

Haemodynamic effects of isoprenaline in acute myocardial infarction

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The haemodynamic effects of isoprenaline were investigated in 10 patients with acute myocardial infarction. Serial measurements of multiple parameters at increasing concentrations of the drug allowed establishment of a dose-response curve.

Significant increase over basal values was observed in cardiac output, stroke volume, and dp/dt . Heart rate increased only moderately. Systemic and pulmonary vascular resistances diminished, without appreciable change in aortic or pulmonary mean pressures.

These results were obtained with concentrations of 2/3 to 1 $\mu\text{g}/\text{min}$. No arrhythmias were induced and the clinical tolerance was uniformly good.

The use of these small doses of isoprenaline and their effectiveness in the management of myocardial failure complicating infarction are particularly emphasized.

The application of standard haemodynamic techniques to the study of patients with acute myocardial infarction, within the framework of coronary care units, has provided a more precise knowledge of the basic alterations in cardiac metabolism and function (Malmcrona and Varnauskas, 1964; Shillingford and Thomas, 1967; Karliner and Ross, 1971), and of the pathophysiology underlying the clinical manifestations and complications of this disease (Weil and Shubin, 1968; Swan *et al.*, 1970).

At the same time, the results of pharmacological interventions utilized in the management of complications, such as congestive heart failure and cardiogenic shock, can be more properly assessed.

Isoprenaline, a catecholamine with inotropic and chronotropic properties and without peripheral vasoconstrictive effect, has been used principally in myocardial infarction complicated by cardiogenic shock (Smith *et al.*, 1967; Morse, Danzig, and Swan, 1967; Gunnar *et al.*, 1967).

Though this agent has been investigated as a cardiotonic in chronic conditions (Dodge, Lord, and Sandler, 1960; Krasnow *et al.*, 1964; Elliot and Gorlin, 1966), there is little information available as to its particular use in congestive heart failure complicating myocardial infarction. Furthermore, generally recommended doses (Weil and Bradley, 1966;

Elliot and Gorlin, 1966; Gunnar *et al.*, 1967) tend to induce undue tachycardia or arrhythmias, clearly deleterious in the acutely ill patient.

The purpose of this study was to investigate the haemodynamic response and tolerance to relatively small and increasing doses of isoprenaline during the acute phase of myocardial infarction. A limited dose-response curve was obtained by serial measurements of haemodynamic parameters at progressive concentrations of the drug. This information could be used as a basis for a more rational administration, in cases of infarction complicated by congestive failure or shock, avoiding untoward effects while still obtaining significant pharmacological action.

Subjects and methods

Ten patients (9 men and 1 woman), whose ages ranged from 36 to 60 years, were studied on the third day after admission to the Coronary Care Unit for acute myocardial infarction. The diagnosis was established on the basis of a typical clinical picture, objective electrocardiographic changes of recent transmural infarction, and serum enzyme rises.

Patients with major complications such as severe arrhythmias, cardiogenic shock, or advanced right heart failure were excluded from this study. The selected patients had not received inotropic or vasoactive agents for the previous two weeks.

Informed consent was obtained from each patient and his attending physician after proper description of the procedure and its aims.

TABLE *Haemodynamic effects of isoprenaline in myocardial infarction*

	Heart rate (min)	Systemic arterial pressure (mmHg)			Systemic vas- cular resistance (units)	Pulmonary arterial pressure (mmHg)		
		Systolic	Diastolic	Mean		Systolic	Diastolic	Mean
Control								
Mean	81 ± 7	118 ± 20	67 ± 10	90 ± 13	18 ± 4	26 ± 5	10 ± 2	15 ± 2
1/3 µg								
Mean	84 ± 14	110 ± 17	61 ± 9	83 ± 13	15 ± 4	24 ± 4	8 ± 1	15 ± 1
Per cent	104	93	91	92	83	92	80	100
P	NS	NS	NS	NS	<0.01	NS	NS	NS
2/3 µg								
Mean	90 ± 18	111 ± 13	62 ± 10	84 ± 10	13 ± 3	25 ± 5	8 ± 2	14 ± 2
Per cent	111	94	92	93	72	96	80	93
P	NS	NS	NS	NS	<0.01	NS	NS	NS
1 µg								
Mean	98 ± 16	119 ± 12	61 ± 5	84 ± 8	12 ± 2	24 ± 7	8 ± 2	13 ± 3
Per cent	121	100	91	93	66	92	80	87
P	<0.01	NS	NS	NS	<0.01	NS	<0.05	NS

