Superiority of Dobutamine over Dopamine for Augmentation of Cardiac Output in Patients with Chronic Low Output Cardiac Failure

HENRY S. LOEB, M.D., JOHN BREDAKIS, M.D., AND ROLF M. GUNNAR, M.D.

SUMMARY Dobutamine is a newly developed catecholamine reported to have minimal direct vascular effects relative to its inotropic activity and to have less chronotropic and arrhythmogenic properties than dopamine. We compared its use in the treatment of low output states. In this study, the acute hemodynamic effects of dobutamine were compared to those of dopamine in 13 patients with chronic low output cardiac failure. At dosages adjusted to achieve similar increments in cardiac output, dobutamine reduced left ventricular filling pressure (LVFP) from 25 ± 2 mm Hg (SEM) to 17 ± 2 mm Hg, while dopamine increased LVFP to 30 ± 3 mm Hg and in six patients caused arterial O₂ saturation to fall below 90%. This poor response to dopamine was probably the result of its vasoconstrictive effects and illustrates the potential advantages of using a cardioselective agent such as dobutamine when the desired goal of therapy is to improve ventricular function by direct inotropic stimulation.

OF THE MANY AGENTS capable of improving cardiac output in patients with low output cardiac failure, the catecholamines are among the most widely used. As a group, these drugs exert similar direct cardiac effects mediated by stimulation of beta adrenergic receptors. Important differences in their peripheral vascular actions are found among them. At times, these vascular effects are undesirable and can offset benefits gained from the inotropic actions. In addition, the catecholamines currently used for treatment of heart failure frequently cause tachycardia and/or arrhythmias. Newer agents have been developed and tested under laboratory conditions with the purpose of finding one that would retain the inotropic activity of the earlier catecholamines without direct vascular, chronotropic and arrhythmogenic actions. Of many such compounds tested, dobutamine appears to come closest to fulfilling these criteria. We and others² ³ have previously described the acute hemodynamic effects of dobutamine in patients with severe left ventricular dysfunction. In the present study, we compared the effects of dobutamine to those of dopamine in 13 such patients. Our studies suggest that dobutamine has important

References

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advantages over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure when hypotension is not present.

**Methods and Materials**

The patients studied were all males, hospitalized for symptoms of chronic cardiac failure due to cardiomyopathy (8), arteriosclerotic heart disease (4), or persisting after prosthetic aortic valve replacement (1). Their ages ranged between 48 and 68 years, averaging 58 years. All patients had received digitalis and diuretic therapy prior to the study and none were in acute pulmonary edema or cardiogenic shock at the time of study. Two patients were in chronic atrial fibrillation and the remainder were in sinus rhythm. Prior to the study, informed consent was obtained from each patient.

On the morning of the study, the patient was brought to a specially equipped hemodynamic study unit in the fasting state without specific pre-medication. A #7F thermal dilution Swan-Ganz catheter was inserted from a surgically-exposed basilic vein and advanced under fluoroscopic control until the catheter tip was situated in the right or left pulmonary artery. It was positioned to yield a reliable wedge pressure (WP) waveform when the balloon was inflated and pulmonary artery systolic (PASP) and diastolic (PADP) pressure waveform when the balloon was deflated. Right atrial pressure (RAP) was measured from the proximal lumen. Cardiac output (CO) was determined by averaging two or more thermal dilution curves obtained by injecting 10 cc of 0° C saline into the right atrium. A Model 9500 Edwards laboratory cardiac output computer was used to give on-line readout of CO. Arterial systolic (ASP) and diastolic (ADP) pressure was measured from an indwelling cannula inserted into the radial, brachial, or femoral artery. All pressures were obtained from Statham 23 Db transducers leveled at the midchest position. Mean pulmonary (MPAP) and systemic arterial (MAP) pressures were determined by electrical dempning. Heart rate (HR) was determined from a standard ECG lead which was monitored continuously. Pressures and ECGs were recorded on a multichannel photographic recorder run at various paper speeds. Arterial (AO2) and pulmonary artery (PAO2) oxygen saturations were determined by oximetry using an American Optical oximeter.

