The Intracranial Pressure Effects of Isoflurane and Halothane Administered Following Cryogenic Brain Injury in Rabbits

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The intracranial pressure (ICP) responses to administration of either halothane or isoflurane were compared in New Zealand white rabbits following a standardized cryogenic brain injury. Animals were tracheally intubated and paralyzed, and background anesthesia was maintained with morphine sulfate and nitrous oxide. Following injury and attainment of an elevated and stable ICP, animals were divided into four groups. Animals in groups I and III were maintained normocapnic throughout the experiment and administered 1 MAC halothane or isoflurane, respectively. Group II and IV animals were made hypocapnic (Pa_{CO_2} = 20 mmHg) prior to the administration of either 1 MAC halothane or isoflurane, respectively. Monitored variables were mean arterial blood pressure, ICP (ventriculostomy), end-tidal (ET) CO_2, ET volatile anesthetic, the electroencephalogram, temperature, and arterial blood gases. Prior to producing the lesion, ICP was approximately 5 mmHg in all animals with no differences among groups. Sixty to ninety minutes after injury, ICP increased significantly to approximately 20 mmHg in all animals. Introduction of either halothane or isoflurane was associated with significant increases in ICP in all groups to approximately 30 mm Hg. These data suggest that further significant increases in ICP may occur following introduction of either halothane or isoflurane in the presence of acute brain injury and elevated ICP. Furthermore, these ICP increases may not be altered by the prior establishment of hypocapnia. (Key words: Anesthetics, volatile: halothane; isoflurane. Brain: cryogenic injury; intracranial pressure.)

HALOTHANE IS A POTENT cerebral vasodilator, and its administration to patients with intracranial pathology can lead to dangerous increases in intracranial pressure (ICP).[1] This occurs presumably because halothane increases cerebral blood flow (CBF) which leads to an increase in the volume of the intracranial contents.[2] Isoflurane may have theoretical advantages over halothane in this respect, because, when administered to normal animals or normal humans, it does not increase cerebral blood flow at end-tidal concentrations near 1 MAC if normocapnia is maintained.[3-6] Studies examining the effects of isoflurane and halothane on ICP in neurosurgical patients with elevated ICP have focused primarily

on patients with chronic processes, such as brain tumors, and not on acutely injured patients. In patients with tumors, it has been suggested that prior institution of hypocapnia will attenuate ICP increases normally seen with either isoflurane or halothane.[7,8] However, other authors have demonstrated that significant ICP increases can occur despite the presence of moderate hypocapnia in neurosurgical patients receiving isoflurane.[9] Animal studies have not helped clarify this issue, since direct comparisons of the effects of halothane and isoflurane on cerebral blood flow and intracranial pressure have been performed only in animals with normal, uninjured brains. We, therefore, compared directly the effects of these two volatile anesthetics during both normocapnia and hypocapnia on intracranial pressure when administered to animals with acutely injured brains and elevated ICP following a standardized brain injury.

Materials and Methods

Following review and approval of the protocol by the animal care committee, 36 New Zealand white rabbits were anesthetized with halothane. Following endotracheal intubation, halothane was discontinued and morphine sulfate (MS) 10 mg/kg and pancuronium 1 mg were administered intravenously. This was followed by an infusion of MS 2 mg · kg⁻¹ · h⁻¹ and pancuronium 1 mg · h⁻¹. The animals were ventilated with a tidal volume of 17 ml/kg at a rate of 30 breaths/min with 70% nitrous oxide (N_2O) in oxygen, and carbon dioxide was added to the inspired gases to maintain normocapnia. All surgical preparations were done following infiltration of the tissue with 0.25% bupivacaine. The scalp tissues were incised longitudinally and reflected laterally to expose the skull. A 2-mm burr hole was made 9 mm posterior to the coronal suture and 8 mm lateral to the sagittal suture over the right hemisphere. Through this hole, a 20-gauge spinal needle was stereotactically placed into the lateral ventricle to measure ICP, and the ICP transducer was zeroed at the level of the interaural line. An aluminum funnel with a neck diameter of 1 cm was fastened to the skull with epoxy glue. The funnel was centered 17 mm anterior to the inion and 6 mm lateral to the sagittal suture over the left half of the skull.

