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Cerebral Functional, Metabolic, and Hemodynamic Effects of Etomidate in Dogs

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The effects of a continuous infusion of etomidate on cerebral function, metabolism, and hemodynamics and on the systemic circulation were examined in six dogs. The infusion rate of etomidate was progressively increased at 20-min intervals from 0.02 to 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$ for 2 h. Cerebral oxygen consumption (CMR_{O_2}) decreased until there was cessation of neuronal function as reflected by the onset of an isoelectric EEG. This occurred during an infusion of 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ etomidate when the animals had received a total of 10.7 $mg \cdot kg^{-1}$ over 91 min. At this time the CMR_{O_2} was 2.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, 48% of control. Thereafter, despite continued administration of etomidate to a total dose of 21.4 $mg \cdot kg^{-1}$, CMR_{O_2} did not decrease further. Cerebral blood flow (CBF) decreased in association with a marked increase in cerebrovascular resistance but was independent of changes in CMR_{O_2}. CBF decreased precipitously from 145 ± 23 to 72 ± 6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ during the lowest infusion rate of 0.02 $mg \cdot kg^{-1} \cdot min^{-1}$ etomidate and stabilized at 34–36 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ during an infusion rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$. CBF remained at this level despite the continued administration of etomidate and a further decrease in CMR_{O_2}. Etomidate produced physiologically minor but statistically significant changes in the systemic hemodynamic variables. Assays of cerebral metabolites taken at the end of the infusion revealed a normal energy state and a very mild but significant increase in cerebral lactate to 1.49 $\mu mol \cdot g^{-1}$. We conclude that etomidate is a potent, direct cerebral vasoconstrictor that appears to be independent of its effect on CMR_{O_2} and that the cerebral metabolic effects of etomidate are secondary to its effect on neuronal function, with little if any direct or toxic effects on metabolic pathways. (Key words: Anesthetics, intravenous: etomidate. Brain: blood flow; electroencephalogram; metabolism; oxygen consumption.)

PREVIOUS STUDIES[1,2] indicate that a variety of anesthetics produce cerebral metabolic depression as a passive effect secondary to a decrease in neuronal activity. In the absence of neuronal function, indicated by an isoelectric EEG, cerebral metabolism is unaffected by most anesthetics, while in the presence of function (active EEG) anesthetics can greatly affect neuronal energy requirements.[3] This has been demonstrated with thiopental[4] and isoflurane,[5] both of which produce dose-related decreases in cerebral oxygen metabolism (CMR_{O_2}) that are correlated with decreasing neuronal function as indicated by changes in EEG activity. Once suppression of neuronal function is achieved, these agents, even at high doses, have no apparent direct or toxic effect on metabolism. In contrast, halothane, in high concentrations, does produce a dose-related toxic alteration in oxidative phosphorylation independent of neuronal function.[6]

Etomidate has been shown to produce marked changes in the EEG similar to those achieved with thiopental.§ A single dose of etomidate (60 mg) has been reported to be a potent cerebral metabolic depressant in humans and to decrease cerebral blood flow (CBF) secondary to the decrease in CMR_{O_2}.[7] However, the effects of a continuous infusion or increasing doses of etomidate on CBF and CMR_{O_2} have not been reported, and no correlation between EEG changes produced by etomidate and cerebral metabolism has been made.

The purpose of the present study was to determine whether etomidate decreases cerebral metabolism in relation to changes in neuronal function, whether etomidate has any direct or toxic effects on cellular metabolic pathways, and whether changes in CBF can be entirely accounted for by changes in CMR_{O_2}. In a dog model similar to that used for the study of isoflurane,[5] we examined the cerebral metabolic effects of a continuous infusion of etomidate both in the presence and absence of neuronal function. The dose of etomidate was progressively increased to and beyond the infusion rate necessary to abolish EEG activity. The data support the conclusion that the cerebral metabolic effects of etomidate are secondary to its effect on neuronal function with little, if any, direct or toxic effects on metabolic pathways and that the effects of etomidate on cerebral blood flow are at least in part independent of its effects on metabolism.

