

Autoregulation of Cerebral Blood Flow during Normocapnia and Hypocapnia in Dogs

Alan A. Artru, M.D.,* Ross A. Katz, M.D.,† Peter S. Colley, M.D.*

The effect of hypocapnia on autoregulation of cerebral blood flow (CBF) and the lower limit of autoregulation (LLA) was determined in dogs anesthetized with nitrous oxide (66%) and halothane (0.2%, end-expired concentration). CBF and cerebral vascular resistance (CVR) were determined during both normocapnia and hypocapnia (P_{aCO_2} , 21–22 mmHg) at control cerebral perfusion pressure (CPP) and after reducing CPP (by hemorrhage) to 80%, 60%, 50%, and 40% of control. At control CPP hypocapnia decreased CBF from 75 ± 5 to 48 ± 3 ml · 100 g⁻¹ · min⁻¹ (mean \pm SEM, $P < 0.05$). During both normocapnia and hypocapnia CVR decreased and CBF did not change as CPP was reduced to 60% of control. When CPP was reduced to 50% or 40% of control, CVR remained decreased and CBF fell sharply. The LLA during hypocapnia, $61 \pm 2\%$ of control CPP, was not different than that during normocapnia, $59 \pm 3\%$ of control CPP. Below the LLA the CBF-CPP slopes differed from zero but did not differ between hypocapnia and normocapnia. Hypocapnia does not produce a substantial shift of the LLA, and over the range of CPP values studied here, autoregulatory cerebral vasodilation only partially abolishes hypocapnia-induced cerebral vasoconstriction. The results suggest that when cerebral autoregulation is intact and in the absence of cerebrovascular disease, hypocapnia does not reduce global CBF to a level that is likely to produce ischemia and remains a useful therapeutic treatment so long as CPP remains above the LLA. (Key words: Blood pressure: hypotension. Brain: autoregulation, blood flow, vascular resistance. Carbon dioxide: hypocapnia.)

AUTOREGULATION of cerebral blood flow (CBF) refers to alterations in cerebral vascular resistance (CVR) that occur so that CBF does not change when cerebral perfusion pressure (CPP) increases or decreases. The lower limit of autoregulation (LLA) is the CPP at which CVR is maximally decreased and below which CBF falls in parallel with reduction of CPP. The decrease in CVR that accompanies reduction of CPP is believed to be mediated primarily by myogenic mechanisms.^{1,2}

Hypocapnia, however, increases CVR. The increase in CVR that accompanies hypocapnia is believed to be mediated primarily by chemical–metabolic mechanisms.^{1,3}

It is not certain which mechanism predominates when CPP is reduced during hypocapnia. Previous work in this area is either incomplete in certain respects or leads to differing conclusions about the interaction between falling

CPP and hypocapnia.^{4–8} Consequently, the effects of hypocapnia on autoregulation of CBF, the LLA, and CBF at CPP below the LLA are not well defined.

Clarification of the effects of hypocapnia on CBF during hypotension is relevant to clinical practice because changes produced by hypocapnia may alter intracranial pressure, the ease of brain visualization and retraction during craniotomy, the likelihood of “cerebral steal,” and the CPP threshold for cerebral ischemia. Because the effects of hypocapnia on CBF during hypotension are not known, safe blood pressure levels during hypocapnia cannot be predicted and it is not known whether hypocapnia should be discontinued during blood pressure reduction.

Accordingly, the present study was designed to examine autoregulation of CBF during normocapnia and hypocapnia in dogs. By defining the relationship between CBF and CPP as CPP was lowered, this study sought to determine whether the LLA is different during hypocapnia than during normocapnia and whether autoregulatory cerebral vasodilation overrides the cerebral vasoconstriction produced by hypocapnia, at CPP either above or below the LLA.

