Effect of Short-Term Hyperventilation on Cerebral Blood Flow Autoregulation in Patients With Acute Bacterial Meningitis

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Background and Purpose—Cerebral blood flow (CBF) autoregulation is impaired in patients with acute bacterial meningitis; this may be caused by cerebral arteriolar dilatation. We tested the hypothesis that CBF autoregulation is recovered by acute mechanical hyperventilation in 9 adult patients with acute bacterial meningitis.

Methods—Norepinephrine was infused to increase mean arterial pressure (MAP) 30 mm Hg from baseline. Relative changes in CBF were concomitantly recorded by transcranial Doppler ultrasonography of the middle cerebral artery, measuring mean flow velocity (Vmean), and by measurement of arterial to jugular oxygen content difference (a-v D O2). The slope of the regression line between MAP and Vmean was calculated. Measurements were performed during normoventilation and repeated after 30 minutes of mechanical hyperventilation.

Results—At normoventilation (median Pa CO2 4.4 kPa, range 3.5 to 4.9), MAP was increased from 68 mm Hg (60 to 101) to 109 mm Hg (95 to 126). Vmean increased with MAP from 48 cm/s (30 to 61) to 65 cm/s (33 to 86) (P<0.01), and a-v DO2 decreased from 2.2 mmol/L (1.0 to 2.7) to 1.4 mmol/L (0.8 to 1.8) (P<0.05). During hyperventilation (PaCO2 3.5 kPa, range 3.3 to 4.1), MAP was increased from 76 mm Hg (58 to 92) to 109 mm Hg (95 to 121). Vmean increased from 45 cm/s (29 to 55) to 53 cm/s (33 to 78) (P<0.01), and a-v DO2 decreased from 2.5 mmol/L (1.8 to 3.0) to 1.8 mmol/L (1.2 to 2.4) (P<0.05). Four patients recovered autoregulation completely during hyperventilation. The slope of the autoregulation curve decreased during hyperventilation compared with normoventilation (P<0.05).

Conclusions—CBF autoregulation is partially recovered during short-term mechanical hyperventilation in patients with acute bacterial meningitis, indicating that cerebral arteriolar dilation in part accounts for the regulatory impairment of CBF in these patients. (Stroke. 2000;31:1116-1122.)

Key Words: autoregulation ■ cerebral blood flow ■ cerebral blood flow velocity ■ meningitis ■ ultrasonography, Doppler, transcranial

In patients with acute bacterial meningitis, elevated intracranial pressure (ICP) appears to be related to cerebral edema.1,2 In addition, changes in global and regional cerebral blood flow (CBF) have been reported in acute bacterial meningitis.3,4 The nature of these CBF fluctuations and the pathophysiological importance for the development of cerebral edema and intracranial hypertension are not fully understood. However, it may be reasonable to assume that meningeal inflammation, with the release of a variety of factors, including oxygen free radicals,5 cerebral interstitial acidosis,6 and nitric oxide,7 results in cerebral arteriolar dilation. Such a decrease in cerebrovascular tone would tend to increase cerebral blood volume and subsequently ICP.

Arteriolar dilation also may be expected to affect the normal relation between perfusion pressure and CBF, that is, autoregulation may be disturbed.8 It has previously been shown that CBF autoregulation is impaired in patients with acute bacterial meningitis9,10 and in the rabbit model of meningitis.11

If cerebral arteriolar dilation is responsible for the impairment of autoregulation in patients with acute bacterial meningitis, acute hyperventilation may be hypothesized not only to mediate vasoconstriction8,12,13 but to restore autoregulation. This study was conducted to investigate the acute effect of mechanical hyperventilation on CBF autoregulation in patients with acute bacterial meningitis. Cerebral perfusion was monitored by transcranial Doppler (TCD) and by measuring cerebral oxygen extraction.

Subjects and Methods

Patients
Mechanically ventilated adult patients with acute bacterial meningitis were consecutively evaluated for entry into the study.

Acute bacterial meningitis was defined by the presence of a neutrophil pleocytosis (>10×10⁶ leukocytes/L) in cerebrospinal fluid.
fluid (CSF) attributable to a bacterial infection and a clinical presentation compatible with meningitis. Exclusion criteria were age <18 years; pregnancy or breast-feeding; a history of stroke; lumbar puncture >48 hours before inclusion; mean arterial pressure (MAP) <40 mm Hg for >2 hours; or cerebral herniation before inclusion.

