Role of Adrenoceptors and Dopamine Receptors in Modulating Left Ventricular Diastolic Function

Roberto M. Lang, John D. Carroll, Shigeru Nakamura, Haruki Itoh, and Sol I. Rajfer

Although both dopamine and dobutamine are potent positive inotropic agents, multiple studies indicate that dopamine may produce a rise in left ventricular (LV) filling pressure, while dobutamine often has the opposite effect. To ascertain the pharmacological and hemodynamic mechanisms responsible for the elevation in LV filling pressure observed with dopamine, we administered incremental infusions (2, 4, and 6 μg/kg/min) of dopamine to 18 open-chest, anesthetized dogs in the presence and absence of rauwolscine (selective α2-adrenoceptor antagonist) (n = 7), terazosin (selective α1-antagonist) (n = 6), and domperidone (selective dopamine, antagonist) (n = 5), while measuring pressures in the LV and left atrium and changes in dimension in the LV short-axis (with ultrasonic piezo crystals). Dobutamine (2, 4, and 6 μg/kg/min) was infused in five additional dogs before and after administration of rauwolscine. The time constant of isovolumic pressure decay, peak lengthening rate (mm/sec), LV end-diastolic pressure, and diastolic pressure-dimension relation were computed. A significant elevation in LV end-diastolic pressure and a parallel increase in LV end-diastolic chamber size was observed with dopamine, while a decline in LV end-diastolic pressure occurred with dobutamine. Yet both dopamine and dobutamine caused a dose-related acceleration of pressure decay and augmentation of peak lengthening rate. Furthermore, heart rate declined during the administration of dopamine but rose with dobutamine. In the presence of either rauwolscine or terazosin, dopamine infusion resulted in a positive chronotropic effect and dose-dependent reductions in LV end-diastolic pressure and end-diastolic chamber dimension; arterial pressure fell only after terazosin administration. The hemodynamic actions of dobutamine, however, were unchanged in the presence of rauwolscine. Moreover, domperidone did not alter the hemodynamic responses to dopamine. The results of the present study suggest that activation of prejunctional α2-adrenoceptors and postjunctional α1- and α2-adrenoceptors play an important role in determining the hemodynamic responses to dopamine. The rise in LV filling pressure produced by dopamine can be attributed to vasoconstriction resulting from stimulation of postjunctional α1- and α2-receptors. The decrease in heart rate observed with dopamine may also contribute toward the development of elevated LV filling pressures. (Circulation Research 1988;63:126–134)

Many clinical studies in congestive heart failure have documented that dopamine frequently causes no reduction or an increase in left ventricular (LV) filling pressure despite its positive inotropic action.1–7 In contrast, the administration of dobutamine may be associated with a reduction in LV filling pressure.1–6,8–10 Dobutamine is a full agonist at the β1-adrenoceptor site (positive inotropic action) and possesses weak activity at the β2-adrenoceptor (produces vasodilation) and α1-adrenoceptor sites (suberves vasoconstriction)11; thus, hemodynamic responses to dobutamine are essentially the result of its cardiotonic action medi-
TABLE 1. Hemodynamic Responses to Dopamine Infusion Before and After Rauwolscine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dopamine</th>
<th>Dopamine + rauwolscine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 µg</td>
<td>4 µg</td>
<td>6 µg</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 ± 4</td>
<td>83 ± 6</td>
<td>72 ± 5*</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>89 ± 10</td>
<td>84 ± 9*</td>
<td>92 ± 12</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>4.8 ± 0.8</td>
<td>5.6 ± 0.9</td>
<td>6.9 ± 1*</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>4.6 ± 0.9</td>
<td>4.9 ± 0.9</td>
<td>5.7 ± 1.2</td>
</tr>
<tr>
<td>End-systolic dimension (cm)</td>
<td>2.82 ± 0.34</td>
<td>2.77 ± 0.34</td>
<td>2.76 ± 0.35</td>
</tr>
<tr>
<td>End-diastolic dimension (cm)</td>
<td>3.57 ± 0.43</td>
<td>3.59 ± 0.43</td>
<td>3.66 ± 0.42*</td>
</tr>
<tr>
<td>Peak positive dP/dt (mm Hg/sec)</td>
<td>3,031 ± 210</td>
<td>3,127 ± 224</td>
<td>4,267 ± 630*</td>
</tr>
<tr>
<td>Peak lengthening rate (mm/sec)</td>
<td>222 ± 61</td>
<td>226 ± 66</td>
<td>265 ± 69*</td>
</tr>
<tr>
<td>Time constant of pressure decay (msec)</td>
<td>27 ± 1.9</td>
<td>25.2 ± 1.7</td>
<td>23 ± 1.3</td>
</tr>
</tbody>
</table>

