Haemodynamic effects of dobutamine in patients with congestive heart failure receiving captopril

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SUMMARY Treatment with captopril has proved effective in some patients with resistant heart failure. Since cardiac output responses to captopril treatment are generally small, we infused the positive inotropic agent dobutamine in six patients already receiving captopril to determine whether cardiac output could be augmented without concomitantly increasing myocardial oxygen demands. At low infusion rates of dobutamine (2.5 and 5 $\mu\text{g/kg}$ per min), a substantial rise in cardiac output was observed yet myocardial oxygen uptake remained well below baseline (pre-captopril/dobutamine) levels. At higher rates of infusion (10 and 20 $\mu\text{g/kg}$ per min) the rise in cardiac output was accompanied by a pronounced increase in myocardial oxygen uptake, and the appearance of chest pain or multifocal ventricular extrasystoles in three patients. These data indicate that captopril treatment combined with low infusion rates of dobutamine can augment cardiac output in the short term, without increasing myocardial oxygen demand.

The prime pathophysiological features of heart failure include reduced myocardial contractility, oedema, and vasoconstriction. Treatment may be directed at these abnormalities singly or in combination. The vasoconstriction aspect has enjoyed particular attention recently with the advent of vasodilator treatment^{1,2} and the oral converting-enzyme inhibitor, captopril.^{3,4} Captopril-induced increases in myocardial performance as assessed by measurements of cardiac output, however, are often not great.³ Under such circumstances the addition of agents which directly increase myocardial contractility should be beneficial provided that the balance of cardiac oxygen demand and supply is not adversely affected. The purpose of this paper is to report the haemodynamic changes induced by short-term incremental infusions of dobutamine, a positive inotropic agent,⁵⁻⁷ in six patients with congestive cardiac failure stabilised on captopril.

Patients and methods

Approval was given by the hospital ethical committee and informed consent was obtained from all patients. Six patients, 54 to 72 years of age, were each studied for seven days. All had congestive heart failure and were in New York Heart Association Functional class III (able to walk only short distances because of

dyspnoea) or class IV (confined to bed by dyspnoea) despite treatment with digoxin (0.0625 to 0.25 mg/day), frusemide (80 to 500 mg/day), and prazosin (15 to 30 mg/day). Additional treatment including hydralazine (100 to 400 mg/day) and spironolactone (75 to 200 mg/day) had been tried in some of the patients, without clinical benefit.

During the study the patients remained in the semi-supine position in bed (trunk approximately 35° to the horizontal). Dietary sodium and potassium intake was constant in each patient (33 to 48 mmol/day and 73 to 100 mmol/day, respectively). All drugs were withdrawn at least 48 hours before the study except for digoxin and frusemide, the doses of which remained unchanged throughout. On the first day a triple lumen Swan-Ganz catheter was positioned in the pulmonary artery for measurements of cardiac output (thermodilution), each reading being made in duplicate, and right heart pressures; a radial artery cannula was inserted for direct arterial pressure measurements. After a two day control period, oral captopril therapy was introduced in an eight hourly regimen (07.30, 14.30, 23.30 hours) beginning with 6.25 mg and rising to a maximum dose of 150 mg three times daily by day 6. On the seventh day, in addition to continuing captopril treatment, dobutamine was administered intravenously using an IVAC pump. Dosages of 2.5, 5, 10, and 20 $\mu\text{g/kg}$ per min were given for 15 minutes each day. Pressures

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and cardiac output were determined at the end of each infusion period. An electrocardiogram was monitored constantly during dobutamine administration.

Statistical analyses were performed using Student's *t* test for paired data.

Results

The addition of captopril to digoxin and frusemide treatment induced beneficial haemodynamic responses and clear-cut hormonal changes, the details of which are reported elsewhere for five of the six patients.³ As shown in the Table and Figure, captopril lowered arterial pressure ($p<0.001$), slowed the pulse rate ($p<0.025$), and thus reduced myocardial oxygen uptake (MVO_2) conspicuously ($p<0.001$) as assessed indirectly (heart rate $\times$ systolic arterial pressure product^{8 9}). A concurrent modest decline in pulmonary artery diastolic pressure (an index of left ventricular end-diastolic filling pressure) was observed. The rise in resting cardiac output was minor but statistically significant ($p<0.01$). Dobutamine infusion on the fifth day of treatment with captopril induced chest pain in one patient (at 10 $\mu\text{g/kg}$ per min) and frequent multifocal ventricular extrasystoles in two others (at 10 and 20 $\mu\text{g/kg}$ per min) so that further dose increments were not employed in these subjects.

