

# Evaluation of haemodynamic effects of intravenous propranolol at low dosage (1 and 2 mg) in acute myocardial infarction

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*The haemodynamic effects of intravenous propranolol at low dosage (1 and 2 mg) have been evaluated on 14 patients in the acute stage of myocardial infarction. The first 1 mg propranolol was not followed by any significant variation in the variables measured. After the second 1 mg propranolol, the heart rate, cardiac index, and stroke index decreased significantly but moderately. Changes in pulmonary wedge pressure were not significant.*

*It is concluded that intravenous propranolol in the small dosage of 1 or 2 mg, at which antiarrhythmic effect is still produced, has only a negligible depressant myocardial effect.*

Propranolol administered intravenously has a potent and rapid antiarrhythmic action but, because of its pronounced negative inotropic effects, its use is limited in conditions in which ventricular function is impaired, particularly in acute myocardial infarction. Nevertheless, the negative inotropic effect appears to be proportional to the amount of the drug administered whereas an appreciable antiarrhythmic action can be obtained with a low dosage which does not induce clinically appreciable myocardial depression.

The aim of the present study was to evaluate the haemodynamic effects of intravenous propranolol at low dosage (1 and 2 mg) given in the acute stage of myocardial infarction.

## Subjects and methods

Studies were made on 14 patients (9 men, 5 women) admitted for acute myocardial infarction. The diagnosis was made on the usual criteria: typical chest pain, significant rise in enzyme levels, and characteristic electrocardiographic abnormalities. The study was performed between the second and the fourth day after admission. At the time of the study, two patients had first degree atrioventricular block with a PR interval of 0.24 s. Nine patients had clinical manifestations of left ventricular failure, which were of varying degree in the different patients, but in 2 they were pronounced (Cases 6 and 14).

The haemodynamic study was carried out on patients

in the fasting state, without premedication. The patients had not received any drugs within the previous 6 hours that could influence cardiovascular function.

A small diameter catheter was inserted percutaneously through the femoral artery into the thoracic aorta for measurement of arterial pressure and for withdrawal of blood for measurement of cardiac output. A 5 F Swan-Ganz catheter was introduced through the femoral vein and advanced until a pulmonary pressure curve was obtained. Pressures were measured by means of P23Db Statham transducers positioned at the level of the mid-axillary line. In 5 cases the pulmonary wedge pressure could not be obtained and the end-diastolic pulmonary pressure was used instead; pulmonary wedge pressure or end-diastolic pulmonary pressures were measured in a total of 11 cases. Cardiac output was measured by the dye-dilution technique (indocyanine green, Harvard 902 Pump, Waters Company XC 302 densitometer, Variant recorder). Two consecutive measurements of cardiac output were made and the mean of these two values was used.

The following variables were measured or derived:

- heart rate (HR) in beats/min
- PR interval of the electrocardiogram in seconds
- pulmonary wedge mean pressure (PWPM) in mmHg
- systolic pulmonary arterial pressure (SPAP), diastolic (DPAP), mean (PAPm) in mmHg
- systolic aortic pressure (SAoP), diastolic (DAoP), mean (AoPm) in mmHg
- cardiac output (CO) in l/min
- cardiac index (CI) in l/min per m<sup>2</sup>
- stroke volume (SV) in ml/beat obtained by dividing CO by HR

- stroke index (SI) in ml/beat per m<sup>2</sup> obtained by dividing CI by HR
- systolic ejection time of the left ventricle (SET) in seconds, measured on the aortic pressure curve between the upstroke of the aortic pressure curve and the dicrotic notch.
- mean systolic ejection rate (SERm) in ml/s, obtained by dividing SV by SET
- left ventricular work (W) in kg m/min calculated with the formula:

$$W = \frac{AoPm \times CO \times 1.26}{100}$$

- total systemic arterial resistances in dynes s cm<sup>-5</sup>, calculated according to the formula:

$$TSAR = \frac{AoPm}{CO} \times 80.$$

Measurements of all the haemodynamic variables were made in the basal state. At 15-minute intervals, two intravenous injections of 1 mg propranolol were then made. Heart rate, PR interval, aortic pressure, and pulmonary arterial pressure were measured just before the second injection was made. Fifteen minutes after this second injection, measurements of the various haemodynamic parameters were made again.

