Effect of Dobutamine on Systemic Capacity in the Dog

RICHARD M. FUCHS, DAVID L. RUTLEN, AND WM. JOHN POWELL, JR.

SUMMARY Dobutamine, a recently synthesized catecholamine, was developed as an agent which would produce increased inotropy in low cardiac output states without major changes in heart rate, cardiac rhythm, or peripheral vascular resistance. However, the effect of dobutamine on the capacitance vasculature is unknown. Since alterations of systemic vascular capacity influence venous return and hence cardiac output, we performed the present study. The muscular capsules of the canine spleen make them representative of the capacitance vasculature. We weighed exteriorized canine spleens continuously in 26 anesthetized dogs. Dobutamine infused for 15 minutes at 4 and 16 μg/kg per min was associated with decreases in splenic weight of 15 ± 2% (SEM) (P < 0.0005) and 33 ± 2% (P < 0.0001) from controls of 249 ± 27 g and 313 ± 42 g. Dobutamine-induced splenic contraction was abolished by phenoxybenzamine but not by propranolol. Injections of dobutamine into the splenic artery produced significant decreases in splenic weight without any change in systemic hemodynamics. In six additional dogs with ganaglionic blockade and supported by total cardiopulmonary bypass, decreases or increases in vascular volume were recorded as changes in oxygenator volume. Dobutamine infusion at 30 μg/kg per min for 10 to 24 minutes in these dogs was associated with decreases in vascular volume of 25 ± 28 ml (P < 0.0001). Selective blockade revealed the dobutamine effect to be mediated by α-adrenergic receptor stimulation alone. Thus, in the intact animal, the administration of dobutamine should increase venous return and hence cardiac output through an α-adrenergic-mediated decrease in systemic vascular capacity. Circ Res 46: 133-138, 1980

DOBUTAMINE, a recently synthesized catecholamine, was developed as an agent that would increase cardiac contractility without producing any major change in heart rate or rhythm, or in peripheral resistance. Several studies have shown that administration of the drug at both low and high doses produces a marked inotropic effect which is accompanied by only moderate increases in heart rate, a low incidence of arrhythmias, and only a modest decrease in total peripheral resistance (Tuttle and Mills, 1975; Vatner et al., 1974; Akhtar et al., 1975; Leier et al., 1977; Gillespie et al., 1977). With regard to its action on adrenergic receptors, dobutamine acts primarily on adrenergic β receptors to increase contractility. In the arterial circulation, both β2 and α receptors are stimulated (Robie et al., 1974; Sonnenblick et al., 1979), but the β-adrenergic dilator response is slightly greater than the α-constrictor response (Sonnenblick et al., 1979) at both high and low doses of dobutamine. Little is known about the effect of dobutamine on the capacitance vasculature, however. Since venous return is a major determinant of cardiac perform-

From the Cardiac Unit, Department of Medicine, Massachusetts General Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts.

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Address for reprints: Wm. John Powell, Jr., M.D., Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114.

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ance, the present investigation was carried out to examine the effect of dobutamine on systemic vascular capacity.

Under physiological conditions, approximately 60-70% of man's circulating blood volume is in veins and venules (Folkow and Neil, 1971a). The smooth muscle in the walls of these capacitance vessels is capable of contraction in response to appropriate stimuli (Shepherd and Vanhoutte, 1978). In the dog, the spleen is surrounded by smooth muscle and thus has the potential to translocate volume to other areas of the dog's circulatory system. Opdyke and Ward (1973) have demonstrated that the response of the smooth muscle surrounding the dog's spleen to neural, pharmacological, and hypotensive stimuli is directionally similar to that of the smooth muscle of the remainder of the capacitance vasculature. Thus, continuous recording of the weight of the exteriorized spleen permits an assessment of changes in splenic capacity which are representative of changes in overall systemic capacity. In the present study we employed the isolated spleen model to examine the effects of dobutamine on intravascular volume. The results then were confirmed in a canine total cardiopulmonary bypass preparation.

