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# *Influence of Venous Return on Baroreflex Control of Heart Rate during Lumbar Epidural Anesthesia in Humans*

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**The role of variation of venous return on baroreflex control of heart rate during lumbar epidural anesthesia was investigated in 12 unpremedicated patients. Group 1 patients (n = 6) received 8 ml of 0.5% plain bupivacaine in the epidural space (L3–4) (mean upper level of analgesia at T10). Group 2 patients (n = 6) received 8 ml of saline at the same level in the epidural space. Following the epidural injection, phenylephrine (PHE) and nitroglycerin (NTG) were employed to alter the stimulation of baroreceptor sites before and during application of lower body positive pressure (LBPP). Plasma bupivacaine, catecholamines, renin activity, and vasopressin were assayed. In contrast to saline, epidural bupivacaine induced a decrease in systolic arterial and right atrial pressures (−11 ± 4 and −3.2 ± 0.7 mmHg, respectively, mean ± SEM) without change in heart rate, an increase in baroreflex slopes during PHE and NTG injections (+5.9 ± 1.6 ms/mmHg and +2.8 ± 0.9 ms/mmHg, respectively), and a decrease in plasma norepinephrine (−248 ± 89 pg/ml). The application of LBPP restored hemodynamic and reflex variables to preepidural analgesia values, whereas plasma catecholamines decreased further. Plasma renin activity and vasopressin were not modified at any time in either groups. This study indicates that lumbar epidural anesthesia enhances cardiac vagal tone mainly through a decrease in venous return. (Key words: Anesthetic techniques: epidural. Blood pressure: hypotension: baroreceptor reflexes. Hormones: catecholamines; renin-angiotensin; vasopressin. Reflexes: baroreceptor. Venous return.)**

THE NORMAL REFLEX tachycardia associated with hypotension often is absent during regional anesthesia, even if the level of blockade is too low to involve cardiac accelerator fibers.[1,2] This suggests an impairment of reflex control of heart rate, which could be influenced by changes in position and resulting variations in the venous return to the heart.[2,3] A previous study under general anesthesis[4] failed to demonstrate any alteration of the baroreflex control of heart rate during lumbar epidural anesthesia. Accordingly, the goals of this study were (1) to reinvestigate the effects of low level epidural anesthesia in young unpremedicated patients on baroreflex control of heart rate, and (2) to assess the role of variations of the venous return in possible alterations of this control. To accomplish these goals, we studied the effects of injections of vasopressor and vasodepressor drugs and the concentrations of plasma catecholamines, renin-activity, and vasopressin before and after application of lower body positive pressure (LBPP) under epidural anesthesia. The same study was conducted on a control group of patients who received only saline in the epidural space.

## Material and Methods

Twelve informed consenting male patients (37 ± 3 yr, mean ± SEM), who were scheduled for orthopedic surgery were studied after approval by our Institutional Committee. They were free of cardiac, renal, and hepatic diseases, had normal sodium intake, and did not take any drugs known to influence the cardiovascular and neuroendocrine systems. They had fasted for 6 h before the procedure. Catheters were inserted in a peripheral vein, in the radial artery, in the lumbar epidural space (L3–L4), and in the right atrium *via* a basilic vein under local anesthesia with 4 to 6 ml of plain 0.5% bupivacaine hydrochlorine. Position of the atrial catheter was confirmed by typical pressure waveforms and by characteristic responses to Valsalva maneuver. Radial and atrial catheters were connected to Statham P23ID® strain gauge manometers. ECG (lead II), arterial, and right atrial pressures were monitored continuously on a multichannel electrostatic recorder (ES 1000, Gould Inc., Instruments division, Cleveland, OH). Patients were wrapped with three-compartment medical antishock trousers (Jobst Institute, Inc., Toledo, OH). Throughout the procedure, patients remained in a 10-degree, head-up, comfortable position and lactated Ringer's solution was slowly infused through the peripheral venous catheter (50 ml/h).

