Comparison of dobutamine and dopamine in treatment of severe heart failure[1]

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The haemodynamic effects of dobutamine, a new synthetic catecholamine, were studied in 12 patients with severe congestive heart failure and compared with those of dopamine in 10 clinically similar patients. Dobutamine produced a distinct increase in cardiac index, while lowering left ventricular end-diastolic pressure and leaving mean aortic pressure unchanged. Dopamine also significantly improved cardiac index, but at the expense of a greater increase in heart rate than occurred with dobutamine. Dopamine was ineffective in lowering left ventricular end-diastolic pressure, but increased mean aortic pressure. We conclude that dobutamine is an effective, positive inotropic agent in patients with severe congestive heart failure. Because it has comparatively little effect on heart rate and aortic pressure, both major determinants of myocardial oxygen consumption, it may be of special value in patients with the low output syndrome associated with coronary heart disease.

The treatment of severe congestive heart failure continues to be a challenging problem in spite of many new and innovative pharmacological, mechanical, and surgical approaches. The sympathomimetic amines remain one of the primary forms of therapy because of their potent inotropic effect, yet none of those currently available for clinical use is wholly satisfactory. Noradrenaline produces excessive systemic vasoconstriction, decreasing tissue perfusion while increasing arterial pressure and cardiac work (Cohn and Luria, 1965; Vatner *et al.*, 1974a). Isoprenaline may increase heart rate and predispose to potentially fatal arrhythmias (Innes and Nickerson, 1975; Smith *et al.*, 1967). Peripherally, it induces beta-adrenergic vasodilatation, diverting cardiac output to noncritical tissues while lowering arterial and coronary perfusion pressure (Elliott and Gorlin, 1966; Gunnar *et al.*, 1967). In patients with coronary artery disease it may worsen myocardial ischaemia and increase infarct size (Maroko *et al.*, 1971; Lipp *et al.*, 1972). Dopamine is associated with considerably less chronotropic effect, but still may produce ventricular arrhythmias (Lipp *et al.*, 1972; Gunnar and Loeb, 1972). Though it lowers renal vascular resistance through stimulation of specific dopamine receptors, it has a predominantly alpha-adrenergic action on other arterial beds and may produce excessive vasoconstriction in high doses (McNay *et al.*, 1965; Goldberg, 1972; Vatner *et al.*, 1973). More importantly, dopamine's inotropic effect is mediated in part through the release of endogenous noradrenaline (Tsai *et al.*, 1967; Nash.*et al.*, 1968). In severe heart failure, when endogenous noradrenaline stores are low, its ability to improve cardiac output may be reduced and unpredictable (Chidsey *et al.*, 1963; Tuttle and Mills, 1975).

Dobutamine ([±]-4-[2-[[3-(p-hydroxyphenyl)-1-methyl propyl] amino] ethyl] pyrocatechol hydrochloride) is a new synthetic sympathomimetic amine developed in an effort to reduce the deleterious effects associated with currently available inotropic agents (Tuttle and Mills, 1975). Though a derivative of dopamine, it acts directly on adrenergic receptors rather than through release of endogenous noradrenaline. Preliminary studies indicate that it dramatically improves cardiac output with relatively little chronotropic or peripheral vascular effect (Gunnar *et al.*, 1973; Vatner *et al.*, 1974b; Robie *et al.*, 1974; Akhtar *et al.*, 1975). It remains to be established, however, whether dobutamine is clinically a more effective therapeutic agent. Accordingly, this study was undertaken to assess the degree of haemodynamic improvement produced by dobutamine in patients with severe heart failure and

to compare its effects with those of dopamine in a similar group of patients.

Methods

Twelve patients undergoing routine diagnostic cardiac catheterisation were studied. All had evidence of severe left ventricular dysfunction, either on the basis of coronary artery disease or cardiomyopathy. None had significant valvular abnormalities.

At the end of the diagnostic cardiac catheterisation, control haemodynamic measurements were made, including right atrial, pulmonary artery, pulmonary capillary wedge, left ventricular, and aortic pressures. Cardiac output was measured using the Fick method. Arterial and mixed venous oxygen content were determined using an Instrumentation Laboratory spectrophotometer. From these, systemic and pulmonary vascular resistances were calculated. Maximal left ventricular dp/dt was obtained by computer analysis of the left ventricular pressure tracing. Left ventricular pressures were recorded through fluid-filled catheters which had been tuned and optimised to provide linear frequency responses up to 16 Hz. These frequency responses have been shown to provide data necessary to obtain high quality left ventricular dp/dt measurements. After recording control values, dobutamine was infused intravenously at a rate of 10 µg/kg per min for 15 minutes and the above measurements were repeated.