Methods

Following approval from the animal care committee, eight unmedicated mongrel dogs, weighing 14–20 kg, were anesthetized with halothane (>1.8%, inspired) and nitrous oxide (66%) in O₂. The trachea was intubated, and ventilation was controlled with a Harvard® pump (Harvard Apparatus Co., Millis, Massachusetts) and adjusted along with the inspired O₂ concentration to maintain initial blood–gas tensions (Radiometer® BMS3 MK 2 electrodes, [Radiometer A/S, Copenhagen, Denmark]) at $P_{aO_2} > 120$ mmHg and P_{aCO_2} of 35–40 mmHg. Thereafter, expired CO₂ was continuously monitored *via* a Beckman LB-2® medical gas analyzer (Beckman Instruments, Inc., Fullerton, California), and ventilation was regulated by a servocontroller (Harvard Apparatus Pump Speed Modulator, Model 552) to maintain expired CO₂ at the desired value. With the animal in the lateral position, a urinary catheter was inserted and both femoral veins were cannulated for fluid and drug administration, and reinfusion of blood collected from a sagittal sinus cannula. An iv infusion of succinylcholine 50–120 mg/h was used to maintain muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood–gas analyses, and for continuous monitoring of

* Associate Professor of Anesthesiology.

† Research Fellow and Acting Instructor of Anesthesiology.

Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Accepted for publication September 13, 1988.

Address reprint requests to Dr. Artru: Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, Washington 98195.

TABLE 1. Cerebral Values and Systemic Variables during Normocapnia and Reduction of Cerebral Perfusion Pressure (mean \pm SEM, n = 8)

	Control CPP	80% of Control CPP	60% of Control CPP	50% of Control CPP	40% of Control CPP
Cerebral values					
CBF (ml \cdot 100 g ⁻¹ \cdot min ⁻¹)	75 \pm 5	72 \pm 4	69 \pm 4	54 \pm 3*	42 \pm 4*
CVR (mmHg \cdot ml ⁻¹ \cdot 100 g \cdot min)	1.49 \pm 0.06	1.28 \pm 0.05*	1.02 \pm 0.05*	1.07 \pm 0.04*	1.13 \pm 0.05*
P _{ss} O ₂ (mmHg)	53 \pm 4	46 \pm 4	38 \pm 4*	33 \pm 3*	30 \pm 3*
CPP (mmHg)	113 \pm 6	92 \pm 4*	70 \pm 4*	58 \pm 3*	48 \pm 3*
Systemic variables					
P _a CO ₂ (mmHg)	37 \pm 2	36 \pm 2	36 \pm 2	37 \pm 2	35 \pm 2
P _a O ₂ (mmHg)	172 \pm 12	162 \pm 11	150 \pm 7	146 \pm 7	146 \pm 10
pH	7.35 \pm 0.02	7.35 \pm 0.02	7.34 \pm 0.02	7.35 \pm 0.02	7.34 \pm 0.02
Bicarbonate (mEq \cdot l ⁻¹)	19.8 \pm 1.2	19.7 \pm 0.8	20.0 \pm 1.6	21.4 \pm 1.5	19.8 \pm 1.6
Hemoglobin (g \cdot dl ⁻¹)	13.3 \pm 1.1	14.0 \pm 1.0	13.5 \pm 1.0	13.1 \pm 0.9	12.9 \pm 0.8
Heart rate (beats \cdot min ⁻¹)	106 \pm 4	105 \pm 4	113 \pm 6	113 \pm 6	115 \pm 5
Temperature nasopharyngeal (°C)	36.8 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2

CBF = cerebral blood flow; CVR = cerebral vascular resistance; P_{ss} O₂ = sagittal sinus oxygen tension; CPP = cerebral perfusion pressure.

* Significant difference compared with control values, P < 0.05.

systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 \pm 0.5° C by heat lamps or ice packs. Depletion of vascular volume was minimized by continuous infusion of saline 4-6 ml \cdot kg⁻¹ \cdot h⁻¹. The animal was then turned to the prone position and the head slightly elevated and fixed in a stereotaxic frame.

The method of measurement of CBF was previously described in detail and is summarized here.⁹ The sagittal sinus was exposed *via* craniectomy and, following systemic iv infusion of heparin 8,000 units, the posterior sagittal sinus was incised and a snug-fitting, tapered nylon catheter (2 mm internal diameter) was passed anteriorly 2-4 mm. The sinus was packed with strips of Surgicel[®] (Johnson and Johnson Products, New Brunswick, New Jersey) through another incision just posterior to the catheter, assuring total diversion of sagittal sinus flow through the catheter. The distal tip of the catheter was placed at the level of the base of the skull, and flow from the catheter was collected in a reservoir and returned by a roller pump to the femoral vein. The reservoir and pump initially were primed with saline and the fluid level in the reservoir was maintained at \pm 2 ml/kg. Sagittal sinus blood samples for measurement of oxygen tension were drawn into syringes through a side-arm at the distal tip of the sagittal sinus outflow catheter by gentle aspiration. At each experimental condition CBF, expressed as ml/min, was determined by 3-5 timed collections of outflow from the sagittal sinus catheter. The duration of each timed collection was 30 s. Conversion of CBF values from ml/min to ml \cdot min⁻¹ \cdot 100 g⁻¹ was based on brain weight and the portion of brain that contributed to sagittal sinus flow, namely, 48%, as reported previously.¹⁰ Three to five CBF values were averaged to provide representative mean CBF

values for each experimental condition. Brains were excised and weighed after the final experimental condition.

