Influence of sepsis on sevoflurane minimum alveolar concentration in a porcine model

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Sevoflurane is widely used in anaesthetic protocols for patients undergoing surgical procedures. However, there are no reports on the influence of sepsis on minimum alveolar concentration of sevoflurane (MACSEV) in animals or in humans. The aim of this study was to test the hypothesis that sepsis could alter the MACSEV in a normotensive septic pig model. Twenty young, healthy pigs were used. After they had received 10 mg kg⁻¹ of ketamine i.m. for premedication, anaesthesia was established with propofol 3 mg kg⁻¹ and the trachea was intubated. Sevoflurane was used as the sole anaesthetic agent. Baseline haemodynamic recording included electrocardiography, carotid artery blood pressure and a pulmonary thermodilution catheter. Baseline MACSEV in each pig was evaluated by pinching with a haemostat applied for 1 min to a rear dewclaw. MACSEV was determined using incremental changes in sevoflurane concentration until purposeful movement appeared. Pigs were assigned randomly to two groups: the saline group (n=10) received a 1-h i.v. infusion of sterile saline solution while the sepsis group (n=10) received a 1-h i.v. infusion of live Pseudomonas aeruginosa. Epinephrine and hydroxyethylstarch were used to maintain normotensive and normovolemic haemodynamic status. In both groups, MACSEV was evaluated 5 h after infusion. Significant increases in mean artery pulmonary pressure, filling, epinephrine and vascular pulmonary resistances occurred in the sepsis group. MACSEV for the saline group was 2.4% (95% confidence interval (CI) 2.1–2.55%) and the MACSEV for the sepsis group was 1.35% (95% CI 1.2–1.45%, P<0.05). These data indicate that MACSEV is significantly decreased in this normotensive septic pig model.

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Patients with sepsis syndrome or septic shock may require general anaesthesia for eradication of a septic focus, often on an emergency basis. Most anaesthetics are cardiodepressant and can alter vascular tone. Nevertheless, ketamine preserves cardiovascular function and oxygen delivery in hypoxic tissues and therefore seems to be the most attractive drug in these circumstances.1 Theoretically, sevoflurane could be an interesting alternative in these patients because of its rapid pharmacokinetics, allowing rapid haemodynamic control.2

The pharmacokinetics of sevoflurane has been well characterized in animals and humans in numerous situations.3 As with other inhaled anaesthetic agents, many parameters can affect the minimum alveolar concentration of sevoflurane (MACSEV) in pigs, including age, hypothermia, additional anaesthetic drugs, acid–base status, carbon dioxide and cerebral electrolyte concentrations, type of supramaximal stimulus and haemodynamics.4–7 Reduced requirement of isoflurane MAC has been demonstrated in a septic canine model,8 but no published data are available on MACSEV requirements in septic animals or patients.

As few studies have evaluated the use of halogenated agents in septic conditions, inappropriately high or low

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doses of volatile agents may have been administered. The aim of this study was to test whether sepsis could modify MACSEV requirements in an animal model of sepsis.

Methods

After approval of the study by the Claude Bernard University Committee on Animal Research, we studied 20 healthy young pigs [3–4 months old; 23 (SD 2) kg]. They were obtained from Morel Farm and housed in the university vivarium for 3–5 days.

