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Increases in inotropic state without change in heart rate: Combined use of dobutamine and zatebradine in conscious dogs

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Abstract

The cardiovascular and left ventricular functional effects of dobutamine (5, 10 and 20 μg kg^{-1} min^{-1}) were examined in conscious, chronically instrumented dogs in the presence and absence of control of heart rate with the specific bradycardic agent, zatebradine. Dobutamine increased heart rate, cardiac output, stroke volume, diastolic coronary blood flow velocity and pressure-work index (calculated myocardial oxygen consumption) and decreased systemic vascular resistance and diastolic coronary vascular resistance. Mean arterial pressure and left ventricular systolic and end-diastolic pressures were unchanged. Dobutamine-induced increases in heart rate and pressure-work index were attenuated by zatebradine. Dobutamine alone increased preload recruitable stroke work slope (63 ± 6 to 116 ± 11 mmHg) and $+dP/dt$. These positive inotropic effects were unaffected by zatebradine. Dobutamine decreased the time constant of isovolumic relaxation (30 ± 3 to 25 ± 2 ms). Dobutamine-induced decreases in the time constant of isovolumic relaxation were not altered by zatebradine, indicating that changes in the time constant occurred independent of heart rate. Dobutamine also increased the maximal segment lengthening velocity to a similar degree in zatebradine-treated versus untreated dogs. Control of dobutamine-induced tachycardia by zatebradine decreases myocardial oxygen consumption but does not alter the positive inotropic and lusitropic effects of dobutamine.

Keywords: Isovolumic relaxation; Ventricular filling; Myocardial contractility; Preload recruitable stroke work; Inotropes; Dobutamine; Bradycardic agents, specific; Zatebradine

1. Introduction

Dobutamine has been shown to enhance myocardial contractility, produce beneficial effects on left ventricular diastolic function and reduce afterload in the failing heart (Ruffolo, 1987; Sonnenblick et al., 1979). However, tachycardia produced by dobutamine may adversely affect myocardial oxygen supply-demand relations in this setting despite concomitant improvements in ventricular loading conditions. The heart rate-dependence of dobutamine-induced enhancement of left ventricular systolic and diastolic function has not been established. This investigation examined the effects of dobutamine on systemic and coronary hemodynamics and left ventricular function in conscious dogs in the presence and absence of zatebradine (UL FS-49), a specific bradycardic agent. Zatebradine has been shown to reduce heart rate by specifically decreasing the rate of sinoatrial node discharge by inhibiting the hyperpolarizing-activated current in sinoatrial tissue (Van Bogaert et al., 1990) without directly altering inotropic and lusitropic state or peripheral vascular tone (Breall et al., 1993; Johnston et al., 1991; Pagel et al., 1995; Riley et al., 1987). The present investigation tested the hypothesis that dobutamine-induced enhancement of left ventricular systolic and diastolic function occurs independent of increases in heart rate produced by this drug.

2. Materials and methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All procedures conformed to the 'Guiding Principles of the Care and Use of Animals' of the American Physiologic Society and were in accordance with the 'Guide for the Care and Use of Laboratory Animals' (DHEW (DHHS) publication (NIH) 85-23, revised 1985).

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2.1. Implantation of instruments

