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Comparison of the Effect of Etomidate and Desflurane on Brain Tissue Gases and pH during Prolonged Middle Cerebral Artery Occlusion

William E. Hoffman, Ph.D., Fady T. Charbel, M.D.,† Guy Edelman, M.D.,‡ Mukesh Misra, M.D.,§ James I. Ausman, M.D., Ph.D.‖*

Background: **The authors compared the effects of etomidate and desflurane on brain tissue oxygen pressure (P_{O_2}), carbon dioxide pressure (P_{CO_2}), and *p*H in patients who had middle cerebral artery occlusion for >15 min.**

Methods: **After a craniotomy, a probe that measures P_{O_2}, P_{CO_2}, and *p*H was inserted into cortical tissue at risk for ischemia during middle cerebral artery occlusion. A burst suppression pattern of the electroencephalogram was induced with etomidate (n = 6) or 9% end-tidal desflurane (n = 6) started before middle cerebral artery occlusion. Mean blood pressure was supported with phenylephrine to 90–95 mmHg.**

Results: **During baseline conditions, tissue P_{O_2}, P_{CO_2}, and *p*H were similar between the two groups (P_{O_2} = 15 mmHg, P_{CO_2} = 60 mmHg, *p*H = 7.1). During administration of etomidate before middle cerebral artery occlusion, tissue P_{O_2} decreased in five of six patients without a change in P_{CO_2} or *p*H. During administration of 9% desflurane, tissue P_{O_2} and *p*H increased before middle cerebral artery clipping. Middle cerebral artery occlusion for an average of 33 min with etomidate and 37 min with desflurane produced a decrease in *p*H with etomidate (7.09 to 6.63, $P < 0.05$) but not with desflurane (7.12 to 7.15).**

Conclusion: **These results suggest that tissue hypoxia and acidosis are often observed during etomidate treatment and middle cerebral artery occlusion. Treatment with desflurane significantly increases tissue P_{O_2} alone and attenuates acidotic changes to prolonged middle cerebral artery occlusion. (Key words: Anesthesia; anesthetics; intravenous; ischemia; neuroanesthesia; volatile.)**

* Associate Professor, Department of Anesthesiology.

† Assistant Professor, Department of Neurosurgery.

‡ Assistant Professor, Department of Anesthesiology.

§ Resident, Department of Neurosurgery.

‖ Professor and Chairman, Department of Neurosurgery.

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Address reprint requests to Dr. Hoffman: Anesthesiology Department, Suite 3200, University of Illinois Hospital, MC 515, 1740 West Taylor, Chicago, Illinois 60612. Address electronic mail to: Whoffman@uic.edu

TEMPORARY brain artery occlusion may be required to facilitate cerebrovascular surgery and to decrease the risk of bleeding. This carries a risk of ischemic brain injury and infarction if occlusion times are prolonged. Treatment with etomidate before brain artery occlusion may allow an occlusion time of 14 min with a good recovery.[1] This is consistent with the hypothesis that anesthetic agents that suppress brain electrical activity decrease brain metabolic demand and attenuate ischemic injury.[2] Recent studies in rats suggest, however, that treatment with etomidate produces greater ischemic injury compared with thiopental or halothane.[3,4] Inhalation anesthetic agents, including isoflurane and desflurane, can suppress brain electrical activity, produce cerebrovasodilation, and enhance brain tissue oxygenation in animal and human studies.[5–9] This raises the possibility that an anesthetic agent such as desflurane may attenuate ischemic changes during prolonged periods of brain artery occlusion by decreasing metabolic demand and enhancing tissue perfusion. The purpose of this study was to compare the effects of etomidate and desflurane on brain tissue oxygen pressure (P_{O_2}), brain tissue carbon dioxide pressure (P_{CO_2}), and *p*H changes in patients with middle cerebral artery (MCA) occlusion longer than 15 min.

