

Dose-related Changes in the Rate of Cerebrospinal Fluid Formation and Resistance to Reabsorption of Cerebrospinal Fluid Following Administration of Thiopental, Midazolam, and Etomidate in Dogs

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The rate of cerebrospinal fluid (CSF) formation (\dot{V}_f) and resistance to reabsorption of CSF (R_a) were determined in dogs at four doses of thiopental (6, 12, 18, and 24 mg · kg⁻¹ · h⁻¹), midazolam (0.5, 1.0, 1.5, and 2.0 mg · kg⁻¹ · h⁻¹), and etomidate (0.86, 1.72, 2.58, and 3.44 mg · kg⁻¹ · h⁻¹). Results were compared within and between groups and to previously reported normal values for \dot{V}_f (0.030–0.054 ml/min) and R_a (220–240 cmH₂O · ml⁻¹ · min) in dogs. At the two lower doses of thiopental, midazolam, or etomidate \dot{V}_f was not significantly different than previously reported normal values. At the two higher doses of each drug \dot{V}_f was 0.019–0.024 ml/min, significantly reduced compared to \dot{V}_f at the two lower doses of each drug. The pattern of R_a data was more varied. With thiopental R_a was elevated at the lowest dose, (354 ± 17 cmH₂O · ml⁻¹ · min, mean ± SD) reduced at the highest dose (156 ± 19 cmH₂O · ml⁻¹ · min), and not significantly different than previously reported normal values at the two intermediate doses. With midazolam R_a was elevated at the lowest and highest doses (332 ± 25 and 378 ± 18 cmH₂O · ml⁻¹ · min) and normal at the two intermediate doses. With etomidate R_a was normal at the three lower doses and reduced at the highest dose (187 ± 13 cmH₂O · ml⁻¹ · min). It is concluded that CSF volume may be increased and the CSF pressure at which CSF volume contracts may be increased by doses of thiopental or midazolam that increase R_a , but not increased by etomidate. (Key words: Anesthetics, intravenous; etomidate; midazolam; thiopental. Brain: intracranial pressure. Cerebrospinal fluid: formation; pressure; reabsorption. Hypnotics: etomidate; midazolam; thiopental.)

THE HYPNOTICS thiopental, midazolam, and etomidate are recommended as part of a balanced anesthetic technique for patients with increased intracranial pressure (ICP) or decreased intracranial compliance.¹⁻³ One factor in determining the suitability of these hypnotics for patients with increased ICP or decreased intracranial compliance is the effect of the drug on cerebrospinal fluid (CSF) dynamics, *i.e.*, the rate of CSF formation (\dot{V}_f) and resistance to reabsorption of CSF (R_a). Previously, there have been no reports on the effects of thiopental, midazolam, or etomidate on these variables.

\dot{V}_f and R_a are important in patients with increased ICP or decreased intracranial compliance because they deter-

mine CSF volume, which, in turn, is one of the principal determinants of ICP. Increase of \dot{V}_f and/or R_a elevates ICP and opposes contraction of CSF volume in response to expansion of cerebral blood volume (CBV) or brain tissue volume. Conversely, decrease of \dot{V}_f and/or R_a lowers ICP and favors contraction of CSF volume in response to expansion of CBV or brain tissue volume. Preservation of normal \dot{V}_f and R_a does not change ICP and permits contraction of CSF volume in response to expansion of CBV or brain tissue volume.

The present studies were designed to determine the effects of thiopental, midazolam, or etomidate on \dot{V}_f and R_a in dogs. Four doses of each drug were examined to determine whether the effects varied with the amount of drug administered.

Methods

ANIMAL PREPARATION

This study was approved by the Animal Care Committee of the University of Washington. Eighteen unmedicated mongrel dogs (15–22 kg) were studied. Anesthesia was induced with halothane (>1.2%, end-expired value determined intermittently by gas chromatography) and nitrous oxide (N₂O, 66%, inspired) in oxygen. The trachea was intubated, expired CO₂ was continuously monitored (Beckman Medical Gas Analyzer, Model LB2, Beckman Instruments, Inc., Fullerton, California), and ventilation was regulated by a servo controller to maintain expired CO₂ at normocapnia. The right femoral artery was cannulated to permit arterial blood sampling for blood gas analysis and to permit continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. A urinary catheter was inserted, the right femoral vein was cannulated for saline and drug administration, and temperature was monitored by a nasopharyngeal thermistor probe. Intravenous infusion of vecuronium 2–4 mg/h maintained muscle relaxation.

