Cerebral Blood Flow and Metabolism During Infusion of Norepinephrine and Propofol in Patients With Bacterial Meningitis

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Background and Purpose—In patients with severe bacterial meningitis, norepinephrine is often infused to increase mean arterial pressure (MAP). This increases cerebral blood flow (CBF), but it is unknown if this increase is caused by impaired cerebral autoregulation or by a cerebral effect of norepinephrine through increased cerebral metabolism. The latter possibility implies a CBF–metabolism coupling. This has not been studied during meningitis. We studied the effect of norepinephrine and propofol on CBF and oxidative metabolism in patients with severe bacterial meningitis.

Methods—In seven patients with pneumococcal meningitis and 7 healthy subjects, norepinephrine was infused intravenously; patients also underwent intravenous propofol infusion. Global CBF was measured by the Kety–Schmidt technique; cerebral oxidative metabolism and net flux of norepinephrine and epinephrine were calculated from measured arterial-to-jugular venous concentration differences (a-vD).

Results—During norepinephrine infusion, MAP increased from a median value of 79 (range, 70 to 89) to 99 (98 to 129) mm Hg in patients, and from 87 (72 to 103) to 123 (112 to 132) mm Hg in controls. CBF increased in patients (51 [48 to 60] to 59 [54 to 77] mL/100 g per minute) but remained unchanged in controls. The cerebral metabolic rate of oxygen (CMRO₂) decreased in patients and remained unchanged in controls. No cerebral net flux of norepinephrine or epinephrine was found at any time in the 2 groups. During propofol infusion, CMRO₂, and the a-vD O₂ decreased whereas CBF was unchanged.

Conclusions—In patients with severe bacterial meningitis, norepinephrine increases both MAP and CBF but not CMRO₂, indicating impaired autoregulation. Propofol reduces CBF relatively less than cerebral metabolism, suggesting a resetting of the CBF–CMRO₂ relationship. (Stroke. 2004;35:1333-1339.)

Key Words: energy metabolism • meningitis • blood flow

Critically ill patients with severe acute bacterial meningitis are often treated with norepinephrine to increase mean arterial pressure (MAP) and thereby maintain adequate organ perfusion. It has previously been shown that patients with acute bacterial meningitis have impaired cerebral blood flow (CBF) autoregulation, because a median increase in MAP of 46% by norepinephrine infusion is associated with a median increase in CBF of 36%, as assessed by transcranial Doppler ultrasonographic measurement of the flow velocity in the middle cerebral artery. However, an alternative explanation could be that norepinephrine leaks over a disrupted blood–brain barrier, known to occur in meningitis, thereby increasing cerebral metabolism and, subsequently, CBF.

Further, sedation is often instituted in patients with bacterial meningitis and impaired consciousness, the objective being to reduce cerebral metabolism and CBF, which in turn is expected to reduce intracranial pressure (ICP) and vasogenic edema. Propofol, a short-acting sedative, is the drug of choice in many intensive care units. However, the effect of propofol on cerebral oxidative metabolism and CBF has not been established in meningitis patients, and it is unknown whether the metabolic coupling is preserved.

The present study addresses the effect of norepinephrine and propofol on global CBF, oxidative metabolism, and net flux of catecholamines in patients with severe bacterial meningitis as compared with healthy volunteers. We hypothesized the following: (1) during a norepinephrine infusion effectively increasing MAP, CBF increases in patients but remains unchanged in volunteers, whereas cerebral oxidative metabolism and net fluxes of catecholamines are unchanged in both groups; and (2) during propofol infusion, cerebral oxidative metabolism and CBF will decrease in parallel in patients with meningitis.
Materials and Methods

Patients

Eligible patients were mechanically ventilated adults with bacterial meningitis, as verified by lumbar puncture <48 hours before inclusion in this study. We included 7 patients (median age, 59 [range, 26 to 72] years) (Table 1) with severe pneumococcal meningitis. The reason for mechanical ventilation was impaired consciousness or uncontrollable agitation, or both; Glasgow coma score before intubation was 8 points (range, 6–10 points). Patients were monitored according to standards of intensive care, which does not include ICP monitoring in this hospital, and received adequate antibiotic treatment, without dexamethasone. Oral and written informed consent was obtained from the next of kin. Seven healthy male volunteers (age, 24 [range, 21–29] years) were included after a thorough medical examination and informed consent. The study was approved by the Scientific-Ethics Committee of Copenhagen and Frederiksberg Municipalities (file number [K.F.] 01-353/96, with amendments [K.F.] 11-059/01, 11-058/01, and 11-055/02).