All values are mean ± SEM; n = 7.
*p < 0.017 for the differences from control values; †p < 0.01 for the differences from the equivalent dose of dopamine, and ‡p < 0.05.

ated by activation of β2-adrenoceptors. Dopamine influences the cardiovascular system by acting directly on β1-adrenoceptors, α1-adrenoceptors, and dopamine receptors (produces vasodilation) and by acting indirectly by releasing norepinephrine from sympathetic nerve endings.7-12,14 Activation of pre-junctional α2-adrenoceptors and dopamine receptors can lead to a decrease in norepinephrine release from sympathetic nerve terminals.13-16 The rise in LV filling pressure occurring with dopamine has generally been attributed to LV dilatation from an increase in LV afterload secondary to activation of postjunctional α-adrenoceptors on arterial vessels.1 However, the relation between the elevation in LV filling pressure and changes in the diastolic properties of the LV have not been assessed. In the present study, we examined the effects of dopamine and dobutamine on LV systolic and diastolic function and attempted to define the pharmacological mechanisms responsible for differential responses to these two drugs.

Materials and Methods
Surgical Preparation and Instrumentation

Twenty-three adult mongrel dogs, weighing 21-32 kg, were anesthetized with morphine, 5 mg/kg s.c., followed by administration of α-chloralose, 100 mg/kg i.v. After endotracheal intubation, ventilation was maintained with a Harvard respirator (South Natick, Massachusetts). A median sternotomy was performed, and the heart was suspended in a pericardial cradle. Systemic arterial pressure was measured with a fluid-filled catheter positioned in the left femoral artery and with a Statham strain-gauge transducer (model P23ID, Los Angeles, California). LV and left atrial pressures were measured with high-fidelity micromanometer-tipped catheters (Millar Instruments, Houston, Texas) inserted retrogradely from the right femoral artery and antegradely from the pulmonary veins, respectively. Before insertion, both micromanometer-tipped catheters were calibrated at 37° C with a mercury manometer. Ultrasonic piezo crystals (2.5 mm diameter; Triton Technology, San Diego, California) were sutured against the endocardium through stab incisions and positioned perpendicular to the long axis of the LV, midway between the apex and the base of the heart; they were used for continuous measurements of LV short-axis dimension. The electrocardiogram, body temperature, and arterial oxygen tension were monitored throughout the study.

LV peak systolic and diastolic pressures, systemic arterial pressure, left atrial pressure, instantaneous peak positive change in LV pressure with time (dP/dt), and LV internal dimensions were recorded with a Hewlett-Packard eight-channel inkpen recorder (Waltham, Massachusetts) at 25, 50, and 100 mm/sec.

Drug Protocol

Eighteen dogs received incremental infusions of dopamine (2, 4, and 6 µg/kg/min) before and 30 minutes after the intravenous administration of one of the following antagonists: the selective α1-adrenoceptor antagonist rauwolscine (0.3 mg/kg, n = 7)17; the selective α1-adrenoceptor antagonist terazosin (0.3 mg/kg, n = 6)18; or the selective dopamine β-antagonist domperidone (40 µg/kg, n = 5).19 Five dogs received incremental infusions of dobutamine (2, 4, and 6 µg/kg/min) before and 30 minutes after the intravenous administration of rau-
The dose of domperidone almost eliminated the decline in arterial pressure induced by the selective dopamine-α,-agonist Aβ disbelief dopamine,21 50 μg/kg i.v. Before administration of any drugs, a 30-minute control period was allotted to ensure hemodynamic stability. Baseline hemodynamic measurements were then obtained. Thereafter, a graded infusion of dopamine or dobutamine was administered at rates of 2, 4, and 6 μg/kg/min. The infusion rate was increased at 15-minute intervals; hemodynamic measurements were obtained just before each increment in dosage and 15 minutes after the peak infusion rate was achieved. After the drug infusion was completed and hemodynamic parameters returned to baseline (minimum of 15 minutes), the antagonist was administered; 30 minutes later, the incremental infusion of dopamine or dobutamine was repeated. Persistent blockade by the antagonist for the duration of the experiment was documented by monitoring the response to the appropriate agonist after the final infusion of dopamine or dobutamine.

