Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies

B. F. Matta and P. J. Stow

Summary

We have studied cerebral autoregulation and vaso-reactivity to carbon dioxide in 10 patients with the sepsis syndrome receiving intensive therapy. All patients were sedated with infusions of midazolam and fentanyl, and their lungs were ventilated mechanically with oxygen–air to maintain normoxia and normocapnia. Inotropic support and antibiotics were administered as necessary. During a period of constant level of sedation and stable haemodynamics, cerebral autoregulation was tested by increasing mean arterial pressure (MAP) by 23 (SD 2) mm Hg from baseline with an infusion of phenylephrine and simultaneously recording middle cerebral artery blood flow velocity (v_mca) using transcranial Doppler ultrasonography. Carbon dioxide reactivity was tested by varying P_aCO_2 between 3.0 and 7.0 kPa and simultaneously recording v_mca.

There was no significant change in v_mca (57 (22) and 59 (23) cm s⁻¹) during the increase in MAP (75 (11) to 98 (10) mm Hg). The mean index of autoregulation (IOR) was 0.92 (SEM 0.03), which was not significantly different from 1, indicating near perfect autoregulation. Although absolute carbon dioxide reactivity was lower than reported previously in awake subjects, relative carbon dioxide reactivity was within normal limits for all patients (11.6 (SEM 0.8) cm s⁻¹ kPa⁻¹ and 20.3 (3) % kPa⁻¹, respectively). We conclude that cerebral carbon dioxide reactivity and pressure autoregulation remained intact in patients with the sepsis syndrome, providing indirect evidence that at least in the early stages of the syndrome, the widespread sepsis-induced vasoparalysis does not involve the cerebral vasculature. (Br. J. Anaesth. 1996; 76: 790–794)

Key words


Sepsis continues to be a common and frequently fatal illness in humans. Although the pathophysiology of generalized sepsis is complex and not yet fully explained, the syndrome is generally associated with multisystem organ impairment and decreased systemic vascular resistance as a result of widespread vasoparalysis [1, 2].

Cerebral pressure autoregulation and carbon dioxide reactivity are dependent on intact cerebral vascular tone and reactivity [3]. It is not known if the vasoparalysis in patients with sepsis involves the cerebral vasculature, and if so, what effect this has on these two important mechanisms for the control of cerebral blood flow (CBF). In this study we aimed to establish if there were disturbances in cerebral autoregulation and carbon dioxide reactivity in patients with the sepsis syndrome. If this were the case, it might explain the pathophysiology of the encephalopathy seen in up to 70 % of patients with sepsis, which has been associated with higher mortality [4, 5]. Furthermore, the information may be beneficial in the management of these patients in whom involvement of the cardiovascular and respiratory systems often leads to arterial pressure instability and carbon dioxide retention.

Patients and methods

After obtaining Human Subjects Committee approval and informed consent from the next of kin, we examined cerebral autoregulation and carbon dioxide reactivity in 10 patients admitted to our intensive care unit with the sepsis syndrome (eight intra-abdominal sepsis, two pneumonias) and altered mental state (confusion or delirium). The sepsis syndrome was diagnosed according to criteria described previously by Bone and colleagues [2] (table 1). Patients who had a pre-existing neurological disease and those receiving psychotropic drugs were excluded. All studies were performed within 24 h of admission to the intensive care unit. Routine monitors included electrocardiography, invasive arterial pressure, central venous and pulmonary artery pressures, and pulse oximetry. All patients received infusions of midazolam 100–300 μg kg⁻¹ h⁻¹ and fentanyl 1–5 μg kg⁻¹ h⁻¹ to maintain adequate sed-
Autoregulation and $CO_2$ reactivity in patients with sepsis