The electroencephalogram (EEG) was recorded using bilateral frontoparietal electrodes and a Beckman Acutrace® polygraph (Beckman Instruments, Inc.) with a bandpass of 0.3–75 Hz. The EEG was recorded to eval-

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TABLE 1. Dose Regimens of Thiopental, Midazolam, and Etomidate

	Initial Infusion Given over 5-10 min (mg/kg)	Subsequent Infusion Rate (mg·kg ⁻¹ ·h ⁻¹)
Thiopental (n = 6)	6.0	6.0
	6.0	12.0
	6.0	18.0
	6.0	24.0
Midazolam (n = 6)	1.6	0.5
	1.6	1.0
	1.6	1.5
	1.6	2.0
Etomidate (n = 6)	0.86	0.86
	0.86	1.72
	0.86	2.58
	0.86	3.44

uate the effects of thiopental, midazolam, and etomidate on cortical activity and to determine whether those effects remained constant throughout each infusion period. Electrodes were adjusted to maintain impedances between electrode pairs at <3 K Ω . Computer (Digital Equipment Corp. MINC-23[®], Digital Equipment Corp., Marlboro, Massachusetts) analysis of the EEG was performed using a Compressed Spectral Array (CSA) program, which averaged the EEG power spectra of four epochs (1 epoch = 4 s) every 30 s.^{4,5} Data from the CSA program were evaluated as the amount of EEG activity in the standard frequency bins: delta (1-4 Hz), theta (4-8 Hz), alpha (8-14 Hz), beta-1 (14-20 Hz), and beta-2 (20-32 Hz).

A burr hole was placed over the left hemisphere and a catheter was directed into the underlying lateral ventricle. The posterior neck muscles were surgically separated to expose the atlanto-occipital membrane, and a catheter was directed into the cisterna magna. A 0.3-ml sample of CSF was obtained from the cisternal cannula for measurement of osmolality using a Wescor Model 5100 B Vapor Pressor Osmometer (Wescor, Inc., Logan, UT). Mock CSF of matching osmolality was prepared by mixing standard solutions⁶ (osmolality 290, 300, or 310 mosm/kg) labeled with blue dextran (1 mg/ml) (Sigma Chemical Co., St. Louis, Missouri). Wound edges were infiltrated with bupivacaine (0.5%) and the concentration of halothane was decreased (N₂O unchanged) to 0.2% (end-expired value determined intermittently by gas chromatography). Details of this animal preparation have been previously reported.^{7,8}

Mock CSF was infused into the ventricle, and the mixture of mock and native CSF was permitted to flow passively out of the cisterna magna through a short length of tubing attached to the cisternal cannula. The infusion rate (\dot{V}_i) was controlled with a roller pump and gradually increased to 0.6 ml/min while ventricular CSF pressure was continuously monitored. The open end of the cister-

nal outflow tubing was placed at the same height as the CSF level present in the cisternal and ventricular cannula before perfusion was begun. This arrangement did not alter CSF pressure from the value normally occurring in the intact animal because the height of the open end of the outflow tubing determines CSF pressure during open ventriculocisternal perfusion. Successful ventriculocisternal perfusion was indicated by outflow of labeled CSF from the cisternal cannula with no increase in ventricular CSF pressure above preperfusion values. This initial period of open ventriculocisternal perfusion allowed for equilibration of labeled mock CSF with native CSF in the intracranial and cisternal CSF spaces of the dog. Details of this modified open ventriculocisternal perfusion technique have been previously reported.^{8,9}

After 1 h of ventriculocisternal perfusion, \dot{V}_i was gradually reduced to 0.3 ml/min. Concentrations of blue dextran in cisternal outflow samples were determined intermittently using light absorbance at 620 nm on a Beckman DU-2 Spectrophotometer (Beckman Instruments, Inc.) (fitted with a Gilford absorbance indicator, Gilford Instrument Laboratories, Inc., Oberlin, Ohio). Equilibration of the tracer was considered complete when measured blue dextran concentrations in three consecutive samples of cisternal outflow (collection time = 4-6 min/sample) agreed within 2%.

