Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction

Haemodynamic study

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In 15 patients with acute myocardial infarction associated with signs of left ventricular dysfunction, phentolamine was infused intravenously in a dose of 10 mg per hour. This therapy induced a substantial reduction in mean right atrial pressure from 10 to 7 mmHg (1.3 to 0.9 kPa) ($P < 0.001$), and in pulmonary capillary wedge pressure from 20 to 13 mmHg (2.7 to 1.7 kPa) ($P < 0.001$). The cardiac index increased from 2.5 to 3.0 l/min per m^2 ($P < 0.001$) accompanied by a fall in both the systemic and pulmonary vascular resistances ($P < 0.001$). On the other hand, the mean stroke work index did not change significantly after phentolamine, because of the combined effects of the increased cardiac output and of the lowered systemic vascular resistance. With the dose used the mean arterial pressure decreased from 112 to 99 mmHg (14.9 to 13.2 kPa) ($P < 0.001$). No adverse effects attributable to the drug treatment were noted.

Benefits of this treatment are probably related to reduction in the impedance to left ventricular ejection and possibly to its relaxant effect on the venous tone. The drug may also improve subendocardial perfusion by decreasing left diastolic ventricular pressure. This could possibly limit extension of necrosis. Thus vasodilator therapy appears to be of particular interest in left ventricular failure complicating acute myocardial infarction, where inotropic agents may be contraindicated.

Left heart failure is a frequent complication of acute myocardial infarction. The treatment of this cardiac insufficiency has hitherto been approached in three different ways: administration of positive inotropic agents, with the aim of increasing the contractility of the remaining unaffected myocardium; vasopressor amines, with the aim of improving coronary perfusion, thus limiting the extent of the infarction; and diuretics, in order to reduce the circulatory volume, thus reducing pulmonary congestion.

These forms of treatment have, in fact, proved disappointing: cardiac output is not always improved by digitalis preparations (Malmcrona, Schröder, and Werkö, 1966; Cohn, Tristani, and Khatri, 1969; Hodges *et al.*, 1972; Rahimtoola *et al.*, 1972), vasopressor amines increase the afterload on an already failing myocardium (Cohn, 1973), and, finally, diuretics can lead to a further fall in cardiac output because of a reduction in

venous return (Cohn *et al.*, 1972; Dikshit *et al.*, 1973).

In earlier work (Enrico, Poli, and Perret, 1971) we were able to observe the beneficial effect of vasodilator therapy in pulmonary oedema resistant to the classic forms of therapy. In hypertensive patients with myocardial infarction a reduction of the afterload, obtained with phentolamine infusion, resulted in the rapid disappearance of pulmonary congestion while at the same time correcting the lactic acidosis secondary to tissue anoxia. Some recent studies have confirmed the benefits of vasodilator therapy in severe chronic cardiac insufficiency (Majid, Sharma, and Taylor, 1971), and in myocardial infarction (Franciosa *et al.*, 1972; Kelly *et al.*, 1973; Chatterjee *et al.*, 1973). The present study was undertaken to determine the haemodynamic effects of phentolamine, administered in low doses with the aim of reducing the afterload without excessively lowering the coronary perfusion pressure.

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Subjects and methods

Selection of patients

Studies were made on 15 patients, 11 men and 4 women, for a period of 24 hours after the onset of symptoms of acute myocardial infarction, in the Intensive Care Unit of the Medical Department of the University of Lausanne. The patients were aged between 34 and 77 years, the average age being 61 years.

The criteria for the diagnosis of acute myocardial infarction included a suggestive clinical history, typical electrocardiographic abnormality, and characteristic increases in the serum aspartate aminotransferase, serum alanine transaminase, and creatinine phosphokinase activity in serial blood samples over the first three days.

Before vasodilator therapy, all but two patients had signs of cardiac failure *viz*: a fourth heart sound gallop rhythm, râles at the lung bases, and radiological signs of pulmonary congestion (Table 1). All these patients had first received oxygen and analgesics. No patients received diuretics or digitalis before administration of phentolamine. Informed consent was obtained from the patients.