Methods

Twenty-six mongrel dogs (18-22 kg) were anesthetized with intravenous chloralose (60 mg/kg) and urethane (600 mg/kg). After induction of anesthesia, an endotracheal tube was inserted and the dogs were ventilated with a Harvard positive pres-
sure respirator (Harvard Apparatus Co., Inc.) at a rate between 14 and 18 cycles/min with a mixture of 95% O2 and 5% CO2.

The spleen was exteriorized through a left subcostal incision. Arterial pressure, central venous pressure, and splenic vein pressure were monitored continuously via catheters inserted into the right subclavian artery, the superior vena cava, and the splenic vein (via a left gastroepiploic vein), respectively. Pressures were monitored with Statham P23Db pressure transducers (Statham Instruments, Inc.) and recorded on a model 7700 Hewlett-Packard 8-channel direct writing recorder (Hewlett-Packard Co.).

The exteriorized spleen was covered with sponges moistened with physiologic saline and placed with its pedicle intact in a specially designed plastic tray which conformed to the spleen’s shape. The tray was suspended from a Harvard Apparatus model 360 isometric force transducer, which was free of any contact with the dog except for the splenic pedicle. The force transducer was sufficiently sensitive to detect changes in weight of 1 g.

In 20 dogs, cannulas were introduced into the right femoral vein for the infusion of dobutamine. In each of two dogs of this group, an electric magnetic flowmeter (Statham SN61770) was placed around the splenic artery; in one case, care was taken to leave the splenic nerves intact; in the other case, they were intentionally severed. In an additional six dogs, a thin plastic cannula was inserted into the left gastroepiploic artery, with its tip at the junction of the splenic artery, to permit injections directly into the splenic artery.

Dobutamine (Eli Lilly Co., Inc.) was dissolved in normal saline at a concentration of 80 μg/ml. The drug was administered either intravenously with a Harvard infusion pump (at rates of 80 and 320 μg/min) or by direct injection into the splenic artery (80 μg injected by hand over 10 seconds). Alpha adrenergic receptor blockade was achieved with phenoxybenzamine (Dibenzyline, Smith, Kline & French), 50 mg, iv, and tested with norepinephrine (Levophed, Winthrop Laboratories), 10 μg iv. This dose of norepinephrine consistently produced more than a 30% reduction in spleen weight in animals without β-adrenergic receptor blockade. Blockade was considered adequate when the splenic constriction effect of norepinephrine was abolished. Beta adrenergic blockade was obtained with 10 mg of propranolol given iv (Inderal, Ayerst Laboratories). Isoproterenol (Isuprel, Winthrop Laboratories) was used as a test drug, with abolition of the tachycardia induced by isoproterenol, 6 μg iv as the criterion for effective β blockade.

To confirm that dobutamine administration is associated with an overall decrease in systemic capacity, an additional seven dogs were placed on total cardiopulmonary bypass. Following anesthesia, intubation, and ventilation, as described above, a median sternotomy was performed, and heparin, 3 mg/kg, was administered intravenously. Total venous return to the reservoir of a pump oxygenator was accomplished by cannulating the superior and inferior venae cavae through the right atrial appendage with Argyle 32 French catheters. The azygos vein was securely ligated. Central venous pressure was measured in the venous return line and was set at 8 cm H2O by adjusting the height of a venous overflow column. Blood from the operative dog and from four donor dogs was oxygenated with a Harvey model H-1000 oxygenator (William Harvey) which was calibrated with whole blood in 100-ml increments up to a total volume of over 3800 ml before each experiment. Thus, any increase or decrease in the dog’s systemic intravascular volume could be measured as a reciprocal change in oxygenator volume. The roller pump (Cardiovascular Instruments) returning the oxygenated blood to the femoral arteries of the dog was set at 1.5 liters/min. The rate was maintained constant throughout the course of each experiment. Arterial pressure was measured via a cannula in the subclavian artery. The aorta was cross-clamped 2 cm above the aortic valve, and the pulmonary hilum were clamped to exclude the coronary, pulmonary, and bronchial circulations. Hence, any contribution of the cardiac chambers or pulmonary vasculature to total systemic capacity was excluded. The adequacy of clamping was demonstrated by the absence of flow from drains placed in both ventricles.