EXPERIMENTAL PERIOD

The experimental period began once tracer equilibration was complete. \dot{V}_f and R_a were determined during thiopental, midazolam, or etomidate in six dogs each. For all three drugs each dog received four dose regimens iv of the drug (table 1). Within each drug group doses were given in sequence, progressing from smallest to largest dose. The duration at each infusion level was about 90 min and there were no intervals between infusions. Drug doses and infusion rates were based on previously reported data with the aim of achieving comparable and steady levels of depression of cerebral cortical activity during each infusion period.^{3,10-12} At each dose of all three drugs dogs were studied at two CSF pressures (normal and elevated) so that R_a could be determined.

Normal CSF pressure was defined as that when the open end of the cisternal outflow tubing was placed at the same height as the CSF level present in the cisternal and ventricular cannula before perfusion was begun. Elevated CSF pressure was defined as CSF pressure when the open end of the cisternal outflow tubing was placed 10 cm above the level used for normal CSF pressure. The sequence of normal and elevated CSF pressures were altered within each group of six dogs so that six different combinations were employed over the four drug doses.

\dot{V}_f and the rate of reabsorption of CSF (\dot{V}_a) were de-

terminated at each of the eight conditions. At least 27 min (the first 17 min with $\dot{V}_i = 0.6$ ml/min followed by at least 10 min with $\dot{V}_i = 0.3$ ml/min) was allowed between conditions to permit reequilibration of the tracer. At each condition three consecutive samples of cisternal outflow were collected (collection time = 4–6 min/sample) for determinations of \dot{V}_f , and $\dot{V}_a \cdot \dot{V}_f$ and \dot{V}_a were calculated as previously described⁹ according to the formulas of Heisey *et al.*¹³ For these calculations concentrations of blue dextran in samples of the labeled mock CSF being perfused into the ventricle also were determined using light absorbance at 620 nm. Values for \dot{V}_a at normal and elevated CSF pressures were used to calculate R_a . By definition R_a is a reciprocal measure of the slope relating \dot{V}_a (expressed as ml/min) to CSF pressure (expressed as cmH₂O).¹⁴ The EEG and systemic variables also were recorded at each experimental condition.

STATISTICAL ANALYSIS

Statistical comparisons within groups were made using repeated-measures analysis of variance (ANOVA), and comparisons between groups were made using one-way ANOVA.¹⁵ Comparisons between the present groups and previously reported normal values for \dot{V}_f and R_a for dogs^{7,16–22} were made using one-way ANOVA. Where the calculated *F* value exceeded the critical value for the 0.05 probability level, the Student-Newman-Keuls' test was used to determine which differences were significant at $P < 0.05$.²³ Values are tabulated as mean \pm SD.

Results

At the two lower doses of thiopental, midazolam, or etomidate \dot{V}_f was not significantly different than previously reported normal values (table 2; fig. 1). At the two higher doses of each drug \dot{V}_f decreased by 33%, 46%, and 39%, respectively, compared to the two lower doses of each drug.

R_a during thiopental increased by 53% at the lowest dose, decreased by 33% at the highest dose, and was not different than previously reported normal values at the two intermediate doses (fig. 2). R_a during midazolam increased by 61% and 41% at the lowest and highest doses, respectively, and was normal at the two intermediate doses. R_a during etomidate was normal at the three lower doses and decreased by 21% at the highest dose.

In all groups \dot{V}_f was not different at elevated CSF pressure than at normal CSF pressure. \dot{V}_f at low drug doses was not different between groups and \dot{V}_f at high drug doses was not different between groups. R_a at intermediate drug doses also was not different between groups. In all groups CSF pressure increased by 10 cmH₂O when the open end of the cisternal outflow tubing was placed 10 cm above the level used for normal CSF pressure.

TABLE 2. Cerebral Variables at Eight Experimental Conditions for the Three Treatment Groups