The following calculations were made:

Cardiac Index (CI) = CO/body surface area (DuBois)

Stroke Index (SI) = CI/HR

*Left Ventricular Stroke Work Index (LVSWI) =

MAP – WP 

\[\text{SI} \times 13.6\]

Right Ventricular Stroke Work Index (RVSWI) =

\[\frac{(\text{MPAP} – \text{RAP}) \times \text{SI} \times 13.6}{1000}\]

Systemic Arterial Resistance (SAR) = (MAP – RAP)/CO

Pulmonary Arterial Resistance (PAR) = (MPAP – WP)/CO

**Protocol**

After control measurements had been obtained and hemodynamic stability established, either dobutamine or dopamine was infused at a constant rate using an IVAC constant infusion pump. Repeat measurements were made and dosages adjusted at 15 to 30 min intervals once a new stable state was achieved. When measurements had been obtained at one or more dosages, the first drug was stopped and the patient allowed to return to control status. After 30 min, the second drug was infused and measurements obtained in a similar manner.

The following considerations were important in determining the dosages used for comparing the two drugs. Since improved cardiac output is a major objective when inotropic agents are given to patients with low output cardiac failure, we thought it necessary that the two drugs be compared if possible, at dosages yielding significant and similar increases in cardiac output. In previous studies of patients with poor left ventricular function, we found that infusions of dobutamine in amounts of 10.7 ± 1.1 μg/kg/min (mean ± SEM) were well tolerated and raised cardiac index by an average of 82% (from 1.9 ± 0.2 L/min/m² to 3.3 ± 0.2 L/min/m²). Accordingly, in the present study, we chose to study dobutamine at an infusion rate of 10 μg/kg/min. Since it was also important that dobutamine not always be the first agent studied, when dopamine was studied first, we gave it at more than one infusion rate (table 1) and then chose for analysis, data obtained at the dopamine infusion rate which yielded a cardiac output closest to that which was present during the 10 μg/kg/min dobutamine infusion. As can be seen, a CI obtained during infusion of dopamine agreed within 0.4 L/min/m² of the CI present during dobutamine infusion in all but three patients.

**Results**

In table 2 are listed the various parameters measured during the control and drug infusion periods for each of the 13

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Cardiac index in L/min/m². Parenthesis refer to the dopamine dosage chosen for comparing to 10 μg/kg/min dobutamine infusion.
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**Mean ± SEM**

- **C** = difference in mean values between dobutamine and dopamine is significant (P < 0.05 by paired t-test)
- **Abbreviations:** ASP = arterial systolic pressure; MAP = mean arterial pressure; ADP = arterial diastolic pressure; P = pulmonary; MPAP = mean pulmonary artery pressure; WP = wedge pressure; RAP = right atrial pressure; CI = cardiac index; HR = heart rate; SI = stroke index; L and RVSWI = left and right stroke work index; SAR = systemic arteriolar resistance; PAR = pulmonary arteriolar resistance; A-Va = cardiac output; DB = dobutamine; DP = dopamine; SEM = standard error of mean.

*References:* 317
patients studied. Dobutamine was the first drug evaluated in eight patients and dopamine the first in five patients. Dosages were 10.3 ± 0.3 μg/kg/min for dobutamine and 5.4 ± 0.8 μg/kg/min for dopamine.

Arterial Pressures. Mean arterial systolic pressure was 109 ± 5 mm Hg during control (12 patients), increased minimally to 112 ± 5 mm Hg with dobutamine and to 124 ± 7 mm Hg during dopamine infusion. Mean arterial pressure was 83 ± 3 mm Hg before the drug infusion, fell to 76 ± 3 mm Hg during infusion of dobutamine, and increased slightly to 86 ± 5 mm Hg with dopamine. ADP (12 pts) was 70 ± 3 mm Hg during control, fell to 56 ± 5 mm Hg during dobutamine infusion, and increased slightly with dopamine to 72 ± 4 mm Hg. Each of the above pressures were significantly higher (P < 0.05) during dopamine infusion than during dobutamine infusion.

