Perioperative concentrations of catecholamines in the cerebrospinal fluid and plasma during spinal anesthesia

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Background: Catecholamine release is a physiological response to stress. The extent to which perioperative stress provokes the central release of catecholamines, which modulate pain perception in the spinal cord, still remains unknown. The perioperative course of catecholamine concentrations in the cerebrospinal fluid (CSF) and plasma was examined.

Methods: A prospective study was performed in 25 patients (ASA III, 60–84 years) undergoing elective hip joint replacement in spinal catheter anesthesia. The concentrations of dopamine, epinephrine and norepinephrine in the CSF and plasma were measured before anesthesia, immediately after surgery, and 6 and 24 h post-operatively.

Results: In most patients, dopamine and epinephrine were not detectable in CSF. CSF–norepinephrine concentrations decreased from median [interquartile-range] 159 [124;216] pre-anesthesia to 116 [79;152] pmol/l immediately post-operatively and were slightly elevated 24 h post-operatively (180 [134;302] pmol/l) (P < 0.05). Dopamine plasma concentrations were not detectable or were barely above the detection threshold. Plasma epinephrine increased from 61 [28;77] pmol/l pre-anesthesia to 112 [69;138] pmol/l 6 h post-operatively and returned to baseline 24 h post-operatively (P = 0.001). Plasma norepinephrine concentrations increased intra-operatively from 298 [249;422] to 556 [423;649] pmol/l and remained elevated 24 h after surgery (P = 0.009). There was no association between changes in CSF or plasma norepinephrine or epinephrine concentrations and changes in heart rate (HR) or mean arterial pressure (MAP).

Conclusion: During spinal anesthesia for elective hip joint replacement, norepinephrine concentrations were greater in plasma than in CSF. CSF dopamine and epinephrine concentrations were essentially undetectable. The changes in CSF-norepinephrine concentrations and the changes of plasma norepinephrine concentrations showed no association with each other; nor were there correlations between clinical stress parameters (HR, MAP) or visual analog scale pain, and the changes in CSF norepinephrine concentrations.

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Anticipation of surgery, even with general anesthesia, triggers physical and psychological stress in patients (1, 2). This results in an endocrine response mediated by the hypothalamic–pituitary–adrenal and renin–angiotensin axes, along with sympathetic nervous system activation (3).

The most basic physiological response to stress, including that resulting from surgical tissue injury, is release of catecholamines (4–7). The major catecholamines, dopamine, epinephrine, and norepinephrine are released both peripherally and centrally (8, 9).

While it is well established that peripheral catecholamine concentrations increase markedly in response to surgical stress, the extent to which surgical stress provokes the central release of catecholamines remains unknown. Because catecholamines modulate pain perception in the spinal cord (10–14), and differences in catecholamine levels may affect analgesia, we chose to investigate the catecholamine concentrations in the cerebrospinal fluid (CSF).

Therefore, this study determined the perioperative changes of catecholamine concentrations in the CSF and plasma in elderly patients undergoing major hip surgery. Possible correlations between CSF and plasma catecholamine concentrations, heart rate (HR), mean arterial pressure (MAP),...
Methods

With the approval of the local Ethics Committee and written informed patient consent, 25 patients were enrolled in this prospective study. Inclusion criteria were an age of 60 years or above with ASA Physical Status III undergoing elective total hip joint replacement with spinal-catheter anesthesia. The surgeon used cemented MS-30 stems and polyethylene screw-in cups (Biomet Deutschland GmbH, Berlin, Germany). Exclusion criteria were decompensated cardiac or circulatory insufficiency, severe renal or hepatic impairment, signs of clotting disorders, neuromuscular dysfunction, diseases of endocrine organs (diabetes, pancreatitis, thyroid problems, hepatitis), known tumors/neo-plasmas, alcohol or drug abuse, use of substances acting on the central nervous system, and use of calcium antagonists, \( \alpha_2 \)- and \( \beta \)-sympathomimetics, or theophylline.

One hour before surgery, 3.75 mg oral midazolam (Dormicum, Hoffmann-La Roche AG, Basel, Switzerland) was administered. During the preparation for anesthesia, a 16G central venous line (Cavafix Certodyn 375, B. Braun, Melsungen, Germany) was placed in the basilic vein and correct placement checked by ECG. A 20G arterial line (B.Braun) was inserted into the radial artery.

HR from the ECG and MAP were recorded at 5-min intervals until the end of surgery, and then 1, 3, 6, 12, and 24 h post-operatively. For anesthesia and sampling, a 20G spinal catheter (Perifix, B. Braun) was placed in the basilic vein and correct placement checked by ECG. A 20G arterial line (B.Braun) was inserted into the radial artery.

