

The Effects of Sevoflurane and Isoflurane on Intracranial Pressure Following Diffuse Brain Injury in Rats

Diffüz Kafa Travması Sonrası Sıçanlarda Sevofluran ve İntrakraniyal Basınca Etkileri

SUNA GOREN, NEVZAT KAHVECİ, TULİN ALKAN, BÜLENT GOREN, ENDER KORFALI

Uludağ University School of Medicine Dept. of Anesthesiology (SG),
Physiology (NK, TA, BG), Neurosurgery (EK) Bursa, Türkiye

Geliş Tarihi: 3.3.1999 ⇔ Kabul Tarihi: 3.8.1999

Abstract: Twenty-four adult Wistar rats weighting 220–290 g were anesthetized with an intraperitoneal injection of 30 mg/kg sodium thiopental and a tracheostomy was performed. Following diffuse impact–acceleration brain injury (BI), animals were paralyzed and mechanically ventilated with %30 O₂ in N₂O. The rats were randomly assigned to two groups. Each group received one of the two volatile anesthetic agents which were administered in 0.5, 0.75, 1.0 and 1.25 MAC end-tidal concentrations for 30 minutes each, respectively. Anesthesia was maintained with 0.75 MAC during last hour of the study period. ICP, MAP, rectal and intrahemispheric temperature and end-tidal volatile anesthetics concentration were monitored continuously for 3 hours. At baseline, there were no significant differences between two groups with regard to the monitored physiologic variables. MAP decreased in the sevoflurane group after 45 minutes and in isoflurane group after 30 minutes ($p<0.05$, $p<0.01$, $p<0.001$). ICP rose significantly at 30 minutes in the sevoflurane group ($p<0.05$) and remain elevated until the end of the study period ($p<0.05$). ICP did not change significantly in the group that received isoflurane. CPP changed in parallel with MAP, with the reduction in the sevoflurane group being more pronounced than that in the isoflurane group ($p<0.05$, $p<0.01$, $p<0.001$). The results showed that, in the presence of diffuse BI, animals that were anesthetized with sevoflurane had higher ICP than those anesthetized with isoflurane. This suggests that, in the clinical setting sevoflurane should not be chosen above isoflurane for anesthetic management of the diffuse BI patient group.

Key Words: Diffuse brain injury, intracranial pressure, isoflurane, rat, sevoflurane.

Özet: Erişkin 220-290 g 24 Wistar sıçanına, 30 mg/kg Na-tiyopental ile anesteziyi takiben trakeostomi açıldı. Diffüz kitle-akselerasyon kafa travmasından sonra hayvanlar paraliz edildi ve % 30 O₂+% 70 N₂O ile mekanik ventilasyona başlandı. Sıçanlar rastgele iki gruba ayrıldı. Volatil anestezi ajanları sırasıyla 0.5, 0.75 1 ve 1.25 MAC end-tidal değerlerinde 30 dk aralıklarla uygulandı. Son 1 saatte ise anestezi idamesi 0.75 MAC değeri ile gerçekleştirildi. Üç saat süresince ortalama arter basıncı (OAB), intrakraniyal basınç (İKB), rektal ve intrahemisferik ısı, end-tidal volatil anestezi konsantrasyonları sürekli monitörize edildi. İki grup karşılaştırıldığında, takip edilen parametrelerde kontrol değerleri arasında anlamlı bir fark saptanmadı. OAB, sevofluran grubunda 90. dk, izofluran grubunda 60. dk'dan itibaren anlamlı derecede azaldı ($p<0.01$; $p<0.001$). İKB artışı sevofluran grubunda 45. dk'dan itibaren başladı ($p<0.05$) ve 3. saatin sonuna kadar sürdü ($p<0.01$; $p<0.001$). İzofluran grubunda anlamlı farklılık gözlenmedi ($p<0.05$). SPB'da iki grupta da OAB ile benzer dönemlerde azaldı. İki grup karşılaştırıldığında azalmanın sevofluran grubunda daha fazla olduğu saptandı ($p<0.05$; $p<0.01$; $p<0.001$). Sonuç olarak, diffüz kafa travmalı sıçanlarda, izofluranla karşılaştırıldığında, sevofluran İKB'ı arttırdığı için klinik uygulamada uygun bir ajan olmadığı, izofluranın tercih edilmesi gerektiği sonucuna varılmıştır.

Anahtar Kelimeler: Diffüz kafa travması, intrakraniyal basınç, izofluran, sevofluran, sıçan.

