARISON BETWEEN CONTROL VALUES AND THOSE OBSERVED DURING INFUSION OF LABETALOL (15, 30, AND 60 MINUTES)

The values given here are those observed after one hour of infusion. Systemic pressures (systolic, diastolic, and mean) and total systemic resistance (Fig. 1) were significantly decreased during infusion at the optimal rate. The decrease in total systemic resistance was highly significant (17·7 to 14 IU; $p<0·001$). Heart rate was significantly lowered during the infusion (94 to 81 beats/min, $p<0·001$); cardiac index (Fig. 2) was significantly reduced (3·1 to 2·7 l/min per m^2; $p<0·001$) but the stroke index was not significantly changed. Left ventricular stroke work index was also significantly decreased (43 to 29·8 g.m/m^2; $p<0·001$) during labetalol administration.

Pulmonary artery pressures (systolic, diastolic, and mean) and pulmonary wedge pressure were slightly decreased (Fig. 3), but not significantly; the right atrial pressure was almost unchanged. The double product (Fig. 4) was greatly reduced throughout the period of labetalol infusion (16 497 to 8598 mmHg×beats/min).

As shown on Fig. 1 to 4, comparable changes are already observed 15 and 30 minutes after the infusion.

COMPARISON BETWEEN HAEMODYNAMIC STATUS OBSERVED AT END OF LABETALOL INFUSION AND VALUES OBSERVED ONE HOUR AND FOUR HOURS AFTER INFUSION WAS STOPPED

There was a significant increase in systemic blood pressure (systolic, diastolic, and mean) after the infu-

Table 1 *Clinical characteristics of 11 patients studied*

No.	*Age (y)*	*Delay from onset (h)*	*Site of infarction*	*Prior hypertension*
1	67	43	Anteroseptal	−
2	50	46	Anteroapical	+
3	60	31	Anteroseptal	−
4†	60	23	Inferior	+
5	41	42	Anteroinferior	+
6	51	16	Anterior	−
7	68	18	Anteroseptal	+
8	51	16	Anterior	+
9†	51	30	Anterior	+
10	51	47	Inferior and lateral	−
11‡	66	23	Subendocardial and posterior	−

† Died in hospital.
‡ Case 11 was a woman.

Table 2 *Comparison of haemodynamic values before (control), during, and after labetalol infusion*

Variables	*Control*	*During infusion*		*After infusion*			
		60 minutes		*One hour*		*Four hours*	
		Mean±SEM	*p*	*Mean±SEM*	*p*	*Mean±SEM*	*p*
Blood pressure (mmHg)							
Systolic	175±5	118±4	<0·001	125±5	<0·02	141±5	<0·001
Diastolic	85±5	63±3	<0·001	69±4	<0·01	74±4	<0·005
Mean	112±5	79±3	<0·001	86±4	<0·005	83±5	<0·005
Total systemic resistance (IU)	17·7±1·2	14±0·9	<0·001	15·6±1·1	<0·005	16·3±1·7	NS
Heart rate (beats/min)	94±3	81±3	<0·001	81±3	NS	87±4	NS
Cardiac index (l/min per m²)	3·1±0·1	2·7±0·2	<0·001	2·6±0·2	NS	2·7±0·2	NS
Stroke index (ml/m²)	32·7±1·6	33±1·9	NS	31·8±2·2	NS	29·6±1·5	NS
LVSWI (g.m/m²)	43±3·1	29·8±2·5	<0·001	31·5±3·3	NS	29·8±3·5	NS
Pulmonary pressures (mmHg)							
Systolic	35±3	30±2	NS	33±3	NS	32±4	NS
Diastolic	18±2	16±1	NS	17±2	NS	16±2	NS
Mean	25±3	21±2	NS	24±2	NS	22±3	NS
Wedge	16±2	13±1	NS	15±2	NS	15±2	NS
Right atrial pressure (mmHg)	7±2	8±1	NS	9±2	NS	8±2	NS
Double product (mmHg beats/min)	16497±703	8598±568	<0·001	10202±545	<0·05	12280±792	<0·001

LVSWI, left ventricular stroke work index; IU, international units. Statistical significance (p) of differences between control values and those during the infusion, and statistical significance of differences between values at 60 minutes of infusion compared with values recorded afterwards are given.

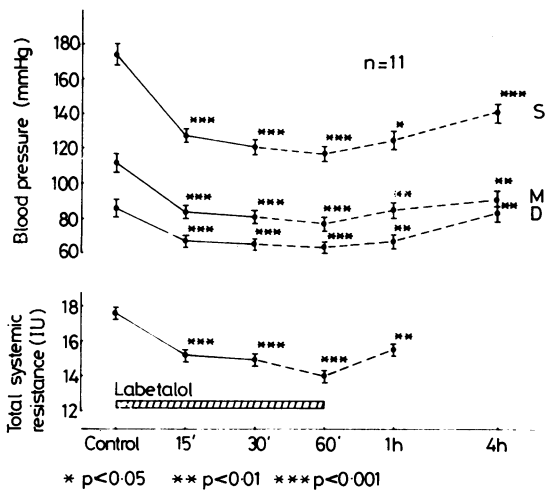

Fig. 1 *Changes in blood pressure (systolic, diastolic, and mean) and total systemic resistance before (control), during (15, 30, and 60 minutes), and after (one and four hours) labetalol infusion. At four hours, the total systemic resistance is not given because it was obtained only in six cases. Values shown are mean ± SEM; p values are indicated.*

sion was stopped. Even after four hours, however, the values remained below those observed before the infusion was started. The total systemic resistance increased but the results were only significant after one hour (14 to 15·6 IU; p<0·005).

