Bupivacaine Inhibits Baroreflex Control of Heart Rate in Conscious Rats

Kyoung S. K. Chang, M.D., Ph.D.,* Don R. Morrow, B.S.,† Kazuyo Kuzume, M.D.,‡ Michael C. Andresen, Ph.D.§

Background: Because exposure to intravenously administered bupivacaine may alter cardiovascular reflexes, the authors examined bupivacaine actions on baroreflex control of heart rate in conscious rats.

Methods: Baroreflex sensitivity (pulse interval vs. systolic blood pressure in ms/mmHg) was determined before, and 1.5 and 15.0 min after rapid intravenous administration of bupivacaine (0.5, 1.0, and 2.0 mg/kg) using heart rate changes evoked by intravenously administered phenylephrine or nitroprusside. The actions on the sympathetic and parasympathetic autonomic divisions of the baroreflex were tested in the presence of a muscarinic antagonist methyl atropine and a β-adrenergic antagonist atenolol.

Results: Within seconds of injection of bupivacaine, mean arterial pressure increased and heart rate decreased in a dose-dependent manner. Baroreflex sensitivity was unaltered after administration of 0.5 mg/kg bupivacaine. In addition, 1 mg/kg bupivacaine at 1.5 min depressed phenylephrine-evoked reflex bradycardia (0.776 ± 0.325 vs. 0.543 ± 0.282 ms/mmHg, P < 0.05) but had no effect on nitroprusside-induced tachycardia. Bupivacaine (2 mg/kg), however, depressed reflex bradycardia and tachycardia (phenylephrine, 0.751 ± 0.318 vs. 0.451 ± 0.265; nitroprusside, 0.839 ± 0.256 vs. 0.564 ± 0.19 ms/mmHg, P < 0.05). Baroreflex sensitivity returned to prebupivacaine levels by 15 min. Bupivacaine (2 mg/kg), in the presence of atenolol, depressed baroreflex sensitivity (phenylephrine, 0.633 ± 0.204 vs. 0.277 ± 0.282; nitroprusside, 0.653 ± 0.142 vs. 0.320 ± 0.299 ms/mmHg, P < 0.05). In contrast, bupivacaine did not alter baroreflex sensitivity in the presence of methyl atropine.

Conclusions: Bupivacaine, in clinically relevant concentrations, inhibits baroreflex control of heart rate in conscious rats. This inhibition appears to involve primarily vagal components of the baroreflex–heart rate pathways. (Key words: Autonomic nervous system; baroreceptors; hypertension; local anesthetics.)

BUPIVACAINE is a potent, long-acting local anesthetic agent. An infrequent but serious complication arises if bupivacaine accidentally enters into the general circulation.1 Sudden cardiovascular collapse (ventricular tachycardia, ventricular fibrillation, cardiac asystole, or complete heart block) can occur immediately after accidental intravenous injection of bupivacaine.1 Despite the well-established peripheral cardiovascular toxic effects of bupivacaine on the heart and blood vessels,2 relatively little is known about its effects on neural regulatory mechanisms. Some evidence seems to support that bupivacaine actions alter neural control of blood pressure and heart rate.3–6 Bupivacaine, when administered intravenously in subconvulsive or convulsive doses, produced hypertension, tachycardia, and arrhythmias in humans3 and in awake or lightly anesthetized animals.3–6 Direct central injection of bupivacaine into the lateral cerebral ventricle of the cat evoked hypertension and ventricular arrhythmias.7 Recently, we demonstrated that bupivacaine, in clinically relevant concentrations, depresses baroreceptor sensory discharge.8 Thus, baroreflex impairment may precede or accompany direct cardiotoxic effects of bupivacaine and contribute to cardiac arrhythmias. In pentobarbital-anesthetized animals, bupivacaine depressed baroreflex control of heart rate.9 Pentobarbital itself depresses baroreflex control of heart rate,10,11 but also modifies the actions of bupivacaine. For example, bupivacaine-induced hypertension or arrhythmias are observed infrequently during pentobarbital-induced anesthesia.12,13 Our current studies were undertaken (1) to determine whether bupivacaine impairs baroreflex control of heart rate in conscious, unanesthetized animals; and (2) if so, to identify which components of the autonomic nervous system (sympathetic or parasympathetic) are responsi-
ble for the baroreflex change. We found that clinically relevant doses of bupivacaine produce hypertension and bradycardia and impair baroreflex control of heart rate in a dose-dependent manner, primarily by affecting cardiac vagal component.

