Does the Choice of Local Anesthetic Affect the Catecholamine Response to Stress during Epidural Anesthesia?

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Background: Previous work has established that 2-chloroprocaine epidural anesthesia has no effect on circulating plasma epinephrine concentrations in young, healthy, resting volunteers, and results in a decrease in norepinephrine concentration only when a level of analgesia to pinprick of C-8 is reached. The current study was performed to evaluate the possibility that this finding is unique to 2-chloroprocaine.

Methods: Nine healthy volunteers were studied on three occasions at least 48 h apart; each received three local anesthetics (0.75% bupivacaine, 2% lidocaine, and 3% 2-chloroprocaine, all without epinephrine). After placement of lumbar epidural and central venous catheters, blood samples were drawn from the central venous catheter at the following stages: (1) 20 min after catheter placement (baseline), (2) during the first cold pressor test (CPT; hand held in an ice water bath for 90 s), (3) 20 min after reaching epidural analgesia to T-1 level of analgesia, and (4) during a second CPT (epidural analgesia to T-1). Monitoring consisted of noninvasive cardiac output (impedance), noninvasive blood pressure, and EKG.

Results: Extensive epidural block (stage 3) altered measured variables only minimally with respect to baseline state. During stage 2 (first CPT), mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), epinephrine, and norepinephrine increased. During stage 4 (second CPT), increases in HR and CI were not attenuated by any of the three local anesthetics. Increases in MAP were attenuated by epidural anesthesia with all three local anesthetics. Bupivacaine and 2-chloroprocaine epidural anesthesia significantly attenuated increases in plasma catecholamines, but lidocaine epidural anesthesia did not.

Conclusions: Epidural anesthesia with all three local anesthetic agents tested resulted in an incomplete sympatholysis in the resting state in healthy young men, judged by plasma catecholamine concentrations and cardiovascular variables minimally changed from resting baseline. Lidocaine epidural anesthesia did not attenuate the catecholamine response to CPT, indicating decreased blockade of sympathetic efferent neural traffic compared with bupivacaine and chloroprocaine epidural anesthesia. (Key words: Anesthesia techniques: epidural. Anesthetics, local: bupivacaine; chloroprocaine; lidocaine. Cold pressor test. Hemodynamic response. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

ONE of the goals of using epidural anesthesia in patients undergoing major surgical procedures is the attenuation of the "stress hormone response."1,2 There is evidence that neural blockade with local anesthetics may attenuate some of the physiologic disturbances associated with surgery of the lower extremities and lower abdomen.3 Additionally, epidural anesthesia is sometimes used to interrupt transmission of neural traffic travelling via preganglionic sympathetic fibers ("sympathectomy") in the treatment of sympathetically mediated pain.4 Because preganglionic sympathetic fibers originate in spinal segments T-1 to L-2,5 and, specifically, the adrenal medulla is innervated by sympathetic fibers originating in the T-6 to L-2 spinal segments,6 an epidural block of these segments would be expected to produce a decreased release of epinephrine and nor-
epinephrine into the circulation. However, there is little information available to quantify the sympathetic block during epidural anesthesia, nor is there information on comparison of degree of sympathectomy produced by different local anesthetics.

One study demonstrated a decrease in circulating plasma concentrations of norepinephrine, but not epinephrine, during epidural anesthesia with 0.5% bupivacaine in elderly men. In a previous study using young, healthy volunteers, we found that epidural anesthesia with 2-chloroprocaine did not change plasma epinephrine concentrations, and only decreased plasma norepinephrine concentrations when an analgesic level to C-8 was reached.

Because this finding was unexpected, we performed the current crossover study in nine volunteers to investigate the possibility that the incomplete sympathetic block observed during epidural anesthesia in our previous study could have been unique to the use of 2-chloroprocaine. In addition, a cold pressor test (CPT) was included in the protocol, so that the sympathoexcitatory response to stress could be evaluated during epidural anesthesia.