A burr hole was placed over the left hemisphere and a catheter was directed into the underlying lateral ventricle for measurement of intracranial cerebrospinal fluid (CSF) pressure. The strain gauges used to measure systemic arterial pressure and intracranial CSF pressure were positioned 12 cm above heart level. The zero reference for the strain gauges was set at the level of the external auditory meatus. CPP was determined as the difference between MAP and CSF pressure. CVR was calculated as the ratio of CBF to CPP. All wound edges were infiltrated with bupivacaine (0.5%).

After completion of the surgical preparation the expired concentration of halothane was decreased to 0.2% (end-expired concentration determined by gas chromatography, nitrous oxide continued). After stable measurements of cerebral and systemic variables were obtained (at least 25 min later), CBF, CVR, and systemic variables were determined at five CPP during normocapnia and at five CPP during hypocapnia (P_aCO₂ of about 20 mmHg). The five CPP were control, 80% of control, 60% of control, 50% of control, and 40% of control. The desired CPP was achieved by controlled hemorrhage, *i.e.*, by allowing sagittal sinus blood from the outflow catheter to accumulate in the reservoir (500 ml capacity), or by returning blood from the reservoir into the femoral vein. Hyperventilation was used to decrease P_aCO₂. Four dogs were examined first at all five CPP during normocapnia, then during hypocapnia, and four dogs were examined first during hypocapnia, then during normocapnia. The order of CPP was randomized for each P_aCO₂ level. The duration at each CPP was 15 min, with the desired CPP being achieved by 5 min and CBF, CVR, and systemic variables being measured at 10 and 15 min during each

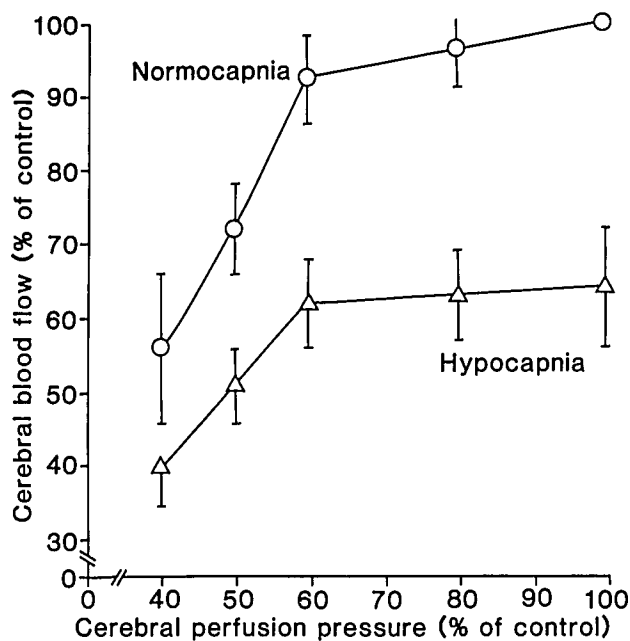


FIG. 1. The results of the present study are shown as mean values \pm SEM. The circles represent cerebral blood flow (percent of control) at five cerebral perfusion pressures (percent of control) during normocapnia, and the triangles represent cerebral blood flow at the same five pressures during hypocapnia. Autoregulation of cerebral blood flow was observed during both normocapnia and hypocapnia. The lower limit of autoregulation did not differ between the two conditions. The cerebral blood flow-cerebral perfusion pressure slope was steeper with normocapnia than with hypocapnia at cerebral perfusion pressures above the lower limit of autoregulation, but not at cerebral perfusion pressures below the lower limit of autoregulation.

15-min period. When changing from hypocapnia to normocapnia or vice versa, 30 min at normal CPP and the desired P_{aCO_2} level were allowed before studies at the five 15-min CPP levels were begun.