Simultaneous with the surgical preparation of the head, a catheter was placed into the right femoral artery

TABLE 1. Intracranial Pressures (mmHg)

	Pre-lesion	Post-lesion	During HV	During VA	
Group 1 N = 10 halothane	4.7 ± 1.5	21.4 ± 11.5*	—	30.2 ± 12.9†	
Group 3 N = 10 isoflurane	5.4 ± 1.5	19.5 ± 10*	—	29.5 ± 14.6†	
Group 2 N = 8 halothane	4.9 ± 2	20.4 ± 8.7*	18.1 ± 7.4‡	28 ± 10†	
Group 4 N = 8 isoflurane	5.3 ± 1.3	23.8 ± 9.4*	20.7 ± 8.6‡	30 ± 13†	

All data expressed as mean ± SD. HV = hyperventilation. VA = volatile anesthetic.

* Denotes significant increases in ICP following cryogenic lesion.

† Denotes significant increases in ICP following addition of either halothane or isoflurane. There were no differences between groups.

‡ Denotes significant decrease in ICP following establishment of hypocapnia.

for the measurement of blood pressure and sampling of arterial blood. Following surgical preparations, 3 cc of 3% Evans Blue dye was administered intravenously, and the animal was left undisturbed for an additional 45 min. In all animals, this insured that the end-tidal (ET) halothane concentration was less than 0.08%. Monitored variables were mean arterial pressure (MAP), ET CO_2, ET volatile anesthetic, temperature (servocontrolled to 37° C), arterial blood gases, and a bipolar fronto-occipital electroencephalogram (EEG).

Following the stabilization period, a cryogenic injury was produced by pouring liquid nitrogen into the funnel. After 1 min, the funnel was detached, and any remaining liquid was quickly removed by blowing on the exposed skull.

One hour after cryogenic injury, animals were evaluated for entry into the study. Animals were entered into the study at 60–90 min if they met the following criteria: 1) ICP was at least 10 mmHg, 2) cerebral perfusion pressure (defined as MAP-ICP) was at least 50 mmHg, 3) ICP had not increased more than 1 mm in the preceding 5 min, and 4) there was no EEG evidence of seizure activity at the time of volatile anesthetic administration. As noted in the Results section, short bursts of seizure activity were noted in some animals which required that we wait a few minutes until it spontaneously subsided before administering the volatile anesthetic. The animals were then assigned to receive halothane or isoflurane on a rotating basis. However, the studies on the normocapnic animals (groups I and III) were completed before those on the hypocapnic animals (groups II and IV). Animals assigned to groups I and III were maintained with Pa_{CO_2} in the normal range (38–42)

mmHg and 1 MAC¶ ET halothane or isoflurane (one anesthetic per animal) was introduced over 10 min. Once a 1 MAC ET value was achieved, it was maintained for 15 min. MAP was supported at pre-volatile anesthetic levels at all times with an intravenous infusion of angiotensin II. Animals in groups II and IV were made hypocapnic (Pa_{CO_2} 18–22 mmHg) by eliminating CO_2 from the inspired gas. Once hypocapnia had been achieved, 10 min was allowed to pass before introduction of 1 MAC halothane (group II) or isoflurane (group IV) in the same fashion as for group I and III animals. The highest ICP in the 15 min period following the achievement of 1 MAC, volatile anesthetic was recorded as the peak ICP. Animals were then killed with KCL, and the brains were removed and placed in formalin for later examination of the lesion.

Statistical analysis of the within group mean ICP values employed a repeated measures analysis of variance. Where indicated, paired t tests corrected for multiple comparisons were performed on the mean ICP values within groups. Within group ICP values before lesioning, 1 h after lesioning, following the induction of hypocapnia (groups II and IV), and the peak ICP following the addition of the volatile anesthetic were evaluated in this manner. Between group comparisons of ICP changes before and following the various experimental maneuvers utilized unpaired t tests to compare either the absolute values (*e.g.*, pre-lesion) or the magnitudes of the ICP changes between groups (all other comparisons). Cardiovascular and arterial blood gas data were similarly evaluated within and between groups. Angiotensin II doses were compared between those groups that received halothane (I and III) and those that received isoflurane (II and IV) at each level of Pa_{CO_2} with unpaired t tests. In all cases, $P < 0.05$ was considered to be statistically significant.