Materials and Methods

After obtaining institutional review board approval from the National Naval Medical Center and written informed consent, nine healthy male volunteers were enrolled in the study. All volunteers were anesthesiologists or nurse anesthetists. Their mean age was 35.8 yr (range: 33–43 yr), height 177.2 cm (range: 170–183 cm), and weight 75.4 kg (range: 63.5–86.2 kg). All were ASA physical status I, and taking no medications. Each subject was studied on three occasions, each time with a different local anesthetic, separated by at least 48 h. Local anesthetics used were 0.75% bupivacaine HCl (Sensorcaine-MPF), 2% lidocaine HCl (Xylocaine-MPF), and 3% 2-chloroprocaine (Nesacaine MPF; all Astra Pharmaceuticals, Westborough, MA). All solutions were without epinephrine. The order of local anesthetics was randomized. Subjects were blinded as to which local anesthetic they received; investigators performing analysis of hemodynamic data and catecholamine analysis were also blinded. Solid food and caffeine-containing beverages were withheld after midnight preceding each study, but clear liquids were allowed until the time of catheter placement.

Catheter Placement

Local anesthesia for catheter placement was obtained using a total of 5 ml pH-adjusted 1% lidocaine HCl. A central venous catheter was inserted via an arm vein for blood sampling. Position of the catheter tip in the right atrium was confirmed by EKG waveform analysis. An epidural catheter was inserted at the second, third, or fourth lumbar interspace. Following a negative aspiration test, a test dose of 60 mg 2-chloroprocaine was given immediately after catheter insertion. Intravenous fluids (Ringer's lactate) were given only to replace blood drawn for blood samples in a 3:1 ratio.

Monitoring

Subjects were monitored with an EKG for heart rate (HR), noninvasive blood pressure (Dinamap; Critikon, Tampa, FL), central venous pressure (CVP) measurement, and a noninvasive impedance cardiac output monitor. Mean arterial blood pressure (MAP) was calculated as \( \frac{1}{3} \times \) (pulse pressure) + diastolic pressure, and was measured every 5 min during the study, except during the CPT, during which it was measured every 30 s. Cardiac output was measured every 10 s during the study using a computer-interfaced impedance device (CIC-1000; Sorba Medical Systems, Milwaukee, WI). The system generates a 50-kHz, 500-ua signal that is applied to patch electrodes located on the forehead and left proximal thigh. Two sensing electrodes applied to the left base of the neck and the left midaxillary line at the level of the xiphoid measured changes in impedance over time (dZ/dt). Cardiac index (CI) and total peripheral resistance (TPR) were calculated by the CIC-1000. The accuracy of changes in CO detected by the CIC-1000 in normal healthy subjects compares favorably with those changes detected using thermodilution.

During local anesthetic injection, frequent aspiration tests were repeated. Local anesthetic was injected incrementally, and subjects were observed and queried for signs and symptoms of intravenous injection. Level of sensory analgesia was determined using a safety pin. After confirming a sharp sensation by testing at the shoulder (C-4 dermatome), the pin was moved up the trunk and the hand in a cephalad direction from anesthetized to unanesthetized dermatomes until the pin again felt as sharp as at the shoulder. The dermatome caudal to that where the pin again felt as sharp as at the shoulder was considered to be the level of analgesia. Level of analgesia was tested bilaterally. Testing was done beginning 20 min after initial local
anesthetic injection, until a T-1 level of analgesia had been attained. Testing was repeated just before drawing the blood samples for stage 3, and just after the second CPT (stage 4).

**Cold Pressor Test**
A CPT was performed on two separate occasions during each testing session. The volunteer was asked to place one hand up to the wrist into an ice-water bucket for 90 s. The maximum MAP, HR, CVP, and CI measured during the CPT were recorded. A blood sample for catecholamine determination was drawn at the end of the 90-s CPT.

**Experimental Protocol**
After catheters were inserted and monitoring devices were attached, a 20-min equilibrium period allowed the subjects to relax. Cardiovascular variables (HR, MAP, CVP, CI, and TPR) were recorded and blood samples for catecholamine measurement were taken at four stages: (1) resting baseline, 20 min after catheter insertion; (2) immediately after stage 1, at the end of the first CPT; (3) 20 min after achieving a T-1 level of epidural analgesia; and (4) immediately after stage 3, at the end of the second CPT (epidural analgesia to T-1). Between stages 2 and 3, local anesthetic was incrementally injected via the epidural catheter (with frequent aspiration tests and observation for signs and symptoms of intravenous injection). For lidocaine and 2-chloroprocaine, an initial dose of 30 ml was given over 5 min. If a T-1 level was not achieved within 20 min, an additional 5–10 ml were injected. For bupivacaine, the initial dose was 25 ml over 5 min, and additional doses were injected if necessary.

