Sympathetic Neural Blockade by Thoracic Epidural Anesthesia Suppresses Renin Release in Response to Arterial Hypotension

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Background: The renin–angiotensin and vasopressin systems, in addition to the sympathetic system, are important backup mechanisms for maintaining arterial blood pressure during circulatory challenges. We tested the hypothesis that preganglionic sympathetic blockade by thoracic epidural anesthesia interferes with the functional integrity of the renin–angiotensin system.

Methods: Renin concentrations were assessed in awake non-sedated patients in response to induced arterial hypotension (n = 10). Heart rate (electrocardiogram) and mean arterial blood pressure (electromancymetry) were recorded continuously. Active renin (radioimmunoassay), vasopressin (radioimmunoassay), and osmolality (osmometry) in arterial blood were measured intermittently: (1) at baseline, (2) during a hypotensive challenge (15 min) induced by sodium nitroprusside (titrated to decrease mean arterial blood pressure by at least 25%) with the sympathetic system intact, (3) during recovery, (4) with epidural anesthesia alone (sensory blockade T1–T11), and (5) during a second hypotensive challenge and sympathetic blockade with sodium nitroprusside titrated to the same mean arterial blood pressure as with the sympathetic system intact.

Results: With the sympathetic system intact hypotension almost doubled renin concentration (34 ± 32 SD to 60 ± 58 pg · ml⁻¹, P = 0.019), while vasopressin concentration remained unchanged. In contrast, during sympathetic blockade and despite identical hypotension (mean arterial blood pressure 68 ± 8 vs. 67 ± 5 mmHg), renin concentration did not change (35 ± 27 vs. 35 ± 29 pg · ml⁻¹, P = 0.5), whereas vasopressin concentration increased (4.6 ± 2.5 to 13.4 ± 9.4 pg · ml⁻¹, P = 0.01). Osmolality remained unchanged.

Conclusion: Our results indicate a key role of renal sympathetic fibers in mediating renin release during hypotension in humans, and that epidural anesthesia interferes with the functional integrity of the renin–angiotensin system. (Key words: Anesthetic techniques: epidural. Complications: hypotension. Hormones: renin; vasopressin. Sympathetic nervous system.)

DURING widespread thoracic epidural anesthesia, sympathetic outflow is attenuated by preganglionic neural blockade. Accordingly, maintenance of arterial blood pressure under these conditions may depend on the integrity of the renin–angiotensin and vasopressin systems. Hence, assessment of whether or not and to what extent the renin system is functional during sympathetic blockade by epidural anesthesia is important for identification of mechanisms potentially responsible for cardiovascular complications during regional anesthesia, as well as important for our understanding of the regulation of renin release in general.

A circulatory challenge such as arterial hypotension evokes renin release in both humans and animals with an intact sympathetic system,1–3 but it is unknown whether this is mediated by a decrease in arterial pressure per se or by reflex activation of sympathetic renal efferent nerves.4,5 That, in principle, sympathetic nerve traffic to the kidney can contribute to renin secretion, at least in animals, has been shown by the increase in plasma renin activity evoked by electrostimulation of the peripheral stump of renal nerves in dogs.6 Accordingly, we tested the hypothesis that preganglionic sympathetic blockade by epidural anesthesia impairs the functional integrity of the renin system. This was accomplished by measuring active renin concentrations in response to sodium nitroprusside (SNP)–induced...

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arrestal hypotension both before and during sympathetic blockade. Vasopressin concentration was also measured since activation of the vasopressin system can support arterial blood pressure when integrity of the renin–angiotensin system and sympathetic vasomotor control is impaired.7–11

Our results show in awake nonseated humans that sympathetic blockade by thoracic epidural anesthesia abolishes the physiologic increase in renin concentration evoked by arterial hypotension, whereas under these conditions the vasopressin system is activated.

Materials and Methods

Patients

The study was approved by the local ethical committee. After having obtained informed written consent ten nonpremedicated patients without cardiovascular disease or electrolyte disturbances (ASA physical status 1 or 2 and mean age 53 yr ± 12 SD [range 29–72 yr]), scheduled for elective upper abdominal surgery, were enrolled.

All experiments were performed in the early morning in a quiet separate room with the ambient temperature held constant around 24°C, i.e., near the thermoneutral range.12 An intravenous catheter for fluid replacement and SNP infusion and a radial artery catheter for blood pressure measurements were inserted under local anesthesia. Normal saline was infused at a rate of 20 ml·h⁻¹ during the course of the study and no blood volume expansion or drugs were used unless specifically stated.