Methods

The clinical review board at our institution approved this study. Patients gave informed consent for brain tissue monitoring and randomization of anesthetic treatment. Before the start of surgery, patients were randomly selected to receive either etomidate or desflurane to produce suppression of electroencephalogram. Eleven patients were scheduled for an extracerebral artery to intracerebral artery bypass. Nine of these patients had a superficial temporal artery-to-MCA bypass, and two patients had a carotid artery-to-MCA bypass

Table 1. Baseline Arterial Gases and *p*H, Clip Time, Hypoxia Time, Acidosis Time, and Outcome

Patient No.	Age (yr)/ Sex	Surgery	MAP (mmHg)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH_a	Brain Temperature (°C)	Clip (min)	Hypoxia (min)	Acidosis (min)
Etomidate										
1	40/F	STA-MCA	96	218	32	7.43	34.0	38	35	NA
2	50/F	Car-MCA	76	319	33	7.39	35.3	32	0	0
3	52/M	STA-MCA	112	97	44	7.34	35.6	50	50	50
4	45/F	STA-MCA	85	193	33	7.46	35.1	18	18	12
5	52/M	STA-MCA	105	103	40	7.43	34.9	42	0	0
6	51/M	STA-MCA	111	241	29	7.47	37.9	22	21	21
Mean ± SD			97 ± 14	195 ± 84	35 ± 5	7.42 ± 0.04	35.4 ± 1.3	33 ± 12	30 ± 14	27 ± 13
Desflurane										
1	71/F	STA-MCA	88	131	38	7.36	35.1	34	0	0
2	40/M	STA-MCA	81	154	33	7.42	34.8	37	0	0
3	31/F	Car-MCA	92	167	41	7.36	36.5	38	37	0
4	51/M	STA-MCA	86	222	38	7.44	36.0	39	0	0
5	64/M	STA-MCA	89	130	39	7.33	34.8	51	0	0
6	47/F	Aneurysm	76	229	31	7.43	34.9	24	22	0
Mean ± SD			85 ± 5	172 ± 43	36 ± 4	7.39 ± 0.04	35.3 ± 0.7	37 ± 8	10 ± 15*	0*

STA = superficial temporal artery; MCA = middle cerebral artery; Car = carotid; NA = not available; MAP = mean arterial pressure; Pa_{CO_2} = arterial CO_2 tension; Pa_{O_2} = arterial oxygen tension; pH_a = arterial *p*H.

* $P < 0.05$ *versus* etomidate.

using a vein graft, which required temporary occlusion of the MCA (table 1). Patient 2 in the etomidate group had a superficial temporal artery-to-MCA bypass when the internal carotid artery was removed during excision of a left sphenoid meningioma. One patient (desflurane patient 6) had a giant MCA aneurysm, which had bled 6 days before surgery. All other patients had a presurgical diagnosis of cerebral occlusive disease. This was determined by neurologic symptoms of regional ischemia and confirmed by single-photon emission computed tomography scans and cerebral angiography.

Patients fasted overnight, and blood glucose was measured intermittently throughout the case and maintained at <200 mg/dl with insulin treatment if necessary. Anesthesia was induced with 3–5 mg/kg thiopental and 10–15 μg/kg fentanyl, and muscle paralysis was achieved with 100 μg/kg vecuronium for tracheal intubation. Patients in group 1 were ventilated with 0.5% isoflurane (n = 6) and in group 2 with 3% desflurane (n = 6) with a fraction of inspired carbon dioxide ($F_{I_{O_2}}$) of 0.4 and the balance nitrogen. A radial artery catheter was inserted for direct measurement of arterial pressure using a Marquette monitor (Milwaukee, WI) and for arterial blood gas samples. Arterial P_{CO_2} was adjusted to 35–40 mmHg. End-tidal CO_2 and anesthetic gas concentration were monitored by a Datex Ultima (Helsinki, Finland). An esophageal temperature probe was inserted, and temperature was allowed to decrease to 34°C during the surgical procedure. Two-channel bifrontal electroencephalography was performed from electrodes placed on the forehead over both hemispheres with the nasion as the reference using an A-1000 Electroencephalography monitor (Aspect, Natick, MA). During a burst suppression electroencephalogram pattern, this monitor indicates the percentage of the electroencephalographic signal that is quiescent.