Materials and Methods

Preparation for Study of Conscious Rats
The study protocol was approved by the Oregon Health Sciences University Animal Care and Use Committee. Experiments were performed in male Sprague-Dawley rats (weight, 300–350 g; Simonsen, Gilroy, CA). For induction of anesthesia, rats were placed in a clear plastic box filled with 5% isoflurane–O₂ for 10 min. After loss of consciousness, an endotracheal tube (14-gauge intravenous catheter; Critikon, Tampa, FL) was placed and adequate anesthesia maintained with isoflurane (2.0–2.5%) and oxygen. Ventilation was controlled. A femoral artery was cannulated with polyethylene tube (PE50; Becton Dickinson, Sparks, MD) to monitor blood pressure, and each femoral vein was cannulated (with PE10; Becton Dickinson), one for injection of bupivacaine and the other for vasoactive drug infusion to test the baroreflex. These catheters were filled with heparinized saline and led subcutaneously to the scruff of the neck and externalized through a small incision. Three stainless wire electrodes were placed under the skin of left and right front legs and left hind leg for electrocardiographic monitoring. After cannulation, animals were extubated when the spontaneous respiration resumed. Rats were treated prophylactically with 30,000 U penicillin given intramuscularly and allowed to recover for 2 days.

Monitoring Hemodynamic Parameters
On the day of the experiment, each rat was placed in a rat restrainer. The arterial catheter was connected to a pressure transducer (Baxter, Round Lake, IL) to monitor blood pressure. Blood pressure was sampled digitally by microcomputer (Hewlett-Packard 310, Pleasanton, CA) at 104 samples/s. Pulse interval, heart rate, and mean arterial pressure (MAP) were derived from the blood pressure signal by an amplifier (Grass Instrument 7DAHJK, Quincy, MA) and continuously recorded on a recorder (Grass Instrument 78). Studies were performed in a quiet room.

Determination of Baroreflex Sensitivity (Slope)
Baroreflex sensitivity (slope, ms/mmHg) was derived from a least-squares linear regression of the relation between systolic blood pressure and succeeding pulse intervals. The slope or gain of the baroreflex was estimated from this linear fit to heart rate changes in response to ramp changes in systolic blood pressure. In all cases, the control correlation coefficient (r) exceeded on average 0.87, and in those during maximal depression with bupivacaine r exceeded on average 0.6, with P < 0.0001. This method has the advantage of assessing the baroreflex in a short period, a necessity as the effects on blood pressure of a bolus intravenous injection of bupivacaine were short-lived (<5 min for 2 mg/kg). Phenylephrine was infused intravenously (50 μg · kg⁻¹ · min⁻¹ for 15 s) to obtain a pressor–bradycardic response and sodium nitroprusside (20 μg · kg⁻¹ · min⁻¹ for 45 s) to test the depressor–tachycardic response. Peak increases or decreases of MAP of 50–60 mmHg were obtained. All reflex changes were almost completely eliminated by ganglionic blockade with chlorisondamine (10 mg/kg given intravenously; peak heart rate before chlorisondamine, ↓125 ± 37 [phenylephrine, n = 5] and ↑160 ± 45 [nitroprusside, n = 3]; after chlorisondamine, ↑18 ± 17 [phenylephrine] and ↓21 ± 4 [nitroprusside]). The total volumes (45–135 μl) and rate of infusion (3 μl/s) were kept minimal, and administration of saline in these ranges had no effect on blood pressure or heart rate.