After a resting period of 30 min, control measurements were performed and followed by epidural injection of either 8 ml of plain 0.5% bupivacaine hydrochloride (group 1, n = 6) or 8 ml of saline (group 2, n = 6) according to a random but unblinded distribution. The second set of measurements was performed 30 min after

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epidural injection in the two groups of patients. At the end of this second set of measurements (*i.e.*, at least 50 min after epidural injection), the leg compartments of the trousers were inflated, according to Payen *et al.*,[5] to provide a circumferential pressure of 40 mmHg, which was below the diastolic arterial pressure in every case. The third and last set of measurements was performed after the tenth minute of sustained LBPP (*i.e.*, at least 60 min after epidural injection). Each set of measurements included the following: (1) upper level of analgesia by change in sensation of pinprinck; (2) heart rate, arterial, and right atrial pressures; (3) baroreflex testing; and (4) collection of arterial blood samples for assay of bupivacaine, catecholamines, renin-angiotensin, and vasopressin.

Baroreflex testing was performed, according to Eckberg,[6] using graded intravenous bolus injections of phenylephrine and nitroglycerin in order to respectively increase (activation of the reflex) or decrease (deactivation of the reflex) systolic arterial pressure by 20–30 mmHg. Each injection was separated by a 5- to 10-min period to allow arterial pressure and heart rate to return to basal values. The set point was defined as the systolic arterial pressure and R-R interval values measured immediately before the injection of the vasoactive drugs. Each R–R interval was plotted as a function of the preceding systolic arterial pressure, beginning after the first noticeable change in the R–R interval. Baroreflex sensitivity was expressed as the slope of the regression line between R–R interval and systolic arterial pressure.

Data analysis was accepted if the correlation coefficient was 0.80 or greater. Arterial blood samples were immediately centrifuged at 4° C for 10 min at 3000 rev/min and plasma stored at −18° C. Plasma epinephrine and norepinephrine were measured by the radioenzymatic method of Da Prada and Zucker.[7] The sensitivity of this method was ±5 pg/ml for both epinephrine and norepinephrine. Plasma renin activity was measured by radioimmunoassay with a sensitivity of $\pm 125$ pg $\cdot$ ml$^{-1}$ $\cdot$ h$^{-1}$.[8] Plasma vasopressin was measured by radioimmunoassay with a minimum detectable level of 0.9 pg/ml.[9] Bupivacaine was measured by the high pressure liquid chromatography technique, which measures bupivacaine between 0.05 and 10 μg/ml with a coefficient of variation of less than 10%.**

All values were expressed as mean ± SEM. Data were analyzed by multifactorial analysis of variance followed by intragroup modified t-test and intergroup unpaired t-test ($P < 0.05$ significant).

** Bishop W, Oppenheim RC, Eyres RL: Analysis of lignocaine, bupivacaine in plasma by high-performance liquid chromatography. Asian J Pharmaceut Sci 2:91–94, 1980

## Results

### Before Epidural Injection

Comparison of the control data for the two groups showed no significant difference for cardiovascular (tables 1 and 2) and humoral (fig. 2) variables. The sensitivities of the baroreflex during either activation (phenylephrine) or deactivation (nitroglycerin) were similar between the two groups (table 2). The insertion of catheters under local anesthesia with bupivacaine resulted in a detectable plasma level of bupivacaine during the control period (table 1).

### After Epidural Injection

Thirty minutes after epidural injection of 8 ml of plain bupivacaine (group 1), the superior level of analgesia ranged from T8 to T12 (mean T10), and plasma level of bupivacaine increased significantly (table 1). At this time, systolic arterial and right atrial pressures were decreased without changes in heart rate (table 1). Baroreflex sensitivities were increased during both activation and deactivation of the reflex (table 2), while the set point was shifted to the left (hypotension without tachycardia) (fig. 1A). Plasma norepinephrine decreased significantly from 558 ± 121 to 331 ± 94 pg/ml, whereas the decrease in epinephrine was not significant (115 ± 33 to 90 ± 22 pg/ml). In group 2, epidural injection of 8 ml of saline induced no changes in hemodynamic, humoral, and reflex variables (tables 1 and 2; figs. 1B and 2).