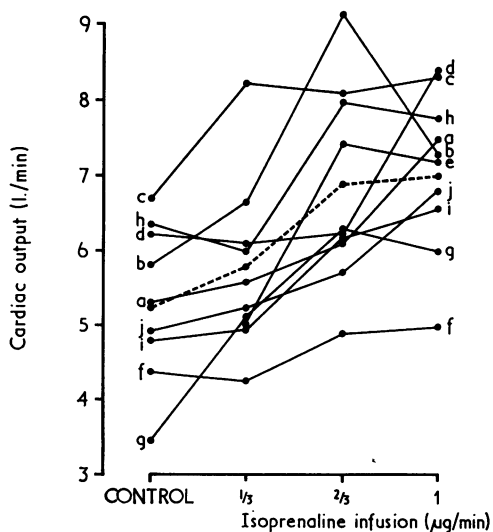
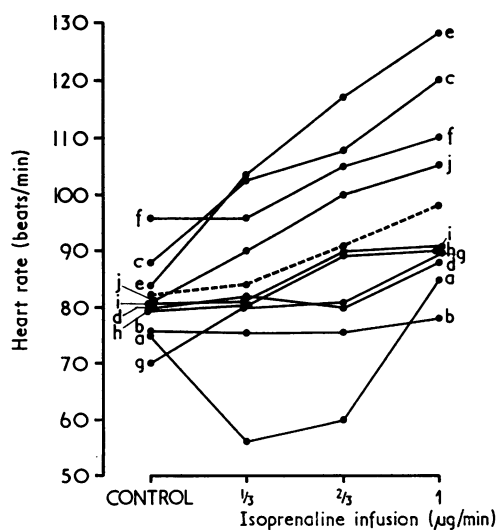
The control measurements are taken as 100 per cent, and the values obtained during the infusion of increasing doses of isoprenaline are expressed both in absolute terms (mean ± SD) and in the percentage by which they differ with the controls. P, Significance for Student's paired 't' test.

Standard haemodynamic techniques and instrumentation were used. Catheters were placed in the superior vena cava, pulmonary artery, and descending aorta. A central venous catheter (polyethylene PE 240) was introduced through a cut-down in an antecubital vein. A pulmonary artery catheter (Courmand No. 7) was introduced by a similar approach and positioned under image intensification fluoroscopy.

An arterial catheter (Kifa-red) was inserted percutaneously through one of the femoral arteries, utilizing Seldinger's technique (Sel-

dinger, 1953). Pulse pressure curves were obtained with P23 DB Statham transducers. Cardiac output determinations were carried out in duplicate by dye dilution of indocyanine green, with injection in the superior vena cava and sampling from the aorta. Values were calculated with a Sanborn computer and by semilogarithmic plotting.

All tracings were recorded with a PR-8 Electronics for Medicine. Haemodynamic measurements consisted of heart rate; central venous, pulmonary artery and aortic pressures; aortic

FIG. 1 *Cardiac output response to increasing concentrations of isoprenaline in 10 patients.*FIG. 2 *Heart rate response to increasing concentrations of isoprenaline in 10 patients.*

Pulmonary vascular resistance (units)	Central venous pressure (mean) (mmHg)	Aortic dp/dt	Cardiac output (l./min)	Cardiac index (l./min/m ²)	Stroke output (ml)
3.0 ± 1.0	5.5 ± 4	1645 ± 705	5.3 ± 1.0	2.8 ± 0.5	66 ± 13
2.7 ± 0.6 90 NS	5.0 ± 4 90 NS	1834 ± 967 111 NS	5.6 ± 1.0 106 NS	3.0 ± 0.6 107 NS	69 ± 18 104 NS
2.1 ± 0.6 70 <0.01	4.8 ± 4 87 NS	2156 ± 1022 131 <0.05	6.8 ± 1.5 128 <0.01	3.6 ± 0.6 128 <0.01	79 ± 24 120 NS
1.9 ± 0.5 63 <0.05	4.8 ± 4 87 NS	2645 ± 1344 160 <0.01	7.0 ± 1.0 132 <0.01	3.8 ± 0.6 135 <0.01	74 ± 18 112 <0.05

dp/dt; cardiac output, cardiac index and stroke output; and pulmonary and systemic vascular resistances (in units).

Isoprenaline, in progressive doses of 1/3, 2/3, and 1 µg/minute, was administered intravenously by the microdrip technique, for periods of 15 minutes each. All haemodynamic parameters were recorded initially with the patient in basal conditions, about one hour after completion of catheterization procedures. Repeat measurements were obtained at the end of each progressive dose of isoprenaline, as periods of infusion of 15

minutes for each concentration were found adequate for stabilization of the parameters under control.