Pulmonary Artery and Right Atrial Pressures. PASP, MPAP, and PADP were 53 ± 4 mm Hg, 39 ± 3 mm Hg and 30 ± 2 mm Hg, respectively, during the control period. During dobutamine infusion, these pressures fell to 46 ± 5 mm Hg, 32 ± 3 mm Hg, and 23 ± 3 mm Hg; and during dopamine infusion they increased to 58 ± 4 mm Hg, 42 ± 4 mm Hg, and 32 ± 3 mm Hg. Each was significantly lower (P < 0.01) during dobutamine infusion than during dopamine infusion. Wedge pressure was measured in eight patients and averaged 24 ± 2 mm Hg during the control period, falling to 16 ± 3 mm Hg during infusion of dobutamine. Wedge pressure increased to 28 ± 5 mm Hg during dopamine infusion, a value significantly higher (P < 0.01) than during dobutamine infusion. Right atrial pressure (12 pts) fell from 11 ± 2 mm Hg to 6 ± 2 mm Hg during dobutamine infusion and was significantly higher during dopamine infusion, averaging 12 ± 3 mm Hg.

Cardiac Index. Cardiac index prior to drug infusion was 1.9 ± 0.1 L/min/m². During dobutamine infusion, CI increased to 2.9 ± 0.2 L/min/m² and as expected, was not significantly different than the average of 2.7 ± 0.2 L/min/m² achieved during dopamine infusion.

Heart Rate. Heart rate averaged 85 ± 2 beats/min during the control period and increased to a similar extent during both dobutamine and dopamine infusions averaging 100 ± 4 and 99 ± 6 beats/min respectively.

Stroke Index. Stroke index was 25 ± 2 cc/beat during the control period and increased by a similar extent during infusion of dobutamine and dopamine averaging 31 ± 2 and 30 ± 3 cc/beat respectively.

Left Ventricular Stroke Work Index (fig. 1). During the control period LVSWI averaged 19 ± 2 g-m/m². During dobutamine infusion, LVSWI increased to 25 ± 2 g-m/m² and during dopamine infusion decreased to 23 ± 3 g-m/m². Differences in LVSWI between dobutamine and dopamine were not significant.

Systemic Arteriolar Resistance. This parameter (measured in 12 pts) fell during infusion of both agents from a control value of 21 ± 2 mm Hg/L/min to 13 ± 1 mm Hg/L/min with dobutamine and to 16 ± 2 mm Hg/L/min during infusion of dopamine. The difference in SAR between dobutamine and dopamine was not significant.

Right Ventricular Stroke Work Index (fig. 2). RVSWI increased from 10 ± 1 g-m/m² to 11 ± 1 g-m/m² during

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**Figure 1.** Left ventricular stroke work index on the vertical axis is plotted against left ventricular filling pressure (wedge or pulmonary artery diastolic pressure) on the horizontal axis. During dobutamine infusion, (unfilled circle) the plot moves upward and to the left suggesting significant improvement in left ventricular function. During dopamine infusion, the plot moves upward and to the right suggesting minimal, if any, change in left ventricular function.

**Figure 2.** Right ventricular stroke work index is plotted against right atrial pressure. As in figure 1 for left ventricular function, right ventricular function seems to have improved significantly more during infusion of dobutamine than during infusion of dopamine.
dobutamine infusion and to 12 ± 1 g·m⁻² during infusion of dopamine. The difference in RVSWI between dobutamine and dopamine was not significant.

**Pulmonary Arteriolar Resistance.** This measurement (8 pts) fell from 5.1 ± 1.0 mm Hg/L/min to 3.9 ± 0.8 mm Hg/L/min during dopamine infusion, which was not significantly different from the mean of 2.9 ± 0.4 mm Hg/L/min present during dopamine infusion.