### Data Analysis

The electrocardiogram, LV systolic and end-diastolic pressures, systemic arterial pressure, mean left atrial pressure, instantaneous peak positive dP/dt, and LV end-diastolic and end-systolic chamber dimensions were measured directly from the tracings. The time constant of LV isovolumic pressure decay was computed as the negative reciprocal of the slope of the linear regression line describing the relation between the natural logarithm of LV pressure and time.22-23 Peak LV diastolic lengthening rate was calculated as the maximal rate of change in dimension measured by the endocardial piezo crystals during diastole.

At each dose of dopamine and dobutamine, a diastolic pressure-dimension relation was constructed from simultaneous pressure and dimension coordinates determined at 5-msec intervals from tracings recorded at a paper speed of 100 mm/sec.

### Statistical Analysis

All values are expressed as mean ± SEM. Statistical analyses involving comparisons of control with posttreatment data were performed with the Student’s t test for paired samples and then by using the Bonferroni correction for multiple comparisons. Statistically significant differences were accepted at a p value less than 0.05/K, where K = number of comparisons. Comparisons of data obtained after the administration of rauwolscine and terazosin were performed with the t test for unpaired samples, and statistical significance was accepted at a p value less than 0.05.

### Results

#### Hemodynamic Responses to Dopamine

The hemodynamic data obtained before and after incremental infusions of dopamine are depicted in Tables 1 and 2. The infusion of dopamine resulted in a significant dose-related negative chronotropic effect (Figure 1). This was accompanied by a small but significant decrease in mean aortic pressure at an infusion rate of 2 μg/kg/min; as the infusion rate

### Table 2. Hemodynamic Responses to Dopamine Infusion Before and After Terazosin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 μg</th>
<th>4 μg</th>
<th>6 μg</th>
<th>Control post terazosin</th>
<th>2 μg</th>
<th>4 μg</th>
<th>6 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>97 ± 12</td>
<td>88 ± 11*</td>
<td>82 ± 11*</td>
<td>75 ± 9*</td>
<td>126 ± 13†</td>
<td>132 ± 11†</td>
<td>142 ± 12†</td>
<td>151 ± 16†</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>89 ± 7</td>
<td>84 ± 7*</td>
<td>89 ± 6</td>
<td>94 ± 4</td>
<td>83 ± 5†</td>
<td>79 ± 6*</td>
<td>78 ± 6*</td>
<td>78 ± 6*</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>4.7 ± 0.7</td>
<td>5.0 ± 0.5</td>
<td>5.9 ± 0.7*</td>
<td>6.6 ± 0.8*</td>
<td>4.9 ± 0.5</td>
<td>4.4 ± 0.6</td>
<td>4.1 ± 0.6*</td>
<td>3.5 ± 0.5*</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.4</td>
<td>2.6 ± 0.4*</td>
<td>2.8 ± 0.5*</td>
<td>1.9 ± 0.3</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.3*</td>
<td>1.9 ± 0.4*</td>
</tr>
<tr>
<td>End-systolic dimension (cm)</td>
<td>3.11 ± 0.34</td>
<td>3.07 ± 0.33</td>
<td>2.89 ± 0.35*</td>
<td>2.79 ± 0.29*</td>
<td>2.99 ± 0.34†</td>
<td>2.95 ± 0.33*</td>
<td>2.93 ± 0.33*</td>
<td>2.89 ± 0.34*</td>
</tr>
<tr>
<td>End-diastolic dimension (cm)</td>
<td>3.93 ± 0.38</td>
<td>3.92 ± 0.37</td>
<td>4.06 ± 0.39*</td>
<td>4.10 ± 0.38*</td>
<td>3.74 ± 0.37</td>
<td>3.64 ± 0.36*</td>
<td>3.59 ± 0.37*</td>
<td>3.56 ± 0.38*†</td>
</tr>
<tr>
<td>Peak positive dP/dt (mm Hg/sec)</td>
<td>2,459 ± 286</td>
<td>2,520 ± 272</td>
<td>3,149 ± 458*</td>
<td>3,979 ± 515*</td>
<td>2,742 ± 256</td>
<td>2,730 ± 265</td>
<td>3,493 ± 470*</td>
<td>4,776 ± 305*</td>
</tr>
<tr>
<td>Peak lengthening rate (mm/sec)</td>
<td>248 ± 49</td>
<td>295 ± 51*</td>
<td>319 ± 55*</td>
<td>469 ± 53*</td>
<td>255 ± 50</td>
<td>270 ± 51</td>
<td>289 ± 50*</td>
<td>307 ± 56*</td>
</tr>
<tr>
<td>Time constant of pressure decay (msec)</td>
<td>22.7 ± 1.3</td>
<td>21.6 ± 1.6</td>
<td>20.8 ± 2</td>
<td>19.3 ± 1.6*</td>
<td>21.4 ± 1.6</td>
<td>19.6 ± 0.6</td>
<td>16.9 ± 1.1*</td>
<td>14.2 ± 0.9*</td>
</tr>
</tbody>
</table>