Systemic variables and cerebral values were compared between CPP conditions using analysis of variance for repeated measures and between CO_2 conditions using analysis of variance.¹¹ Where the calculated *F* value exceeded the critical value for 0.05 probability, the Student-Newman-Keuls' test was employed.¹² A *P* value of less than 0.05 was considered significant. Autoregulation of CBF was determined from the slope of the relationship between CBF and CPP. CBF-CPP slopes were determined by linear regression analysis. CBF values were normalized to offset the mathematical bias toward steeper slopes with the data for normocapnia. Such a bias would have resulted from the fact that, at control CPP, CBF during hypocapnia was expected to be 33–50% lower than CBF during normocapnia.^{10,13,14} CBF-CPP slopes at normocapnia were compared with those at hypocapnia using analysis of variance.¹¹ Where the calculated *F* value exceeded the critical value for 0.05 probability, the Student-

Newman-Keuls' test was employed.¹² A *P* value of less than 0.05 was considered significant.

Results

Mean CBF was 75 ± 5 ml \cdot 100 g⁻¹ \cdot min⁻¹ (mean \pm SEM) and mean CVR was 1.49 ± 0.06 mmHg \cdot ml⁻¹ \cdot 100 g \cdot min at normocapnia and control CPP (table 1). CVR decreased so that CBF did not change as CPP was reduced to 80% and 60% of control. At below 60% of control CPP, CVR remained low and CBF decreased as CPP was reduced to 50% and 40% of control (fig. 1).

CBF at hypocapnia and control MAP was 48 ± 3 ml \cdot 100 g⁻¹ \cdot min⁻¹, significantly lower than CBF at normocapnia and control CPP (table 2). CVR at hypocapnia and control MAP was 2.35 ± 0.08 mmHg \cdot ml⁻¹ \cdot 100 g \cdot min, significantly higher than CVR at normocapnia and control CPP. During hypocapnia CVR decreased so that CBF did not change as CPP was reduced to 80% and 60% of control. At below 60% of control CPP, CVR remained low and CBF decreased as CPP was reduced to 50% and 40% of control.

The lower limit of autoregulation of CBF was calculated from the regression equations. At normocapnia the lower limit of autoregulation occurred when CPP was reduced to $61 \pm 2\%$ of control CPP. This value was not significantly different from the lower limit of autoregulation during hypocapnia, which occurred when CPP was reduced to $59 \pm 3\%$ of control MAP.

During normocapnia the slope of the regression equation relating CBF to CPP was $y = (x) 0.21 \pm 0.08$ for CPP values above the LLA and $y = (x) 1.80 \pm 0.33$ for CPP values below the LLA, where $y =$ CBF, percent change from control, and $x =$ CPP, percent change from control. During hypocapnia the slope of the regression equation relating CBF to CPP was $y = (x) 0.05 \pm 0.04$ for CPP values above the LLA and $y = (x) 1.68 \pm 0.26$ for CPP values below the LLA. Below the LLA the slopes relating CBF to CPP were significantly different from zero but did not differ between normocapnia and hypocapnia.

As regards systemic variables, arterial blood pH increased and bicarbonate decreased with hypocapnia. The other systemic variables did not differ between conditions other than the intended changes in CPP and P_{aCO_2} . Cerebral values and systemic variables at 10 min after altering MAP were not significantly different from those at 15 min after altering MAP.

Discussion

The results of the present study indicate that at CPP greater than the LLA, autoregulation of CBF was present during hypocapnia as well as during normocapnia. At both P_{aCO_2} levels CVR fell progressively as CPP was lowered

TABLE 2. Cerebral Values and Systemic Variables during Hypocapnia and Reduction of Cerebral Perfusion Pressure (mean \pm SEM, n = 8)

