Vasodilator therapy in acute myocardial infarction

Use of sublingual isosorbide dinitrate

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The haemodynamic effect of a long-acting vasodilator isosorbide dinitrate has been studied in 10 patients after an acute myocardial infarct, all of whom had evidence of left ventricular failure. Left ventricular filling pressure measured as the mean pulmonary artery wedge pressure was raised in all patients and fell significantly from 20 ± 6 to 13 ± 5 mmHg ($P < 0.001$) within 10 minutes of sublingual isosorbide dinitrate. This 35 per cent fall in left ventricular preload was accompanied by significant fall in mean pulmonary artery pressure from 30 ± 7 to 20 ± 4 mmHg ($P < 0.001$) and mean right atrial pressure from 11 ± 3 to 6 ± 2 mmHg but cardiac output measured by thermodilution was unchanged. Mean systemic blood pressure was also significantly reduced. This improvement in left ventricular performance resulting from a reduction in left ventricular filling pressure and systemic blood pressure indicates that there may be a place for long-acting vasodilators in the treatment of acute myocardial infarction.

The relief of angina pectoris by vasodilators may be partly the result of the reduction in left ventricular work consequent upon a fall in venous and systemic blood pressure. The effect of such a reduction in left ventricular preload and afterload (both of which are determinants of myocardial oxygen consumption) has been reported in patients with acute myocardial infarction, using vasodilators such as sodium nitroprusside (Franciosa *et al.*, 1972) and phentolamine (Kelly *et al.*, 1973) but, recently, interest has been renewed in the use of nitrates (Delgado *et al.*, 1975; Williams *et al.*, 1975). A limiting factor is the short duration of action of glyceryl trinitrate though a topical ointment (Reichek *et al.*, 1974) and intravenous infusions have been used to overcome this (Flaherty *et al.*, 1976). Isosorbide dinitrate is an alternative nitrate with similar but much longer action, and has been used in angina pectoris and chronic left ventricular failure (Kovick *et al.*, 1976; Mantle *et al.*, 1976). Its effect was, therefore, investigated in patients with acute myocardial infarction, in whom there was evidence of acute left ventricular failure.

Patients and methods

Ten patients (9 male and 1 female) with a mean age of 62 (± 9) years who had been admitted to the

coronary care unit with an acute myocardial infarct were studied. The diagnosis was based on a typical history, serial changes in a 12-lead electrocardiogram with new Q waves, and an appropriate rise and fall in cardiac enzymes (World Health Organization, 1959). All patients had a portable posteroanterior chest x-ray film shortly after admission.

Six patients had anterior myocardial infarcts, three inferior infarcts, and one left bundle-branch block. Two patients had also had a previous myocardial infarction. Clinical evidence of left ventricular failure was present in all patients. Seven had third or fourth heart sounds, 9 had radiological changes of pulmonary oedema, and most had audible basal crepitations.

HAEMODYNAMIC MEASUREMENTS

After informed consent had been obtained, a 7F Swan Ganz flow directed thermodilution catheter was passed under fluoroscopic control from an antecubital vein into the pulmonary artery. The patency of the catheter was maintained by a slow infusion of heparin in 5 per cent dextrose (5000 units 12-hourly). The catheter was connected to an Elcomatic transducer and electromanometer from which measurements of mean right atrial, pulmonary artery, and pulmonary artery wedge pressure were made, the latter being obtained by inter-

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mittent inflation of the catheter balloon. All measurements were made with the patient supine and free from pain, using the midpoint of the antero-posterior diameter of the chest as the zero reference level. The initial study was made within 24 hours of infarction in 9 patients, 4 of whom had a second study on the following day. No diuretics or analgesics had been administered within 4 hours of the study.

Cardiac output was measured using the thermodilution technique (Ganz and Swan, 1972) and the St. Thomas's Cardiac Output Computer (Cardiovascular Instruments Ltd. 3750). On each occasion the cardiac output was measured in triplicate and the mean calculated. The patients were attached to a Sanborn bedside electrocardiographic monitor from which the heart rate was recorded. Systemic blood pressure was measured with a standard sphygmomanometer cuff using the first and fourth Korotkoff sounds for systolic and diastolic pressure, respectively.

The intracardiac pressures, cardiac output, heart rate, and systemic blood pressure were measured at the start and at the end of a 30-minute control period. If the baseline measurements were unchanged 5 mg isosorbide dinitrate was given sublingually and further measurements made after 5 to 10 minutes, 25 to 30 minutes, 1 hour and 2 hours.

The following calculations were made:

Cardiac index (CI)=

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

Systemic vascular resistance=

$$\frac{\text{mean BP} - \text{mean RAP}}{\text{CO}} \quad (\text{units})$$

where RAP=right atrial pressure

Left ventricular stroke work index (LVSWI)

$$= \text{SI} \times (\text{MSP} - \text{LVFP}) \times 0.0136 \quad \text{g m/beat per m}^2$$

BSA where SI (stroke index)=

$$\frac{\text{CI}}{\text{heart rate}}$$

MSP (mean systolic blood pressure)

= 0.8 (systolic BP - diastolic BP) × diastolic BP
and LVFP (left ventricular filling pressure) = mean pulmonary artery wedge pressure (Walker *et al.*, 1973).

