Improvement in exercise haemodynamics by isosorbide dinitrate in patients with severe congestive cardiac failure secondary to ischaemic heart disease

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SUMMARY Seven patients with severe chronic congestive cardiac failure secondary to ischaemic heart disease performed submaximal supine exercise before and after 5 mg sublingual isosorbide dinitrate at the time of cardiac catheterisation. Exercise before isosorbide dinitrate produced a poor response in left ventricular performance. After isosorbide dinitrate this response was significantly improved. Compared with the control exercise period, cardiac index increased from mean 2.6 to 3.1 l/min per m² ($P < 0.0025$), stroke volume index from mean 22 to 27 ml/m² ($P < 0.0025$), and left ventricular stroke work index from mean 21 to 30 g m/m² ($P < 0.01$). Mean left ventricular filling pressure fell from 37 to 26 mmHg ($P < 0.01$).

Although isosorbide dinitrate reduced left ventricular filling pressure at rest from mean 26 to 17 mmHg ($P < 0.005$), there was no significant change in mean cardiac index or stroke volume index, while left ventricular stroke work index decreased from mean 29 to 22 g m/m² ($P < 0.05$).

Isosorbide dinitrate effectively reduces left ventricular filling pressure in the resting patient with congestive cardiac failure but produces a more comprehensive improvement in left ventricular performance during exercise.

Vasodilating agents have been shown to improve left ventricular performance in patients with congestive cardiac failure after acute myocardial infarction (Gold *et al.*, 1972; Chatterjee *et al.*, 1973; Bussmann *et al.*, 1977) and with chronic congestive cardiac failure (Majid *et al.*, 1971; Guiha *et al.*, 1974; Miller *et al.*, 1975; Rossen *et al.*, 1976). Of the orally available agents, isosorbide dinitrate has been shown to be effective in reducing left ventricular filling pressure in congestive cardiac failure for 4 to 5 hours after administration (Franciosa *et al.*, 1974; Williams *et al.*, 1977). Sublingual isosorbide dinitrate appears to be effective in this respect for 1½ hours (Gray *et al.*, 1975). In the ambulant patient with congestive cardiac failure an important therapeutic objective is the improvement of his exercise tolerance. This study was designed to assess further the possible usefulness of long-term treatment with isosorbide dinitrate in this respect.

Patients and methods

Seven patients with chronic congestive cardiac failure undergoing cardiac catheterisation were studied. Severe exertional dyspnoea was the predominant symptom, though angina pectoris was a feature in some. All were receiving treatment with large doses of diuretics. In addition, some patients were receiving digoxin. Chest x-ray films showed cardiomegaly and upper lobe blood redistribution in all patients. The aetiology of the congestive cardiac failure was judged to be ischaemic heart disease in all on historic and electrocardiographic evidence (Table 1). Forty-eight hours before cardiac catheterisation digitalis therapy was withdrawn. Diuretic therapy was continued. Pre-medication was with diazepam 10 mg. Informed consent was obtained in all cases. Left ventricular angiography was performed in the right anterior oblique position via a right brachial arteriotomy using a NIH catheter. Coronary arteriography was subsequently performed in 6 patients. A thermodilution catheter was advanced to the pulmonary

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Table 1 Patient data

Case No.	Age and sex	Presenting symptom	Electrocardiogram	Level of exercise (kpm)	Coronary arteriogram No. of vessels with > 50% stenosis	Left ventricular ejection fraction (%)
1	65 M	Dyspnoea, angina	Old DMI, old AMI	75	3	24
2	58 M	Dyspnoea, angina	Diffuse ST-T changes	75	3	31
3	67 M	Dyspnoea	Old DMI, old AMI	150	2	21
4	50 M	Dyspnoea	Old AMI	75	Not performed	32
5	52 M	Dyspnoea	Old DMI, old AMI	150	3	18
6	57 M	Dyspnoea, angina	Old DMI, old AMI	75	3	17
7	45 F	Dyspnoea	Old AMI	75	1	19

Abbreviations: AMI, anterior myocardial infarction; DMI, diaphragmatic myocardial infarction.

artery. Pressures were measured using Bell and Howell transducers with zero set at mid-chest and recorded on a Mingograf 82 recorder at paper speeds of 25 mm/s (50 mm/s for left ventricular pressure). Cardiac output was measured in triplicate¹ by the thermodilution technique (Ganz and Swan, 1972) using a Waters cardiac output computer.