### After LBPP Application

In group 1, the application of LBPP increased systolic arterial and right atrial pressures, but the latter remained less than its control value (table 1). Baroreflex sensitivities during activation and deactivation of the reflex and the set point returned to control values (table 2; fig. 1A), while heart rate remained unchanged (table 1). Plasma norepinephrine (from 331 ± 94 to 234 ± 40 pg/ml) and epinephrine (from 90 ± 22 to 43 ± 11 pg/ml) showed further significant decrease (fig. 2). In group 2, LBPP increased both systolic and diastolic arterial pressures and right atrial pressure without change in heart rate (table 1). Baroreflex sensitivity during activation of the reflex was decreased (table 2), while the set point was shifted to the right (hypertension without bradycardia) (table 2; fig. 1B). Plasma norepinephrine increased significantly from 358 ± 32 to 620 ± 80 pg/ml (fig. 2). Plasma renin activity and vasopressin remained unchanged in both groups (fig. 2).

## Discussion

The major finding of this study is that lumbar epidural anesthesia induces an enhancement of cardiac vagal ac-

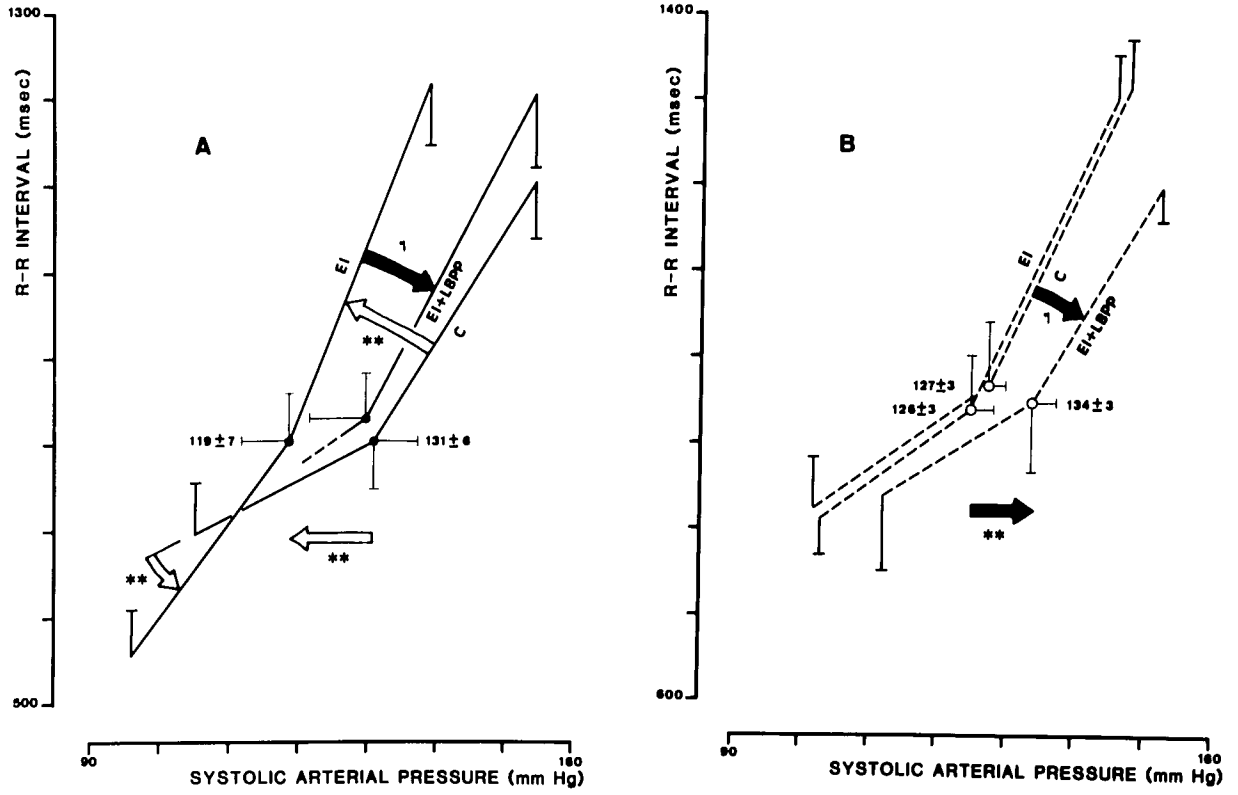


FIG. 1. Linear regressions between increases in systolic arterial pressure and lengthening of the R–R interval induced by phenylephrine, and between reductions in systolic arterial pressure and shortening of the R–R interval induced by nitroglycerin. Data are shown as means ± SEM of single regression lines obtained in each of the six subjects of each group. The circles (full and open) between the regression slopes represent average control values (±SEM) for systolic arterial pressure and R–R interval. *A* (group 1). C = control period; EI = 30 min after epidural injection of bupivacaine; EI + LBPP = 60 min after epidural injection of bupivacaine + 10 min of LBPP. *B* (group 2): C = control period; EI = 30 min after epidural injection of saline; EI + LBPP = 60 min after epidural injection of saline + 10 min of LBPP. Significant change from C: $*P < 0.05$, $**P < 0.01$. Significant change between EI and EI + LBPP: 1 $P < 0.05$.

tivity due to decreased venous return. The epidural dose of plain bupivacaine (group 1) was chosen to produce a low level of segmental blockade, that would cause vasodilation, but avoid blockade of cardiac sympathetic nerves. The increase in the slope of the linear relation between R–R interval and systolic arterial pressure after an intravenous bolus of phenylephrine is a pure index of enhanced cardiac parasympathetic tone.[10] Moreover, the decrease in plasma norepinephrine in the presence of concomitant decreases in arterial and right atrial pressures reflects a reduction in peripheral sympathetic tone.[11–13]

