Endogenous Vasopressin and Renin-Angiotensin Systems Support Blood Pressure after Epidural Block in Humans

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Background: Studies in experimental animals show that endogenous Arg-vasopressin (AVP) and the renin–angiotensin system support blood pressure when the sympathetic system is impaired pharmacologically or after epidural anesthesia. However, extrapolation to humans is uncertain. Therefore, we administered an AVP type V1 receptor antagonist and an angiotensin-converting enzyme inhibitor to volunteers and measured the effect on blood pressure after epidural anesthesia.

Methods: Healthy volunteers in whom epidural catheters were placed were randomly assigned to receive 1.25 mg intravenous enalapril or saline placebo followed by 0.5 mg AVP type V1 antagonist/β-mercapto-β-cyclopentamethylene-proprionyl-o-Met-Tyr-Arg-vasopressin (AVPA) or saline placebo. Finally, 2% lidocaine was injected to obtain a T2 level. Controls received intramuscular lidocaine.

Results: Blood pressure did not significantly change after T2 epidural anesthesia in subjects treated with saline placebo, AVPA or enalapril alone (n = 10, for each treatment). In contrast, combined treatment with enalapril and AVPA resulted in a 36 ± 11% decrease in blood pressure after epidural dosing (n = 6). Controls given intramuscular lidocaine, in place of the epidural did not develop hypotension after AVPA and enalapril treatment (n = 10).

Conclusions: Endogenous AVP and the renin–angiotensin system play important roles in maintaining blood pressure after epidural anesthesia in healthy subjects. (Key words: Anesthetic techniques: epidural. Blood pressure: Hormones: renin; vasopressin.)

HIGH-RISK obstetric and vascular surgical patients may be particularly sensitive to the hypotensive effects of epidural anesthesia.1 In contrast, epidural anesthesia rarely produces hypotension in healthy, nonpregnant subjects.2,3 Understanding the role that endogenous vasopressors play in maintaining blood pressure after epidural anesthesia in healthy, nonpregnant subjects may help us understand why certain high-risk patients become hypotensive when this anesthetic technique is used.

Blood pressure is maintained by the combined effects of three major neurohumoral vasopressor systems: the sympathetic nervous system, the renin–angiotensin system (RAS), and the Arg-vasopressin (AVP) system.1–6 Under conditions in which the sympathetic nervous system is impaired, the RAS and the AVP system assume more important roles in maintaining blood pressure.1–6

Experimentally, the roles of the RAS and AVP in maintaining blood pressure can be studied by administering specific antagonists of these vasopressor systems and measuring the resultant effect on blood pressure. Two such antagonists are enalapril, an angiotensin-converting enzyme inhibitor, which decreases production of the potent vasoconstrictor angiotensin II,7,8 and β-mercapto-β-cyclopentamethylene-proprionyl-o-Met-Tyr-Arg-Vasopressin (AVPA), a specific competitive antagonist of the vascular AVP type V1 receptor.9 Activation of the V1 receptor is responsible for the vasopressor effects of AVP.5,10 In fact, experiments in animals using these antagonists demonstrate that AVP and/or the RAS play important roles in maintaining blood pressure after pharmacologic ganglionic blockade,5 spinal cord transection,6 and epidural anesthesia.11 However, extrap-
olation of these results to humans cannot be made with certainty.

Therefore, we administered AVPA and enalapril to healthy volunteers and measured the effects on blood pressure after epidural anesthesia. Knowledge of the magnitude of the change in blood pressure after administration of the antagonists should aid in establishing the relative contribution that AVP and the RAS play in supporting blood pressure after epidural anesthesia in humans.

Materials and Methods

The study was approved by the Committee on Human Research at the Oregon Health Sciences University, and informed consent was obtained from all subjects. The subjects were healthy volunteers solicited by public advertisement at our medical center. Subjects who had a history of alcohol or drug abuse or of cardiovascular, pulmonary, renal, or endocrine disease; who weighed more than 100 kg or were shorter than 152 cm; who were pregnant; or who were taking any medications were excluded from the study. The subject group is described in table 1.