After completion of the angiograms, a 40-minute rest period was allowed. Previous studies indicate that this is an adequate period for recovery from the effects of angiographic contrast material (Mullins *et al.*, 1972). Control recordings of heart rate, pulmonary arterial and left ventricular pressures, and cardiac output were made. The patient then performed supine leg exercise on a bicycle ergometer at a submaximal work rate (determined on a separate occasion before catheterisation) for a period of 2½ to 3 minutes, after which time recordings were repeated. Exercise was discontinued and a 5-minute rest period allowed. Isosorbide dinitrate, 5 mg, was then administered sublingually after a second series of control recordings. Ten minutes after isosorbide dinitrate administration recordings were repeated at rest and during exercise at the same work rate and for the same time as before.

Left ventricular end-diastolic pressure was measured at the intercept of the downstroke of the 'a' wave and the upstroke of the left ventricular pressure curve averaged for 10 beats. The time from the onset of the upstroke of the curve to the point on its downstroke where left ventricular pressure was equal to the left ventricular end-diastolic pressure was taken to represent the left ventricular ejection period.² Mean left ventricular systolic pressure was obtained by dividing the area between these points by the left ventricular ejection period. Left ventricular stroke work index, $g\ m/m^2 = (\text{mean}$

left ventricular systolic pressure—left ventricular end-diastolic pressure) $\times$ stroke volume index $\times$ 0.0136. Tension-time index, $mmHg\ s/min = \text{left ventricular area} \times \text{heart rate}$. Left ventricular ejection fraction was calculated from the left ventricular cineangiogram (Sandler and Dodge, 1968).

Results

CINEANGIOGRAPHIC DATA (Table 1)

Left ventricular cineangiography showed severe reduction in ejection fraction in all patients. The contraction pattern was diffusely abnormal in all patients, there being no areas where motion was paradoxical, i.e. aneurysmal.

Coronary arteriography showed significant stenosis of one or more major coronary arterial branches in all 6 patients in whom this was performed.

HAEMODYNAMIC DATA

Effects of exercise (Table 2)

The degree of exercise achieved was modest (75 to 150 kpm—Table 1). The resting left ventricular end-diastolic pressure was greater than 16 mmHg in all but one patient. Supine exercise was associated with a 29 per cent increase in mean heart rate. Changes in cardiac index and stroke volume index were variable, increasing in some patients and decreasing in others, there being no change in mean values. Mean left ventricular end-diastolic pressure and mean pulmonary arterial pressures rose significantly (57% and 48%, respectively). Left ventricular stroke work index increased in some patients and decreased in others, there being no change in the mean. Mean tension-time index rose by 18 per cent. Mean left ventricular systolic pressure did not change significantly.

Effects of isosorbide dinitrate on resting haemodynamics (Table 3)

The principal haemodynamic effect of isosorbide

¹Technically unsatisfactory thermal curves were repeated giving < 10 per cent variation in values accepted.

²This slightly overestimates left ventricular ejection period derived from the aortic pressure trace.