Methods

Six unmedicated fasting dogs of either sex, weighing 12–13 kg, were studied. Anesthesia was induced and maintained during the surgical preparation with halothane, 1% inspired; nitrous oxide, 70%; and oxygen. Succinylcholine, 40 mg, was given intravenously to facilitate endotracheal intubation and thereafter was continued at an infusion rate of 150 $mg \cdot h^{-1}$ to maintain muscle paralysis. Ventilation was controlled with a Harvard Pump® to maintain normocarbia. Cannulae were inserted into a

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femoral artery for pressure measurements and blood sampling, into a femoral vein for fluid and drug administration and for blood return from the direct cerebral blood flow measurements, and into a pulmonary artery via the right external jugular vein for pressure measurements, blood sampling, and measurement of cardiac output by thermodilution.¶ A peripheral intravenous catheter was placed for the administration of lactated Ringer's solution at a rate of 75 ml · h^{-1}. The electrocardiogram was recorded continuously from limb leads. Core temperature was measured by a thermistor in the pulmonary artery, and brain temperature was monitored by a parietal epidural thermistor. Both temperatures were maintained near 37° C with heating pads and lamps as necessary. Intracranial pressure (ICP) was measured with an epidural fiberoptic device,** and a four-lead bilateral EEG was recorded continuously from electrodes cemented to the skull.

After heparinization (300–400 units · kg^{-1} intravenously), the sagittal sinus was exposed, isolated, and cannulated as previously described[8,9] for direct measurement of cerebral blood flow (CBF) by a square-wave electromagnetic flowmeter.[10]†† Thereafter, the cranium was rigidly closed by sealing the cranial openings with Surgicel® and Super Line® adhesive.‡‡ Arterial, sagittal sinus, and mixed venous blood gas values were measured by electrodes at 37° C. Blood oxygen contents were calculated from measurements of hemoglobin and oxyhemoglobin concentration and oxygen tension.[11] Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated as the product of CBF and the arterial–sagittal sinus blood oxygen content difference, while whole body oxygen consumption ($\dot{V}_{O_2}$) was calculated as the product of cardiac index (CI, expressed as 1 · min^{-1} · m^{-2}) and the arterial–mixed venous blood oxygen content difference. Cerebral perfusion pressure (CPP) was calculated as the difference between mean arterial pressure (MAP) at the head level and ICP. Cerebral vascular resistance (CVR) was calculated as the quotient of CPP and CBF, while systemic vascular resistance index (SVRI) was calculated as the quotient of MAP and CI. Blood glucose, serum lactate, and pyruvate contents were determined by standard enzymatic techniques.

After completion of the surgical preparation, a period of 30 min was allowed for the animals to eliminate the halothane to an end-expired concentration of 0.1%, before control measurements were obtained. During the subsequent 20-min control period and during the period of the etomidate infusion, CBF and CMR_{O_2} were measured at 5-min intervals. Blood gas values, CI, $\dot{V}_{O_2}$, MAP, mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), heart rate, core and brain temperatures, ICP, hemoglobin concentration (Hb), blood glucose, and serum lactate and pyruvate concentrations were measured at 20-min intervals.

Following the control measurements, etomidate was infused at a rate of 0.02 mg · kg^{-1} · min^{-1} for 20 min. Thereafter the infusion rate was increased in stepwise fashion at 20-min intervals to rates of 0.05, 0.1, 0.2, 0.3, and 0.4 mg · kg^{-1} · min^{-1}. Once the etomidate infusion was started, nitrogen was substituted for nitrous oxide.

At the end of the infusion period, the dura was exposed and incised, and simultaneous bilateral cortical biopsies were taken by a technique that deposits a sample of brain (200–400 mg) into liquid nitrogen within 1 s.[12] The tissue was prepared for analysis in a refrigerated box (−25° C) as described by Folbergrova *et al.*[13] Tissue extracts were analyzed by enzymatic fluorometric techniques for phosphocreatine (PCr), ATP, ADP, AMP, glucose, lactate, and pyruvate.[14] The energy charge (EC) of the brain tissue was expressed as ([ATP] + 0.5 [ADP])/([ATP] + [ADP] + [AMP]).[15]

Results were compared between control and at each infusion rate of etomidate by analysis of variance, and significant differences were tested by the Bonferroni *t* test for multiple comparisons of paired data. Cerebral concentrations of metabolites obtained at the end of the etomidate infusion were compared with canine normal values for our laboratory by Student's *t* test for unpaired data.