Study Design

The patients were studied as soon after inclusion as possible; volunteers reported to the department after an overnight fast. The patients were studied as soon after inclusion as possible; volunteers reported to the department after an overnight fast. The patients were monitored according to standards of intensive care, which does not include ICP monitoring in this hospital, and received adequate antibiotic treatment, without dexamethasone. Oral and written informed consent was obtained from the next of kin. Seven healthy male volunteers (age, 24 [range, 21–29] years) were included after a thorough medical examination and informed consent. The study was approved by the Scientific-Ethics Committee of Copenhagen and Frederiksberg Municipalities (file number [K.F.] 01-353/96, with amendments [K.F.] 11-059/01, 11-058/01, and 11-055/02).

Study After Lumbar Puncture (h) Outcome

*This patient was transferred to a rehabilitation unit 2 months after admission and died 5 months after the primary admission because of cancer.

Patient Study

Global CBF, cerebral metabolic rates (CMR) of glucose (glu), and lactate (lac) and cerebral net fluxes (J) of norepinephrine and epinephrine were measured sequentially during 3 conditions: baseline, norepinephrine infusion, and propofol infusion.

Norepinephrine Infusion

Norepinephrine was infused intravenously at rates sufficient to increase MAP by at least 20 mm Hg from baseline. The infusion rate was titrated so that the target MAP was reached 18 minutes after the start of tracer infusion (10 minutes before start of blood sampling) and maintained unchanged until the end of blood sampling.

Propofol Infusion

Propofol was infused intravenously at rates routinely used for deep sedation. The infusion rate was superimposed on the baseline settings of sedatives and analgesics. The target infusion rate of propofol was set at the start of tracer infusion (28 minutes before blood sampling) and maintained until the end of blood sampling. Norepinephrine was infused whenever needed to maintain MAP unchanged from baseline.

The order of measurements was not randomized. Measurements were spaced 1 hour apart (30-minute washout phase plus 30-minute tracer infusion), ie, total study duration was 3 hours. The position of the patient, ventilator settings, and infusion rates of sedatives and sympathomimetics, except for the changes stated previously, were maintained unchanged throughout the study (Table 2). A physician was present in the room at all times during the study, continuously monitoring the patient for hemodynamic and neurological changes; no complications occurred.

Volunteer Study

CBF, CMR, and J were measured at baseline and during an infusion of norepinephrine at rates as stated for patients. No propofol was

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TABLE 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, Age</th>
<th>Cerebrospinal Fluid Leukocyte Count (10⁶ L⁻¹)</th>
<th>Time of Baseline Study After Lumbar Puncture (h)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 26</td>
<td>1120</td>
<td>30</td>
<td>Survived, no sequelae</td>
</tr>
<tr>
<td>2</td>
<td>F, 59</td>
<td>7987</td>
<td>18</td>
<td>Survived, no sequelae</td>
</tr>
<tr>
<td>3</td>
<td>M, 42</td>
<td>6450</td>
<td>26</td>
<td>Survived, slight cognitive sequelae</td>
</tr>
<tr>
<td>4</td>
<td>F, 69</td>
<td>1495</td>
<td>20</td>
<td>Survived, no sequelae</td>
</tr>
<tr>
<td>5</td>
<td>F, 72</td>
<td>1424</td>
<td>26</td>
<td>Survived meningitis*, moderate cognitive sequelae</td>
</tr>
<tr>
<td>6</td>
<td>M, 46</td>
<td>627</td>
<td>27</td>
<td>Survived, severe hearing deficit</td>
</tr>
<tr>
<td>7</td>
<td>F, 64</td>
<td>5645</td>
<td>17</td>
<td>Survived, slight hearing deficit</td>
</tr>
</tbody>
</table>

*This patient was transferred to a rehabilitation unit 2 months after admission and died 5 months after the primary admission because of cancer.

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TABLE 2. Infusion Rates of Sedatives, Analgesics, and Sympathomimetics

<table>
<thead>
<tr>
<th>Sedative/Analgesic</th>
<th>Meningitis (N=7)</th>
<th>Control (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infusion Rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>(µg kg⁻¹ min⁻¹)</td>
<td>(µg kg⁻¹ min⁻¹)</td>
</tr>
<tr>
<td>Baseline</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>0–200</td>
<td>0.2</td>
<td>0.12</td>
</tr>
<tr>
<td>0–6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N*</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>0–200</td>
<td>6</td>
<td>0.10</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.10</td>
<td>0.40</td>
</tr>
<tr>
<td>0.2</td>
<td>(0.07–0.50)</td>
<td>(0.22–0.80)</td>
</tr>
<tr>
<td>0.1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>0.2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>0.2</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Values are medians with ranges in parentheses. ND indicates not done.