Statistical analysis and paired tests for significance were applied to all values obtained.

Results

The Table summarizes the mean values for all parameters measured in this series of patients. Individual values are represented in Fig. 1 to 6.

FIG. 3 Stroke output response to increasing concentrations of isoprenaline in 10 patients.

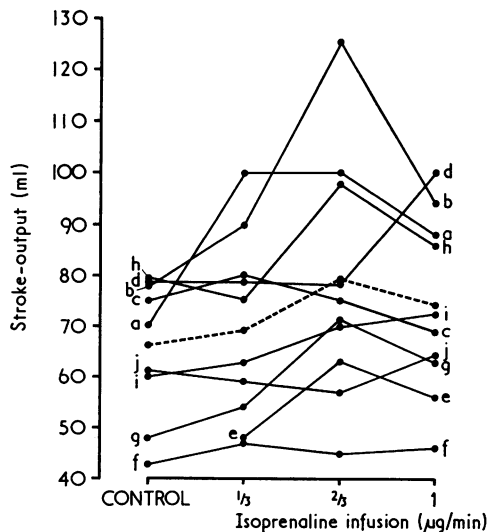
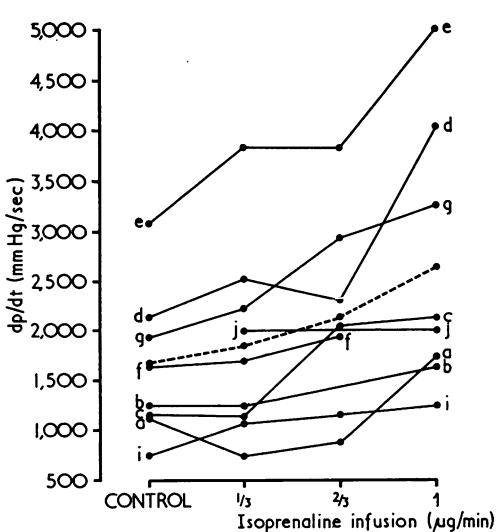


FIG. 4 Measurement of aortic dp/dt at increasing doses of isoprenaline in 9 patients.



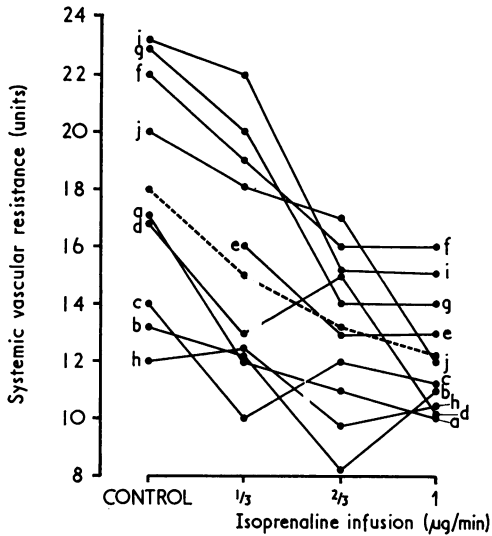


FIG. 5 Variation of systemic vascular resistance with progressive concentrations of isoprenaline in 10 patients.

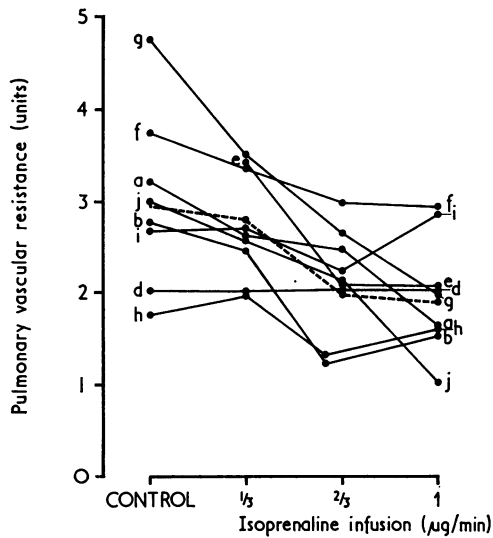


FIG. 6 Variation of pulmonary vascular resistance with progressive concentrations of isoprenaline in 9 patients.