Baroreflex sensitivity was determined before and 1.5 and 15.0 min after intravenous bolus injection of bupivacaine (0.5, 1.0, and 2.0 mg/kg). Because acute tolerance developed with multiple injections of bupivacaine, each rat received only a single dose of bupivacaine on a given test day. Each rat was tested first with either pressor (phenylephrine) or depressor (nitroprusside) drug. The order of vasoactive drug delivery was random. On the subsequent day, the baroreflex test was repeated with the vasoactive challenge not tested the previous day.

To partition the autonomic basis of the observed changes in heart rate during exposure to bupivacaine, the baroreflex was tested in separate experiments in the presence of either the peripherally acting muscarinic antagonist methyl atropine (given intravenously, 0.5 mg/kg in 50 μl saline) or the β-adrenergic antagonist atenolol (given intravenously, 1 mg/kg in 50 μl in distilled water). Vehicle injections of this volume (50 μl) had no effect on blood pressure and heart rate. The appropriate dose range for effective antagonism was determined in preliminary experiments with intravenously administered acetylcholine (0.25–2.0 μg/kg) and isoprotenerol (0.05–0.10 μg/kg). Blockades lasted more than 1 h, a time sufficient to complete our protocols.
The full autonomic antagonist protocol was as follows: (1) the control baroreflex–heart rate was tested; (2) an antagonist was injected; (3) 10 min later, baroreflex was tested again; (4) bupivacaine (2.0 mg/kg) was injected intravenously; and (5) baroreflex tests were repeated at 1.5 and 15.0 min. A separate animal was used for each autonomic antagonist.

Studies of Blood Plasma: Arterial Blood Gas, Hematocrit, Plasma Sodium, Potassium, Bupivacaine, and Catecholamine Assays

To determine whether bupivacaine altered acid-base balance, electrolytes, or hematocrit, arterial blood samples (0.5 ml) were drawn at intervals in separate groups of experimental rats, as it was difficult to draw blood samples and to test baroreflex simultaneously 1.5 min after injection of bupivacaine. In one group, concentrations of catecholamine in plasma were measured to assess the effects of bupivacaine (2 mg/kg) on systemic sympathetic neurotransmitter levels. In another group, concentrations of bupivacaine in plasma were measured to correlate to baroreflex effects. In the latter group of animals, arterial blood samples (0.5 ml) were drawn before administration of bupivacaine at the peak of the blood pressure response to bupivacaine (30 s) and at the time corresponding to maximal baroreflex depression (1.5 min) after administrations bupivacaine. After plasma was separated from the blood samples, it was frozen at −80°C for assay of total concentrations of bupivacaine by gas chromatography (Hewlett-Packard 5890A) and catecholamine by high-pressure liquid chromatography (Hewlett-Packard 1090L).16

Drugs

Isoflurane was purchased from Abbott Laboratories (North Chicago, IL). Acetylcholine chloride, isoprotene-
nol, bupivacaine hydrochloride, phenylephrine hydrochloride, sodium nitroprusside, methyl atropine bromide, and atenolol were purchased from Sigma Chemical Co. (St. Louis, MO). Chlorisondamine was a gift from Ciba-Geigy (Summit, NJ). Bupivacaine (15 mg/ml) was prepared in distilled water. Varying doses were delivered by injecting appropriate volumes (10–45 \( \mu l \)) of this solution to yield the three bupivacaine test doses (0.5, 1.0, and 2.0 mg/kg).

![Image](fig2.png)

**Fig. 2.** Summary of averages of peak changes in mean arterial pressure (MAP; top) and heart rate (HR; bottom) during rapid intravenous administration of 0.5, 1.0, and 2.0 mg/kg bupivacaine (BUP) in conscious rats. Results are expressed as change from baseline values to the peak response. Values represent mean ± SD. \( n = \) number of animals studied.