Statistical significance was determined by using the Student paired t-test between basal values and values obtained after the first and the second 1 mg propranolol injections.

### Results

The haemodynamic effects of the first and the second 1 mg propranolol injections are shown in Table 1. Mean values, mean differences, percentage variations, and paired t-test probability values between the basal measurements and the measurements after the second 1 mg injection are given in the lower part of the Table.

The first 1 mg propranolol injection was not followed by any significant variation of the measured parameters. The only noticeable variation was a slight tendency for heart rate to decrease.

After the second 1 mg propranolol injection, some parameters (PR interval, aortic pressure, ejection time) changed only very slightly (not significant). Irregular variations of the pulmonary wedge pressure were observed but these changes were not significant. In only one case (Case 4) the pulmonary wedge pressure increased conspicuously, from 12 to 18 mmHg (1.6 to 2.4 kPa), though symptoms of cardiac insufficiency were not prominent in this case. Systemic arterial resistance showed large individual variations, without significance.

The variables which changed significantly were, heart rate, cardiac output, cardiac index, stroke volume, stroke index, ejection rate, left ventricular work. No correlation was observed between the

haemodynamic effects of propranolol and the initial severity of the clinical symptoms and haemodynamic abnormality. On the whole, decrease in cardiac output was moderate (-20%,  $P < 0.01$ ). In one case (Case 3), cardiac output decreased by more than a half, but this produced no clinical deterioration.

In all cases, there was no occurrence or aggravation of symptoms of cardiac insufficiency after intravenous administration of propranolol in the dosage used.

### Discussion

It is well known that at the acute stage of myocardial infarction there is an increase of circulating catecholamines which may induce arrhythmias by their action on the myocardial beta-receptors (Jewitt *et al.*, 1969). Propranolol has a potent antiarrhythmic effect, on the one hand by its action of blockade on the beta-receptors, and on the other hand by an intrinsic membrane stabilizing action or 'quinidine-like effect' (Vaughan-Williams, 1971). Propranolol induces also a decrease in myocardial contractility and in coronary blood flow (Wolfson and Gorlin, 1969; Stein *et al.*, 1968; Lewis and Brink, 1968). These latter effects have been considered a contraindication to the use of propranolol in myocardial infarction because of the possibility that they may dangerously increase the ventricular failure resulting from the myocardial damage.

Sloman, Robinson, and McLean (1965) and Rothfeld *et al.* (1968) have used propranolol for the treatment of major ventricular arrhythmias in the acute phase of myocardial infarction. The antiarrhythmic effect was striking, achieving prompt interruption of persistently recurring ventricular fibrillation, but serious haemodynamic consequences of the negative inotropic effect were observed. In these cases, the dosage used by the intravenous route was high, being more than 15 mg. Because of the hazards of the increased myocardial depression, the authors advised using not more than 10 mg propranolol intravenously (Sloman *et al.*, 1965; Rothfeld *et al.*, 1968).

In fact, an intravenous dose of 10 mg propranolol still has a profound myocardial negative inotropic effect. Bay *et al.* (1967) have measured the haemodynamic effects in 8 patients of 5 mg propranolol given intravenously, and showed a considerable decrease in cardiac output from 5.2 l/min to 1.5 l/min, together with a diminution of the heart rate from 93 to 68. Pulmonary wedge pressure was not measured in this study, but the right atrial pressure increased moderately. Of the 8 patients studied, 3 exhibited severe accentuation of the clinical symptoms of pre-existing cardiac failure.