Surgical implantation of instruments has been described in detail previously (Pagel et al., 1995). Briefly, a left thoracotomy was performed in the fifth intercostal space under sterile conditions in conditioned mongrel dogs of either sex weighing between 25 and 30 kg. The dogs used in the present investigation were similar to those used in our previous studies (Pagel et al., 1995). The relatively large size of the dogs facilitates implantation of instruments. Heparin-filled catheters were placed in the descending thoracic aorta and the right atrium for measurement of aortic blood pressure and fluid or drug administration, respectively. An ultrasonic flow probe was positioned around the ascending thoracic aorta for measurement of relative cardiac output. A pair of miniature ultrasonic segment length transducers (percent segment shortening) were implanted within the subendocardium of the left ventricular anterior free wall. A high-fidelity, miniature micromanometer was inserted into the left ventricular chamber for measurement of continuous left ventricular pressure and the maximum rate of increase and decrease of left ventricular pressure ($+dP/dt_{max}$ and $-dP/dt_{min}$, respectively). A heparin-filled catheter was inserted in the left atrial appendage and the left ventricular micromanometer calibrated in vivo against pressures measured via arterial and left atrial catheters. A single port, 16-gauge, heparin-filled catheter was placed in the apex of the left thoracic cavity between the lung and the chest wall through the thoracotomy incision for measurement of continuous intrathoracic pressure. A precalibrated Doppler ultrasonic flow transducer was positioned around the left anterior descending coronary artery for measurement of diastolic coronary blood flow velocity. A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of left ventricular preload. All instrumentation was secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube.

All dogs received systemic analgesics (fentanyl) as needed after surgery. Dogs were allowed to recover a minimum of 7 days prior to experimentation. All dogs were treated with intramuscular antibiotics (cephalothin (40 mg kg^{-1}) and gentamicin (4.5 mg kg^{-1})) and trained to stand quietly in a loose restraining sling during hemodynamic monitoring. Coronary blood flow velocity and segment length signals were monitored by a mainframe sonomicrometer. End-systolic and end-diastolic segment lengths were measured at 30 ms before maximum negative left ventricular dP/dt and just prior to the onset of left ventricular isovolumic contraction, respectively. Percent segment shortening was calculated using the equation: percent segment shortening = (end-diastolic length − end-systolic length) · 100 · end-diastolic $length^{-1}$. Relative diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow velocity. The pressure-work index, a calculated estimate of myocardial oxygen consumption, was determined using a previously validated formula (Rooke and Feigl, 1982). All hemodynamic data were continuously recorded on a polygraph and digitized by a computer interfaced with an analog to digital converter.

2.2. Experimental protocol

Each dog was fasted overnight, and fluid deficits were replaced prior to experimentation with crystalloid (500 ml Lactated Ringer's) that was continued at 3 ml kg^{-1} h^{-1} for the duration of each experiment. Left ventricular pressure, intrathoracic pressure and segment length waveforms were digitally recorded for later off-line analysis of left ventricular diastolic function. Left ventricular pressure-segment length diagrams used to assess myocardial contractility were generated by mechanical reduction of left ventricular preload. This was accomplished by abruptly constricting the inferior vena cava, resulting in an approximately 25 mmHg decline in left ventricular systolic pressure over 10 to 15 cardiac cycles. Respiratory variation in left ventricular pressure was later reduced by digital subtraction of the continuous intrathoracic pressure waveform from the left ventricular pressure waveform (Pagel et al., 1995). The inferior vena caval occlusion was released immediately after recording of the waveforms.

Baseline systemic and coronary hemodynamics and left ventricular pressure-segment length waveforms and diagrams were recorded under control conditions in the conscious state. Intravenous infusions of dobutamine at 5, 10, or 20 μg kg^{-1} min^{-1} were then administered in a sequential fashion. Hemodynamics were recorded, and left ventricular pressure-segment length waveforms and diagrams were obtained using the techniques described above after 20 min equilibration at each dose of dobutamine (total cumulative doses = 0.1, 0.3 and 0.7 mg kg^{-1}). The dobutamine infusion was then discontinued and each dog was monitored until hemodynamics had returned to baseline values. Dobutamine infusions were then repeated using zatebradine to prevent increases in heart rate. Intravenous infusions of dobutamine (5, 10 and 20 μg kg^{-1} min^{-1}) were administered in a sequential fashion and data were recorded as described above. In contrast to the experiments with dobutamine alone, however, intravenous boluses of zatebradine (1–3 mg per injection) were administered during dobutamine infusions as required to maintain heart rate at control levels. The total zatebradine dose was calculated at the completion of the dobutamine infusions. The range of zatebradine doses was 5 to 17 mg. In most dogs, the majority of zatebradine was administered during the 10 and 20 μg kg^{-1} min^{-1} doses of dobutamine in 3 to 6 boluses. Thus, a total of 9 experiments were performed that examined the systemic and coronary hemodynamic effects and left ventricular functional actions of dobu-

tamine in the presence and absence of heart rate control with zatebradine.