Table 1 Criteria for definition of the sepsis syndrome [2]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Hypothermia &lt; 35.1°C or hyperthermia &gt; 38.3°C</td>
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<td>Tachycardia &gt; 90 beat min$^{-1}$ in the absence</td>
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<td>of hypovolaemia or beta-adrenergic block</td>
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<tr>
<td>Tachypnoea &gt; 20 b.p.m. or requirement for</td>
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<td>ventilatory support</td>
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Clinical evidence of an infection site

At least one end-organ showing evidence of inadequate perfusion or dysfunction:

- Poor or altered cerebral function (inattention, confusion, disorientation, delirium, coma)
- Hypoxaemia $Pa_{O_2} < 10$ kPa breathing room air, not caused by overt pulmonary disease
- Elevated plasma lactate > 2.2 mmol litre$^{-1}$
- Oliguria (urine output < 30 ml h$^{-1}$) without corrective therapy for at least 1 h

Results

Patient characteristics are shown in table 2. There were no significant changes in body temperature, haemoglobin concentration and partial pressure of oxygen ($Pa_{O_2}$) in arterial blood during the study (table 3). There was no change in $Pa_{CO_2}$ during the autoregulation part of the study and no change in MAP during the carbon dioxide reactivity part of the study.

<table>
<thead>
<tr>
<th>Data (mean (SD or range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Sex (M : F)</td>
</tr>
<tr>
<td>Admission APACHE score</td>
</tr>
<tr>
<td>Haemoglobin (g dl$^{-1}$)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
</tr>
<tr>
<td>Cardiac index (litre min$^{-1}$ m$^{-2}$)</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dyn s cm$^{-1}$ m$^{-2}$)</td>
</tr>
</tbody>
</table>

| $Pa_{CO_2}$ (kPa) | 4.7 (0.3) |
| $Pa_{O_2}$ (kPa) | 13.3 (1.8) |
| $v_{mca}$ (cm s$^{-1}$) | 57 (22) |

Table 3 Data (mean (SD)) during pressure autoregulation. **P < 0.01 compared with baseline (t test)

<table>
<thead>
<tr>
<th>Data (mean (SD))</th>
<th>Baseline</th>
<th>Autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>75 (11)</td>
<td>98 (10)**</td>
</tr>
<tr>
<td>HR (beat min$^{-1}$)</td>
<td>95 (36)</td>
<td>92 (35)</td>
</tr>
<tr>
<td>$Pa_{CO_2}$ (kPa)</td>
<td>4.7 (0.3)</td>
<td>4.8 (0.3)</td>
</tr>
<tr>
<td>$Pa_{O_2}$ (kPa)</td>
<td>13.3 (1.8)</td>
<td>13.4 (1.8)</td>
</tr>
<tr>
<td>$v_{mca}$ (cm s$^{-1}$)</td>
<td>57 (22)</td>
<td>59 (23)</td>
</tr>
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</table>

The index of autoregulation (IOR) was calculated as the ratio of percentage change in estimated cerebral vascular resistance (CVRe) to percentage change in MAP, using the equations CVRe = MAP/$v_{mca}$ and IOR = $\%$ (CVRe)/$\%$ MAP, where MAP = mean arterial pressure at the time of $v_{mca}$ measurement [6]. Perfect autoregulation is present when the percentage change in CVRe is equal to the percentage change in MAP; no change in $v_{mca}$ with change in MAP, and IOR = 1. An IOR of 0 signifies complete absence of autoregulation. Based on studies published previously [6, 7], we considered a 15% change in IOR to be clinically insignificant. We then performed a power analysis which indicated that for a power of 0.80, an alpha value of 0.05 and a beta value of 0.20, the required number of patients to reject the null hypothesis was 10. The computed IOR and data recorded before and after the phenylephrine-induced increase in MAP were analysed using Student’s t test. P < 0.05 was considered statistically significant.