Results

The etomidate infusion produced dose-related EEG changes similar to those reported for most general anesthetics (fig. 1). The EEG of the control state (high frequency—15 Hz, low amplitude 5 × 10^{-5}V activity) (A) changed to faster activity (20–30 Hz) within 15 min of the lowest infusion rate (B). High-amplitude slow waves (30 × 10^{-5}V, 5–10 Hz) occurred at 26 min during an infusion rate of 0.05 mg · kg^{-1} · min^{-1} (C). Burst suppression occurred at 68 min during an infusion rate of 0.2 mg · kg^{-1} · min^{-1} (E) while an isoelectric EEG with occasional isolated spikes occurred at approximately 91 min during an infusion rate of 0.3 mg · kg^{-1} · min^{-1} (F). Continued administration of etomidate maintained an isoelectric EEG (G).

During the infusion of etomidate, CMR_{O_2} decreased progressively until an isoelectric EEG indicated that neuronal function had been suppressed (fig. 2). Although the total dose required to produce an isoelectric EEG varied

¶ Instrumentation Laboratory Cardiac Output Computer 701.
** LADD Research Industries Inc., Burlington, VT.
†† EP 300 API, Carolina Medical Electronics.
‡‡ Rawn Company.

with each dog, once electrical silence was produced, CMR_{O_2} stabilized at 2.6 ± 0.15 ml · min^{-1} · 100 g^{-1} (mean ± SE), approximately 48% of control (fig. 2, table 1). Continued administration of etomidate at progressively increasing infusion rates had no further effect on CMR_{O_2}.

Unlike the CMR_{O_2}, which decreased progressively over a large dose range, CBF decreased precipitously with the start of the etomidate infusion and was half the control value within 7 min of the start of the lowest infusion rate (fig. 3). CBF decreased further to 36 ml · min^{-1} · 100 g^{-1} (during an infusion rate of 0.1 mg · kg^{-1} · min^{-1} and remained approximately at this value throughout the remainder of the study, despite further increases in the dose of etomidate (table 1, fig. 3). The decrease in CBF was

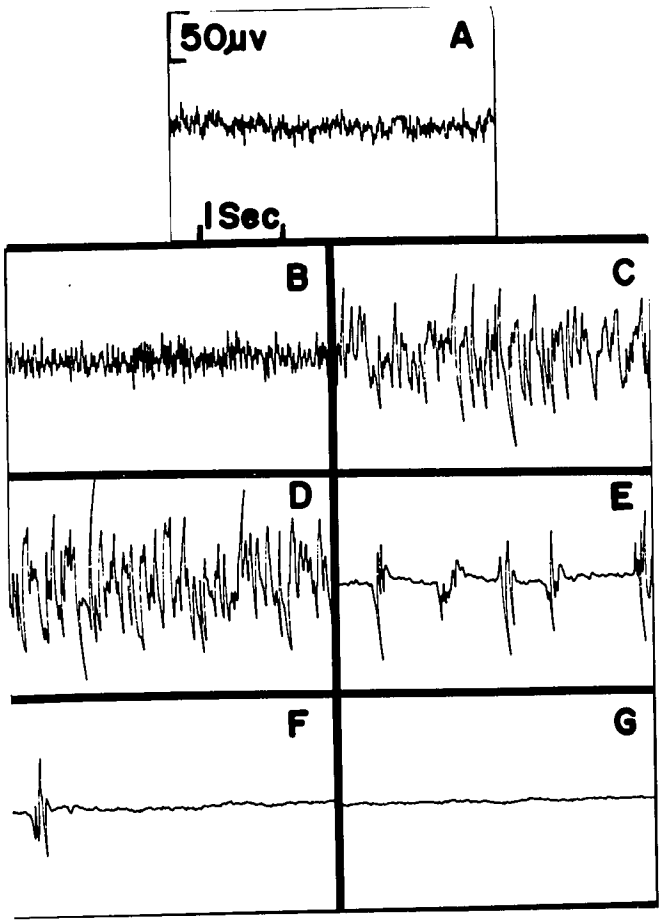

FIG. 1. EEG changes during etomidate administration in one dog. *A.* control period: high-frequency low-amplitude activity. *B.* At 15 min: etomidate infusion at 0.02 mg · kg^{-1} · min^{-1}. *C.* At 30 min: etomidate infusion at 0.05 mg · kg^{-1} · min^{-1}. *D.* At 45 min: etomidate infusion at 0.1 mg · kg^{-1} · min^{-1}. CBF had reached a plateau of 36 ml · min^{-1} · 100 g^{-1}. *E.* at 70 min: etomidate infusion at 0.2 mg · kg^{-1} · min^{-1}. *F.* At 95 min: etomidate infusion at 0.3 mg · kg^{-1} · min^{-1}. CMR_{O_2} reached a plateau of 2.6 ml · min^{-1} · 100 g^{-1} at this time. *G.* At 100 min: etomidate infusion at 0.3 mg · kg^{-1} · min^{-1}.