No appreciable changes were observed in aortic, pulmonary, or central venous pressures. Cardiac output increased significantly up to 32 per cent from a mean basal measurement of 5.3 l./min to 7 l./min at an infusion rate of 1 $\mu\text{g}/\text{min}$ of isoprenaline. In 60 per cent of the cases a maximal response had been already reached with $2/3$ $\mu\text{g}/\text{min}$ (Fig. 1).

Heart rate increased only moderately. From a mean basal control of 81 it rose to 98 a minute at 1 $\mu\text{g}/\text{min}$; only 3 patients reached a rate over 100 a minute at this concentration (Fig. 2).

Stroke output increased 20 per cent, from a mean control of 66 ml to 79 ml at $2/3$ $\mu\text{g}/\text{min}$, with subsequent drop at a higher infusion rate. In fact, practically 80 per cent of the cases had their maximal response at the $2/3$ $\mu\text{g}/\text{min}$ level (Fig. 3), though the values are of borderline statistical significance.

The dp/dt changed from an average basal value of 1645 to 2645 with 1 $\mu\text{g}/\text{min}$, representing a significant augmentation of 60 per cent (Fig. 4).

Systemic vascular resistance diminished by 34 per cent during maximal infusion rates (Fig. 5), while pulmonary vascular resistance decreased 37 per cent at a similar concentration of isoprenaline (Fig. 6).

No arrhythmias were induced throughout the investigation, and the clinical tolerance was uniformly good.

Discussion

A number of agents have been used for their inotropic properties in acute myocardial infarction complicated by congestive heart failure or cardiogenic shock.

The use of digitalis, though the best known of these agents, is limited by an increased risk of intoxication due to a reduced threshold at the onset of severe rhythm disturbances. This has been observed in man (Selzer, 1968), and clearly documented in the experimental animal (Bellet, Johnston, and Schechter, 1934; Travell, Gold, and Modell, 1938; Morris *et al.*, 1969). Furthermore, patients during the acute stage of a myocardial infarction may require defibrillation as a form of management of primary life-threatening arrhythmias, and this procedure is more hazardous in the presence of digitalization (Kleiger and Lown, 1966).

The use of non-glycoside agents such as glucagon (Warembourg *et al.*, 1969; Puri and Bing, 1969; Murtagh *et al.*, 1970; Parmley and Sonnenblick, 1971) or dopamine (Talley *et al.*, 1969) can still be considered to be in an experimental phase.

The pharmacological properties of isoprenaline, leading to an increase in cardiac output, diminution of peripheral vascular resistance, improved perfusion of vital organs, and little change in mean pulmonary or systemic pressures (Kaufman, Iglauer, and Herwitz, 1951; Sandler, Dodge, and Murdaugh,

1961), may be desirable in patients with myocardial failure. An advantage, in comparison to digitalis, is the flexibility of administration and withdrawal.

The usefulness of isoprenaline, however, has been limited by the development of conspicuous tachycardia and arrhythmias, poorly tolerated in the condition under discussion.

Our study shows that, with the administration of relatively small doses of isoprenaline, a significant improvement of myocardial performance can be obtained without undue tachycardia or arrhythmias. In fact, cardiac output increased up to 32 per cent. This was accomplished with a relatively minor chronotropic effect and an inotropic action suggested by the increased stroke volume and aortic dp/dt.

The majority of patients evidenced a statistically significant and very adequate haemodynamic response to an infusion rate of only $\frac{2}{3}$ $\mu\text{g}/\text{min}$ isoprenaline, results quite comparable to those described by other investigators for higher concentrations (Elliot and Gorlin, 1966; Morse *et al.*, 1967; Gunnar *et al.*, 1967). In our experience, a dose of 1 $\mu\text{g}/\text{min}$ did not contribute a significant increase in cardiac output, compared to the $\frac{2}{3}$ $\mu\text{g}/\text{min}$ dosage, while further increasing heart rate and reducing stroke output in a number of patients. It is reasonable to believe, therefore, that at higher concentrations myocardial efficiency will diminish.

Though these results have been obtained in a selected group of patients with clinically uncomplicated myocardial infarction, for purposes of standardization of the method, our untabulated experience in patients complicated by congestive failure is similar. Furthermore, there is no doubt that irrespective of the clinical stability of a patient, detailed haemodynamic studies will reveal early and consistent impairment of myocardial function (Karlner and Ross, 1971).

It may be concluded that isoprenaline, apart from its value as an adjunct in the management of patients with hypotension or shock, may find application in the treatment of congestive heart failure, particularly if initial heart rates are not too high. As shown by a concentration-response curve, this can be achieved with relatively small doses and with avoidance of untoward effects.

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