*N* of patients receiving the drug at baseline.

†One patient was given methadone.
infused. The order of the baseline and norepinephrine studies was randomized with a 1-hour interval between measurements. No complications occurred.

**Measurements**

Global CBF, CMR, and J were measured using the Kety-Schmidt technique in the desaturation mode using 133Xe as previously described. Paired blood samples were drawn at prespecified times and counted on a scintillation counter (Cobra II; Packard Instruments) yielding background-corrected and decay-corrected activity of 133Xe in cpm/g blood.

Paired full-blood samples were analyzed on a blood gas analyzer (ABL 715; Radiometer) for arterial (a) and jugular venous (v) oxygen tension (P aO2), oxygen saturation (S aO2), and carbon dioxide tension (p CO2).

Glucose and lactate concentrations were measured on fluoride-treated plasma, which was stored at −20°C until analyzed by an enzymatic method (YSI 2700; Yellow Spring Instruments). Plasma glucose concentrations were converted to whole-blood concentrations.

Glutathione-treated and EGTA-treated plasma were stored at −80°C until measurement of norepinephrine and epinephrine concentration by high-performance liquid chromatography (Hewlett-Packard) with electrochemical detection. For calculation of J, plasma concentrations were converted to whole-blood concentrations.

**Calculations**

Calculations were performed as previously described. Briefly, global CBF was calculated from the height-over-area equation, using a hemoglobin (Hb)-corrected A as given by Heedt-Rasmussen et al. Arterial and jugular venous concentrations and the arterial-to-jugular venous concentration difference (a-vD) of O2 were calculated from measured values of Hb, P O2, and S O2. CMRO2, CMRglu, and CMRlac and the cerebral net flux, J, of catecholamines were calculated by the Fick principle of multiplying CBF by the a-vD of the substance. By definition, positive values of CMR or J indicate consumption or net influx, and negative values indicate production or net efflux.

The index of autoregulation and the index of metabolic coupling were calculated as follows. First, the estimated cerebrovascular resistance, CVRe, was calculated as

\[
CVRe = \frac{MAP}{CBF}
\]

This equation substitutes MAP for cerebral perfusion pressure, i.e., it assumes that the ICP is zero. This assumption was made because ICP monitoring was not available. In patients with increased ICP, MAP will be higher than the cerebral perfusion pressure, i.e., the absolute value of CVR will be overestimated. This will be of less importance during repeated measurements, provided that the ICP is unchanged between measurements.

The autoregulation index (ARI) was calculated from the values obtained at baseline and during norepinephrine infusion as relative change in CVR, divided by relative change in MAP, i.e.,

\[
ARI = \frac{\frac{CVR_{NE} - CVR_{base}}{CVR_{base}}}{\frac{MAP_{NE} - MAP_{base}}{MAP_{base}}}
\]

Base and NE indicate values measured at baseline and during norepinephrine infusion, respectively. If CBF values are identical at baseline and during norepinephrine infusion (perfect autoregulation), the relative change in CVR will be identical to the relative change in MAP, and the resulting ARI is 1.0. Conversely, if the relative change in CBF is identical to the relative change in MAP, i.e., if autoregulation is severely impaired, CVR will remain unchanged, and the resulting ARI is zero. The ARI was not adjusted for changes in P CO2.

The metabolic coupling index (MCI) was calculated from values obtained at baseline and during propofol infusion as relative change in CBF divided by relative change in CMRO2, i.e.,

\[
MCI = \frac{\frac{CMRO2_{SED} - CMRO2_{base}}{CMRO2_{base}}}{\frac{CBF_{SED} - CBF_{base}}{CBF_{base}}}
\]

SED indicates values measured during propofol infusion. If CBF decreases in proportion to CMRO2 during propofol infusion (perfect metabolic coupling), the MCI is 1.0; conversely, if no change in CBF is observed (total absence of metabolic coupling), the MCI is zero.