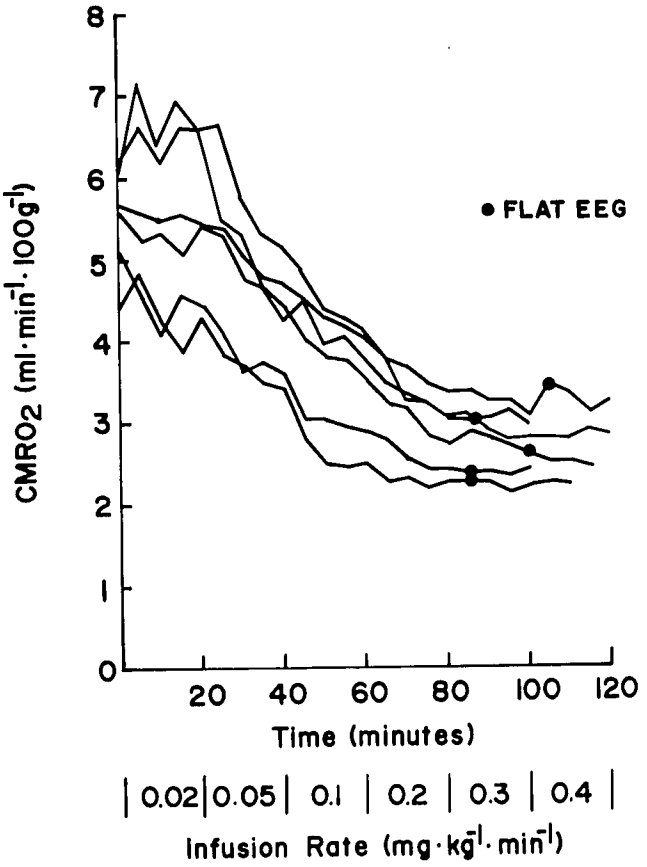

FIG. 2. Effect of increasing doses of etomidate on CMR_{O_2} for each of six dogs. CMR_{O_2} decreased progressively until the EEG became isoelectric. At this point, CMR_{O_2} remained approximately constant, despite continued infusion of etomidate. This change in CMR_{O_2} paralleled the effect on neuronal function manifested on EEG.

associated with a marked increase in cerebrovascular resistance (table 1). CVR doubled from 2.1 to 4.5 mmHg · ml^{-1} · min within 7 min of the start of the etomidate infusion (at which time the CBF was halved) and was tripled to 6.3 mmHg · ml^{-1} · min by the end of the infusion (table 1). CBF achieved a minimum value before CMR_{O_2}. The minimum CBF occurred after approximately 45 min of etomidate infusion (total dose infused 1.9 mg · kg^{-1}), and the minimum CMR_{O_2} occurred after approximately 91 min (total dose infused 10.7 mg · kg^{-1}) (compare figs. 2 and 3). Despite the discrepancy in the rates at which CMR_{O_2} and CBF decreased, oxygen delivery to the brain appeared adequate as evidenced by a CBF of greater than 30 ml · min^{-1} · 100 g^{-1} and by an oxygen tension in the sagittal sinus blood of 37 ± 1 mmHg at the end of the etomidate infusion.

Following the etomidate infusion, the cerebral metabolic state was essentially normal (table 2). ATP and phosphocreatine concentrations and the energy charge

TABLE 1. Cerebral Metabolic and Hemodynamic Values before and after Etomidate Infusion

Variable	Before Infusion	At 45 min (minimum CBF)	End of Infusion
CMR_{O_2} ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	5.52 ± 0.27	3.62 ± 0.30	2.63 ± 0.15*
CBF ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	145 ± 23	36 ± 1*	34 ± 2*
CPP (mmHg)	106 ± 9	93 ± 10	78 ± 11*
ICP (mmHg)	9 ± 2	4 ± 1	1 ± 0*
CVR ($mmHg \cdot ml^{-1} \cdot min$)	2.1 ± 0.3	6.7 ± 0.8	6.3 ± 1.3*
Pss_{O_2} (mmHg)	58 ± 4	38 ± 1	37 ± 1*

Mean ± SE for six dogs.
* Value significantly different from before infusion ($P < 0.05$).