The increase in slope of the linear relation between R-R interval and systolic arterial pressure after an hypotensive *iv* bolus of nitroglycerin was unexpected because the hypotension induced by epidural anesthesia was associated with a lack of reflex tachycardia. However, the tachycardic response to hypotension is not linear: the initial portion of the stimulus-response curve is flatter than the second part of the slope.[14] Thus, this increase in the so-called baroreflex sensitivity might be due to the shift to the left of the set point in such a way that the decrease in systolic arterial pressure came to work on the steeper portion of the curve.[14] Consequently, any interpretation of variations in baroreflex sensitivity after nitroglycerin injection may be erroneous.

The increase in vagal tone, evidenced by the increase in the baroreflex slope during phenylephrine injection, may explain the absence of cardiac acceleration in the presence of systemic hypotension induced by epidural anesthesia. The age-related alteration in baroreflex function[15] cannot be implicated in our work in contrast with previous studies on middle-aged or elderly patients.[1,2] The observed imbalance in autonomic nervous system in group 1 cannot be attributed to prolonged bed rest and a contracted blood volume because the patients of group 2 did not exhibit it. A role of circulating bupivacaine can be excluded because higher plasma levels in humans have no action on sympathetic and parasympathetic systems.[16,17] Therefore, the alteration in baroreflex control of heart rate can be related solely to the extradural blockade. A previous study failed to demonstrate such an alteration during lumbar epidural anesthesia.[4] However,

TABLE 1. Hemodynamic Effects of Lumbar Epidural Injection of Bupivacaine (Group 1) or Saline (Group 2) with and without Lower Body Positive Pressure (LBPP) and Plasma Levels of Bupivacaine

| | Control Values | 30 Min after Epidural Injection | 60 Min after Epidural Injection (10 min LBPP) |
|---|---|---|---|
| Systolic arterial pressure (mmHg) | | | |
| Group 1 | 131 ± 6 | 119 ± 7* | 130 ± 9† |
| Group 2 | 127 ± 3 | 126 ± 3 | 134 ± 3*‡ |
| Diastolic arterial pressure (mmHg) | | | |
| Group 1 | 70 ± 4 | 63 ± 3 | 67 ± 4 |
| Group 2 | 68 ± 2 | 68 ± 2 | 72 ± 2*‡ |
| Mean arterial pressure (mmHg) | | | |
| Group 1 | 90 ± 4 | 84 ± 4 | 88 ± 5 |
| Group 2 | 87 ± 2 | 87 ± 2 | 92 ± 1*‡ |
| Right atrial pressure (mmHg) | | | |
| Group 1 | 3.8 ± 0.8 | 0.7 ± 0.8* | 2.6 ± 0.8†§ |
| Group 2 | 4.1 ± 0.8 | 3.9 ± 0.7 | 6.9 ± 0.8*‡ |
| Heart rate (beats/min) | | | |
| Group 1 | 75 ± 4 | 75 ± 5 | 74 ± 6 |
| Group 2 | 67 ± 5 | 66 ± 4 | 66 ± 6 |
| Plasma bupivacaine (μg/ml) | | | |
| Group 1 | 0.12 ± 0.02 | 0.40 ± 0.04* | 0.30 ± 0.04*† |
| Group 2 | 0.10 ± 0.02 | 0.03 ± 0.01* | 0 |