The patient was placed supine in a park bench position with the head in pins and turned. After a pterional craniotomy and dural reflection, a Paratrend 7 probe (Diametrics Medical, Minneapolis, MN), which measures P_{O_2}, P_{CO_2}, *p*H, and temperature, was inserted by the neurosurgeon. The probe was always placed in the same region in the midfrontal gyrus, close to the frontal operculum. The probe is 0.5 mm in diameter and must be inserted 4 cm for all of the sensors to be in brain tissue.[10] The brain surface surrounding the tissue was covered with sterile gauze to prevent light contamination of the sensors. The P_{O_2}, P_{CO_2}, and *p*H sensors were calibrated using precision gases before insertion into the tissue, and a 30-min equilibration period was allowed after insertion before recording baseline values. Tissue gases and *p*H are reported with body temperature corrected to 37°C. Tissue hypoxia was defined as $P_{O_2} < 10$ mmHg and acidosis as *p*H < 7.0 during the

time of MCA occlusion. A laser Doppler flow probe (Vasamedics, St. Paul, MN) was placed on the cortex surface adjacent to the Paratrend probe in three patients in the etomidate group and two patients in the desflurane group.

Before MCA occlusion, patients in group 1 (n = 6) received etomidate as 0.1–0.15 mg/kg intravenous bolus doses to induce and maintain burst suppression electroencephalogram. Electroencephalographic quiescence of 50% was maintained. Isoflurane was continued during the treatment with etomidate. In group 2, end-tidal desflurane concentration was increased to 9% to produce the same burst suppression pattern.[9] Arterial blood pressure was maintained at baseline levels or higher in both groups with intravenous phenylephrine infusion during the period of burst suppression electroencephalogram. In both groups, MCA occlusion was produced 10–20 min after the start of burst suppression electroencephalogram. Arterial blood gas was measured at the start of recording, and all other variables, including blood pressure, electroencephalogram, end-tidal gases, and Paratrend measurements were recorded by computer every 10 s using a Labview program (National Instruments, Austin, TX).

Each patient was evaluated 3–5 days after surgery to determine if a new ischemic injury occurred. An ischemic injury was determined if the patient showed a new neurologic deficit that was confirmed by an infarct on the postoperative computed tomographic scan.

Statistics tests of normality and equal variance were performed initially on each data set to determine whether parametric or nonparametric analyses should be performed. Comparisons of treatments within each group were made by repeated-measures analysis of variance with Tukey's *post hoc* tests or a repeated-measures analysis of variance on ranks with Dunnett's tests used for *post hoc* comparison if the data were not parametric. Statistical comparisons of changes in P_{O_2}, P_{CO_2}, and *p*H during MCA occlusion between etomidate and desflurane groups were made using *t* tests or a rank sum test. A Pearson product–moment correlation was used to evaluate the relation between temperature and the length of hypoxia or acidosis during MCA occlusion.

Results

There was no difference in blood pressure, arterial blood gas levels, and *p*H or brain temperature between the etomidate and desflurane treatment groups during baseline conditions (table 1). A burst suppression electroencephalogram was seen in all patients during treatment with etomidate or desflurane for brain protection with 50% electrical silence.

An example of tissue changes in patient 4 in the etomidate group is shown in figure 1. This patient showed a decrease in laser Doppler flow and P_{O_2} after treatment with etomidate alone. Middle cerebral artery occlusion further decreased flow and P_{O_2} and produced an increase in P_{CO_2} and a decrease in *p*H to 6.6 after 18 min of temporary clipping.

An example of patient 3 in the desflurane group is shown in figure 2. Treatment with 9% desflurane produced an immediate increase in laser Doppler flow, P_{O_2}, and *p*H and a decrease in P_{CO_2}. Middle cerebral artery occlusion decreased P_{O_2} to hypoxic levels but produced only modest, transient ischemic changes in P_{CO_2} and *p*H.

