Comparative Systemic and Regional Hemodynamic Effects of Dopamine and Dobutamine in Patients with Cardiomyopathic Heart Failure

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SUMMARY  Thirteen patients with severe cardiac failure underwent a single crossover study of dopamine and dobutamine in order to compare the systemic and regional hemodynamic effects of the two drugs. The dose-response data demonstrated that dobutamine (2.5-10 µg/kg/min) progressively and predictably increases cardiac output by increasing stroke volume, while simultaneously decreasing systemic and pulmonary vascular resistance and pulmonary capillary wedge pressure. There was no change in heart rate or premature ventricular contractions (PVCs)/min at this dose range. Dopamine (2-8 µg/kg/min) increased the stroke volume and cardiac output at 4 µg/kg/min. Dopamine at >4 µg/kg/min provided little additional increase in cardiac output and increased the pulmonary wedge pressure and the number of PVCs/min. At >6 µg/kg/min, dopamine increased heart rate. During the 24-hour maintenance-dose infusion of each drug (dopamine 3.7-4, dobutamine 7.3-7.7 µg/kg/min), only dobutamine maintained a significant increase of stroke volume, cardiac output, urine flow, urine sodium concentration, creatinine clearance and peripheral blood flow. Renal and hepatic blood flow were not significantly altered by the maintenance dose of either drug. Systemic and regional hemodynamic data suggest that dobutamine has many advantages over dopamine when infused in patients with cardiac failure.

DOPAMINE HAS REPLACED most other catecholamine preparations (e.g., isoproterenol, norepinephrine) in clinical situations where inotropic and circulatory support is required. The popularity of dopamine has, as its basis, several studies showing that dopamine is less chronotropic and has less dramatic peripheral vascular effects than the other catecholamines. In addition, dopamine appears to have a unique property of stimulating renovascular receptors (dopaminergic receptors) directly. Tuttle and Mills have systematically formulated and synthesized a new catecholamine, dobutamine, designed to selectively increase cardiac contractility without altering heart rate and blood pressure. Animal and human data indicate that dobutamine increases stroke volume, cardiac output and overall cardiocirculatory performance in a dose range that does not elicit significant chronotropic and peripheral vascular responses. Dobutamine has also improved some parameters of renal function in patients with severe cardiac failure. Acute hemodynamic studies (catheterization laboratory data) comparing dopamine and dobutamine suggest that the ventricular function of patients with heart failure improves with both agents; however, dobutamine appears to be less chronotropic and, in contrast to dopamine, tends to lower left ventricular filling pressure. This study was designed to compare the dose-hemodynamic response curves, the maintenance dose-systemic and regional responses (during a 24-hour infusion) and the withdrawal responses of dopamine and dobutamine in 13 patients with low output cardiac failure.

Methods and Materials

Patients

Thirteen patients with moderately severe-to-severe left ventricular failure were studied. The mean age was 58 years (range 30-70 years), and all subjects were male. All patients had a form of congestive cardiomyopathy (10 idiopathic, two alcohol, one post-viral). The congestive cardiomyopathy diagnosis was confirmed in each patient with cardiac catheterization. Twelve patients were categorized as Functional Class IV (New York Heart Association), and one patient as Functional Class III. All patients were on a digitalis preparation (daily oral digoxin dose of 0.25 mg in eight patients, 0.125 mg in two patients and digitoxin 0.1 mg in three patients) and furosemide (daily oral dose range 40-240 mg). Five patients were receiving oral quinidine sulfate (daily dose range of 800-2000 mg). The digitalis, furosemide and quinidine were continued throughout the study. Written informed consent was obtained from the patients before each study.