**Statistical Analysis**

Measures of MAP, heart rate, and baroreflex sensitivity were compared before and after administration of bupivacaine or after autonomic antagonists by a repeated-measures analysis of variance, and a Scheffé F test was used for post hoc comparisons (StatView II; Abacus Concepts, Berkeley, CA). Comparisons between the groups (doses) were analyzed by analysis of variance followed by Scheffé F test. \( P \) values < 0.05 were considered significant. All data are expressed as mean ± SD.

**Results**

**Bupivacaine Dose–Response**

Intravenous injection of bupivacaine increased MAP and decreased heart rate in a dose-dependent manner (figs. 1 and 2). Typically, blood pressure began to increase approximately 3–5 s after the injection and

![Image](fig3.png)

**Fig. 3.** Representative baroreflex relations for pressor (PE = phenylephrine) and depressor (NP = nitroprusside) responses during control (top), 1.5 min bupivacaine (BUP, 2 mg/kg; middle), and 15-min recovery (bottom). Least-squares linear regression analysis (\( y = mx + b \)) was performed on beat-to-beat values of systolic blood pressure and succeeding pulse interval. Thick lines represent the linear fit and broken lines the 95% confidence limits. For all fits, \( P < 0.0001 \). Respective fit r values were 0.90767 (control PE), 0.92765 (control NP), 0.81485 (BUP PE), 0.8321 (BUP NP), 0.88337 (recovery PE), and 0.90909 (recovery NP).
peaked 10–30 s later. Blood pressure returned to baseline levels within 1.5–5.0 min depending on the dose of bupivacaine. Increasing the dose of bupivacaine delayed the time of the peak response and prolonged the duration of the hypertension. Bradycardia became severe at 2 mg/kg bupivacaine, and electrocardiographic changes became complex. Transient, complex electrocardiographic changes developed in the first few seconds after the 1- and 2-mg/kg doses. At 2 mg/kg bupivacaine, most rats (86%) convulsed briefly. Although by 1.5 min most of the increase in MAP had subsided (fig. 1E), heart rate remained strongly depressed (> 15 min).

Baroreflex Sensitivity after Intravenously Administered Bupivacaine

Baroreflex sensitivity was assessed during exposures to bupivacaine with vasoactive drug challenges (figs. 3 and 4). At the times of these baroreflex tests, control baseline hemodynamic conditions before injection of bupivacaine were similar across all groups (table 1). After injection of bupivacaine, the average prevailing MAP at 1.5 min was significantly higher only with the highest dose (2 mg/kg). In contrast, heart rate remained lower with the 1- and 2-mg/kg doses. Baroreflex sensitivity to increases and decreases in pressure were similar and averaged ~0.8 ms/mmHg in control conditions. Bupivacaine-induced changes in baroreflex sensitivity, however, were dependent on the direction of the evoked reflex changes. At 1.5 min, the 0.5-mg/kg dose had no effect on the baroreflex sensitivity. The 1-mg/kg dose depressed baroreflex sensitivity assessed only during pressor–bradycardic responses elicited by phenylephrine, but it had no effect on depressor–tachycardic responses by nitroprusside. The 2-mg/kg dose, however, decreased baroreflex sensitivity to pressor and depressor tests (figs. 3 and 4). At 15 min, the baroreflex sensitivity returned to the predrug value. Baroreflex sensitivity assessed in time-matched controls in preliminary studies was equivalent throughout the experimental period at three time intervals, before and 1.5 and 15.0 min after injection of 50 μl vehicle (0.667 ± 0.083, 0.690 ± 0.139, 0.760 ± 0.017 ms/mmHg for phenylephrine [n = 3], and 0.723 ± 0.215, 0.703 ± 0.045, 0.704 ± 0.045 ms/mmHg for nitroprusside [n = 3]). Increases in MAP were a prominent effect of intravenously administered bupivacaine. To assess the potential contribution of changes in pressure itself on baroreflex control of heart rate, we tested baroreflex responses during sustained increases in MAP, which replicated the short-term increase in MAP observed during the highest dose of bupivacaine (2 mg/kg; fig. 5). Heart rate–baroreflex sensitivity was not significantly altered by increasing MAP by an equivalent amount (fig. 5). Arterial blood gas (pH, carbon dioxide partial pressure, oxygen partial pressure), electrolytes (Na+ and K+), and hematocrit measured at 1.5 min after injection of 2 mg/kg bupivacaine were also not different from predrug control values (table 2).