Treatment with etomidate produced a decrease in tissue P_{O_2} in five of six patients but no change in tissue P_{CO_2} or *p*H (fig. 3). During MCA occlusion, four of six patients had tissue hypoxia ($P_{O_2} < 10$ mmHg) or acidosis (*p*H < 7.0) for 12–50 min. Tissue P_{CO_2} and *p*H data were not available for patient 1 in the etomidate group because of inadequate light shielding. All four etomidate-treated patients who had extended periods of tissue hypoxia and acidosis during MCA occlusion had new neurologic deficits after surgery.

Elevating the concentration of desflurane from 3% to 9% increased tissue P_{O_2} and *p*H and decreased P_{CO_2} (fig. 4). Middle cerebral artery occlusion produced tissue hypoxia in two patients but not acidosis. The decrease in *p*H during MCA occlusion in patients treated with etomidate (median = −0.32) was different from the small increase seen in desflurane-treated patients (median = 0.05, $P < 0.05$). Changes in P_{O_2} and P_{CO_2} were not different between the two groups. There was no relation between the brain temperature at the time of MCA occlusion and the length of hypoxia or acidosis with both groups considered together. No desflurane-treated patient showed a new neurologic deficit.

Discussion

These results are consistent with a previous report that the use of etomidate in the setting of cerebral ischemia may lead to a decrease in tissue P_{O_2}.[11] Ischemic changes were seen here in P_{CO_2} and *p*H in etomidate-treated patients during MCA occlusion, and a new ischemic injury was seen in these patients. This agrees with the work of Samson *et al.*,[1] who reported that even when etomi-