INTRODUCTION

Sevoflurane (fluoromethyl 2,2,2-trifluoro 1-[trifluoromethyl] ethyl ether) is a commonly used, non-flammable volatile anesthetics that has a low blood-gas partition coefficient of 0.63, which is lower than that of many other volatile anesthetics (1). As an added benefit, this agent is not a respiratory irritant. These favorable properties lead to smooth and rapid anesthetic induction recovery with this agent. In particular, use of sevoflurane would seem to be of particular advantage in neurosurgical patients, since intra- or postoperative awakening is required for neurologic evaluation during many neurosurgical procedures. Animal experiments have shown that sevoflurane is similar to isoflurane in its effects on cerebral blood flow (CBF), cerebral metabolism rate of oxygen ($CMRO_2$), intracranial pressure (ICP), and electroencephalography (EEG) (2,3). It decreases $CMRO_2$ and causes a minimal to moderate increase in CBF and ICP in rabbits and dogs. As has been reported for isoflurane, it is possible to prevent this increase in ICP for any anesthetic concentration with prior establishment of hypocapnia (4,5). However, these studies were performed in animals that had normal intracranial compliance, and may not necessarily reflect the responses that would occur in the presence of compromised intracranial compliance or in an abnormal brain. We designed this study to investigate the effects of sevoflurane on mean arterial pressure (MAP), ICP, and cerebral perfusion pressure (CPP) in a diffuse brain injury (BI) rat model, and compared these effects to those seen with isoflurane.

MATERIALS AND METHODS

This study was reviewed and approved by the Animal Care and Use Committee at the Uludağ University School of Medicine. Twenty four adult male Wistar rats, weighting 220–290 g were fasted overnight with free access to water.

Minimum alveolar anesthetic concentration (MAC) for sevoflurane and isoflurane (Sevorane and Forane, Abbott Lab. Country) were determined in 16 rats using the up and down method with a tail-clamp technique (6,7). The expired volatile anesthetic concentration (Datex, Capnomac-ultimate, Finland) was then changed by 0.2% increments depending on the presence or absence of purposeful movement of the animal. MAC was considered the concentration midway between the highest concentration that allowed movement and the lowest concentration that

prevented movement.

After anesthetic induction with an intraperitoneal injection of 30 mg/kg sodium-thiopental, A tracheostomy was performed. All surgical procedures were performed following infiltration of the tissue with 2% lidocaine. The diffuse BI was delivered according to the weight-drop traumatic BI model described by Marmarou et al (8). A midline incision was made in the skin over the cranium and the periosteum covering the vertex was reflected. We dried the area, and then, using dental acrylic, fixed a 10 mm diameter metallic disk to the central portion of the rat's cranial vault between the coronal and lambdoid sutures. The animal was placed in prone position on a foam bed (of known spring constant) contained within a Plexiglass frame, and was secured in place with two belts. The lower end of the Plexiglass tube was then positioned directly above the helmet. The moderate BI was induced using a 450 g weight that fell freely by gravity through the 1 m vertical section of the transparent Plexiglass tube (held in place with a ring stand) onto the fixed helmet.

Following the BI, the animals were ventilated mechanically with 70% nitrous oxide (N_2O) and 30% O_2 (Harvard Rodent Ventilator-model 683, USA). The femoral artery was cannulated to measure blood pressure and sample arterial blood gases. A femoral vein catheter was inserted for administration of fluid (0.9% NaCl solution was infused 2-3 ml/h during the study) and drugs. Vecuronium infusion (0.1 mg/kg/h) was used for neuromuscular block and 0.02 mg/kg atropin was administered intramuscularly to reduce tracheal secretions. ICP was monitored with an intraparenchymal fiberoptic transducer which was placed through a small burr-hole 3 mm to the left of midline and 2 mm posterior to the bregma (Camino V420, USA). Another burr-hole was drilled on the controlateral side for intraparenchymal temperature monitoring (Mallinckrodt, Mon-A-Therm, 6510, USA). Rectal temperature (Protocol, Propaq-104, USA) and the end tidal concentrations of volatile anesthetics, were also monitored. Normothermia (36-37°C) was maintained using radiant heating lamp and normocapnia (36-40 mmHg) was maintained by adjusting tidal volume and respiratory frequency during the study period. Increments of sodium bicarbonate of 0.25 mEq were administered intravenously as necessary to maintain arterial pH > 7.30.

