Comparative effects of propofol vs dexmedetomidine on cerebrovascular carbon dioxide reactivity in patients with septic shock

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Background. The use of sedative drugs is reportedly related to altered cerebrovascular CO2 reactivity. The present study examined the comparative effects of propofol vs dexmedetomidine on cerebrovascular CO2 reactivity in patients with septic shock.

Methods. A total of 20 patients with septic shock who required mechanical ventilation were included in this study. Sedation during mechanical ventilation was maintained using either propofol or dexmedetomidine. A 2.5 MHz pulsed transcranial Doppler probe was attached to the head of the patient at the right temporal window for continuous measurement of mean blood flow velocity in the middle cerebral artery ($V_{\text{mca}}$). After establishing baseline values of $V_{\text{mca}}$ and cardiovascular haemodynamics, end-tidal CO2 was increased by decreasing ventilatory frequency by 5–8 bpm.

Results. The absolute and relative CO2 reactivity values in patients with septic shock were lower for both propofol and dexmedetomidine than those for control groups, with significant differences between these values in the two septic shock groups (absolute CO2 reactivity in septic shock under propofol: 2.6 (0.3) cm s$^{-1}$ mm Hg$^{-1}$; absolute CO2 reactivity in septic shock under dexmedetomidine: 2.0 (0.3) cm s$^{-1}$ mm Hg$^{-1}$; P<0.01).

Conclusions. This study showed that cerebrovascular CO2 reactivity was lower under dexmedetomidine sedation than under propofol sedation during almost identical sedation in patients with septic shock.

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young subjects. These findings indicate that different sedatives are likely to exert different effects on cerebrovascular CO2 reactivity. We thus hypothesized that cerebrovascular CO2 reactivity would differ between propofol and dexmedetomidine sedation in patients with septic shock. As no previous studies have provided such data, this study compared the effects of propofol and dexmedetomidine on cerebrovascular CO2 reactivity in patients with septic shock.

Methods

After obtaining approval from the ethics committee of our institution, written, informed consent was obtained from all patients. Subjects comprised 20 patients with septic shock within 72 h of admission to the ICU. In addition, all studies were performed within 24 h after the diagnosis of septic shock.

Patients with septic shock were defined according to American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) criteria. Routine monitoring, including electrocardiography, invasive arterial pressure, central venous pressure, end-tidal CO2 (PtCO2) and pulse oximetry, was done for all patients.

The 20 septic shock patients were prospectively randomized into two groups: the propofol group (n=10), receiving 1.0 mg kg\(^{-1}\) i.v. bolus of propofol over 10 min, followed by continuous infusion at a rate of 1–3 mg kg\(^{-1}\) h\(^{-1}\); and the dexmedetomidine group (n=10), receiving 0.01 μg kg\(^{-1}\) i.v. bolus of dexmedetomidine over 10 min, followed by continuous infusion of 0.3–0.5 mg kg\(^{-1}\) h\(^{-1}\). As controls, 20 patients without sepsis were also monitored. These control patients were ICU patients who required mechanical ventilation for respiratory failure. Control patients were likewise randomized into propofol and dexmedetomidine groups (n=10 each). Sedation regimens for control patients were identical to those for septic shock patients. To maintain haemodynamic stability, all patients in control and septic shock groups received isotropic agents such as dopamine, dobutamine, or adrenaline. Target systolic arterial blood pressure for all patients was >80 mm Hg. All patients received mechanical ventilation using a Servo 300 ventilator (Siemens, Danvers, MA, USA) in volume-controlled ventilation mode with a PEEP of 5–10 cm H\(_2\)O. Target oxygenation variables were \(P_{aO2}\) >60 mm Hg and arterial oxygen saturation was >90%. Measurement of cerebrovascular CO2 reactivity was performed ≥1 h after haemodynamic and respiratory variables stabilized.

To assess the severity of disease and organ dysfunction, Acute Physiology and Chronic Health Evaluation (APACHE II) and multiple organ dysfunction syndrome (MODS) scores were registered.

Target sedation levels in all patients in both groups were Ramsay Score 4 sedation. A bispectral index (BIS) monitor (Aspect Medical Systems, Natic, MA, USA) was used to assess the effects of equipotent doses of propofol and dexmedetomidine in each group.

A 2.5 MHz pulsed transcranial Doppler probe was attached to the head of the patient at the right temporal window and mean blood flow velocity in the middle cerebral artery (V\(_{mca}\)) was measured continuously using a SONOS 5500 2.5 MHz transducer (Hewlett Packard, Andover, MA, USA). After signals were identified at a depth of 45–60 mm, the probe was fixed using a probe folder, to avoid changes to insonating angle. V\(_{mca}\) values at end-expiration were recorded.