Upon arrival in the anesthesia clinical research area, after an overnight fast, the subjects were placed supine on a well-padded hospital bed, and a 14-G peripheral venous catheter was placed after administration of local anesthesia. Next, the subjects in the epidural study groups were turned to the lateral decubitus position, and with local anesthesia, a 17-G Tuohy-Weiss needle was inserted into the epidural space via a midline approach at the L2 or L3 interspace by the loss of resistance to air technique. An 18-G catheter was then inserted 3–4 cm into the epidural space and secured with tape. In subjects in the intramuscular catheter groups, a 22-G butterfly-type needle was inserted intramuscularly into the right upper gluteal region after administration of local anesthesia. This catheter was secured with tape and was used for the subsequent administration of intramuscular lidocaine. After epidural or intramuscular catheter insertion, the patients were placed in the supine position for the remainder of the study.

Next, monitoring devices and face-mask oxygen were applied to the subjects. The ECG, heart rate, and oxygen saturation were measured continuously during the study. Throughout the study blood pressure was measured every 3 min by an automated monitor (Dinamap Vital Signs Monitor 1846 SX, Critikon, Tampa, FL). Changes in mean blood pressure greater than 10% compared to the mean of the baseline readings were always confirmed by two additional readings taken 1 min apart. The level of sensory analgesia was determined by pin prick and loss of cold sensation and was tested bilaterally every 5 min after epidural or intramuscular catheter dosing. When there was a difference between sides, the most caudal level was used.

After catheters and monitors were positioned the subjects were permitted to rest, undisturbed, for 30

### Table 1. Description of Healthy Volunteer Study Groups, Epidural Block, and Lidocaine Levels*

<table>
<thead>
<tr>
<th>Study Group†</th>
<th>Saline Placebo + Epidural</th>
<th>AVPA + Epidural</th>
<th>ENAL + AVPA + Epidural</th>
<th>Saline Placebo + IM LIDO</th>
<th>AVPA + IM LIDO</th>
<th>ENAL + IM LIDO</th>
<th>ENAL + AVPA + IM LIDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29 ± 8</td>
<td>30 ± 6</td>
<td>32 ± 8</td>
<td>29 ± 7</td>
<td>31 ± 6</td>
<td>33 ± 6</td>
<td>26 ± 9</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>7/3</td>
<td>7/3</td>
<td>7/3</td>
<td>4/2</td>
<td>7/3</td>
<td>7/3</td>
<td>7/3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 9</td>
<td>68 ± 10</td>
<td>70 ± 13</td>
<td>73 ± 17</td>
<td>72 ± 18</td>
<td>63 ± 9</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 ± 3</td>
<td>172 ± 3</td>
<td>174 ± 5</td>
<td>179 ± 5</td>
<td>173 ± 6</td>
<td>171 ± 5</td>
<td>173 ± 4</td>
</tr>
<tr>
<td>Preliminary (L)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Epidural LIDO (mg)</td>
<td>530 ± 94</td>
<td>532 ± 90</td>
<td>504 ± 72</td>
<td>492 ± 82</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IM LIDO (mg)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>545</td>
<td>545</td>
<td>545</td>
</tr>
<tr>
<td>Plasma LIDO (µg/ml)</td>
<td>2.2 ± 0.3</td>
<td>2.4 ± 0.4</td>
<td>1.9 ± 0.3</td>
<td>2.0 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>2.1 ± 0.5</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>Maximal block height</td>
<td>T2</td>
<td>T2</td>
<td>T2</td>
<td>T2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Time to T4 block (min)</td>
<td>28 ± 10</td>
<td>28 ± 13</td>
<td>22 ± 7</td>
<td>24 ± 7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NPO (h)</td>
<td>9.8 ± 1.2</td>
<td>9.9 ± 1.5</td>
<td>10.8 ± 2.1</td>
<td>8.9 ± 1.1</td>
<td>10.1 ± 1.6</td>
<td>10.0 ± 2.0</td>
<td>9.1 ± 1.8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39 ± 5</td>
<td>42 ± 4</td>
<td>41 ± 5</td>
<td>42 ± 3</td>
<td>43 ± 3</td>
<td>39 ± 4</td>
<td>39 ± 3</td>
</tr>
</tbody>
</table>

All data are mean ± SD. AVPA: arginine vasopressin antagonist; ENAL: Enalaprilat; IM: Intramuscular; EPID: epidural block; NA: not applicable.