Ganglionic blockade was produced in all dogs on cardiopulmonary bypass by the administration of 100 mg of mecamylamine (Inversine, Merck, Sharpe & Dohme) to the pump reservoir over 10 minutes. In preliminary experiments, this dose was shown to be adequate to abolish entirely the 50 mm Hg rises in perfusion pressure caused by clamping a single carotid artery below the bifurcation. Bilateral cervical vagectomy also was performed. Since the mean systemic pressure in these animals on total cardiopulmonary bypass was in the range of 65–75 mm Hg, the ganglionic blockade and vagotomy eliminated possible reflex changes secondary to systemic hypotension.

Dobutamine was infused into the femoral arteries with a parenteral fluid delivery system (IV 5000, Valleylab) at a rate of 600 μg/min and, for a period of time, that allowed all hemodynamic changes to stabilize. The drug was dissolved in normal saline at a concentration of 2 ml/min. Reservoir volume and arterial pressure were unchanged from the baseline during 20-minute infusions of normal saline alone at 2 ml/min in two dogs. Alpha- and β-adrenergic receptor blockade was achieved with 0.5 to 1.0 g of phenoxybenzamine and 20 mg of propranolol, respectively, added to the blood reservoir containing 3800 to 4000 ml and allowed to circulate through the dog. The adequacy of blockade was assessed by the absence of reflex changes secondary to systemic arterial pressure responses to 300 μg of phenylephrine (Neosynephrine, Winthrop Laboratories).
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DOBUTAMINE 80;ig/min I.V.

SPLEEN WT (% control)

Δ MAP (mm Hg)

Δ SVP(cm H2O)

Δ CVP(cm H2O)

Δ HR (bpm)

MINUTES

FIGURE 1 Effects of a low dose of dobutamine. Note the significant decrease in splenic weight. Each bar represents ± 1 standard error of the mean. Asterisks indicate data points significantly different from preinfusion control points at the P < 0.05 level. Abbreviations: ΔMAP = change in mean arterial pressure, ΔSVP = change in splenic vein pressure, ΔCVP = change in central venous pressure, ΔHR = change in heart rate, bpm = beats per minute, I.V. = intravenously.

and 12 µg of isoproterenol, respectively, administered intraarterially before and after blockade. Complete blockade was confirmed before and after each infusion administered in the presence of α- or β-adrenergic blockade by noting the absence of changes in blood pressure with either phenylephrine or isoproterenol.

Dunnett’s procedure was performed between control values and all the specified experimental values in each series shown in Figures 1–4. The mean squares for error required for Dunnett’s t-statistic was calculated from a two-way analysis of variance upon columns consisting of the column of actual control values followed by one column of values for each experimental sample point up to 30 minutes. Percent and delta values are used for display in figures, not for statistical tests. Differences in column means were significant if P < 0.05 (two-tailed critical points of Dunnett’s t-distribution).

Results

In 10 dogs, dobutamine was infused intravenously at a rate of 80 µg/min (approximately 4 µg/kg per min) for a period of 15 minutes. In all 10 dogs, spleen weight decreased, and the decrease was maintained for the duration of the infusions (Fig. 1). At the end of the infusions, spleen weight had declined by an average of 15.0 ± 2.4% (SEM) (P < 0.0005). The control data are given in Table 1. As shown in Figure 1, mean arterial pressure decreased slightly and splenic vein pressure increased slightly. The greatest effect on splenic vein pressure was seen at 5 minutes, although the pressure remained significantly elevated throughout the period of infusion. Central venous pressure and heart rate both increased slightly but not significantly. All parameters returned toward control values after the infusions were discontinued, except heart rate, which was not assessed during the postinfusion control period.

In eight experiments in six dogs, dobutamine was infused intravenously at a rate of 320 µg/min (approximately 16 µg/kg per min) for a period of 15 minutes. All hemodynamic parameters were affected in the same direction as with the low dose infusion but to a greater extent. Spleen weight decreased by 32.5 ± 2.1% (P < 0.0001). As illustrated in Figure 2, all parameters changed by a statistically significant amount during the infusions. The control data are given in Table 1. As with the low dose infusions, all parameters returned toward control values after the infusions were discontinued.