**Oxygen Saturation.** Arterial and pulmonary oxygen saturation was measured in 12 patients. During control, AO₂ was 90% or above in every patient averaging 96 ± 0.4%. During dobutamine, AO₂ remained above 90% in 11 patients averaging 93 ± 0.8%. During dopamine infusion, AO₂ was significantly lower (P < 0.01) averaging 87 ± 2% and was below 90% in six patients. As can be seen in figure 3, in each of these six patients, the fall in AO₂ which occurred during dopamine infusion was associated with LVFP above 35 mm Hg which, in four of the six patients, was due to a large increase in LVFP, ranging from 15 to 21 mm Hg. In contrast, four of the six patients whose AO₂ remained above 90% during dopamine infusion, had a fall in LVFP and in none was LVFP above 28 mm Hg.

PAO₂ averaged 45 ± 5% during the control period and increased during both dobutamine and dopamine infusions, averaging 64 ± 2% and 57 ± 4%, respectively. Although PAO₂ was higher with dopamine than with dopamine, the AO₂ − PAO₂ difference, which averaged 51 ± 5% prior to infusion of either drug, was narrowed similarly with both dobutamine and dopamine, averaging 30 ± 2% and 30 ± 3%, respectively.

**Adverse Effects.** No serious adverse effects resulted from the study. In a few patients, shortness of breath developed during dopamine infusion, and in one patient, chest pain occurred during infusion of dopamine at a dosage of 5 μg/kg/min but he responded promptly to nitroglycerin and discontinuation of the infusion. Although arrhythmias were uncommon, some patients had more ventricular ectopic beats noted during administration of the drugs. Since ectopic beats were not counted during the study, a comparison of the two agents with regard to arrhythmogenic effects was not possible.

**Discussion.**

In 1963, Goldberg, McDonald, and Zimmerman⁴ reported improved sodium diuresis in patients with congestive heart failure during dopamine infusion. Subsequently, dopamine has become popular for the treatment of patients with various types of shock⁵ and low output states.⁶ The popularity of dopamine is largely due to its potent inotropic activity coupled with its unique ability to selectively vasodilate vessels in splanchnic and renal vascular beds by a mechanism other than adrenergic stimulation.⁷ In addition, when used in moderate dosages, dopamine, although exerting both alpha- and beta-adrenergic peripheral vascular effects, seems less likely to cause either excessive vasodilatation and hypotension than isoproterenol or excessive vasoconstriction and increased cardiac work, as norepinephrine does. In spite of these theoretical advantages, the direct peripheral vascular effects of dopamine which are largely dose dependent⁸ may, as in the case of isoproterenol and norepinephrine, limit its usefulness under certain conditions.

In order to eliminate some of these problems, Tuttle and Mills⁹ modified the chemical structure of isoproterenol in an attempt to develop a substance having potent inotropic activity with minimal chronotropic, arrhythmogenic, or direct peripheral vascular effects. Among several substances evaluated, dobutamine, a derivative of dopamine, appeared to best fit these requirements. Experimental studies have shown dobutamine to be a direct-acting compound with its action being independent of stored catecholamines. When compared to other catecholamines at dosages producing equivalent inotropic effects, dobutamine also appears to have less arrhythmogenic activity and to exert less effect on peripheral vascular resistance. Although both alpha- and beta-adrenergic actions on peripheral vasculature can be elicited by dobutamine during selective adrenergic blockade, these effects seem to be slight in comparison to its direct cardiac effects.¹⁰⁻¹¹

Clinical studies have shown dobutamine to increase cardiac output in patients with and without heart failure¹²⁻¹⁴ without substantially raising heart rate. Isoproterenol caused greater rate increases with comparable increases in cardiac output.¹³⁻¹⁴

In the present study, we compared the acute hemodynamic effects of dobutamine to those of dopamine in patients with chronic low output cardiac failure. It is important to note that none of these patients were in clinical shock and perfusion pressure was considered to be adequate in all patients prior to infusion of either drug. Augmentation of cardiac output and not arterial pressure was therefore a desired therapeutic endpoint in addition to reduction in the elevated left ventricular filling pressure.