	Low Dose		Low-intermediate Dose		High-intermediate Dose		High Dose	
	Normal CSF Pressure	Elevated CSF Pressure	Normal CSF Pressure	Elevated CSF Pressure	Normal CSF Pressure	Elevated CSF Pressure	Normal CSF Pressure	Elevated CSF Pressure
	Thiopental group (n = 6)	0.039 \pm 0.011	0.033 \pm 0.005	0.028 \pm 0.006	0.029 \pm 0.005	0.024 \pm 0.004*	0.024 \pm 0.005*	0.020 \pm 0.007*
\dot{V}_f (ml \cdot min ⁻¹)	354 \pm 17†	17.7 \pm 0.9	239 \pm 26	17.5 \pm 1.3	225 \pm 23	17.6 \pm 1.0	156 \pm 19*†	17.4 \pm 1.3
R_a (cmH ₂ O \cdot ml ⁻¹ \cdot min)	7.7 \pm 0.9	17.7 \pm 0.9	7.5 \pm 1.3	17.5 \pm 1.3	7.6 \pm 1.0	17.6 \pm 1.0	7.4 \pm 1.3	17.4 \pm 1.3
CSF pressure, intraventricular (cmH ₂ O)								
Midazolam group (n = 6)	0.040 \pm 0.011	0.038 \pm 0.007	0.035 \pm 0.007	0.035 \pm 0.004	0.021 \pm 0.004*	0.019 \pm 0.005*	0.020 \pm 0.005*	0.019 \pm 0.004*
\dot{V}_f (ml \cdot min ⁻¹)	378 \pm 18†	18.0 \pm 1.4	217 \pm 23	18.0 \pm 1.4	253 \pm 17	18.5 \pm 1.5	332 \pm 25†	18.5 \pm 1.5
R_a (cmH ₂ O \cdot ml ⁻¹ \cdot min)	8.0 \pm 1.4	18.0 \pm 1.4	8.0 \pm 1.4	18.0 \pm 1.4	8.5 \pm 1.5	18.5 \pm 1.5	8.5 \pm 1.5	18.5 \pm 1.5
CSF pressure, intraventricular (cmH ₂ O)								
Etomidate group (n = 6)	0.041 \pm 0.011	0.034 \pm 0.005	0.031 \pm 0.004	0.029 \pm 0.005	0.022 \pm 0.003*	0.020 \pm 0.004*	0.021 \pm 0.004*	0.019 \pm 0.005*
\dot{V}_f (ml \cdot min ⁻¹)	237 \pm 11	17.5 \pm 1.6	249 \pm 9	17.7 \pm 1.6	229 \pm 17	17.7 \pm 1.6	187 \pm 13*†	17.4 \pm 1.3
R_a (cmH ₂ O \cdot ml ⁻¹ \cdot min)	7.5 \pm 1.6	17.5 \pm 1.6	7.7 \pm 1.6	17.7 \pm 1.6	7.7 \pm 1.6	17.7 \pm 1.6	7.4 \pm 1.3	17.4 \pm 1.3
CSF pressure, intraventricular (cmH ₂ O)								

Values are given as mean \pm SD.

* Significant difference from low dose values, $P < 0.05$.

† Significant difference from intermediate dose values, $P < 0.05$.

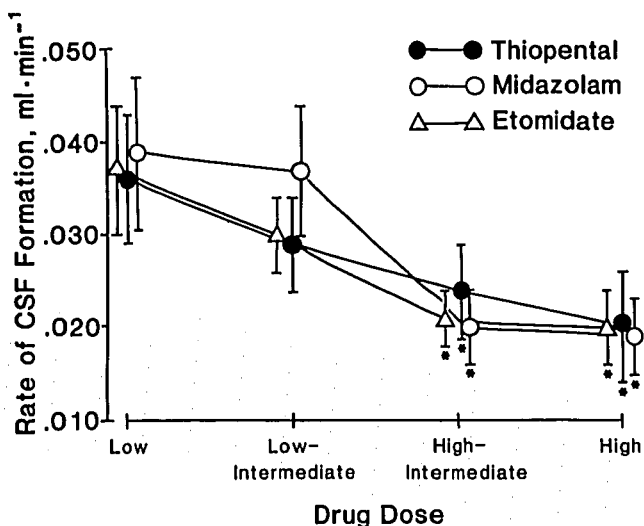


FIG. 1. Rates of CSF formation are shown for all four doses of thiopental (solid circles), midazolam (open circles), and etomidate (open triangles). For each drug, rates of CSF formation at the two higher doses were less than rates of CSF formation at the two lower doses; $*P < 0.05$. Previously reported normal values for \dot{V}_f range from 0.30 ± 0.11 to 0.54 ± 0.10 $\text{ml} \cdot \text{min}^{-1}$ (mean \pm SD) for dogs.^{7,16-22}

With thiopental the EEG showed loss of high frequency activity and a decrease of theta, alpha, and beta-1 activity that decreased as the dose of thiopental was increased. With midazolam the EEG showed loss of high frequency activity and either continued moderate theta and alpha activity or variable, alternating periods of minimal and