2.3. Calculation of indices of systolic and diastolic left ventricular function

The slope of the regional preload recruitable stroke work relation was used to determine myocardial contractility (Glower et al., 1985). The time constant of isovolumic relaxation was determined using the derivative method (Raff and Glantz, 1981). Maximum segment lengthening velocity during rapid ventricular filling was determined by differentiation of the continuous segment length waveform. Regional myocardial chamber stiffness (β) was determined using a best-fit Gauss–Newton algorithm (ASYST version 4.01, Metrabyte, Rochester, NY) from the left ventricular end-diastolic pressure–segment length relationship obtained during brief occlusion of the inferior vena cava: $P_{ed} = \alpha e^{\beta * EDL} + \gamma$, where P_{ed} = left ventricular end-diastolic pressure, α and γ = curve fitting constants, and EDL = end-diastolic segment length.

2.4. Statistical analysis

Statistical analysis of data under control conditions and during infusions of dobutamine in the presence and absence of zatebradine was performed by multiple analysis of variance (MANOVA) with repeated measures, followed by Student's t-test with Duncan's correction for multiplicity. Changes were considered statistically significant when the probability (P) value was < 0.05. All data are reported as mean ± S.E.M.

3. Results

The systemic and coronary hemodynamic effects of dobutamine with and without maintenance of a constant heart rate with zatebradine are summarized in Table 1. No differences in hemodynamics were observed between the first and second control periods. Dobutamine caused a significant ($P < 0.05$) increase in heart rate (Fig. 1), rate-pressure product, pressure-work index, cardiac output (2.4 ± 0.3 during control 1 to 4.0 ± 0.3 l min^{-1} during the high dose; Fig. 2), stroke volume and diastolic coronary blood flow velocity. Dobutamine also decreased systemic (3410 ± 360 during control 1 to 1970 ± 190 dyn s cm^{-5} during the high dose) and diastolic coronary vascular resistances and end-systolic segment length. Mean arterial pressure, left ventricular systolic and end-diastolic pressures, and end-diastolic length were unchanged. Dobutamine caused dose-dependent increases in the slope of preload recruitable stroke work (63 ± 6 during control to 116 ± 11 mmHg during high dose), $+dP/dt_{max}$ and percent segment shortening indicating a direct positive inotropic effect (Fig. 3). The length intercept of the regional