Parasympathetic and Sympathetic Contributions to Bupivacaine Baroreflex–Heart Rate Response

Pretreatment with either methyl atropine or atenolol had no effect on resting MAP. In contrast, methyl atropine increased and atenolol decreased resting heart rate.
These observations indicate the presence of significant basal vagal and sympathetic tones in these animals at rest. For assessment of baroreflex, 2 mg/kg bupivacaine was selected for testing because our preliminary work indicated that this dose depressed baroreflex sensitivity to increases and decreases in pressure. Pretreatment with either antagonist had no effect on bupivacaine-induced hypertension. In contrast, bupivacaine-induced bradycardia was significantly attenuated by methyl atropine but not by pretreatment with atenolol. As with controls, prevailing MAP 1.5 min after administration of bupivacaine during the presence of either antagonist was significantly higher (tables 3 and 4).

Phenylephrine-evoked reflex bradycardia was severely attenuated by methyl atropine but unaffected by pretreatment with atenolol (fig. 6). In contrast, nitroprusside-evoked reflex tachycardia was attenuated by methyl atropine (64%) and atenolol (36%). Thus, although hypotensive bradycardia is primarily vagal, reflex tachycardia elicited by hypotension is attributable to parasympathetic inhibition and sympathetic stimulation. Bupivacaine (2 mg/kg), in the presence of atenolol, depressed baroreflex sensitivity as assessed by phenylephrine and nitroprusside. In contrast, in the presence of methyl atropine, bupivacaine had no effects on baroreflex sensitivity (fig. 6).

Concentrations of Bupivacaine and Catecholamine in Plasma

At the peak of the blood pressure response (30 s) after injection of 2 mg/kg bupivacaine, concentrations of bupivacaine in plasma reached an average 7.9 μg/ml and decreased to 1.8 μg/ml at 1.5 min, corresponding to the time when the baroreflex sensitivity was depressed (n = 3, data not shown). Concentrations of epinephrine and norepinephrine in plasma increased maximally at the peak of blood pressure responses. Concentrations of epinephrine remained increased up to 20 min, whereas concentrations of norepinephrine returned to resting by 5–8 min (fig. 7).

Discussion

The results of the current study demonstrate that, in conscious rats, baroreflex control of heart rate was depressed in clinically relevant concentrations. Concentrations in plasma ranging up to 2.5 μg/ml are observed from slow intravenous absorption after regional block with bupivacaine.17

Our results are consistent with studies in pentobarbital-anesthetized rats9 that suggested that bupivacaine depresses baroreflex sensitivity. Pentobarbital-induced anesthesia itself, however, is known to depress baroreflex control of heart rate10,11 and, in addition, to interact with bupivacaine.9,12,13 One difference, however, is that in pentobarbital-anesthetized animals, bupivacaine often does not change arterial pressure.9,12,13 Further, severe and potentially lethal ventricular arrhythmias develop more frequently in conscious but not in pentobarbital-anesthetized animals.4,6,13 Together, these results suggest that the central nervous system (CNS) is a critical factor.
component of the mechanisms by which bupivacaine generates hypertension and arrhythmias. Because general anesthesia modifies the response of the circulation and CNS, studies of awake, unpremedicated animals are essential to understand the clinical ramifications of exposure to intravenously administered bupivacaine.