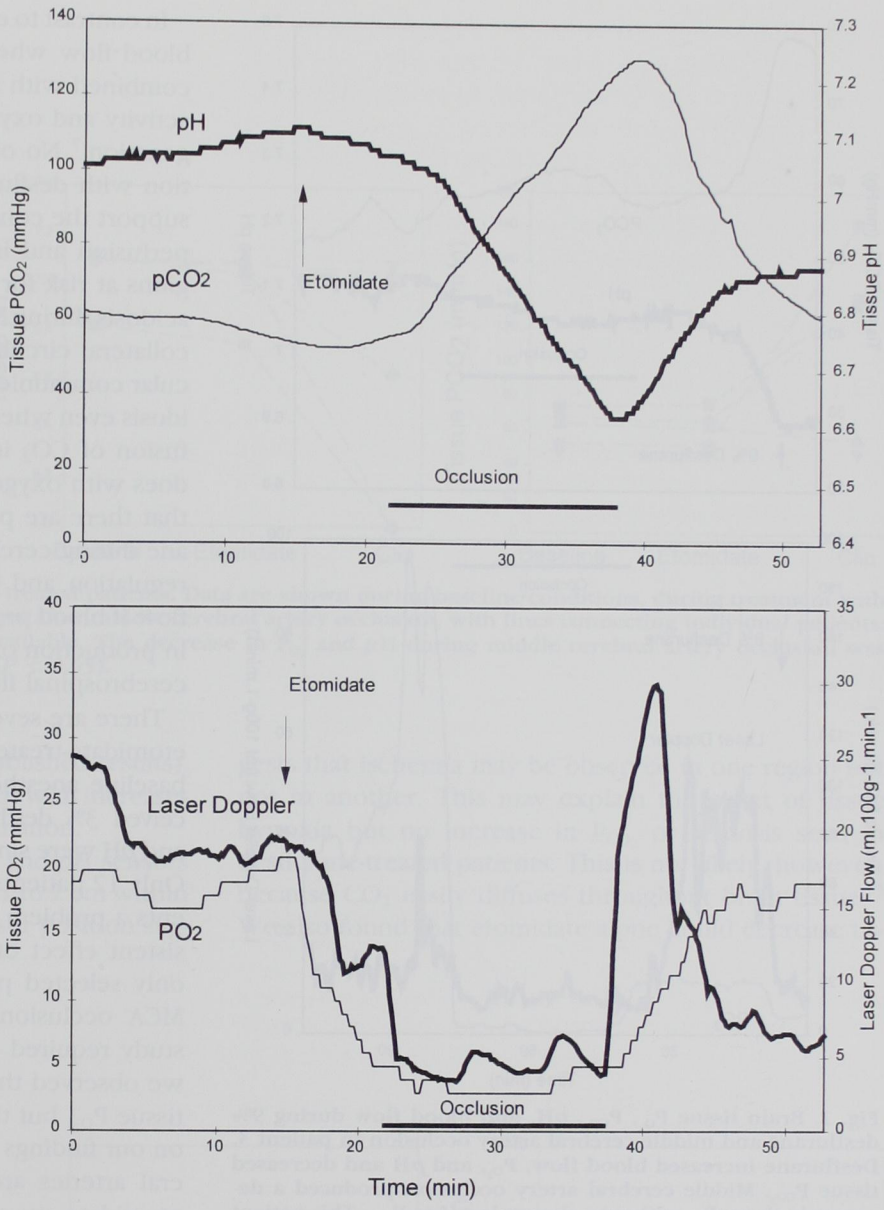

Fig. 1. Brain tissue P_{O_2}, P_{CO_2}, *p*H, and blood flow during etomidate and middle cerebral artery occlusion in patient 4. Each tracing is identified in the graph. Laser Doppler flow and *p*H are shown with bold lines. At the time of treatment with etomidate, P_{O_2} and blood flow decreased without a change in *p*H or P_{CO_2}. Middle cerebral artery occlusion produced a further decrease in P_{O_2} and blood flow and an increase in P_{CO_2} and acidosis. This patient showed a severe neurologic deficit postoperatively.

date is used, lengths of brain artery occlusion >14 min produced a high incidence of ischemic injury and a 100% infarction rate with durations of occlusion >30 min. In contrast to etomidate, 9% desflurane increased P_{O_2} and *p*H in this study, and MCA occlusion produced hypoxia but no acidosis. Because both etomidate and desflurane may have decreased brain electrical activity and metabolic demand, we believe the contrast between changes in tissue gases and *p*H with each agent may be due to differences in tissue perfusion.

It has been reported that etomidate suppresses electroencephalographic activity, decreases cerebral oxygen demand, and attenuates neuronal injury during ischemia.[12–17] Other reports, however, have questioned the ability of etomidate to protect the brain from ischemia, particularly when high doses are used that produce electroencephalographic quiescence but also can produce hemolysis.[3,4,18–20] Drummond *et al.*[4] speculated that etomidate may increase ischemia by decreasing release of nitric oxide and attenuating collateral blood flow. Etomidate may produce this effect by inhibition of nitric oxide synthesis or by nitric oxide binding by

