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Sympathetic Blockade by Epidural Anesthesia Attenuates the Cardiovascular Response to Severe Hypoxemia

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Blood pressure is usually well maintained during epidural or spinal anesthesia even in the presence of extensive sympathetic blockade. The authors investigated whether hormonal systems support arterial pressure and how the circulation copes with a hypoxic challenge when activation of the sympathetic nervous system is selectively impaired by neural blockade. Accordingly, the effects of high epidural anesthesia alone and combined with hypoxia were evaluated in seven awake trained dogs. On different days, either bupivacaine 0.5% (8–12 ml) or saline (placebo) were randomly injected epidurally and the effects evaluated on cardiovascular (arterial pressure, heart rate) and respiratory (blood gases, oxygen consumption) variables, as well as on hormone plasma concentrations (vasopressin, norepinephrine, epinephrine, renin) during both normoxia and hypoxia. During epidural anesthesia alone, vasopressin increased tenfold (1.7 pg/ml ± 1.0 SD to 16.8 ± 13.8, $P < 0.05$), norepinephrine decreased (90 pg/ml ± 31 to 61 ± 28, $P < 0.05$) while epinephrine and renin concentrations remained unchanged. Mean arterial and pulse pressure decreased by 13 mmHg and 23 mmHg ($P < 0.05$), respectively. In dogs without sympathetic blockade (saline group), hypoxemia (Pa_{O_2}: 31 ± 4 mmHg) evoked an increase in mean blood pressure by 37 mmHg ± 8 and heart rate by 50 beats per min ± 17. In contrast, in the presence of sympathetic blockade but with a similar degree of hypoxemia, blood pressure failed to increase (+1 mmHg ± 14) and heart rate rose by only 15 beats per min ± 11. These differences between groups were statistically significant ($P < 0.001$). Hypoxemia induced a similar hypocarbia (Pa_{CO_2}:25 mmHg) in both groups, indicating that the ventilatory response to hypoxemia was preserved after epidural blockade. During hypoxemia vasopressin concentrations increased 35-fold to 64 pg/ml ± 38 ($P < 0.0001$) compared to base line only during epidural anesthesia, but not after epidural saline (2 pg/ml ± 2), while other hormones showed no significant differences. The authors conclude that high epidural anesthesia in awake unsedated dogs: 1) almost completely abolishes the normal cardiovascular response to hypoxemia while promoting vasopressin secretion; 2) preserves the ventilatory response to hypoxemia; and 3) is associated with increased vasopressin concentrations, most likely to compensate for decreased cardiac filling and/or arterial blood pressure when sympathoadrenal responses are impaired. Thus, the changes in cardiovascular vital signs in response to severe hypoxemia are markedly blunted when spinal sympathetic outflow is selectively eliminated by epidural anesthesia. (Key words: Anesthetic techniques: epidural. Complications: hypoxemia. Hormones: vasopressin (ADH); catecholamines; Renin. Sympathetic nervous system: sympathectomy. Ventilation: hypoxemia, response.)

EXTENSIVE BLOCKADE of vasomotor and cardiac sympathetic efferents following high epidural and spinal anesthesia is usually associated with a surprisingly small decrease in arterial blood pressure in healthy supine humans.[1–5] This could relate to the release of vasoactive hormones such as renin or vasopressin when neural circulatory control is impaired, since recent experimental evidence indicates that hormonal support systems can contribute to circulatory stability under conditions such as pharmacological blockade of the autonomic nervous system,[6] hemorrhage,[7,8] or dehydration.[9]

However, it is not known how the circulation copes with challenges such as hypoxemia under conditions of sympathetic blockade during epidural anesthesia when activation of the efferent sympathetic system may no longer be possible. The answer to this question may have some bearing on the etiology of unexpected cardiac arrest during spinal anesthesia.[10] In these cases, cyanosis apparently preceeded cardiac arrest leading the authors to suggest unappreciated hypoxemia as a possible precipitating event.[10] This and evidence[11] that sympathetic blockade is more widespread in relation to the level of sensory block than hitherto assumed stimulated us to explore three questions: 1) Are hormonal support systems involved in the maintainance of arterial pressure during epidural blockade? 2) Does epidural anesthesia alter the normal cardiovascular response to hypoxic hypoxemia? and 3) Does hypoxemia during epidural anesthesia, *i.e.*, in the presence of diminished or absent sympathetic drive, invoke other hormonal systems for stabilizing blood pressure?

Accordingly, we evaluated the effects of high epidural anesthesia alone and combined with hypoxic hypoxemia in awake unsedated dogs. Epidural anesthesia almost completely abolished the physiological increases in blood pressure and heart rate in response to hypoxemia, and promoted vasopressin secretion during epidural anesthesia alone as well as during hypoxemia in the presence of sympathetic blockade.

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Methods

Twenty experiments were performed in seven trained mongrel dogs (weight: 21–25 kg) housed in the local animal care facility under supervision of veterinarians and treated according to the Guidelines by the American Physiological Society. The study was approved by the Governmental Animal Protection Commission. The effects of epidural anesthesia alone and combined with hypoxia on arterial pressure and heart rate as well as on vasopressin (ADH), norepinephrine, epinephrine, and renin plasma concentrations were evaluated and compared with those of epidural saline (placebo) in the same dogs studied on a different day. To avoid any time- or order-dependent bias, the experiments were performed in a randomized cross-over fashion with each dog serving as its own control. At least one day elapsed before a dog was studied again. The dogs, which were aquainted with the laboratory setting and had been trained to lie unrestrained in the lateral position on a cushioned table, had been repeatedly subjected to epidural anesthesia before.[12] For measuring of arterial blood pressure and blood sampling, six of the animals had one or both carotid arteries exteriorized in skin loops several months or years before the experiments.

