The effects of etomidate on cerebral metabolism and blood flow in a canine model for hypoperfusion


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The effects of etomidate, a nonbarbiturate cerebral metabolic depressant, on cerebral metabolism and blood flow were studied in 29 dogs during cerebral hypoperfusion. Three groups of animals were studied during a 45-minute normotensive and a 30-minute hypotensive period: 10 control animals without etomidate, 11 animals receiving a 0.1-mg/kg etomidate bolus followed by an infusion of 0.05 mg/kg/min etomidate (low-dose group), and eight animals receiving doses of etomidate sufficient to suppress electroencephalographic bursts (high-dose group). The mean arterial pressure fell to similar levels (p < 0.05) during hypotension in all three groups (40 ± 5, 38 ± 3, and 27 ± 6 mm Hg, respectively). The mean cerebral oxygen extraction fraction rose (p < 0.05) from 0.23 ± 0.02 to 0.55 ± 0.08 in the five control animals tested and from 0.33 ± 0.02 to 0.53 ± 0.02 in the seven animals tested in the low-dose group, but did not increase (p > 0.05) in the four animals tested in the high-dose group (0.24 ± 0.03 to 0.23 ± 0.05). Mean cerebral blood flow levels decreased in all groups during hypotension (p < 0.05): 42 ± 3 to 21 ± 4 ml/100 gm/min (52% ± 12% decrease) in the five animals tested in the control group, 60 ± 8 to 24 ± 6 ml/100 gm/min (56% ± 13% decrease) in the four animals tested in the low-dose group, and 55 ± 8 to 22 ± 3 ml/100 gm/min (60% ± 4% decrease) in the four animals tested in the high-dose group. In summary, the cerebral oxygen extraction fraction increased in the control animals and low-dose recipients during hypotension, suggesting the presence of threatened cerebral tissue. In contrast, the cerebral oxygen extraction did not change during hypotension when high-dose etomidate was administered. It is concluded that high-dose etomidate may preserve the cerebral metabolic state during hypotension in the present model.

KEY WORDS • etomidate • cerebral metabolism • cerebral blood flow

Etomidate is an intravenously administered carbamoylated imidazole derivative (nonbarbiturate) agent which has cerebral metabolic depressant properties. Previous reports have indicated that, like barbiturate agents, etomidate decreases cerebral oxygen consumption (CMRO₂) by 35% to 50%. In distinction to barbiturates, however, etomidate does not have marked cardiac depressant properties. For this reason, its use may be advantageous during surgically induced temporary cerebral ischemia.

With regard to the specific metabolic actions of etomidate, Milde, et al., reported that etomidate lowers cerebral blood flow (CBF) and CMRO₂ proportionately during normotension. In addition, Milde and Milde also reported that etomidate maintains phosphocreatine and adenosine triphosphate content at relatively normal levels during a short hypotensive period in dogs. The metabolic effects of etomidate, however, have not been thoroughly established during a hypoperfusion insult. For this reason, the aim of the present studies was to develop an animal model in which a stereotypical hypotensive insult could be produced and to define the effects of etomidate on cerebral metabolism and CBF in this setting.

Materials and Methods

Animal Preparation

Experiments were carried out on 29 mongrel dogs, weighing 19.0 to 36.2 kg each (mean ± standard error of the mean: 24.8 ± 1.9 kg), of either sex that were housed in an approved surgical facility. Laboratory protocol was approved by the University of Texas South-
western Medical Center Investigational Review Board. All animals were fed at 3 p.m. on the day prior to the study and the food was not removed prior to the study. An induced ischemic insult is reported to be more severe in fed than in fasted animals.

On the day of the procedure, each dog was anesthetized with a short-acting barbiturate (thiamylal 20 mg/kg), then endotracheally intubated and ventilated at an approximate volume of 18 cc/kg using a Harvard pump. Anesthesia was maintained with 1.5% inspired isoflurane (Forane), 5% to 10% N₂O (in the studies measuring CBF only) and an N₂/O₂ mixture so as to maintain PaO₂ at 150 to 250 mm Hg. Paralysis was maintained with vecuronium bromide, approximately 0.1 mg/kg/hr. Isoflurane was chosen as the anesthetic agent in the present studies because it is preferentially used in the clinical setting in which cerebral ischemia is produced. Isoflurane employed at this concentration has less significant effects on CBF than does halothane, does not markedly depress CMRO₂, and does not suppress electroencephalographic (EEG) bursts.