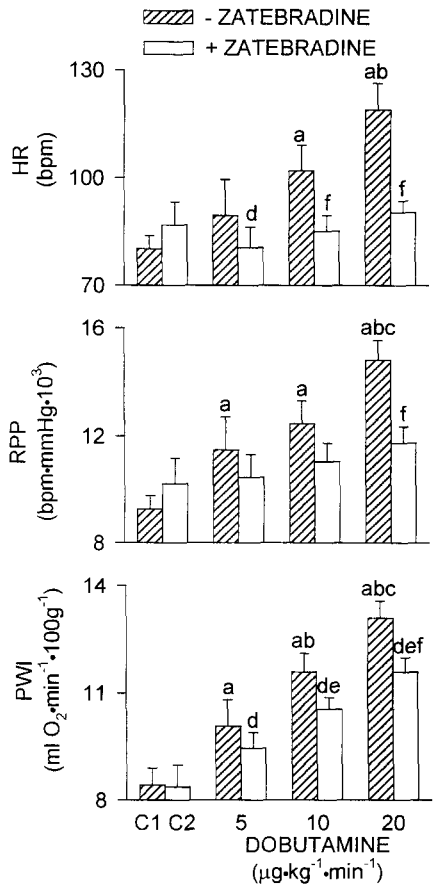

Fig. 1. Histograms illustrating the effects of dobutamine on heart rate (HR; top panel), rate–pressure product (RPP; middle panel) and pressure–work index (PWI; bottom panel) in the absence (hatched bars) and presence (open bars) of zatebradine. (a) Significantly ($P < 0.05$) different from control 1 (C1); (b) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine alone; (c) significantly ($P < 0.05$) different from 10 μg kg^{-1} min^{-1} dobutamine alone; (d) significantly ($P < 0.05$) different from control 2 (C2); (e) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine plus zatebradine; (f) significantly ($P < 0.05$) different from corresponding value in dobutamine alone experiments.

preload recruitable stroke work relationship remained unchanged. Decreases in the time constant of ventricular relaxation (30 ± 3 during control 1 to 25 ± 2 ms during the high dose) and increases in the magnitude of $-dP/dt_{min}$ were observed with dobutamine alone, indicating a positive lusitropic effect. Increases in maximum segment lengthening velocity (47 ± 7 during control to 72 ± 11 mm s^{-1} during the high dose) were also observed, suggesting that early ventricular filling was augmented. No change in regional myocardial chamber stiffness was observed during administration of dobutamine alone.

A total zatebradine dose of 9.8 ± 1.0 mg (0.38 ± 0.05 mg kg^{-1}; mean ± S.E.M.) was used to maintain heart rate at control levels during the administration of dobutamine (Fig. 1). Dobutamine-induced increases in calculated indices of myocardial oxygen consumption (rate-pressure product and pressure-work index) were attenuated but not

Table 1
Hemodynamic effects of dobutamine with and without heart rate control by zatebradine

	Dobutamine ($\mu g\ kg^{-1}\ min^{-1}$)					Dobutamine with Zatebradine ($\mu g\ kg^{-1}\ min^{-1}$)			
	n	control 1	5	10	20	control 2	5	10	20
MAP (mmHg)	9	92 ± 2	95 ± 4	92 ± 3	95 ± 4	92 ± 4	99 ± 4	95 ± 5	92 ± 4
LVSP (mmHg)	9	118 ± 3	121 ± 4	123 ± 5	126 ± 7	116 ± 5	126 ± 5	120 ± 5	129 ± 8
LVEDP (mmHg)	9	9 ± 1	9 ± 1	9 ± 1	8 ± 1	10 ± 2	12 ± 1 [f]	12 ± 2	13 ± 2 [f]
$+dP/dt_{max}$ ($mmHg\ s^{-1}$)	9	2438 ± 214	3249 ± 266 [a]	3819 ± 26 [a]	4556 ± 335 [abc]	2273 ± 169	3035 ± 150 [d]	3710 ± 207 [de]	4079 ± 400 [de]
$-dP/dt_{min}$ ($mmHg\ s^{-1}$)	9	−2245 ± 103	−2630 ± 122 [a]	−2723 ± 78 [a]	−3068 ± 125 [abc]	−2263 ± 103	−2600 ± 107 [d]	−2744 ± 131 [d]	−2791 ± 213 [d]
DCBFV (Hz 10^2)	8	38 ± 5	44 ± 6	49 ± 7 [a]	54 ± 7 [ab]	38 ± 5	42 ± 5	46 ± 6 [d]	49 ± 7 [de]
DCVR (ru)	8	2.22 ± 0.31	2.05 ± 0.32	1.79 ± 0.34 [ab]	1.77 ± 0.34 [ab]	2.36 ± 0.41	2.11 ± 0.31	1.98 ± 0.43 [d]	1.74 ± 0.38 [de]
EDL (mm)	9	19.1 ± 2.6	19.2 ± 2.8	19.1 ± 2.8	18.7 ± 2.7	19.3 ± 2.7	19.9 ± 2.8 [d]	19.7 ± 2.7	19.4 ± 2.7
ESL (mm)	9	15.4 ± 2.1	15.0 ± 2.2	14.6 ± 2.1 [ab]	14.3 ± 2.1 [ab]	15.8 ± 2.2	15.5 ± 2.3	15.0 ± 2.2 [de]	14.7 ± 2 [de]
SS (%)	9	19.8 ± 2.0	21.9 ± 1.9 [a]	24.0 ± 1.9 [a]	23.8 ± 2.2 [a]	18.7 ± 2.3	22.1 ± 2.1 [d]	24.3 ± 2.2 [d]	24.1 ± 1.5 [d]
L_w (mm)	9	13.4 ± 1.8	13.3 ± 2.0	13.3 ± 1.8	14.2 ± 1.9	14.9 ± 2.5	12.3 ± 2.1	13.5 ± 1.7	13.9 ± 1.8
β (mm^{-1})	9	0.69 ± 0.16	0.80 ± 0.16	0.62 ± 0.10	0.65 ± 0.09	0.78 ± 0.14	0.74 ± 0.17	0.59 ± 0.09	0.68 ± 0.11

