Cerebral blood flow autoregulation in early experimental \textit{S. pneumoniae} meningitis

Michael Pedersen,1 Christian T. Brandt,3 Gitte M. Knudsen,2 Christian Østergaard,3 Peter Skinhøj,1 Niels Frimodt-Møller,3 and Kirsten Møller1

1Department of Infectious Diseases and 2Neurobiology Research Unit, Rigshospitalet, Copenhagen University Hospital; and 3National Center for Antimicrobial and Infection Control, Copenhagen, Denmark

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\section*{MATERIALS AND METHODS}

\textbf{Experimental pneumococcal meningitis.} We used a previously described model of pneumococcal meningitis in rats (3). All experiments were carried out in accordance with the European Communities Council Resolves of 24 November 1986 (86/609/EEC). The experimental protocol was approved by the Danish State Research Inspectorate (J. No. 2002/651–527).

\textit{Bacteria.} \textit{S. pneumoniae} serotype 3 [strain 68034; Statens Serum Institut (SSI), Copenhagen, Denmark] was used for the experiments. Before experiments, bacteria were passed through rats to ensure virulence. A culture from rat CSF was obtained and stored at \(-80\,^\circ\text{C}$. For experiments, bacteria were thawed and grown on 5% blood agar plates (SSI) for 18 h at 35$^\circ$C, diluted in cold sterile isotonic saline to an optical density of 0.5 (546 nm, Sherwood Colorimeter 254), and thereafter diluted 10-fold to achieve a final concentration of $1 \times 10^7$ colony-forming units (CFU)/ml, as confirmed by quantitative cultures.

\textit{Rats.} Young adult male Wistar rats (Harlan) weighing 250–350 g were used for the experiments. Normal day-night cycles were provided for the rats with food and water ad libitum.

\textit{Inoculation.} On the day before the autoregulation studies, the rat was anesthetized with a subcutaneous injection of a mixture of fentanyl (0.1 mg/kg body wt), fluanisone (3.3 mg/kg), and midazolam (1.6 mg/kg). Intracisternal inoculation was performed by an injection of 30 µl of bacterial suspension (meningitis rats) or of normal saline (control rats) by using a 25-gauge butterfly needle. Following anesthesia, the rat was returned to a cage to recover.

\textit{Clinical assessment.} Rats were assessed for clinical signs of infection at 12 and 24 h after inoculation. Severity of illness was classified by the

In healthy humans, a constant blood supply to the brain despite changes in cerebral perfusion pressure (CPP) is secured during by CBF autoregulation (14). If CBF autoregulation is lost, CBF will vary in parallel with the CPP even within the normal range of autoregulation. This may lead to an increased risk of cerebral ischemia and infarction during hypotensive episodes and to an increased risk of vasogenic edema during hypertension. Hypocapnia triggers vasoconstriction in healthy subjects, thereby leading to an increase in cerebrovascular resistance and a reduction in CBF (30). If this effect is also present during meningitis, it may counteract the vasodilatation possibly associated with meningitis, thereby restoring CBF autoregulation.

The objective of this study was to investigate CBF autoregulation in an adult rat model of early \textit{S. pneumoniae} meningitis. We hypothesized that CBF autoregulation is impaired early in the course of meningitis but is restored during acute hyperventilation.

\section*{RESULTS}

\textbf{CBF autoregulation and intracranial pressure (ICP) during normo- and hyperventilation in a rat model of \textit{Streptococcus pneumoniae} meningitis.} Meningitis was induced by intracisternal injection of \textit{S. pneumoniae}. Mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP, defined as MAP – ICP), and laser-Doppler CBF were measured in anesthetized infected rats and saline-inoculated controls. CPP was either incrementally reduced by controlled hemorrhage or increased by intravenous norepinephrine infusion. Twelve hours postinoculation, rats were studied solely during normocapnia, whereas rats studied after 24 h were exposed to either normocapnia or to acute hyperventilation. CPP was either unchanged at 12 h but increased at 24 h postinoculation (not significant and $P < 0.01$, respectively); hypocapnia did not lower ICP compared with normocapnia. Twelve hours postinoculation, CBF autoregulation was lost in all infected rats but preserved in all control rats ($P < 0.01$). Twenty-four hours after inoculation, 10% of infected rats had preserved CBF autoregulation during normocapnia compared with 80% of control rats ($P < 0.01$). In contrast, 60% of the infected rats and 100% of the control rats showed an intact CBF autoregulation during hypocapnia ($P < 0.05$ for the comparison of infected rats at normocapnia vs. hypocapnia). In conclusion, CBF autoregulation is lost both at 12 and at 24 h after intracisternal inoculation of \textit{S. pneumoniae} in rats. Impairment of CBF autoregulation precedes the increase in ICP, and acute hyperventilation may impair autoregulation of CBF.