Measurements

Electrocardiogram, heart rate (ECG triggered cardiotachometer), whole-body oxygen consumption ($\dot{V}O_2$), and arterial blood pressure (Statham 23 id transducer) were measured continuously, the latter through a catheter inserted percutaneously into a carotid loop (six dogs) or femoral artery (one dog). Central venous pressure was assessed (Statham 23 id) in four experiments in two dogs through a catheter introduced percutaneously from a limb vein and positioned close to the right atrium under fluoroscopy. Pressures were zeroed to atmospheric pressure and referenced to the level of the thoracic vertebral spinous processes. $\dot{V}O_2$ was measured with an open circuit flow-through technique as described previously.[13] Briefly, the dog's head and upper trunk remained under a transparent plastic hood through which a constant flow of ambient air was sucked with a precision pump, the dogs breathing freely from it. Room air entered the hood at the edges of the hood, whereas the expired gas/air mixture was removed at the top of the hood. $\dot{V}O_2$ (STPD) was then derived from the air flow and the O_2 difference (paramagnetic principle) between in- and out-flowing gas mixtures. The apparatus has a time constant of 30 s. The oxygen concentration under the hood was measured using a calibrated oxygen analyser (Oxydig, Dräger AG, Lübeck, West Germany).

Arterial blood samples were collected in chilled tubes, placed immediately in crushed ice, processed further within 10 min, and stored at −20° C until analysis. Sodium bisulfite was added to blood used for catecholamine assays to prevent degradation of catecholamines. Norepinephrine and epinephrine were extracted[14] from plasma (recovery > 95%) and their free concentrations measured using HPLC and electrochemical detection (Coulochem 5100 A, Biotronik). Sensitivity was 10 pg/ml plasma with an intra- and interassay variability of less than 10%. Arg^8-Vasopressin was measured in duplicate by radioimmunoassay (^{125}I vasopressin, Euro-Diagnostics) using rabbit anti-Vasopressin antiserum calibrated against the World Health Organization standard and with a sensitivity of 0.8 pg/ml. Cross reactivity with Lys^8-Vasopressin and Oxytocin was 0.1%. Renin activity was measured as generated angiotensin I ($ng \cdot ml^{-1} \cdot h^{-1}$) by radioimmunoassay (GammaCoat ^{125}I Plasma Renin Activity, Baxter, Cambridge, Massachusetts) at a *p*H of 6.0. Intra- and interassay varibility was less than 10%. Plasma bupivacaine concentrations were determined by gas chromatography as described previously.†† Arterial blood gases (Pa_{O_2}, Pa_{CO_2}) and pH_a were determined using standard electrodes (Radiometer, Kopenhagen) at 37° C.

Epidural Anesthesia

One to three days before an experiment, a radiopaque wire reinforced flexible tip epidural catheter was introduced through a 16 G Tuohy needle inserted percutaneously into the lumbar epidural space (usually between L_5 and L_6) under sterile conditions during anesthesia with methohexital (4 mg/kg iv). Under fluoroscopy the catheter was placed in the low thoracic or lumbar epidural space. The catheter was sutured to the skin and secured with plaster of Paris.

Experimental Protocol

The experiments were performed under basal metabolic conditions. The dogs were always studied in the morning in a dimmed laboratory after an overnight fast but with free access to water until 2 h before an experiment. Room temperature was kept between 23–25° C, which is the thermoneutral temperature range of dogs.[15] No drugs or fluids were given at any time unless stated specifically. After insertion of the various catheters and fluoroscopic confirmation of their proper epidural (tip: T8-L4) or central venous position, the dog's head and upper trunk was placed under the plastic hood to measure oxygen consumption and recordings commenced. Thereafter, to ensure a stable base line before measurements were taken, at least 45 min were allowed to elapse: the dogs were then either drowsy or sleeping.

†† Bongartz H: Pharmakokinetische Untersuchungen am Menschen mit dem Lokalanaesthetikum Bupivacain. Doctoral Thesis, University of Bonn, Cologne, 1979.

After a further control period of 15 min, either 8–12 ml bupivacaine 0.5% (n = 7) or an equal volume of normal saline (n = 7) stored at room temperature were injected into the epidural space over 2 min. The volume injected depended on the dogs' length, catheter position, and individual spread of nerve block as tested during previous studies.[12] This volume was sufficient to block most, if not all sympathetic outflow, as evidenced by paresis of the nictitating membrane of the eye which derives its sympathetic innervation from the most cranial part of the spinal sympathetic system, *i.e.*, the upper three thoracic segments.[16] In our previous studies, this volume of bupivacaine had increased both front and hind limb skin temperatures and abolished the baroreflex-mediated blood pressure increase to bilateral carotid artery clamping.[12] Analgesia, assessed by unresponsiveness to pin prick at the end of the experiments (*i.e.*, approximately 70 min after epidural injection), extended up to the first intercostal space. The hind limbs were paralysed, while front limb motor function appeared unimpaired. Most dogs changed their mode of inspiration from a thoracic to a diaphragmatic pattern of breathing indicating at least partial motor block of the intercostal musculature.

Data were recorded for 45 min after epidural injection of bupivacaine or saline, *i.e.*, for a time sufficient to allow full spread of epidural blockade.

Hypoxic Challenge

Hypoxemia was then induced over the course of 5–10 min and titrated to achieve an oxygen concentration of 7–10% under the hood by blowing nitrogen under the hood *via* four large-bore tubings and a rotameter. This concentration was maintained for 5 min, blood samples taken, and the nitrogen flow terminated. This resulted in a similar decrease in both groups in arterial oxygen partial pressures to 30–35 mmHg and respiratory alkalosis.

Blood Samples

Arterial blood samples for measurements of vasopressin, catecholamines, renin, blood gases, and pH_a were collected at specified time intervals before (base line), 45 min after epidural injection of bupivacaine or saline, and at the end of the hypoxic phase. A total of 45 ml of blood was collected for analysis during each experiment and replaced by equal volumes of saline.

Additional Experiments

Plasma bupivacaine concentrations were determined at specified time intervals in separate experiments in five conscious dogs after epidural injection of 10 ml bupivacaine 0.5%. In one dog, the effect of an intramuscular injection of 12 ml bupivacaine 0.5% on hormones, plasma bupivacaine concentrations, and the response to hypoxemia was studied in the absence of sympathetic blockade to exclude any effects secondary to elevated local anesthetic blood levels *per se*.

Data Evaluation

Data are reported as mean ± one standard deviation (SD). Two *a priori* null hypotheses were tested statistically: 1) There is no difference in effects 45 min after epidural injection, regardless of whether bupivacaine or saline are injected; and 2) Changes in variables induced by the hypoxic challenge are not altered by epidural anesthesia. Hypotheses were evaluated by analysis of variance for repeated measurements (ANOVA) followed by further analysis using Scheffe's test if indicated,[17] and by Student's two-tailed *t* test for paired samples. A null hypothesis was rejected and statistical significance assumed when $P < 0.05$.