	Control CPP	80% of control CPP	60% of Control CPP	50% of Control CPP	40% of Control CPP
Cerebral values					
CBF ($\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)	48 \pm 3*	48 \pm 4*	47 \pm 3*	38 \pm 3*†	30 \pm 3*†
CVR ($\text{mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g} \cdot \text{min}$)	2.35 \pm 0.08*	1.93 \pm 0.08*†	1.49 \pm 0.06*†	1.55 \pm 0.07*†	1.56 \pm 0.07*†
P _{ss} O ₂ (mmHg)	33 \pm 3*	30 \pm 3*	31 \pm 3*	25 \pm 3*	22 \pm 2*†
CPP (mmHg)	113 \pm 6	92 \pm 4†	70 \pm 4†	59 \pm 3†	47 \pm 3†
Systemic variables					
Pa _{CO₂} (mmHg)	22 \pm 1*	21 \pm 2*	22 \pm 2*	22 \pm 2*	21 \pm 2*
Pa _{O₂} (mmHg)	167 \pm 6	158 \pm 10	146 \pm 12	146 \pm 12	144 \pm 13
pH	7.50 \pm 0.02*	7.49 \pm 0.02*	7.48 \pm 0.02*	7.48 \pm 0.02*	7.47 \pm 0.02*
Bicarbonate ($\text{mEq} \cdot \text{l}^{-1}$)	15.6 \pm 0.5*	15.3 \pm 0.7*	15.2 \pm 0.6*	15.5 \pm 1.6*	15.0 \pm 1.2*
Hemoglobin ($\text{g} \cdot \text{dl}^{-1}$)	12.9 \pm 1.0	13.2 \pm 1.4	14.0 \pm 1.5	14.3 \pm 1.5	13.9 \pm 1.5
Heart rate ($\text{beats} \cdot \text{min}^{-1}$)	111 \pm 4	110 \pm 6	114 \pm 5	110 \pm 5	114 \pm 4
Temperature, nasopharyngeal ($^{\circ}\text{C}$)	36.6 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2	36.6 \pm 0.2

* Significant difference compared with respective values during normocapnia, $P < 0.05$.

† Significant difference compared with control values, $P < 0.05$.

from control to 60% of control MAP, then remained low as CPP was lowered to 40% of control. CBF did not change significantly as CPP was lowered from control to 60% of control, then fell sharply as CPP was lowered to 40% of control.

In addition, the calculated LLA was not significantly different during hypotension combined with hypocapnia than during hypotension at normocapnia. These two results indicate that the mechanisms of cerebral vascular regulation responsible for hypocapnia-induced vasoconstriction do not reset or substantially alter the mechanisms of cerebral vascular control that are responsible for autoregulation. This conclusion is consistent with the view that autoregulation is mediated primarily by neurogenic mechanisms,^{1,2} whereas cerebral CO₂ reactivity is mediated primarily by chemical/metabolic mechanisms.^{1,3}

At CPPs below the LLA CBF was lower during hypocapnia than at normocapnia. These data indicate that even with complete autoregulatory cerebral vasodilation, some CO₂ reactivity remained. Our finding of hypocapnia-induced reduction of CBF coexistent with reduction of CBF due to hypotension is consistent with previous metabolic studies.⁴ When the CBF-CPP slopes from below the LLA were extrapolated, they were found to intersect at 20–25 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Considering that ischemia generally does not occur until CBF falls below 20 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, the intercept of these extrapolated slopes suggests that hypocapnia does not affect CBF when hemorrhagic reduction in CPP threatens ischemia.¹⁵

Analysis of the CBF data at CPP greater than the LLA provides additional information. The smaller change in CBF as CPP was lowered in hypocapnic dogs likely reflects loss of hypocapnia-induced vasoconstriction as autoregulatory cerebral vasodilation overrides CO₂ reactivity of CBF. In addition, the CBF-CPP slope during hypocapnia

did not converge with the CBF-CPP slope during normocapnia. This indicates that even though autoregulatory cerebral vasodilation overrides CO₂ reactivity, some CO₂ reactivity remains. The above conclusions, that autoregulation of CBF is present during hypocapnia, that autoregulatory vasodilation partially reverses hypocapnia-induced cerebral vasoconstriction, and that some CO₂ reactivity remains despite autoregulatory vasodilation are consistent with previous reports of partial preservation of CO₂ reactivity of CBF during reduction of MAP to about 67% of control.^{8,9}

This study examined the effects of hypocapnia on autoregulation of CBF only during reduction of CPP by hemorrhagic hypotension. The effects of hypocapnia on autoregulation of CBF may be different under conditions in which CPP was reduced either by increased intracranial pressure or by pharmacologically induced hypotension, Pa_{CO₂} was altered without changing minute ventilation, the sympathetic nervous system was stimulated, or different anesthetics were used.¹⁶