The study was approved by the Scientific Ethics Committee of Copenhagen and Frederiksberg Municipalities (jr. no. KF 01 to 353/96). Informed consent was obtained from the patient or the patient’s next of kin, according to the Declaration of Helsinki.

Twenty-three patients with acute bacterial meningitis were admitted from December 1997 to February 1999 and fulfilled the inclusion criteria. Fourteen patients were excluded from the study because the next of kin declined consent (4 patients) or because of the presence of ≥1 exclusion criteria (10 patients). Thus, 9 patients (median age 53 years, range 19 to 74) were included in the study (Table 1). The CSF leukocyte count was 3000 (109 to 19000)×10⁶/L. Five patients had septic shock necessitating inotropic and/or vasopressor support.

**Treatment of Meningitis**

The treatment of the patients followed local guidelines for treatment of acute bacterial meningitis. Empiric antibiotic treatment for acute bacterial meningitis was intravenous ceftriaxone and ampicillin. If specific microorganisms were demonstrated in blood or CSF, treatment was changed according to type of microorganism and resistance pattern. The duration of treatment was 7 to 14 days, depending on the causative agent. Steroids were not given.

All patients were sedated, endotracheally intubated, and mechanically ventilated. Ventilator settings were adjusted to maintain an arterial carbon dioxide tension (PaCO₂) of 4 to 4.5 kPa during the first 24 to 48 hours. Sedation was maintained with infusions of propofol (50 to 150 mg/h) and fentanyl (0.05 to 0.10 mg/h), or sufentanil (0.05 to 0.10 mg/h) during the first 24 to 48 hours. Thereafter, midazolam (5 to 10 mg/h) and fentanyl or sufentanil was infused.

All patients had a central venous catheter for administration of fluids and drugs and a radial artery catheter for blood pressure monitoring and arterial blood gas analysis. Seven patients had a retrograde jugular venous catheter (5F single-lumen) on one side, with the tip located in the jugular bulb. This catheter was used for concomitantly recorded. Where possible, ≥2 simultaneous measurements of MAP, TCD parameters, and blood gas parameters were performed during each autoregulation measurement.

**Transcranial Doppler Ultrasonography**

Unilateral TCD of the middle cerebral artery was performed with a 2-MHz pulsed probe placed over the temporal window and secured by a headband. Measured parameters included systolic, diastolic, and mean flow velocities (Vₚ, Vₚₑ, and Vₑₑ [in cm/s]), respectively. Calculated parameters included Gosling’s pulsatility index (PI), defined as (Vₚₑ−Vₑₑ)/Vₑₑ.⁶

Assuming an unchanged caliber of the middle cerebral artery, Vₑₑ will change in proportion with CBF. Thus, Vₑₑ may be used to measure relative changes in CBF.

**Arterial and Jugular Vein Blood Gas Analysis**

Blood samples for blood gas analysis were drawn simultaneously from the radial artery catheter and the retrograde jugular vein catheter. Blood gases were measured on an ABL 605 and OSM 3 (Radiometer). Blood hemoglobin content (Hb, in mmol/L) was measured by standard methods.
Arterial oxygen content (CaO₂) (in mmol/L) was calculated as

\[ \text{CaO}_2 = 0.96 \times \text{Hb} \times \text{SaO}_2 + 0.01 \times \text{PaO}_2 \]

where SaO₂ denotes arterial oxygen saturation (measured as a fraction of 1) and PaO₂ denotes arterial oxygen tension (in kPa).

Jugular venous oxygen content (CJV O₂) was similarly calculated as

\[ \text{CJV O}_2 = 0.96 \times \text{Hb} \times \text{SJV O}_2 + 0.01 \times \text{PJV O}_2 \]

The arterial to jugular oxygen content difference (a-v D O₂) was calculated as

\[ \text{a-v D O}_2 = \text{CaO}_2 - \text{CJV O}_2 \]

Assuming an unchanged metabolic rate of oxygen (CMRO₂), a-v D O₂ changes in inverse proportion to CBF, since, according to the Fick principle, CMRO₂ = CBF × (CaO₂ - CJV O₂) = CBF × (a-v D O₂). Thus, an increase in CBF will elicit a proportional decrease in a-v D O₂, which may be used to estimate relative changes in global CBF.¹⁶,¹⁷

Statistical Analysis and Criteria for Evaluation of Autoregulation

All results are presented as medians and ranges. A value of \( P < 0.05 \) was considered statistically significant.