Results

Cardiovascular data, initial ICP, and arterial blood gases were not different among groups except for the expected alterations due to the institution of hypocapnia. Following cryogenic injury, but before the introduction of the volatile anesthetic, the ICP had increased significantly from approximately 5 mmHg to 20 mmHg in all four groups with no differences between groups (tables 1, 2). In all but a few animals, the ICP was stable and met the criteria outlined in Materials and Methods at 60 min. In the remaining animals, we waited until the

¶ MAC values for halothane and isoflurane in the New Zealand white rabbit have been previously determined in our laboratory according to the method of Eger.[10] The values were 1.39% and 2.05, respectively.[11]

TABLE 2. Cardiovascular and ABG Data

		MAP	Pao₂	Paco₂	pH	Angio
Group 1 HAL	PreLe	90 ± 8	142 ± 28	38 ± 2	7.45 ± .07	—
	VA	89 ± 8	138 ± 17	38 ± 2	7.48 ± .10	1.09 ± .32*
Group 3 ISO	PreLe	97 ± 15	151 ± 31	39 ± 1	7.42 ± .05	—
	VA	98 ± 12	151 ± 37	39 ± 2	7.43 ± .06	.65 ± .45
Group 2 HAL	PreLe	99 ± 10	183 ± 12	38 ± 2	7.43 ± .03	—
	VA	95 ± 6	179 ± 14	21 ± 2	7.57 ± .05	1.15 ± .21*
Group 4 ISO	PreLe	93 ± 14	175 ± 17	40 ± 2	7.43 ± .04	—
	VA	92 ± 13	171 ± 20	21 ± 2	7.59 ± .04	.37 ± .33

All data expressed as mean ± SD. PreLe = pre-lesion values; VA = values during volatile anesthetic; HAL = halothane group; ISO = isoflurane group; MAP = mean arterial pressure; Angio = angiotensin dose. MAP, Pao₂, and Paco₂ expressed in mmHg. Angiotensin

doses expressed in $\mu g \cdot kg^{-1} \cdot min^{-1}$.

* Denotes significant difference between halothane and isoflurane groups at each Paco₂ level (I vs. III, II vs. IV).

ICP met the criteria before proceeding with either administration of the volatile anesthetic (groups I and III) or the induction of hypocapnia (groups II and IV). Therefore, in these animals, the initial ICP (INIT in fig. 1) was slightly different than the 60 min ICP. In no animal did we need to wait longer than 90 min after lesioning to achieve the ICP criteria. The induction of hypocapnia in animals in groups II and IV reduced ICP

by 2–9 mmHg in all animals except one group II animal (halothane). The mean decreases in both group II and IV were significant when analyzed statistically. Following the administration of either halothane or isoflurane, the peak ICP achieved was significantly greater than the pre-volatile anesthetic ICP in all four groups with no differences among the groups (figs. 2, 3). The time course of the ICP rises in the various groups following