Measurements

Arterial blood pressure was measured electromanometrically, and heart rate was derived from the electrocardiogram. The electrocardiogram and blood pressure were recorded continuously on both ink recorder (Gould brush) and tape.

As an indicator for the spread of sympathetic blockade, skin temperatures were measured by infrared telethermography on the hand (thumb) and foot (big toe). Skin temperatures were recorded intermittently every 5 min, and ambient and rectal temperatures were recorded continuously with thermistors (model 402, Yellow Springs Instruments, Yellow Springs, OH), as described previously.13

Blood for measurement of active renin, vasopressin, and bupivacaine concentrations was withdrawn into chilled tubes and immediately placed in crushed ice. After centrifugation plasma samples were stored at −20°C until analysis. Active renin was measured by radioimmunoassay with two anti-renal monoclonal antibodies (Renin Irma Pasteur, Marnes-la-Coquette, France). Intra- and interassay coefficients of variation range from 3–6% and 6–9%, respectively, with a detection limit of 3.5 pg·ml⁻¹. The reference values for healthy, normally hydrated, supine adults in our laboratory are up to 30 pg·ml⁻¹. Pilot experiments had shown that incubation of the plasma of two volunteers with bupivacaine in vitro at concentrations of 1, 2.5, and 5 µg·ml⁻¹ did not affect active renin measurements, i.e., did not interfere with the renin assay.

Arg⁵-Vasopressin was measured by radioimmunoassay (125I vasopressin, Euro-Diagnostics) using rabbit antivasopressin antiserum calibrated against the World Health Organization standard and with a sensitivity of 0.8 pg·ml⁻¹. Cross-reactivity with Lys⁸-Vasopressin and Oxytocin was 0.1%. Total bupivacaine plasma concentrations were measured by high-pressure liquid chromatography and ultraviolet detection, as described previously.14 Serum osmolality was measured by freezing-point osmometry (Knauer, Bad Homburg, Germany).

Epidural Anesthesia

Thoracic epidural catheterization was performed with the patient lying in the right decubitus position. The epidural space was identified in the seventh or eighth interspace by the loss-of-resistance technique and a catheter advanced. Thereafter, the patient was turned supine in a comfortable position and the trunk covered with a blanket.

Epidural anesthesia was induced by injection of 0.75% bupivacaine (mean dose 7.4 ± 0.7 ml) into the epidural catheter. This dose of bupivacaine 0.75% was expected to be sufficient to achieve a dermatomal spread of 10–12 segments based on clinical experience and our previous studies in humans.13 To minimize potential complications of accidental intrathecal or intravascular injection the dose was given in two increments, injected 5 min apart.

Extension of sensory blockade was assessed by the pin prick method (22 gauge needle) and defined as the most cranial and the most caudal dermatomes insensitive to the stimulus.

Hypotensive Challenge

Arterial hypotension was induced by continuous intravenous infusion of SNP (Schwarz Pharma, Monheim,
Germany) with a motor syringe (Braun, Melsungen, Germany). SNP was diluted to a final concentration of 200 µg·ml⁻¹ and the infusion rate adjusted to achieve an approximately 25% reduction in mean arterial pressure for at least 10 min. After thoracic epidural anesthesia was fully established the challenge was repeated with the SNP dose adjusted to achieve the same mean arterial blood pressure as with the sympathetic system intact. The mean infusion dose of SNP necessary for the target reduction of mean arterial pressure was 1.5 ± 0.6 µg·kg⁻¹·min⁻¹ before and 0.3 ± 0.3 µg·kg⁻¹·min⁻¹ during epidural anesthesia.

Study Protocol
Each patient was studied under five experimental conditions, i.e., (1) at baseline (15 min); (2) during a hypotensive challenge (15 min) with the sympathetic system intact; (3) recovery (20 min); (4) during thoracic epidural anesthesia alone (35 min); and (5) during a second hypotensive challenge and sympathetic blockade by epidural anesthesia (15 min).

Arterial blood (30 ml) for the measurement of active renin, vasopressin, and bupivacaine concentrations in plasma as well as serum osmolality was withdrawn at the end of each intervention period and replaced by equal amounts of lactated Ringer's solution.

Data Analysis
Data are presented as means ± SD. Two a priori null hypotheses were tested: there is no difference between variables with the various interventions over time; and there is no difference in hormone responses during the hypotensive challenge with and without sympathetic blockade by thoracic epidural anesthesia. Mean values of variables were evaluated statistically by Friedman's analysis of variance for repeated measures followed by a post hoc Wilcoxon's test. Null hypotheses were rejected and statistically significant differences assumed with an α error (P) of less than 5%.