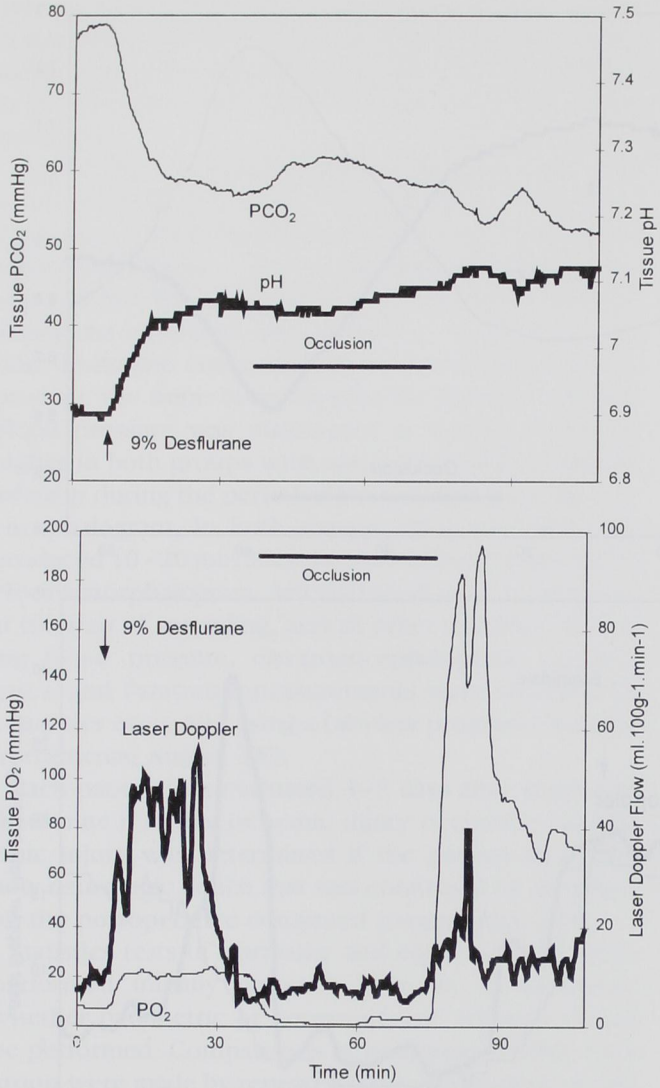

Fig. 2. Brain tissue P_{O_2}, P_{CO_2}, *p*H, and blood flow during 9% desflurane and middle cerebral artery occlusion in patient 3. Desflurane increased blood flow, P_{O_2}, and *p*H and decreased tissue P_{CO_2}. Middle cerebral artery occlusion produced a decrease in tissue P_{O_2} without a change in *p*H or P_{CO_2}. This patient had a good recovery.

free hemoglobin. This was supported by a more recent study in rats showing that treatments that enhance nitric oxide attenuate ischemic injury associated with etomidate.[3] Milde *et al.*[12] reported that sagittal sinus oxygen saturation decreases with etomidate treatment because of decreases in cerebral blood flow. Although our results and those of others indicate that the cerebrovasoconstrictor effects of etomidate do not produce ischemic changes alone,[21,22] tissue oxygenation may be decreased.[11,12]

In contrast to etomidate, desflurane increases cerebral blood flow when blood pressure is supported.[5] This, combined with a decrease in electroencephalographic activity and oxygen demand, may improve tissue oxygenation.[7] No one has examined the ischemic protection with desflurane in animals, however. Our results support the conclusion that desflurane enhances tissue perfusion and improves tissue metabolic status in regions at risk for ischemia. The attenuation of ischemic acidosis during MCA occlusion may be due to enhanced collateral circulation mediated by leptomeningeal vascular communications. CO_2 clearance may attenuate acidosis even when oxygenation is decreased because diffusion of CO_2 in tissue proceeds more readily than it does with oxygen.[23] It should also be noted, however, that there are potential disadvantages of using desflurane during cerebral ischemia, including impaired autoregulation and a possible decrease in cerebral blood flow if blood pressure is not maintained,[24,25] an increase in production of cerebrospinal fluid, and an increase in cerebrospinal fluid pressure.[26,27]

There are several weaknesses in this study. First, the etomidate-treated group received 0.5% isoflurane for baseline anesthesia, whereas the desflurane group received 3% desflurane. The baseline levels of P_{O_2}, P_{CO_2}, and *p*H were similar between the two groups, however. Only 12 patients were evaluated in this study; this presents a problem with statistical evaluation of the inconsistent effect of etomidate on tissue P_{O_2}. Because we only selected patients for this study who underwent MCA occlusion for >15 min, however, the current study required 2 yr to complete. In a previous study, we observed that treatment with etomidate decreased tissue P_{O_2}, but this effect was also inconsistent.[11] Based on our findings here that patients with adequate collateral arteries are less likely to develop hypoxia with etomidate, we suggest that the variable effects of etomidate on P_{O_2} are related to the adequacy of collateral circulation.