FIG. 1. ICP responses in animals subjected to a cryogenic lesion, the induction of hypocapnia (panels C and D), and the administration of either 1 MAC halothane (panels A and C) or isoflurane (panels B and D). INIT = initial ICP before the induction of hypocapnia (groups II and IV) or initial ICP immediately before addition of the volatile anesthetic (groups I and III). HV indicates ICP after induction of hypocapnia, but before the addition of the volatile anesthetic (groups II and IV). Double bars indicate where the time axis was not continuous. For example, "peak" ICP was not continuous along the time axis, but rather was the highest ICP observed following the achievement of a 1 MAC ET concentration. *Denotes significant increase in ICP compared to pre-lesion (TIME 0). @Denotes significant decrease in ICP compared to pre-hypocapnia (INIT). #Denotes significant increase in ICP compared to pre-volatile anesthetic (groups I and III INIT, groups II and IV HV).
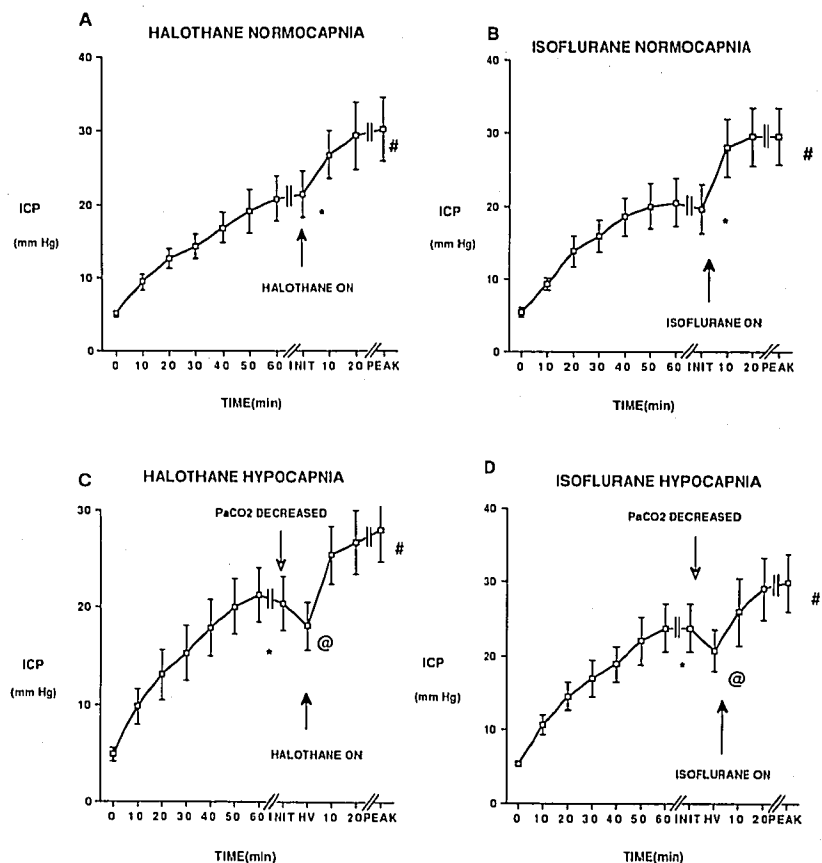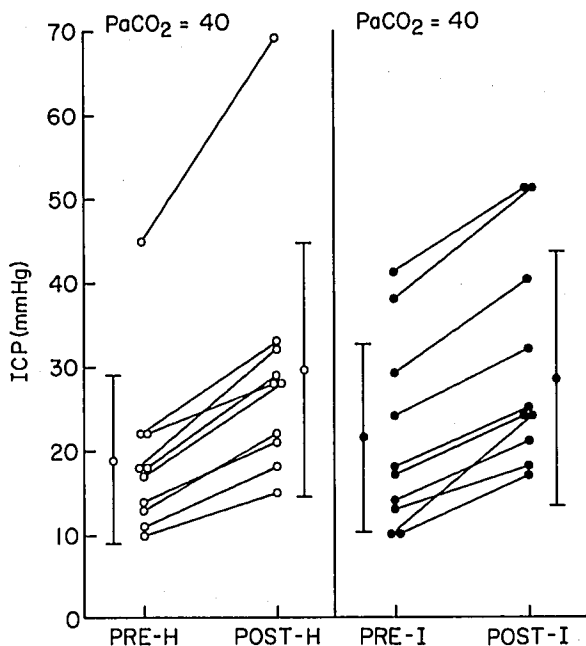
FIG. 2. ICP responses of individual animals to the administration of halothane (H) or isoflurane (I) during normocapnia (mean ± SD).

the addition of the volatile anesthetics are detailed in figure 1, panels A thru D. It can be seen that nearly all of the eventual rise in ICP in all four groups occurred by 10 min, the time at which 1 MAC ET concentration was generally achieved.

Angiotensin II doses were significantly greater in the groups (I and II) that received halothane compared to those that received isoflurane (III and IV) at the same Pa_{CO_2} level.
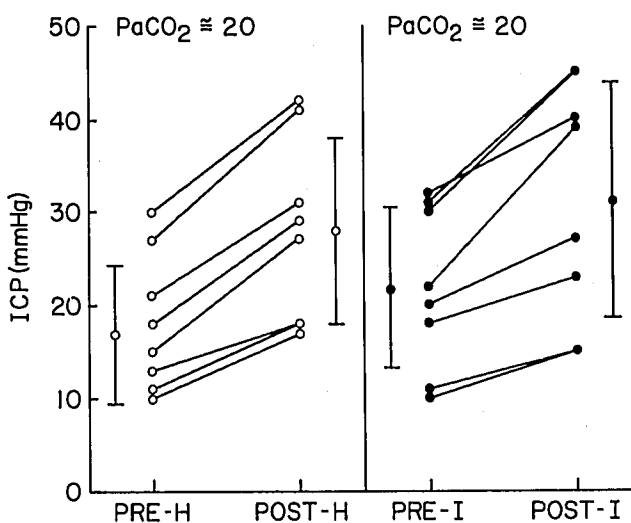

FIG. 3. ICP responses of individual animals to the administration of halothane or isoflurane during hypocapnia (mean ± SD).

At autopsy, a well-circumscribed, dark blue area was observed over the left cerebral hemisphere corresponding to the area of penetration of Evans Blue dye into injured brain. Measurements of the front-back and medial-lateral dimensions were not different in those animals receiving halothane and those receiving isoflurane, nor were there differences between the normocapnic and hypocapnic animals (fig. 4).