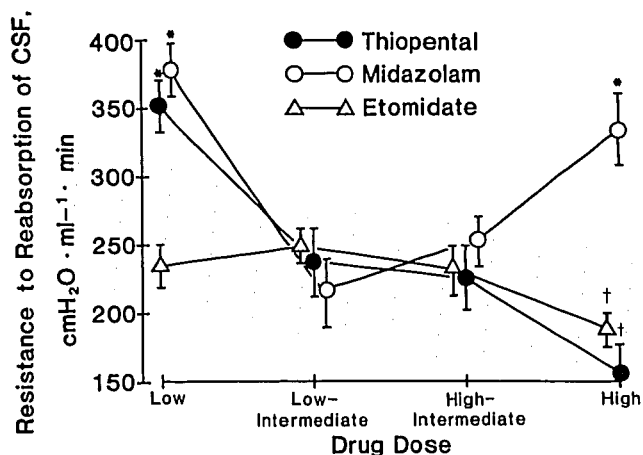


FIG. 2. Resistance to reabsorption of CSF is shown for all four doses of thiopental (solid circles), midazolam (open circles), and etomidate (open triangles). Compared to resistance values at the two intermediate doses, resistance to reabsorption of CSF was increased at the lowest doses of thiopental and midazolam and at the highest dose of midazolam ($*P < 0.05$), and decreased at the lowest doses of thiopental and etomidate ($\dagger P < 0.05$). Previously reported normal values for R_a range from ~ 220 to 240 ± 5 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{min}$ (mean \pm SD) for dogs.^{21,22,24,25}

moderate theta and alpha activity. With etomidate the EEG showed prominent theta, alpha, and beta-1 activity that increased as the dose of etomidate was increased. At all four rates of infusion of the three drugs the pattern of EEG activity characteristic of each dose remained constant throughout each infusion period.

Within each treatment group systemic variables were not significantly different between conditions. Systemic variables were therefore combined within groups (table 3). Combined systemic variables did not differ between treatment groups, although a trend toward lower heart rate values was observed with etomidate.

Discussion

In previous studies of CSF dynamics control or normal values for \dot{V}_f and R_a were determined during inhalation of N_2O and low concentrations of volatile anesthetic or administration of pentobarbital.^{7,9,16-21,24-32,\dagger} The reported range of control or normal values for \dot{V}_f was 0.030 ± 0.011 to 0.054 ± 0.010 ml/min (mean \pm SD) for dogs.^{7,16-22} Assuming that 0.030 – 0.054 ml/min represents normal canine \dot{V}_f , the results of the present study indicate that \dot{V}_f is unchanged at the two lower doses of thiopental, midazolam, or etomidate and is reduced at the two higher doses of each drug.

The reported range of control or normal values for R_a for dogs is ~ 220 – 240 ± 5 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{min}$.^{21,22,24,25} Assuming that 220 – 240 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{min}$ represents normal canine R_a , the results of the present study indicate that R_a is elevated at the lowest dose of thiopental, unchanged at the intermediate doses, and reduced at the highest dose. With midazolam R_a is elevated at the lowest and highest doses and unchanged at the intermediate doses. With etomidate R_a is reduced at the highest dose and unchanged at the other three doses.

It should be noted that in the present studies the sequence of administration of thiopental, midazolam, and etomidate always proceeded from lowest dose to highest dose. Consequently, it is possible that the reduction of \dot{V}_f observed with the two higher doses of each drug occurred because of time-related changes rather than drug effect. However, previous studies with this model reported no time-related change in \dot{V}_f during inhalation of N_2O and low concentrations of halothane^{7,17,18,21} (the "background" anesthetic used here), inhalation of 1 MAC halothane,^{17,18} or inhalation of N_2O and low concentrations of halothane combined with iv infusion of fentanyl.^{17,18} Thus, it seems likely that the reduction of \dot{V}_f

[†] VanLandingham KE, Maffeo CJ, Jackson H, Butler AB: Cerebrospinal fluid dynamics in the cat under halothane and pentobarbital anesthesia. Abstracts of Scientific Papers, Annual Meeting of the Society for Neuroscience, 1981, p 89.