Haemodynamic data from 10 different patients with similar haemodynamic derangements previously studied in our laboratory during dopamine administration are presented for comparison (Holloway *et al.*, 1975). All had severe left ventri-

cular dysfunction without evidence of significant valvular abnormalities. Control haemodynamic measurements were made as described above. An infusion of dopamine (100 µg/ml) was begun at a rate of 2 µg/kg per min for 5 minutes, then increased by 2 µg/kg per min every 5 minutes until mean aortic pressure increased by 15 mmHg or heart rate by 30 beats/min. When either of these limits was reached, the infusion rate was kept constant for an additional 5 minutes and the haemodynamic measurements were repeated. The rate required to obtain the desired end-point ranged from 2 to 16 µg/kg per min.

All statistical analyses were performed using Student's t-test for paired samples, or for unpaired samples with equal variance, and a P value of less than 0·05 was taken as indicative of statistical significance.

Results

The haemodynamic response to dobutamine infusion in 12 patients with severe left ventricular dysfunction is summarised in Table 1. The cardiac index increased dramatically from 1·9 to 3·5 1/min per m², largely because of an increase in stroke index (P < 0·001). This was accompanied by a fall in left ventricular end-diastolic pressure from 28·3 to 21·5 mm (P < 0·001) and a nearly 60 per cent rise in left ventricular dp/dt (P < 0·005). Mean aortic pressure remained constant, while calculated systemic vascular resistance fell by 36 per cent. Mean pulmonary artery pressure was unchanged, while pulmonary vascular resistance was reduced by 31 per cent. Heart rate was increased by a mean of 13 beats/min.

The haemodynamic response to dopamine infusion in 10 similar patients with left ventricular dysfunction is summarised in Table 2. These results form part of an earlier report (Holloway

Table 1 *Haemodynamics in 12 patients with severe left ventricular failure before and after dobutamine infusion (mean ± SEM)*

	Control	Dobutamine
Heart rate (beats/min)	90·1 ±4·0	102·7 ±4·0*
Right atrial mean (mmHg)	5·0 ±1·9	2·0 ±1·0*
Pulmonary artery mean (mmHg)	36·8 ±2·9	34·9 ±4·1
Pulmonary capillary wedge mean (mmHg)	22·0 ±2·4	17·9 ±3·2*
Left ventricular end-diastolic (mmHg)	28·3 ±2·4	21·5 ±2·9*
Aorta mean (mmHg)	82·0 ±3·3	82·0 ±5·6
Cardiac index (l/min per m²)	1·9 ±0·1	3·5 ±0·4*
Stoke index (ml/beat per m²)	22·2 ±1·7	32·1 ±2·5*
Systemic vascular resistance (Wood units)	22·1 ±1·4	14·2 ±2·0*
Pulmonary vascular resistance (Wood units)	4·2 ±0·5	2·9 ±0·4*
Left ventricular dp/dt (mmHg/s)	842·5 ±99·9	1337·9 ±228·0*

*P < 0·05.

Table 2 *Haemodynamics in 10 patients with severe left ventricular failure before and after dopamine infusion (mean ± SEM)*

	Control	Dopamine
Heart rate (beats/min)	82·1 ±4·1	110·9 ±5·9*
Right atrial mean (mmHg)	6·3 ±1·2	7·9 ±1·5
Pulmonary artery mean (mmHg)	38·2 ±2·3	48·5 ±4·2*
Pulmonary capillary wedge mean (mmHg)	24·4 ±1·3	28·4 ±2·6
Left ventricular end-diastolic ((mmHg)	28·8 ±1·4	30·4 ±2·9
Aorta mean (mmHg)	85·4 ±3·1	98·4 ±4·6*
Cardiac index (l/min per m²)	2·0 ±0·2	3·0 ±0·3*
Stroke index (ml/beat per m²)	24·4 ±1·9	27·0 ±2·4
Systemic vascular resistance (Wood units)	24·0 ±2·2	17·4 ±1·7*
Pulmonary vascular resistance (Wood units)	4·5 ±0·9	4·3 ±0·8

*P < 0·05.

et al., 1975). Control cardiac index, left ventricular end-diastolic pressure, mean aortic and pulmonary arterial pressures, systemic vascular resistance, pulmonary vascular resistance, and heart rate are similar to those of the 12 patients receiving dobutamine. Cardiac index increased significantly after dopamine administration, though to a lesser degree than with dobutamine. Left ventricular end-diastolic pressure was unchanged, while mean aortic and pulmonary arterial pressures increased. Heart rate rose by a mean of 29 beats/min, significantly greater than with dobutamine ($P < 0.05$). while stroke index increased by only 11 per cent.