Results

Effects of Epidural Anesthesia Alone

Epidural nerve block evoked a small decrease in arterial pressure, but a significant increase in plasma vasopressin concentrations. Concentrations of norepinephrine decreased significantly, while those of epinephrine and renin remained unchanged.

The time course of cardiovascular effects is shown in figure 1. From 15–45 min after epidural injection, mean arterial blood pressure was lower in the bupivacaine group reaching a mean of 85 mmHg *versus* 98 mmHg in the saline group 45 min after epidural injection. This represented a small but statistically significant 14% decrease in mean arterial blood pressure with epidural anesthesia both relative to base line and to the saline group. Differences in absolute pressures between groups, however, could not be detected by Scheffe's test following a significant ($P = 0.038$) ANOVA. Heart rate decreased over time from a base line of 65 to 58 beats per min 45 min after epidural saline, but increased from 71 to 76 beats per min in the bupivacaine group. These differences were statistically significant. Pulse pressure, an estimate of stroke volume, significantly fell by 23 mmHg after epidural nerve block. Central venous pressure in two dogs decreased from 3 mmHg to −1 mmHg. Whole-body oxygen consumption (4.3 *vs.* 4.6 $ml \cdot kg^{-1} \cdot min^{-1}$), Pa_{O_2} (93 *vs.* 90 mmHg), Pa_{CO_2} (35 *vs.* 34 mmHg), and pH_a (7.37 *vs.* 7.38) did not differ between groups before or after epidural injections and remained within the normal range.

Hormone concentrations are shown in figure 2. In every dog, vasopressin increased after epidural injection of bupivacaine. On the average, vasopressin concentrations increased tenfold from 1.7 to 16.8 pg/ml (range: 3.3–

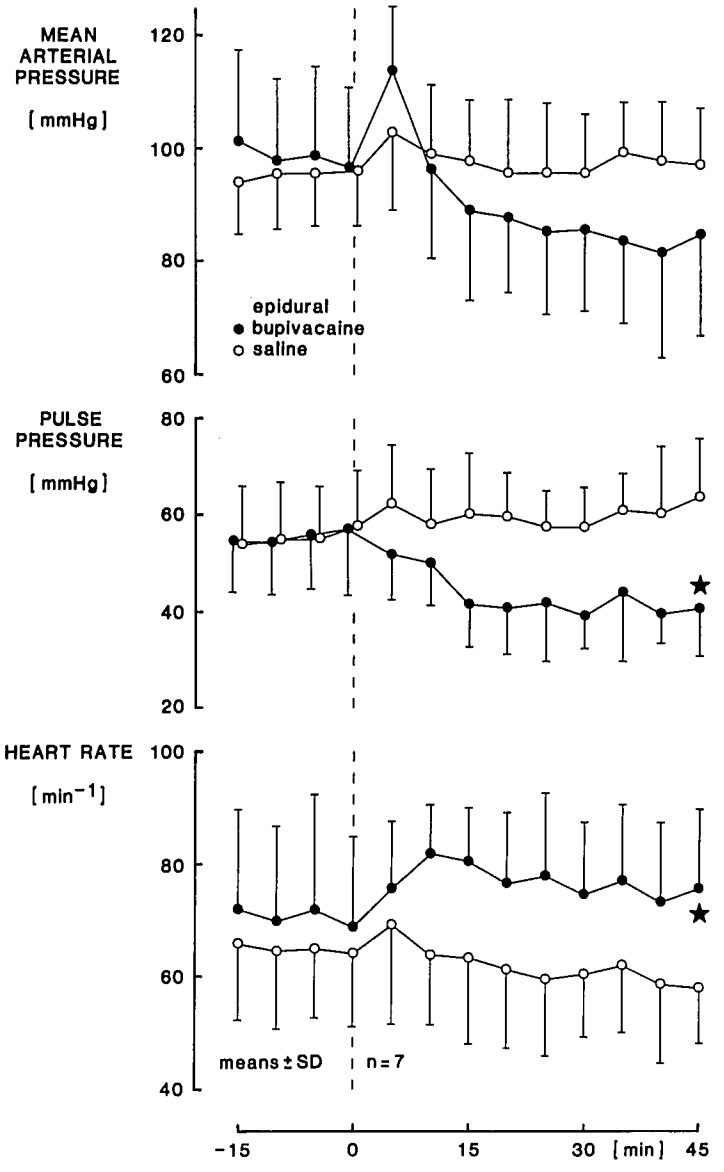

FIG. 1. Time course of cardiovascular changes after epidural injection of either epidural bupivacaine 0.5% (full symbols) or epidural saline (control group, open symbols) in seven awake unsedated dogs. Data represent mean ± SD. Time of epidural injection is indicated by the vertical stippled line. Arterial blood pressure (upper panel) and pulse pressure (middle panel) decreased after epidural anesthesia, while heart rate showed a small but significant increase. Although mean arterial pressure decreased significantly after epidural bupivacaine relative to base line and to the saline group, differences in absolute pressures between groups could not be detected following detection of a significant difference by ANOVA (*$P < 0.05$, ANOVA followed by Scheffe's test).

40.8) after epidural anesthesia, but not after epidural saline (1.2 *vs.* 1.5 pg/ml). Norepinephrine concentrations decreased significantly from 89–61 pg/ml during epidural anesthesia compared with saline, while epinephrine and renin concentrations remained unchanged.

Epidural Blockade and the Cardiovascular and Hormonal Response to Hypoxemia

Sympathetic blockade by epidural anesthesia almost completely abolished the physiological cardiovascular response to hypoxemia, *i.e.*, the increase in blood pressure and heart rate. An original recording is shown in figure 3. The blood pressure and heart rate responses from all experiments are shown in figure 4. With innervation intact (epidural saline), hypoxemia evoked an average increase in mean arterial blood pressure of 37 mmHg and in heart rate of 50 beats per min. In contrast, changes in arterial blood pressure and heart rate were attenuated markedly in each dog after sympathetic blockade. Mean arterial pressure did not increased while heart rate increased by only 15 beats per min. These differences between experimental groups were highly significant. Thus, epidural anesthesia abolished completely the pressure response, and attenuated by 70% the heart rate response to hypoxemia.