* Thoracic dermatome sensory level to cold following epidural dosing. IM lidocaine did not produce a sensory block.
† See Methods for a description of the sequence of drug administration and the doses administered.

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min before beginning the study period. During this rest period the subjects received 1000 ml 0.9% saline, after which the intravenous infusion was maintained at a 50 ml/h. Hemodynamic values recorded during the “rest” period were not included in the study analysis. The remainder of the study was divided into four periods totaling 150 min: (1) 30 min, baseline; (2) 30 min, antagonist or placebo administration; (3) 30 min, epidural or intramuscular catheter dosing; and (4) 60 min postepidural or postintramuscular dosing monitoring.

During the first period, baseline hemodynamic values were recorded for 30 min, after which the subjects were randomly assigned to one of four epidural or four intramuscular lidocaine study groups by opening sealed envelopes containing the group assignments (table 1), previously placed in random order.

Next, subjects received 1.25 mg intravenous enalapril (Enalaprilat, Merck, Sharpe and Dohme, West Point, PA) contained in 10 ml saline or received 10 ml saline alone. After 15 min, the subjects received 0.5 mg intravenous AVPA dissolved in 10 ml saline or received 10 ml saline alone. AVPA was supplied as a lyophilized powder by H. Gavris, Boston University School of Medicine (IND 21862). AVPA, enalapril, and saline were each administered intravenously over 2 min. The investigators performing the study procedures and the subjects were blinded to the identity of the antagonist drugs administered. After an additional 15 min of monitoring, the 30-min drug administration interval was completed.

Epidural or intramuscular catheter dosing with lidocaine was performed over the next 30-min period. Epidural or intramuscular injection was begun with aspiration of the catheter for blood or spinal fluid, after which a 3-ml test dose of 1.5% lidocaine containing epinephrine 1:200,000 was given. In the absence of signs of intrathecal or intravenous injection after 5 min of observation, the epidural or intramuscular catheters were dosed with lidocaine.

In the epidural groups, 2% lidocaine (plain) was injected in 5-ml increments (over 30 s) every 2 min for an initial dose of 20 ml. After 20 min an additional 5 or 10 ml lidocaine was injected when the sensory level was below T4 or T6, respectively. Only patients in the epidural groups with at least a T4 sensory level at the end of the 30-min epidural or intramuscular catheter dosing period were included in the study. No intravascular or intrathecal catheters were detected. One subject was excluded from the study because of inadequate block, and one subject withdrew from the study before epidural dosing. Data from these subjects are not included in table 1.

In the intramuscular catheter groups, 10% lidocaine was used to administer lidocaine in a total volume compatible with intramuscular injection. Five minutes after injection of a test dose injection (vda supr), 10% lidocaine (plain) was injected intramuscularly in 1-ml increments (over 30 s) every 2 min for a dose of 4 ml. After 20 min, an additional 1 ml 10% lidocaine was injected for a total of 5 ml.

Thirty minutes after the initial injection the epidural or intramuscular catheter dosing period was over, and the vital signs were monitored for an additional 60 min, after which the study was completed. Any decrease in mean blood pressure greater than 20% compared to baseline was treated with 5–10 mg intravenous ephedrine every 3 min and 500 ml intravenous 0.9% saline administered as a bolus every 5 min.