All values are mean ± SEM; n = 6.

*fp<0.017 for the differences from control values; tp<0.01 for the equivalent dose of dopamine; and tp<0.05.

wolscine (0.3 mg/kg). The doses used for rauwolscine and terazosin have been determined previously in our laboratory to provide selective α₂- and α₁-adrenoceptor antagonism, respectively.20 The dose of domperidone almost eliminated the decline in arterial pressure induced by the selective dopamine-α,-agonist N,N-di-n-propyldopamine,21 50 μg/kg i.v. Before administration of any drugs, a 30-minute control period was allotted to ensure hemodynamic stability. Baseline hemodynamic measurements were then obtained. Thereafter, a graded infusion of dopamine or dobutamine was administered at rates of 2, 4, and 6 μg/kg/min. The infusion rate was increased at 15-minute intervals; hemodynamic measurements were obtained just before each increment in dosage and 15 minutes after the peak infusion rate was achieved. After the drug infusion was completed and hemodynamic parameters returned to baseline (minimum of 15 minutes), the antagonist was administered; 30 minutes later, the incremental infusion of dopamine or dobutamine was repeated. Persistent blockade by the antagonist for the duration of the experiment was documented by monitoring the response to the appropriate agonist after the final infusion of dopamine or dobutamine.

### Data Analysis

The electrocardiogram, LV systolic and end-diastolic pressures, systemic arterial pressure, mean left atrial pressure, instantaneous peak positive dP/dt, and LV end-diastolic and end-systolic chamber dimensions were measured directly from the tracings. The time constant of LV isovolumic pressure decay was computed as the negative reciprocal of the slope of the linear regression line describing the relation between the natural logarithm of LV pressure and time.22-23 Peak LV diastolic lengthening rate was calculated as the maximal rate of change in dimension measured by the endocardial piezo crystals during diastole.

At each dose of dopamine and dobutamine, a diastolic pressure-dimension relation was constructed from simultaneous pressure and dimension coordinates determined at 5-msec intervals from tracings recorded at a paper speed of 100 mm/sec.
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HEART RATE PEAK\(\frac{dP}{dt}\)

\(p<0.01\)

FIGURE 1. Bar graph depicting percent change in heart rate during dopamine infusion before and after rauwolscine and terazosin. Dopamine infusion resulted in a dose-dependent negative chronotropic effect. In the presence of rauwolscine or terazosin, dopamine produced a dose-related increase in heart rate. This augmentation in heart rate was greater after rauwolscine than terazosin. CTR, control; DA, dopamine; R, rauwolscine; T, terazosin; DA2, 4, and 6, dopamine at 2, 4, and 6 \(\mu g/kg/min\), respectively.

was increased further, mean aortic pressure rose gradually and was elevated above control values at the 6 \(\mu g/kg/min\) rate.

Dopamine augmented overall LV systolic performance as evidenced by a progressive increase in peak positive \(dP/dt\) (Figure 2). It also produced an elevation in LV end-diastolic chamber dimension, which occurred in parallel with a rise in LV end-diastolic pressure. The increase in LV end-diastolic pressure and mean left atrial pressure occurred despite accelerated pressure decay and a reduction in end-systolic chamber dimension. In Figure 3A, the LV diastolic pressure-dimension relation before and after dopamine (6 \(\mu g/kg/min\)) is shown for a representative experiment. In early diastole, dopamine caused a leftward and downward shift because of reduced end-systolic chamber size and reduced LV pressure relative to chamber dimension. In late diastole, the administration of dopamine resulted in an increase in LV end-diastolic dimension accompanied by an elevation in LV end-diastolic pressure.