In the presence of sympathetic nerve block, hypoxemia evoked a further significant increase (35-fold relative to

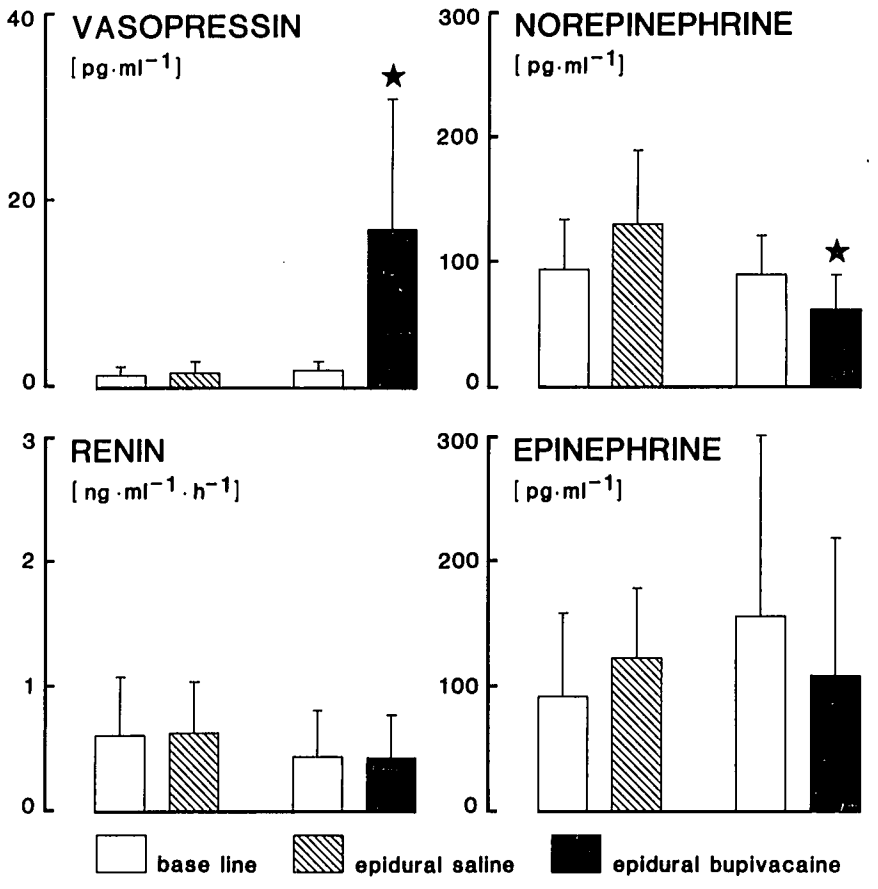

FIG. 2. Hormone concentrations at base line and 45 min after epidural injection of either saline or bupivacaine 0.5%. Data represent mean ± SD from six awake unsedated dogs. With sympathetic blockade by epidural anesthesia vasopressin concentrations increased tenfold, while norepinephrine concentrations decreased by 20%. There was no detectable change in epinephrine or plasma renin levels (*$P < 0.05$, ANOVA followed by Scheffe's test).

base line) in vasopressin concentrations to 63.8 pg/ml, but vasopressin levels remained unchanged (1.8 pg/ml ± 1.6) following hypoxemia in the epidural saline group (fig. 5). Plasma norepinephrine and epinephrine (fig. 5) tended to increase slightly with hypoxemia but there was no statistical difference whether epidural bupivacaine or saline had been injected. Nevertheless, in all but one experiment the increment in norepinephrine was less with hypoxemia after epidural blockade. Epinephrine and renin did not appreciably change with hypoxemia in either group.

Epidural blockade did not alter the animals ability to increase their alveolar ventilation in response to hypoxemia as evidenced by equal hypocapnia in the epidural bupivacaine (Pa_{CO_2}: 25 mmHg ± 5) and saline (Pa_{CO_2}: 25 mmHg ± 4) groups. Arterial hypoxemia was not significantly different between groups (35 mmHg ± 4 *vs.* 31 ± 4).

ADDITIONAL EXPERIMENTS

Bupivacaine concentrations (fig. 6) in five dogs were generally low, peaked at 0.74 μg/ml ± 0.2 shortly after epidural injection, and declined to 0.25 μg/ml ± 0.08 by 60 min postinjection. With intramuscular injection of 12 ml of bupivacaine 0.5%, bupivacaine was 0.46 μg/ml 45 min postinjection. Similar to the epidural saline group, mean arterial blood pressure increased by 45 mmHg and heart rate by 40 beats per min during hypoxemia while vasopressin concentrations remained unchanged at 0.9 pg/ml throughout the experiment. Plasma bupivacaine was 0.9 μg/ml at the time of hypoxemia.

Discussion

Epidural anesthesia abolished almost completely the physiological cardiovascular response to severe hypoxemia, while the ventilatory response was preserved. Epidural blockade was also accompanied by an increase in the vasopressin plasma concentration with an additional increase observed during hypoxemia, but only in the presence of sympathetic blockade.

These results emerged when sympathetic efferents were largely, if not completely, eliminated by epidural anesthesia (see Methods section). The abolition of sympathoadrenal outflow is also indicated by the 20% decrease in plasma norepinephrine concentrations after epidural anesthesia. If some residual sympathetic outflow had remained or reappeared during the experiments, our findings would even underestimate the role of sympathetic blockade in blunting the response to hypoxia.