* $P < 0.01$. Significant change from control value.
† $P < 0.05$. Significant change between pre-LBPP and post-LBPP after epidural injection.
‡ $P < 0.01$. Significant change between pre-LBPP and post-LBPP after epidural injection.
§ $P < 0.05$. Significant change from control value.

that study was conducted under general anesthesia, which is well-known to reduce parasympathetic tone and to modify the balance between the cardiac vagal restraint and the sympathetic peripheral tone.[18]

Two explanations may account for the enhancement in vagal tone that we observed during epidural anesthesia. First, increase in α-adrenergic activity on baroreceptor areas, unaffected by the blockade, has been shown to increase baroreceptor sensitivity in animals.[19,20] However, the adrenergic stimulation used in those animal experimental studies was intense, while in our work the sympathetic tone during epidural anesthesia, reflected by

TABLE 2. Effects of Lumbar Epidural Injection of Bupivacaine (Group 1) or Saline (Group 2) with and without Lower Body Positive Pressure (LBPP) on the Set Point and the Sensitivity of Baroreflex during Activation (PHE = Phenylephrine) and Deactivation (NTG = Nitroglycerin)

| | Control Values | 30 Min after Epidural Injection | 60 Min after Epidural Injection (10 min LBPP) |
|---|---|---|---|
| Set point | | | |
| Systolic arterial pressure (mmHg) | | | |
| Group 1 | 131 ± 6 | 119 ± 7* | 130 ± 9† |
| Group 2 | 127 ± 3 | 126 ± 3 | 134 ± 3*‡ |
| R-R interval (ms) | | | |
| Group 1 | 812 ± 46 | 806 ± 43 | 836 ± 55 |
| Group 2 | 967 ± 75 | 940 ± 77 | 947 ± 75 |
| Baroreflex sensitivity (ms/mmHg) | | | |
| After PHE injection | | | |
| Group 1 | 14.4 ± 3.1 | 20.3 ± 4.4* | 16.4 ± 3.8† |
| Group 2 | 17.0 ± 2.3 | 17.3 ± 2.2 | 14.7 ± 2.2*† |
| After NTG injection | | | |
| Group 1 | 4.7 ± 1.4 | 7.6 ± 1.8* | 5.9 ± 1.4† |
| Group 2 | 5.9 ± 1.4 | 5.4 ± 1.1 | 4.8 ± 1.9 |

Significant change from control value: *$P < 0.01$.
Significant change between pre- and post-LBPP after epidural injection: †$P < 0.05$, ‡$P < 0.01$.
No significant difference between the control values of the two groups.