Because data could not be assumed to be normally distributed, as evaluated by calculation of Shapiro-Franzia W', nonparametric statistical analysis was performed. Wilcoxon’s test for paired data was used for comparison of MAP, a-v D O₂, Vmean, PI, and PaCO₂ at initial and maximum levels of MAP and at normoventilation and hyperventilation. This method was also used for comparison between slopes of autoregulation regression lines at normoventilation and hyperventilation.

For evaluation of autoregulation in each patient, MAP was plotted against Vmean. A computer program was used to search for a possible lower limit of autoregulation. This program has previously been validated for this purpose.¹⁸ The program fits a linear regression line for MAP below the lower limit of autoregulation and a horizontal line above the lower limit by the least sum of squares method, comparing the result with that of fitting a single linear regression line to the data.

The slope of the autoregulation curve was calculated as the slope of the single linear regression line, that is, the relative increase in Vmean in percent divided by the increase in MAP. In the case of preserved autoregulation with identification of a lower limit of autoregulation (defined below), the slope was calculated for the regression line fitting only those points with MAP values exceeding the lower limit.

Preservation of CBF autoregulation was assessed by predefined criteria.¹⁰ Since the coefficient of variation during measurements of Vmean is \( \approx 9\% \),¹⁹ autoregulation was classified as preserved (1) if the slope of the single linear regression line was \( \leq 0.33\%/\text{mm Hg} \) (ie, Vmean increased \( \leq 10\% \) per increase in MAP of 30 mm Hg), or (2) in the case of identification of a physiologically acceptable lower limit, if it was determined with a standard error of \( < 25\% \), and the MAP interval used exceeded the MAP value of the lower limit by \( \geq 10 \text{ mm Hg} \), and the sum of squares for 2 lines was less than the sum of squares for 1 single regression line. Conversely, autoregulation was classified as impaired if no lower limit of autoregulation was identified and the slope of the single linear regression line increased \( > 0.33\%/\text{mm Hg} \), that is, if Vmean increased \( > 10\% \) per increase in MAP of 30 mm Hg.

To evaluate how well changes in Vmean reflected changes in global CBF, the correlation between Vmean and a-v D O₂ was examined. If both parameters are a reflection of global CBF, Vmean will change in inverse proportion to a-v D O₂. These parameters are not direct measures of CBF, but relative changes may be assumed to reflect equal changes in global CBF. Hence, Spearman’s \( \rho \) was calculated for the correlation between relative changes in Vmean and \( 1/(\text{a-v D O}_2) \).

Results

Clinical Outcome

Seven patients survived and were extubated after a median of 7 (3 to 12) days. Three patients had mild neurological...
sequelae and 4 recovered completely. Two patients died. Patient 2 had severe pneumococcal meningitis with septic shock and died of cerebral herniation on day 3. Patient 5 had meningitis and septic shock with positive blood and CSF cultures for *Listeria monocytogenes* and died on day 6 of cerebral hemorrhage and herniation.

**Autoregulation Measurement During Normoventilation and Hyperventilation**

During normoventilation, PaCO₂ remained unchanged throughout the MAP range used (Figures 1 and 2, Table 2). The median MAP increase achieved during norepinephrine infusion was 35 (25 to 41) mm Hg, corresponding to a relative increase of 45% (25% to 61%). $V_{\text{mean}}$ increased in all patients by a median of 32% (8% to 59%) ($P<0.01$). Simultaneously, the a-v $DO_2$ decreased, corresponding to a relative increase in CBF of 51% (27% to 88%) ($P<0.05$).

In 8 patients, the increase in $V_{\text{mean}}$ exceeded 10% per 30–mm Hg increase in MAP, and no lower limit of autoregulation was identified. Thus, autoregulation was impaired in these 8 patients at normoventilation. In the remaining patient (patient 8), as the slope of the regression line was $<0.33\%$ per mm Hg (0.24% per mm Hg), autoregulation was preserved at normoventilation; however, the a-v $DO_2$ did decrease from 2.5 to 1.8 mmol/L from baseline to peak values of MAP (during norepinephrine infusion) in this patient.