Confounding influences on hormone release or the re-

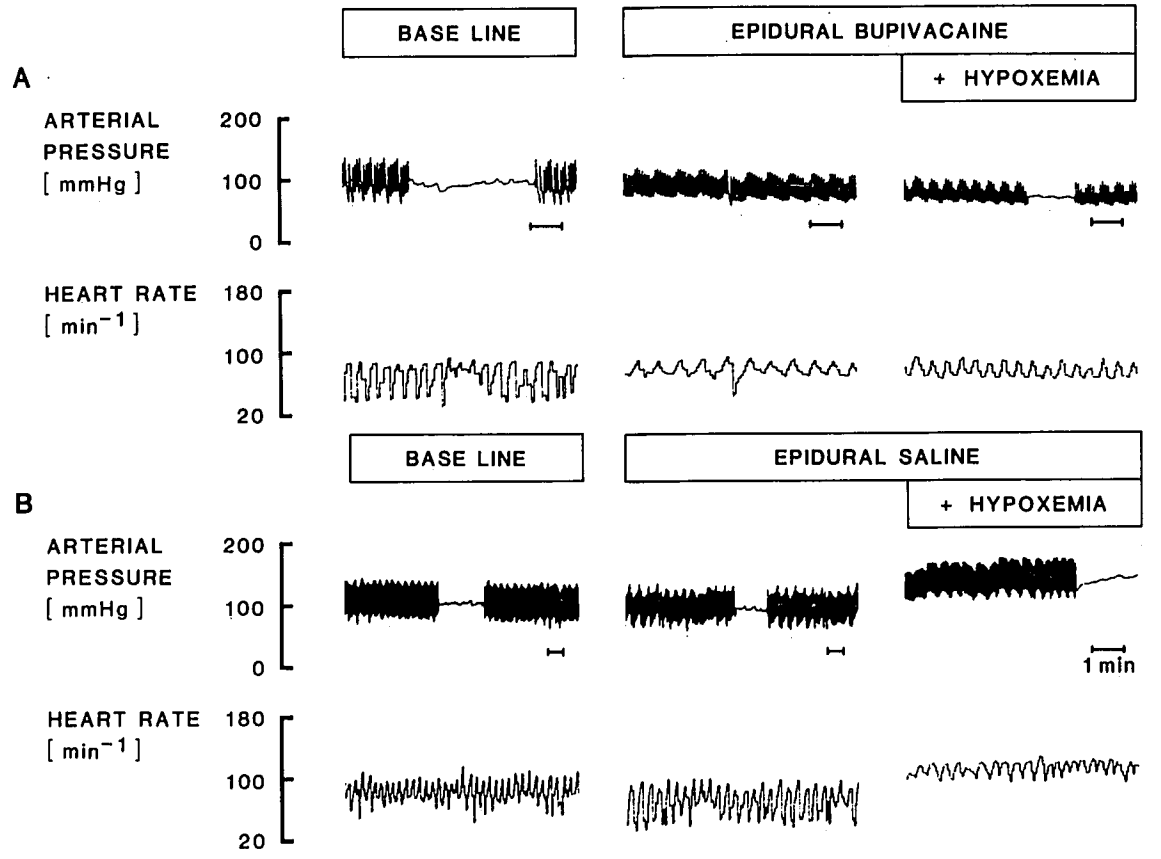

FIG. 3. Effects of epidural anesthesia alone and in combination with hypoxemia on arterial blood pressure and (beat-to-beat) heart rate (panel A) in an awake unsedated dog. Changes are contrasted with the response in the intact innervated state after injection of epidural saline in the same dog (panel B). Original recordings, representing the states at base line (left), 45 min after epidural injection of either bupivacaine or saline (middle), and during additional hypoxemia (right). Mean arterial blood pressure is obtained and shown for each state by briefly activating an electrical filter. With epidural blockade alone arterial blood pressure is slightly decreased, while heart rate increased. During hypoxemia in the presence of sympathetic blockade by epidural nerve block the normal marked increase in arterial blood pressure and tachycardia is no longer seen. In fact, in this dog, pressure decreased slightly with hypoxemia in the denervated state.

sponse to hypoxia, such as anesthetics, mechanical ventilation, surgery, ambient temperature, fluid balance, or drug interventions were either excluded or kept constant.[18–23] Before epidural anesthesia, concentrations of catecholamines and also of vasopressin and renin were in the normal range for awake normally hydrated dogs.[22,24] Finally, the low base line values of blood pressure, heart rate, and $\dot{V}O_2$, the latter corresponding to the basal metabolic rate,[13] are evidence that the animals were calm and accustomed to the experiments.

We infer that the described effects result from the blockade of efferent sympathetic drive rather than the presence of bupivacaine in the blood. Several arguments support the former alternative. First, bupivacaine plasma concentrations after epidural injection of 10 ml bupivacaine 0.5% were rather low, reaching values of only 0.25 μg/ml by 60 min postinjection. These concentrations are lower than those observed after epidural anesthesia in humans[3,25] and are believed to exert no appreciable cardiovascular effects when achieved by intravenous infusion.[26] Second, intramuscular injection of 12 ml bupivacaine 0.5% in one dog, similar to epidural saline, failed to influence either vasopressin levels or the cardiorespiratory response to hypoxia, despite a plasma bupivacaine concentration fourfold higher than after epidural administration. Third, increased bupivacaine concentrations cannot explain the additional increase in vasopressin due to hypoxemia, since by that time bupivacaine concentrations had fallen. Our findings, therefore, most likely represent the effects of sympathetic blockade alone.

Epidural Anesthesia and Vasoactive Hormones

In spite of the blockade of most, if not all sympathetic efferents, blood pressure decreased surprisingly little. This is not simply a matter of species differences. In healthy supine humans, blood pressure is usually well maintained when, during epidural or spinal anesthesia reaching the upper thoracic dermatomes, sympatholysis is almost com-