During the 1-min period of liquid nitrogen application, all animals demonstrated seizure activity (fig. 5). Seizure activity was noted occasionally during the 1-h waiting period following the lesion. This consisted of short bursts of activity lasting only a few seconds. Following the induction of hypocapnia in group II and IV animals, seizure activity recurred in some animals. Again, these were short bursts of activity which did not persist nor lead to status epilepticus in any of the animals. Animals receiving 1 MAC isoflurane had distinctively different EEG patterns compared to those receiving halothane. This has been described previously.[3] Generally, the EEG of the animals receiving 1 MAC isoflurane demonstrated a burst suppression pattern, whereas the EEGs of the animals receiving 1 MAC halothane remained active with some slowing.

Discussion

In this animal model of acute brain injury, the administration of either 1 MAC halothane or isoflurane to a rabbit receiving a MS/N_2O anesthetic caused significant increases in ICP regardless of whether or not hypocapnia had been previously established. There has been only one animal investigation comparing the effects of volatile anesthetics on ICP following acute cerebral injury. In that study, Smith and Marque determined that prolonged (5 h) administration of halothane, isoflurane, or enflurane following a cryogenic brain injury was associated with elevations of ICP when compared to intravenous anesthetic techniques.[12] They also demonstrated that cerebral white matter water content was greater in animals anesthetized with volatile anesthetics, and they concluded that this was the probable cause of the elevations in ICP. In the present study, the volatile anesthetic was added rapidly to the background anesthetic, and ICP increases were seen immediately in all four groups (fig. 1A–D). This is more consistent with a cerebrovascular effect rather than with edema formation. The other widely quoted studies in the anesthesiology literature that compare the effects of isoflurane and halothane on ICP were performed in humans with brain tumors or vascular malformations. These studies clearly showed that the inducement of hypocapnia simultaneously with the administration of isoflurane would offset any ICP increases, and that, in many pa-

tients, ICP would actually decrease. Furthermore, the prior establishment of hypocapnia abolished halothane induced ICP increases.[7,8] However, more recently, Grosslight et al. found that isoflurane could significantly increase ICP even during moderate hypocapnia in some patients with brain tumors.[9] Their observations suggest that hypocapnia may not prevent volatile anesthetic-induced increases in ICP in some patients with intracranial pathology.

Experimental cryogenic cerebral injury closely resembles a severe focal brain contusion in terms of blood-brain barrier breakdown and vasogenic cerebral edema formation.[13] The lesions in the present study were relatively uniform, judging by the homogeneity of their dimensions.

Although we attempted to pick a point in time at which the ICP had reached a plateau after lesioning before administering the volatile anesthetics, it is quite possible that some of the eventual ICP increases can be ascribed to the passage of time alone. Nonetheless, ICP increases were seen immediately following the introduction of the volatile anesthetic in all four groups, and the ICP elevations seen when 1 MAC ET concentrations were achieved after 10 min were very nearly equal to the peak ICPs observed in the ensuing 15-min period. Therefore, the passage of time and the natural progression of the lesion probably had a very small effect in terms of elevating the ICP soon after the introduction of the volatile anesthetic. Furthermore, because the time course of the introduction of the volatile anesthetic was the same in all animals, the effect of the passage of time was likely evenly distributed across all groups.