(0.89)—which is a quantitative estimate of the adenine nucleotide pool and more accurately reflects the amount of energy available to the cells—were normal or above normal. However, cerebral lactate was slightly but significantly increased to 1.49 ± 0.1 μmol/g, and the lactate/pyruvate ratio was significantly increased.

Intracranial pressure decreased significantly from 9 mmHg to 1 mmHg by the end of the etomidate infusion (table 1). The decrease in ICP accompanied the increase in CVR and is presumed to result from a decrease in cerebral blood volume.

Etomidate produced largely unimportant changes in the systemic variables, even at the greatest doses (table 3). Mean arterial pressure was decreased from a control of 126 mmHg but was well maintained at approximately 110 mmHg throughout most of the etomidate administration. Only at the highest infusion rate did the MAP decrease to a nadir of 89 ± 12 mmHg. The maintenance of MAP was due to both maintenance of cardiac output and systemic vascular resistance throughout most of the etomidate infusion. Only at the highest infusion rate did all three variables decrease slightly (table 3). Pulmonary artery and pulmonary capillary wedge pressures remained the same throughout the study, as did whole-body oxygen consumption.

There were no changes in arterial blood gas values except for a mild metabolic acidosis, as reflected by a significant decrease in *p*H and buffer base and a significant increase in the lactate/pyruvate ratio (table 4). The hemoglobin decreased significantly from withdrawal of blood samples and hemodilution from fluid administration.

Discussion

The results of this study further support the premise that changes in cerebral metabolism occurring with the administration of general anesthetics are primarily the result of changes in neuronal function produced by those anesthetics. As long as EEG activity persisted, etomidate produced a dose-related decrease in cerebral metabolism that correlated with progressive changes in neuronal electrical activity. Upon suppression of electrical activity (flat EEG), a minimal metabolic rate was established and maintained despite continued administration of etomidate in increasing doses. This is similar to the effect produced by both thiopental[4] and isoflurane.[5] With the use of the Bonferroni *t* test for comparison of three groups (5% confidence level = $P < 0.0167$), this minimal metabolic rate (2.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) was numerically higher but not

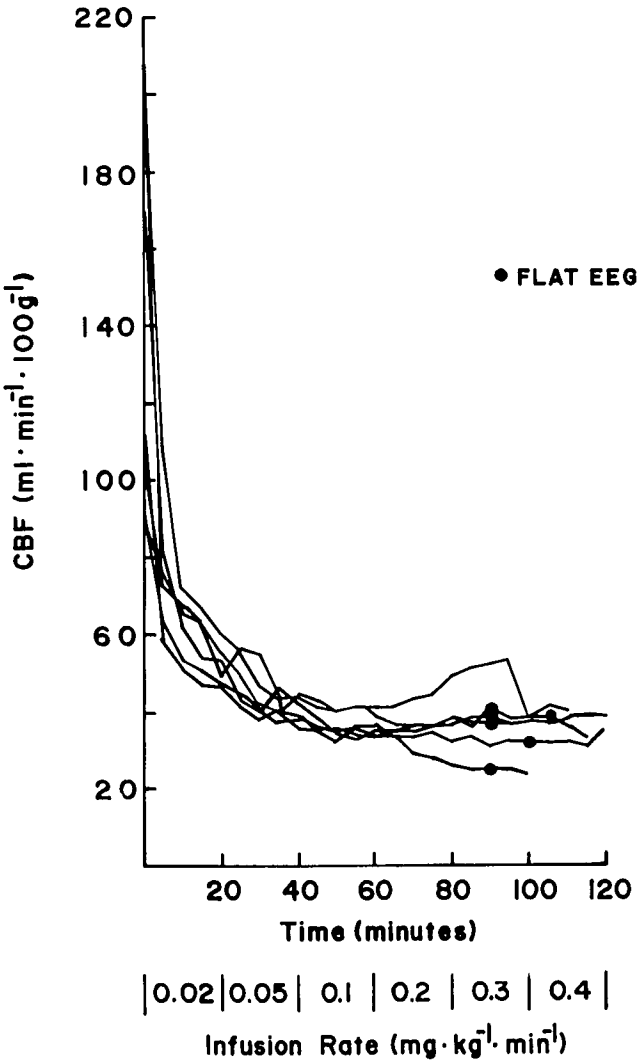

FIG. 3. Effect of increasing doses of etomidate on CBF for each of six dogs. CBF decreased rapidly with the infusion of etomidate to approximately 36 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. It remained at this value throughout the study, despite increasing infusion rates of etomidate. This change in CBF occurred independent of the effect on EEG or CMR_{O_2}.