Heart rate, cardiac index, stroke index, and left ventricular stroke work index were not significantly altered. Pulmonary pressures including wedge pressure and atrial pressure remained unchanged. Double product increased slightly after one hour, and significantly after four hours (8598 to 12 280 mmHg×beats/min).

INDIVIDUAL EVOLUTION OF LEFT VENTRICULAR FUNCTION

In Fig. 5, the pulmonary wedge pressure was plotted against the cardiac index showing the individual evolution of the left ventricular function between the control values and those observed after one hour of infusion with the optimal dose. The cardiac index decreased in all but two cases; this fall was particularly important in one case (from 2·5 to 1·7 l/min per m²), most probably related to the pronounced decrease in pulmonary wedge pressure (from 21 to 5 mmHg). The curves of the six patients who initially had raised pulmonary wedge pressures greater than 15 mmHg shifted to the left; this beneficial effect on preload may be favourable in patients with mild left heart failure.

TOLERANCE

No serious side effects were observed. Headache, vomiting, and facial flush were observed each in one patient; they were transient despite continuation of treatment. All but two patients left the hospital in

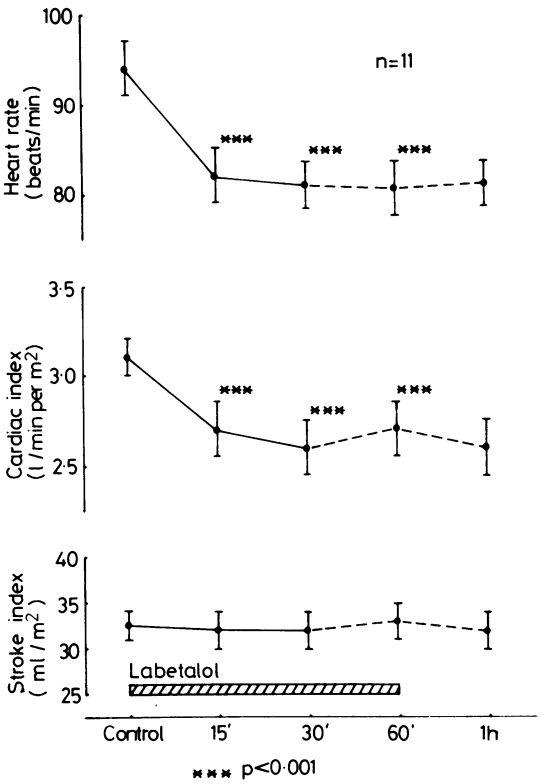

Fig. 2 *Changes in heart rate, cardiac index, and stroke index before (control), during (15, 30, and 60 minutes), and after (one hour) labetalol infusion. Values shown are mean ± SEM; p values are indicated.*

good condition: one died from refractory ventricular fibrillation secondary to recurring acute myocardial infarction on day 5, the other from cardiogenic shock on day 3 after completion of the labetalol treatment.

Discussion

Systemic hypertension is frequent during the first hours of acute myocardial infarction; blood pressure normalises spontaneously in most cases, however, during the first six hours as the pain is relieved and the patient becomes relaxed.[1] In some cases blood pressure remains high; many consider it should be treated rapidly because it is a major factor of myocardial oxygen demand[8] and is potentially deleterious.[2-4] Vasodilators are effective in reducing the high blood pressure but they generally increase the heart rate, which is unfavourable.[9-11] Beta blockers decrease blood pressure and heart rate but they increase systemic resistance when they are injected; furthermore, $beta_2$ blockers may promote constriction of the coronary arteries which would also be deleterious.[12] Labetalol which combines alpha and beta adrenoreceptor blockade should prevent any vasoconstrictive effect associated with pure beta blockade[13] and should thus be a drug useful in the treatment of hypertension in acute myocardial infarction. Marx and Reid[5] have given labetalol to 15 patients with acute myocardial infarction and hypertension and observed a return to normal of blood pressure in all cases with a decrease in heart rate and pulmonary wedge pressure. Timmis *et al.*[6] have used labetalol to treat hypertension in seven patients with acute