Table 2 *Haemodynamic effects of exercise*

Case No.	HR		CI		SVI		MPA		LVSP		LVEDP		LVSWI		TTI	
	R	E	R	E	R	E	R	E	R	E	R	E	R	E	R	E
1	90	135	2.1	2.4	23	18	27	50	122	114	25	45	30	17	4312	5465
2	70	115	3.0	3.6	43	31	25	50	116	106	30	42	50	27	3964	3814
3	100	130	2.7	2.5	27	19	18	50	72	84	12	38	22	12	2673	3360
4	86	97	1.7	1.2	20	12	40	50	—	—	24	26	—	—	—	—
5	90	115	1.8	2.9	20	25	40	48	92	115	32	36	16	27	994	1587
6	100	110	2.1	2.4	21	22	35	44	99	103	32	38	19	19	1972	2266
7	103	120	2.8	3.2	27	27	28	40	80	103	22	35	21	25	1318	1487
Mean	91	117	2.3	2.6	26	22	30	47	97	104	25	37	26	21	1540	2996
± SEM	4.6	5.2	0.2	0.3	3.3	2.6	3.3	1.6	8.8	5.0	2.9	2.4	5.6	2.7	613	684
P	<0.0025		NS		NS		<0.0025		NS		<0.005		NS		<0.025	

Abbreviations: HR, heart rate in beats/min; CI, cardiac index (l/min per m²); SVI, stroke volume index (ml/m²); MPA, mean pulmonary arterial pressure (mmHg); LVSP, mean left ventricular systolic pressure (mmHg); LVEDP, left ventricular end-diastolic pressure (mmHg); LVSWI, left ventricular stroke work index (g m/m²); TTI, tension-time index (mmHg-s/min); ± SEM, standard error of mean; P, P value; R, rest; E, exercise; NS, not significant.

Table 3 *Effects of isosorbide dinitrate on resting haemodynamics*

Case No.	HR		CI		SVI		MPA		LVSP		LVEDP		LVSWI		TTI	
	R	R ^I	R	R ^I	R	R ^I	R	R ^I	R	R ^I	R	R ^I	R	R ^I	R	R ^I
1	90	87	2.4	2.0	27	23	25	15	142	89	30	18	41	22	4666	3055
2	70	78	3.1	2.6	44	33	25	14	113	91	30	8	50	37	3808	3741
3	100	100	2.7	2.8	27	16	18	18	72	65	12	12	22	12	2673	2592
4	90	84	2.6	1.7	19	19	45	40	—	—	26	17	—	—	—	—
5	87	80	2.0	1.9	23	24	45	28	100	85	34	24	21	20	1044	1088
6	96	96	2.1	2.4	21	25	36	27	101	86	27	22	21	22	1946	1816
7	105	110	2.8	2.5	27	23	28	20	86	85	25	17	22	21	1445	1496
Mean	91	91	2.5	2.3	27	23	32	23	102	83	26	17	29	22	2597	2298
± SEM	4.6	4.8	0.2	0.2	3.3	2.2	4.2	3.8	10.7	4.2	2.8	2.2	5.7	3.6	630	451
P	NS		NS		NS		<0.0025		<0.025		<0.005		<0.05		NS	

Abbreviations: R, rest; R^I, rest after isosorbide. Other abbreviations are the same as for Table 2.

Table 4 *Effects of isosorbide dinitrate on exercise haemodynamics*

Case No.	HR		CI		SVI		MPA		LVSP		LVEDP		LVSWI		TTI	
	E	E ^I	E	E ^I	E	E ^I	E	E ^I	E	E ^I	E	E ^I	E	E ^I	E	E ^I
1	135	135	2.4	2.7	18	20	50	20	114	128	45	20	17	29	5465	4838
2	115	105	3.6	4.2	31	40	50	30	106	119	42	33	27	47	3814	4614
3	130	120	2.5	2.6	19	22	50	16	84	65	38	15	12	15	3360	3087
4	97	94	1.2	1.6	12	17	50	45	—	—	26	23	—	—	—	—
5	115	120	2.9	3.5	25	29	48	48	115	112	36	33	27	31	1587	1619
6	110	110	2.4	3.3	22	30	44	38	103	97	38	28	19	28	2266	2343
7	120	130	3.2	4.1	27	32	40	32	103	104	35	28	25	33	1487	1888
Mean	117	116	2.6	3.1	22	27	47	33	104	104	37	26	21	30	2996	3065
± SEM	5.2	5.8	0.3	0.4	2.6	3.2	1.6	4.9	5.0	9.9	2.4	2.7	2.7	4.6	624	618
P	NS		<0.0025		<0.0025		<0.0125		NS		<0.01		<0.01		NS	