To determine carbon dioxide reactivity, regression lines were constructed for paired $Pa_{CO_2}$-$v_{mca}$ data for each patient. Carbon dioxide reactivity was expressed in both absolute (change in $v_{mca}$ per kPa change in $Pa_{CO_2}$) and relative (percentage change in $v_{mca}$ at $Pa_{CO_2}$ 5.3 kPa per kPa change in $Pa_{CO_2}$) values.
obtained during sedation and anaesthesia [6, 18, 19].

awake values, they were consistent with values in this study were slightly lower than reported primarily through dilatation of arterioles and not the arteries of the circle of Willis [17].

Changes in cerebral vascular resistance occur primarily through dilatation of arterioles and not the arterioles of the circle of Willis [17].

Although the absolute carbon dioxide reactivity values in this study were slightly lower than reported awake values, they were consistent with values obtained during sedation and anaesthesia [6, 18, 19].

When the carbon dioxide reactivity values were normalized to v_{mca} at P_{aCO2} of 5.3 kPa, the percentage change in v_{mca} per kPa approximated the awake value. Normalizing all v_{mca} values by expressing them as a percentage of v_{mca} at a P_{aCO2} of 5.3 kPa allows comparisons with previously published studies and reduces the dependence on the baseline v_{mca} value, which is reported to vary between 30 and 90 cm s\(^{-1}\) in awake individuals [20]. Bowton and colleagues have shown that in septic patients, CBF is reduced [21]. Although it is not possible to estimate absolute CBF accurately, v_{mca} values obtained in this study were within the normal range.

We could only estimate cerebral vascular resistance (CVRe) because we measured v_{mca} and not absolute CBF. This estimation of CVRe depends on our previous assumption that changes in CBF correlate with changes in v_{mca}. We then calculated the index of autoregulation by dividing the percentage change in CVRe by the percentage change in MAP. An IOR of 1 indicates that the percentage change in CVRe is the same as the percentage change in MAP and no change in CBF results (complete autoregulation). Complete absence of autoregulation gives an IOR of 0. IOR was 0.92 (SEM 0.03), which indicated that near complete autoregulation was present in patients with the sepsis syndrome. This deviation from an IOR of 1 is clinically unimportant and within normal limits, as dynamic autoregulation in normal volunteers has been shown to have an SD of 15% [22]. Power analysis ensured that 10 patients were sufficient to reject the null hypothesis with a power of 0.80, an alpha error of 0.05 and a beta error of 0.20.

Although we only examined autoregulation in one direction (increase in pressure), we chose a level of MAP which normally lies in the middle of the autoregulation curve. Therefore, there is no reason to assume that a decrease instead of an increase in MAP would have yielded different results. This has been confirmed recently by Tiecks and colleagues who found that the ability of the cerebral circulation to autoregulate is similar whether MAP is increased or decreased [23].

Encephalopathy may be present in up to 70% of patients with sepsis [4]. The severity ranges from impaired attention and concentration to delirium and coma. The electroencephalograph (EEG) is a valuable tool in the intensive care of these patients. The EEG is a sensitive indicator of the severity of the encephalopathy. Four main patterns of increasing severity are seen: diffuse theta, intermittent rhythmic delta, triphasic waves, and suppression or burst suppression [24]. Although EEG patterns and the clinical grade of encephalopathy may be associated with a poor outcome, complete recovery is possible despite the presence of suppression and burst suppression EEG patterns [24, 25]. All patients in this study had a mild degree of encephalopathy and made a complete recovery. The size of the study does not allow speculation on the grade of the encephalopathy, autoregulation and carbon dioxide reactivity, and outcome.

The pathogenesis of septic encephalopathy is unknown. A reversible “metabolic” mechanism has

Figure 1 Relative middle cerebral artery velocity (v_{mca}) vs corresponding P_{aCO2} for all patients. Relative v_{mca} was calculated by expressing flow velocity values as a percentage of v_{mca} at a P_{aCO2} of 5.3 kPa. The respective linear regression is shown.