Results
SNP-induced hypotension increased plasma renin concentrations with the sympathetic system intact but not during sympathetic blockade by thoracic epidural anesthesia. In contrast, vasopressin concentrations remained unchanged with SNP-induced hypotension before epidural anesthesia but increased significantly during neural blockade. The time course of cardiovascular variables and hormones is shown in figure 1 and table 1, respectively. With sympathetic innervation intact SNP infusion significantly increased heart rate from 75 ± 14 to 97 ± 16 beats·min⁻¹ (P = 0.0059) and decreased mean arterial pressure from 91 ± 6 to 68 ± 8 mmHg (P = 0.0059). Concomitantly, active renin plasma concentration nearly doubled to 60 ± 58...
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Table 1. Plasma Hormone and Bupivacaine Concentrations, Mean Arterial Pressure, and Serum Osmolality with Sodium–Nitroprusside-Induced Hypotension before and during Sympathetic Blockade by Epidural Anesthesia

<table>
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<tr>
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<th>Sympathetic Innervation Intact</th>
<th>Sympathetic Blockade by Epidural Anesthesia</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Hypotensive Challenge</td>
</tr>
<tr>
<td>Active renin (pg/ml)</td>
<td>34 ± 32</td>
<td>60 ± 58*</td>
</tr>
<tr>
<td>Vasopressin (pg/ml)</td>
<td>4.9 ± 7.4</td>
<td>6.4 ± 4.6</td>
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<tr>
<td>Bupivacaine (μg/ml)</td>
<td>0.16 ± 0.09</td>
<td>0.16 ± 0.08</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>91 ± 6</td>
<td>68 ± 8*</td>
</tr>
<tr>
<td>Osmolality (mosm/kg)</td>
<td>299 ± 8</td>
<td>303 ± 10</td>
</tr>
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</table>

Data from 10 awake undated patients without cardiovascular disease prior to elective surgery; mean ± SD.

* P < 0.05 versus preceding value (Friedman and Wilcoxon rank tests).

pg·ml⁻¹ (P = 0.019), whereas vasopressin plasma concentrations remained unchanged (table 1).

After cessation of SNP infusion, heart rate and mean arterial pressure returned to baseline values within 5 min (fig. 1) and at the end of the 20-min recovery period renin concentration had reached its baseline value (table 1).

After epidural anesthesia, sensory blockade developed gradually and after 50 min extended from dermatomes T1 ± 3.5 to T11 ± 3.2. As an indicator of the widespread sympathetic blockade, regional skin temperatures increased significantly on both hand (+3.8 ± 2.9°C, P = 0.014) and foot (+3.6 ± 2.5°C, P = 0.0059) at constant ambient (24.0 ± 0.5°C) and rectal (37.0 ± 0.6°C) temperatures (fig. 2).

Not unexpected, sympathetic blockade by thoracic epidural anesthesia alone (fig. 1) lead to a decrease of both heart rate (72 ± 15 vs. 66 ± 13 beats·min⁻¹) and mean arterial pressure (94 ± 7 vs. 77 ± 7 mmHg). However, neither active renin nor vasopressin plasma concentrations changed significantly (table 1).

With sympathetic blockade by epidural anesthesia and titration of SNP to the same mean arterial pressure (67 ± 5 mmHg) as with the sympathetic system intact, heart rate again increased significantly, albeit to a much smaller extent (66 ± 13 to 75 ± 19 beats·min⁻¹; fig. 1). However, despite the same degree of hypotension, active renin concentration remained unchanged (table 1). In contrast, during hypotension and with sympathetic blockade vasopressin concentrations increased significantly, from 4.6 ± 2.5 to 13.4 ± 9.4 pg·ml⁻¹ (P = 0.01).

The changes of active renin and vasopressin plasma concentrations in response to SNP-induced hypotension before and during sympathetic blockade are contrasted in figure 3. Sympathetic blockade abolished the increase in renin concentration (P = 0.01), but increased vasopressin plasma concentrations (P = 0.041).

Serum osmolality remained unchanged throughout the study (table 1).

Bupivacaine plasma concentrations were quite low, but nevertheless detectable even after local infiltration anesthesia for placement of the various catheters (table 1).

No complications resulted from the study and, in all patients, the epidural catheter was used subsequently to provide postoperative analgesia.

Discussion

The principle finding from this study is that neural sympathetic blockade by thoracic epidural anesthesia abolished the increase in renin activity in response to arterial hypotension. This indicates, in humans, that the renal sympathetic system plays a key role in mediating renin release in response to hypotension. Furthermore, the data show that thoracic epidural anesthesia, in addition to blockade of sympathetic vasoconstrictor tone, also impairs the functional integrity of the renin–angiotensin system, leaving endogenous vasopressin as the last line of blood pressure defense.