**Measurement of Plasma Catecholamine Concentrations**
Whole blood was drawn into heparinized syringes, cooled on ice for 10 min, and then centrifuged for 10 min at 3,000 rpm at 2°C. Plasma was frozen and stored at −70°C until assay. The catecholamine assays were performed using single isotope radioenzymatic method with a lower limit of sensitivity of 10 pg/ml for norepinephrine and epinephrine. Specificity of this assay is greater than 0.98.

**Plasma Local Anesthetic Concentrations**
For each experiment, a single whole blood sample for determination of plasma local anesthetic concentrations was drawn at stage 3. Whole blood samples were treated as above. Plasma bupivacaine concentrations were measured by capillary gas chromatography using nitrogen phoshate detection, with sensitivity of 0.05 μg/ml. Plasma lidocaine concentrations were measured using fluorescence polarization method (Therapeutic Drug Monitoring Systems, "TDX"; Abbott Diagnostics, North Chicago, IL) with a sensitivity of 0.1 μg/ml. Plasma chloroprocaine concentrations were not measured.

**Data Analysis**
Data are presented as means ± SEM. For CPT #1, data are presented as change from stage 1 to stage 2. For CPT #2, data are presented as change from stage 3 to stage 4. Multivariate analysis of variance (MANOVA) test was used to detect any significant differences between local anesthetic trials. If significant differences were detected, paired t test was used to detect differences between any two local anesthetic trials. Additionally, paired t test was used whenever appropriate. SAS GLM software was used (SAS Institute, Cary, NC). Level of analgesia was coded from 1–19 for T-1 to C-2 dermatomes, respectively. If a difference between left and right sides was found, the most caudal level of analgesia was used. Statistical significance was set at P < 0.05.

**Results**

**Effects of Epidural Anesthesia Alone**
There were no differences in baseline resting (stage 1) catecholamine concentrations or any cardiovascular variables among the three groups (table 1). One subject was excluded from the 2-chloroprocaine trial because of an unusually high level of block. A subdural catheter placement was suspected. Another subject was excluded from the bupivacaine trial because an adequate arm vein for CVP catheter placement could not be located. Volumes of local anesthetic injected were 35.3 ± 1.5 ml (lidocaine trial), 25 ± 0 ml (bupivacaine), and 33.5 ± 1.2 ml (2-CP). There were no significant differences between level of block on right and left sides with any local anesthetic trial by MANOVA testing. Extent of analgesia (see materials and methods section) was slightly below the C-8 dermatome for lidocaine (12.8 ± 0.4 dermatomes blocked) and bupivacaine (12.9 ± 0.1), and slightly above the C-8 dermatome for 2-chloroprocaine (13.5 ± 0.3). There were no statistical differences in level of analgesia between these
Table 1. Effects of Epidural Anesthesia on Resting Hemodynamic Variables and Plasma Catecholamine Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine (mg·h⁻¹)</th>
<th>Norepinephrine (mg·h⁻¹)</th>
<th>Heart Rate (beats·min⁻¹)</th>
<th>Mean Arterial Pressure (mmHg)</th>
<th>Cardiac Index (l·min⁻¹·m⁻²)</th>
<th>Total Peripheral Resistance (dyne·s·cm⁻⁵)</th>
<th>Central Venous Pressure (mmHg)</th>
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<td><strong>Lidocaine</strong></td>
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<tr>
<td>Stage 1 (n = 9)</td>
<td>53 ± 7</td>
<td>288 ± 69</td>
<td>59 ± 3</td>
<td>87 ± 3</td>
<td>3.9 ± 0.3</td>
<td>1,000 ± 100</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Stage 3 (n = 9)</td>
<td>74 ± 13</td>
<td>299 ± 54</td>
<td>69 ± 4</td>
<td>84 ± 4</td>
<td>3.9 ± 0.4</td>
<td>900 ± 90</td>
<td>1.0 ± 0.4</td>
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<td><strong>Bupivacaine</strong></td>
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<tr>
<td>Stage 1 (n = 8)</td>
<td>81 ± 21</td>
<td>271 ± 27</td>
<td>61 ± 3</td>
<td>85 ± 3</td>
<td>3.5 ± 0.2</td>
<td>1,040 ± 100</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Stage 3 (n = 8)</td>
<td>47 ± 12</td>
<td>215 ± 40</td>
<td>63 ± 4</td>
<td>83 ± 3</td>
<td>3.1 ± 0.2</td>
<td>1,140 ± 100</td>
<td>0.9 ± 0.6</td>
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<tr>
<td><strong>2-Chloroprocaine</strong></td>
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</tr>
<tr>
<td>Stage 1 (n = 8)</td>
<td>65 ± 7</td>
<td>302 ± 37</td>
<td>61 ± 3</td>
<td>86 ± 2</td>
<td>4.1 ± 0.3</td>
<td>930 ± 100</td>
<td>3.1 ± 1.2</td>
</tr>
<tr>
<td>Stage 3 (n = 8)</td>
<td>51 ± 16</td>
<td>247 ± 53</td>
<td>65 ± 6</td>
<td>75 ± 4⁺</td>
<td>4.0 ± 0.3</td>
<td>800 ± 65⁺</td>
<td>2.5 ± 1.0</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