Protocol

A single crossover design was utilized. The sequence of study for each patient consisted of a 24-hour baseline period (control data for drug I), a 24-hour drug I infusion period (dose-response and maintenance dose infusion parts), a four-hour drug I discontinuation phase, a 24-hour re-equilibration period (control data for drug II), a 24-hour drug II infusion period (dose-response and maintenance dose in-
fus ion parts) and a four-hour drug II discontinuation phase. Odd-numbered patients received dobutamine as drug I and dopamine as drug II, and even-numbered patients received dopamine as drug I and dobutamine as drug II. The infusions were administered into a peripheral vein by a calibrated Harvard pump. The volume of infusion admixture (drug in 5% dextrose in water) was less than 275 ml/24 hours. The dose range of the dose-response phase of the infusions was selected on the basis of the infusion doses generally used clinically. Dopamine was started at 2 μg/kg/min and was increased every 30 minutes in 2 μg/kg/min dose increments until the maximal dose of 8 μg/kg/min was achieved. Dobutamine was started at 2.5 μg/kg/min and was increased every 30 minutes in 2.5 μg/kg/min dose increments up to a maximal dose of 10 μg/kg/min. After the dose-response phase of the infusion period, a maintenance dose was administered for the remainder of the 24-hour infusion period. The maintenance dose for each patient was determined on the basis of data derived from the dose-response phase and had to meet the following criteria: heart rate increase of ≤120% control, systolic blood pressure ≤120% control, pulmonary capillary wedge pressure ≤140% control, and premature ventricular contractions of ≤12/min. The dose was also lowered if intolerable symptoms (vomiting, severe headache, etc.) developed. After 12 hours of the maintenance dose infusion, the dose was re-evaluated for each patient, and was adjusted based on the above criteria. The maintenance dose range for dopamine was 2–6 μg/kg/min and for dobutamine was 5–10 μg/kg/min.

Before the study period, a triple-lumen thermodilution Swan-Ganz catheter was introduced percutaneously into the subclavian vein and placed in the pulmonary artery for the measurement of pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP, pulmonary arterial occlusive pressure) and cardiac output (thermodilution technique). The pulmonary artery and capillary wedge pressures were measured by Electronics for Medicine M2101 pressure amplifier units. Pulmonary capillary wedge positioning was verified by the development of a pulmonary capillary wedge pressure wave form and a mean pressure lower than the mean pulmonary artery pressure upon inflation of the balloon. The cardiac outputs were computed with an Instrumentation Laboratory computer unit 601 and recorder unit 602. Each cardiac output value represents the mean of at least three measurements. Noninvasive assessment of left ventricular (LV) function was made by performing systolic time intervals and echocardiography. Systolic time intervals were obtained with an Electronics for Medicine VR6 unit using the specifications previously outlined. The pre-ejection period/left ventricular ejection time (PEP/LVET) was used as a measure of LV performance. Echocardiograms were performed with a Unirad series C echoscope and an Electronics for Medicine VR6 recorder. The %ΔD and Vcf were used as the echocardiographic determinants of LV function and were derived from the formulae,

$$\% \Delta D = \frac{EDD-ESD}{EDD} \times 100 \quad \text{and}$$

$$Vcf = \frac{EDD-ESD}{EDD \times LVET},$$

where EDD and ESD are end-diastolic and end-systolic diameters, respectively. The ECG was continuously monitored during the study. The mean heart rate and frequency of premature ventricular contractions per minute (PVCs/min) were determined from 1-minute monitor recordings taken every 5 minutes during the dose-response phase of each drug, and every 30 minutes during the baseline and maintenance dose periods of each drug. The systemic blood pressure was measured indirectly with a calibrated sphygmomanometer. The hemodynamic, noninvasive and ECG data (i.e. pulmonary artery and capillary wedge pressures, systemic blood pressure, cardiac output, PEP/LVET, %ΔD, Vcf, heart rate and PVCs/min) were obtained 1 hour before drug infusion (control data), after each dose increment of the dose-response phase, every 12 hours of the maintenance dose period and 30 minutes, 1, 2 and 4 hours after discontinuation of the study drug. The same data were then obtained on drug II following the same schedule.

Regional hemodynamic studies were performed during the baseline and maintenance dose periods of each drug. Forearm and hand blood flow was measured in six patients by the venous occlusive method using a water-containing plethysmograph (Szanati Engineering, Columbus, Ohio). The limb blood flow is expressed as cc blood/100 cc tissue/min, and each value for each patient represents a mean of three determinations. Hepatic blood flow was determined in six patients by the indocyanin green clearance method and renal blood flow was measured in seven patients by the PAH clearance method. Twenty-four hour urine collections were obtained during the baseline and re-equilibration periods and the two infusion (drug I and II) periods for the determinations of urine flow (cc/min) and creatinine clearance. Urine sodium concentration (meq/l) was measured every 8 hours throughout the study. The hemodynamic, noninvasive and ECG data were compared to control values for each drug, with analysis of variance of repeated measures. Analysis of inter-drug and regional blood flow data and of changes in urine flow, urine sodium concentration and creatinine clearance was performed by using the t test for paired and unpaired data. Data points with P values <0.05 were considered significant.

