BENEFICIAL EFFECTS OF CAPTOPRIL IN LEFT VENTRICULAR FAILURE IN PATIENTS WITH MYOCARDIAL INFARCTION

J.P. BOUNHOURE, J.G. KAYANAKIS, J.M. FAUVEL & J. PUEL

Departments of Clinical and Experimental Cardiology and Heart Disease, C.H.U. of Toulouse Rangueil 31054, France

1 Ten patients with acute myocardial infarction and left ventricular failure were studied. Acute myocardial infarction was anterolateral in eight patients, posterolateral in one, and anteroseptal in one. Three patients were grade II, 4 grade III, and 3 grade IV of Killip's classification. None presented with arterial hypertension but mean values of plasma renin activity and serum aldosterone were 20.7 ng/ml/h and 13.5 ng/100 ml. Haemodynamic measurements were performed by using a flow-directed catheter. Cardiac output was determined in triplicate by thermo-dilution (Edwards computer). Classic haemodynamic measurements included: heart rate, cardiac index, stroke volume index, stroke work index, blood pressure, right atrial pressure, pulmonary vascular resistance, systemic vascular resistance, and pulmonary diastolic blood pressure. Curves of ventricular function correlating stroke work index and pulmonary diastolic blood pressure were constructed. Haemodynamic changes after drug therapy were tested for significance using the paired *t* test. All patients received heparin, oxygen, and an intravenous infusion of isosorbide dinitrate.

2 Haemodynamic measurements were repeated at 30 min intervals and after isosorbide infusion until values returned to normal. The infusion was then discontinued and pressures returned to control values. At this time, oral captopril was administered, the first dose being 12.5 mg. Subsequent doses of 12.5 mg up to 50 mg were given if systolic blood pressure remained above 100 mm Hg and pulmonary diastolic pressure greater than 18 mm Hg. When the most effective oral dose was determined it was administered at six hourly intervals. This therapy resulted in an improvement of functional class, with a reduction in Killip's grade from class III to 1.7 (mean value). Heart rate, mean atrial pressure, and pulmonary diastolic pressure decreased by 10%, 32% and 41%. Cardiac index increased from 2.4 ± 0.8 l/min/m² to 2.8 ($p < 0.02$) and stroke volume index increased by 37.2%. Pulmonary vascular resistance decreased by 22.14% ($p < 0.001$) and the product of heart rate $\times$ blood pressure decreased by 33.6% ($p < 0.001$).

3 Haemodynamic effects of oral captopril treatment were beneficial in left ventricular failure and acute myocardial infarction without immediate side effects. In acute left ventricular failure the renin angiotensin system was appreciably stimulated. All ten patients who were treated for a mean of 6.5 days showed a significant subjective, clinical, and haemodynamic improvement. After discharge from the coronary care unit anterolateral infarctions produced by ventricular fibrillation resulted in four deaths.

4 These data suggest that captopril may be an effective therapy in acute myocardial infarction with left ventricular failure and that it is more effective than other vasodilators. Nevertheless, more patients need to be studied for a longer period before definite conclusions can be drawn.

Introduction

The evaluation of haemodynamic and clinical responses to the oral enzyme inhibitor captopril in patients with chronic heart failure has been the subject of many recent investigations. In long-term therapy treatment for patients with chronic and refractory heart failure captopril improves haemodynamic state, with a decline in vascular resistance and left end diastolic ventricular pressure and an increase in cardiac output. (LeJemtel *et al.*, 1982).

But there are no studies in the acute left ventricular failure of recent myocardial infarction. Enhanced activity of the sympathetic nervous system and increasing concentrations of circulating catecholamines have been thought to contribute to arteriolar vasoconstriction and an increase in systemic vascular resistance and in impedance of ejection, reducing cardiac output. (Chatterjee & Parmley, 1977). In acute and sudden ventricular failure the

renin-angiotensin-aldosterone system is intensively stimulated. The goal of our study was to evaluate clinical and haemodynamic effects of repeated administration of captopril in the acute phase of ischaemic left ventricular failure.

Methods

Eighteen patients were treated but eight patients dropped out so that in them no sequential haemodynamic studies were carried out. Ten patients with acute myocardial infarction were treated and studied. The age range was 51–74 (mean 66). Acute myocardial infarction was anterolateral in eight patients, inferior and lateral in one and septal in one. Three patients were grade II, four grade III, and three grade IV of Killip's classification. None presented with arterial hypertension but mean values of plasma renin activity were 20.7 ng/ml/h and serum aldosterone 13.5 ng/dl. All classic haemodynamic measurements were studied in the coronary care unit after cannulation of the brachial artery for invasive measurement of mean arterial pressure. A Swan-Ganz balloon-tipped thermodilution catheter was advanced to the pulmonary artery. Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were determined by using Thompson-Telco transducers and recorders. Cardiac output was determined in triplicate by using the thermodilution technique and Edwards computer. Haemodynamic indexes were calculated and left ventricular function curves were constructed correlating stroke work index and diastolic pulmonary pressure before and after treatment.