There were no significant differences in baseline variables (stage 1) among local anesthetic trials by MANOVA.

* P < 0.05 versus baseline (stage 1) by paired t test.

† P < 0.05 versus lidocaine and bupivacaine by paired t test.

trials (MANOVA test, P = 0.2789), nor were any differences in level of analgesia between stages 3 and 4 detected (t test, P = 0.1690, 0.3506, and 0.3506 for lidocaine, bupivacaine, and 2-chloroprocaine, respectively).

Twenty minutes after achieving analgesia to the T-1 dermatome (stage 3), there were no significant differences compared with resting baseline in any measured variable or in catecholamine concentration with any local anesthetic, except for a modest decrease in MAP and TPR in the 2-chloroprocaine trial (table 1). At this time, mean plasma local anesthetic concentrations were 5.20 ± 0.35 μg/ml (lidocaine) and 1.53 ± 0.12 μg/ml (bupivacaine).

**Effects of the Cold Pressor Tests**

The first CPT (no epidural anesthesia) produced increases in HR, MAP, CI, epinephrine, and norepinephrine in all local anesthetic trials (figs. 1 and 2; table 2), except for CI during the bupivacaine trial, which was not significantly increased. Central venous pressure and TPR did not significantly change in any trial.

During the second CPT (epidural anesthesia), significant increases in HR were seen compared with stage 3 (resting epidural state) during lidocaine and bupivacaine epidural anesthesia. The mean HR increase during 2-chloroprocaine epidural anesthesia was not significantly changed. However, there was no difference between CPT #1 and CPT #2 for the 2-chloroprocaine trial. The increases in HR and CI seen during CPT #2 also did not differ from CPT #1 with any local anesthetic. Increases in MAP during CPT #2 with all three local anesthetics were significantly less when compared with CPT #1. Total peripheral resistance decreased during CPT #2 with both lidocaine and bupivacaine epidural anesthesia, but, otherwise, TPR and CVP did not significantly change with any local anesthetic during the second CPT.

During lidocaine epidural anesthesia, the increases in epinephrine and norepinephrine with the second CPT were not different than those seen with the first CPT (no epidural anesthesia; figs. 1 and 2). However,

![Fig. 1. Changes in plasma epinephrine concentrations (means ± SEM) during CPT #1 (before epidural anesthesia) and CPT #2 (during epidural anesthesia with three different local anesthetics). * = P < 0.05 for stage 2 versus stage 1 (resting baseline); delta = P < 0.05 versus bupivacaine and 2-CP trials; † = P < 0.05 for stage 4 versus stage 3 (resting epidural anesthesia); and ‡ = P < 0.05 versus CPT #1 (preepidural anesthesia). Differences (CPT #1–CPT #2) were significantly less for lidocaine than for bupivacaine or 2-CP, by paired t test. Bupivacaine and 2-CP trials did not differ.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931318/ on 11/10/2018)
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![Graph showing changes in plasma norepinephrine concentrations.](image)

Fig. 2. Changes in plasma norepinephrine concentrations (means ± SEM) during CPT #1 (before epidural anesthesia) and CPT #2 (during epidural anesthesia) with three different local anesthetics. * = P < 0.05 for stage 2 versus stage 1 (resting baseline); † = P < 0.05 for stage 4 versus stage 3 (resting epidural anesthesia); and ‡ = P < 0.05 versus CPT #1 (preepidural anesthesia). There were no differences among local anesthetic trials by MANOVA.