After premedication with ketamine 10 mg kg\(^{-1}\) i.m., general anaesthesia was induced with propofol 3 mg kg\(^{-1}\) infused in an auricular vein. The trachea was intubated with a 6.0 mm cuffed tube and mechanical ventilation was started. Ventilation was performed (Sa 2; Dräger, Lübeck, Germany) in a pure oxygen non-rebreathing system with sevoflurane as the sole anaesthetic agent, delivered with a calibrated vaporizer (Vapor 19.1; Dräger). Fresh gas flow was delivered at 4.5 litre min\(^{-1}\) in this open circuit, and ventilation was adjusted to maintain end-tidal normocapnia at baseline values. A 7 Fr pulmonary artery thermodilution catheter (Arrow, PA, USA) was introduced via the internal jugular vein, positioned under fluoroscopy into the pulmonary artery for measurement of pulmonary arterial pressure (MPAP) and cardiac output. A common carotid artery catheter was inserted for continuous monitoring of systemic arterial pressure and blood sampling. Inspired and expired gases, including end-tidal anaesthetic concentrations and carbon dioxide concentrations, were measured with a recently calibrated gas analyser (Dräger). Sevoflurane was measured with an infrared analyser (PM 8050; Dräger). This analyser was calibrated before the study according to the manufacturer’s guidelines with specific software using anaesthetic gas mixtures of known concentration: oxygen, carbon dioxide, nitric oxide and halogenated volatiles. During the whole procedure, hydration was maintained with a 9% solution of NaCl 5 ml kg\(^{-1}\) h\(^{-1}\) as the sole perfusate.

MACSEV was then assessed in each pig as previously described,\(^5\)\(^6\) beginning with a 3.5% end-tidal concentration of sevoflurane, according to previous studies.\(^2\)\(^7\) Each pig was pinched with a haemostat clamped with full ratchet lock to the back limb and moved cranially and caudally for 1 min. If no response was obtained, the expired concentration of sevoflurane was decreased by 0.1% over 10 min for equilibration (FA/FI=1) and MACSEV was evaluated. Once MACSEV had been determined, the following data were recorded: heart rate, systemic arterial pressure, MPAP, central venous pressure, end-tidal carbon dioxide, central core temperature, filling levels, cardiac output. An arterial blood sample was collected simultaneously for immediate gas analysis on an automated blood gas analyser (ABL5; Radiometer, Neuilly, France). Another arterial blood sample was collected and centrifuged (E82S; Jouan, Lyon, France) for measurements of plasma lactate levels.

Once the MACSEV had been determined and haemodynamic data collected, pigs were allocated randomly to two groups. The saline group received a 1-h infusion of sterile saline solution (1 ml kg\(^{-1}\)) and the sepsis group a 1-h intravenous infusion of live \textit{Pseudomonas aeruginosa}. This pure strain was isolated from an abscess and remained unchanged during the entire study. The inoculum was evaluated with a turbidity analyser: 1.5 McFarland units corresponding to \(5 \times 10^8\) colony-forming units (c.f.u.) per ml. In keeping with previous studies, 0.3 ml 20 kg\(^{-1}\) min\(^{-1}\) of \(5 \times 10^9\) c.f.u. per ml live bacteria was infused.\(^9\)\(^10\)

In both groups, haemodynamic status and core temperature were assessed 30, 60, 120, 180, 240 and 300 min after bacterial or saline infusion. Epinephrine and hydroxyethylstarch were used to maintain a pulmonary artery occlusion pressure between 8 and 15 mm Hg and a mean arterial...
pressure (MAP) between 60 and 70 mmHg.11 MACSEV was assessed again 5 h after the end of the infusion. MACSEV data were compared using the Mann–Whitney U-test (Fig. 1) and Kaplan–Meier curve analysis (Fig. 2). Dose–response curves were constructed in which the percentage of animals that had a demonstrated response was plotted against the sevoflurane concentration. Median MACSEV and the 95% confidence intervals were calculated. The haemodynamic data were compared using the Friedman test (Table 1). When differences were observed, a pairwise comparison using the Student–Newman–Keuls test was performed to determine which groups differed. Results are presented as mean (SEM) in Table 1 and as percentages of values for the control group. MACSEV is expressed as median and 95% confidence interval.

Results

Significant differences in MACSEV were found between the sepsis and saline groups: MACSEV for the saline group was 2.4% (2.1–2.55%) and the MACSEV for the sepsis group was 1.35% (1.2–1.45%) (P<0.05) (Figs 1 and 2).