Critique of Methods

Other factors such as vasoactive drugs, anesthetics, ambient temperature, osmolality, and fluid balance which might influence hormone concentrations were either controlled for or excluded. That, in some patients, baseline renin values were slightly greater than reference values, is most likely explained by the patients' prolonged overnight fast. However, this did not influence the renin response to hypotension.
Increased bupivacaine concentrations in the blood after epidural anesthesia can be excluded from influencing renin measurements. In the absence of sympathetic blockade neither intravenous infusion of bupivacaine nor incubation of plasma with bupivacaine, in concentrations even greater than those measured in our patients after epidural anesthesia, altered renin concentrations at rest, in response to hypotension, or \textit{in vitro}, respectively. Increased bupivacaine concentrations in the blood can also be excluded from influencing vasopressin concentrations since during lumbar epidural anesthesia with a more restricted sensory blockade (upper dermatomal level T10) and comparable plasma bupivacaine concentrations, neither arterial pressure nor vasopressin concentrations changed.\textsuperscript{18} Finally, SNP \textit{per se} could hypothetically stimulate renin release \textit{via} release of nitric oxide,\textsuperscript{19} independent of other mechanisms. However, this is very unlikely since recent \textit{in vitro} and \textit{in vivo} experiments in animals suggest that nitric oxide, if anything, inhibits renin release.\textsuperscript{20,21}

Most important, each of our patients served as its own control, excluding any bias with regard to interindividual variabilities in the response to hypotension. Thus, the suppression of renin release during epidural anesthesia despite substantial hypotension as well as

\begin{figure}
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\includegraphics[width=\textwidth]{diagram.png}
\caption{Spread of sensory blockade and regional skin and ambient temperatures during epidural anesthesia (means ± SD from ten awake patients). Vertical stippled lines indicate the start and end of hypotensive challenge by sodium nitroprusside (SNP). Injection of bupivacaine into the thoracic epidural space (vertical solid line) resulted in a sensory blockade (tested by pin prick) extending from dermatome T1 to T11. Compared to baseline (open circles), skin temperatures increased markedly and significantly after epidural anesthesia (filled circles) on the thumb and big toe, indicating widespread sympathetic blockade. Ambient temperature remained constant. *P < 0.05.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{chart.png}
\caption{Changes in plasma hormone concentrations evoked by hypotensive challenge}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart2.png}
\caption{Changes in plasma renin and vasopressin concentrations evoked by the hypotensive challenge before (open bars) and during (filled bars) neural sympathetic blockade (means ± SD from ten awake patients). Sympathetic blockade by thoracic epidural anesthesia abolished the hypotension-induced physiologic increase in active renin that had been observed with the sympathetic system intact. In contrast, vasopressin plasma concentrations increased significantly with the hypotensive challenge during sympathetic blockade but not with the sympathetic system intact. *P < 0.05.}
\end{figure}

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the increase in vasopressin concentration in all likelihood result from the widespread sympathetic blockade by epidural anesthesia. This is consistent with our previous observations in conscious dogs.11,22

Efferent sympathetic fibers innervating the kidneys are supposed to emerge from the lower thoracic spinal cord.23 Accordingly, attenuation of evoked or tonic renal sympathetic drive can be assumed when bupivacaine is injected into the thoracic epidural space resulting in widespread sympathetic blockade. This assumption is confirmed by the substantial and significant increase in skin temperatures on both hand and foot. Moreover, the increase in heart rate with the hypertensive challenge during sympathetic blockade was significantly less than with intact sympathetic system, suggesting also widespread sympathetic blockade. Finally, the dose of SNP required for induced hypotension was substantially less after sympathetic blockade by epidural anesthesia, suggesting impaired sympathetic outflow. However, the observed suppression of renin release might have also contributed. Thus, the unchanged renin plasma concentrations after thoracic epidural anesthesia observed in this study despite substantial hypotension is most likely caused by attenuation of sympathetic drive to the kidneys.