After measurement of baseline V\(_{mca}\) and cardiovascular haemodynamic values, PtCO2 was increased by reducing ventilatory frequency by 5–8 bpm. This increased PtCO2 by ~7–10 mm Hg from 34 (3) to 43 (4) mm Hg within several minutes. All measurements were repeated after PtCO2 increase and had remained stable for 5–10 min. To confirm alterations in \(P_{aCO2}\) by reducing ventilatory frequency, \(P_{aCO2}\) was also measured.

Cerebral vasodilatory response to hypercapnia in each patient was calculated as both the absolute change in V\(_{mca}\) and the percentage change from baseline V\(_{mca}\) per millimetre of mercury change in \(P_{aCO2}\) using the following formulae:

\[
\text{Absolute CO2 reactivity} = \frac{V_{mca \text{ at hypercapnia} } - V_{mca \text{ at baseline}}}{\Delta P_{aCO2}}
\]

\[
\text{Relative CO2 reactivity} = \frac{\text{absolute CO2 reactivity}}{V_{mca \text{ at baseline}}} \times 100
\]

where \(\Delta V_{mca}\) is the difference between flow velocity after \(P_{aCO2}\) elevation and baseline flow velocity, and \(\Delta P_{aCO2}\) is the difference between final and baseline \(P_{aCO2}\). The generally accepted value for absolute CO2 reactivity is a 2.0–5.0 cm change in flow velocity per second per millimetre of mercury under anaesthesia. In addition, the generally accepted value for relative CO2 reactivity is a 2.5–6.0% change in flow velocity per millimetre of mercury.

Pulsatile index (PI) and V\(_{mca}\) were calculated for all study participants using the following formulae:

\[
\text{PI} = \frac{\text{systolic velocity} - \text{diastolic velocity}}{\text{mean velocity}}
\]

\[
V_{mca} = \frac{\text{systolic velocity} - \text{diastolic velocity}}{3 + \text{diastolic velocity}}
\]

Examiners who measured V\(_{mca}\) were blinded to group assignment for each patient. Data obtained in this study were analysed later by an independent researcher who was likewise blinded to group assignment.

Statistical analysis

All data are expressed as mean (sd). A paired t-test or Fisher exact test was used for comparisons between
propofol and dexmedetomidine groups. After confirmation of equal variance among groups using the Bartlett test, one-way factorial measure analysis of variance was performed with multiple comparisons. When the F-value was significant, the Bonferroni method was used for multiple comparisons. To eliminate type II errors, each individual P-value was adjusted. Sample size was evaluated after completion of the study, and was calculated based on the hypothesis that absolute CO₂ reactivity in propofol and dexmedetomidine patients would be decreased by 0.5 cm s⁻¹ mm Hg⁻¹ compared with that in control patients. The sample size provided 80% power to detect a 20% difference between propofol or dexmedetomidine and control groups with a 5% probability of type I error. P<0.05 was considered statistically significant. All calculations were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA) and StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1 shows patient characteristics for each group. All patients in propofol and dexmedetomidine groups displayed readily detectable V_mca flow velocities. All groups were well matched for age, weight, and height. APACHE II and MODS scores were significantly higher in patients with septic shock than those in control patients, but no significant differences in these values were seen among septic shock patients in propofol and dexmedetomidine groups. No significant differences in MAP were identified among any groups.

Table 2 shows the cerebrovascular CO₂ reactivity data in all groups. Values are expressed as mean (SD). APACHE II, acute Physiology and Chronic Health Evaluation; MODS, multiple organ dysfunction syndrome; MAP, mean arterial pressure; HR, heart rate, CVP, central venous pressure. *P<0.05 compared with control groups. **P<0.05 compared with propofol group with sepsis.

FIO₂ and PEEP were significantly higher in patients with septic shock than those in control patients. No significant differences in FIO₂ or PEEP were seen between propofol and dexmedetomidine groups with or without septic shock. Dosages of vasopressor drugs were higher in patients with septic shock than those in control patients, but were well matched between septic shock patients in propofol and dexmedetomidine groups.

Table 2 Comparative effects of propofol and dexmedetomidine on cerebrovascular CO₂ reactivity in each group. Values are expressed as mean (SD). BIS, bispectral index; V_mca, mean blood flow velocity in the middle cerebral artery; BP, blood pressure; PI, pulsatile index. *P<0.05 compared with control; **P<0.05 compared with propofol group with sepsis.

Discussion

The present study showed that cerebrovascular CO₂ reactivity was lower under dexmedetomidine sedation than under propofol sedation in patients with septic shock. In contrast, no differences in cerebrovascular CO₂ reactivity were found in control patients under propofol or dexmedetomidine sedation.
The American College of Critical Care Medicine and the SCCM practice parameters for the optimal use of sedatives and analgesics, which were published in 1995 and revised in 2000, recommend a tiered approach to the use of sedatives and analgesics. These guidelines recommend that drugs of choice in patients >12 yr old requiring prolonged sedation and analgesia during mechanical ventilation include morphine and fentanyl for i.v. opiate analgesia and propofol for rapid awakening from sedation. The selective α-2 agonist, dexmedetomidine, has recently been approved for use as a sedative with analgesic-sparing activity for short-term (<24 h) use in patients receiving mechanical ventilatory support. In addition to sedative effects, dexmedetomidine reduces concurrent analgesic and sedative requirements and produces anxiolytic effects comparable with benzodiazepines.