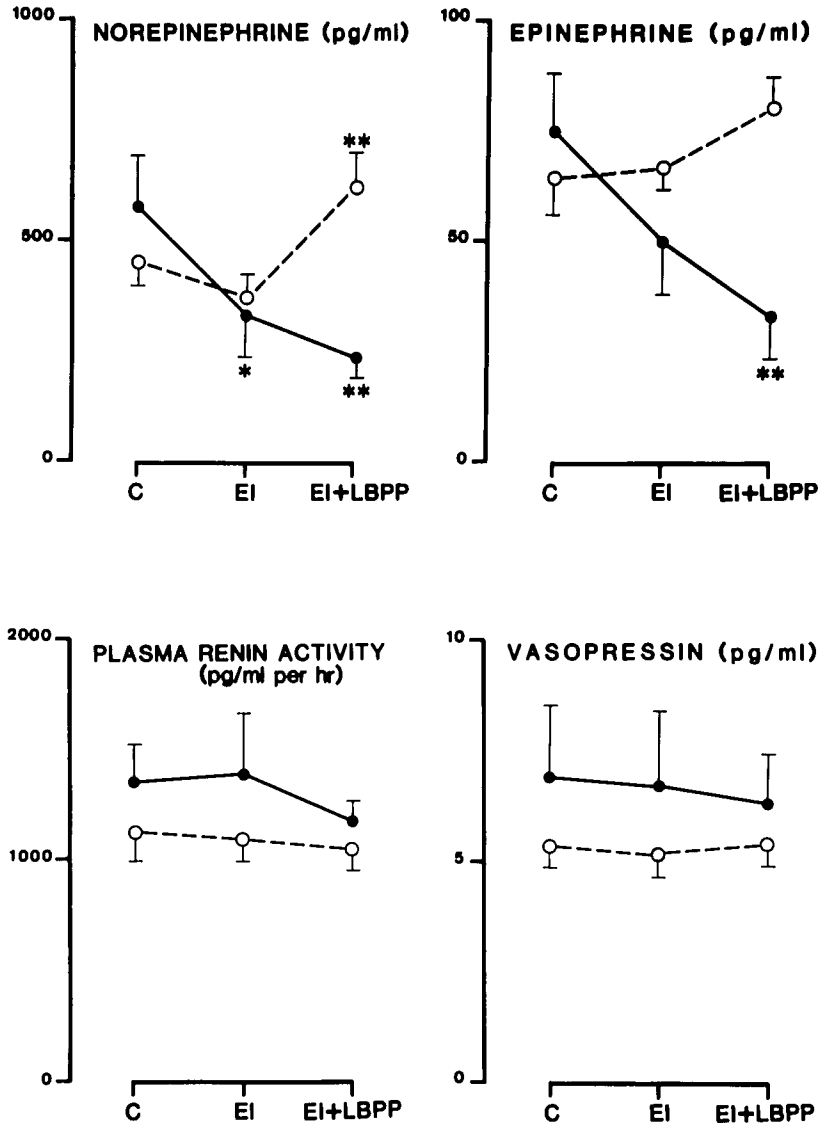


FIG. 2. Plasma norepinephrine, epinephrine, renin activity, and vasopressin 30 min after epidural injection (EI) and 60 min after EI + 10 min of LBPP (EI + LBPP). ● —— ● EI of bupivacaine (group 1); ○ - - - ○ EI of saline (group 2). Significant change from control values: $*P < 0.05$, $**P < 0.01$. No significant difference between the control values of the two groups.

plasma norepinephrine level, was rather low. The second, and more likely, explanation is a decrease in venous return to the heart. Stimulation of cardiopulmonary receptors tonically inhibits baroreflex responses.[21] If these inputs are reduced by the epidural anesthesia-induced decrease in the venous return to the heart, tonic inhibition of baroreflex response should decline also, especially if the sympathetic tone was reduced.[22]

An additional argument in favor of this hypothesis is the effect of LBPP, which decreased the vagal tone, as reflected by the baroreflex sensitivity after phenylephrine injection in both groups. This effect probably was related to the shift of blood from peripheral to central compartment,[23] even if this movement was so moderate that neither plasma renin activity nor vasopressin was decreased at any time of the study in the two groups. We chose application of LBPP as a nonpharmacological way to increase the venous return to the heart. This maneuver induces a prompt and sustained augmentation in venous return[5] free of changes in hematocrit, osmolality, and blood temperature that accompany intravenous fluid infusions.[24] This technique, however, has undoubtedly an arterial effect because mean arterial pressure increased in the unblocked group 2 patients during LBPP. The slight increase in norepinephrine depicted in the group 2 patients is unusual,[24] and might be related to the discomfort of LBPP without epidural analgesia.

In conclusion, lumbar epidural anesthesia confined to the lower spinal segments induces an enhancement of cardiac vagal tone due to venous pooling. This modulation of baroreceptor control of heart rate is abolished by mechanical volume increase of the central blood compart-

ment. The absence of cardiac acceleration in our patients who received epidural anesthesia corresponds to a relative bradycardia because heart rate should have increased due to the hypotension. Absolute bradycardia may occur during epidural anesthesia, even if the upper level of analgesia is low, when venous return is greatly decreased by an acute blood loss[25] or a head-up position.[2] These data support the clinical evidence that, during regional anesthesia, changes in position and, consequently, variations in venous return to the heart may modify heart rate.

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