Abbreviations: E, exercise; E^I, exercise after isosorbide. Other abbreviations are the same as for Table 2.

dinitrate was a reduction in mean left ventricular end-diastolic pressure (19%). A fall in left ventricular end-diastolic pressure was observed in all but one patient in whom it did not change. There was a corresponding fall in mean pulmonary arterial pressure (mean 28%). There was a significant fall in mean left ventricular stroke work index (24%) and mean left ventricular systolic pressure (19%).

There were no significant changes in mean cardiac index or stroke volume index. Mean tension-time index did not change significantly.

Effects of isosorbide on exercise haemodynamics (Table 4)

Compared with the control exercise period there were significant increases in mean cardiac index

Fig. 1 Haemodynamic effects of isosorbide dinitrate. Mean values ($n=7$) for heart rate (HR) beats per minute; cardiac index (CI) l/min per m²; stroke volume index (SVI) ml/m²; left ventricular filling pressure (LVFP) mmHg. Bars represent standard error of the mean.

(19%), stroke volume index (23%), and left ventricular stroke work index (43%). In association there were pronounced falls in mean left ventricular end-diastolic pressure (19%) and mean pulmonary arterial pressure (mean 30%). There were no significant changes in mean values for heart rate, mean left ventricular systolic pressure, and tension-time index.

The effects of isosorbide dinitrate on haemodynamic variables are illustrated in Fig. 1 and 2.

Discussion

The most important cardiovascular stress is that of exercise. In ambulant patients with congestive

Fig. 2 Haemodynamic effects of isosorbide dinitrate. Mean values ($n=7$) for left ventricular stroke work index, g m/m² and tension-time index (TTI) mmHg s/min. Bars indicate standard error of the mean.

cardiac failure a reduction in exercise tolerance caused by fatigue or dyspnoea constitutes their major disability. The response to exercise of the failing heart has been characterised by pronounced rises in left ventricular end-diastolic pressure together with a much diminished or even negative response in cardiac output, stroke volume, left ventricular stroke work, and left ventricular contractile state. This is in distinct contrast to the response of the normal heart where exercise is associated with increases in cardiac output, stroke volume, and stroke work with little or no increase in left ventricular end-diastolic pressure (Ross *et al.*, 1966; Krayenbuehl *et al.*, 1972).

The rise in left ventricular end-diastolic pressure may be regarded as a compensatory mechanism (Frank-Starling principle) in congestive cardiac failure, by which cardiac output is maintained. During exercise, however, this mechanism fails possibly because of the ventricle reaching the peak or entering the 'descending limb' of its Starling curve.

High levels of circulating noradrenalin have been observed in patients with congestive cardiac failure at rest and more strikingly during exercise compared

with normals (Chidsey *et al.*, 1962). Further, though myocardial noradrenalin stores are depleted in congestive cardiac failure (Chidsey *et al.*, 1963), there is evidence that the failing heart is super-sensitive to circulating noradrenalin (Spann *et al.*, 1967). Thus, two further supportive mechanisms exist in congestive cardiac failure, tending on one hand to maintain systemic arterial pressure by augmentation of peripheral vascular tone, while on the other to augment myocardial contractility. However, these mechanisms may be inadequate or even deleterious during exercise. Though an increase in peripheral vascular tone preserves arterial pressure, this together with the reduced arterial compliance known to occur in congestive cardiac failure (Zelis *et al.*, 1973) increases arterial impedance, that is left ventricular afterload (Milnor, 1975). This increase in afterload is poorly tolerated by the failing left ventricle, resulting in a further rise in left ventricular filling pressure, systolic wall tension and thus myocardial oxygen consumption. This chain of events would tend to oppose the inotropic effects of circulating catecholamines.