Data are mean ± S.E.M. Abbreviations: MAP = mean aortic pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressures; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; EDL and ESL = end-diastolic and end-systolic segment lengths; SS = segment shortening; L_w = length intercept of preload recruitable stroke work; β = end-diastolic myocardial stiffness constant.

[a] Significantly ($P < 0.05$) different from control 1.

[b] Significantly ($P < 0.05$) different from 5 $\mu g\ kg^{-1}\ min^{-1}$ dobutamine alone.

[c] Significantly ($P < 0.05$) different from 10 $\mu g\ kg^{-1}\ min^{-1}$ dobutamine alone.

[d] Significantly ($P < 0.05$) different from control 2.

[e] Significantly ($P < 0.05$) different from 5 $\mu g\ kg^{-1}\ min^{-1}$ dobutamine plus zatebradine.

[f] Significantly ($P < 0.05$) different from corresponding value in dobutamine alone experiments.

completely abolished by zatebradine. Dobutamine caused dose-related increases in cardiac output (2.2 ± 0.2 during control 2 to 3.7 ± 0.2 l min^{-1} during high dose) and stroke volume and decreases in systemic vascular resistance (3450 ± 240 during control to 2070 ± 170 dyn s cm^{-1} during high dose; Fig. 2). Changes in these variables were similar to those occurring with dobutamine alone. Dobutamine-induced increases in diastolic coronary blood flow velocity and decreases in diastolic coronary vascular resistance in the presence of zatebradine were also similar to those observed in the absence of heart rate control. Dose-related increases in the slope of preload recruitable stroke work (66 ± 5 during control to 110 ± 10 during the high dose), $+dP/dt_{max}$ and percent segment shortening were observed, indicating that myocardial contractility had been enhanced. Dobutamine-induced increases in contractility were similar in the presence and absence of zatebradine (Fig. 3). Decreases in the time constant of isovolumic relaxation (31 ± 1 during control 2 to 24 ± 2 ms during the high dose) and increases in the magnitude of $-dP/dt_{min}$ occurred in dogs receiving dobutamine and zatebradine. Dobutamine-induced decreases in the time constant of isovolumic relaxation were similar with and without heart rate control with zatebradine. Dobutamine also increased maximum segment lengthening velocity (44 ± 7 during control 2 to 85 ± 12 mm s^{-1} during the high dose) in the presence of zatebradine. This enhancement of early ventricular filling was similar to that caused by dobutamine alone. No changes in regional myocardial chamber stiffness were produced by dobutamine and zatebradine.