Mean MPAP in the sepsis group had increased significantly (+131%, P<0.05) 30 min after the end of the bacterial perfusion. It then decreased continuously to a steady state with persistent pulmonary hypertension for the remainder of the study in comparison with the control group (+78%) (Table 1). Pulmonary vascular resistance had increased significantly (+179%; P<0.05) in the sepsis group 30 min after the end of the bacterial perfusion; it then declined but remained significantly higher compared with baseline (+114%, P<0.05) (Table 1). Filling level increased significantly in the sepsis group during the entire study after the end of bacterial infusion (+300%, P<0.05) (Table 1). Epinephrine infusion increased significantly in the sepsis group during the whole study after the end of bacterial infusion (Table 1).

In both groups, before and after infusion, no statistically significant differences were observed for MAP, cardiac output, systemic vascular resistance, heart rate, central venous pressure, pulmonary artery occlusion pressure, filling, end-tidal carbon dioxide, arterial gas values, core temperature or plasma lactate concentration (Table 1).

### Table 1 Influence of sepsis on sevoflurane MAC. Data are mean (SEM). MPAP=mean pulmonary artery pressure; PAOP=pulmonary arterial occlusion pressure; cumulative filling=hydroxyethylstarch and saline infusion. *P<0.05 vs animals with saline