Discussion

Previous work has shown dobutamine to be a potent and relatively selective inotropic agent with only minor chronotropic and peripheral vascular effect (Vatner *et al.*, 1974b; Robie *et al.*, 1974; Akhtar *et al.*, 1975; Gunnar *et al.*, 1973; Tuttle and Mills, 1975). This study extends these findings to a group of patients with severe heart failure resulting from coronary artery disease or cardiomyopathy, in whom dobutamine might be clinically indicated. When infused at a rate of 10 μg/kg per min, dobutamine dramatically improved left ventricular function, increasing left ventricular dp/dt by over 50 per cent, nearly doubling cardiac index, and lowering left ventricular end-diastolic pressure. Dobutamine reduced peripheral vascular resistance and some of its effect could be attributed to this reduction in afterload. The increase in cardiac output and the drop in left ventricular end-diastolic pressure would be influenced by this peripheral vasodilatation. In contrast, the administration of dopamine failed to reduce left ventricular end-diastolic pressure. This lack of reduction of left ventricular end-diastolic pressure could be attributed to the observation that there was an increase in arterial pressure or afterload, since by other measures dopamine clearly produced an inotropic effect. Heart rate rose by 14 per cent, while a nearly 50 per cent increase in stroke index accounted for the majority of the improvement in cardiac output. Mean systemic arterial pressure remained unchanged because of a 36 per cent decline in systemic vascular resistance, the latter reflecting either a reflex reduction in sympathetic tone or a direct effect of dobutamine on the peripheral vasculature.

Comparison of these findings with the haemodynamic effects of dopamine in a similar group of patients, previously studied in our laboratory, reveals several important differences. Dopamine, while administered in doses that significantly increased cardiac index, was ineffective in lowering left ventricular end-diastolic pressure from levels commonly associated with pulmonary oedema. As a result its use may be associated with continued pulmonary vascular congestion and arterial desaturation (Loeb *et al.*, 1975).

Although both drugs produced similar increases in cardiac index with the doses employed, dopamine accomplished this at the expense of a significantly greater increase in heart rate. Systemic arterial pressure also rose with dopamine administration, in spite of a slight decrease in systemic vascular resistance. Since both heart rate and arterial pressure are important determinants of myocardial oxygen consumption (Sonnenblick and Skelton, 1971), these findings suggest that dobutamine may be preferable in treating patients with coronary artery disease. Animal studies using epicardial ST segment mapping and coronary sinus lactate determinations have shown that dopamine may worsen myocardial ischaemia and injury after coronary occlusion (Stemple *et al.*, 1976). In contrast, when dobutamine was administered to patients in clinical heart failure with evolving myocardial infarctions, there was no detectable increase in myocardial injury as determined by hourly serum-CK determinations and a plot of the CK-kinetic curves (Gillespie *et al.*, 1975).

Similarly, dobutamine's pharmacological actions offer distinct advantages over the other currently available inotropic agents. In equivalent doses it induces far less tachycardia than isoprenaline and is not associated with excessive vasodilatation or hypotension (Tuttle and Mills, 1975; Vatner *et al.*, 1974b; Robie *et al.*, 1974). At the other end of the spectrum, the pronounced vasoconstriction that occurs with noradrenaline is also avoided. Instead, dobutamine acts more selectively to improve myocardial contractility and left ventricular function, with tissue perfusion increasing in proportion to cardiac output.

While it is difficult to extrapolate directly to patients treated in the hospital with low cardiac output resulting from cardiomyopathy, we believe that our studies clearly show the effectiveness of dobutamine. Because of its predictable inotropic effects while producing little in the way of increased myocardial oxygen demands, we believe it deserves use in patients with the low output syndrome associated with coronary heart disease.

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