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Statistical analysis

Because the variability of the target parameter was unknown, sample size calculation was not possible. Nonetheless, 25 patients were included in the study, which seemed likely to be sufficient for this sort of natural history study. Statistical analysis was explorative. We calculated the minimum, maximum, median, arithmetic mean, interquartile
range, and standard deviation for each numeric parameter. Results are presented as median [interquartile range].

Because most parameters were not normally distributed, non-parametric tests were used for the analyses. First we determined whether the catecholamine concentrations in plasma and CSF changed during the observation period using Friedman’s analysis of variance (ANOVA) by ranks. Then absolute changes between the differences of catecholamine concentrations and the differences in vital parameters or VAS during time intervals were calculated using Spearman’s rank correlation. A correlation coefficient lower than 0.5 was termed no association.

Results

Sixteen of the 25 patients were evaluated (six women, 10 men). Nine patients were excluded from data analysis due to discontinuation of the study (technical problems in placing spinal catheter \( n = 1 \), administration of amezinium metilsulfate \( n = 7 \), dislocation of spinal catheter \( n = 1 \)). The 16 patients included in the data analysis were ASA Physical Status III; their characteristics are listed in Table 1.

Anesthesia and surgery of the evaluated patients were performed without complications. The heart rate was (median [interquartile range]) 75 [71;81] beats per minute at the beginning of the examination period and 70 [65;74] beats per minute at the end of the period. The mean arterial pressure was 103 [95;107] mmHg versus 93 [84;100] mmHg. SaO\(_2\) ranged from 95% to 99% during the entire study period. The upper level of the blockade varied from T6 to T10 immediately before surgery started and from T10 to L1 right after skin closure. Midazolam was administered intra-operatively to 11 patients. Pre-LA the median pain score (VAS) was 1 [0;2]. Immediately after surgery the median pain score (VAS) was 0 [0;2.5]. During the 24 h post-OP study period, patients received 6–32 mg morphine i.v., resulting in a median pain score of VAS 3 [2;4] 6 h post-OP, and VAS 2 [1;3] 24 h post-OP.

In most patients, dopamine, and epinephrine were not detectable in the CSF: dopamine was not detectable in 11 patients, in three patients it was detected immediately pre-LA, and in two patients it was detected 6 h and 24 h post-OP. CSF epinephrine concentrations were detectable in just a single patient. Norepinephrine was detectable in all patients in both CSF and plasma. Its concentrations in the CSF decreased intra-operatively from 159 [124;216] pmol/l pre-LA to 116 [79;152] pmol/l 0 h post-OP and increased from 111 [71;283] pmol/l 6 h post-OP to 180 [134;302] pmol/l 24 h post-OP (\( P < 0.05 \)).

Dopamine plasma concentrations were not detectable or were barely above the detection threshold. Plasma epinephrine increased from 61 [28;77] pmol/l pre-LA to 112 [69;138] pmol/l 6 h post-OP and returned to baseline 24 h post-OP (\( P = 0.001 \)). Plasma norepinephrine concentration increased from 298 [249;422] pmol/l pre-LA to 556 [423;649] pmol/l 0 h post-OP, and remained nearly stable for up to 24 h (\( P = 0.009 \)) (Figs 1–3).

The changes in the detectable CSF catecholamine concentrations were not associated with changes in plasma catecholamine concentrations and there was no association between changes of the vital parameters (HR, MAP) and VAS. The known clinical effects of plasma catecholamine concentrations

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics and operation data.</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>128 ± 36</td>
</tr>
<tr>
<td>Volume substitution (ml)</td>
<td>2719 ± 587</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>881 ± 351</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. \( n = 16 \) (six females, 10 males).
on the vital parameters (HR, MAP) at each measurement point were correlated, as expected.

Median values of venous blood pH were between 7.37 [7.36;7.39] and 7.41 [7.39;7.45]. The median values for pO₂ were between 4.6 and 4.9 kPa (34 and 37 mmHg) and the values for pCO₂ were between 5.3 and 6.1 kPa (40 and 46 mmHg) in venous blood. Glucose concentrations remained within the normal range (3.3–3.8 mmol/l in CSF and 4.9–6.0 mmol/l in blood).

**Discussion**

A group of elderly patients who were scheduled for hip surgery with spinal catheter analgesia was examined, giving us continuous access to CSF and the opportunity to describe the perioperative time-course of catecholamines in humans for the first time. The study showed that in this group of patients, catecholamine concentrations were higher in plasma than in CSF.

Catecholamines are produced in the brain, adrenal medulla, extramedullar chromaffine tissue, the gray matter of the spinal cord, and sympathetic nerve endings. They are stored in vesicles and liberated via central catecholaminergic impulses, eventually making their way into plasma and CSF. This is of particular interest because catecholamines modulate pain perception in the spinal cord (10–14), and differences in catecholamine concentrations may affect analgesia. The mechanism of this process is an effect of epinephrine or norepinephrine on α₂-receptors causing hyperpolarization of the transmission cells of the substantia gelatinosa in the spinal cord dorsal horn (14). Several clinical studies demonstrated that administering epinephrine or norepinephrine during epidural analgesia causes an elevation of the nociceptive threshold (11–13). However, in this case the vasoconstrictive effect that inhibits systemic absorption and therefore prolongs the effect of local anesthetics or morphines also plays a role.