Although the physicians performing the study procedures were blinded to the group assignments, the study was monitored by the principal investigator and by a physician-monitor not directly involved with the study. The records of all subjects were reviewed periodically by the principal investigator to identify complications and to ensure adherence to the study protocol. In addition, the records of all subjects requiring treatment for hypotension were reviewed by the monitor before additional subjects were enrolled. As an additional safeguard, a prospective decision was made by the principal investigator to terminate any treatment group after five individuals in that group required treatment for hypotension. We believed that this limitation would still permit statistically and scientifically valid conclusions to be made, without exposing subjects to additional risk. Only subjects in the combined AVPA–enalapril group required treatment for hypotension (fig. 1). In fact, study of this group was terminated and the group removed from randomization after five of the first six subjects required treatment for hypotension. No subjects suffered morbidity as a result of the hypotension experienced during the study.

Blood was drawn from an indwelling antecubital venous catheter for renin and AVP measurements at the following times: (1) end of the baseline period, (2) end of the antagonist or placebo administration, and (3) end of the epidural or intramuscular catheter dosing. Epinephrine and norepinephrine concentrations were measured only at times (1) and (3). Lidocaine concentrations were measured only at time (5) and hematocrit only at time point (1). Lidocaine, renin,
AVP, epinephrine, and norepinephrine concentrations were determined using radioimmunoassay techniques. The lower limits of sensitivity for the assays were 0.5 μg/ml, 0.1 ng·ml⁻¹·h⁻¹, 0.8 pg/ml, 10 pg/ml, and 10 pg/ml for lidocaine, renin, AVP, epinephrine, and norepinephrine, respectively. The intra- and interassay variabilities were less than 10% in all cases. AVP concentration could not be measured in subjects receiving AVPA because this antagonist cross-reacts with the radioimmunoassay for AVP. In addition, after enalapril administration, renin concentration is increased as a result of a loss of feedback inhibition by angiotensin and so no longer reflects the activity of the RAS (i.e., angiotensin II release). Therefore, values for AVP and renin concentration were not included in our data analysis of subjects receiving AVPA and/or ENAL, respectively.

Data were analyzed by analysis of variance for repeated measurements and followed by further analysis by Scheffé's test to correct for multiple comparisons. Differences were considered to be statistically significant if $P$ was <0.05.

**Results**

The subjects were demographically matched, and the maximum epidural block level, onset time, plasma lidocaine concentrations, and baseline blood pressure were similar in all groups (table 1). As shown in figure 1, T2 epidural block did not result in significant hypotension in healthy volunteer subjects with an intact AVP system and intact RAS treated only with saline placebo. Similarly, subjects in whom the AVP system or the RAS were blocked individually by treatment with either the V₁ receptor antagonist AVPA or the angiotensin-converting enzyme inhibitor enalapril did not develop hypotension after T2 epidural block (fig. 1A). In contrast, subjects in whom both the AVP system and the RAS were blocked by combined treatment with enalapril and AVPA had a significant decrease in mean blood pressure after epidural dosing (fig. 1A). In the absence of an epidural block, subjects treated with AVPA and enalapril did not develop hypotension after administration of a similar dose of intramuscular lidocaine in place of epidural lidocaine (fig. 1B). In addition, as shown in figure 1C, decreases in heart rate were not responsible for the decrease in blood pressure after epidural dosing in subjects treated with enalapril and AVPA.

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The time course of the hypotensive effect of epidural block after combined AVP and RAS blockade is shown in figure 2. As the block approached a T2 sensory level, each of the six subjects in the group treated with AVPA and enalapril developed hypotension. In five of the six subjects the blood pressure decreased by greater than 20% (range 22%-45%) after epidural dosing compared to the baseline blood pressure. Only these five subjects developed symptoms associated with central nervous system hypoperfusion (i.e., altered sensorium, scotomata, or limb dysesthesia) and were treated, according to our protocol, with a mean dose of 25 ± 5 mg ephedrine and 985 ± 110 ml lactated Ringer’s solution to restore blood pressure to baseline values and relieve symptoms (fig. 2).