In four dogs, dobutamine was infused both before and after α-adrenergic blockade with phenoxybenzamine. In three dogs, dobutamine was infused intravenously at a rate of 320 µg/min for 15 minutes; in one dog, the dose was 80 µg/min. In all cases, splenic contraction was eliminated entirely by α blockade (see Table 2 and Figure 3). To exclude the possibility of tachyphylaxis, control experiments were done in two dogs without prior α blockade, in which a second infusion of dobutamine in each animal produced a decrease in spleen weight which was identical to that produced by the first infusion. Dobutamine produced a greater decrease in mean arterial pressure after α-adrenergic receptor blockade. The data indicate the influence of α receptor stimulation in maintaining arterial pressure during the infusion of dobutamine in the absence of block-

<table>
<thead>
<tr>
<th>Dobutamine iv infusion</th>
<th>Splenic wt (g)</th>
<th>MAP (mm Hg)</th>
<th>SVP (cm H2O)</th>
<th>CVP (cm H2O)</th>
<th>HR (bpm)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>249 ± 27</td>
<td>149 ± 4.1</td>
<td>8.5 ± 1.2</td>
<td>3.2 ± 0.4</td>
<td>150 ± 9</td>
<td>10</td>
</tr>
<tr>
<td>320</td>
<td>313 ± 42</td>
<td>139 ± 4.2</td>
<td>6.3 ± 0.4</td>
<td>1.4 ± 0.6</td>
<td>137 ± 10</td>
<td>8</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. Abbreviations are as in Figure 1.
Figure 2  Effects of a high dose of dobutamine. Note the significant decrease in splenic weight. Asterisks and abbreviations are as in Figure 1.

Figure 3  High dose dobutamine before and after α-adrenergic blockade. The dobutamine associated decrease in splenic weight is abolished after α-adrenergic blockade. Asterisks and abbreviations are as in Figure 1.

In four dogs, a high dose of dobutamine (320 µg/min) was infused intravenously before and after intravenous propranolol (10 mg, iv). In these dogs, the high dose of dobutamine produced decreases in splenic weight which were not significantly different before and after α-adrenergic receptor blockade (see Fig. 4). Before propranolol, mean arterial pressure fell below control during dobutamine infusion and after β blockade, mean pressure rose above control, reflecting the capability of dobutamine to stimulate α-adrenergic receptors in the arterial circulation. The alterations of splenic vein pressure, central venous pressure, and heart rate produced by the infusion of dobutamine before and after blockade are also shown in Figure 4. The control data for pressures and heart rate prior to the infusion of dobutamine are in Table 2. Patterns of response of splenic vein pressure were not significantly different before and after blockade.

In three dogs, a low dose of dobutamine (80 µg/min) was infused intravenously both before and after β-adrenergic receptor blockade with propranolol (10 mg, iv). In these low dose experiments, there was no consistent difference in the response of spleen weight to dobutamine before and after β blockade. Spleen weight fell by 11.3 ± 3.3% before propranolol and 12.3 ± 4.1% after β blockade. All the other responses were similar to, but less pronounced than, the response to the high dose dobutamine infusions noted above.

Ligation of the splenic artery was performed in two dogs to establish whether a diminution of arterial inflow could, by itself, diminish splenic