Surgical Procedure

Following the induction of anesthesia, each animal was placed in the prone position with the head supported. A cephalic intravenous catheter was placed for the infusion of maintenance fluids (0.9% normal saline), and a polyethylene catheter (0.12 cm internal diameter) was inserted in the left femoral artery for physiographic monitoring. A biparietal craniectomy was performed in order to expose the superior sagittal sinus, and the sinus was cannulated with a No. 20 polyethylene catheter so that the tip was placed proximal to the torcular herophili.Michenfelder, et al.,¹⁹ and Hegedus and Shackelford²⁰ have previously reported that samples obtained from this site are preferred in the assessment of CBF and metabolism in the dog. Four needle scalp electrodes were inserted transdurally to record cortical electrical activity. A bipolar montage was used, and hemispheric electrical activity was recorded on a Lifescan brain activity monitor, allowing continuous analysis of EEG frequency spectrum as well as raw EEG data.

Experimental Design

Each experiment consisted of a normotensive (baseline) period (0 to 45 minutes), a hypotensive period (45 to 75 minutes), and a recovery period (75 to 120 minutes). Baseline samples were taken in triplicate from the femoral artery and sagittal sinus at 10 to 15 minutes in the etomidate protocols and at 40 to 45 minutes in all three groups. Hypotension (27 to 40 mm Hg) was then induced for 75 minutes by administration of trimethaphan (Arfonad, 0.1 to 1.0 mg/min) and sodium nitroprusside (1 to 8 μg/kg/min). Metabolic samples were taken at 70 to 75 minutes. Recovery period samples were obtained at 90 to 120 minutes. In approximately 20% of the animals, the mean arterial blood pressure (MABP) could not be lowered below 60 mm Hg despite maximum pharmacological doses of hypotensive agents. Since it is likely that these animals were not subjected to an insult similar to that of the more hypotensive animals, their data were not included in the results reported here.

The first protocol (control) was designed to assess the cerebral metabolic responses (five dogs) and the CBF responses (five dogs) during a hypoperfusion insult. The purpose of the second protocol (low-dose etomidate) was to assess the effect of etomidate (Amidate) on the cerebral metabolic responses (seven dogs) and CBF responses (four dogs) during hypotension. This dose of etomidate (which did not suppress the EEG bursts of the animals) was employed for two reasons. First, Milde, et al.,¹⁹ reported that cerebral metabolism is dissociated from CBF at low but not high doses of etomidate, and it was of interest to further investigate this finding. Second, it appeared clinically important to assess the effects of different doses of etomidate on cerebral metabolism during hypoperfusion since burst-suppressive doses of etomidate are not routinely administered during temporary arterial occlusion. In this group, metabolic samples were drawn at 10 to 15 minutes, and a 1.0-mg/kg etomidate bolus was given at 15 minutes followed by a 0.05-mg/kg/min infusion which was continued throughout the remainder of the study. The purpose of the third protocol (high-dose etomidate) was to assess the effect of burst-suppressive doses of etomidate on cerebral metabolism (four dogs) and blood flow (four dogs). In this protocol, 3.0 ± 0.6 mg/kg etomidate was administered at 15 minutes to achieve EEG burst suppression, a state defined as an isoelectric interval interrupted by bursts of activity of 8 to 12 Hz, which diminish to 1 to 4 Hz prior to electrical silence.³ A continuous etomidate infusion (0.1 mg/kg/min) was then begun, supplemented with bolus infusions as necessary to maintain EEG burst suppression throughout the study.

Collection and Processing of Blood Samples

Samples for arterial and venous blood gases and O₂ content were collected as noted above and run on a Corning 278 blood gas analyzer and a 2500 CO-oximeter. The intra-assay coefficient of variation (CV) was 3%. Plasma glucose samples were analyzed; the
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FIG. 1. Effect of hypotension on mean arterial blood pressure (left) and cerebral oxygen extraction fraction (right) without etomidate (control), with low-dose etomidate, or with high-dose etomidate. Asterisk indicates that the data for the high-dose etomidate group was significantly less than for the control and low-dose etomidate groups (p < 0.05).

intra-assay CV was 3%. Whole blood lactate concentrations were analyzed in triplicate using the methods developed by Lloyd, et al.; the intra-assay CV was 8%