The method of statistical analysis used was the paired t test.

Results

A total of 14 studies was made in the 10 patients all of whom had a raised mean pulmonary artery wedge pressure (greater than 12 mmHg) during the control period. The striking haemodynamic effect was a 37 per cent reduction in mean pulmonary artery wedge pressure from 20 ± 6 to 13 ± 5 mmHg within 10 minutes of drug administration. This change which is highly significant ($P < 0.001$) was accompanied by a highly significant reduction in mean pulmonary artery pressure from 29 ± 7 to 21 ± 6 mmHg ($P < 0.001$) (Fig. 1). There was also a fall in the mean right atrial pressure from 11 ± 3 to 6 ± 2 mmHg. This effect persisted for between 1 and 2 hours and for some patients longer.

Fig. 2 shows a small rise in heart rate of 5 beats per minute at 10 minutes and a significant fall in mean blood pressure. The change in systolic blood pressure was greater than in diastolic pressure and indeed diastolic blood pressure was not significantly altered.

Cardiac output in individual patients varied after isosorbide dinitrate but the maximal reduction in mean cardiac output for the group of 3.4 to 3.3 l/min was not significant (Fig. 2). Systemic vascular resistance and left ventricular stroke work index both fell slightly but did not reach levels of statistical significance (Fig. 3) but a significant fall in pulmonary vascular resistance occurred at 30 minutes.

There were no complications of treatment. Two patients had a diuresis during the 4 hours after isosorbide; both these patients were breathless and were symptomatically improved.

Fig. 1 This shows the mean ($\pm$ SD) change in mean pulmonary artery and pulmonary artery wedge pressures after 5 mg isosorbide dinitrate.

Fig. 2 This shows the mean ($\pm$ SEM) change in heart rate, mean blood pressure, mean right atrial pressure, and cardiac output after 5 mg isosorbide dinitrate.

Discussion

The management of left ventricular failure after acute myocardial infarction remains a therapeutic problem. Patients with raised left ventricular end-diastolic pressure and low cardiac index have a higher mortality than other patients in spite of conventional therapy with inotropic agents (Scheidt *et al.*, 1973). In addition not all patients respond to diuretics, and studies with frusemide (Kiely *et al.*, 1973) suggest that as many as 50 per cent fail to obtain reduction in left ventricular filling pressure.

In the present study we have shown the beneficial haemodynamic effect of alternative treatment using a long acting nitrate as a vasodilator. Sublingually, isosorbide dinitrate produces a rapid fall in left ventricular preload and systemic blood pressure in all patients within 10 minutes, with a significant effect persisting for 2 hours. This occurred with only a slight initial increase in heart rate and no significant alteration in cardiac output. The likely benefits to the myocardium of the considerable fall in left ventricular filling pressure are a reduction in left ventricular end-diastolic volume (Willis *et al.*, 1976) and left ventricular wall tension with a subsequent fall in myocardial oxygen demand. This effect on oxygen requirement is in direct contrast to that produced by positive inotropic agents. Nitrates are in addition coronary vasodilators and, either by this mechanism or as a result of the fall in preload, increase blood flow to the ischaemic areas of myocardium (Becker *et al.*, 1971). The net effect

Fig. 3 This shows the mean ($\pm$ SEM) change in pulmonary vascular resistance (PVR), left ventricular stroke work index (LVSWI), and systemic vascular resistance (SVR).

after acute myocardial infarction may be a limitation in infarct size, and recent ST segment mapping studies by Flaherty *et al.* (1976) lend support to this theory.

Response to vasodilators may depend on the initial haemodynamic measurements. Their effect in reducing left ventricular preload is similar in all patients, but those with the highest initial left ventricular filling pressure appear to obtain the greatest reduction. The effect on left ventricular stroke work is more variable. Chatterjee *et al.* (1972) and Gold *et al.* (1972) report a decrease in left ventricular stroke work when this is normal before treatment, but an increase in left ventricular stroke work in patients with severe pump failure, in whom this is low before treatment. Similar findings have been reported in chronic cardiac failure (Mikulic *et al.*, 1975; Mantle *et al.*, 1976).

Little is known of the renal effects of isosorbide and other vasodilators, but a diuresis was observed in 2 patients in our series and by other authors (Mantle *et al.*, 1976). Isosorbide has been regarded as a mild osmotic diuretic (Lant, 1975) but this requires further study.

The exact place of vasodilators has still to be defined in acute myocardial infarction, but isosorbide dinitrate appears to be an alternative therapeutic agent in those patients with left ventricular failure who do not respond to diuretics. Some improvement in short-term prognosis has been achieved with chronic vasodilator treatment in patients with 'pump' failure (Chatterjee *et al.*, 1976), but its use

in less severe cases of myocardial infarction will depend on further evaluation of its effect in limiting infarct size.

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