\section*{DISCUSSION}

STREPTOCOCCUS PNEUMONIAE is a common cause of bacterial meningitis and carries a high mortality and morbidity (5, 23, 27, 37, 38). Although antibiotics rapidly sterilize the cerebrospinal fluid (CSF) in pneumococcal meningitis within hours to 1 day of initiation (8), intrathecal inflammation persists for a longer time and is associated with the development of cerebral edema and elevated intracranial pressure (ICP) (12, 21). Bacterial constituents as well as certain mediators of the inflammatory response are known to be potent vasodilators (32), which may increase cerebral blood flow (CBF), cerebral blood volume, and ICP (15); moreover, this vasodilatation may impair normal cerebrovascular reactivity, affecting the regulation of CBF.

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following score (0–4): 0 = no signs of illness; 1 = affected activity; 2 = without activity, but able to turn if laid on the back (intact righting reflex); 3 = without activity and unable to turn if put on the back (loss of righting reflex); and 4 = lethargic and lying on the side.

**Surgical procedures.** At 12 or 24 h after inoculation, rats were anesthetized by induction with 5% isoflurane (Forane vapour; Dräger, Lübeck, Germany); anesthesia was maintained with 2.5% isoflurane in a mixture of 30% O2-70% N2O during the following experimental procedures. After tracheotomy, rats were artificially ventilated on a small animal respirator (Harvard Apparatus, Kent, UK), and isoflurane was maintained at 1.7%. End-tidal CO2 was monitored continuously (Brüel & Kjær, Copenhagen, Denmark) and adjusted to the desired level (normoventilation, 5–6 kPa; hyperventilation, 3–4 kPa) by varying the tidal volume. Femoral veins and arteries were cannulated bilaterally for continuous blood pressure measurement (Simonsen and Weel, Herlev, Denmark), blood sampling, administration of drugs, and blood transfusion to avoid hypovolemia. Rats were placed on a heating pad (HB 101/2 Panlab, Barcelona, Spain), and rectal temperature was kept at 37°C. The head was immobilized in a stereotactic frame (Kopf Instruments), and the parietal bone was thinned over an area of 3 mm2, and a 1-mm laser-Doppler probe (probe 407; Perimed, Stockholm, Sweden) was placed on the thinned bone over an area of the cerebrum; great care was taken to avoid regions with major blood vessels. Following surgical procedures, rats rested for 30 min before CBF measurements.

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**CBF measurement.** Relative changes in CBF were measured by laser-Doppler flowmetry at a wavelength of 780 nm. Simultaneous values of CBF, mean arterial pressure (MAP), and ICP were collected at a sampling rate of 35 s–1 both at baseline and throughout the experiment that lasted ~1.5 h.

**Autoregulation studies.** The rats were divided into the following groups: 1a) 12 h postinoculation (saline), lower limit of autoregulation, normoventilated control (n = 5); 1b) 12 h postinoculation, lower limit of autoregulation, normoventilated meningitis (n = 5); 2a) 24 h postinoculation (saline), lower limit of autoregulation, normoventilated meningitis (n = 5); 2b) 24 h postinoculation, lower limit of autoregulation, normoventilated meningitis (n = 10); 3a) 24 h postinoculation (saline), lower limit of autoregulation, hyperventilated meningitis (n = 10); 3b) 24 h postinoculation, lower limit of autoregulation, hyperventilated meningitis (n = 10); 4a) 24 h postinoculation (saline), upper limit of autoregulation, normoventilated control (n = 5); and 4b) 24 h postinoculation, upper limit of autoregulation, normoventilated meningitis (n = 5).

In rats subjected to hyperventilation, the rats were hyperventilated from shortly after intubation and catheterization but before placing the laser-Doppler flow probe. This was done because pilot studies indicated that ICP did not decrease during short-term (i.e., 15 to 30 min) hyperventilation, so that a longer period of hyperventilation might be warranted. The total duration of hyperventilation in these rats before autoregulation measurements was 60–90 min.