The CBF was assessed in a separate group of animals using the Kety-Schmidt method with N₂O dilution. These studies were performed to document that there was a decrement in CBF in response to hypotension. It should be noted that metabolic data from these animals were similar to data in the first group of animals (data not shown). A 5% to 10% N₂O mixture was administered during a 30- to 40-minute period until a steady-state concentration occurred as defined by a stable blood N₂O concentration. The N₂O was stopped at this point and arterial and venous decay curves were drawn. The N₂O concentrations were determined on an infrared analyzer as described by Swedlow and Lewis using an infrared N₂O analyzer; the intra-assay CV was 3%. The CBF values were corrected for PaCO₂, but the uncorrected data are included because these alterations led to an estimated change in CBF of only 2.5%.

Calculations and Statistical Analysis

The cerebral oxygen extraction fraction was calculated as follows: O₂ content (arterial) - O₂ content (venous)/O₂ content (arterial). The glucose extraction fraction was calculated in a similar fashion. The CBF was calculated from the N₂O decay curves using a one-compartmental model. All summary statistics are reported as mean ± standard error of the mean. Two-factor repeated-measures analysis of variance was used to compare the control, low-dose, and high-dose groups over three time periods (baseline, hypotension, and recovery). If there was a significant interaction across time periods (p < 0.10), appropriate multiple comparisons were made using a Bonferroni approach. Pairwise comparisons were considered statistically significant at p < 0.05.

Results

Heart Rate, MABP, and Blood Gases During Hypotension

The MABP fell from 156 ± 10 to 40 ± 5 mm Hg during hypotension in the control studies (p < 0.05) and rose to 87 ± 16 mm Hg during the recovery period (p < 0.05) (Fig. 1 left). The MABP fell (p < 0.05) similarly in the low- and high-dose etomidate studies, from 151 ± 6 to 38 ± 3 mm Hg and from 142 ± 11 to 27 ± 6 mm Hg, respectively. In these groups, the MABP increased to 84 ± 15 and 72 ± 10 mm Hg, respectively, during the recovery period (p < 0.05). Mean heart rates were similar in all groups during the baseline, hypotension, and recovery periods: 141 ± 13, 127 ± 5, and 151 ± 9/min (control group); 150 ± 15, 122 ± 16, and 132 ± 7/min (low-dose group); and 128 ± 14, 106 ± 9, and 108 ± 12/min (high-dose group). The blood gas data are listed in Table 1.

<table>
<thead>
<tr>
<th>PaO₂ (mm Hg)</th>
<th>Baseline</th>
<th>Hypotension</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>control</td>
<td>189 ± 5</td>
<td>128 ± 17</td>
<td>152 ± 20</td>
</tr>
<tr>
<td>low-dose etomidate</td>
<td>174 ± 8</td>
<td>97 ± 10</td>
<td>136 ± 21</td>
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<tr>
<td>high-dose etomidate</td>
<td>256 ± 12</td>
<td>166 ± 14†</td>
<td>213 ± 94†</td>
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</table>

<table>
<thead>
<tr>
<th>PₐCO₂ (mm Hg)</th>
<th>Baseline</th>
<th>Hypotension</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>37 ± 1</td>
<td>42 ± 3</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>low-dose etomidate</td>
<td>37 ± 1</td>
<td>42 ± 2</td>
<td>48 ± 3</td>
</tr>
<tr>
<td>high-dose etomidate</td>
<td>32 ± 2</td>
<td>41 ± 3</td>
<td>45 ± 5</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard error of the means.
† High-dose etomidate group data were significantly less than control group data (p < 0.05).

TABLE 1

Effect of hypotension on PaO₂, PₐCO₂, and pH in groups without, with low-dose, or with high-dose etomidate

Infrared N₂O analyzer manufactured by Vital Signs, Inc., East Rutherford, New Jersey.
Cerebral Oxygen Changes During Hypotension

Figure 1 right shows the changes in cerebral oxygen extraction fraction for the three animal groups. The mean cerebral oxygen extraction fraction increased from 0.23 ± 0.02 to 0.55 ± 0.08 during hypotension (p < 0.05) then decreased to 0.31 ± 0.04 during the recovery period (p < 0.05) in the control studies. In the low-dose etomidate group, the mean cerebral oxygen extraction fraction increased from 0.33 ± 0.02 to 0.53 ± 0.02 during hypotension (p < 0.05) and decreased to 0.35 ± 0.06 during the recovery period (p < 0.05). In the high-dose etomidate studies, the mean cerebral oxygen extraction fraction remained constant (p > 0.05) during the baseline, hypotension, and recovery periods (0.24 ± 0.03, 0.23 ± 0.05, and 0.22 ± 0.04, respectively).