The following haemodynamic variables were measured: mean arterial pressure, heart rate, right atrial pressure, cardiac output, cardiac index, stroke volume index, stroke work index, systemic arterial resistances $80 \times (\text{mean arterial pressure} - \text{right atrial pressure})/\text{cardiac output}$ (dyne/s/cm^{-5}); pulmonary arterial resistances $80 \times (\text{mean pulmonary pressure} - \text{pulmonary wedge pressure})/\text{cardiac output}$ (dyne/s/cm^{-5}); double product = heart rate $\times$ mean arterial pressure mm Hg $\text{min} \times 10^{-2}$.

There were four periods in our study:

- On entry to the coronary care unit catheters were inserted for haemodynamic measurements after a six-hour period of stability;
- Infusion of 10 mg of isosorbide dinitrate diluted with isotonic serum and perfused by electric infusion pump. The dose range was 40–70 $\mu\text{g/h}$. Haemodynamic measurements were performed and indexes calculated every 30 min;
- After 24 hours of isosorbide dinitrate infusion and if haemodynamic variables returned to normal or near normal, the infusion was discontinued and

pressures curves were allowed to return to control values;

- After this period of washout oral captopril was given to each patient at a dose of 12.5 mg, repeated half an hour later. If systolic blood pressure was higher than 100 mm Hg and diastolic pulmonary pressure higher than 18 mm Hg another dose of 12.5 mg was given half an hour later. The optimal dose of the drug was considered that which caused the greatest increase of cardiac output without producing hypotension.

When the effective oral dose has been determined captopril was given every six hours. The mean daily dose was 80 mg in four doses and the mean duration of treatment was six days (range 5–10).

Student's paired *t* test was used to determine the statistical significance of the haemodynamic data. Results are expressed as the mean $\pm$ SD and are considered significant at the $p < 0.05$ level. The protocol was approved by the local ethical committee of our institution.

Results

Clinical data

Captopril produced an improvement in functional classes with a mean reduction in Killip's grade from class III to about 1.7. Most patients reported an improvement in their dyspnoea with cessation of their sweating. The major functional effect appeared on the second day of treatment with captopril.

Haemodynamic results (Table 1)

Heart rate fell in all patients on captopril (mean value before 97 ± 2.56 beats/min and 78.2 ± 2.26 beats/min (after treatment), but there was no significant variation with isosorbide dinitrate.

A significant reduction in mean arterial systemic pressure occurred with the two vasodilators. (Control 96.2 ± 5.06 mm Hg; 81 ± 3 mm Hg with isosorbide 94.2 ± 4 mm Hg before captopril; 77.6 ± 5.86 mm Hg after captopril. But there was no significant variation between isosorbide and captopril on the mean value reduction. Right atrial pressure decreased significantly by 3 mm Hg with isosorbide and by 2.7 mm Hg with captopril ($p < 0.001$). Diastolic pulmonary artery pressure fell from its control value of 28 mm Hg to 16 mm Hg with captopril (-41.6%) and from 28 to 19.5 mm Hg with isosorbide ($p < 0.001$ for captopril).

Cardiac output increased with isosorbide and captopril at the same level. Stroke volume index increased by 37.2% with captopril (26.76 ± 0.59 ml a 36.7 ± 1.10 ml/syst/m²). This gain was very significant ($p < 0.001$). Stroke work index was very low

Table 1 Variations in haemodynamic mean values

	<i>Basal</i>	<i>Isosorbide</i>	<i>Captopril</i>
Mean arterial pressure	96.20 ± 11.5	81 ± 11.2***	77.60 ± 13.3***
Heart rate	97.70 ± 18.80	97 ± 11.66	78.20 ± 2.26**
Right atrial pressure	8.50 ± 2.5	5.50 ± 1.16****	5.80 ± 1.6****
Diastolic pulmonary pressure	28.50 ± 4.6	19.50 ± 3.37***	16.80 ± 2.6****
Cardiac output	4.43 ± 0.93	5.03 ± 1.01***	5.05 ± 1.03**
Cardiac index	2.50 ± 0.59	2.86 ± 0.56***	2.86 ± 0.68**
Stroke volume	26.76 ± 7.76	30.20 ± 8.63	36.72 ± 8.44****
Stroke work index	27.38 ± 10.71	26.59 ± 8.5	31.51 ± 9.03*
Pulmonary arterial resistance	197.640 ± 77	160.640 ± 115.39	153.880 ± 152.6****
Systemic arterial resistance	1630.5 ± 367.2	1275.8 ± 489***	1236.3 ± 575.6***
Double product	120.21 ± 24.3	101.5 ± 16.14	79.77 ± 29****

* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$; **** $p < 0.001$

Figure 1 Percentage variations in heart rate (H.R.), mean arterial pressure (M.A.P.) right atrial pressure (R.A.P.), diastolic pulmonary pressure (D.P.P.), pulmonary and systemic arterial resistance (P.A.R. and S.A.R.), stroke work index (S.W.I.), cardiac output (C.O.), cardiac index (C.I.), and stroke index (S.I.). (Results are mean values after 24 hours of infusion of 10 mg of isosorbide dinitrate diluted with isotonic serum and infused with electric pump). Dose range 40–70 µg/h.

Figure 2 Effects of captopril treatment. Percentage variations in same haemodynamic variables as in Figure 1. The more important result in the decrease of diastolic artery pulmonary pressure and of the heart rate, which results in an improvement of stroke work index.

before the treatment—a sign of a bad prognosis. (27.38 ± 1.11 gm/syst/ m^2). The index increased insignificantly with isosorbide and by 15% with captopril ($p = 0.05$).

The reduction in pulmonary arterial resistance of 22% with captopril was very significant ($p < 0.001$). Systemic arterial resistance fell from 1630 ± 106 dyne/s/ cm^{-5} to 1275 ± 91 dyne/s/ cm^{-5} with isosorbide and from 1630 to 1236 dyne/s/ cm^{-5} with captopril—very significant reductions.

Discussion

Captopril in the left ventricular failure of myocardial infarction produced beneficial haemodynamic responses. Its effects were observed within one or two hours. Pulmonary diastolic pressure fell and remained at a lower level than the control value for about six hours. There was a reduction of systemic resistance and an increase in cardiac output, stroke volume, and stroke work index. In left ventricular failure decreasing systemic vascular resistance to improve cardiac performance is the basis for the use of vasodilator therapy (Chatterjee & Parmley, 1977). With captopril ventricular function curves correlating stroke work index and diastolic pulmonary pressure show the displacement on the left of points of ventricular function before and after treatment. While the increase in stroke volume induced by this angiotensin-converting-enzyme inhibitor may be explained by the reduction of impedance of cardiac ejection, the

decrease in both atrial pressure and pulmonary pressure is not fully understood. Captopril may affect venous capacitance but this effect is controversial and angiotensin has no direct effect on venous capacitance.

LeJemtel *et al.* (1982) found that captopril treatment (by improving cardiac performance) resulted in reflex sympathetic withdrawal and attenuation of noradrenaline-induced vasoconstriction. Vrobel & Cohn (1980) reported a decrease in circulating noradrenaline concentrations after administration of angiotensin-converting-enzyme inhibitor in heart failure.

Captopril is an effective possible treatment of the most dangerous complication of acute myocardial infarction—left ventricular failure. All patients showed an initial improvement, with reduction of pulmonary congestion and reduction of signs of low cardiac output. The treatment requires serial haemodynamic measurements of pulmonary and mean systemic arterial pressure for assessing left ventricular function. Like other vasodilators such as isosorbide dinitrate, phentolamine, and sodium nitroprusside, oral captopril treatment is effective without an exacerbation of ischaemic signs.

Right atrial and pulmonary pressure fell, systemic and pulmonary resistance decreased, and cardiac output and stroke volume increased. One significant difference between the haemodynamic effects of other vasodilators and captopril was the tendency to slow the heart rate. In our experience results are better with oral captopril than with nitrates. Like

Nicholls *et al.* (1982) we found that on withdrawal of captopril there was little rebound haemodynamic deterioration or worsening of left ventricular function. During treatment neither anginal attacks nor extension of myocardial ischaemia occurred. The prognosis of acute left ventricular failure is, however, very poor and correlates with the extension of myocardial necrosis. Left ventricular failure

corresponds to a severe impairment of myocardial function and is chiefly related to extensive loss of left ventricular muscle. All studies with pharmacological agents, mechanical circulatory assistance, or surgery show a high mortality of 50% to 70%. Our experience with captopril is too brief for firm conclusions but this treatment seems to be worth evaluating with serial haemodynamic monitoring.

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