In rats subjected to lower-limit (LL) studies, MAP was reduced in decrements of 5 mmHg to the lowest possible level by controlled hemorrhage. For upper-limit (UL) autoregulation studies, MAP was elevated in increments of 10–20 mmHg to the highest possible level by controlled hemorrhage. For upper-limit (UL) autoregulation studies, MAP was elevated in increments of 10–20 mmHg to the highest possible level by controlled hemorrhage. For upper-limit (UL) autoregulation studies, MAP was elevated in increments of 10–20 mmHg to the highest possible level by controlled hemorrhage.}

**Blood analysis.** Arterial blood from the femoral artery was analyzed for pH (pH), oxygen tension (PaO2), carbon dioxide tension (PaCO2), oxygen saturation (SaO2), lactate, and glucose (ABL 605; Radiometer, Copenhagen, Denmark). Values of pH, PaO2, and PaCO2 were temperature corrected.

**Microbiological analysis.** Bacterial load in the CSF and blood were determined by plating 10-fold serial dilutions of 10 μl of CSF and 40 μl of undiluted blood, respectively. As removal of CSF and blood was done at the end of experiments, this was 2–4 h delayed compared with the start of experiments, i.e., at 14–18 h for the 12-h groups and at 26–28 h for the 24-h groups. Cultures were grown on 5% blood-agar plates (SSI) for 18 h at a temperature of 35°C, and the number of CFU was counted.

**Autoregulation analysis.** Values of laser-Doppler blood flow (arbitrary units) were normalized to the baseline level equalling 100. Autoregulation curves in individual rats were plotted with CPP (calculated as MAP – ICP) on the x-axis and normalized laser-Doppler flow values on the y-axis. As manual identification of the exact value of the limits of autoregulation is difficult and subjected to bias (31), it was calculated by computer software as previously described (26, 35). Briefly, this program uses the corresponding values of CPP and laser-Doppler flow in each individual rat to fit a pair of regression lines. Fitting is done in a repetitive manner, starting at the baseline CPP and continuing at 1-mmHg decrements to the lowest measured value. For identification of the lower limit of autoregulation, the pair of regression lines consists of a line with a positive slope through the points below the given CPP value and a horizontal line through the points above that CPP. Finally, the corresponding sum of squares is calculated. The pair of regression lines yielding the least sum of squares is defined as the autoregulation curve, and the CPP corresponding to their intersection is defined as the lower limit of autoregulation. The same procedure was applied for calculation of the upper limit of autoregulation, with the difference that the horizontal regression line was fitted to the data below the CPP value and the sloped regression line to those above that value.

For autoregulation studies to be accepted for computer analysis, the range of CPP values measured was required to be at least 40 mmHg. Thereafter, autoregulation was recorded as present or absent for each individual rat according to the following criteria.

In studies in which the software identified an upper or lower limit of autoregulation, this limit was accepted and autoregulation was classified as preserved if the following criteria were fulfilled: 1) the sum of squares obtained by the two calculated regression lines was lower than that of a single linear regression line fitted to all pressure-flow data of that animal; 2) the CPP value of the autoregulation limit identified by the software was physiologically acceptable with a SE of <25% of the value of the limit; and 3) the CPP value at the limit of CBF autoregulation was at least 10 mmHg higher than the lowest CPP measured in the lower limit experiment, or at least 10 mmHg lower than the highest CPP value measured in the upper limit experiment.

If the criteria were not fulfilled, a single linear regression was identified, and CBF autoregulation was considered to be preserved if the CBF increase for this line was <10% per millimeter Hg increase in CPP, and abolished if the CBF increase was >10% per millimeter Hg increase in CPP. After CBF autoregulation curves were classified as abnormal and normal, all data were pooled for each group, and mean values of CBF and autoregulatory limits were calculated for the groups.

**Statistics.** Pooled data of autoregulation limits are presented as means ± SE; the remaining data are presented as medians and quartiles. The Kruskal-Wallis and the Mann-Whitney U-tests were used for comparison between groups. Fisher’s exact test was used for comparison of categorical data. P < 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (version 11.5; SPSS; Chicago, IL).

**RESULTS.** Sixty-seven rats were prepared for the study. Three infected rats died during induction of anesthesia before surgery and were excluded from analysis. Data from two rats in the infected group and two in the control group were excluded because of measurement difficulties. Thus a total of 60 rats was studied.
after inoculation with pneumococci (n = 30) or saline (n = 30), respectively.