The animals were left undisturbed for 15

minutes before baseline measurements were recorded. They were then randomly assigned to one of two groups to receive isoflurane (n=12) or sevoflurane (n=12). The respective volatile anesthetics were administered at 0.5, 0.75, 1.0 and 1.25 MAC end-tidal concentrations for 30 minutes each. In the third hour, the anesthesia was maintained at 0.75 MAC.

Measured variables included MAP, ICP, end-tidal concentrations of volatile anesthetics, intrahemispheric and rectal temperature all of which were recorded every 15 minutes. CPP was calculated as the difference between MAP and ICP. Arterial blood gases were analyzed at 1-hour intervals.

All data were expressed as mean ± SEM. The data were compared within groups using the Wilcoxon test, and between two groups at equianesthetic MAC values using unpaired t-test. For all analyses, p<0.05 was considered statistically significant.

RESULTS

The baseline values of the physiological variables recorded immediately after diffuse BI were similar in both groups (Table I). We found no differences between the two anesthetic groups with regard to mean arterial pH, arterial carbon dioxide and oxygen pressures, base excess, hematocrit, or rectal and intrahemispheric temperature values in any of the measurement periods. The MAC value for sevoflurane was 2.18% ± 0.05, and for isoflurane was 1.37% ± 0.07.

We found that increasing the percentage of both volatile anesthetics caused a drop in MAP (Figure 1). In animals receiving 0.5 MAC isoflurane, MAP was significantly decreased at 30 minutes. This

Table I: The physiological control values of both groups (mean±SEM). No significant difference was found between the groups.

	Sevoflurane	Isoflurane
Weight (g)	260.4 ± 4.7	261.2 ± 6.6
PaO ₂ (mmHg)	102.2 ± 9.5	115.4 ± 13.7
PaCO ₂ (mmHg)	36.3 ± 3.1	36.5 ± 2.8
pH	7.44 ± 0.03	7.44 ± 0.04
BE (mmol/L)	1.2 ± 1.1	0.9 ± 0.9
Hct (%)	41.2 ± 1.6	39.0 ± 1.2
Rectal temp (°C)	37.4 ± 0.2	37.4 ± 0.2
Intrahemispheric temp (°C)	36.1 ± 0.2	36.4 ± 0.1

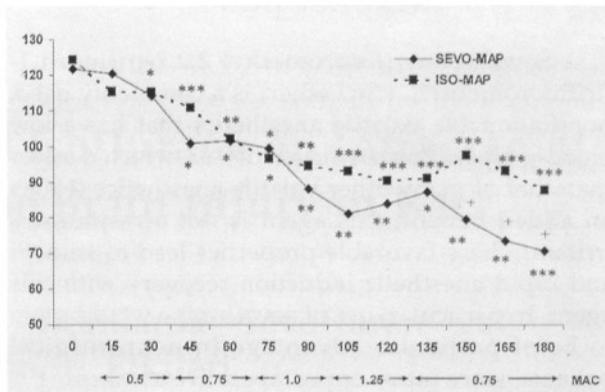


Figure 1: Mean changes in mean arterial pressure (mmHg) with isoflurane and sevoflurane *p<0.05; **p<0.01; ***p<0.001, compared with control. +p<0.05 compared intergroup MAC: Minimal alveolar anesthetic concentration

reduction continued until the end of the third hour (p<0.05, p<0.01, p<0.001). The same changes were observed in the sevoflurane group starting at 45 minutes (p<0.05, p<0.01, p<0.001). The MAP values at 150 min, 165 min, and 180 min were significantly lower in the sevoflurane group than in the isoflurane group (p<0.05).

We observed only a minimal increase in ICP in the isoflurane group throughout the whole study period, but the rise did not differ significantly from baseline values (Figure 2). In contrast, ICP began to increase at 30 minutes in the animals receiving sevoflurane, and this elevation in pressure grew

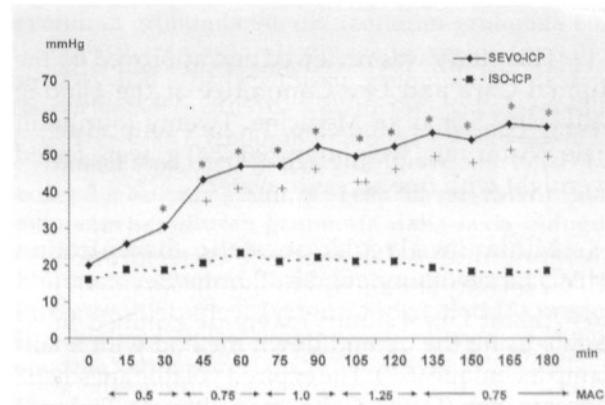


Figure 2: Mean changes in intracranial pressure (mmHg) with isoflurane and sevoflurane *p<0.05; **p<0.01; ***p<0.001, compared with control. +p<0.05; ++p<0.01, compared intergroup. MAC: Minimal alveolar anesthetic concentration

constantly to the end of the study period ($p < 0.05$). The differences between the groups with regard to ICP after 45 minutes were statistically significant ($p < 0.05$, $p < 0.01$).