Haemodynamic measurements

In all patients right atrial (RA), mean pulmonary arterial (MPA), and pulmonary capillary wedge (PCW) pressures were recorded through a balloon-tip triple-lumen 7 F catheter (Ganz and Swan, 1972). The catheter was introduced via an antecubital or an internal jugular vein, by means of a venous 8 F percutaneous catheter introducer. Pressures were measured with Statham P230B transducers, and recorded on a three-channel thermal writing recorder (Cardiopan 3 T, Philips). The common zero reference level for all pressures was set at 4 cm below the sternal angle, with the patient in the supine position.

Arterial pressures were measured in several patients by an indwelling brachial artery 3 F 'teflon' catheter

inserted percutaneously. In the other cases arterial pressure was measured by the normal cuff from which the mean arterial pressure (MA) was calculated (diastolic pressure plus one-third of the pulse pressure).

Cardiac output (CO) was measured in triplicate by the thermodilution technique using the triple-lumen balloon catheter (Ganz and Swan, 1972). A direct display of cardiac output was provided by a computer (9500 cardiac output computer¹). The results were verified by direct planimetry of the thermal curves.

The haemodynamic variables were calculated from the basic data, as follows:

Cardiac index (CI):

$$\frac{\text{Cardiac output (CO)}}{\text{body surface area (BSA)}} \text{ (l/min per m}^2 \text{ BSA)}$$

$$\text{Stroke volume index (SVI): } \frac{\text{SV}}{\text{BSA}} \text{ (ml per m}^2 \text{ BSA)}$$

Stroke work index (SWI):

$$\text{SVI} \times (\text{MA} - \text{PCW}) \times 0.0136 \text{ (g M per m}^2 \text{ BSA)}$$

Systemic vascular resistance index (SVRI):

$$\frac{\text{MA} - \text{RA}}{\text{CI}} \text{ (mmHg/l min}^{-1} \text{ per m}^2 \text{ BSA)}$$

Pulmonary vascular resistance index (PVRI):

$$\frac{\text{MPA} - \text{PCW}}{\text{CI}} \text{ (mmHg/l min}^{-1} \text{ per m}^2 \text{ BSA)}$$

Procedure

After the balloon had been placed in the correct position, confirmed radiologically, and the patient was in a steady state, as defined by serial haemodynamic measurements, phentolamine, diluted in a solution of 5 per cent dex-

¹Edwards Laboratories, Santa Ana, Calif., U.S.A.

TABLE 1 Clinical data

Case No.	Age (yr)	Sex	Site of infarct	S ³ gallop	S ⁴ gallop	Clinical pulmonary congestion	Chest x-ray
1	68	F	Anterior + inferior	+	+	+++	Pulmonary oedema
2	74	M	Inferior	—	+	++	Pulmonary venous congestion
3	64	M	Inferior	+	+	+++	Pulmonary oedema
4	77	F	Inferior	+	+	+++	" "
5	75	M	Anterior	—	+	+	Pulmonary venous congestion
6	41	M	Anterior	—	+	++	" " "
7	57	M	Anterior	+	+	+	" " "
8	65	M	Inferior	+	+	++	" " "
9	54	M	Inferior	—	+	—	—
10	73	F	Anterior	—	+	++	Pulmonary venous congestion
11	42	M	Anterior	—	—	+	" " "
12	34	M	Anterior	—	+	+	" " "
13	58	F	Anterior + inferior	—	+	+	" " "
14	62	M	Inferior	+	+	++	Pulmonary oedema
15	71	M	Anterior	—	—	—	—

Clinical pulmonary congestion: + = mild; ++ = severe; +++ = pulmonary oedema.

S³ = Third heart sound; S⁴ = Fourth heart sound.

trose, was administered into the right atrium at a rate of 10 mg per hour, for one hour.

All the measurements were repeated at the end of each phentolamine infusion. In 5 patients (Cases 3, 6, 7, 8, and 10), the same procedure was repeated once or twice with a minimum interval of one hour between two successive tests.