During bupivacaine and 2-chloroprocaine epidural anesthesia, increases in norepinephrine and epinephrine concentrations were attenuated compared with CPT #1.

**Bradycardia After Stage 4**

Five subjects developed sudden bradycardia after the second CPT. Heart rates ranged from 38 to 45 beats/min, and were associated with sweating, nausea, and impending syncope. All subjects responded to intravenous atropine 0.4–0.8 mg with prompt resolution of bradycardia and other symptoms. No other treatment was necessary. Bradycardia occurred during lidocaine epidural anesthesia (five subjects), 2-chloroprocaine (three subjects), and bupivacaine (one subject). Hypotension (systolic BP approximately 80 mmHg) associated with this bradycardia did occur, which resolved with treatment of bradycardia. However, hemodynamic data was not entered into the database at the time of the experiments, and could not be retrieved.

**Discussion**

There are two major findings of this study. The first is that lumbar epidural anesthesia extending to the T-1 dermatome using plain solutions of local anesthetic provides only a partial block of the sympathetic nervous system. The second finding is that the choice of the local anesthetic may influence the degree of sympathetic block during epidural anesthesia. This difference, however, is not apparent in the resting state, but only becomes apparent when the patient is subjected to stress. Both of these findings may have clinical importance.

The heart rate response to the CPT did not appear to be altered by epidural anesthesia, despite analgesia of the T-1–T-4 dermatomes. During the CPT, circulating

**Table 2. Change in Hemodynamic Variables in Response to Cold Pressor Test before and during Epidural Anesthesia**

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats · min⁻¹)</th>
<th>Mean Arterial Pressure (mmHg)</th>
<th>Cardiac Index (l·min⁻¹·m⁻²)</th>
<th>Total Peripheral Resistance (dyne·s⁻¹·cm⁻⁵)</th>
<th>Central Venous Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lidocaine</strong></td>
<td></td>
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</tr>
<tr>
<td>CPT 1 (n = 9)</td>
<td>16 ± 5*</td>
<td>18 ± 4*</td>
<td>0.8 ± 0.2*</td>
<td>58 ± 64</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>CPT 2 (n = 9)</td>
<td>10 ± 4†</td>
<td>6 ± 2†‡</td>
<td>1.1 ± 0.4†</td>
<td>-147 ± 54†</td>
<td>0.0 ± 0.3</td>
</tr>
<tr>
<td><strong>Bupivacaine</strong></td>
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<tr>
<td>CPT 1 (n = 8)</td>
<td>20 ± 4*</td>
<td>19 ± 3*</td>
<td>0.7 ± 0.3</td>
<td>57 ± 78</td>
<td>0.4 ± 0.7</td>
</tr>
<tr>
<td>CPT 2 (n = 8)</td>
<td>14 ± 4†</td>
<td>5 ± 5†‡</td>
<td>0.7 ± 0.2†</td>
<td>-189 ± 75††</td>
<td>-0.5 ± 0.3</td>
</tr>
<tr>
<td><strong>2-Chloroprocaine</strong></td>
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<tr>
<td>CPT 1 (n = 8)</td>
<td>17 ± 3*</td>
<td>18 ± 4*</td>
<td>1.0 ± 0.3*</td>
<td>-26 ± 54§</td>
<td>0.3 ± 1.3</td>
</tr>
<tr>
<td>CPT 2 (n = 8)</td>
<td>13 ± 12</td>
<td>1 ± 5†‡</td>
<td>0.5 ± 0.4</td>
<td>-24 ± 30§</td>
<td>-0.3 ± 0.5</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

CPT = cold pressor test.

MANOVA test yields no significant difference among local anesthetic trials for CPT 1 (stage 2–stage 1) or for CPT 2 (stage 4–stage 3) given any hemodynamic variable, except for TPR during CPT 2.

* P < 0.05 for stage 2 versus baseline (stage 1) by paired t test.
† P < 0.05 for stage 3 versus stage 4 by paired t test.
‡ P < 0.05 versus CPT 1 (stage 2–stage 1) by paired t test.
§ P < 0.05 versus CPT 2 during bupivacaine epidural anesthesia by paired t test.