Previous work in our laboratory with normal rabbits has shown that 1 MAC halothane administered against a background of MS/N$_2$O anesthesia increased CBF equally during both normocapnia and hypocapnia.[3] Increases in CBF are generally associated with increases in cerebral blood volume (CBV), and, thus, increases in ICP might be expected to occur.[14] In that same study, however, 1 MAC isoflurane administered in the same fashion as was done in the present experiment did not alter CBF during normocapnia, and decreased CBF significantly when hypocapnia had been previously established. Thus, the increases in ICP seen during hypocapnia and the administration of isoflurane in the present experiment may appear paradoxical. Possible mechanisms for this effect may include an alteration of the normal CBF response to CO$_2$, a response known to be impaired frequently in humans who have sustained closed head injuries.[15] In the present experiment, induction of hypocapnia did successfully lower ICP in all but one animal, although the average reductions in ICP were slight or modest, perhaps suggesting impairment
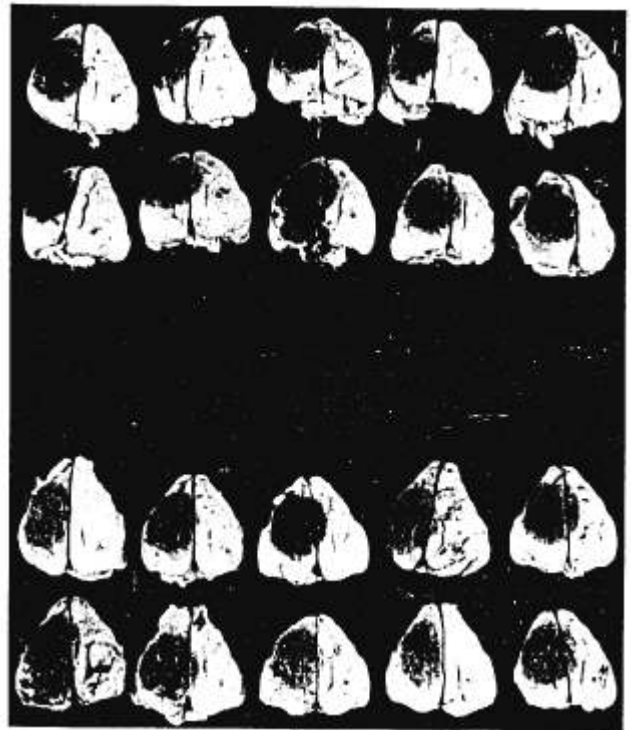

FIG. 4. The brains of animals given cryogenic injury centered over left hemisphere. Upper brains from animal given halothane (group 1). Lower brains from animals given isoflurane (group 3). Lesion sizes were the same in both groups.

of the CBF response to CO$_2$. Alternatively, the increases in ICP may be related solely to volatile anesthetic-induced increases in CBV and relatively independent of the effects of the volatile anesthetic on CBF. Although CBV responses to volatile anesthetics have not been studied in animals with injured brains, CBV increases following halothane and isoflurane have been shown to be the same in normal animals during normocapnia.[16,17]
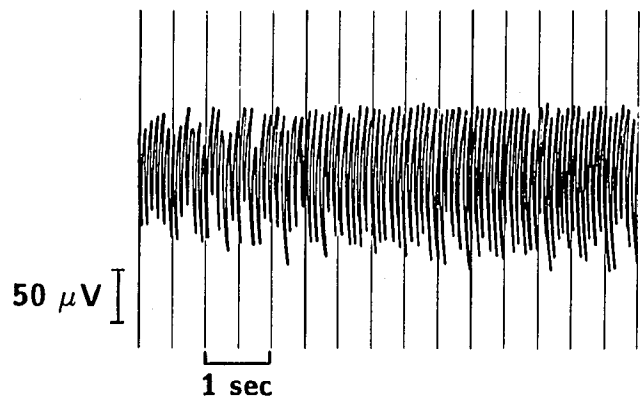

50 μV

1 sec

FIG. 5. Typical EEG recording during cryogenic injury showing clear cut seizure activity.

MS/N$_2$O anesthesia was essential to insure that the animals were treated humanely. Extensive experience with this anesthetic in our laboratory indicates that cardiovascular variables and CBF remain stable for prolonged periods of time.[3]

Angiotensin II was used to maintain MAP constant during the period of volatile anesthetic administration. Angiotensin II is a direct acting vasoconstrictor which, like other pressor agents, is known to affect cerebral as well as peripheral vessels, although its cerebral effects are thought to be modest.[18,19] Nonetheless, in comparing cerebrovascular effects of anesthetics, it is important to maintain blood pressure at equivalent levels in all groups, since anesthetics may affect autoregulation to different degrees. This has been demonstrated to be the case for halothane and isoflurane in cats.[4] At the same time, however, it must be kept in mind that the greater doses of angiotensin required in the halothane-anesthetized animals may have limited halothane-induced CBF or CBV increases. This might serve to artificially lower ICP compared to the isoflurane-anesthetized animals who received less angiotensin to maintain MAP.

In summary, following acute cryogenic cerebral injury resulting in an elevated ICP, the addition of 1 MAC halothane or isoflurane to a MS/N$_2$O anesthetic caused immediate further significant increases in ICP regardless of whether or not hypocapnia had been previously established when MAP was maintained at pre-volatile anesthetic levels. If these data are relevant to the practice of human anesthesia, they suggest that ICP responses to the administration of either halothane or isoflurane may not be substantially different, and that hypocapnia may not invariably attenuate these possibly deleterious ICP responses in patients with acute, rapidly progressive brain injury.

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