TABLE *Haemodynamic effects of intravenous propranolol (1 mg and 2 mg)*

Case no.	HR	PR	PWPM	AoP	CO	CI	SV	SI	SERm	SET	W	TSAR
1	100*	0.13	10	110/70	4.40	2.47	44	24.7	—	—	6.57	—
	93	0.13	8	—	—	—	—	—	—	—	—	—
	85	0.13	8	100/70	4.03	2.25	47	26.3	—	—	5.5	—
2	100	0.16	4	85/50	6.48	3.9	64.8	39	324	0.20	7.35	740
	90	0.17	5	90/50	—	—	—	—	—	—	—	—
	95	0.16	4	80/45	4.76	2.84	49	29	245	0.20	5.32	925
3	135	0.13	11	85/45	5.40	3.35	40	24	190	0.21	6.25	815
	135	0.13	21	100/70	—	—	—	—	—	—	—	—
	120	0.13	10	75/48	2.5	1.5	21	12.6	100	0.21	2.55	1920
4	80	0.24	12	120/60	5.4	2.7	67.5	33.7	337.5	0.20	8.75	1260
	74	0.24	15	120/60	—	—	—	—	—	—	—	—
	70	0.24	18	105/55	4.4	2.2	63	31.5	286	0.22	6.3	1455
5	100	0.12	—	125/75	4.15	2.52	41.5	25.2	207.5	0.20	7	1735
	90	0.12	—	120/75	—	—	—	—	—	—	—	—
	88	0.12	—	120/80	3.20	1.96	37.6	23.2	189	0.20	5.2	2250
6	† 165	—	18	115/60	3	1.6	18	9.9	103	0.17	4.7	2000
	150	—	16.5	90/50	—	—	—	—	—	—	—	—
	150	—	22	80/55	3	1.6	20	11	117	0.17	3.26	1430
7	95	0.13	2	85/50	6.1	3.2	64.2	33.7	397	0.17	7.3	810
	92	0.13	3	90/55	—	—	—	—	—	—	—	—
	95	0.13	3	80/45	7.2	3.84	90	44.2	530	0.17	7.82	610
8	100	0.24	9	180/90	4.4	2.78	44	27.8	183	0.24	10.08	2550
	95	0.24	8	200/100	—	—	—	—	—	—	—	—
	90	0.24	9	200/100	3.55	2.25	41.7	26.4	174	0.24	9.2	3150
9	75	0.20	12	90/50	5.20	2.78	69	36.8	275	0.25	6.38	1000
	70	0.20	13	90/50	—	—	—	—	—	—	—	—
	70	0.20	13	90/50	4.08	2.18	62.8	33.4	247	0.25	5	1335
10	90	0.16	11	100/55	5.5	2.94	64.5	34.5	292	0.22	7.5	1160
	95	0.16	10	—	—	—	—	—	—	—	—	—
	80	0.16	9	100/55	4.5	2.42	56	30	233	0.24	6.1	1240
11	90	0.12	12	90/55	3.73	2.3	41.4	25.5	206	0.20	4.55	1600
	90	0.13	12	95/55	—	—	—	—	—	—	—	—
	80	0.13	12	90/50	3.6	2.22	45	27.7	187	0.24	4.4	1555
12	80	0.13	—	170/90	5.50	3.10	68.6	38.2	286	0.24	12.35	1600
	—	—	—	—	—	—	—	—	—	—	—	—
	82	0.13	—	200/100	5.2	2.88	72	40	287	0.25	14	2400
13	100	0.13	18	150/105	5.17	2.78	51.7	27.8	257	0.20	10.5	1845
	—	—	—	—	—	—	—	—	—	—	—	—
	88	0.16	14	160/100	3.25	1.75	16.8	19	184	0.20	6.85	1720
14	90	0.13	—	105/70	3.55	2	39.4	22	218	0.18	5.08	1900
	—	—	—	—	—	—	—	—	—	—	—	—
	80	0.16	—	115/70	2.9	1.64	36.2	20.5	200	0.19	3.55	2340
<i>Average</i>												
Basal	100	13.6	10.9	84	4.8	2.7	50.3	28.4	242	0.20	7.6	1425
After 2 mg propranolol	91	14	11.5	81.3	3.8	2.15	45.2	25.4	202	0.21	6.25	1715
Difference	-9%	+2.8%	+5.2%	-3%	-21%	-20%	-10%	-10%	-16%	+5%	-18%	—
Paired t-test	<0.01	NS	NS	NS	<0.01	<0.01	<0.05	<0.05	<0.01	NS	<0.01	—

\* For each case: top row is basal; next row is after 1 mg; third row is after 2 mg. † Atrial fibrillation. NS=Not significant; for other abbreviations, see text. Pressures are in mmHg - to convert to SI units: 1 mmHg  $\approx$  0.133 kPa.