**Clinical presentation.** Clinical signs of meningitis were observed in all rats inoculated with *S. pneumoniae* (n = 30). In rats studied at 12 h after inoculation, all (n = 5) had a clinical score of 1 before anesthesia; in the infected rats studied at 24 h (groups 2a, 3a, and 4a), 5 rats had a score of 2, and 20 rats had a score of 3. Saline-inoculated rats (n = 30) exhibited no signs of disease, as indicated by a score of 0 in all animals. Body weight measured immediately before CBF recording was 261 (245–278) g (median and quartiles) in the infected rats vs. 278 (257–318) g in the control rats (Kruskal-Wallis test, P < 0.01).

**Microbiology.** Meningitis rats were inoculated with a bacterial concentration of 2.75 (1.60–4.00) × 10^7 CFU/ml. In infected rats, the resulting bacterial concentration in the CSF was 5.00 (2.49–27.75) × 10^7 CFU/ml (n = 5) in the 12-h group and 3.50 (0.59–7.75) × 10^7 CFU/ml (n = 19) in the 24-h groups. Bacterial concentrations in blood were 7.75 (6.00–55.00) × 10^7 CFU/ml (n = 5) in the 12-h and 1.63 (0.56–15.61) × 10^7 CFU/ml in the 24-h groups, respectively. No difference was found in the bacterial concentration in CSF or blood between the 12-h and 24-h groups (P = 0.37 and 0.06, respectively). In the control rats, all blood and CSF cultures were negative.

**Blood gas analysis and body temperature.** Baseline blood gas values and temperature are given in Table 1. There was no difference between groups with regard to baseline levels of PaO₂, SaO₂, or glucose.

**PaCO₂** did not differ between controls and meningitis rats during normoventilation (groups 1a, 1b, 2a, 2b, 4a, and 4b). Hyperventilated rats had lower PaCO₂ than normoventilated rats, with no difference between hyperventilated controls (group 3a) and hyperventilated infected rats (group 3b). Similarly, pH did not differ between normoventilated groups but was higher in hyperventilated than in normoventilated rats.

**Despite the attempt to control temperature,** infected rats of groups 2b and 3b had slightly, but significantly, lower rectal temperatures than their corresponding controls (groups 2a and 3a). Lactate was increased in all meningitis groups compared with controls and was increased more in hyperventilated meningitis rats than in the normoventilated meningitis rats.

**ICP.** At 12 h after inoculation, baseline ICP values were 2 (2–3) mmHg in the infected group vs. 2 (2–4) mmHg in the control group (NS). By contrast, at 24 h ICP was higher in the infected group than in the controls [11 (5–18) vs. 4 (2–8) mmHg (P < 0.01)]. During hyperventilation at 24 h, ICP was 9 (3–17) mmHg in infected rats [not significant (NS) compared with infected rats at normoventilation] and 3 (2–7) mmHg in control rats (NS) compared with normoventilated control rats.

**MAP and CPP.** During normoventilation, baseline MAP was higher in rats than in infected rats both at 12 h [98 (95–100) vs. 93 (91–95) mmHg; P < 0.001] and at 24 h [pooled normoventilated groups, 114 (97–118) vs. 95 (87–107) mmHg; P < 0.001]. During hyperventilation at 24 h, however, MAP was lower in controls than in infected rats [111 (104–114) vs. 117 (99–130) mmHg; P < 0.05]. Moreover, MAP at baseline in infected rats was lower during normoventilation than hyperventilation [98 (91–107) vs. 117 (99–130) mmHg; P < 0.001].

CPP in control rats was unaffected by hyperventilation compared with normoventilation [108 (98–116) vs. 105 (87–113) mmHg; NS]. In contrast, baseline CPP in hyperventilated infected rats was higher than in normoventilated infected rats [91 (80–111) vs. 88 (69–95) mmHg; P < 0.001] but lower than in hyperventilated controls (P < 0.001).

**Lower limit of CBF autoregulation.** The computer-calculated limits from the analysis of the pooled CBF data are shown in Table 2. At 12 h after inoculation, autoregulation was present in all five control rats (Fig. 1A) and in none of five

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**Table 1. Baseline blood gas variables**