Results

The results of the haemodynamic studies are presented in Table 2. The values were measured in steady state before and after a one-hour phentolamine infusion. Response was indicated by an average increase in the cardiac index of 0.5 l/min per m² BSA, secondary to simultaneous increases in both the heart rate and stroke index. This increase in cardiac output was accompanied by a reduction in the mean pulmonary capillary wedge and right atrial pressures from 20 mmHg (2.7 kPa) and 10 mmHg (1.3 kPa) to 13 mmHg (1.7 kPa) and

7 mmHg (0.9 kPa) respectively. The mean pulmonary arterial pressure fell from 32 mmHg (4.3 kPa) to 24 mmHg (3.2 kPa). With the doses used in this study the mean arterial pressure fell, on average, from 112 mmHg (14.9 kPa) to 99 mmHg (13.2 kPa). The systemic vascular resistance fell by an average of 25 per cent. All these changes are highly significant ($P < 0.001$). The mean stroke work index, on the other hand, did not change significantly after phentolamine, because of the combined effects of the lowered peripheral vascular resistance and increased cardiac output.

There is a positive correlation between the fall in mean arterial pressure induced by the phentolamine and the initial mean arterial pressure: $r = -0.81$, $P < 0.001$. On the other hand, there is no simple relation between the changes in the impedance to ejection or the mean arterial pressure and the initial cardiac index or pulmonary capillary wedge pressure values.

TABLE 2

Case No.	Heart rate (beats/min)		Pressures								Cardiac index (l/min per m ² BSA)		Stroke work index (g m per m ² BSA)		Systemic vascular resistance index (mmHg/l min ⁻¹ per m ² BSA)	
			Mean arterial (mmHg)		Right atrium (mmHg)		Mean pulmonary arterial (mmHg)		Pulmonary capillary wedge (mmHg)							
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	120	124	100	90	13	5	40	30	22	14	1.5	1.9	13.5	16	57	45
2	112	120	97	88	13	9	38	34	20	18	2.7	3.1	25	24	31	26
3 a)	84	96	98	93	11	9	34	30	26	20	2.0	3.3	24	34	43	26
b)	80	86	88	92	9	9	34	26	27	15	2.6	3.0	27	36	30	28
c)	80	84	93	93	9	7	29	22	20	15	2.4	2.6	29	33	36	33
4	85	94	140	127	12	9	38	25	28	16	2.5	3.1	44	50	52	38
5	82	96	173	130	8	4	35	25	23	14	3.0	3.4	74	55	56	37
6 a)	82	90	88	84	12	7	30	24	21	12	2.7	3.7	31	41	28	21
b)	85	90	94	84	11	7	32	24	20	12	2.8	3.7	33	41	29	21
7 a)	84	96	127	107	9	5	37	16	18	5	2.5	3.6	45	51	46	29
b)	80	86	107	108	7	5	29	21	12	7	2.5	3.0	41	47	40	35
c)	100	108	117	95	10	8	29	21	20	14	2.6	3.6	34	36	41	25
8 a)	100	110	115	101	5	5	25	20	15	10	2.2	2.6	37	29	49	37
b)	100	105	120	105	6	5	31	20	17	11	2.4	2.6	34	32	48	38
c)	96	108	110	107	5	1	28	15	18	6	2.3	2.5	30	33	49	41
9	52	54	125	115	8	6	19	15	14	10	1.9	2.4	56	62	62	46
10 a)	82	96	110	87	14	8	28	29	20	19	2.7	3.6	40	34	36	22
b)	88	96	113	87	11	10	22	16	14	10	2.5	2.6	38	29	41	29
11	90	98	90	90	16	13	28	25	20	20	2.4	3.5	26	34	30	22
12	84	82	125	107	12	8	40	32	23	15	2.7	3.2	45	49	42	31
13	100	100	118	103	9	9	40	36	20	15	2.4	2.7	32	32	45	36
14	68	68	90	80	12	7	40	32	27	20	2.8	3.0	36	35	28	25
15	125	135	130	108	9	6	34	21	21	10	2.3	2.5	28	25	52	41
Mean	90	97	112	99	10	7	32	24	20	13	2.5	3.0	36	37	42	32
± SEM	3.3	3.6	4.2	2.8	0.6	0.5	1.2	1.3	0.9	0.9	0.07	0.10	2.5	2.3	2.1	1.6
P <	0.001		0.001		0.001		0.001		0.001		0.001		NS		0.001	

Conversion factor from Traditional Units to SI Units: 1 mmHg ≈ 0.133 kPa.