Interpretation of Results

In humans, the role of the sympathetic nervous system in regulation of renin release is largely unknown. In conscious dogs renin release, as estimated by the venoarterial renin concentration difference across the kidney in response to isolated (renal artery cuff occluder) decrements in renal artery pressure, appears to be mediated preferentially by nonneural mechanisms with a threshold pressure of about 94 mmHg for release.24,25 Bilateral carotid occlusion, presumably by activation of sympathetic efferent nerves, increased the threshold pressure by 17 mmHg, however, without influencing peak renin values or the slope of the pressure-renin release relationship.24 Systemic β blockade in combination with carotid occlusion still increased the threshold pressure for renin release in response to renal artery hypotension, but reduced peak renin concentrations by around 50%.24 In turn, infusion of the α1-blocking agent prazosin into the renal artery eliminated this increase in threshold pressure, but did not alter renin release in response to a decrease in renal artery pressure below the threshold.26 On the other hand, an intact renal sympathetic nervous system is by no means a necessary precondition for renin release in animals, since reduction of renal arterial pressure by suprarenal aortic constriction from 130 to 50 mmHg in anesthetized dogs with acutely denervated kidneys quadrupled arterial renin activity.27 Thus, the prevailing opinion was that, in animals, activation of sympathetic renal efferent nerves interact with a dominant intrarenal pressure-dependent mechanism only by increasing to a minor degree the threshold pressure for renin release.5,4,27

In contrast to these data, obtained in animals, our results in humans strongly suggest that an intact renal sympathetic system plays a key role in mediating renin release in response to arterial hypotension. That an increase in renal sympathetic drive rather than a decrease in renal perfusion pressure per se mediated the physiologic increase in renin concentration in response to hypotension is also consistent with anecdotal observations in humans. In patients with essential hypertension renin activity doubled in response to a 19-mmHg decrease in mean arterial pressure induced by injection of hydralazine, but did not change in a patient with a transplanted, i.e., presumably denervated kidney.2 Also, renin activity failed to increase during head-up tilt in three individuals with severe autonomic nervous system disease despite decreases in mean arterial pressure to values as low as 40 mmHg.28,29 Together, all these findings indicate that in humans integrity of the renal sympathetic system plays an important role in mediating renin release in response to hypotension.

Nevertheless, renin may still be released, independent of central sympathetic drive, with even greater decreases in arterial pressure. In fact, when in four patients with traumatic transection of the cervical spinal cord mean arterial pressure was decreased from 81 to 52 mmHg by head up tilting (two patients fainted) renin activity increased fourfold.30 Even during epidural anesthesia, renin may still be released in response to hypotension when epidural blockade is confined to caudal body parts, leaving unimpaired sympathetic nerve supply to the kidneys. In fact, in elderly humans receiving lumbar epidural anesthesia with a variable cranial extent of sensory blockade, plasma renin activity (measured as generated angiotensin I) tended to increase during simulated hypovolemia induced by a head-up tilt.31 For obvious ethical reasons, we did not determine whether renin concentration would increase during sympathetic blockade with a hypotensive challenge resulting in a mean arterial pressure much less than

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60 mmHg. Nevertheless, our results clearly demonstrate suppression of renin release during thoracic epidural anesthesia despite substantial arterial hypotension.

Vasopressin plasma concentration increased during hypotension with widespread sympathetic blockade but not with the sympathetic system intact. This can be attributed to the fact that, according to our results, sympathetic blockade by epidural anesthesia eliminates two (the sympathetic and the renin–angiotensin system) of the organism’s three major pressor systems, leaving unimpaired solely the vasopressin system. Both a decrease in cardiac volume, secondary to redistribution of blood into denervated body regions and/or a diminution in arterial pressure could be responsible for vasopressin release, since a decrease in baroreceptor activity as well as cardiopulmonary receptor discharge increase plasma vasopressin concentrations. Since vasopressin is a potent vasoconstrictor even at normal physiologic concentrations, the increase in vasopressin concentrations most likely supported to some degree arterial blood pressure. This is deduced from the finding that the decrease in arterial blood pressure after epidural anesthesia doubles, when, in addition to widespread sympathetic blockade, the vasoconstrictive effects of endogenous vasopressin are prevented by intravenous administration of a vasopressin-1 receptor antagonist in conscious dogs.

A body of experimental evidence indicates in animals that arterial blood pressure is supported by the renin–angiotensin as well as the vasopressin system, when the organism’s main defense against hypotension, activation of the sympathetic nervous system, is exhausted. Our data show that an intact renal sympathetic nervous system seems to play a key role in mediating renin release during hypotension in awake humans. Furthermore, they reveal that thoracic epidural anesthesia, in addition to diminution of efferent sympathetic drive, also interferes with the functional integrity of the renin–angiotensin system, leaving activation of the vasopressin system as the last line of circulatory defense in response to hypotension. Finally, interference of epidural anesthesia with neurohumoral regulation likely explains why, in the clinical setting, arterial blood pressure can be quite unstable during central neuraxial blockade, in particular during diminution of cardiac filling, e.g., with blood loss, positioning, head-up tilt, or increased pleural pressure (mechanical ventilation).

References


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