Like MAP, CPP fell in both groups (Figure 3). The decrease began at 30 minutes in the isoflurane group ($p < 0.05$, $p < 0.01$, $p < 0.001$) and at 45 minutes in the sevoflurane group ($p < 0.01$, $p < 0.001$), and continued to the end of the third hour in both groups. The rate of decrease in CPP in the sevoflurane group was significantly greater than that observed in the isoflurane group ($p < 0.05$, $p < 0.01$, $p < 0.001$).

DISCUSSION

This study shows that both sevoflurane and isoflurane have similar impact on MAP, ICP, and CPP in rats that have sustained diffuse BI. As anesthetic concentrations rose, ICP increased and MAP and CPP decreased. However, the changes in the sevoflurane group were more pronounced than those seen in the isoflurane group. The MAC values of volatile anesthetics determined in this study are in agreement with those noted in previous studies (9,10).

Sevoflurane and isoflurane are commonly used volatile anesthetics. Both agents reduce MAP in dose-related fashion. Increasing concentrations of sevoflurane progressively decrease blood pressure in a manner similar to other volatile anesthetics, but the reported changes in MAP have varied when equianesthetic concentrations of isoflurane and

sevoflurane have been compared (11,12,13). In our study, the MAP reduction was similar in both groups, apart from the final 45 minutes of the study period. It has been reported that the decrease in arterial pressure results from a decrease in systemic vascular resistance rather than lower cardiac output (3,13,14,15). In the presence of intracranial hypertension, increasing the MAP seems to be beneficial in terms of improving CPP, but it has been shown that increases in blood pressure are often associated with further increases in ICP (16).

Animal experiments have demonstrated that isoflurane increases ICP minimally in normal subjects and in those with intracranial hypertension (15,17,18,19). However, a substantial increase in ICP has been reported when isoflurane and N_2O are used in combination (20). ICP elevation with 1% isoflurane was partially blocked by hypocapnia (5,20). Cerebral blood volume (CBV), which is an indirect measure of ICP, has been reported to be increased with the use of isoflurane, even during hypocapnia (22). Sevoflurane has similar effects to those of isoflurane with regard to $CMRO_2$, CBF, ICP, and the EEG. Scheller et al. (3) showed that, like isoflurane, increasing concentrations of sevoflurane (0.5, 1.5, and 2.15 MAC) had minimal effect on CBF but significantly reduced $CMRO_2$ in dogs. They also compared isoflurane and sevoflurane in rabbits, and determined that, despite causing no change in CBF and a decrease in $CMRO_2$ at 0.5-1.0 MAC, both anesthetics increased ICP (2). Sevoflurane and isoflurane at different MAC values (0.5, 1.0, 1.5, 2.0) caused cerebral arteriolar dilatation, as well as a decrease in CBF, in rats with high ICP; however, sevoflurane had a more profound effect at higher MAC values (21).

The literature contains several animal experiments that have compared the effects of volatile anesthetics on ICP following acute BI. Smith and Marque (23) observed that prolonged (5-hr) administration of isoflurane, halothane, or enflurane following cryogenic BI was associated with elevations of ICP above that associated with intravenous anesthetic techniques. Scheller et al. (19) also demonstrated that significant increases in ICP may occur following introduction of either 1 MAC halothane or isoflurane in the presence of acute cryogenic BI, resulting in elevated ICP. Kaieda et al. (17) compared the effects of halothane and isoflurane on ICP and the development of cerebral edema after cryogenic BI in rabbits. They observed ICP elevation in all animals. In the present study, the administration