During hyperventilation, PaCO₂ decreased in all patients to 3.5 kPa (3.3 to 4.1) ($P<0.01$). There was a slight but statistically significant change in PaCO₂ of $-0.20$ kPa ($-0.15$ to $+0.67$) from the lowest to the highest value of MAP during norepinephrine infusion at hyperventilation ($P<0.05$) (data not shown).

The MAP range at hyperventilation was 33 mm Hg (29 to 43). With a MAP increase of 41% (31% to 74%) during norepinephrine infusion, $V_{\text{mean}}$ increased by 18% (2% to 51%) ($P<0.01$) (Figure 1), and a-v $DO_2$ decreased, corresponding to a relative increase in CBF of 30% (10% to 60%) ($P<0.05$).

The slope of the regression lines decreased during hyperventilation compared with the slope at normoventilation ($P<0.05$). In 4 patients (patients 5, 7, 8, and 9), autoregulation was completely recovered during hyperventilation. In 1 patient (patient 5), the lower limit of autoregulation was identified at 108 mm Hg, and the slope of the regression line above the lower limit was 0. In 3 patients (patients 7, 8, and 9), the slope of the single linear regression line was $<0.33\%$ per mm Hg. In patients 7 and 8, a lower limit of autoregulation appeared to be present at 71 and 89 mm Hg, respectively, but the standard error of the MAP value exceeded 25%. In 3 patients, the slope decreased but autoregulation was not completely recovered; in 2 patients, the slope increased slightly.

At the lowest MAP level, $V_{\text{mean}}$ and a-v $DO_2$ were not significantly altered at hyperventilation compared with normoventilation, although there was a trend toward decreased $V_{\text{mean}}$ and increased a-v $DO_2$. However, $V_{\text{mean}}$ and a-v $DO_2$ were significantly reduced and increased, respectively, at peak MAP values.

Absence of cerebral ischemia both during normoventilation and hyperventilation was indicated by the jugular venous oxygen content. Ischemia would cause a high oxygen extraction and, consequently, a low jugular venous oxygen content. During normoventilation, values of $P_{\text{JvO}_2}$ and $S_{\text{JvO}_2}$ at the lowest MAP were 4.6 kPa (3.9 to 5.8) and 0.62 (0.56 to 0.83), respectively, and at high MAP 5.4 kPa (4.9 to 6.7) and 0.78 (0.70 to 0.86), respectively. During hyperventilation, $P_{\text{JvO}_2}$ and $S_{\text{JvO}_2}$ at the lowest MAP were 3.9 kPa (3.4 to 4.4) and 0.60 (0.51 to 0.70) and at high MAP 4.8 kPa (4.0 to 5.3) and 0.70 (0.60 to 0.79). Compared with values measured in healthy subjects ($S_{\text{JvO}_2}$ 0.55 to 0.70, calculated as mean±2 SD), these values are within or slightly above normal ranges; one measurement in patient 7 was slightly below the normal range. This indicates that global cerebral oxygen delivery was sufficient to meet cerebral metabolic requirements in the patients both during normoventilation and hyperventilation.
TABLE 2. Autoregulation Measurements During Normoventilation and Hyperventilation

<table>
<thead>
<tr>
<th></th>
<th>PaCO₂</th>
<th>Baseline MAP</th>
<th>Peak MAP</th>
<th>vmean at Baseline MAP</th>
<th>vmean at Peak MAP</th>
<th>a=a-v DO₂ at Baseline MAP</th>
<th>a=a-v DO₂ at Peak MAP</th>
<th>Slope of Autoregulation Regression Line, % per mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoventilation</td>
<td>4.4</td>
<td>68 (60–101)</td>
<td>109*</td>
<td>48 (30–61)</td>
<td>65* (33–86)</td>
<td>2.2 (1.0–2.7)</td>
<td>1.4† (0.8–1.8)</td>
<td>1.10 (0.23–1.62)</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>3.5‡</td>
<td>76 (58–92)</td>
<td>109†</td>
<td>45 (29–55)</td>
<td>53*§ (33–78)</td>
<td>2.5 (1.8–3.0)</td>
<td>1.8‡§ (1.2–2.4)</td>
<td>0.45§ (0–1.27)</td>
</tr>
</tbody>
</table>

All values are presented as medians and ranges.
*P<0.01 compared with values at baseline MAP.
†P<0.05 compared with values at baseline MAP.
‡P<0.01 compared with normoventilation.
§P<0.05 compared with normoventilation.
|Not significant compared with normoventilation.