Effects of Rauwolscine and Terazosin on Hemodynamic Responses to Dopamine

The effects of rauwolscine and terazosin on the hemodynamic responses to dopamine are depicted in Tables 1 and 2 and Figures 1, 2, 4, and 5.

Before the infusion of dopamine, the administration of rauwolscine elicited an increase in heart rate from 88±4 to 101±6 beats/min (\(p<0.01\)); other hemodynamic variables did not change significantly. In the presence of rauwolscine, dopamine produced a further increase in heart rate and a greater augmentation in peak positive \(dP/dt\). Mean aortic pressure fell slightly at an infusion rate of 2 \(\mu g/kg/min\) but exhibited no significant change from control values at higher infusion rates. In contrast to measurements obtained before the administration of rauwolscine, LV end-diastolic and left atrial pressures declined with dopamine. The increase in peak lengthening rates and reduction in the time constant of pressure decay induced by dopamine persisted after rauwolscine administration, the change in the latter parameter actually being more exaggerated.

Before the infusion of dopamine, the administration of terazosin evoked an increase in heart rate (from 97±12 to 126±13 beats/min, \(p<0.01\)), a decline in mean arterial pressure (from 89±7 to 83±5 mm Hg, \(p<0.05\)), and a reduction in LV end-systolic dimension (from 3.11±0.34 to 2.99±0.34 cm, \(p<0.05\)). In the presence of terazosin, a significant positive chronotropic effect of
dopamine was observed and was accompanied by a decline in mean aortic, LV end-diastolic and mean left atrial pressures. The increase in peak positive dP/dt and peak shortening rates and the reduction in time constant of pressure decay observed with dopamine persisted in the presence of terazosin.

Comparisons of the hemodynamic responses to dopamine in the presence of rauwolscine and terazosin revealed a greater increase in heart rate after rauwolscine than terazosin (p<0.05) (Figure 1). The augmentation in heart rate after rauwolscine occurred when no alteration in arterial pressure occurred, while a decline in arterial pressure was documented after terazosin. The elevation in peak positive dP/dt evoked by dopamine was also greater after rauwolscine than terazosin (p<0.01) (Figure 2). Both rauwolscine and terazosin prevented the increase in LV end-diastolic pressure, LV end-diastolic dimension, and mean left atrial pressure produced by dopamine (Figure 4). The augmentation in peak shortening rate and decrease in end-systolic chamber dimension induced by dopamine was maintained after rauwolscine and terazosin; however, the acceleration in LV pressure decay evoked by dopamine was greater after rauwolscine when compared with values obtained in the presence of terazosin (p<0.01) (Figure 5).

Effects of Domperidone on Hemodynamic Responses to Dopamine

The hemodynamic responses to dopamine were not altered in the presence of domperidone (data not shown).

Hemodynamic Responses to Dobutamine

The hemodynamic data obtained before and after the administration of rauwolscine are depicted in Table 3.

The infusion of dobutamine resulted in an increase in heart rate and mean arterial pressure. LV end-diastolic pressure was decreased marginally at an infusion rate of 6 µg/kg/min, while mean left atrial pressure remained unchanged. LV systolic performance improved as evidenced by an increase in peak
FIGURE 5. Bar graph depicting percent change in pressure decay during dopamine infusion before and after rauwolscine and terazosin. Dopamine produced an acceleration in left ventricular pressure decay. After rauwolscine, dopamine elicited an even greater acceleration in left ventricular pressure decay that did not occur in the presence of terazosin. DA, dopamine; R, rauwolscine; T, terazosin; CTR, control; and DA2, 4, and 6, dopamine at 2, 4, and 6 μg/kg/min.

positive dP/dt and a decrease in end-systolic chamber size. These alterations were associated with an acceleration of pressure decay and augmentation of peak LV lengthening rate.

In Figure 3B, the LV diastolic pressure-dimension relation before and after dobutamine (6 μg/kg/min) is shown for a representative experiment. In early diastole, dobutamine caused a leftward and downward shift because of reduced end-systolic chamber dimension and reduced LV pressure relative to chamber dimension. With dobutamine, after the initial diastolic pressure nadir, no significant shift in the ventricular pressure-dimension relation was noted.

No significant changes in the hemodynamic responses to dobutamine were noted after rauwolscine.