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epinephrine or norepinephrine concentrations are poorly correlated with the changes in heart rate. This finding is in agreement with another study of the sympathetic response to the CPT.\textsuperscript{12} The increase in heart rate observed evoked by CPT during lidocaine and bupivacaine epidural anesthesia in this study cannot, therefore, be attributed to an increased release of catecholamines. The most likely explanation for this observation is the persistence of unblocked cardiovascular fibers. Further evidence for the persistence of unblocked sympathetic cardiovascular fibers is the observation that sudden bradycardia after the second CPT was rapidly corrected by atropine.

The role of vagal tone is unclear. It is possible that the CPT may have caused withdrawal of high vagal tone in our young, healthy subjects, accounting for increased heart rate. Rapid changes in vagal tone could also explain the bradycardia observed in several subjects after completion of the second CPT. However, one study (in humans with intact cardiovascular) of the hemodynamic response to CPT has shown that vagal blockade with atropine has no effect on the magnitude of heart rate increase during CPT.\textsuperscript{15} Another study in healthy volunteers showed that $\beta$ blockade with propranolol abolished the heart rate increases in response to CPT.\textsuperscript{12} Taken together, these two studies leave one with the impression that sympathetic activation (and not vagal inhibition) must be responsible for cardiovascular activity during CPT. This argument, however, does not rule out vagal influences in determining the heart rate at rest during epidural anesthesia.

Measurement and interpretation of plasma catecholamine concentrations in humans is, at best, an inexact science. However, changes in plasma catecholamine concentrations do provide a window through which one can make observations regarding sympathetic nervous system activity. Our results clearly show that the use of terms such as “sympathectomy” and “complete sympathetic block” to describe epidural anesthesia are inappropriate.

Bromage wrote, in 1978, that he suspected that the sympathetic block accompanying epidural anesthesia represented a reduction in neural traffic in sympathetic nerve, not a complete block.\textsuperscript{14} Evidence for this hypothesis can be found in several studies of patients or volunteers undergoing cervical or thoracic epidural anesthesia.\textsuperscript{15-20} These studies demonstrate that, despite epidural anesthesia of upper thoracic dermatomes (including T-1–T-5), sympathetic stressors, such as CO$_2$ breathing,\textsuperscript{15,16,17} exercise,\textsuperscript{18,19} or laryngoscopy,\textsuperscript{19} resulted in increases in blood pressure and heart rate similar to those changes seen in the unblocked states. Sundberg and Watwil\textsuperscript{16} attributed an unattenuated heart rate response, despite anesthesia of T-1–T-5 dermatomes, to presumed catecholamine release by the “unblocked” adrenal medulla (they did not measure catecholamines). Although our observations do not support Sundberg’s postulated explanation, the failure of epidural anesthesia to completely block hemodynamic changes in these studies agrees with our observations.

Experiments in trained resting dogs have shown that there is little change in plasma catecholamine concentrations, despite extensive lumbar epidural anesthesia with 0.5% bupivacaine.\textsuperscript{21} Other experiments in trained dogs showed that the catecholamine response to a combination of hypoxia and hypercarbia (a potent sympathetic challenge) is attenuated, but not completely abolished, by 2% lidocaine epidural anesthesia.\textsuperscript{22} In both of these experiments, extensive motor and sensory blockade was present. The weight of experimental evidence strongly argues against the concept of a complete sympathetic block associated with epidural anesthesia. Indeed, the available evidence indicates that sympathetic efferent nerves may be more difficult to block than somatosensory nerves.