Changes in the prevailing baseline blood pressure during exposure to bupivacaine are unlikely to contribute to the observed depression of baroreflex. Briefly sustained increases in blood pressure by slow infusion of phenylephrine failed to alter baroreflex sensitivity (fig. 5). Furthermore, low doses of bupivacaine (1 mg/kg), which had no effect on baseline blood pressure, clearly depressed baroreflex sensitivity. Brief increases in arterial pressure lasting from 15–20 min reset rat aortic baroreceptors acutely so that higher threshold pressures are required to activate them, although baroreceptor discharge slope (sensitivity) is unchanged. Such results are consistent with our present reflex data. Acute resetting of baroreflex control of systemic blood pressure and heart rate similarly shifts the set point without affecting its slope. In contrast, chronic hypertension in rats not only resets arterial baroreceptors to higher pressure thresholds but also decreases their sensitivities. Potentially complicating factors, such as acid–base abnormality or hyperkalemia, which could affect baroreflex control of heart rate, were within normal ranges (table 2).

Bupivacaine might potentially depress baroreflex–heart rate responses by affecting any of several components of the baroreflex–heart rate pathways: the sensory limb at arterial baroreceptors or the vessel wall in which these sensory endings are embedded; the CNS portions of the reflex, including synaptic transmission or associated ion channels; and the efferent pathways or the peripheral effectors themselves such as cardiac myocytes. Concentrations of bupivacaine comparable to

![Baroreflex Sensitivity vs. Blood Pressure](chart.png)

**Fig. 5.** Influence of short-term increase in MAP on mean heart rate (HR)–baroreflex sensitivity (slope) assessed by phenylephrine (PE, top) and sodium nitroprusside (NP, bottom) in six conscious rats. Blood pressure (BP) was increased with a low-dose infusion of PE (1.0–1.5 µg·kg⁻¹·min⁻¹) to match the BP elicited by bupivacaine 2 mg/kg at 1.5 min. Mean arterial pressure (MAP) increased from 118 ± 2 mmHg (basal) to 139 ± 2 mmHg (high), whereas HR decreased from basal 390 ± 7 to 302 ± 14 beat/min. Values represent mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PaCO₂ (mmHg)</th>
<th>PaO₂ (mmHg)</th>
<th>HCO₃⁻</th>
<th>O₂ Saturation (%)</th>
<th>Hct (%)</th>
<th>Na (mEq/l)</th>
<th>K (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>7.49 ± 0.03</td>
<td>38 ± 4</td>
<td>88 ± 20</td>
<td>30 ± 2</td>
<td>97 ± 1</td>
<td>44 ± 3</td>
<td>144 ± 3</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>BUP 1.5 min (n = 8)</td>
<td>7.47 ± 0.05</td>
<td>37 ± 4</td>
<td>88 ± 5</td>
<td>28 ± 2</td>
<td>97 ± 1</td>
<td>43 ± 4</td>
<td>144 ± 2</td>
<td>4.2 ± 0.6</td>
</tr>
<tr>
<td>BUP 15 min (n = 8)</td>
<td>7.49 ± 0.03</td>
<td>38 ± 2</td>
<td>88 ± 5</td>
<td>30 ± 2</td>
<td>97 ± 1</td>
<td>42 ± 3</td>
<td>143 ± 3</td>
<td>3.9 ± 0.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

pH₅₆ = arterial blood pH; PaCO₂ = arterial carbon dioxide partial pressure; PaO₂ = arterial oxygen partial pressure; HCO₃⁻ = bicarbonate; Hct = hematocrit; Na = plasma sodium; K = plasma potassium; BUP = bupivacaine.

Anesthesiology, V 92, No 1, Jan 2000
those that depress baroreflex control of heart rate (1.8 μg/ml) cause direct cardiac depression as indicated by slowed conduction and depressed contractility\textsuperscript{25,26} and depression of baroreceptor discharge.\textsuperscript{8} Other evidence indicates additional potential neuronal sites within cardiovascular reflexes. Bupivacaine may have CNS actions.\textsuperscript{7,27,28} Direct injection of bupivacaine into the cerebral ventricle of experimental animals induced cardiac arrhythmias and hypertension,\textsuperscript{7,27} which were prevented by ganglionic blockade with hexamethonium.\textsuperscript{27} Bupivacaine microinjected into nucleus tractus solitarius in medulla where baroreceptors first synapse in the CNS produced cardiac arrhythmias and hypotension in anesthetized rats.\textsuperscript{28} Such results indicate that bupivacaine can potentially induce CNS-mediated arrhythmias and abnormalities in blood pressure. These effects are consistent with a blunting of baroreflex control of blood pressure and heart rate, which may precede its direct cardiotoxic effect.