Discussion
To analyze the specific pharmacological actions of dopamine and dobutamine that influence LV diastolic function, we examined the hemodynamic responses to dopamine in the presence and absence of selective dopamine, α₁- and α₂-adrenoceptor antagonists, and dobutamine in the presence and absence of a selective α₂-antagonist. Our findings demonstrate the importance of α-receptor activation in modulating the effects of dopamine on diastolic and systolic performance.

Heart Rate
Previous studies have demonstrated that the administration of dopamine, a β₁-adrenoceptor agonist, is frequently not accompanied by an increase in heart rate.1,2-5,8-13 We have also recently observed no significant change in heart rate during the administration of dopamine to patients with dilated cardiomyopathy.24 In the present study, the infusion of dopamine resulted in a dose-dependent negative chronotropic effect. This cannot be attributed solely to a baroreflex-mediated response to a rise in arterial pressure since a decline in heart rate was noted at infusion rates when no alteration in arterial pressure had occurred. Since no significant changes in the hemodynamic responses to dopamine were observed after the administration of domperidone, activation of prejunctional dopamine₂ receptors (stimulation of dopamine receptors leads to a reduction in the release of norepinephrine from sympathetic nerve endings15,16) did not appear to be responsible for the decrease in heart rate seen with dopamine. However, in the presence of rauwolscine, the administration of dopamine resulted in a dose-related increase in heart rate that occurred even when mean arterial pressure was rising. Terazosin also reversed the negative chronotropic effect of dopamine, but the increase in heart rate occurred in conjunction with a reduction in arterial pressure.

In contrast, dobutamine produced an augmentation in heart rate that was unaffected by rauwolscine. These observations suggest that blockade of prejunctional α₂-adrenoceptors, the activation of which inhibits neuronal release of norepinephrine,16 unmask the positive chronotropic activity of dopamine; stimulation of β₁-adrenoceptors is probably responsible for the increase in heart rate. The augmentation in heart rate occurring after terazosin probably represents a baroreflex-mediated response to the decrease in arterial pressure resulting from postjunctional α₁-adrenoceptor blockade. Our findings are consistent with the data of Heyndrickx et al25 who demonstrated that prejunctional α₂-adrenoceptors played an important role in modulating the heart rate and myocardial contractile response to exercise. These investigators reported that the administration of phentolamine (nonselective α-adrenoceptor antagonist) or yohimbine (selective α₂-antagonist) resulted in the potentiation of the heart rate and peak positive dP/dt responses to exercise because of the exaggerated release of norepinephrine from sympathetic nerves.

Myocardial Contractility
Peak positive dP/dt increased in a dose-dependent manner during the infusion of dopamine and dobutamine. Neither terazosin nor domperidone altered the augmentation in peak positive dP/dt evoked by dopamine. In contrast, the increase in peak positive dP/dt elicited by dopamine was significantly greater in the presence of rauwolscine.
junctional \( \alpha_2 \)-adrenoceptors may not occur under basal conditions. Thus, it appears that extensive activation of prejunctional \( \alpha_2 \)-adrenoceptor agonist activity of dopamine, which may blunt expression of its full cardiotonic effect, is unmasked in the presence of rauwolscine.

**Myocardial Relaxation and Diastolic Properties**

The administration of dopamine and dobutamine resulted in an acceleration of LV pressure decay. Isolated muscle studies have demonstrated that isoproterenol, a \( \beta \)-adrenoceptor agonist, also accelerates tension decay. Activation of \( \beta_1 \)-adrenoceptors leads to an increase in intracellular cyclic adenosine monophosphate. This messenger accelerates the rate of calcium reuptake by the sarcoplasmic reticulum, thereby enhancing ventricular relaxation. A reduction in end-systolic dimension may be an additional factor favoring more rapid pressure decay by augmenting elastic recoil from a smaller chamber size. The infusion of dopamine after rauwolscine resulted in an even greater acceleration of pressure decay presumably as a result of greater activation of \( \beta_1 \)-adrenoceptors because of increased neuronal release of norepinephrine.