Plasma concentrations of AVP, renin, and catecholamines in the study subjects are shown in figure 3. Epidural block did not result in statistically significant increases in AVP or renin concentrations in subjects with an intact AVP system and intact RAS treated only with saline placebo. After AVP or RAS blockade, however, a significant increase in the concentration of the unblocked vasopressor occurred after epidural block. As a result of this effect, subjects first treated with enalapril had significantly increased concentrations of AVP after epidural block (fig. 3A). Similarly, subjects first treated with AVPA had significantly increased concentrations of renin after epidural block (fig. 3B). (Because AVP and enalapril interfere with the AVP assay and the renin values, respectively, analysis of these values was not possible in subjects receiving the combination of AVPA and enalapril.) In the absence of an epidural block, AVPA or enalapril treatment did not increase AVP or renin concentrations after administration of intramuscular lidocaine (data not shown). Finally, we observed no change in epinephrine and norepinephrine concentrations after epidural block in subjects with or without intact AVP system and intact RAS (fig. 3C).

Discussion

The results of the current study in human subjects are consistent with the results of previous studies in animals demonstrating that the AVP system and RAS assume important roles in blood pressure maintenance only under conditions in which the sympathetic nervous system is impaired. For example, combined blockade of the AVP system and RAS resulted in significant hypotension after pharmacologic ganglionic blockade, spinal cord transection, and halothane anesthesia in experimental animals. Furthermore, Peters et al. provided evidence that AVP plays an important role in supporting blood pressure after epidural block in dogs. This conclusion was based largely on the ability of AVP to produce profound hypotension after upper thoracic level epidural block in dogs. In contrast, in the current study in humans, we did not observe a hypotensive effect of AVPA administration, alone, after T2 epidural block. Furthermore, AVPA alone did not produce hypotension after administration to 11 patients receiving T1 spinal block before surgery. The lack of effect of AVPA on blood pressure in the current study may be the result of the compensatory activation of the RAS we observed in our subjects after AVPA administration. In contrast, Peters et al. did not observe an increase in renin after AVPA administration in dogs. Similarly, the lack of effect of enalapril alone on blood pressure in the current study may be the result of the compensatory increase in AVP concentrations we observed after enalapril administration. Peters et al. did not study the role of the RAS by administering an angiotensin-converting enzyme inhibitor (e.g.,

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Fig. 3. continued not included in our analysis of subjects receiving AVPA and/or ENAL. *Vasopressin and renin concentrations were measured at three time points: (a) end of the baseline period, before any treatment, (b) end of the antagonist or placebo administration, and (c) end of epidural dosing. Epinephrine and norepinephrine were measured at (a) and (c). All data are expressed as mean ± SEM, **P < 0.05 compared to baseline values in each group and between groups. Unless otherwise noted, there were no other statistically significant differences in values between or within groups at any time point.

Fig. 3. Analysis of plasma vasopressin, renin, epinephrine, and norepinephrine concentrations after epidural block in subjects treated with vasopressin antagonist (AVPA), enalapril (ENAL), or saline placebo. (A) Vasopressin concentrations. (B) Renin concentrations. (C) Epinephrine and norepinephrine concentrations. *Because AVPA and ENAL interfere with the vasopressin assay and renin values, respectively, these values were

alapril) in their animal model.11 We believe that the differences between their study in dogs and the current study in humans may be attributable to species differences in the hierarchy of blood pressure regulation. In support of this notion, previous reports have demonstrated species differences with respect to the relative importance that the sympathetic and AVP systems and the RAS play in blood pressure maintenance.5 Taken together, our results in humans suggest that in addition to AVP, the RAS plays an important role in maintaining blood pressure after epidural block.

The conclusions of our study depend on the pharmacologic specificity of the vasopressor antagonists used. AVPA, an antagonist of the vasopressor action of AVP mediated by activation of vascular V_{1} receptors, does not affect the antidiuretic action of AVP on V_{2} receptors.9,10,16 V_{1} receptors are coupled to specific G proteins, and activation of these receptors increases the hydrolysis of phosphatidylinositol, leading to mobilization of intracellular calcium with a resultant vasoconstrictor response.10