C = Control; P = Phentolamine; S = Survived; D = Died.

In Fig. 1 the changes in the cardiac index in relation to the pulmonary capillary wedge pressure after phentolamine can be seen. In all but one patient (Case 11) the increased output was accompanied by a reduction in the pulmonary capillary wedge pressure. However, if one studies the changes in the stroke work index in relation to the pulmonary capillary wedge pressure (Fig. 2), it can be seen that the significant increase in the cardiac index is not always accompanied by an increase in stroke work. In 3 patients (Cases 5, 8, and 10) there was a slight reduction in the stroke work index. Overall, the same stroke work is obtained with a lower filling pressure.

In 5 patients the test was carried out twice (Cases 6 and 10) or three times (Cases 3, 7, and 8). The second and third tests were carried out between 1 and 24 hours after the end of the previous phentolamine infusion. The haemodynamic response to the vasodilator is comparable in each test (Fig. 3). The

Pulmonary
vascular
resistance
index
(mmHg/l min⁻¹
per m² BSA)

C	P	
12	8	S
7	5	D
4	3	S
4	3	
4	3	
4	3	S
4	3	S
3	3	S
4	3	
8	3	S
7	5	
4	2	
4	4	S
6	3	
4	3	
3	2	S
3	3	S
3	2	
3	1	S
5	5	S
8	8	S
5	4	D
6	4	S
4.9	3.6	
0.5	0.4	

0.001

FIG. 1 Individual changes in cardiac index (CI) and the pulmonary capillary wedge (PCW) pressure after phentolamine intravenous infusion. The dots represent the baseline recordings and the arrow heads the recordings at the end of the infusion. (1 mmHg = 0.133 kPa.)

FIG. 2 Individual changes in the stroke work index (SWI) and pulmonary capillary wedge (PCW) pressure after phentolamine intravenous infusion. The dots represent the baseline recordings and the arrow heads the recordings at the end of the infusion. (1 mmHg = 0.133 kPa.)

effect of phentolamine was seen to wear off in the 30 minutes after the end of the infusion.

The phentolamine infusions were well tolerated. No patient had any chest pain, nausea, or vomiting. No arrhythmia was observed. Of the 15 patients studied, 2 died, 1 from irreversible cardiac insuffi-

FIG. 3 Haemodynamic response to two successive perfusions of phentolamine showing the reproducibility of the effects (Case 6). (1 mmHg = 0.133 kPa.)

ciency, secondary to septal perforation, and the other as a result of ventricular fibrillation.

Discussion

This study indicates that administration of a small dose of phentolamine to patients in the acute phase of myocardial infarction, complicated by left ventricular failure, results in a reduction in the mean systemic arterial blood pressure and pulmonary wedge pressure, with an increase in the cardiac output. For the majority of the patients studied this meant an improvement in left ventricular performance, as shown by the fact that the left ventricular work was maintained or increased, at a lower filling pressure. Similar results have been published by other authors (Kelly *et al.*, 1973; Chatterjee *et al.*, 1973), though the doses used were generally higher. The present study also shows that the haemodynamic improvements are of short duration after cessation of the infusion and that subsequent infusions produce similar haemodynamic effects. The overall clinical course of the cases treated was satisfactory; the mortality rate of 13 per cent in this group of high risk patients was surprisingly low.