Discussion

We found that CBF autoregulation was impaired in 8 of 9 patients with acute bacterial meningitis, by use of TCD and the a-v DO₂ method to determine relative changes in CBF during manipulation of MAP. This finding is in accordance with previous studies performed in patients in the early phase of acute bacterial meningitis with the use of identical methods as well as the 133Xe clearance technique.

Spontaneous hyperventilation is a characteristic clinical feature of patients with acute bacterial meningitis before coma and intracranial hypertension ensue, and it is possible that the arterial hypocapnia helps maintain a normal cerebral vascular tone and prevents a further rise in ICP in the setting of cytotoxic cerebral edema. The pathogenesis of the impaired CBF autoregulation is unclear, but cerebral interstitial acidosis is present in acute bacterial meningitis and may account for development of cerebral vasodilation. In the present study, we expected CBF autoregulation to be restored during mechanical hyperventilation. Indeed, autoregulation was partially or completely recovered in 6 of the 8 patients in whom CBF autoregulation was absent at normoventilation.

The recovery of autoregulation induced by short-term hyperventilation is suggested to result from alkalization of the interstitial fluid. An alternative explanation for the partial or complete recovery of autoregulation is that a decrease in ICP induced by hyperventilation may have improved cerebral perfusion pressure. If ICP were high during normoventilation, the true perfusion pressure would be markedly lower than MAP, and the autoregulation measurement might then have been performed at perfusion pressures located below the lower limit of autoregulation. With a decrease in ICP during hyperventilation, perfusion pressure would approach MAP, and the resulting autoregulation curve might then be located above the lower limit, causing the slope to decrease in comparison with that obtained at normoventilation. The present data, however, show that during the normoventilation study a-v DO₂ was within or below the normal range, indicating that global CBF was adequate or relatively high even at the initial (low) MAP. This would be an unlikely finding in a patient in whom CBF was compromised by a high ICP and whose cerebral perfusion pressure was located below the lower limit of autoregulation.

Recovery of autoregulation during hyperventilation has been described in patients with acute liver failure and in patients with intracerebral tumors or infarction. In patients with head trauma, Cold et al reported that autoregulation was preserved at a PaCO₂ of 4.5 kPa but was lost when the PaCO₂ was reduced to 3.0 kPa. In contrast, Newell et al found an improvement in dynamic cerebral autoregulation as measured by TCD, with a reduction in PaCO₂ from 4.9 to 3.7 kPa in head-injured patients.

In this study, although there was a trend toward decreased cerebral perfusion during hyperventilation, as estimated by vmean and a-v DO₂, this decrease was not statistically significant at baseline MAP values. At least 3 different explanations are possible for the apparent paradox that CBF autoregulation was affected during hyperventilation, whereas cerebral perfusion appeared to be unaffected. First, hyperventilation may have mediated a decrease in ICP and hence an increase in cerebral perfusion pressure. If ICP were high during normoventilation, the true perfusion pressure would be markedly lower than MAP, and the autoregulation measurement might then have been performed at perfusion pressures located below the lower limit of autoregulation. With a decrease in ICP during hyperventilation, perfusion pressure would approach MAP, and the resulting autoregulation curve might then be located above the lower limit, causing the slope to decrease in comparison with that obtained at normoventilation. The present data, however, show that during the normoventilation study a-v DO₂ was within or below the normal range, indicating that global CBF was adequate or relatively high even at the initial (low) MAP. This would be an unlikely finding in a patient in whom CBF was compromised by a high ICP and whose cerebral perfusion pressure was located below the lower limit of autoregulation.