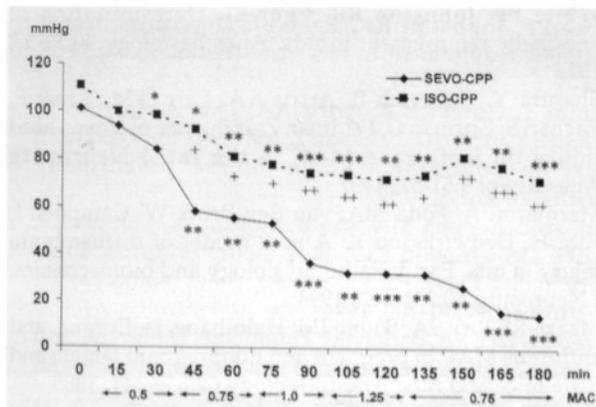


Figure 3: Mean changes in cerebral perfusion pressure (mmHg) with isoflurane and sevoflurane * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, compared with control. + $p < 0.05$; ++ $p < 0.01$ compared intergroup. MAC: Minimal alveolar anesthetic concentration

of isoflurane or sevoflurane at different MAC values (0.5, 0.75, 1.0, and 1.25) caused ICP to rise. In accordance with the results of previous studies, the ICP increase observed in the isoflurane group was less than that in the sevoflurane group. ICP increased progressively in the sevoflurane group, even though the sevoflurane concentration was reduced to 0.75 MAC during the last hour of the study period. These significant changes in MAP and ICP with sevoflurane caused a more pronounced decrease in CPP than that observed with isoflurane.

The inconsistency of experimental results to date can be explained in part by species differences and differences in experimental models, that is, intact versus injured brain. In this study, we opted to use the diffuse BI model. This simple, reproducible weight-drop model of rodent closed BI is capable of producing a graded traumatic BI without a focal lesion, a massive hypertensive surge, or excessive brainstem damage. It also produces a pronounced diffuse axonal injury consistent with features of human diffuse axonal injury (24).

The main limitation of our study was that we used sevoflurane and isoflurane in combination with N₂O and sodium thiopental. N₂O is a potent vasodilator that increases CBV and ICP (25,26,27,28); however, it is likely that the effects of N₂O on ICP are attenuated by prior administration of sodium thiopental.

There are several possible explanations for the observed difference in ICP alteration caused by these two agents. ICP increases in response to change in either CBF or Cerebrospinal fluid (CSF) volume. Isoflurane increases CBV but decreases CSF volume, and, therefore, prevents major increases in ICP (29). Isoflurane has no effect on CSF production rate, and is known to decrease resistance to the reabsorption of CSF in the dog (30). To date, the effect of sevoflurane on CBF has been reported, but the effects of this agent on CBV and CSF dynamics remain unclear. Based on its negligible influence on CBF, it is speculated that sevoflurane may increase CBV independent of changes in CBF, similar to the effect of isoflurane. A second possibility is that sevoflurane and isoflurane may have different effects on the formation and reabsorption of CSF. Also, the rate of edema development after traumatic BI may be another important factor. Thus, further studies are

required to identify the role of these factors in the changes in ICP that occur under sevoflurane anesthesia.

In conclusion, our findings show that, after sustaining diffuse BI, animals that receive sevoflurane have higher ICP than animals anesthetized with isoflurane. This suggests that, in the clinical setting, sevoflurane should not be chosen as an alternative to isoflurane for the anesthetic management of patients with diffuse BI.

Correspondence: Ender Korfalı

Uludağ University School of Medicine
Dept. of Neurosurgery
Görükle Bursa/Turkey
Phone: 0.225-442 80 81
Email : Tunev@uludağ.edu.tr

REFERENCES

1. Wallin RF, Regan BM, Napoli MD, Stern IJ: Sevoflurane: a new inhalational anesthetic agent. *Anesth Analg* 54:758-766, 1975
2. Scheller MS, Tateishi A, Drummond JC, Zornow MH: The effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of isoflurane in the rabbit. *Anesthesiology* 68:548-551, 1988
3. Scheller MS, Nakakimura K, Fleischer JE, Zornow MH: Cerebral effects of sevoflurane in the dog: comparison with isoflurane and enflurane. *Br.J Anaesth.* 65:388-392, 1990
4. Takahashi H, Murata K, Ikeda K: Sevoflurane does not increase intracranial pressure in hyperventilated dogs. *Br J Anaesth* 71:551-555, 1993
5. Scheller MS, Todd MM, Drummond JC: Isoflurane, halothane, and regional cerebral blood flow at various levels of PaCO₂ in rabbits. *Anesthesiology* 64:598-604, 1986
6. White PF, Johnston RR, Eger EI: Determination of anesthetic requirement in rats. *Anesthesiology* 40:52-57, 1974
7. Shapira Y, Gurevich B, Artru AA, Lam AM, Israel E, Zachari S, Gurman G, Feldman Z: Influence of closed head injury on isoflurane MAC in the rat. *J Neurosurg Anesthesiol* 9:51-57, 1997
8. Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K: A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. *J Neurosurg* 80:291-300, 1994
9. Mazze RI, Rice SA, Baden JM: Halothane, isoflurane, and enflurane MAC in pregnant and nonpregnant female and male mice and rats. *Anesthesiology* 62:339-341, 1985
10. Nakajima Y, Moriwaki G, Ikeda K, Fujise Y: The effects of sevoflurane on recovery of brain energy metabolism after cerebral ischemia in the rat: a comparison with isoflurane and halothane. *Anesth Analg* 85:593-599, 1997
11. Ebert TJ, Harkin CP, Muzi M: Cardiovascular responses to sevoflurane: a review. *Anesth Analg* 81:S11-S22, 1995