<table>
<thead>
<tr>
<th>Time after infusion (min)</th>
<th>Before infusion</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic vascular resistance (dyne s cm⁻²)</strong>&lt;br&gt;Saline</td>
<td>1918 (140)</td>
<td>2208 (156)</td>
<td>2134 (144)</td>
<td>1987 (144)</td>
<td>2170 (152)</td>
<td>2079 (210)</td>
<td>2165 (176)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2025 (110)</td>
<td>1735 (89)</td>
<td>1825 (101)</td>
<td>1944 (78)</td>
<td>1972 (134)</td>
<td>2085 (128)</td>
<td>2061 (193)</td>
</tr>
<tr>
<td><strong>PAOP (mm Hg)</strong>&lt;br&gt;Saline</td>
<td>11 (0.2)</td>
<td>10 (0.3)</td>
<td>12 (0.5)</td>
<td>11 (0.3)</td>
<td>9 (0.1)</td>
<td>11 (0.2)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>12 (0.5)</td>
<td>11 (0.3)</td>
<td>10 (0.3)</td>
<td>8 (0.2)</td>
<td>10 (0.3)</td>
<td>12 (0.4)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td><strong>MPAP (mm Hg)</strong>&lt;br&gt;Saline</td>
<td>16.4 (1.2)</td>
<td>18 (1.5)</td>
<td>14.7 (1.4)</td>
<td>16.1 (1.2)</td>
<td>15.7 (1.4)</td>
<td>14.5 (1.4)</td>
<td>14.6 (1.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>19.5 (1.8)</td>
<td>45 (3.4)*</td>
<td>43.2 (1.5)*</td>
<td>38.9 (1.6)*</td>
<td>36.5 (1.1)*</td>
<td>37.1 (1.7)*</td>
<td>34.2 (1.8)*</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance (dyne s cm⁻²)</strong>&lt;br&gt;Saline</td>
<td>211 (26)</td>
<td>198 (41)</td>
<td>179 (21)</td>
<td>214 (29)</td>
<td>202 (19)</td>
<td>230 (28)</td>
<td>189 (32)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>242 (38)</td>
<td>722 (102)*</td>
<td>690 (64)*</td>
<td>654 (45)*</td>
<td>589 (31)*</td>
<td>603 (63)*</td>
<td>554 (100)*</td>
</tr>
<tr>
<td><strong>Heart rate (beats min⁻¹)</strong>&lt;br&gt;Saline</td>
<td>89 (5)</td>
<td>95 (4)</td>
<td>87 (7)</td>
<td>92 (4)</td>
<td>111 (9)</td>
<td>98 (3)</td>
<td>105 (2)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>101 (6)</td>
<td>104 (6)</td>
<td>94 (4)</td>
<td>106 (9)</td>
<td>88 (5)</td>
<td>84 (10)</td>
<td>90 (9)</td>
</tr>
<tr>
<td><strong>MAP (mm Hg)</strong>&lt;br&gt;Saline</td>
<td>78 (12)</td>
<td>79 (16)</td>
<td>77 (11)</td>
<td>70 (9)</td>
<td>71 (10)</td>
<td>81 (13)</td>
<td>80 (14)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>85 (15)</td>
<td>61 (9)</td>
<td>69 (8)</td>
<td>71 (14)</td>
<td>77 (31)</td>
<td>93 (17)</td>
<td>86 (11)</td>
</tr>
<tr>
<td><strong>Cardiac output (litre min⁻¹)</strong>&lt;br&gt;Saline</td>
<td>2.8 (0.3)</td>
<td>2.5 (0.4)</td>
<td>2.4 (0.3)</td>
<td>2.4 (0.5)</td>
<td>2.2 (0.6)</td>
<td>2.7 (0.2)</td>
<td>2.5 (0.2)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.9 (0.3)</td>
<td>2.3 (0.7)</td>
<td>2.5 (0.6)</td>
<td>2.6 (0.4)</td>
<td>2.7 (0.8)</td>
<td>3.1 (0.3)</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td><strong>Core temperature (°C)</strong>&lt;br&gt;Saline</td>
<td>38 (0.2)</td>
<td>38.2 (0.3)</td>
<td>38.2 (0.4)</td>
<td>38.4 (0.2)</td>
<td>38.1 (0.4)</td>
<td>38.8 (0.7)</td>
<td>38.6 (0.6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>38.1 (0.2)</td>
<td>38.3 (0.3)</td>
<td>38.3 (0.2)</td>
<td>38.4 (0.5)</td>
<td>38.6 (0.5)</td>
<td>38.3 (0.4)</td>
<td>38.7 (0.6)</td>
</tr>
<tr>
<td><strong>Plasma lactate concentration (mmol litre⁻¹)</strong>&lt;br&gt;Saline</td>
<td>1.1 (0.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.9 (0.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.5 (0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Epinephrine (μg kg⁻¹ min⁻¹)</strong>&lt;br&gt;Saline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>1.1 (0.2)*</td>
<td>0.9 (0.3)*</td>
<td>0.8 (0.2)*</td>
<td>0.6 (0.2)*</td>
<td>0.7 (0.3)*</td>
<td>0.6 (0.3)*</td>
</tr>
<tr>
<td><strong>Cumulative filling (ml)</strong>&lt;br&gt;Saline</td>
<td>30 (0)</td>
<td>60 (0)</td>
<td>90 (0)</td>
<td>120 (0)</td>
<td>150 (0)</td>
<td>180 (0)</td>
<td>210 (0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>30 (0)</td>
<td>114 (16)*</td>
<td>197 (23)*</td>
<td>264 (27)*</td>
<td>367 (39)*</td>
<td>398 (33)*</td>
<td>454 (42)*</td>
</tr>
</tbody>
</table>

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No statistically significant differences were observed for all parameters and MAC$_{SEV}$ in the saline group when values before and after perfusion of sterile saline were compared (Table 1) (Figs 1 and 2).

Discussion

In comparison with the non-septic group (saline group), septic animals had a decreased inhalation requirement for sevoflurane, corresponding to a lower MAC$_{SEV}$.

The experimental model used has several limitations. First, of the numerous models of experimental sepsis found in the literature, only a few have been described to assess MAC of volatile or intravenous anaesthetic needs or haemodynamic effects. Intravasal or intraperitoneal injection of live microorganisms or purified endotoxin and many methods of caecal ligation have been used, but no ideal model of sepsis is available. Injection of a defined amount of microorganisms can provide simple and satisfactory standardization of the inoculum and consequently a constant pure strain.