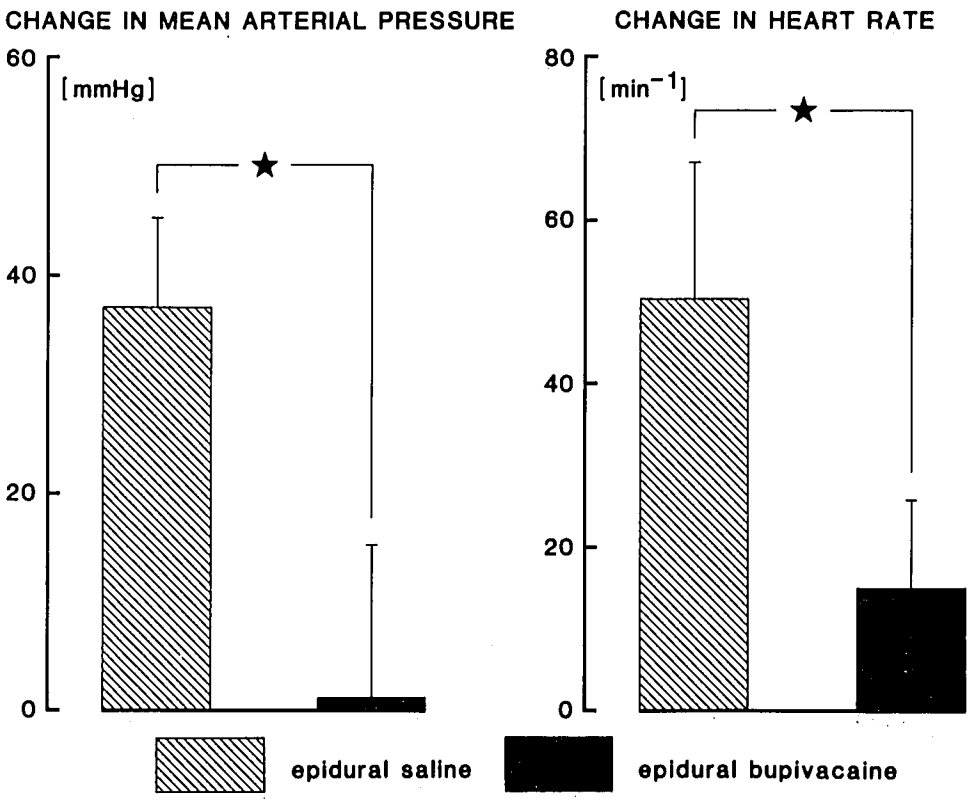

FIG. 4. Cardiovascular response to hypoxemia during either epidural nerve block (full columns) induced by epidural bupivacaine or with epidural saline (striped columns) in seven awake unsedated dogs. Data represent average changes (±SD) induced by hypoxemia relative to the values obtained after fully established nerve block but before hypoxemia, *i.e.*, 45 min after epidural bupivacaine and saline, respectively. The increase in arterial blood pressure evoked by hypoxemia is completely abolished after epidural blockade with bupivacaine, while the rise in heart rate is markedly attenuated (*$P < 0.05$).

plete.[1-5] The impaired adrenergic vasomotor control is also reflected by the decrease in norepinephrine concentrations in our experiments much like those in humans after spinal or epidural anesthesia.[27,28] This raises the question whether hormonal systems such as the renin/angiotensin and/or vasopressin system can partially compensate for the loss of neurogenic vasomotor control and so maintain arterial blood pressure. In our experiments, vasopressin concentrations increased, but renin activity did not change. Since vasopressin is a potent vasoconstrictor even at physiological concentrations, the tenfold greater vasopressin concentrations observed during epidural anesthesia are certainly vasoactive.[29,30]

We do not know with certainty what stimulus caused vasopressin release in our experiments. The decrease in both arterial and central venous pressure could have reflexly triggered vasopressin release *via* arterial baroreceptors[31] and/or cardiopulmonary stretch receptors.[7,32] In fact, the drive for vasopressin secretion appears to be mediated almost entirely *via* cardiac stretch receptors in awake dogs[7] and rabbits.[8] This is an important link to the consequences of epidural anesthesia for cardiac filling since the cardiopulmonary blood volume decreases during epidural anesthesia in humans,[33] due to blood pooling in the denervated body regions. Vasopressin concentrations also increased markedly during application of lower body negative pressure in humans.[34] Moreover, during epidural anesthesia in elderly men with a sensory block between T4 and T10, vasopressin concentrations increased, albeit not statistically significant,[27] possibly because of incomplete sympathetic block. However, vasopressin but not renin concentrations did increase significantly, when the circulation was stressed by an upright tilt of the subjects. Regardless of the mechanisms involved, the principle stimulus for the increase in vasopressin concentrations is the loss of efferent sympathetic tone evoked by epidural anesthesia. Similar to our observations, vasopressin concentrations increased after hemorrhage in anesthetized nephrectomized dogs with spinal cord destruction and evidently supported arterial pressure since severe hypo-