Our results indicate that catecholamine concentrations are greater in plasma than in CSF. Eldrup et al. (16) observed a similar relationship in their control group. However, we could not confirm their conclusion that CSF and plasma norepinephrine concentrations are correlated, and Miura et al. (17) similarly failed to show such a correlation in their work with rats. This is in accordance with the work of Oldendorf (18) stating that catecholamines do not pass the blood–brain barrier and must originate in individual compartments, such as the plasma or brain. Plasma catecholamine concentrations in rats (17) and humans thus provide little if any estimate of CSF catecholamine concentrations and possible associated changes in the cerebrum.

Elevated perioperative plasma catecholamine concentrations signal a stress reaction associated with the operation and perioperative procedure. Plasma norepinephrine remained elevated 24 h after surgery, while plasma epinephrine rapidly normalized. There was an intra-operative reduc-

![Fig. 2. Median values and interquartile ranges of epinephrine concentrations in pmol/l in cerebrospinal fluid (CSF) and plasma, at the measurement points: pre-LA, right before spinal administration of the local anesthetic; 0 h post-OP, immediately post-operative; 6 h post-OP, 6 h post-operatively; 24 h post-OP, 24 h post-operatively. Both curves are based on 16 patients (median) but only one had a CSF epinephrine concentration above the detection threshold.

![Fig. 3. Median values and interquartile ranges of norepinephrine concentrations in pmol/l in cerebrospinal fluid and plasma at the measurement points: pre-LA, right before spinal administration of the local anesthetic; 0 h post-OP, immediately post-operative; 6 h post-OP, 6 h post-operatively; 24 h post-OP, 24 h post-operatively.](image-url)
tion in CSF norepinephrine, which was statistically significant. However, it remains unclear as to whether this reduction is clinically important and whether norepinephrine CSF concentrations are a sensitive marker of stress. This is especially the case because the reduction in CSF norepinephrine concentration during surgery was minimal and the absolute changes did not correlate with the differences in plasma norepinephrine concentrations or VAS.

Kanto and Scheinin (5) recommend using basic parameters such as MAP and HR to evaluate stress. Consistent with their recommendation, we did not observe an association between changes in plasma epinephrine concentrations and changes in HR or MAP or between changes in plasma norepinephrine concentrations and changes in CSF norepinephrine concentrations. Furthermore, there was no association between the changes in VAS score and the changes of plasma epinephrine concentrations or plasma norepinephrine concentrations or CSF norepinephrine concentrations, respectively. This might be due to an effective analgesia and the evaluation of pain by VAS where the chosen number depends on many factors varying from person to person.

To rule out age-related differences in catecholamine concentration, only older patients (above 60 years) were included in the study (19). Postural changes as the cause of increased catecholamine concentrations were improbable because all patients were supine during the examination phase. Patients receiving pre-/intra-operative medication that directly affected catecholamine concentration (e.g. amezinium metilsulfate) were excluded from the study. The administration of benzodiazepines has little (5, 20) or no effect (21, 22) on circulating catecholamine levels, and we deduce that there has little (5, 20) or no effect (21, 22) on circulating catecholamine levels, and we deduce that there was no significant pharmacological influence on perioperative catecholamine concentrations. Nor do we think the sampling procedure affected the measured levels, because all samples were centrifuged and then frozen at – 20 °C immediately after obtaining them and catecholamines are usually stable when frozen (23). As analgesia was effective in all cases, pain-induced increase of catecholamine concentrations seem highly unlikely.

The values for central venous pO₂, pCO₂, SaO₂, and hemodynamic parameters, as signs of general hypoxia or hypercapnia, did not show pathological alterations during the operation. Furthermore, CSF and blood glucose concentrations were monitored to rule out or detect potential cerebral le-

sions caused by intra- or post-operative hypo- or hyper-glycemia.

A limitation of the study is the method of anesthesia. This investigation reflects the actual situation during spinal anesthesia. But it would be interesting to evaluate CSF catecholamine concentrations during general anesthesia.

In conclusion, changes in perioperative catecholamine concentrations were observed in CSF and plasma norepinephrine as well as in plasma epinephrine and plasma dopamine concentrations. The changes in CSF norepinephrine concentrations and the changes of plasma norepinephrine concentrations showed no association to each other; nor were there correlations between clinical stress parameters (HR, MAP) or pain (VAS) and the changes in CSF norepinephrine concentrations.

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