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<th>12 h</th>
<th>24 h</th>
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<tr>
<td></td>
<td>Infected normoventilated (n = 5)</td>
<td>Control normoventilated (n = 5)</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.7 (36.1–37.3)</td>
<td>36.5 (35.7–37.3)</td>
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<tr>
<td>PaCO₂, kPa</td>
<td>5.3 (4.9–5.5)</td>
<td>5.7 (4.9–5.8)</td>
</tr>
<tr>
<td>PaO₂, KPa</td>
<td>19.6 (17.4–21.3)</td>
<td>18.5 (17.4–22.0)</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>99.1 (98.6–99.2)</td>
<td>99.0 (98.8–99.3)</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>11.6 (10.1–12.8)</td>
<td>12.3 (12.1–13.4)</td>
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<tr>
<td>Lactate, mmol/l</td>
<td>2.5* (2.2–2.6)</td>
<td>1.2 (1.0–1.4)</td>
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**Table 2. Lower and upper limits of CBF autoregulation**

<table>
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<th>12 h</th>
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<tr>
<td></td>
<td>Infected normoventilated LL (n = 5)</td>
<td>Control normoventilated LL (n = 5)</td>
</tr>
<tr>
<td>CPP, mmHg</td>
<td>NLI 55 ±1.1</td>
<td>NLI 54 ±1.2</td>
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Values are means ± SE; n = no. of rats. LL and UL, lower and upper limits, respectively, of cerebral blood flow (CBF) autoregulation; CPP, cerebral perfusion pressure; NLI, no limits identified. *P < 0.05 compared with both normo- and hyperventilated LL controls.
infected rats (Fig. 1B, Fisher’s exact test, \( P < 0.01 \)). The lower limit was identified by the computer program in the control rats but not in any of the infected rats, consistent with a loss of autoregulation in this group.

During normocapnia at 24 h after inoculation, the lower limit of autoregulation could be identified in 8 of 10 control rats (Fig. 2A) but in only 1 of 10 rats with meningitis (Fig. 2B, \( P < 0.01 \)). In the single infected rat in which preserved autoregulation was identified, the lower limit was identified at a CPP of 50 \( \pm \) 0.6 mmHg. Since the autoregulation was lost in the majority of meningitis rats, the lower limit was not calculated for the group.

During acute hypocapnia at 24 h after inoculation, the lower limit of autoregulation was present in all 10 control rats (Fig. 3A) and in 6 of the 10 infected rats (Fig. 3B, \( P < 0.05 \) for comparison with normoventilated meningitis rats). The lower CPP limit in hyperventilated control rats did not differ from that of normoventilated controls. By contrast, the lower limit of hyperventilated meningitis rats was higher than that of both hyperventilated (\( P < 0.05 \)) and normoventilated (\( P < 0.01 \)) controls.

Upper limit of CBF autoregulation. The upper limit was only studied at normocapnia, at 24 h postinoculation. The upper limit (Table 2) was present in all five control rats (Fig. 4A) and in none of the five meningitis rats (Fig. 4B, \( P < 0.01 \)).

**DISCUSSION**

We found that CBF autoregulation was lost before the increase in ICP in rats with acute pneumococcal meningitis. Moreover, acute hypocapnia partially restored autoregulation, although the lower limit was higher than in control rats. In contrast, ICP was not reduced by hypocapnia.

In this study, we used continuous laser-Doppler flowmetry during blood pressure changes to evaluate the lower and upper limits of static CBF autoregulation. Laser-Doppler flowmetry has been used previously to study relative changes in cortical CBF during rat meningitis (28) and estimates the limits of autoregulation correctly when validated against the \( ^{133}\text{Xe} \) clearance method (35).

Blood pressure was manipulated by hemorrhage and norepinephrine infusion, respectively. Although hemorrhage may...
elicit minor changes in hematocrit, which may be corrected by fluid therapy, it is preferable to pharmacological induction of hypotension in this model because it allows for rapid and easy control of blood pressure and is devoid of intrinsic cerebrovascular effects. Intravenous norepinephrine does not constrict cerebral vessels in vivo at least in humans (22), does not pass the blood-brain barrier either in healthy subjects or in patients with severe pneumococcal meningitis (18), and has been used previously to study CBF autoregulation in rats (4); therefore, it was considered suitable for the study of effects of a blood pressure increase in itself on CBF. Finally, since isoflurane did not affect autoregulation in control rats, this anesthetic was not responsible for the loss of autoregulation in the meningitis rats. Thus we suggest that the pressure-passive variation of CBF, as measured by laser-Doppler flowmetry, with the CPP in this study reflected a true loss of autoregulation.