Our selective autonomic receptor antagonist studies indicate that bupivacaine depresses baroreflex sensitivity primarily by inhibiting the cardiac parasympathetic input while leaving intact the sympathetic component of the heart rate–baroreflex pathways. This conclusion is based on the following observations. First, high doses of bupivacaine (2 mg/kg) decreased baroreflex sensitivity in rats pretreated with the cardiac β-adrenergic antagonist atenolol. In rats pretreated with the muscarinic antagonist methyl atropine, bupivacaine did not alter baroreflex sensitivity. Second, low-dose bupivacaine (1 mg/kg) depressed only reflex bradycardia elicited by phenylephrine but not the tachycardia in response to nitroprusside. The phenylephrine-induced reflex bradycardia used in our study is, however, primarily attributable to vagal activation, as these responses were not significantly altered by atenolol and nearly completely blocked by methyl atropine. In contrast, however, the nitroprusside-induced reflex tachycardia requires decreases in cardiac parasympathetic activity and increases in cardiac sympathetic activity for full expression, as each antagonist alone blocked only a portion of the responses as reported by others.\textsuperscript{29} Third, concentrations of catecholamine in plasma, which reflect sympathetic activity, were increased at the time of baroreflex depression. Decreased vagal tone probably mediates the tachycardia-associated actions of another local anesthetic.

### Table 3. Baseline Hemodynamic Values for Baroreflex Test—2 mg/kg Bupivacaine + Atenolol

<table>
<thead>
<tr>
<th>BRX Test Drug</th>
<th>Variables</th>
<th>Control</th>
<th>Atenolol 1.5</th>
<th>Atenolol 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP (n = 14)</td>
<td>MAP</td>
<td>122 ± 7</td>
<td>126 ± 11</td>
<td>143 ± 15†</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>366 ± 30</td>
<td>304 ± 11*</td>
<td>264 ± 41†</td>
</tr>
<tr>
<td>PE (n = 6)</td>
<td>MAP</td>
<td>116 ± 5</td>
<td>115 ± 7</td>
<td>130 ± 17†</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>374 ± 17</td>
<td>334 ± 17*</td>
<td>268 ± 37†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

BRX = baroreflex; BUP = bupivacaine; NP = sodium nitroprusside; MAP = mean arterial pressure; HR = heart rate; PE = phenylephrine.

* Significant difference between controls and atenolol pretreatment (\(P < 0.05\)).
† Significant difference between atenolol pretreatment and atenolol + bupivacaine (\(P < 0.05\)).

### Table 4. Baseline Hemodynamic Values for Baroreflex Test—2 mg/kg Bupivacaine + Methyl Atropine

<table>
<thead>
<tr>
<th>BRX Test Drug</th>
<th>Variables</th>
<th>Control</th>
<th>MetATR 1.5</th>
<th>MetATR 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP (n = 12)</td>
<td>MAP</td>
<td>129 ± 17</td>
<td>128 ± 7</td>
<td>148 ± 7†</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>365 ± 31</td>
<td>427 ± 24*</td>
<td>414 ± 35</td>
</tr>
<tr>
<td>PE (n = 10)</td>
<td>MAP</td>
<td>119 ± 10</td>
<td>125 ± 7</td>
<td>134 ± 7†</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>381 ± 45</td>
<td>448 ± 31*</td>
<td>420 ± 31</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

BRX = baroreflex; MetAT = methyl atropine; BUP = bupivacaine; NP = sodium nitroprusside; MAP = mean arterial pressure; HR = heart rate; PE = phenylephrine.