Some controversial findings have been reported regarding cerebrovascular CO2 reactivity in patients with septic shock. Matta and Stow showed that cerebral CO2 reactivity and pressure autoregulation remained intact in patients with sepsis syndrome, providing indirect evidence that at least in the early stages of the syndrome, widespread sepsis-induced vasoparalysis does not involve the cerebral vasculature. In contrast, Terborg and colleagues showed that severe sepsis and septic shock severely reduced CO2-induced vasomotor reaction, independent of changes in MAP. In addition, this impaired vasomotor reactivity was not observed in the absence of sepsis, leading to speculation that such impaired vasomotor reactivity might contribute to the pathogenesis of septic encephalopathy. Terborg and colleagues showed that severe sepsis and septic shock severely reduced CO2-induced vasomotor reaction, independent of changes in MAP. In addition, this impaired vasomotor reactivity was not observed in the absence of sepsis, leading to speculation that such impaired vasomotor reactivity might contribute to the pathogenesis of septic encephalopathy. Terborg and colleagues showed that severe sepsis and septic shock severely reduced CO2-induced vasomotor reaction, independent of changes in MAP. In addition, this impaired vasomotor reactivity was not observed in the absence of sepsis, leading to speculation that such impaired vasomotor reactivity might contribute to the pathogenesis of septic encephalopathy. Terborg and colleagues showed that severe sepsis and septic shock severely reduced CO2-induced vasomotor reaction, independent of changes in MAP. In addition, this impaired vasomotor reactivity was not observed in the absence of sepsis, leading to speculation that such impaired vasomotor reactivity might contribute to the pathogenesis of septic encephalopathy.

Bowie and colleagues studied 12 sedated and ventilated patients in whom sepsis had been established for >24 h, and found that established sepsis profoundly affects vascular tone and reactivity, not only of the systemic circulation, but also of the cerebral vasculature. They concluded that discrepancies regarding impaired cerebrovascular CO2 reactivity were attributable to differences in the timing of measurements in relation to the onset of sepsis or disease severity. Brian and colleagues studied the probable mechanisms of impaired vasomotor reactivity during sepsis, and suggested that impaired mechanisms of vasomotor reactivity during sepsis are not accounted for by group B streptococcus-induced reductions in cardiac output or blood pressure, and are mediated by nitric oxide, not prostanooids. The present findings suggest that the degree of intactness of vasomotor reactivity during sepsis must be considered when attempting to control CBF by changing arterial CO2 levels.

Several studies have evaluated the effects of propofol and dexmedetomidine on cerebrovascular circulation and CO2 reactivity. Matta and colleagues examined the cerebral CO2 reactivity during propofol-induced electrical silence of the electroencephalography in 10 patients, and found that the cerebral CO2 reactivity remained intact during propofol anaesthesia. In a study on sheep, Myburgh and colleagues reported that although constant propofol infusion at 15 mg min\(^{-1}\) kg\(^{-1}\) significantly decreased CBF compared with awake conditions, CO2 reactivity remained intact. In regard to dexmedetomidine, few data are available for the effects of dexmedetomidine on cerebral autoregulation. Zornow and colleagues showed in dogs that despite increased arterial pressure, dexmedetomidine caused marked reductions in CBF when dexmedetomidine has no effect on the cerebral metabolic rate for oxygen. Our study is the first to compare the effects of sedative doses of dexmedetomidine and propofol on CO2 reactivity in patients with septic shock. The results show that cerebrovascular CO2 reactivity is lower under dexmedetomidine sedation than under propofol sedation during almost identical levels of sedation in patients with septic shock. This suggests that propofol has a sparing effect on cerebrovascular CO2 reactivity compared with dexmedetomidine when used as a sedative in patients with septic shock, and thus represents the preferred sedative agent in these patients. In contrast to the differential results between propofol and dexmedetomidine in patients with septic shock, no differential effects were found in controls. This finding has clinical implications in that hypercapnic lung-protective ventilation is currently widely accepted as a ventilatory strategy for acute respiratory distress syndrome. Hypercapnic ventilation has no adverse effect on intracranial pressure (ICP) in patients without septic shock under propofol or dexmedetomidine. In addition, neuroprotective ventilation is sometimes used for patients with raised ICP in patients with brain injury. In patients without septic shock, both propofol and dexmedetomidine would be effective to control ICP. Several mechanisms should be considered for our results. First, dexmedetomidine has a more profound cerebrovascular constrictor effect compared with propofol at our study dosage. Secondly, patient characteristics may have affected our results. In a previous study, we found that the cerebrovascular CO2 reactivity was lower in elderly patients than in young patients. Hartl and colleagues reported markedly lower absolute and relative mean CO2 reactivities in elderly subjects compared with young subjects, suggesting that aging might have some effects on cerebrovascular CO2 reactivity. Finally, the use of different dosages compared with those used in our study may have yielded differential effects. Indeed, we have previously shown that differential dosages of propofol exert differential effects on CO2 reactivity. Altering the dose of dexmedetomidine used in septic shock patients in our study may thus have resulted in different effects on CO2 reactivity. Therefore, further study is necessary to clarify the differential effects of propofol and dexmedetomidine on cerebrovascular CO2 reactivity in patients with septic shock.