**Statistical Analysis**

Values are medians and ranges. Nonparametric methods, i.e., Mann–Whitney U test and Wilcoxon test for paired samples were used. P<0.05 was considered significant. Analysis was performed using SPSS Base and Advanced Models Version 11.0 for Windows (SPSS Inc).
Results

Systemic Parameters

Meningitis patients and controls had similar MAP values at baseline (79 [70 to 89] and 87 [72 to 103] mm Hg, respectively). During norepinephrine infusion, MAP increased in both groups (patients: 99 [98 to 129] mm Hg, \( P<0.05 \) compared with baseline; controls: 123 [112 to 132] mm Hg, \( P<0.05 \)).

Figure 1. Effect of norepinephrine infusion on mean arterial pressure (MAP), cerebral blood flow (CBF), and cerebral metabolic rate of oxygen (CMRO\(_2\)). Individual values and medians (transverse bars) are given.
At baseline, patients had lower $P_{a}$ CO$_2$ than controls (4.5 [4.1 to 4.8] versus 5.4 [5.3 to 5.5] kPa, $P<0.001$). $P_{a}$ CO$_2$ was unchanged in patients but decreased slightly during norepinephrine infusion in controls (5.0 [4.5 to 5.3] kPa; $P<0.05$, compared with baseline). Core temperature was 38.4°C (37.0 to 40.1) in patients and did not change during measurements; temperature was not measured in controls.

Cerebral Blood Flow and Metabolism

At baseline, patients had lower CBF ($P<0.01$), $a$-$v$ DO$_2$ ($P<0.001$), CMRO$_2$ ($P<0.001$), and CMR$_{glu}$ ($P<0.05$) than controls (Table 3). CMR$_{lac}$ did not differ between patients and controls.

In patients, CBF increased during norepinephrine infusion ($P<0.05$), whereas CMRO$_2$ decreased slightly ($P<0.05$; Table 3; Figure 1); CMR$_{glu}$ and CMR$_{lac}$ were unchanged. In controls, CBF and CMR remained unchanged.

During propofol infusion in meningitis patients (Table 3; Figure 2), CMRO$_2$ and CMR$_{glu}$ decreased from baseline values (for both, $P<0.05$), and CMR$_{lac}$ remained unchanged. CBF was not reduced during propofol infusion ($P=0.06$). The $a$-$v$DO$_2$ and the $a$-$v$D$_{glu}$ (0.43 [0.26 to 0.49] versus 0.30 [0.18 to 0.42] mmol/L, $P<0.05$) decreased.

The ARI was higher in controls (1.17 [0.76 to 1.29]) than in meningitis patients (0.76 [−0.19 to +0.89]; $P<0.01$, compared with controls). The MCI in meningitis patients was 0.74 (−0.06 to +1.01). The MCI was not measured in controls.

Norepinephrine and Epinephrine

At baseline, the arterial plasma concentration of norepinephrine did not differ between groups, whereas patients had higher concentrations of epinephrine than controls ($P<0.05$;
Schmidt technique, we found matter flow. Using the Kety may have been overrepresented as compared with white

21 Moreover, hypocapnia partially restores 

sion, or during propofol infusion. 21 Moreover, hypocapnia partially restores 

concentrations. This indicates that the increase in CBF was 

increased without a concomitant increase in cerebral oxida-

ted nor the presence of hypocapnia relative to controls 

explain the disturbed CBF autoregulation in the patients. 

We believe that neither the sedatives–analgesics adminis-

tered nor the presence of hypopcapnia relative to controls 

explain the disturbed CBF autoregulation in the patients. 

Thus, preserved autoregulation has been demonstrated in humans during sedation with midazolam and fentanyl20 and with propofol.21 Moreover, hypocapnia partially restores autoregulation in meningitis patients.18 In contrast, the high temperature in most patients may be of some significance, because hypothermia restores autoregulation in patients with fulminant hepatic failure.22

The use of norepinephrine in meningitis patients has been viewed as problematic, because it may traverse the disrupted blood–brain barrier, increase global cerebral metabolism and CBF, and aggravate vasogenic edema. We found that at clinically relevant doses of norepinephrine, global CBF increased without a concomitant increase in cerebral oxidative metabolism. Moreover, no net cerebral uptake of norepi-

nephine was observed over a wide range of arterial plasma concentrations. This indicates that the increase in CBF was not mediated by an increase in brain metabolism, but rather was a consequence of impaired CBF autoregulation present in the early stages of acute bacterial meningitis.