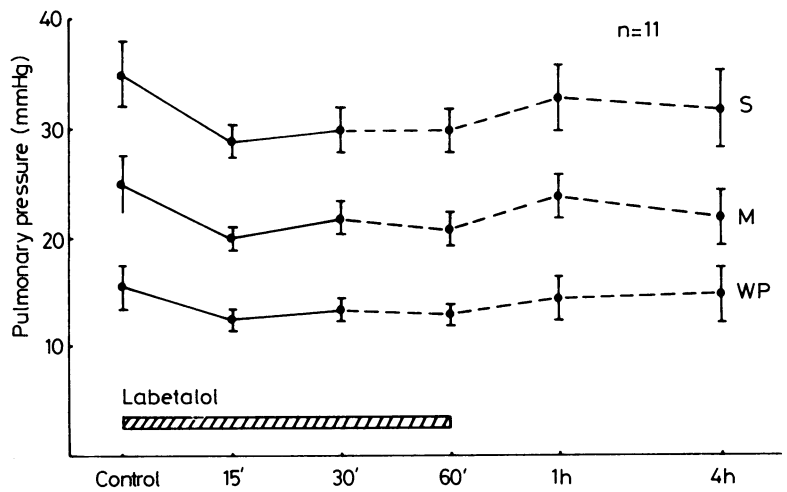

Fig. 3 *Changes in pulmonary pressures (systolic, mean, and wedge pressure) before (control), during (15, 30, and 60 minutes), and after (one and four hours) labetalol infusion. Values shown are mean ± SEM; p values are indicated.*

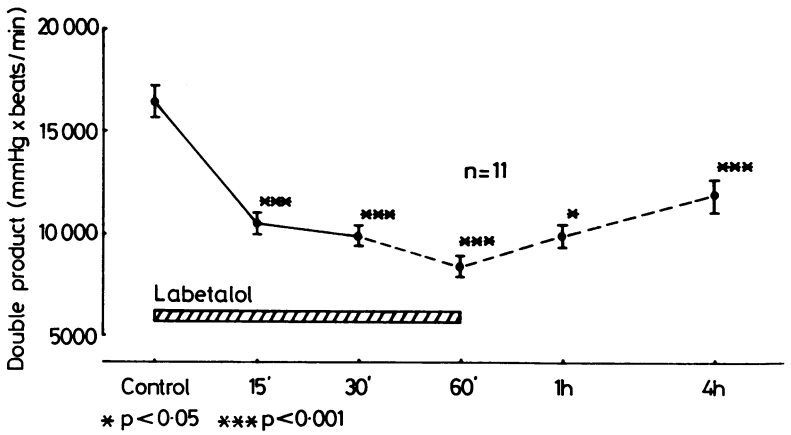

Fig. 4 *Changes in double product (systolic blood pressure × heart rate) before (control), during (15, 30, and 60 minutes), and after (one and four hours) labetalol infusion. Values shown are mean ± SEM; p values are indicated.*

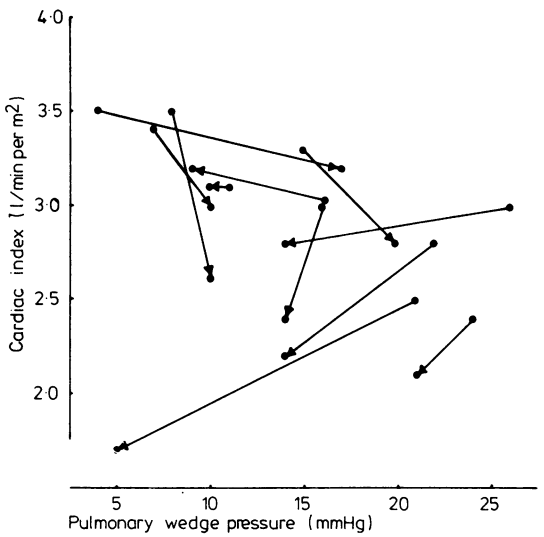

Fig. 5 *Left ventricular function curve: the cardiac index is plotted against the pulmonary wedge pressure; individual evolution from control values to those at one hour infusion is shown.*

myocardial infarction. They normalised blood pressure with a decreased heart rate and pulmonary wedge pressure but the total systemic resistance did not change. In our study labetalol rapidly returned the blood pressure to normal in all cases with a decrease in the heart rate and in the total systemic resistance. There were no consistent changes in mean pulmonary wedge pressure but it decreased in the patients in whom it was initially high (≥15 mmHg). The very conspicuous decrease in the double product observed during labetalol infusion suggests that myocardial oxygen demand is reduced.

The drug activity was observed within a few minutes of infusion and the haemodynamic variables were influenced for at least four hours after the infusion.

We conclude that labetalol is an effective and well tolerated drug in the management of hypertension in the acute stage of myocardial infarction. Its haemodynamic effects are likely to reduce myocardial oxygen requirements, though the response of coronary flow to the lowered blood pressure is at present unknown. Data so far available suggest that administration does not worsen moderate left sided heart failure, but the drug may reduce the cardiac output.

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Requests for reprints to Dr M Renard, Saint-Pierre University Hospital, 322 Rue Haute, 1000 Brussels, Belgium.