Experimentally, dobutamine and dopamine exert similar inotropic responses when given at low dosages and at a respective ratio of one to four.⁹ With increasing dosages of dopamine, however, its pressor effects become important. In the present study, it was not possible to measure inotropic activity per se and we therefore elected to compare the two

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**Figure 3.** Arterial oxygen saturation is plotted against left ventricular filling pressure in each of 12 patients. Solid circles are control values, unfilled circles are values obtained during dobutamine infusion and unfilled squares are values obtained during infusion of dopamine. In six of the 12 patients, dopamine infusion was associated with an arterial oxygen saturation under 90% and in each of these six patients, the low arterial oxygen saturation was associated with a left ventricular filling pressure above 35 mm Hg.
agents at dosages yielding similar, and in most instances, physiologically significant increases in cardiac output. Under these conditions, it becomes apparent that dobutamine would be preferred to dopamine if the desired goal in such patients is to temporarily improve ventricular function. As can be seen in figures 1 and 2, dobutamine shifted the plot of stroke work to filling pressure upward and to the left for both left and right ventricles, whereas dopamine shifted this relationship upward and to the right. This difference suggests that considerably more improvement in ventricular function occurred with dobutamine than with dopamine. Furthermore, LVFP fell in 12 of the 13 patients during dobutamine infusion (increasing by 1 mm Hg in one patient) but increased in eight of the 13 patients during dopamine infusion. In several instances, the elevated LVFP was associated with arterial hypoxemia, dyspnea, and auscultatory evidence of early pulmonary edema. These undesirable effects of dopamine occurred primarily in patients receiving infusion rates above 5 μg/kg/min.

When given to patients with shock, dopamine has been well tolerated at dosages above 10 μg/kg/min. From our early experience with dopamine in 62 patients with shock of various etiologies we reported a mean increase in cardiac output of 37% during dopamine given at an average infusion rate of 10 μg/kg/min (assuming the average patient weighs 78 kg). In 38 of these patients, left ventricular end-diastolic pressure (LVEDP) was measured directly and although LVEDP increased slightly from 13 to 16 mm Hg during dopamine infusion, the drug was generally well tolerated and clinical evidence of worsening ventricular function with pulmonary edema was not seen. We think it important to emphasize this difference in response to dopamine between hypotensive patients with clinical shock and normotensive patients with chronic low output cardiac failure. In the shock patient, especially when sepsis or miscellaneous factors are responsible, vascular resistance may not be elevated and cardiac function may be only moderately depressed. Under such circumstances, large dosages of dopamine are consistent with satisfactory ventricular performance since the adverse effect of increased afterload on ventricular function can be counterbalanced by the inotropic response to the drug coupled with restoration of arterial pressure favoring improved coronary and systemic perfusion.

On the other hand, patients with advanced heart failure not complicated by a reduction in coronary perfusion pressure frequently respond well to vasodilator therapy and are made worse by interventions causing vasoconstriction. Unlike dobutamine, the inotropic effects of dopamine are in part mediated by release of stored myocardial catecholamines, which may be depleted in patients with chronic heart failure. Therefore, although vasoconstriction may be avoided in such patients by using dopamine in low dosages, the dosage may be insufficient for achieving the desired inotropic effect and increase in cardiac output.

In contrast to dopamine, dobutamine is said to have minimal direct vascular activity even when used at higher dosages. In our patients, systemic arteriolar resistance fell in 11 (average from 21 to 13 mm Hg/L/min) during its infusion, while mean arterial pressure fell slightly (from 83 to 76 mm Hg). This reduction in SAR during dobutamine infusion may have been due to recruitment of latent vessels and/or withdrawal of compensatory vasoconstriction as has been observed following administration of digitalis to patients with heart failure. It is also possible that, in spite of experimental evidence to the contrary, dobutamine acted directly to vasodilate vascular smooth muscle. If present, this effect would, in light of our current concepts, be considered desirable with regard to improving ventricular function. Although for the group, SAR also fell during infusion of dopamine, it remained above 18 mm Hg/L/min in the eight patients who also had an increase in LVFP.