Norepinephrine increases glycolysis and oxidative metab-

olism in astrocytes.23 Its penetration over the intact blood–brain barrier is poor24 but increases in animal models after barrier disruption by intracarotid injection of hypertonic urea; simultaneously, CBF and metabolism increase.5 In bacterial meningitis, a certain extent of barrier disruption is likely to occur.2,3 However, 2 separate lines of evidence from the present study suggest that at clinically relevant dosing rates, intravenously infused norepinephrine does not enter the brain to an extent that increases global cerebral metabolism. First, no net flux was observed in patients or healthy subjects at baseline, during norepinephrine infusion, or in patients during propofol infusion. Secondly, even during high infusion rates of norepinephrine no effects were observed to suggest an independent cerebral action of norepinephrine. The slight reduction in CMRO2 observed during norepinephrine infusion may be caused by an underestimation of the CBF change inherent in the Kety-Schmidt technique.9

Sedatives such as propofol are often used in meningitis patients; a reduction in cerebral metabolism is suggested to be beneficial as it is assumed to be accompanied by a parallel reduction in CBF, cerebral blood volume, and ICP. This assumption has not previously been tested in humans with bacterial meningitis. In this study, propofol reduced CMRO2 but failed to reduce CBF. The change in the a-vDO2 also indicates a resetting of the relationship between CMRO2 and CBF. Several studies have found an unchanged a-vDO2 in healthy subjects during propofol sedation,25,26 even at doses leading to an isoelectric electroencephalogram.27 Taken together, the results suggest that cerebral metabolic coupling is impaired in patients with bacterial meningitis.

The low a-vDO2 and CMRO2 in meningitis patients at baseline agree with previous findings in these patients.10,17 Patients were infused with sedatives and analgesics throughout the study, which probably contributed to the low CMRO2. In contrast, the hyperthermia observed in patients would be

| TABLE 4. Arterial Plasma Concentration and Cerebral Net Flux of Catecholamines |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Arterial Plasma Concentration    | Cerebral Net Flux               |                                |
|                                | Norepinephrine (nmol·L⁻¹)        | Epinephrine (nmol·L⁻¹)          | Norepinephrine (pmol·g⁻¹·min⁻¹) | Epinephrine (pmol·g⁻¹·min⁻¹)    |
|                                | Baseline Meningitis 1.3 (0.65–32) | 0.79* (0.15–8.1)               | −0.02 (−0.17–+0.92)           | −0.02 (−0.52–+2.1)             |
|                                | Control 0.73 (0.67–1.2)          | 0.29 (0–0.86)                  | −0.02 (−0.15–+0.15)           | 0 (−0.08–+0.03)                |
|                                | Norepinephrine infusion Meningitis 25† (15–119) | 1.1 (0.16–2.7)               | +0.49 (−0.46–+2.7)           | +0.05 (−0.13–+0.32)           |
|                                | Control 77† (35–151)            | 0 (0–0.47)                    | −3.1 (−0.52–+5.9)            | −0.01 (−0.08–0)                |
|                                | Propofol infusion Meningitis† 9.1† (2.0–29) | 1.3 (2.2–3.3)               | +0.15 (−0.60–+1.0)           | +0.04 (−0.01–+0.39)           |

*Significantly higher compared to control group at baseline.  †Significantly higher compared to same group at baseline.  ††N=6 because of unsuccessful measurement in 1 subject.
expected to increase CMRO₂.⁸ Patients were hypocapnic compared with controls; this reduces CBF in meningitis patients and volunteers but affects CMRO₂ in neither patients nor volunteers.¹⁰

We studied sedated and mechanically ventilated patients early during pneumococcal meningitis. The major pathophysiological events of bacterial meningitis, intrathecal inflammation and blood-brain barrier dysfunction, occur irrespective of bacterial cause.²⁹ Accordingly, the findings can probably be generalized also to patients with meningitis caused by other bacteria than pneumococci. However, extrapolation of the results to less severely affected patients or to the late phase of meningitis may not be justified.¹

The clinical implications of this study are that the cerebrovascular effect of norepinephrine in meningitis patients is mediated solely through its influence on MAP. Thus, increasing MAP by norepinephrine infusion will increase CBF because of impaired autoregulation, and not because of an increase in cerebral metabolism. Secondly, the reduction in a-vDO₂ during propofol infusion suggests that cerebral metabolic coupling is impaired during the early phase of meningitis; thus, global CBF decreases relatively less than oxidative metabolism during propofol sedation.

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References

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