* Significant difference between controls and MetAT pretreatment (\(P < 0.05\)).
† Significant difference between MetAT and MetAT + bupivacaine (\(P < 0.05\)).
agent, cocaine. Such differential actions are similar to reports for other, general anesthetic agents, such as isoflurane and pentobarbital, which appear to depress vagal activity to a greater extent than sympathetic activity, but the mechanisms underlying this differential action are not known.

Inhibitory actions by bupivacaine that compromise baroreflex function at the arterial baroreceptors or the nucleus of the solitary tract would be expected to increase blood pressure and heart rate by dual reciprocal actions to inhibit parasympathetic activity while facilitating sympathetic activation. Surgical elimination of arterial baroreceptors in experimental animals greatly increases blood pressure lability. Bilateral electrolytic lesions of the nucleus of the solitary tract eliminate entry of baroreceptor inputs to the brain stem and can produce a lethal, fulminating neurogenic hypertension. In the current study, despite increased blood pressure and concentrations of catecholamine in plasma during exposure to bupivacaine, we have not observed tachycardia after administration of bupivacaine. Bradycardia was consistently observed after administration of bupivacaine, and this response was partially blocked by methyl atropine, indicating activation of the parasympathetic

---

**Fig. 6. Contribution of autonomic divisions to changes in heart rate (HR)–baroreflex sensitivity (slope) in conscious rats induced by intravenously administered bupivacaine (BUP, 2 mg/kg): cardiac β-adrenergic blockade (left) and parasympathetic blockade (right). Baroreflex sensitivity was assessed by phenylephrine (PE) or sodium nitroprusside (NP) before (C = control), after 10 min of pretreatment with autonomic receptor antagonist (atenolol [ATN] or methyl atropine [MetAT]), and after intravenous administration of BUP at 1.5 and 15.0 min. These BUP tests are indicated as ATN + BUP for atenolol or MetAT + BUP for methyl atropine. Values represent mean ± SD. n = number of animals studied; * = significant differences between control and antagonist (ATN or MetAT), P < 0.05; + = significant differences between antagonist and BUP + antagonist, P < 0.05.**
nervous system by bupivacaine. Further, preliminary data indicate that bupivacaine-induced bradycardia originated, at least in part, from the CNS, as it was reduced by ganglionic block (chlorisondamine, data not shown). The bupivacaine-induced increase in blood pressure also could stimulate the baroreflex and contribute to the bradycardia if reflex activity is not completely blocked. In addition, direct cardiac depressant actions of bupivacaine on cardiac conduction may mask the effects of increased sympathetic outflow to the heart.

The precise mechanisms by which intravenously administered bupivacaine depresses heart rate-baroreflexes are unknown. Bupivacaine is a potent local anesthetic agent, and baroreflex depression by bupivacaine is most likely attributable to these local anesthetic properties. Other local anesthetic agents, such as lidocaine and cocaine, also inhibit the baroreflex.\(^54^{55}\) It is not known whether axonal blockade, which is conventionally attributed to sodium channel blockade,\(^2\) or other mechanisms are primarily involved in baroreflex depression (e.g., inhibition of synaptic transmission in the CNS). Evidence indicates that synaptic transmission in the CNS is more susceptible to local anesthetic agents than axonal conduction.\(^36^{37}\)

Recent studies indicate an association between baroreflex dysfunction and susceptibility to cardiac arrhythmias and sudden death during myocardial infarction.\(^38^{40}\) Reduced cardiac vagal tone has been correlated with increased susceptibility to ventricular fibrillation.\(^40\) Because bupivacaine given systemically has multiple effects, including direct actions on the heart and vascular smooth muscle,\(^2\) the compromise of baroreflex function may in addition jeopardize patients at risk. Our study suggests that bupivacaine, in clinically relevant concentrations, inhibits baroreflex control of heart rate in conscious rats. This inhibition appears to involve primarily the vagal component of the heart rate-baroreflex pathways.

References

1. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979; 51:285–7