Dopamine can improve renal and mesenteric perfusion by selective nonadrenergic vasodilatation and this unique property of dopamine is not shared by dobutamine. Since we did not measure urine flow or sodium excretion, it is possible that dopamine may have exerted beneficial renal effects not apparent from hemodynamic measurements alone. It should be noted, however, that these beneficial effects on regional perfusion can be reversed, when dopamine is given in amounts large enough to cause alphaadrenergically mediated vasoconstriction. Thus, if in addition to improved ventricular function, selective vasodilatation in mesenteric and renal vascular beds is desired, one might consider using dopamine in low dosages of 1.2 to 2.5 μg/kg/min, combined, if necessary, with an agent such as dobutamine, or with a vasodilator to achieve optimal hemodynamic improvement.

Although the effects of dobutamine and dopamine on myocardial oxygen consumption and coronary blood flow were not assessed in the present study, production of myocardial ischemia with either drug is a potential hazard when the drugs are given to patients with coronary artery disease. Tuttle et al. have reported a favorable effect with dobutamine on the relationship between myocardial oxygen delivery and demand following experimental coronary ligation and Gillespie et al. found no evidence of increasing myocardial ischemia in 12 patients with acute myocardial infarction infused with dobutamine in dosages of 1 to 40 μg/kg/min. On the other hand, Willerson et al. have shown increased epicardial ST-segment elevation during infusion of dobutamine in anesthetized dogs following coronary ligation, in spite of concurrent increase of blood flow to all areas of the heart. Experimental studies during dopamine infusion have not found consistent changes in the net effect on the relationship between myocardial oxygen delivery and demand.

In summary, our study has shown that, when given in sufficient amounts, both dobutamine and dopamine can improve cardiac output in patients with chronic low output cardiac failure. Dopamine is more likely to cause persistent elevation of vascular resistance, increased left ventricular filling pressure, and clinical evidence of pulmonary congestion and edema. For these reasons, dopamine should be favored over dopamine for increasing of cardiac output in such patients.

References
Sustained Hemodynamic and Antianginal Effect of High Dose Oral Isosorbide Dinitrate

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SUMMARY Twenty-one patients with documented coronary atherosclerotic heart disease were studied to determine the effect of high dose oral isosorbide dinitrate (ISDN) on heart rate, blood pressure, and exercise time until angina pectoris. Patients were tested in two phases, initially with 0.4 mg of sublingual nitroglycerin and with sublingual placebo, and then with oral ISDN, mean dose 29 mg, and oral placebo. Both phases of the study were conducted in a randomized, double-blind, crossover manner. After ISDN was compared to oral placebo, heart rate increased at 30 to 300 min (P < 0.01)

have generated a long history of controversy, still unresolved. Oral administration of nitrates in particular have been subject to attack. Needleman and associates, working with rats, reported rapid and nearly complete degradation by the liver of orally administered nitrates. Thus it has been argued that there is no rational basis for the use of orally administered nitrates.

More recent hemodynamic studies, however, have caused us to reexamine this issue. Decreases in arterial blood pressure and left ventricular filling pressure following oral isosorbide dinitrate (ISDN) have been demonstrated in several carefully conducted studies in cardiac patients. These hemodynamic effects suggested that an antianginal effect might also be present. Careful review of previous studies on the antianginal effect of oral isosorbide dinitrate

peak increase 18 beats/min at 60 min), and systolic blood pressure decreased from 45 to 300 min (P < 0.005) (peak decrease 18 mm Hg at 60 min). Exercise time at 2 min after sublingual nitroglycerin increased 51% as compared to sublingual placebo (P < 0.001). After ISDN was compared to oral placebo, exercise time increased 54% at 1 hr (P < 0.005), 37% at 3 hr (P < 0.01), and 12% at 5 hr (NS). Twelve of 21 patients (57%) improved their exercise time until angina ≥ 25% at 1 hr after oral ISDN. The exercise response to sublingual nitroglycerin was a good predictor of this response to oral ISDN.

SUBLINGUAL NITROGLYCERIN has enjoyed long-standing and almost universal acceptance as an antianginal agent. The remarkable efficacy of this drug has led to its use not only as a therapeutic agent but also as a standard for evaluating other antianginal agents and even as a diagnostic tool. Many attempts have been made to prolong the brief action of sublingual nitroglycerin by altering both molecular structure and method of administration. These attempts

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Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure.
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