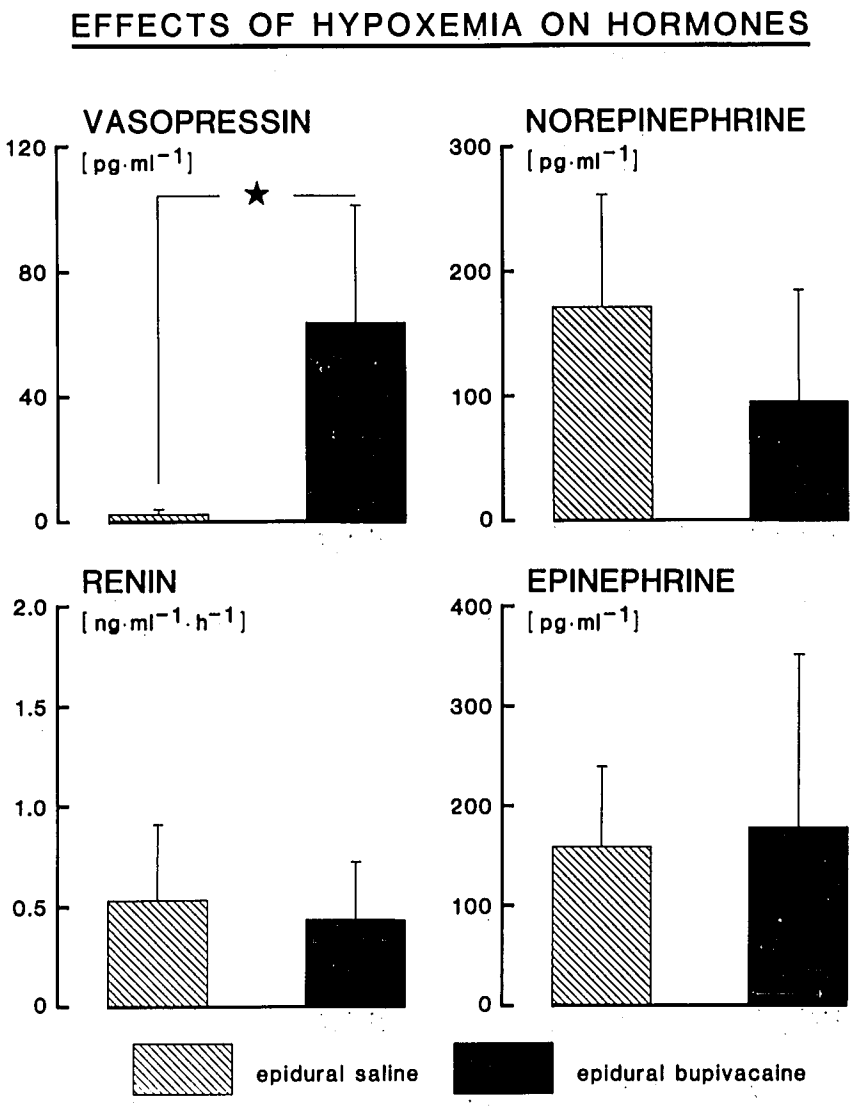

FIG. 5. Hormonal response to hypoxemia during either epidural nerve block induced by epidural bupivacaine (full columns) or epidural saline (striped columns) in six awake unsedated dogs. Data represent average concentrations ± SD during hypoxemia. Hypoxemia resulted in a significant increase in vasopressin concentrations only when combined with epidural nerve block, but not with innervation intact (saline group). No significant differences in catecholamines and renin between groups were found (*$P < 0.05$).

tension occurred only after vasopressin receptor blockade.[35] Together these findings suggest that endogenous vasopressin can support blood pressure when neurogenic vasomotor control is abolished by the blockade of spinal sympathetic outflow during epidural anesthesia.

The predominant role of vasopressin in the face of unchanged renin is probably a unique feature of blockade of sympathetic efferents which *via* renal β_1 receptors[36] can stimulate renin secretion. That renin activity increased during epidural anesthesia in anesthetized ventilated dogs[37] seems to be at odds with our observations. However, in these experiments arterial hypotension was rather severe (halving of mean blood pressure to ~60 mmHg), so that renin release probably resulted from the fall in renal perfusion pressure independent of sympathetic drive.[38] Thus, although the renin system may be invoked by hypotension in both dogs and humans, our results show that it fails to respond to sympathectomy *per se* as long as blood pressure remains above the renal autoregulatory range.

EPIDURAL ANESTHESIA AND THE RESPONSE TO HYPOXIA

Despite severe hypoxemia, epidural anesthesia almost completely abolished tachycardia and hypertension, most likely by preventing efferent sympathetic activity from reaching the target organs. In both dogs[39] and humans[40] hypoxemia is known to increase markedly efferent sympathetic nerve activity. Although it is thought that peripheral chemoreceptors reflexly mediate this activation of the sympathetic system, perfusion with desaturated blood of the brain itself may also contribute.[41] Tachycardia and hypertension are the typical physiological responses to hypoxemia in conscious dogs,[42,43] with the pressure increase somewhat less pronounced in hu-

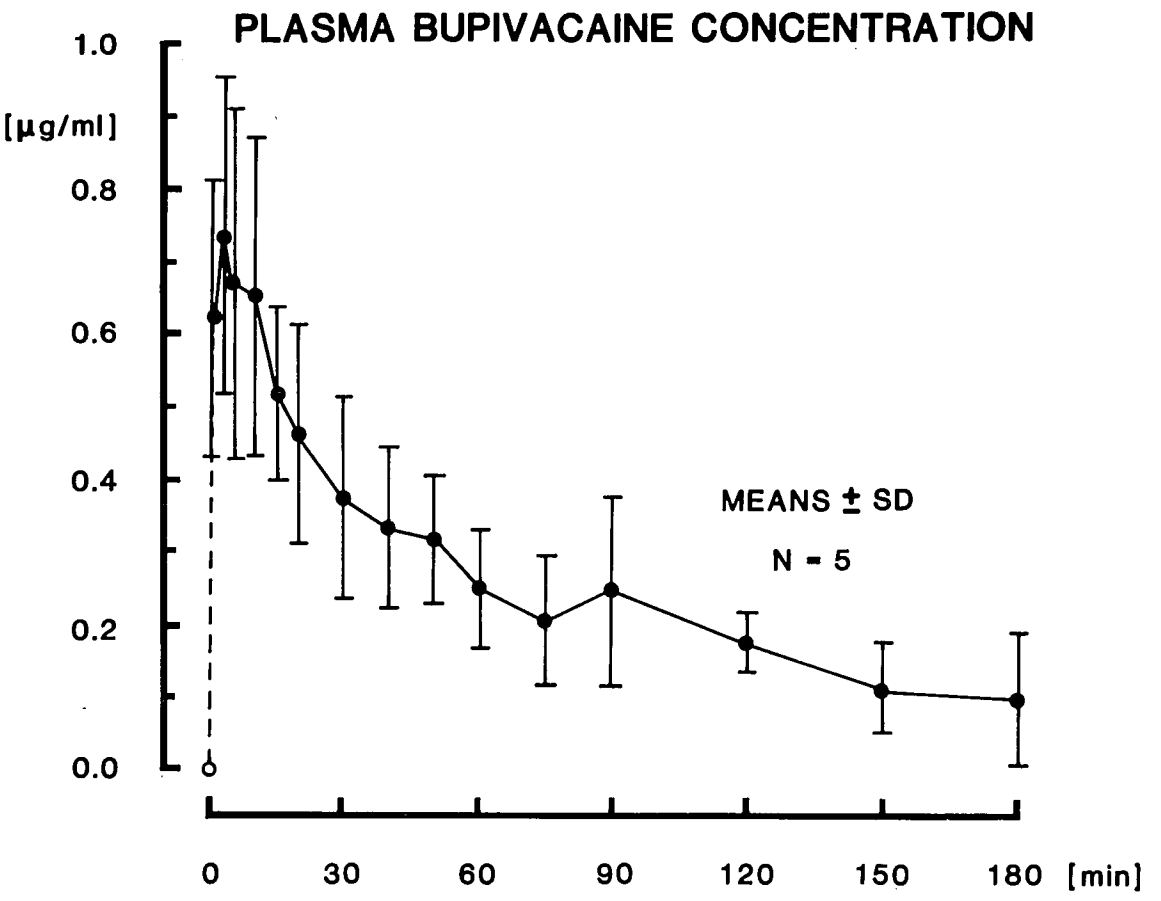

FIG. 6. Time course of plasma bupivacaine concentrations after epidural injection of 10 ml bupivacaine 0.5% in five conscious dogs. Averages ± SD. Concentrations peaked within 5 min postinjection and rapidly declined over time. At 50–60 min postinjection, *i.e.*, at the time when hypoxemia was induced in the main experimental series, concentrations had fallen to a mean around 0.3 µg/ml.

mans.[40,42] The small increase in heart rate persisting in response to hypoxemia after epidural anesthesia was presumably caused by withdrawal of efferent cardiac vagal tone, which appears more tonically active in resting dogs[44] than in humans.