The rationale of treating congestive cardiac failure with vasodilators is primarily to reduce left ventricular afterload according to Cohn (1973). A fall in left ventricular end-diastolic pressure appears to be the most commonly observed response to vasodilators. This may result from improved ejection fraction or from reduced venous return, as vasodilators have been shown to produce venodilatation as well as arteriolar dilatation (Mason and Braunwald, 1965). Reported changes in cardiac output and left ventricular stroke work have however been variable. While improvement has been observed in some patients, falls have been observed in others (Chatterjee *et al.*, 1973; Williams *et al.*, 1977). The latter may be related to a reduction of left ventricular end-diastolic pressure below optimal levels (Crexells *et al.*, 1973).

The present study shows the characteristic haemodynamic responses to exercise of patients in congestive cardiac failure discussed above. Mild exertion produced large increases in left ventricular end-diastolic pressure with no significant change in cardiac index, stroke volume index, left ventricular stroke work index, or mean left ventricular systolic pressure. A significant rise in tension-time index suggests, however, an increase in myocardial oxygen consumption (Sarnoff *et al.*, 1957).

After the administration of isosorbide dinitrate at rest, distinct falls in left ventricular end-diastolic pressure were observed. Other aspects of left ventricular performance however were not uniformly improved. Indeed, there were falls in cardiac index and left ventricular stroke work index in some

Fig. 3 Relation between left ventricular filling pressure (LVFP) mmHg and cardiac index (CI) l/min per m². The values indicated are mean values (n=7). The arrows indicate the direction of change from control (pre-isosorbide-closed circles) to the intervention indicated (open circles).

patients. In contrast, isosorbide dinitrate produced a more comprehensive improvement in left ventricular performance during exercise (Fig. 3). A possible explanation for these observations is that isosorbide dinitrate reduces left ventricular end-diastolic pressure (preload) to below optimal levels at rest but that an optimal level is achieved during exercise by an increase in venous return. The parallel reduction in afterload decreases left ventricular wall tension and increases left ventricular ejection fraction. Inotropic stimulation by circulating catecholamine may now act to augment left ventricular performance.

These changes would have variable effects on myocardial oxygen consumption. For example, decreased wall tension would reduce myocardial oxygen consumption while increased contractility would have the opposite effect (Graham *et al.*, 1968). It is of interest to observe that the improvement in exercise left ventricular performance by isosorbide dinitrate was achieved without further increase in the tension-time index, suggesting that these influences were balanced with respect to myocardial oxygen demand.

Improved regional myocardial blood supply (Becker *et al.*, 1971; Horwitz *et al.*, 1971) may be an additional factor in the observed improvement in exercise haemodynamics after isosorbide dinitrate administration, since all patients had coronary artery disease as the primary disorder.

The results of this study stress the need for caution in the use of isosorbide dinitrate in the treatment of the patient confined to bed with congestive cardiac failure. Although pulmonary congestion

may be effectively relieved through the lowering of the left ventricular end-diastolic pressure, perfusion of vital organs, such as kidneys and brain, may be compromised by further reduction in cardiac output. In patients with severe impairment of left ventricular function where such considerations may be important, careful haemodynamic assessment of the individual's response to isosorbide dinitrate is, therefore, desirable. The effects of isosorbide dinitrate on exercise haemodynamics, however, provides evidence that long-term treatment with this agent may be effective in improving exercise tolerance in ambulant patients with chronic congestive cardiac failure, making a useful alternative to the use of digitalis glycosides which have been shown to produce only a modest overall improvement in cardiac function at rest and during exercise (Cohn *et al.*, 1975).

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