**Results**

**Hemodynamic and Noninvasive Data**

The effects of dopamine and dobutamine on cardiac index, stroke volume index and PCWP are presented
in Figure 1. The control cardiac index (2.45 L/min/m²) was the same for both drugs. Dobutamine progressively increased the cardiac index at all dose increments. Dopamine required an infusion of 4 μg/kg/min before the cardiac index rose significantly above baseline. Increasing the dopamine infusion to 6-8 μg/kg/min resulted in an insignificant further increase in the cardiac index. The cardiac index curve of dopamine remained below the dobutamine curve throughout the dose-response portion of the study, and was significantly different at dopamine doses of 2, 6 and 8 μg/kg/min. The maintenance dose cardiac index values for dobutamine remained significantly above baseline and significantly greater than dopamine values. Only the 12-hour maintenance dose (4 μg/kg/min) of dopamine was significantly increased above baseline. The values for each drug returned toward baseline upon discontinuation with...
the 2 and 4-hour post-dopamine values dropping significantly below control. The mean heart rate during the entire dobutamine infusion did not change from control, so that the increase in cardiac output for this drug was secondary to an increase in stroke volume (fig. 1B). Dopamine significantly increased stroke volume only at the 4 μg/kg/min infusion of the dose-response phase, indicating that the significant increases of cardiac output at dopamine doses of 6 and 8 μg/kg/min were in part secondary to increases in heart rate. The mean PCWP (fig. 1C) rose dramatically with dopamine at doses ≥4 μg/kg/min, while dobutamine significantly lowered the PCWP at infusion rates ≥5 μg/kg/min. The PCWP returned toward control for each drug during the maintenance dose and discontinuation periods. Figure 2 illustrates
the changes in systemic blood pressure and total systemic and pulmonary resistances during the infusions. Dopamine significantly increased the systolic blood pressure at $\geq 4 \text{ug/kg/min}$ and the diastolic pressure at $8 \text{ug/kg/min}$. Dobutamine did not alter diastolic pressure, but significantly increased systolic pressure at $10 \text{ug/kg/min}$ and during the maintenance period. Post-dobutamine and dopamine pressures returned toward baseline values with 1- and 2-hour post-dopamine diastolic pressures falling below control. Total systemic resistance dropped significantly at all dose increments of dobutamine, and remained at this level during the maintenance dose period. The total systemic resistance during the dopamine infusion did not differ from control, but was significantly higher than dopamine values at $8 \text{ug/kg/min}$ and during the maintenance period. Total pulmonary resistance decreased at dobutamine infusion rates $\geq 7.5 \text{ug/kg/min}$. While dopamine did not increase total pulmonary resistance above control, the $8 \text{ug/kg/min}$, maintenance dose, and the 1- and 4-hour discontinuation values were significantly higher than corresponding dobutamine values.

Dopamine at $8 \text{ug/kg/min}$ significantly increased the mean heart rate above control and above the 10 $\text{ug/kg/min}$ dobutamine values (fig. 3A). No heart rate changes were noted with dobutamine. Dopamine at $\geq 4 \text{ug/kg/min}$ significantly increased the number of PVCs/min above control and above the number noted during the dobutamine infusion (fig. 3B). During the respective maintenance dopamine and dobutamine doses of 3.7 and 7.7 $\text{ug/kg/min}$, the mean number of PVCs/min were the same. However, because of the wider range of PVCs/min for dobutamine at this point, the mean value was significantly increased for dopamine only.

The noninvasive LV function data is presented in figure 4. The PEP/LVET decreased significantly at all dose levels of dobutamine, and was significantly lower than most of the corresponding dopamine points during the entire infusion period. The ratio decreased at $\geq 4 \text{ug/kg/min}$ of dopamine and rose above baseline 1 and 2 hours after the drug was discontinued. The $\%\Delta D$ and Vcf rose significantly at all infusion rates of dobutamine and remained above baseline after the drug was discontinued. Dopamine at $\geq 4 \text{ug/kg/min}$ increased the $\%\Delta D$ and Vcf, but the values remained significantly lower than the corresponding dobutamine values during most of the infusion period.