Dobutamine-haemodynamic dose-response curves were produced for cardiac output, heart rate, and MVO_2 , a plateau being reached at a dose of 10 $\mu\text{g/kg}$ per min (Fig.). At the lowest infusion rate of dobutamine (2.5 $\mu\text{g/kg}$ per min), cardiac output increased in each of five patients the mean increment being 0.77 l/min, yet arterial pressure, pulse rate, and MVO_2 did not increase and pulmonary artery diastolic pressure tended to decline. The cardiac outpatient measurement at this infusion rate for the sixth patient was lost. Doubling the dobutamine infusion (5 $\mu\text{g/kg}$ per min) further increased cardiac

Table Haemodynamic results

		Before captopril		Before dobutamine		Dobutamine ($\mu\text{g/kg}$ per min)			
		Mean	SEM	Mean	SEM	2.5	5	10	20
Cardiac output (l/min)	Mean	3.1		3.4		4.1	4.4	5.1	5.1
	SEM	0.9		0.6		0.8	0.6	0.4	0.3
	No	6		6		5	6	5	3
Heart rate (beats/minute)	Mean	85.0		74.3		73.7	80.2	91.6	93.0
	SEM	11.6		2.3		2.6	1.6	6.4	12.8
	No	6		6		6	6	5	3
Mean arterial pressure (mmHg)	Mean	77.1		60.2		60.4	60.2	57.2	60.0
	SEM	1.8		3.5		3.3	2.7	3.7	4.1
	No	6		6		6	6	5	3

Fig. Haemodynamic data, presented as mean $\pm$ SEM from six patients with severe congestive heart failure. The first data point for each index ("control") represents baseline levels before captopril treatment, while the second data point represents each index on the fifth day of captopril treatment. All other results were obtained on the fifth day of captopril administration during and 15 minutes after an incremental intravenous infusion of dobutamine each rate lasting 15 minutes. For the 10 and 20 $\mu\text{g/kg}$ per min infusion rates of dobutamine ($n=4$ and 3, respectively): for cardiac output at the 2.5 $\mu\text{g/kg}$ per min infusion ($n=5$; otherwise $n=6$).

output ($p < 0.001$ compared with levels before dobutamine) but MVO_2 also increased significantly ($p < 0.01$) because of a rise in heart rate. Nevertheless, MVO_2 was still well below that for the control (pre-captopril) period ($p < 0.001$). Higher rates of dobutamine administration (10 and 20 $\mu\text{g/kg}$ per min) again increased cardiac output but at the expense of chest pain or arrhythmia in three patients and a further rise in heart rate and MVO_2 . Mean arterial pressure and pulmonary artery diastolic pressure showed no tendency to increase during dobutamine infusion, and the decline in the latter index reached levels of statistical significance at the 2.5 ($p < 0.05$) and the 10 $\mu\text{g/kg}$ per min infusion rates ($p < 0.01$) compared with values before dobutamine.

All indices had returned to near baseline values 15 minutes after stopping dobutamine infusion.

Discussion

In the treatment of heart failure, vasodilators theoretically should decrease myocardial oxygen demand by lowering preload and/or afterload and thereby reducing left ventricular end-diastolic volume and wall tension. Captopril, by altering the circulating levels of vasoactive hormones, induces arterial (and perhaps venous) dilatation and is reportedly effective in patients with otherwise resistant heart failure.^{3 4 10 11}

The use of sympathomimetic amines for their positive inotropic effect is well established.^{5 6} These are not, however, without theoretical disadvantages. Apart from their obvious arrhythmogenic potential, myocardial oxygen demands would be expected to rise as a result of increased heart rate and peripheral vasoconstriction. In this respect dobutamine appears to be a most attractive agent in that it minimises the increase in myocardial oxygen demand.⁷ We surmised that dobutamine administration at certain dose levels, added to a baseline of treatment with captopril, should increase cardiac output yet retain myocardial oxygen requirements at or below baseline (pretreatment) levels. The current study confirms that this is indeed possible. Therefore, the use of captopril combined with low doses of dobutamine appears to offer a rational, safe, and effective means of increasing cardiac performance, in the short term. It remains to be seen whether similar beneficial effects are possible with longer-term combination treatment of converting-enzyme inhibitors and orally active positive inotropic drugs, a number of which are currently under investigation.

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