Epidural anesthesia not only prevented blood pressure and, to a large extent, also heart rate from increasing in response to hypoxemia, but was also associated with a further increase in plasma vasopressin relative to epidural anesthesia alone and even a 35-fold rise relative to base line or to the intact dogs (saline group). Vasopressin concentrations of this magnitude are very high and correspond, for example, to those seen after a loss of more than 35% of blood volume.[8] In all likelihood, therefore, vasopressin also supported blood pressure when, in addition to the loss of efferent sympathetic drive, hypoxemia caused a further stress on the circulation. Neither the vasopressin nor the renin/angiotensin system was brought into play in the dogs with intact innervation, so that here an enhanced sympathetic tone was probably responsible for the increase in blood pressure and heart rate. That this was not reflected in plasma catecholamines is not too surprising because hypoxemia has been shown to change sympathetic spike traffic, the neurophysiologic correlate of sympathetic tone, in a nonuniform fashion, *i.e.*, an increase to the splanchnic region but at the same time a decrease to the skin.[45] Also in humans, plasma norepinephrine concentrations failed to rise when during hypoxemia efferent sympathetic activity in the peroneal nerve increased.[40] Since the dogs in the denervated and innervated state were equally hypoxemic, and because of hyperventilation, also equally hypocarbic, the mechanism that evoked vasopressin release during hypoxemia is probably related to epidural anesthesia rather than respiration or hypoxemia alone. Even prolonged hypoxemia does not trigger an important rise in vasopressin concentrations in either awake intact[46] or anesthetized spontaneously breathing dogs,[47] but it does so in anesthetized mechanically ventilated dogs,[48] provided their carotid sinus and vagi nerves are intact. In fact, only when the vagi nerves, which carry afferent information from cardiopulmonary receptors, were sectioned in addition to carotid sinus nerves, could vasopressin release be prevented in the latter experiments. Again, this finding ar-

gues for a causal link between cardiac filling and vasopressin. Thus, decreased cardiac filling may be the principle stimulus for vasopressin release both during epidural anesthesia alone and in combination with hypoxemia. However, we could not find direct evidence in the literature as to how hypoxemia influences cardiac filling in the presence or absence of neurogenic control. Nevertheless, it is noteworthy that hypoxemia attenuates markedly the increase in forearm vascular resistance evoked by lower body negative pressure in man.[49] Also, chemoreceptor stimulation by hypoxic blood can dilate canine cutaneous veins.[50] Thus, as the heart is already depleted of blood during epidural anesthesia,[33] adding hypoxemia could, in the presence of sympathetic blockade, lead to unopposed metabolic peripheral vasodilation, and a further fall in cardiac filling when active mobilization of blood by sympathetic vasoconstriction is no longer possible. That hypoxemia in the presence of an intact sympathetic system can *via* an increase in regional sympathetic discharge result rapidly in a substantial mobilization of blood from the splanchnic vascular bed has been shown.[39] Regardless of the specific mechanisms involved, our observations demonstrate that dogs can maintain blood pressure during severe hypoxemia even in the absence of efferent sympathetic cardiovascular control, most likely due to vasopressin release.

Possible Relation of Results to Cardiac Arrest during Spinal Anesthesia in Humans

Our experiments were designed primarily to evaluate the role of hormonal support systems and the response to hypoxemia in the presence or absence of sympathetic vasomotor control in dogs. Although humans could react in a different manner to epidural blockade and/or hypoxemia than dogs, it is nevertheless tempting to speculate on the potential implications in relation to the recently described[10] cases of unexpected cardiac arrest during spinal anesthesia in healthy subjects. Since cyanosis appeared to be the first clue of impending cardiac arrest in half of the patients, the authors speculated that "respiratory changes produced by sedation may have played an important role."

Our results would fit this scenario by showing that in dogs, epidural anesthesia, even in the absence of sedation, severely blunts the cardiovascular response to hypoxemia. To our knowledge, this potential hazard has not attracted attention. Thus, if hypoxemia did occur in these cases, regional anesthesia may have obscured changes in cardiovascular vital signs. However, although the attenuation of changes in vital signs during sympathetic blockade associated with unappreciated hypoxemia is an attractive explanation, our results also demonstrate that, when during extensive sympathetic blockade severe hypoxemia occurred, arterial blood pressure was maintained. Also, despite widespread blockade, the ventilatory response to hypoxemia was well preserved. Thus, if the cardiac arrests described by Caplan *et al.*[10] were secondary to respiratory compromise, it appears that additional factors, possibly direct drug action or hypercarbia have played a role. Nonetheless, it is still difficult to invoke detrimental changes in respiration as a cause of cardiac arrest in those patients receiving either no sedation or supplemental oxygen. In a previous study[33] in volunteers, we evaluated blood volume distribution during epidural anesthesia. Among the subjects were two with syncope and near syncope, who showed a simultaneous marked increase in splanchnic blood volume at the expense of the heart. This argues strongly for a primary deficit in cardiac filling. Our present study supports this view by showing marked and hemodynamically relevant increases in vasopressin concentrations, the release of which is intimately linked to cardiac filling.

In summary, our results show that high epidural anesthesia in awake unsedated dogs: 1) almost completely abolishes the normal cardiovascular response to hypoxemia while promoting vasopressin secretion; 2) preserves the ventilatory response to hypoxemia; and 3) is associated with increased vasopressin concentrations, most likely to compensate for decreased cardiac filling and/or arterial pressure when sympathoadrenal responses are selectively eliminated. Thus, the changes in cardiovascular vital signs in response to severe hypoxemia are blunted markedly when spinal sympathetic outflow is impaired by epidural anesthesia.

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