Renal Function and Regional Blood Flow Data

Urine flow, urine sodium concentration and creatinine clearance increased significantly during the maintenance dose infusion of dobutamine (fig. 5). While the mean values also increased with maintenance dose dopamine, the wide range of individual responses kept the data at $P > 0.05$. Mean renal blood flow did not increase significantly during maintenance dose infusions of either drug in the seven
patients tested. Of the renal function parameters studied, only the mean change in creatinine clearance for dobutamine was significantly greater than that for dopamine. Mean hepatic blood flow did not change significantly from control (fig. 6A) for either drug, and the mean values of the two drugs were not significantly different from each other. Mean upper extremity blood flow (fig. 6B) increased with dobutamine and did not change significantly with dopamine. The change in upper extremity blood flow elicited by dobutamine was significantly greater than that of dopamine.

Clinical Information

Five of seven patients with severe dyspnea at rest noted a reduction of this symptom with the maintenance dose of either dobutamine or dopamine. Orthopnea improved in one of eight patients during maintenance dopamine and four of eight patients with dobutamine. Significant somnolence developed in four patients during the dopamine infusion and in one patient with dobutamine. One patient experienced mild nausea with dobutamine. Another patient noted mild nausea and two other patients developed severe
nausea and vomiting with dopamine. Dobutamine caused a headache in one patient; dopamine produced the same reaction in another.

**Discussion**

While Loeb and colleagues\(^9\) and Stoner et al.\(^8\) found that the hemodynamic effects of dobutamine were superior to dopamine at one matched cardiac output or at one dose, this study demonstrates the advantages of dobutamine over dopamine over the entire dose-response curve, during the continuous maintenance dose infusion period, and upon discontinuation of the drugs. Data derived from the dose-response phase of each drug of this study are shown in figure 7. The graphs in this figure illustrate for each agent the relationship between cardiac index (as a standard of improved cardiac function) and the other cardiovascular parameters known to be affected by inotropic agents, namely, heart rate, ventricular irritability (PVCs/min), systemic and pulmonary resistances, PCWP and myocardial oxygen consumption (estimated by the heart rate-systolic blood pressure product). Dobutamine in doses up to 10 µg/kg/min progressively increases cardiac output while decreasing systemic and pulmonary resistances and PCWP, and without affecting heart rate or ventricular irritability. Dopamine at doses ≥4 µg/kg/min increases the PCWP and the number of PVCs/min, and at doses >6 µg/kg/min increases heart rate and systemic and pulmonary resistances. Undesirable effects occur with dopamine at doses as low as 4 µg/kg/min and, infusion rates <4 µg/kg/min do not appear to improve cardiac output or ventricular performance (PEP/LVET, %ΔD or Vcf) above baseline.

**Figure 5.** Graphs showing the changes in urine flow (A), urine sodium concentration (B), creatinine clearance (C), and renal blood flow (D) elicited by the maintenance doses of dobutamine and dopamine. The values are mean ± SD and statistical analysis (t test for paired data) was applied to changes from baseline. n = number of patients studied; NS = not significant.

**Figure 6.** Panel A shows that maintenance dose dobutamine and dopamine did not significantly alter hepatic blood flow, while panel B shows improvement of limb blood flow with maintenance dose dobutamine and no significant change with dopamine. n = number of patients studied; NS = not significant.
Figure 7. Graphs generated from the dose-response data of dopamine and dobutamine showing the relationship between cardiac index and other cardiovascular parameters for each drug. The doses in µg/kg/min are indicated next to the data points. Dopamine values are designated by closed dots (●) and dobutamine by open triangles (△).
Dopamine doses of >4 μg/kg/min increase the undesirable effects with very little further improvement of cardiac output. While the heart rate-systolic blood pressure product (HR × SBP) increases with both agents, the increase with dopamine is more dramatic than with dobutamine. The HR × SBP product for dopamine at 4 μg/kg/min was the same as that for dobutamine at 10 μg/kg/min, while their respective cardiac outputs increased by 0.60 and 1.13 l/min/m². Thus, compared with dopamine, the increase in cardiac output with dobutamine is nearly twice as great with the same energy expenditure, with no increase in PVCs/min and with a decrease in LV filling pressure and systemic and pulmonary resistances.

Although this study was performed in patients without coronary artery disease, it appears that dobutamine should be the catecholamine of choice in patients with the combination of low output failure and atherosclerotic heart disease. Gillespie and colleagues administered dobutamine to patients with acute myocardial infarction and found that the drug improved hemodynamic parameters without provoking undesirable effects, and without increasing the extent of myocardial injury. However, because Meyer et al. noted that dobutamine elicited inhomogeneous myocardial perfusion in two of three patients with triple-vessel coronary artery disease, this drug should be administered with caution in the setting of severe coronary artery disease.