(\text{SEM 0.8}) \text{ cm s}^{-1} \text{ kPa}^{-1} \text{ and 20.3 (3) % kPa}^{-1}, respectively. Figure 1 shows the relative cerebral vaso-reactivity for all patients (relative v_{mca} vs P_{aCO2}).

**Discussion**

In this study, we have shown that cerebral pressure autoregulation and vasomotor reactivity to carbon dioxide remained intact in patients with the sepsis syndrome. This suggests that at least in the early stages of sepsis, the widespread sepsis-induced vasoparalysis does not involve the cerebral vasculature.

Steady-state conditions were maintained during both parts of the study. There was no change in patient body temperature or haemoglobin concentration; MAP was maintained constant during the carbon dioxide reactivity part of the study, and P_{aCO2} was unchanged between normotension and phenylephrine-induced hypertension phases. The drugs used for sedation (fentanyl and midazolam) have no direct cerebrovascular effects [8, 9].

Transcranial Doppler ultrasonography (TCD) is a particularly suitable tool for assessing cerebral vaso-reactivity to carbon dioxide [10]. The device is inexpensive, non-invasive and non-radioactive. Multiple paired measurements can be obtained and linear regression lines constructed more accurately than with a limited number of conventional blood flow measurements [10–12]. Furthermore, despite TCD not providing a direct measure of CBF, it provides an accurate measure of relative changes in CBF [10–12]. There is now ample direct and indirect evidence to support the contention that MCA is a conductance vessel and its diameter does not change significantly with changes in arterial pressure, P_{aCO2}, or the use of anaesthetic or vasoactive agents [11–16]. Changes in cerebral vascular resistance occur primarily through dilatation of arterioles and not the arterioles of the circle of Willis [17].
been proposed to explain the presence of encephalopathy without direct infection of the brain and without consistent neuropathological changes [4]. Cytokines, the chemical messengers released from macrophages and lymphocytes, are likely to be responsible for this “metabolic” derangement, with increased permeability of the blood-brain barrier, increased capillary leakage and tissue oedema, interference with microcirculation, increased procoagulant activity, and direct effects on tissue metabolism [24–26]. Cytokines (interleukin-1 and-2) may also directly affect the brain [26–29]. There is evidence to suggest that at least in animals, there is differential impairment of pulmonary and systemic vascular contractility in hyperdynamic sepsis [30].

Robert and colleagues have shown that interleukin-1, a cytokine released during septic shock, reduces the noradrenaline-induced arterial vessel contraction in rabbit renal and pulmonary beds, but not in hepatic vessels [31]. This hyporeactivity may affect the mechanisms regulating cerebral blood flow, cerebral autoregulation and vasoreactivity to carbon dioxide, which are dependent on the ability of the cerebral vasculature to regulate its tone. In this study, we have shown that in patients without severe encephalopathy, these mechanisms remained intact. Although the exact mechanisms responsible for autoregulation and vasoreactivity to carbon dioxide remain unclear, this study suggests that cerebral vessels were not hyporeactive to changes in MAP or $P_{a,CO_2}$. However, carbon dioxide reactivity and autoregulation studies were performed during a period of optimal systemic haemodynamic state (table 2), with patients receiving vasoactive agents (dobutamine, dopamine and noradrenaline) that theoretically could have been responsible for restoring cerebrovascular reactivity. Although it is important to identify if these mechanisms are affected by the disease process, or if they can be restored by optimizing systemic haemodynamic state, it is at least reassuring that when systemic haemodynamics are optimized, the cerebral circulation is able to respond to changes in arterial pressure and carbon dioxide tension. This is important for the management of those patients in whom the involvement of the cardiovascular and respiratory systems often leads to arterial pressure instability and carbon dioxide retention.

Acknowledgement

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References

27. Jeppsson B, Freund HR, Gimmon Z, James JH, Vonnreyenfeldt MF, Fischer JE. Blood brain barrier de-