The haemodynamic changes observed after phentolamine are the opposite of those described by Ross and Braunwald (1964), following angiotensin administration in patients with non-ischaemic cardiac insufficiency. The response to an increase in afterload induced by angiotensin is characterized by an increase in left ventricular filling pressure and a decrease in stroke volume. This leads to ventricular dilatation and therefore to an increase in ventricular wall tension, which represents one of the factors determining oxygen consumption in the myocardium. This effect could theoretically be counterbalanced by the increased coronary perfusion pressure caused by increased aortic diastolic pressure. However, according to Maroko and Braunwald (1973) there is an optimal coronary perfusion pressure beyond which the increased oxygen requirement exceeds the increased supply, thus leading to relative ischaemia. It appears that in patients with myocardial infarction the optimal pressure is usually within the normal range of arterial blood pressure. It is probable that in these patients even a moderate increase in the impedance to ventricular ejection is sufficient to aggravate the imbalance between the oxygen supply and demand of the myocardium.

Acute arterial hypertension is common in the first few hours after infarction. It is classically ascribed to an intense sympathetic stimulation and to the release of catecholamines. The resulting increased peripheral vascular resistance has the effect of raising metabolic requirements by increasing the left ventricular wall tension. To this is added the oxygen wasting effect of catecholamines (Raab *et al.*, 1962; Braunwald, 1971). Finally, it is possible that the rise in left ventricular diastolic pressure, if great enough, may impair the oxygen supply to the subendocardial area resulting in extension of the necrosis.

Therefore, under these conditions one may expect a reduction in the impedance to ventricular ejection to improve the myocardial performance and reduce the extent of myocardial damage by improving the balance between the coronary perfusion and the local metabolic requirements of the myocardium. If this is the case, then phentolamine would have the dual effect of preventing or correcting the heart failure, and possibly preventing extension of the necrosis. The effects of phentolamine on ventricular performance are explained essentially by its action on the resistance vessels, though not entirely. Phentolamine in fact combines antagonism toward catecholamines (alpha-blocking properties) with a direct action leading to relaxation of the smooth muscle of the vessels. This results in vasodilatation with a reduction in the systemic

vascular resistance (Taylor *et al.*, 1965; Nickerson, 1965). This reduction in the impedance to left ventricular ejection leads to a fall in pulmonary capillary pressure parallel to the fall in left ventricular end-diastolic pressure and consequently to a reduction in the residual ventricular volume (Cohn *et al.*, 1972).

Furthermore, because of its relaxant effect on the venous tone (Abboud and Eckstein, 1968; Villani *et al.*, 1974), phentolamine can induce a shift of blood volume to the periphery which could also lead to a further fall in left ventricular filling pressure. However, this mechanism only plays an accessory role, since the reduced preload obtained with tourniquets, bleeding, or diuretics, is itself accompanied by a reduction in cardiac output (Cohn *et al.*, 1972).

There is no conclusive evidence that phentolamine has any inotropic effect (Chatterjee *et al.*, 1973; Abboud and Eckstein, 1968), but the possibility that the fall in left ventricular end-diastolic pressure induced by phentolamine may indirectly improve the myocardial performance, by improving the subendocardial perfusion, cannot be excluded. Vasodilator therapy with phentolamine has no adverse effect on the overall myocardial oxygen metabolism, as may be seen from the absence of any significant reduction in the extraction of lactate by the myocardium (Chatterjee *et al.*, 1973). This suggests that the effect of a possible reduction in coronary perfusion secondary to the fall in aortic pressure is largely compensated by the reduction in the oxygen requirement of the myocardium, resulting from the reduction in the afterload.

Vasodilator therapy with phentolamine is not necessarily reserved for hypertensive patients. In low doses (10 mg per hour) it has proved beneficial in normotensive subjects in whom the reduced cardiac output was masking the increased peripheral resistance. With such small doses it has never been necessary to discontinue the treatment as a result of arterial hypotension. It should, therefore, be emphasized that one of the principal advantages of phentolamine administered by infusion is its short duration of action, which renders it easily manageable. Nevertheless, such a therapeutic procedure should only be employed where haemodynamic monitoring facilities are available. In this respect, surveillance of the pulmonary wedge pressure is an extremely useful index for assessing the response to the treatment.

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