The inability of dopamine to further improve stroke volume (and cardiac output) at doses >4 μg/kg/min in these patients was probably related to the increase in systolic pressure (t afterload) and the increase in cumulative heart rate (sinus beats plus PVCs/min) in a failing ventricle. While Beregovich and colleagues reported that the mean cardiac output increased (five patients) as the dopamine dose was increased from 5–10 μg/kg/min, the mean stroke volume did not increase, indicating that the improvement in cardiac output was secondary to an increase in the mean heart rate. They noted that the cardiac output decreased in two of the patients. The elevation of the PCWP with dopamine in our patients was also probably related to an increase in afterload and cumulative heart rate in a severely impaired ventricle, although one cannot exclude the possibility that dopamine may increase LV filling pressure independently of the above factors by diminishing ventricular compliance.

In accordance with the clinical guidelines for inotropic dose selection (e.g., heart rate and blood pressure), the maximal mean maintenance infusion doses for dopamine were 4 and 3.7 μg/kg/min, and for dobutamine 7.3 and 7.7 μg/kg/min. Dopamine maintained an improved cardiac output and PEP/LVET only with the 4 μg/kg/min infusion at 12 hours. The number of PVCs/min was still higher than baseline for both the 4 and 3.7 μg/kg/min maintenance dose dopamine infusions. At these doses, dopamine did not improve renal, hepatic or peripheral blood flow, creatinine clearance, urine flow or renal sodium excretion. At maintenance doses, dobutamine maintained an improved cardiac index, stroke volume, PEP/LVET, %ΔD, and Vcf, while decreasing pulmonary and systemic resistances and without increasing the number of PVCs/min. Maintenance doses of dobutamine significantly increased peripheral blood flow, urine flow, renal sodium excretion and creatinine clearance. At maintenance doses, dobutamine also did not significantly alter renal or hepatic blood flow. The HR × SBP product of maintenance dose dopamine and dobutamine were not significantly different.

Beregovich and colleagues noted an increase in urine flow and renal sodium excretion in patients with heart failure only at dopamine doses of ≥5 μg/kg/min. This suggests that in the low cardiac output heart failure population the beneficial renal properties of dopamine are dose-related (i.e. ≥5 μg/kg/min). Using the criteria generally used to determine the maintenance dose of an inotropic agent, the maximal safe and tolerable maintenance dose of dopamine in our patients was 4 μg/kg/min. Increasing the infusion rate elicited undesirable side effects and, in fact, the mean maintenance dose of dopamine had to be reduced to 3.7 μg/kg/min when PVCs, vomiting and somnolence occurred in some of the patients. The beneficial renal effects of dopamine at ≥5 μg/kg/min thus appear to be of little use in these patients if this dose range cannot be safely achieved or is not tolerated.

Because a previous study from this laboratory showed that cardiac performance remained improved after a 72-hour dobutamine infusion (10–15 μg/kg/min) and because studies have suggested that dopamine may, in part, act through the release of endogenous norepinephrine, measurements were performed over a 4-hour period after discontinuing each drug. While none of the parameters deteriorated below control when dobutamine was discontinued, only Vcf and %ΔD remained significantly above control, suggesting that a 24-hour infusion at 7.3 and 7.7 μg/kg/min will not result in improved hemodynamic function in this patient population upon discontinuation of the drug. After discontinuation of dopamine, the cardiac index fell (P < 0.05 at 2 and 4 hours), the stroke volume decreased (P < 0.05 at 30 minutes), the systemic diastolic pressure fell below baseline at 1 and 2 hours and the PEP/LVET increased significantly at 1 and 2 hours. The mechanism of the transient cardio-circulatory deterioration after dopamine is discontinued is not clear; however, myocardial and peripheral vascular norepinephrine depletion could be a factor.

The superiority of dobutamine over dopamine in low output congestive cardiomyopathy is apparent in the dose-response phase, the maintenance dose period and the discontinuation phase of administration. If an inotrope is to improve cardiac performance without provoking deleterious or intolerable side effects, then dobutamine appears to be the best inotrope available. The next step in the advancement of pharmacology for heart failure should be the development of a safe, effective inotropic agent which can be administered orally.
Acknowledgments

The authors wish to thank Ms. Barbara Metzner and Mr. Fred Davis for their technical assistance.

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Circulation. 1978;58:466-475
doi: 10.1161/01.CIR.58.3.466

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/58/3/466

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