TABLE 2. Brain Metabolites Following Etomidate Infusion

	Phosphocreatine (μmol/g)	Adenosine Triphosphate (μmol/g)	Energy Charge	Lactate (μmol/g)	Lactate/Pyruvate
Normal*	2.99 ± 0.12	2.01 ± 0.01	0.87 ± 0.001	1.23 ± 0.04	11 ± 0.4
Etomidate	3.84 ± 0.13†	1.98 ± 0.04	0.89 ± 0.004†	1.49 ± 0.10†	23 ± 2†

Mean ± SE.
* Normal values obtained from six dogs under spinal anesthesia (25).
† Value significantly different from normal value ($P < 0.05$).

significantly different from the CMR_{O_2} measured in dogs when neuronal function was abolished by thiopental (2.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$)[4] but was statistically greater than that obtained with isoflurane (2.1 $ml \cdot min^{-1} \cdot 100\ g^{-1}$).[5] The reason for this is unknown. However, the cerebral actions of isoflurane and etomidate may differ. Isoflurane suppresses activity in both the cortex and subcortical structures,[16] whereas etomidate has been reported to inhibit only the cortex.§§ The global CMR_{O_2} measured in the present study may reflect a composite CMR_{O_2} of cortex and some subcortical structures. A greater CMR_{O_2} in these areas may have contributed to the greater total CMR_{O_2} observed for etomidate.

Cerebral oxygen delivery was considered adequate throughout the study because CBF was maintained above 30 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ (range 31–40 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) and Pss_{O_2} above 36 mmHg. However, the significant decrease in Pss_{O_2} during the infusion indicates increased oxygen extraction, reflecting a lower CBF/CMR_{O_2} ratio. There was no evidence that etomidate altered normal metabolic pathways. Normal levels of ATP and phosphocreatine and a normal energy charge provide evidence that energy production adequately supplied the energy requirements of the brain. However, etomidate did produce small but statistically significant increases in lactate and in the lactate/pyruvate ratio. In the presence of a normal brain energy state we consider these changes to be unimportant.

This study also indicates that etomidate is a potent direct vasoconstrictor, *i.e.*, its vasoconstrictive effect does not seem to be secondary to its effect on cerebral metabolism. After just 7 min at the lowest infusion rate, CBF was half of that in the control period. This initial rapid decrease in CBF was exaggerated by the high values for CBF obtained during the hyperdynamic state of the control period associated with nitrous oxide analgesia,[17] and by the elimination of this N_2O during the infusion of etomidate. However, by 7 min the N_2O was eliminated so that any subsequent changes in CBF were due to the etomidate infusion. CBF subsequently decreased to a nadir of 36 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ over the next 38 min and remained at approximately this level throughout the study, despite a progressively increasing administration of etomidate. This plateau in CBF indicates that etomidate produced its maximum effect on cerebral vasoconstriction at 45 min so that any additional administration of etomidate had no further change in CBF. Even a continued decrease in CMR_{O_2} did not produce a concomitant decrease in CBF.

In contrast, changes in CMR_{O_2} reflected changes in EEG activity. CMR_{O_2} decreased more slowly than did CBF during the etomidate infusion and reached a minimum level after approximately twice the time it took for CBF to reach a minimum level. This lack of coupling between changes in CBF and CMR_{O_2} is in disagreement with the conclusion of Renou *et al.*,[7] who studied a single dose of etomidate in patients undergoing diagnostic carotid angiography. They reported that etomidate produced a 45% decrease in CMR_{O_2} and a 34% decrease in CBF when compared with awake control values and concluded that the decrease in CBF was secondary to the decrease in CMR_{O_2} produced by etomidate. This represents the pitfall of drawing conclusions from a response curve constructed from two points (control and 60 mg etomidate). With additional points on the curve (figs. 2 and 3) it can be observed that CBF decreased independently of CMR_{O_2}.