Parker, West, and Di Giorgi (1968) have shown that an intravenous dose of 0.15 mg/kg (i.e. approximately a total dose of 10 mg) impairs myocardial contractility as shown by a decrease in cardiac output and systolic ejection rate, with an increase of the left ventricular filling pressure.

On the other hand, Ikram (1968) has noted that doses of 10 mg or even 5 mg intravenously are

unnecessarily high, and that an efficient anti-arrhythmic effect can be achieved with a smaller dosage of propranolol. In 4 cases of persistently recurring ventricular fibrillation in acute myocardial infarction, this author obtained stable rhythm with an electric shock after an intravenous injection of only 1 mg propranolol. Our experience, in daily practice in our coronary care unit, confirms that

intravenous propranolol at this small dose of 1 or 2 mg has a potent antiarrhythmic effect and a negative inotropic action which is negligible or absent or without detrimental consequences.

In this study, it has been demonstrated that the haemodynamic effects of a dose of 1 mg propranolol intravenously are negligible and statistically non-significant. At the dosage of 2 mg, the haemodynamic consequences become significant though they are moderate. There was a small decrease in heart rate. The diminution of the cardiac output was appreciable (mean - 20%), resulting in part but not exclusively from the decrease of the heart rate. The stroke index and the systolic ejection rate are also significantly diminished. These changes result from an impairment of myocardial contractility by the direct action of propranolol. However, the negative chronotropic and inotropic effects which are observed do not have any clinically evident deleterious consequences. There is no increase in symptoms of cardiac insufficiency. From the haemodynamic point of view, the aortic pressure and the left ventricular filling pressure do not change significantly. The absence of any significant increase in the latter indicates that there is no occurrence or aggravation of the cardiac failure. This absence of increase of ventricular filling pressure, and even sometimes its decrease, with propranolol in the coronary patient has already been underlined by Wolfson and Gorlin. This effect has not received definitive explanation but it may result from the decrease of the venous return resulting from a peripheral venous vasodilatation (Wolfson and Gorlin, 1969).

The use of intravenous propranolol in the small dose of 1 or 2 mg is, therefore, justified in the treatment of arrhythmias with acute myocardial infarction. The other antiarrhythmic agents in current use in coronary care units are not free of myocardial depressant action. For instance, the combination lignocaine and procainamide, which is commonly used, has a cardiodepressant effect, as shown by Côté *et al.* (1973), probably greater than that of 2 mg intravenous propranolol.

Furthermore, it is not proved yet that the moderate depressive action seen with the use of a 2 mg dose of propranolol is deleterious in the acute stage of myocardial infarction. This action induces a decrease in cardiac work and therefore a decrease in myocardial oxygen needs. Maroko, Libby, and Braunwald (1973) have shown that propranolol decreases the size of myocardial infarction resulting from coronary occlusion in the dog and that there is an improvement of myocardial function by a reduction of the oxygen demand (Maroko *et al.*, 1973; Becker, Ferreira, and Thomas, 1972). It has also

been shown that propranolol improves the myocardial metabolism in myocardial insufficiency (Mueller, Mazzara, and Ayres, 1972), though it has been demonstrated that propranolol decreases coronary blood flow. This latter potentially dangerous effect is in fact caused by the adjustment of coronary flow to the decreased metabolic demand and not solely by inhibition of sympathetic tone of coronary vessels (Wolfson and Gorlin, 1969; Stein *et al.*, 1968; Lewis and Brink, 1968). The lactate extraction rate increases, which indicates that the decrease in cardiac work and in oxygen needs is more than that of coronary blood flow.

In conclusion, intravenous propranolol at the small dosage of 1 or 2 mg, at which antiarrhythmic effect is still very pronounced, has only a negligible depressant myocardial effect. Its use may be indicated in acute myocardial infarction, particularly when other antiarrhythmic agents are ineffective.

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