Table 2  Splenic Weight, Pressure, and Heart Rate Data before Dobutamine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Spleen wt (g)</th>
<th>MAP (mm Hg)</th>
<th>SVP (cm H₂O)</th>
<th>CVP (cm H₂O)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-α-adrenergic</td>
<td>386 ± 58</td>
<td>133 ± 4</td>
<td>7.0 ± 1.6</td>
<td>6.3 ± 0.9</td>
<td>146 ± 26</td>
</tr>
<tr>
<td>Post-α-adrenergic</td>
<td>390 ± 73</td>
<td>95 ± 4</td>
<td>8.8 ± 1.3</td>
<td>6.3 ± 1.2</td>
<td>133 ± 11</td>
</tr>
<tr>
<td>Pre-β-adrenergic</td>
<td>222 ± 39</td>
<td>138 ± 7</td>
<td>6.4 ± 1.1</td>
<td>3.9 ± 0.7</td>
<td>140 ± 15</td>
</tr>
<tr>
<td>Post-β-adrenergic</td>
<td>226 ± 42</td>
<td>119 ± 15</td>
<td>6.0 ± 0.6</td>
<td>4.1 ± 0.7</td>
<td>101 ± 80</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. Abbreviations are as in Figure 1.
The present study demonstrates that the administration of dobutamine, a recently synthesized catecholamine, is associated with a reduction in venous capacity in the dog. The effect is dose-related and occurs over the dosage range administered clinically. Furthermore, the decrease in capacity is the result of a direct effect on smooth muscle in the capacitance vasculature and is mediated by α-adrenergic receptor stimulation.

Evidence for dobutamine-induced contraction of the capacitance vasculature is provided by findings of splenic contraction in the present experiments. The decrease in splenic weight is not a passive phenomenon mediated by decreased arterial inflow or by decreased venous tone. Evidence for this is provided by the findings that splenic arterial flow and splenic vein pressure both increased during dobutamine administration. The splenic contraction is not due to an autonomic reflex secondary to changes in systemic hemodynamics. Contraction of the spleen occurred with splenic arterial injections of dobutamine of a dose sufficiently small to produce no change in systemic hemodynamics. Furthermore, although systemic blood pressure decreased with dobutamine infusion and increased with dobutamine after β-adrenergic receptor blockade (Fig. 4), the associated changes in splenic weight were nearly identical.

Dobutamine-induced splenic contraction appears to be mediated by stimulation of α-adrenergic receptors alone, as evidenced by the complete elimination of the splenic contraction response after α-adrenergic receptor blockade with phenoxybenzamine and the essentially unaltered response after β-adrenergic receptor blockade with propranolol. Thus, whereas the net affect of the drug on the resistance vasculature is predominantly mediated through β-adrenergic receptor stimulation, on the capacitance vasculature α-adrenergic effects predominate.
The use of the canine splenic weight model is an accurate and sensitive method of assessing humorally induced changes in systemic vascular capacity. Whereas much of man's vascular capacity is in the legs, the dog has relatively little capacity in its thin limbs. The dog's spleen, unlike that of man, has a muscular capsule with the capability of contracting to release 10-20% of the animal's total blood volume (Folkow and Neil, 1971b). In addition to Opdyke and Ward (1973), other investigators have demonstrated the appropriateness of the splenic weight model for investigating contractile properties of the capacitance system (Davis and Withrington, 1973). In our experiments, the dobutamine-induced increase in splenic vein and central venous pressures may be additional manifestations of venoconstriction, lending further support to the validity of the model. The splenic weight model allows an assessment of the effects of dobutamine on vascular capacity in a preparation in which the heart and lungs and reflexes are intact; in spite of variation in control splenic weight, which may reflect some variation in the level of anesthesia from animal to animal, there was a consistent splenic contraction produced in each dog by dobutamine.

The validity of the data obtained with the splenic weight model is confirmed in the present study by the data obtained from the dogs on total cardiopulmonary bypass. Dobutamine administration is associated with a significant decrease in total systemic capacity in these animals. The effect appears mediated entirely through $\alpha$-adrenergic receptor stimulation, because the decrease in systemic capacity is abolished after $\alpha$-adrenergic receptor blockade and is unaltered after $\beta$-adrenergic blockade. The manifestation of the capacity-decreasing effect of dobutamine in the presence of ganglionic blockade and in a bypass preparation in which the heart and lungs are removed from the circulation is further evidence that the observed decrease in total systemic capacity is not mediated through peripheral or central volume receptors or baroreceptors.

Thus, the present study indicates that dobutamine administration is associated with an $\alpha$-adrenergic-mediated decrease in vascular capacity. In the intact organism, it would be expected that dobutamine would be associated with an increase in venous return and, hence, depending on the functional state of the heart, would tend to increase ventricular filling pressure and ventricular performance.

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