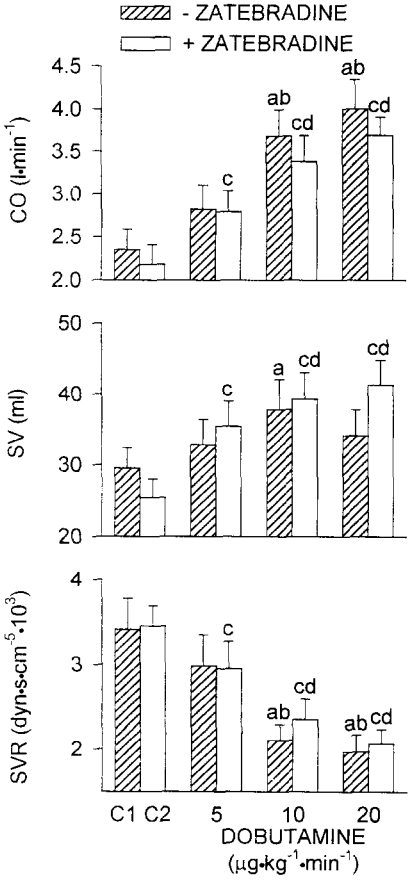

Fig. 2. Histograms illustrating the effects of dobutamine on cardiac output (CO; top panel), stroke volume (SV; middle panel) and systemic vascular resistance (SVR; bottom panel) in the absence (hatched bars) and presence (open bars) of zatebradine. (a) Significantly ($P < 0.05$) different from control 1 (C1); (b) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine alone; (c) significantly ($P < 0.05$) different from control 2 (C2); (d) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine plus zatebradine.

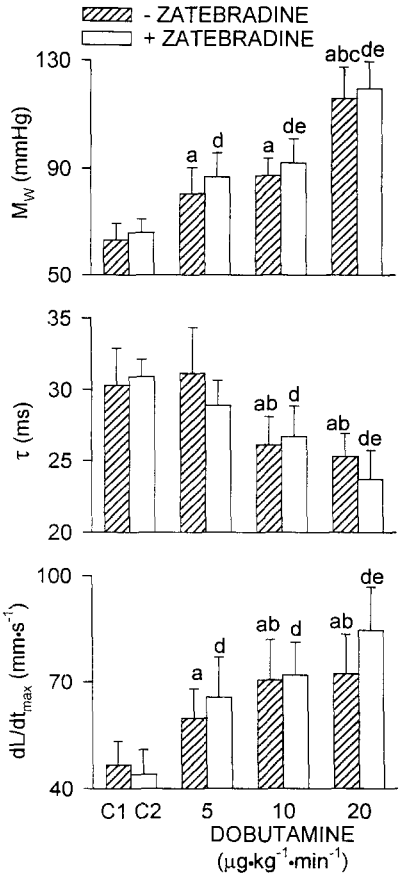

Fig. 3. Histograms illustrating the effects of dobutamine on regional preload recruitable stroke work slope (M_w; top panel), the time constant of isovolumic relaxation (τ; middle panel) and maximum segment lengthening velocity (dL/dt_{max}; bottom panel) in the absence (hatched bars) and presence (open bars) of zatebradine. (a) Significantly ($P < 0.05$) different from control 1 (C1); (b) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine alone; (c) significantly ($P < 0.05$) different from 10 μg kg^{-1} min^{-1} dobutamine alone; (d) significantly ($P < 0.05$) different from control 2 (C2); (e) significantly ($P < 0.05$) different from 5 μg kg^{-1} min^{-1} dobutamine plus zatebradine.

4. Discussion

Dobutamine has been shown to enhance cardiac output, myocardial contractility and coronary perfusion with minimal effects on heart rate and blood pressure at lower doses,