The filling dynamics of the LV are mainly determined by the atrioventricular pressure gradient. This pressure gradient determines the inflow filling pattern in early diastole. Both dopamine and dobutamine accelerated pressure decay, thereby increasing the left atrial-LV pressure gradient in early diastole and as a result, an augmentation of peak LV lengthening rate occurred. This more rapid and complete tension decay is reflected in the leftward and early downward shift of the LV pressure–dimension relation in early diastole. Thus, the rise in filling pressures observed with dopamine cannot

### Table 3. Hemodynamic Responses to Dobutamine Infusion Before and After Rauwolscine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>Control post rauwolscine</th>
<th>Dobutamine + rauwolscine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 ( \mu )g</td>
<td>4 ( \mu )g</td>
<td>6 ( \mu )g</td>
<td>2 ( \mu )g</td>
</tr>
<tr>
<td><strong>Heart rate</strong> (beats/min)</td>
<td>99±12</td>
<td>107±17</td>
<td>111±17</td>
<td>115±23*</td>
</tr>
<tr>
<td><strong>Aortic mean pressure</strong> (mm Hg)</td>
<td>82±4</td>
<td>88±4*</td>
<td>91±4*</td>
<td>94±5*</td>
</tr>
<tr>
<td><strong>Left ventricular end-diastolic pressure</strong> (mm Hg)</td>
<td>3.3±1.2</td>
<td>3.5±1.4</td>
<td>3.1±1.4</td>
<td>2.9±1.3*</td>
</tr>
<tr>
<td><strong>Mean left atrial pressure</strong> (mm Hg)</td>
<td>3.3±1.3</td>
<td>3.5±1.6</td>
<td>3.8±1.9</td>
<td>3.6±1.7</td>
</tr>
<tr>
<td><strong>End-systolic dimension (cm)</strong></td>
<td>2.97±2.8</td>
<td>2.88±2.9</td>
<td>2.77±3.3*</td>
<td>2.71±3.4*</td>
</tr>
<tr>
<td><strong>End-diastolic dimension (cm)</strong></td>
<td>3.92±1.8</td>
<td>3.92±1.8</td>
<td>3.89±2.88</td>
<td>3.96±1.8</td>
</tr>
<tr>
<td><strong>Peak positive dp/dt</strong> (mm Hg/sec)</td>
<td>2,141±156</td>
<td>2,674±240*</td>
<td>3,582±303*</td>
<td>4,340±483*</td>
</tr>
<tr>
<td><strong>Peak lengthening rate</strong> (msec)</td>
<td>357±19</td>
<td>383±36</td>
<td>437±48*</td>
<td>489±45*</td>
</tr>
<tr>
<td><strong>Time constant of pressure decay</strong> (msec)</td>
<td>23±1</td>
<td>21±1*</td>
<td>18.5±1*</td>
<td>16±1*</td>
</tr>
</tbody>
</table>

All values are mean±SEM; \( n = 5 \). \(*p<0.017\) for the differences from control values.
be attributed to a primary effect on myocardial relaxation.

**Vascular Effects**

Arterial vasoconstriction due to α-adrenoceptor activation has been postulated to be the mechanism responsible for the increased LV filling pressures observed with dopamine. A secondary increase in LV end-diastolic dimension in response to the increase in vascular load would mediate this rise in end-diastolic pressure. In the present study, dopamine increased end-diastolic dimension and pressure even before mean arterial pressure rose. The rise in LV filling pressure observed during the infusion of dopamine was abolished by rauwolscine and terazosin. The absence of vasoconstriction and a reversal of heart rate slowing could account for the effects of the α-adrenoceptor antagonists on the responses to dopamine. While the present study did not directly demonstrate that dopamine produced venoconstriction, previous work from our laboratory and others' has demonstrated this hemodynamic effect of dopamine that is mediated through activation of postjunctional α₁- and α₂-adrenoceptors. Vasodilation in arterial vessels resulting from stimulation of these receptors will be counterbalanced by dopamine-mediated vasodilation, which has not been described in the venous system. Accordingly, a rise in LV end-diastolic pressure may be observed at concentrations of dopamine that are not associated with an elevation in arterial pressure.

**Conclusion**

The infusion of dopamine resulted in heart rate slowing, augmentation of peak positive dP/dt, enhanced LV pressure decay, and an elevation in LV filling pressure. The rise in LV end-diastolic pressure observed with dopamine is probably related to both vasoconstriction and heart rate slowing. The greater positive chronotropic and inotropic effects of dopamine in the presence of rauwolscine can be attributed to enhanced release of norepinephrine from sympathetic nerve endings due to blockade of prejunctional α₂-adrenoceptors.

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