Glucose Changes During Hypotension

Arterial plasma glucose and cerebral fractional extraction of glucose during hypotension are shown in Fig. 2. The mean arterial plasma glucose level rose (p < 0.05) in the control studies from 161 ± 19 to 215 ± 30 mg/dl during hypotension and decreased (p < 0.05) to 160 ± 25 mg/dl in the recovery period. The mean glucose level rose (p < 0.05) from 133 ± 11 to 182 ± 32 mg/dl in the low-dose etomidate group and was 171 ± 32 mg/dl in the recovery period. In the high-dose etomidate group, the mean glucose level increased (p < 0.05) from 117 ± 13 to 163 ± 15 mg/dl during hypotension and was 148 ± 27 mg/dl during the recovery period. The mean glucose extraction fraction rose (p < 0.05) from 0.10 ± 0.01 to 0.24 ± 0.06 during hypotension in the control studies and decreased (p < 0.05) to 0.10 ± 0.03 during the recovery period. In the low-dose etomidate group, it rose (p < 0.05) from 0.16 ± 0.02 to 0.35 ± 0.06 during hypotension and decreased (p < 0.05) to 0.20 ± 0.04 in the recovery period. In the high-dose etomidate studies, the mean glucose extraction fraction remained constant (p > 0.05) during the baseline, hypotensive, and recovery periods (0.06 ± 0.01, 0.10 ± 0.03, and 0.06 ± 0.01, respectively).

Arterial Blood Lactate Levels

The mean arterial blood lactate concentration rose from 1.6 ± 0.6 to 3.7 ± 0.5 mmol/liter during hypotension (p < 0.05) and was 3.3 ± 0.5 mmol/liter during the recovery period in the control group. In the low-dose etomidate group, the mean lactate concentration rose (p < 0.05) from 1.5 ± 0.3 to 4.3 ± 0.4 mmol/liter and remained at 5.4 ± 0.5 mmol/liter during the recov-
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TABLE 3

Effect of etomidate and hypotension on CBF, MABP, and PaCO₂

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Normotension</th>
<th>Normotension + Etomidate</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 gm/min)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>control (n = 5)</td>
<td>42 ± 3 (100% ± 8%)</td>
<td>—</td>
<td>21 ± 4 (48% ± 12%)</td>
</tr>
<tr>
<td>low-dose etomidate (n = 4)</td>
<td>60 ± 8 (100% ± 13%)</td>
<td>48 ± 7 (82% ± 12%)</td>
<td>24 ± 6 (44% ± 13%)</td>
</tr>
<tr>
<td>high-dose etomidate (n = 4)</td>
<td>55 ± 8 (100% ± 14%)</td>
<td>38 ± 1 (73% ± 8%)</td>
<td>22 ± 3 (40% ± 4%)</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>145 ± 11</td>
<td>—</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>low-dose etomidate</td>
<td>177 ± 13</td>
<td>174 ± 13</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>high-dose etomidate</td>
<td>164 ± 6</td>
<td>169 ± 10</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>33 ± 2</td>
<td>—</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>low-dose etomidate</td>
<td>34 ± 2</td>
<td>32 ± 4</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>high-dose etomidate</td>
<td>34 ± 3</td>
<td>32 ± 2</td>
<td>38 ± 5</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard error of the means. CBF = cerebral blood flow; MABP = mean arterial blood pressure. Numbers in parentheses are percentages of normotension data.

The brain electrical activity was abolished during hypotension in more than 90% of the animals. Cerebral oxygen extraction fraction was augmented during hypotension in the control and low-dose etomidate groups. In contrast, cerebral oxygen extraction fraction was unchanged during hypotension in the high-dose etomidate group, suggesting that the present model may be useful in screening the efficacy of proposed cerebral metabolic protectant drugs. Although CBF did not fall below 20 cc/100 gm/min in these animals (a level usually associated with ischemia), this could have resulted from the use of the Kety-Schmidt method of determination in the dog and its associated problems (small amounts of noncerebral blood and heterogeneity of brain tissue). In support of the present model is its simplicity in design and reproducibility (80% in the present studies) in the production of a hypoperfusion insult. Also, the severity of ischemia can be limited and the effects are potentially reversible. A global model, therefore, should be useful in the initial evaluation of an agent, while more specific modalities (regional CBF measurements, autoradiography, and positron emission tomography) may be indicated in subsequent studies to determine if the agent's actions are homogeneously distributed and therefore applicable to the various anatomic situations encountered in clinical practice.