Enalapril is an inhibitor of angiotensin-converting enzyme7,8 that catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor whose production is reduced after the administration of enalapril.7,8 Although the bulk of experimental and clinical evidence suggests that enalapril produces its effects as a result of decreases in angiotensin generation, under certain conditions this drug may also affect concentrations of kinins and prostaglandins.7,8

Although enalapril is an antihypertensive drug when administered chronically, and AVPA has been studied for its antihypertensive effects, neither drug significantly affects blood pressure after acute administration in healthy volunteers with an intact sympathetic nervous system.7,8,16,17

The dose of AVPA used in the current study has been shown to be capable of blocking the hypertensive ef
fects of doses of exogenous vasopressin, in excess of those likely to be produced physiologically. These results suggest that the dose of AVPA we administered would be capable of blocking the pressor effect of AVP released in response to epidural block in the current study, although we did not specifically test the antagonism by administering exogenous vasopressin and observing the response. In addition, the rapid onset of action of AVPA and the long duration of action (3–4 h) imply that AVPA was exerting its maximal effect throughout the study period. Similarly, the dose of enalapril administered in the current study has been shown to produce complete inhibition of circulating converting enzyme within 30 min of administration, for a period exceeding the duration of the study.

To determine the effect of systemically absorbed lidocaine, in the absence of a sympathetic block, we included a control group receiving intramuscular lidocaine in place of the epidural lidocaine. Our results demonstrated a lack of effect on blood pressure of AVPA and enalapril administered to control subjects receiving intramuscular lidocaine in place of epidural lidocaine. These results demonstrate that in the absence of an epidural sympathetic block, AVPA and enalapril do not pharmacologically interact with the lidocaine in the circulation after epidural block to produce hypotension directly.

In contrast to the healthy nonpregnant subjects who participated in the current study, parturient women are particularly sensitive to the hypotensive effects of epidural block, and decreased maternal blood pressure may also decrease fetal perfusion. Because the concentration of vasopressinase, a placentially derived AVP-degrading enzyme, is increased during pregnancy, the availability of vasopressin to exert vasopressor effects should be decreased. In addition, the vasopressor effect of angiotensin is decreased during normal pregnancy. Taken together, the decreased activity of these vasopressor systems may help to explain the increased incidence of hypotension after epidural block in obstetric patients. Currently, we are conducting studies to determine whether there is a correlation between concentrations of AVP and renin in the plasma and the subsequent development of hypotension after epidural block for cesarean delivery.

Before conducting the current study, we reviewed the results of previous studies and case reports conducted in humans measuring the effects of AVPA and enalapril on blood pressure. Three of these reports studied the effects of AVPA and enalapril (or the related drug, captopril) in the presence of drugs that block the sympathetic system and found modest effects of these agents on blood pressure; no patients required treatment for hypotension. In addition, the results of our own preliminary study demonstrated that AVPA did not significantly affect blood pressure in healthy patients after T1 spinal block. Furthermore, we believed that the specificity of AVPA and enalapril made it likely that hypotension could be treated using ephedrine, because this vasopressor does not depend on AVP or the RAS for its action. In fact, the subjects in our study responded to ephedrine administration with an increase in blood pressure and resolution of symptoms.

Even though the blood pressure changes produced in our study were clinically significant and required treatment, the degree of hypotension was similar to that which may be encountered after the induction of regional anesthesia in clinical practice. For example, the symptomatic hypotension observed transiently in a significant number of parturient women undergoing spinal anesthesia for elective cesarean delivery is similar in magnitude to the hypotension produced in the current study.

Although the study protocol was approved by our institutional review board and no subject suffered morbidity as a result of the hypotension produced in our study, research in which healthy subjects are exposed to a risk of significant hypotension is controversial. However, taken as a whole, we believe that the current study represents an acceptable balance between scientific investigation and patient safety.

In summary, our results suggest that the AVP system and the RAS play important roles in maintaining blood pressure after epidural block in healthy subjects. Understanding the role that endogenous vasopressors play in maintaining blood pressure after epidural block in healthy subjects may improve our understanding of why certain high-risk patients become hypotensive when this technique is used and may allow us to use this form of anesthesia more safely in these patients.

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