Secondly, the haemodynamic values in our study had no significant differences were found for MAP, cardiac output, systemic vascular resistance, CVP and pulmonary artery occlusion pressure in the septic group (Table 1). Moreover, heart rate did not increase significantly in the septic pig group because of the negative lusitropic effect of sevoflurane (Table 1). Finally, because of the microorganism infusion, early pulmonary hypertension appeared and a slight decrease in MPAP was observed over the whole period of the study, even after bacterial perfusion. Overall, we obtained a normotensive resuscitated septig model with normal systemic resistances and cardiac output, close to that found in patients undergoing surgical procedures. Thirdly, because of the short delay after bacterial infusion, septic myocardiopathy probably did not occur. In cases of haemodynamic failure, MAC$_{SEV}$ is likely to be altered more profoundly.

Three basic variables can influence the MAC: the nociceptive stimulus, the response and the end-tidal anaesthetic concentrations. Two types of stimulus have been used to assess the MAC in animals: clamping the dewclaw and clamping the tail. Minimum alveolar concentration values obtained by clamping the tail were more variable and lower than those obtained by clamping the dewclaw. Therefore, the stimulus that was applied in our study was dewclaw clamping, which has been reported to be a supramaximal stimulus. This stimulus remained constant during the entire study. Thus, the nature of the stimulus could not influence MAC$_{SEV}$. The response to this supramaximal stimulus has already been described in the pig model as the ‘pedal reflex’. It is obtained when contralateral clamping is performed. This type of response was used in our study in order not to underestimate MAC$_{SEV}$.

Many pathophysiological conditions can affect MAC$_{SEV}$ values, including additional anaesthetic drugs, differences in core temperature, age, acid–base status, cerebral electrolyte concentrations, hypotension and prolonged anaesthesia. MAC$_{SEV}$ values in the control group were close to values reported by Eger. The MAC$_{SEV}$ reduction in the septic group could not be explained by core temperature modification. Values under 36°C define hypothermia in pigs. Therefore, both groups were normothermic. In addition, there were no statistical differences between core temperature values in the two groups (Table 1).

Suspected occult tissue hypoxia associated with sepsis, producing metabolic acidosis and indicating anaerobic metabolism, probably contributed to the decreased anaesthetic requirement. In our study, there was no difference in arterial lactate concentrations or acid–basis status. However, lactate is an unreliable indicator of tissue hypoxia during sepsis and in our septic model, because of the short delay after bacterial infusion, tissue hypoxia could have occurred without metabolic modifications.

Another potential cause of discrepancy in the reduction of MAC$_{SEV}$ is fluid and drug resuscitation. Hydroxyethylstarch and epinephrine were administered according to the anaesthetist’s normal practice in order to sustain blood pressure. Steffey and Eger investigated the effect of various vasopressors on halothane MAC in normal dogs and found no effect of epinephrine. Our results support the hypothesis that changes in anaesthetic requirement might be related, in part, to the use of hydroxyethylstarch. However, the influence of hydroxyethylstarch on MAC requirements has never been explored.

Differences in MAC$_{SEV}$ could result from variation in the duration of the experimental procedure. This was not the case in this study as the duration of experiments was constant throughout the study.

Hypotension has been reported to decrease the MAC of volatile anaesthetic agents. In our study, because of epinephrine and filling, septic pigs remained normotensive and had normal systemic vascular resistances.

Differences in MAC$_{SEV}$ can also result from central nervous system dysfunction associated with sepsis. Encephalopathy, alterations in neurotransmitter levels, changes in receptor function and brain Ca$^{2+}$ accumulation occur early during sepsis. Furthermore, changes in regional blood flow and skeletal muscle energy status appear during sepsis. Thus, anaesthetic requirements could be reduced in these models and could possibly explain the lower MAC$_{SEV}$ in the septic group.
In summary, surgical procedures can be performed in patients with sepsis. Improvement in early diagnosis and fluid resuscitation has changed septic shock into severe normotensive sepsis. In this normotensive pig model, the MAC of sevoflurane is decreased. Further studies are needed to determine the effect of hepatic and renal alterations on sevoflurane metabolism in septic patients.

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References
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