12. Manohar M, Parks CM: Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. *J Pharmacol Exp Ther* 231:640-648, 1984
13. Bernard JM, Wouters PF, Doursout MF, Florence B, Chelly JE, Merin RG: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. *Anesthesiology* 72:659-662, 1990
14. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K: Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. *Anesth Analg* 74:79-88, 1992
15. Crawford MW, Lerman J, Saldivia V, Carmichael FJ: Hemodynamic and organ blood flow responses to halothane and sevoflurane anesthesia during spontaneous ventilation. *Anesth Analg* 75:1000-1006, 1992
16. Kim HK, Zornow MH, Illievich UM, Strnat MA, Scheller MS: Sevoflurane versus halothane anesthesia after acute cryogenic brain injury in rabbits: relationship between arterial and intracranial pressure [see comments]. *J Neurosurg Anesthesiol* 6:260-264, 1994
17. Kaieda R, Todd MM, Weeks JB, Warner DS: A comparison of the effects of halothane, isoflurane, and pentobarbital anesthesia on intracranial pressure and cerebral edema formation following brain injury in rabbits. *Anesthesiology* 71:571-579, 1989
18. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. *Anesthesiology* 60:276-282, 1984
19. Scheller MS, Todd MM, Drummond JC, Zornow MH: The intracranial pressure effects of isoflurane and halothane administered following cryogenic brain injury in rabbits. *Anesthesiology* 67:507-512, 1987
20. Sakabe T, Nakakimura K: Effects of anesthetic agent and other drugs on cerebral blood flow, metabolism and intracranial pressure. In: *Anesthesia and Neurosurgery*, Cotrell JE, Smith DS (eds) 3rd Edition, Mosby Philadelphia, 1994 p149-74.
21. Lu GP, Elkholy W, Gibson JA, Saubermann AJ: Effects of sevoflurane vs isoflurane MAC on cerebral blood flow and microcirculation during intracranial hypertension. 87: A590, 1997
22. Archer DP, Labrecque P, Tyler JL, Meyer E, Trop D: Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. *Anesthesiology* 67:642-648, 1987
23. Smith AL, Marque JJ: Anesthetics and cerebral edema. *Anesthesiology* 45:64-72, 1976
24. Foda MA, Marmarou A: A new model of diffuse brain injury in rats. Part II: Morphological characterization. *J Neurosurg.* 80:301-313, 1994
25. Henriksen HT, Jorgensen PB: The effect of nitrous oxide on intracranial pressure in patients with intracranial disorders. *Br J Anaesth* 45:486-492, 1973
26. Moss E, McDowall DG: I.c.p. increases with 50% nitrous oxide in oxygen in severe head injuries during controlled ventilation. *Br J Anaesth.* 51:757-761, 1979
27. Sakabe T, Kuramoto T, Inoue S, Takeshita H: Cerebral effects of nitrous oxide in the dog. *Anesthesiology* 48:195-200, 1978
28. Reasoner DK, Warner DS, Todd MM, McAllister A: Effects of nitrous oxide on cerebral metabolic rate in rats anaesthetized with isoflurane. *Br J Anaesth.* 65:210-215, 1990
29. Artru AA: Relationship between cerebral blood volume and CSF pressure during anesthesia with isoflurane or fentanyl in dogs. *Anesthesiology* 60:575-579, 1984
30. Artru AA: Isoflurane does not increase the rate of CSF production in the dog. *Anesthesiology* 60:193-197, 1984