Etomidate and Cerebral Glucose Extraction During Hypotension

Cerebral glucose extraction fraction increased more than twofold during hypotension with or without low-dose etomidate infusion but not during high-dose etomidate infusion. Hoyer, et al., have reported that glucose extraction fraction also increased during hypotension in their canine experimental studies. Analogous to the situation with cerebral oxygen extraction fraction, this increase may have reflected a response of threatened cerebral tissue. Although the arterial plasma glucose level was slightly but not significantly greater in
the control group than in the high-dose etomidate group, it is unlikely that such a large increment in glucose extraction fraction resulted from a greater cerebral supply of glucose in those groups (mass action effect).

Unexpectedly, systemic acidosis was enhanced in the high-dose etomidate studies, an effect which may be related to the greater dose of hypotension in this group or the etomidate per se. It is likely that etomidate directly induced metabolic acidosis since its administration during normotension lowered the pH of the animals. There was no concomitant increase in net cerebral lactate balance, however. The effect of this drug-induced acidosis on the clinical recovery of the animals was not examined.

**Etomidate and Cerebral Oxygen Extraction During Normotension and Hypotension**

Following the administration of either low- or high-dose etomidate, the cerebral oxygen extraction fraction did not change, whereas CBF showed a tendency to decrease (20% to 30%). The present findings with regard to low-dose etomidate were unexpected based on the report of Milde, et al., that cerebral oxygen extraction fraction increased in this setting. The explanation for the discrepancy between the present findings and those of Milde, et al., remains unclear but may relate to the experimental design. Milde, et al., employed incremental doses of etomidate in the same animal, increasing the dose every 20 minutes. In the present studies, blood flow and metabolic samples were taken 30 minutes after the etomidate infusion was started since the transcranial Doppler ultrasound velocity measurements had fallen to a steady-state value (average 14% decrease) over the first 20 minutes of the infusion (data not shown). If etomidate acts to decrease CBF and CMRO2 by a similar extent but lowers CBF more rapidly (for example, by vasoconstriction), the difference in experimental design may help to explain this discrepancy.

The present findings should not be interpreted to suggest that all cerebral depressant agents work by decreasing CBF proportionately to CMRO2, only that etomidate appeared to act by this mechanism at the two doses tested.

During hypotension without etomidate infusion, CBF fell by approximately 50% whereas cerebral oxygen extraction fraction increased by about twofold. Hoyer, et al., and Moyer and Morris have previously reported that the cerebral oxygen extraction fraction increased in hypotensive dogs. Likewise, Michenfelder and Theye also reported that sodium nitroprusside- or trimethaphan-induced hypotension resulted in an increase in cerebral oxygen extraction fraction, which is a response of threatened cerebral tissue to ischemia.

High-dose etomidate infusion completely blunted the increase in cerebral oxygen extraction fraction during hypotension. Milde and Milde reported that the cerebral energy state remained normal during a short (9-minute) period of oligemic hypotension during etomidate-induced EEG burst suppression. The present data support their conclusion that etomidate maintained the cerebral metabolic state during a period of hypotension.

In contrast, low-dose etomidate infusion during hypotension resulted in an increase in cerebral oxygen extraction fraction. It remains open to investigation whether low doses of etomidate would be more deleterious to the animal than high doses. If true, the use of pharmacologically induced cerebral metabolic suppression in patients undergoing temporary arterial occlusion without the concomitant use of EEG control could be seriously questioned.

**Acknowledgments**

We express our thanks to Leticia Molina for her secretarial assistance. We also appreciate the assistance of Dr. Gary Bowman and the Department of Anesthesiology for the use of the blood gas analyzer and for suggestions regarding the experimental design. In addition, we thank Dr. Craig Branch and Dr. Claudia Robertson for assistance with CBF measurement and Patricia Franklin for statistical programming.

**References**


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J. Neurosurg. / Volume 74 / February, 1991
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Manuscript received May 31, 1990.

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