Loss of CBF autoregulation has previously been found in a rabbit model of experimental meningitis at 16–20 h after inoculation (36), as well as in humans with bacterial meningitis regardless of whether CBF was measured with $^{133}$Xe injection, the arteriovenous $O_2$ difference method, or transcranial Doppler ultrasonography (17, 24). None of these studies, however, examined the timing between the loss of autoregulation and the ICP increase. The first study demonstrated an increase in ICP concomitantly with loss of autoregulation but did not examine the timing between the two phenomena (36); according to the two clinical studies, ICP was either increased at the time of the study (24) or not measured (17). The present study suggests that autoregulation is lost before the ICP increase in meningitis, which implies that loss of autoregulation is neither due to nor dependent on an increase in ICP. Conversely, it remains to be established whether the loss of autoregulation is a necessary prerequisite for a subsequent increase in ICP.

One possible explanation for loss of autoregulation during meningitis may be cerebral arteriolar dilatation, leading to a state of vasoparalysis; this is supported by the finding that hyperventilation, which promotes arterioloconstriction (13), partially restored autoregulation. Moreover, Koedel et al. (11), using pneumococcal cell walls in a rat model of meningitis, found that laser-Doppler flow increased significantly from baseline at 5 h after inoculation. Arteriolar dilatation during meningitis, in turn, may be triggered by the presence of oxygen...
free radicals (16), cerebral interstitial acidosis (2), or nitric oxide (NO) (9). The role of NO may be particularly important, as this substance has been shown to have both a direct influence on the cerebral vasculature during pneumococcal meningitis (6, 10) and an indirect influence in normal rats via inhibition of the production of the vasoconstrictor 20-hydroxyeicosatetraenoic acid (1, 7). A characteristic clinical finding in patients with severe bacterial meningitis is spontaneous hyperventilation (20). Acute hyperventilation reduces CBF (29) through an increase in interstitial pH that triggers cerebrovascular constriction (13). It is possible that this vasoconstriction reduces cerebrovascular reactivity and thus is instrumental in the partial recovery of autoregulation observed in the present experimental study, as well as in meningitis patients (19). However, laser-Doppler flowmetry is less suitable for measuring absolute values of CBF (35); therefore, the results of the present study do not in themselves indicate whether vasoconstriction and a concomitant CBF reduction occurred during hyperventilation, and whether this or another mechanism induced by, e.g., the resulting alkalosis was the reason for the partial restoration of autoregulation.

The limits of cerebral autoregulation may be modulated by a number of different physiological, pharmacological, and pathological conditions. Normally, the CBF autoregulation limits are located at a MAP of approximately 60 mmHg and 150 mmHg, respectively (14, 33, 34), which is close to what we observed in the healthy rats. In healthy humans, hyperventilation shifts the lower limit to the left, widens the autoregulatory plateau, and reduces baseline CBF (25). Albeit not statistically significant, we found that the lower limit was lower in hyperventilated than in normoventilated control rats. In the hyperventilated infected group, the lower limit was located at a CPP that was higher than that of both normo- and hyperventilated controls, indicating a partial rather than a full recovery of autoregulatory capacity, even in those rats in which the lower limit was present during hyperventilation. It remains to be established whether a more pronounced hypocapnia is able to restore CBF autoregulation completely.

At 24 h postinoculation, ICP was significantly higher in infected than in control rats. In the infected group, we found a substantial variation in the ICP values, despite the fact that all rats were seriously ill as evaluated by a rough clinical scale. Although median ICP was lower in infected hyperventilated rats, there was no significant difference between normoventilated and hyperventilated meningitis rats. This may be due to a considerable variation in observed ICP values. In general, hyperventilation causes a rapid lowering of the ICP (29); however, this has never been shown in humans with meningitis.

The clinical implications of the present study are, first, that the demonstrated loss of autoregulation renders the infected brain more vulnerable during fluctuations in perfusion pressure. These fluctuations may be associated with an increased risk of hypoperfusion and ischemia during episodes of low blood pressure and of hyperperfusion, cerebral vasogenic edema, and subsequent ICP increases during high blood pressure. Second, with acute hyperventilation autoregulation is partially restored, which may reduce the risk of perfusion disturbances during MAP excursions in these patients. However, the present study was designed to address neither the clinical usefulness of acute hyperventilation nor its potential risks.

In conclusion, CBF autoregulation is abolished in a rat model of early pneumococcal meningitis before the increase in ICP. Partial recovery of autoregulation occurred during acute hyperventilation as indicated by two findings: first, autoregulation was present only in some of the hyperventilated rats, and, second, the lower limit in these rats was located at a higher CPP value in meningitis compared with control rats. This partial recovery of autoregulation occurred in the absence of a significant change in the ICP during hyper- compared with normoventilation.

GRANTS

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REFERENCES