This observation that a decreasing cerebral metabolic rate is not invariably accompanied by a simultaneous decline in CBF may be unique. The effect of the barbiturates on CBF is coupled to their effect on neuronal electrical

TABLE 3. Systemic Metabolic and Hemodynamic Values before and after Etomidate Infusion

Variable	Before Infusion	At 45 min (minimum CBF)	End of Infusion
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	149 ± 13	150 ± 16	150 ± 16
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.32 ± 0.04	2.41 ± 0.36*	2.70 ± 0.17
MAP (mmHg)	126 ± 11	107 ± 10	89 ± 12*
PAP (mmHg)	17 ± 2	17 ± 1	17 ± 2
PCWP (mmHg)	9 ± 1	9 ± 1	9 ± 1
SVRI ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	39 ± 3	47 ± 4	33 ± 3

Mean ± SE for six dogs.
* Value significantly different from before infusion ($P < 0.05$).

§§ Kugler J, Doenicke A, Laub M: The EEG after etomidate. Anesthesiology and Resuscitation 106:31–48, 1977.

TABLE 4. Systemic Blood Values before and at the End of Etomidate Infusion

Variable	Before Infusion	End of Infusion
Pa_{O_2} (mmHg)	172 ± 1	167 ± 6
Pa_{CO_2} (mmHg)	39 ± 1	39 ± 1
*p*H	7.40 ± 0.01	7.31 ± 0.01*
BB+ (mEq/l)	46 ± 1	40 ± 1*
Hb (g/dl)	16 ± 1	12 ± 1
Glucose (mg/dl)	112 ± 3	94 ± 6
Lactate (μmol/ml)	4.0 ± 0.8	4.6 ± 0.7
Lactate/pyruvate	20 ± 3	47 ± 9*
Brain temp (°C)	37.0 ± 0	37.0 ± 0.1

Mean ± SE for six dogs.
* Value significantly different from before infusion ($P < 0.05$).

activity and CMR_{O_2}.[4] While volatile anesthetic agents clearly alter the coupled relationship between CBF and metabolism, a relationship remains.[18,19] Likewise, during ketamine anesthesia there is a dramatic increase in CBF with less increase in CMR_{O_2}, but CMR_{O_2} does not decrease.[20] It remains to be seen whether an increase in CMR_{O_2} produced during etomidate anesthesia would be accompanied by an increase in CBF.

The parallel change in ICP and CBF observed in the present study also has been demonstrated in patients with normal[21] and increased intracranial pressure.[22] This further supports the assumption that etomidate decreases ICP primarily through its effect on CBF.

The changes noted in the EEG are similar to those observed for both thiopental[4] and isoflurane.[5] While we observed a progressive decrease in electrical activity because of the constant infusion of increasing doses of etomidate, this same pattern, including an isoelectric EEG, has been reported to occur transiently following a single induction dose (0.3 $mg \cdot kg^{-1}$) of etomidate in humans.¶¶

Etomidate in clinical doses is reported to have minimal effects on cardiac function, heart rate, myocardial contractility, blood pressure, and myocardial oxygen consumption. We too observed little change in systemic hemodynamic variables, despite the massive doses of etomidate that the dogs received (table 3). This is in agreement with another canine study in which two doses of etomidate 1.25 $mg \cdot kg^{-1}$ and 2.5 $mg \cdot kg^{-1}$ each decreased systolic and diastolic pressure slightly but significantly without change in dp/dt_{max} or mean coronary artery flow.[23] It should be noted that the systemic variables that were depressed remained within acceptable physiologic limits at all times. This finding also has been reported in studies in humans with normal cardiovascular function[24,25] and in patients with ischemic or valvular cardiac disease[26] and is an obvious advantage of etomidate over other intravenous hypnotic agents.

In conclusion, etomidate, given by continuous infusion in the dog, provides the advantages of systemic hemodynamic stability, decreased cerebral metabolism, and decreased cerebral blood flow, resulting in decreased ICP. If these same changes are found to occur in humans, etomidate may prove to be a useful anesthetic for neurosurgery.

¶¶ Kugler J, Doenicke A, Laub M: The EEG after etomidate. Anesthesiology and Resuscitation 106:31–48, 1977.

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