Bonica \textit{et al.}, in a similar study,\textsuperscript{23} attributed cardiovascular stability during extensive epidural block to cardiovascular stimulating properties of rather high plasma lidocaine concentrations (\textit{4–7 \mu g/ml}). In the current study, comparing epidural anesthesia alone (stage 3) to baseline (stage 1), we saw no significant changes, except for a 16% decline in TPR and a resultant 13% decrease in MAP with 2-CP. Bonica \textit{et al.} used a lumbar, as well as a thoracic, epidural catheter for attaining a T-1 level of block. They found cardiac output and heart rate to remain near baseline values, while both TPR (−16%) and mean arterial pressure (−19%) showed a moderate decrease. Injection via a high thoracic epidural catheter may have resulted in a more intense block of sympathetic fibers to the upper extremity than did our injection of the entire local anesthetic via a lumbar epidural catheter. Furthermore, Bonica used multiple repeated injections, without allowing the block to dissipate. This probably resulted in a much more dense blockade than did our single lumbar epidural injection. The methodology used probably explain the differences between our observations and those of Bonica \textit{et al.}
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Evidence from in vitro experiments and experiments in anesthetized animals show that high plasma concentrations of lidocaine result in myocardial depression. Conclusions from the in vitro data must be tempered by the knowledge that desheathed nerve preparations and very high concentrations of lidocaine (10–20 µg/ml) were used. Data from awake, chronically instrumented dogs show that plasma lidocaine concentrations of about 4 µg/ml (similar to the concentrations observed in our study) produce a central stimulation of both components of the autonomic nervous system, which modulate the direct depressant effects of lidocaine, resulting in increased cardiac chronotropism and inotropism. Further evidence from volunteer studies indicates that the depressant action of systemically administered lidocaine (approximately 3–4 µg/ml) on sympathetic nerves is minimal, and these plasma concentrations of lidocaine may even result in an enhancement of sympathetic tone. Plasma bupivacaine concentrations of 1–2 µg/ml also result in positive chronotropism and vasoconstriction in resting volunteers receiving intravenous bupivacaine infusions, although plasma catecholamine concentrations were not changed. Thus, sympathoexcitatory effects of circulating local anesthetics may compensate for a partial sympathetic block produced by epidural anesthesia.

Because of its rapid metabolism by plasma cholinesterase, 2-chloroprocaine is usually not detectable in the plasma 20 min after epidural injection in normal individuals. Therefore, the data from the 2-chloroprocaine trials probably represent the effects of epidural anesthesia alone, without confounding systemic effects of circulating local anesthetic. We are unaware of any evidence that clinical concentrations of the metabolites of 2-chloroprocaine have systemic hemodynamic effects.

Because analgesia to pinprick was present in a portion of the hand immersed in ice water during CPT #2, the question may arise of whether the sympathetic stimulus was comparable to that during CPT #1. All subjects reported profound discomfort during CPT #2, indicating that analgesia of the ulnar nerve did little to decrease the intensity of the stimulus. As an example of this undiminished stimulus, increases in heart rate and cardiac index during CPT #2, were not different from CPT #1. Additionally, the extent of analgesia did not differ among trials, so that, even if the ulnar analgesia would have had an effect, it would have been the same with each local anesthetic. Therefore, this would not explain differences seen between local anesthetic trials. Circulating local anesthetic concentrations may have an analgesic action. Despite this analgesic action, lidocaine epidural anesthesia did not attenuate increases, either of catecholamines or of heart rate, during the second CPT. Therefore, analgesia of the ulnar nerve distribution of the hand, or analgesia action of circulating local anesthetics, does not appear to have been a factor influencing the results of this study.

Our data support the conclusion that epidural anesthesia produces an incomplete block of sympathetic efferent nerves. Cardiovascular variables, as well as plasma catecholamine concentrations, are minimally changed in young, healthy, resting volunteers, despite high levels of lumbar epidural anesthesia. Increases in catecholamine responses to stress were attenuated by epidural anesthesia with 2-chloroprocaine and bupivacaine, but not with lidocaine. The explanation for this difference may be the central stimulatory effects of therapeutic plasma concentrations of lidocaine. Alternatively, less intense neural blockade with lidocaine may result, despite similar extent of analgesia. We are not aware of any studies attempting to compare the in vivo intensity of blockade produced during epidural anesthesia with these three agents. Thus, it is impossible to say whether the concentration, per se, of the local anesthetics used could be a contributing factor in the differences observed. Because we used the maximum available concentrations of each local anesthetic, and used doses larger than those usually used in clinical practice, we believe it is unlikely that one could produce a more dense blockade, unless one adopted Bonica's methodology. Currently, there is no accepted methodology for measuring "blockade density" in vivo. Perhaps, somatosensory evoked potentials could be used to measure differences in "block density." Effects of age or addition of epinephrine to local anesthetic solutions were not addressed in this study. Either or both of these two factors could, conceivably, alter the cardiovascular or catecholamine changes seen during epidural anesthesia. We suggest that future studies of patient outcome with epidural anesthesia consider that the choice of local anesthetic agent can alter the catecholamine response to stress, and, therefore, the choice of local anesthetic should be controlled.

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References