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Second, cerebrovascular CO₂ reactivity may have been absent or impaired in some of the patients. However, absence of CO₂ reactivity should have been evident at all levels of MAP and not only at low levels. The third possibility is that the number of patients was too small for statistical significance, even though CBF was really reduced at all levels of MAP, that is, a type 2 error occurred. This also may explain why PI remained unchanged throughout the measurements. PI has been suggested to indicate cerebrovascular impedance. Hence, PI would be expected to increase during hyperventilation compared with normoventilation. An increase in PI would also be expected at peak MAP compared with baseline MAP during hyperventilation in the patients who recovered CBF autoregulation during hyperventilation.

With the slight increase in PaCO₂ during norepinephrine infusion observed during hyperventilation, the slope of the regression lines would tend to increase slightly. Accordingly, it is likely that an even more pronounced decrease in the slope of the regression lines might have been expected during hyperventilation if the PaCO₂ had remained constant. CO₂ reactivity was not calculated, and hence no correction was performed for the observed increase in PaCO₂. Despite this, the decrease in the slope of the regression lines from normoventilation to hyperventilation was significant.

The correlation coefficients between relative changes in Vmean and 1/(a-v DO₂) decreased somewhat from normoventilation to hyperventilation. This may be explained by the partial or complete recovery of autoregulation, which decreased the range of variation in both Vmean and a-v DO₂ during hyperventilation compared with normoventilation; accordingly, the correlation coefficient between these 2 parameters will tend to decrease during hyperventilation.

Measuring Vmean by transcranial Doppler provides reliable estimates of relative changes in CBF if the cross-sectional diameter of the insonated artery remains constant during the examination. We used an infusion of norepinephrine to increase MAP in the patients. A constant diameter of the middle cerebral artery during norepinephrine infusion has been reported in healthy volunteers and in patients with neurological diseases as well as in patients with acute liver failure. Changes in the diameter of the insonated artery do not explain the increase in Vmean because a-v DO₂ would then have been expected to remain unchanged despite changes in Vmean. In contrast, Vmean increased and a-v DO₂ decreased with increasing MAP, and there was a good correlation between relative changes in Vmean and 1/a-v DO₂.

Changes in a-v DO₂ will be inversely proportional to changes in CBF only if CMRO₂ remains constant throughout the study period. CO₂ reactivity should have been demonstrated during norepinephrine infusion in patients with acute liver failure and is usually present during short study intervals. If the blood-brain barrier is dysfunctional or defective, as is probably the case in acute bacterial meningitis, the cerebrovascular and cerebral metabolic response to norepinephrine may be altered. To our knowledge, no studies have been performed regarding the effect of norepinephrine on cerebral blood flow and metabolism in acute bacterial meningitis. However, an increase in cerebral oxidative metabolism caused by norepinephrine infusion should be unaffected by the PaCO₂. Also, the relation between MAP, Vmean, and a-v DO₂ should be unaltered from normocapnia to hypocapnia. Hence, an increase in CMRO₂ does not explain our results.

The study was carried out in patients in the early phase of severe acute bacterial meningitis, necessitating sedation and mechanical ventilation for clinical reasons. Five patients had severe septic shock concurrently with acute bacterial meningitis, and all were sedated, but neither septic shock nor sedation appears to affect the integrity of autoregulation.

From a clinical point of view, the recovery of CBF autoregulation during mechanical hyperventilation may protect the brain from fluctuations in perfusion pressure. The stabilization of CBF may be important in patients with acute bacterial meningitis, since vasogenic edema is more likely to result from an increase in perfusion pressure if the blood-brain barrier is disrupted. Unfortunately, the cerebrovascular effects of “prophylactic” hyperventilation will be compensated during long-time hyperventilation. Moreover, hyperventilation may critically reduce blood flow in endangered brain areas if carbon dioxide reactivity is preserved in these areas. Regionally compromised CBF has been reported in patients with acute bacterial meningitis, whereas the CO₂ reactivity in these areas awaits further study.
Although none of our patients had critically low jugular venous oxygen saturation, this may be an important cause for concern in some patients. The potential clinical benefit of a more stable CBF may thus be achieved at the cost of an overall reduction in global CBF during hyperventilation compared with normoventilation. Further studies in patients with acute bacterial meningitis are warranted before general recommendations can be made regarding therapies that reduce CBF, for example, hyperventilation or the administration of vasoactive drugs such as indomethacin. If such therapies are instituted, we suggest that cerebral oxygen consumption should be closely monitored to help avoid cerebral ischemic complications.

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