however, inotropic selectivity is lost at higher doses as positive chronotropic effects become more apparent (Meyer et al., 1995; Vatner et al., 1974). Dobutamine-induced tachycardia may represent an important limitation of the use of this drug in patients with congestive heart failure because of detrimental alterations of myocardial oxygen supply–demand relations or regional maldistribution of coronary blood flow (Warltier et al., 1981). In fact, a previous data (Wynsen et al., 1994) has indicated that heart rate control with zatebradine enhances the positive inotropic effects of dobutamine in ischemic myocardium via favorable alterations in myocardial supply–demand balance and an improvement in subendocardial blood flow. Control of dobutamine-induced tachycardia by zatebradine may also produce favorable effects in the failing heart via similar mechanisms provided that the positive inotropic and lusitropic actions of dobutamine are not substantially reduced by concomitant administration of the specific bradycardic agent. The present investigation tested the hypothesis that enhancement of cardiac performance produced by dobutamine occurs independent of increases in heart rate produced by this drug in conscious dogs with normal left ventricular function.

The present results indicate that although dobutamine produces systemic hemodynamic effects that are partially mediated by tachycardia, this drug enhances left ventricular systolic and diastolic function independent of increases in heart rate in conscious dogs. Dobutamine-induced increases in heart rate probably resulted from a combination of positive chronotropic effects mediated by β_1-adrenoceptors and baroreceptor reflex activation resulting from decreases in afterload. Dobutamine did not alter indices of left ventricular preload, confirming the previous findings in conscious dogs and patients with normal left ventricular function (Meyer et al., 1995; Vatner et al., 1974). In the presence of control of heart rate with zatebradine, dobutamine-induced increases in left ventricular end-diastolic pressure were observed concomitant with maintenance of left ventricular filling time. These increases in left ventricular end-diastolic pressure observed with dobutamine and zatebradine may be detrimental in the presence of elevated left ventricular filling pressures in the failing heart. However, a majority of previous studies (Colucci et al., 1988; Leier et al., 1978; Loeb et al., 1977; Mikulic et al., 1977; Nagata et al., 1995) have indicated that dobutamine reduces left ventricular end-diastolic pressure in this setting concomitant with enhanced myocardial contractility and reductions in both left ventricular preload and afterload. Dobutamine also reduced systemic vascular resistance consistent with declines in left ventricular afterload. Heart rate control with zatebradine did not alter dobutamine-induced reductions in systemic vascular resistance, suggesting that afterload-reducing properties of dobutamine occur independent of changes in heart rate. Increases in cardiac output resulting from simultaneous increases in heart rate and stroke volume were observed in dogs receiving dobutamine alone. Dobutamine produced similar increases in cardiac output in the presence of zatebradine. These findings probably occurred because of relative increases in stroke volume in dogs receiving dobutamine and zatebradine secondary to enhanced contractility and reduced afterload.

Increases in diastolic coronary blood flow velocity and decreases in diastolic coronary vascular resistance were produced by dobutamine. These effects occurred concomitant with increases in rate–pressure product and pressure–work index, suggesting that myocardial oxygen supply and demand were appropriately matched. Changes in coronary hemodynamics produced by dobutamine were unaffected by heart rate control with zatebradine. However, zatebradine partially attenuated increases in calculated indices of myocardial oxygen consumption produced by dobutamine. These findings suggest that dobutamine may cause modest direct coronary vasodilation concomitant with positive inotropic effects, confirming the previous findings (Meyer et al., 1976; Vatner et al., 1974). Increases in pressure–work index observed with dobutamine in the presence and absence of zatebradine indicate that the heart rate response to dobutamine alone is not the sole determinant of increases in myocardial oxygen consumption associated with this drug. These findings also suggest that the influence of the positive inotropic effects of dobutamine on myocardial oxygen consumption were not completely balanced by declines in afterload in dogs receiving zatebradine.