TABLE 3. Combined Systemic Variables from Eight Experimental Conditions and CSF Osmolality for the Three Treatment Groups

Systemic Variables	Thiopental Group (n = 6)	Midazolam Group (n = 6)	Etomidate Group (n = 6)
PaO ₂ (mmHg)	133 ± 11	141 ± 10	145 ± 13
PaCO ₂ (mmHg)	35 ± 3	36 ± 3	34 ± 2
pH	7.39 ± 0.03	7.40 ± 0.02	7.37 ± 0.03
Bicarbonate (mEq · l ⁻¹)	21.1 ± 1.4	21.8 ± 1.2	19.4 ± 1.8
Hemoglobin (g · dl ⁻¹)	14.8 ± 2.4	12.1 ± 2.0	14.0 ± 1.3
Mean arterial blood pressure (mmHg)	114 ± 6	100 ± 9	110 ± 8
Heart rate (beats · min ⁻¹)	112 ± 7	98 ± 14	80 ± 18
Temperature, nasopharyngeal (°C)	37.4 ± 0.6	37.2 ± 0.4	37.2 ± 0.4
CSF osmolality (mosm · kg ⁻¹)	293 ± 17	296 ± 14	298 ± 17

Values are given as mean ± SD. Values are the combined results of

determinations made at four drug doses, each at normal and elevated (+10 cmH₂O) CSF pressure.

observed in the present study with the two higher doses of thiopental, midazolam, and etomidate was not due solely to the effect of time of this model. Regarding R_a no consistent pattern was observed at the highest dose of each drug in this study (elevation of R_a with midazolam, reduction of R_a with thiopental and etomidate). Thus, no time-related effect on R_a is suggested. Because each drug was given in sequence, progressing from smallest to largest dose, the results at all but the lowest infusion rate include the influence of preceding drug doses.

About two-thirds of CSF formation occurs *via* energy-dependent, active transport processes and about one-third of CSF formation occurs *via* passive filtration.^{33,34} The reduction of \dot{V}_f that occurred at the two higher doses of thiopental, midazolam, and etomidate in this study may be related to decrease of choroid plexus blood flow and/or metabolism. Some authors have reported that thiopental, midazolam, and etomidate decrease cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMRO₂) in dogs.^{10,11,35} Decrease of CBF reduces \dot{V}_f , presumably due to impaired delivery of water, ions, and the substrate needed for energy production for active transport processes at the choroid plexus.^{33,34} Decrease of CBF also may reduce \dot{V}_f due to impaired delivery of water and ions to sites of passive filtration of CSF, *i.e.*, the choroid plexus and ependyma.³⁴ Decrease of CMRO₂ reduces \dot{V}_f , presumably due to a slowing in the rate of the energy-requiring processes necessary for active CSF formation.^{28,34,36} It is also possible that these hypnotics reduce \dot{V}_f by direct action (not related to slowing of metabolism) to impair the activity of the catalytic enzymes or membrane pumps of the choroid plexus, or to decrease the permeability of membranes to water or ions at the choroid plexus or ependyma.³⁴

The increase or reduction of R_a that occurred in this study may result from changes in conductance at the arachnoid granulations or changes in the pressure gradient across the arachnoid granulations. Conductance at the arachnoid granulations is altered by changes in the

architecture of the one-way valves or changes in transport across the basement membrane.³⁴ The pressure gradient across the arachnoid granulations is altered by changes in cerebral venous pressure (sagittal sinus and lateral lacunae) and CSF pressure.³⁷ It is unlikely that changes in CSF pressure altered the pressure gradient across the arachnoid granulations in this study because CSF pressure was fixed at the value determined by the height of the distal end of the cisternal outflow tubing.

In summary, the principal findings of this study were that thiopental, midazolam, and etomidate caused no change in \dot{V}_f at the two lower doses and decreased \dot{V}_f at the two higher doses. R_a was elevated at the lowest and highest dose of midazolam and at the highest dose of thiopental, and unchanged or decreased with etomidate. Drug-induced changes in \dot{V}_f and/or R_a are of interest because the balance between \dot{V}_f and R_a is a major determinant of CSF volume. The present results indicate that, under the conditions of this study, CSF volume should be increased at the lowest doses of midazolam and thiopental and may be increased at the highest dose of midazolam. CSF volume should be normal or decreased at the other doses of midazolam and thiopental and with all four doses of etomidate. Also, drug-induced changes in R_a are of interest because R_a is a major determinant of the response of CSF volume to changes in CBV and brain tissue volume. Increased R_a should be disadvantageous when intracranial compliance is reduced because CSF volume can contract in response to increase of CBV or brain tissue volume only if CSF pressure rises. In contrast, unchanged or lowered R_a should be advantageous because a rise in CSF pressure is not needed to permit CSF volume to contract.

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