A number of findings indicate that the present model was suitable to demonstrate normal physiologic responses and characteristics of the cerebral circulation. First, CVR was significantly higher and CBF was significantly lower at hypocapnia and control CPP than at normocapnia and control CPP, demonstrating that the model preserved CO₂ reactivity.⁷ The magnitude of these changes in CVR and CBF were similar to those previously reported to occur with hypocapnia in dogs.^{10,13,14} Second, at CPP greater than the LLA, CVR fell and CBF remained unchanged as CPP was reduced, and at CPP below the LLA, CVR remained low and CBF fell as CPP was reduced. These findings demonstrate that the present model preserved autoregulation of CBF.¹⁷ Third, for each CPP level, CBF at 10 min (CPP stable for ≥ 5 min at the desired level)

was similar to CBF at 15 min (CPP stable for ≥ 10 min at the desired level). These findings demonstrate that the present model preserved rapid autoregulatory responses, which normally are complete at less than 2 min.²

The results of this study suggest that when cerebral autoregulation is intact and in the absence of cerebrovascular disease, there should be no added risk for reduction of CBF to ischemic levels when CPP is lowered during hypocapnia, so long as CPP remains above the LLA. Hypocapnia should remain an effective treatment for reducing intracranial pressure or improving visualization of the surgical field during craniotomy or during reduction of CPP, providing CPP does not fall below the LLA. In cases in which a patient's LLA is estimated as a means to guide blood pressure control intraoperatively, that estimated LLA need not be changed when hypocapnia is employed.

The authors acknowledge the help of the Department of Statistics, University of Washington, in analyzing the CBF-CPP slopes from this study.

References

1. Siesjö BK: Circulation and oxygen consumption in the brain, *Brain Energy Metabolism*. Edited by Siesjö BK. Chichester, John Wiley & Sons, 1978, pp 56-100
2. Symon L: Pathological regulation in cerebral ischemia, *Cerebral Blood Flow*. Edited by Wood JH. New York, McGraw-Hill, 1987, pp 413-424
3. Pickard JD: Ionic and eicosanoid regulation of cerebrovascular smooth muscle contraction, *Cerebral Blood Flow*. Edited by Wood JH. New York, McGraw-Hill, 1987, pp 131-144
4. Levin RM, Zadigian ME, Hall SC: The combined effect of hyperventilation and hypotension on cerebral oxygenation in anaesthetized dogs. *Can Anaesth Soc J* 27:264-273, 1980
5. Paulson OB, Olesen J, Christensen MS: Restoration of autoregulation of cerebral blood flow by hypocapnia. *Neurology* 22: 286-293, 1972
6. Häggendal E, Johansson B: Effects of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. *Acta Physiol Scand* 66(suppl 258):27-53, 1965
7. Harper AM, Glass HI: Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. *J Neurol Neurosurg Psychiatry* 28:449-452, 1965
8. Okuda Y, McDowall DG, Ali M, Lane JR: Changes in CO₂ responsiveness and in autoregulation of the cerebral circulation during and after halothane-induced hypotension. *J Neurol Neurosurg Psychiatry* 39:221-230, 1976
9. Michenfelder JD, Messick JM Jr, Theye RA: Simultaneous cerebral blood flow measured by direct and indirect methods. *J Surg Res* 8:475-481, 1968
10. Artru AA, Colley PS: Cerebral blood flow responses to hypocapnia during hypotension. *Stroke* 15:878-883, 1984
11. Brunning JL, Kintz BL: *Analysis of variance, Computational Handbook of Statistics*. Edited by Brunning JL, Kintz BL. Glenview, Scott, Foreman, 1977, pp 18-106
12. Steel RGD, Torrie JH: *Analysis of variance. I. The one-way classification, Principles and Procedures of Statistics*. Edited by Steel RGD, Torrie JH. New York, McGraw-Hill, 1960, pp 99-131
13. Artru AA: Cerebral vascular responses to hypocapnia during nitroglycerin-induced hypotension. *Neurosurgery* 16:468-472, 1985
14. Artru AA: Partial preservation of cerebral vascular responsiveness to hypocapnia during isoflurane-induced hypotension on dogs. *Anesth Analg* 65:660-666, 1986
15. Lassen NA: *Cerebral and spinal cord blood flow, Anesthesia and Neurosurgery*. Edited by Cottrell JE, Turndorf H. St. Louis, CV Mosby, 1986, pp 1-21
16. Fitch W, MacKenzie ET, Harper AM: Effects of decreasing arterial blood pressure on cerebral blood flow in the baboon; influence of the sympathetic nervous system. *Circ Res* 37:550-557, 1975
17. Harper AM: Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 29:398-403, 1966