The cerebrovascular CO2 reactivity under dexmedetomidine sedation in patients with septic shock was almost within the normal range according to results from our previous studies, even when more profound depression of cerebrovascular CO2 reactivity occurred with
dexmedetomidine than with propofol. However, for clinical situations in ICUs, CBF or volume is sometimes used to manipulate $P_aCO_2$. The change in $P_aCO_2$ has larger effects on CBF and volume under propofol sedation than under dexmedetomidine sedation. The clinical relevance of our findings is that maintaining adequate cerebral circulation is important in patients with septic shock, to avoid septic encephalopathy. Extra caution in the choice of sedatives is thus warranted, as these agents might alter cerebral autoregulation in patients with septic shock.

**Study limitations**

In patients with septic shock, large doses of catecholamines were used to maintain adequate haemodynamics. These large doses of catecholamines may have had some effects on our results. Stephan and colleagues showed that norepinephrine and phenylephrine infused to increase arterial pressure in anaesthetized patients failed to show any significant vasoconstrictor effects on cerebral circulation. Although catecholamine dosage was almost identical between propofol and dexmedetomidine groups in septic shock patients, the effects of catecholamines on vasoconstrictor effects in the cerebral circulation cannot be ignored. Further study is needed to clarify the effects of propofol and dexmedetomidine on cerebral circulation using high-dose catecholamines.

This study focused on the comparative effects of propofol and dexmedetomidine on CO2 reactivity in patients with septic shock, without examining the direct effects of propofol or dexmedetomidine on vasomotor CO2 reactivity in patients with and without septic shock.

The present study used BIS monitors to achieve identical sedation levels. Whether BIS monitors are suitable for monitoring sedation in the ICU remains controversial. Weatherburn and colleagues assessed the effectiveness of a BIS monitor in supporting clinical sedation management decisions in mechanically ventilated ICU patients, and concluded that the use of BIS monitoring did not reduce the amount of sedation used, duration of mechanical ventilation, or duration of ICU stay. Frenzel and colleagues examined the utility of BIS in assessing depth of sedation for sedated and mechanically ventilated ICU patients, compared with clinical sedation scores, and showed that BIS was unsuitable for monitoring sedation in a heterogeneous group of surgical ICU patients. However, Venn and colleagues showed the efficacy of BIS monitors for defining sedation levels in comparisons between dexmedetomidine and propofol for sedation in the ICU.

Another problem is that the present study did not directly measure the cerebral metabolic rate of oxygen (CMRO2), and so cannot rule out the possibility that CMRO2 might have changed during the study period, although factors related to changing CMRO2, such as anaesthetic depth as assessed by BIS and clinical sedation score or rectal temperature, may not have changed throughout the study period.

Hypocapnia-induced hyperventilation is commonly used to treat increased ICP in the operation theatre or ICU. A recent review raised questions about the efficacy of hyperventilation-induced hypocapnia. Laffey and Kavanagh suggested that the reduction in ICP might be life-saving in patients with severely elevated ICP. However, hypocapnia-induced brain ischaemia may occur because of vasoconstriction (impaired cerebral perfusion), reduced oxygen release from haemoglobin, and increased neuronal excitability, with the possible release of excitotoxins such as glutamate. In contrast, hypercapnia has been proposed to be beneficial in cases of focal ischaemia by causing vasodilation and increasing blood flow in the ischaemic brain. Conversely, hypercapnia may also decrease blood flow to the ischaemic brain by causing vasodilation in the normal brain and diverting blood flow away from the ischaemic brain. According to the present findings, controlling CBF by altering $P_aCO_2$ can be more effectively achieved using propofol rather than dexmedetomidine sedation in the ICU.

In conclusion, we found that cerebrovascular CO2 reactivity in patients with septic shock was impaired compared with that in patients without septic shock, and that cerebrovascular CO2 reactivity was lower under dexmedetomidine sedation than under propofol sedation in patients with septic shock.

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