It is possible that increases in tissue P_{O_2} may be due to changes in the concentration of desflurane rather than tissue P_{O_2}. We do not know if desflurane can change the current, and therefore the P_{O_2} measurement, by a direct action at the Clark electrode. Other measures of tissue metabolic status, including decreases in P_{CO_2} and increases in *p*H during desflurane, would be consistent with an increase in oxygenation. In addition, we have observed similar increases in tissue P_{O_2} with treatment with desflurane with a fiberoptic measure of tissue P_{O_2}

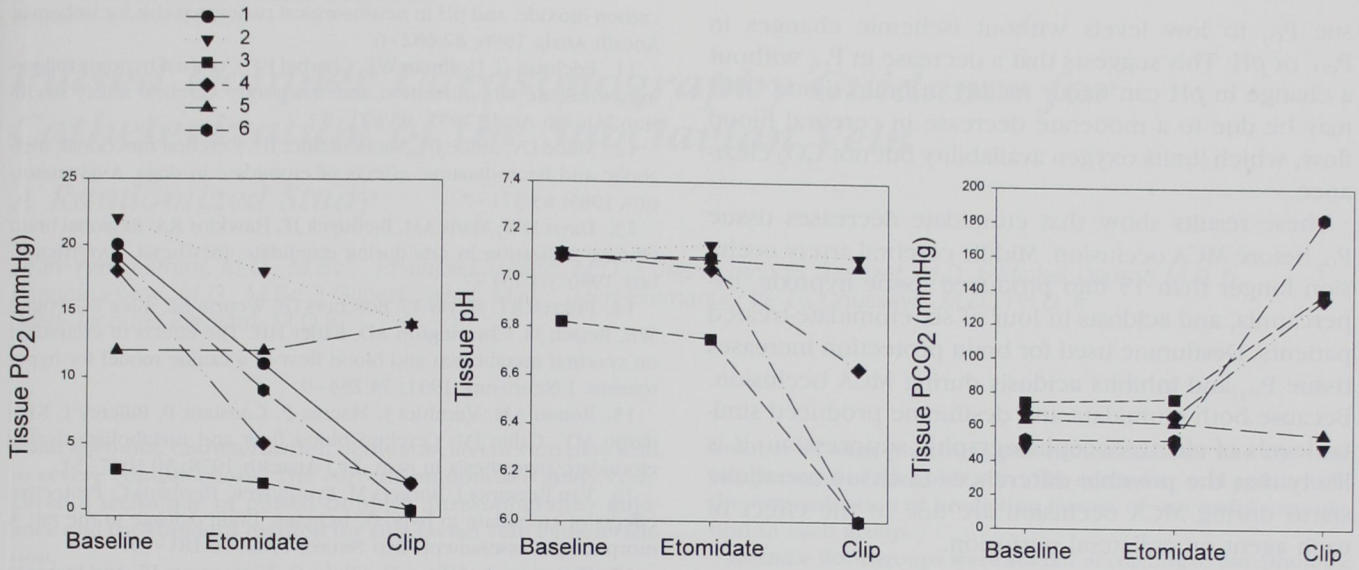

Fig. 3. Tissue P_{O_2}, *p*H, and P_{CO_2} in etomidate-treated patients. Data are shown during baseline conditions, during treatment with etomidate, and for peak or minimum changes after middle cerebral artery occlusion, with lines connecting individual patients. P_{CO_2} and *p*H data for patient 1 were not available. The decrease in P_{O_2} and *p*H during middle cerebral artery occlusion was significant compared with baseline values ($P < 0.05$).

rather than a Clark electrode (our unpublished results). This suggests that the elevation in P_{O_2} seen with increases in desflurane is due to enhanced oxygenation.