Dobutamine increased myocardial contractility in the presence and absence of zatebradine as assessed with the slope of the regional preload recruitable stroke work relationship, indicating that increases in heart rate caused by dobutamine do not contribute to the positive inotropic effects of this drug. The data also suggest that the combination of dobutamine and zatebradine increased myocardial efficiency (the ratio of myocardial contractility to myocardial oxygen consumption) compared to the findings with dobutamine alone because zatebradine partially attenuated dobutamine-induced increases in rate–pressure product and pressure–work index. Dobutamine decreased the time constant of isovolumic relaxation and increased the magnitude of $-\mathrm{d}P/\mathrm{d}t_{\min}$ in the presence and absence of zatebradine, indicating that the positive lusitropic effects of dobutamine also occur independent of heart rate concomitant with increases in myocardial contractility. Dobutamine enhanced maximum segment lengthening velocity to an equivalent degree in dogs with and without zatebradine. The rate of rapid ventricular filling (as evaluated regionally by maximum segment lengthening velocity) has been shown to be inversely related to the rate and extent of isovolumic relaxation and directly proportional to inotropic state, left ventricular preload and the pressure gradient between the left atrium and left ventricle during this phase of the cardiac cycle. Thus, increases in maximum segment lengthening velocity during the administration of dobutamine in the presence and absence of zatebradine may

have occurred because of increases in preload recruitable stroke work slope and decreases in the time constant of isovolumic relaxation. These conclusions should be qualified, however, because the left atrial–ventricular pressure gradient during rapid ventricular filling was not specifically measured in the present investigation and alterations in this gradient by dobutamine may have influenced maximum segment lengthening velocity. No changes in the regional chamber stiffness constant were observed, indicating that dobutamine in the presence and absence of dobutamine does not affect regional chamber compliance in the range of left ventricular end-diastolic pressures occurring in the present investigation.

The present results with dobutamine and zatebradine are similar but not identical to the findings obtained with levosimendan, a new myofilament calcium sensitizer with cardiac phosphodiesterase III inhibiting activity, in the presence and absence of the specific bradycardic agent (Pagel et al., 1995). Levosimendan increased heart rate, produced venous and arterial vasodilation, and enhanced left ventricular systolic and diastolic function in conscious dogs. In contrast to the findings with dobutamine, maintenance of heart rate by zatebradine partially attenuated the positive inotropic and lusitropic effects of levosimendan. Levosimendan, but not dobutamine, decreased left ventricular preload as indicated by reductions in left ventricular end-diastolic pressure and end-diastolic segment length. This levosimendan-induced venodilatation promoted increases in heart rate that were relatively greater in dogs receiving levosimendan compared to those treated with dobutamine. Thus, marked tachycardia associated with levosimendan, but not dobutamine, probably contributed to the positive inotropic and lusitropic effects of the myofilament calcium sensitizer but not the β_1-adrenoceptor agonist.

Previous investigations from this (Pagel et al., 1995) and other laboratories (Breall et al., 1993; Johnston et al., 1991) have demonstrated that zatebradine causes minimal circulatory effects in conscious dogs. A total zatebradine dose of 0.38 ± 0.05 mg kg^{-1} (mean $\pm$ S.E.M.) maintained heart rate at baseline levels during the administration of dobutamine. This dose of zatebradine does not alter hemodynamics or left ventricular systolic and diastolic function (Breall et al., 1993; Johnston et al., 1991; Pagel et al., 1995). Thus, it is unlikely that the total dose of zatebradine used to control heart rate during dobutamine infusions adversely influenced overall changes in left ventricular mechanics.

In summary, the present results indicate that dobutamine increased heart rate, rate–pressure product and pressure–work index, reduced left ventricular afterload and caused positive inotropic and lusitropic effects in conscious, chronically instrumented dogs. Zatebradine-induced maintenance of heart rate during dobutamine administration partially attenuated increases in myocardial oxygen consumption. However, dobutamine augmented cardiac output and enhanced left ventricular systolic and diastolic function independent of increases in heart rate. These findings suggest that zatebradine improves myocardial efficiency during administration of dobutamine. The results demonstrate that the beneficial actions of dobutamine on left ventricular mechanical function are independent of increases in heart rate in the normal heart. The hypothesis that the combined use of dobutamine and a specific bradycardic agent represents a useful therapeutic approach in patients with heart failure requires further evaluation.

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