It should be noted that the P_{O_2}, P_{CO_2}, and *p*H sensors of the Paratrend probe are separated by 1 to 2 cm within the tissue.[10] The spatial disparity in sensor position suggests that ischemia may be observed in one region but not in another. This may explain the onset of tissue hypoxia but no increase in P_{CO_2} or acidosis seen in desflurane-treated patients. This is not likely, however, because CO_2 easily diffuses throughout brain tissue.[23] We also found that etomidate alone could decrease tis-

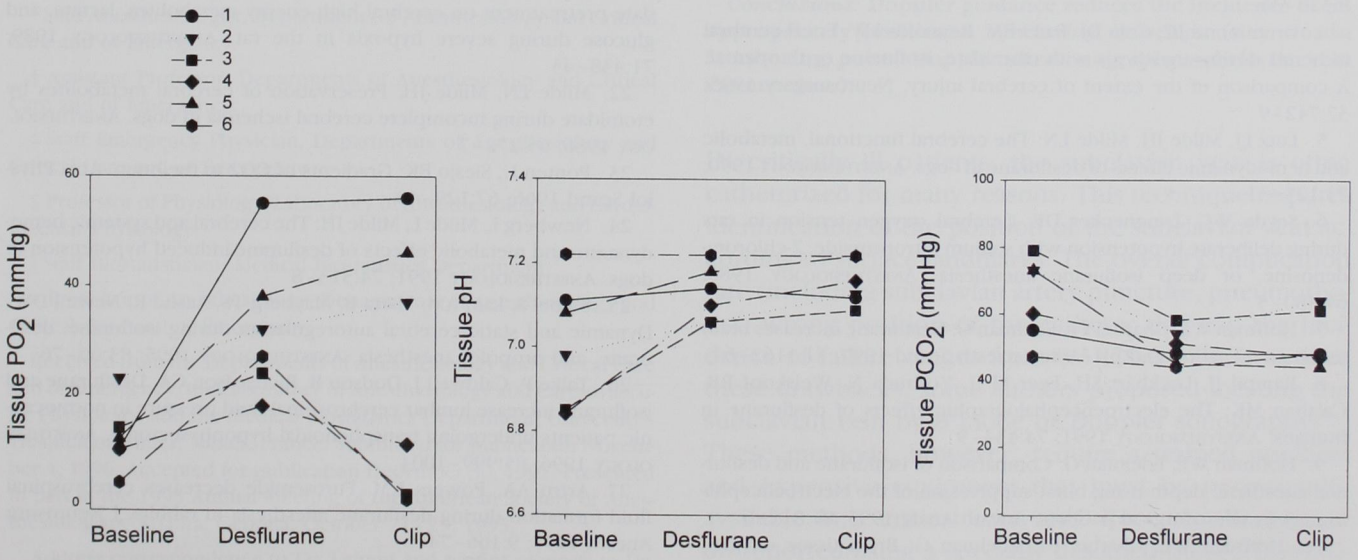

Fig. 4. Tissue P_{O_2}, *p*H, and P_{CO_2} in desflurane-treated patients. Data are shown during baseline conditions, during treatment with desflurane, and for peak or minimum changes after middle cerebral artery occlusion, with lines connecting individual patients. Desflurane treatment increased P_{O_2} and *p*H and decreased P_{CO_2} ($P < 0.05$). Middle cerebral artery occlusion produced no significant change in any parameter.

sue P_{O_2} to low levels without ischemic changes in P_{CO_2} or *p*H. This suggests that a decrease in P_{O_2} without a change in *p*H can occur readily in brain tissue. This may be due to a moderate decrease in cerebral blood flow, which limits oxygen availability but not CO_2 clearance.

These results show that etomidate decreases tissue P_{O_2} before MCA occlusion. Middle cerebral artery occlusion longer than 15 min produced tissue hypoxia, hypercapnia, and acidosis in four of six etomidate-treated patients. Desflurane used for brain protection increases tissue P_{O_2} and inhibits acidosis during MCA occlusion. Because both etomidate and desflurane produced similar levels of electroencephalographic suppression, it is likely that the possible differences in tissue metabolic status during MCA occlusion are due to the effect of each agent on collateral perfusion.

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