

## Halothane, Hypocapnia, and Cerebrospinal Fluid Pressure in Neurosurgery

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The effects of halothane and hypocapnia on cerebrospinal fluid pressure (CSFP) were examined in 48 patients undergoing craniotomy for tumors (36 patients) or vascular lesions (12 patients). All patients were hyperventilated to  $P_{aCO_2}$  levels less than 30 mm Hg (mean 26). Twenty-one patients (Group I) received halothane (0.5 to 1.0 per cent) simultaneously with the onset of hyperventilation, and 17 patients (Group II) received halothane (0.5 to 1.0 per cent) after hyperventilation had been established for 10 minutes. Large increases in CSFP occurred only in Group I (seven patients, mean increase = 260 mm H<sub>2</sub>O). Only small increases in CSFP occurred in Group II (10 patients, mean increase = 26 mm H<sub>2</sub>O). The pressure increases in all patients were transient (10 to 30 minutes). A third group (10 patients) was given Innovar in the absence of halothane, and no increases in CSFP occurred. The authors conclude that halothane is capable of increasing CSFP in patients with intracranial disease, but that these increases are transient and can be minimized or abolished by the prior induction of hypocapnia. (Key words: Halothane; CSF pressure; Hypocapnia; Neurosurgery.)

RECENT STUDIES by McDowall, Jennett, Barker, and Fitch<sup>1-4</sup> demonstrated that halothane may increase intracranial pressure, especially in patients with intracranial space-occupying lesions, and suggested that hypocapnia may not prevent such increases. A subsequent editorial<sup>5</sup> concluded that halothane may be contraindicated for intracranial surgery. The validity of this conclusion can be questioned, because in the patients studied by the McDowall group the levels of induced hypocapnia were inconstant, awake cerebrospinal fluid pressure (CSFP) was not measured, and the effect of halothane was observed for only 10 minutes. The present study was designed to examine the effect of continuous administration of halothane on CSFP at a constant level of hypocapnia induced either before or together with the introduction of halothane. In addition, the combined effect of droperidol, fentanyl, nitrous oxide, and hypocapnia on CSFP was examined.

### Materials and Methods

CSFP was measured continuously in 48 adult patients undergoing craniotomy for tumors (36 patients) or vascular lesions (12 patients). Patients were informed that a subarachnoid needle would be inserted and used for measurement of pressure and, if necessary, for removal of fluid during the surgical procedure. An hour after premedication (meperidine, 25 to 75 mg, and atropine, 0.4 mg), a 19-gauge malleable needle was placed in the lumbar subarachnoid space of each patient. With care to avoid the loss of CSF, the needle was connected to a saline-solution-filled catheter system, and the pressure was transduced by a calibrated strain gauge and recorded on a direct writer. The patient was placed in the position to be used for operation (supine or

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lateral), and the height of the strain gauge was adjusted, the midcranial level being used as the zero reference point. After awake baseline measurements (1 to 2 minutes), and without altering the position of the patient, anesthesia was induced with thiopental (200 to 500 mg), followed by succinylcholine (100 mg) and endotracheal intubation. Thereafter, muscle relaxation was maintained with gallamine triethiodide (100 to 200 mg), and the patient was hyperventilated with 60 per cent nitrous oxide and oxygen, using a Bird ventilator adjusted to produce  $P_{aCO_2}$  levels of 20 to 30 mm Hg, as determined by an IL blood-gas analyzer. Arterial and central venous pressures (CVP) were also transduced by strain gauges and were recorded from catheters inserted in the radial artery and superior vena cava, respectively. The patency of the CSF system between the head and lumbar subarachnoid space was confirmed at the start of each study by observing the expected increase in CSFP in response to passive elevation of the head and was reconfirmed at the end of the recording period by observing the pressure increase in response to digital pressure on the dura. Mean CSFP was calculated from the tracing as being diastolic CSFP plus one third the pulse pressure during the end-expiratory phase of respiration. Mean arterial pressure (MAP) was similarly derived.

The patients were divided into three groups, based on the random selection of one of three possible anesthetic-maintenance regimens. In Group I (21 patients), halothane (0.5 to 1.0 per cent inspired) was administered immediately after endotracheal intubation and simultaneously with the onset of hyperventilation. In Group II (17 patients), halothane (0.5 to 1.0 per cent inspired) was administered 10 minutes after endotracheal intubation and the onset of hyperventilation, when  $P_{aCO_2}$  levels of 20 to 30 mm Hg had been established. Group III (10 patients) received no halothane, but anesthesia was maintained with an initial intravenous injection of a combination of fentanyl and droperidol (1 ml of Innovar/20 to 25 lb) and intermittent supplemental injections of fentanyl (0.05 mg every 15 to 45 minutes). In every patient, CSFP was re-

corded continuously from prior to induction of anesthesia through removal of the bone flap.

The frequencies of CSFP increases of more than 50 mm H<sub>2</sub>O in the three groups were compared, and the significances of differences determined using the chi-square test. Significances of differences in CSFP, CVP, and MAP values were compared within and between groups using Student's *t* tests for paired and unpaired data, respectively.

### Results

The awake mean CSFP's were similar in the three groups and were essentially unchanged immediately after induction, intubation, and onset of mechanical ventilation. Thereafter, the responses of CSFP in the three groups differed. In Group I (fig. 1), with simultaneous onset of halothane and hyperventilation, CSFP increased in seven patients, and in each instance the increase exceeded 50 mm H<sub>2</sub>O (range 55 to 500 mm H<sub>2</sub>O). In Group II (fig. 2), with delayed administration of halothane (after 10 minutes of hyperventilation), small increases in CSFP occurred in 10 patients, exceeding 50 mm H<sub>2</sub>O in only one patient (to 90 mm H<sub>2</sub>O). The difference between the frequencies of CSFP increases of more than 50 mm H<sub>2</sub>O in the two groups is significant. In Group III (fig. 3), no increases in CSFP occurred after the use of Innovar, and in 8 of 10 patients, small statistically significant decreases were observed (table 1).

These differences were not related to identifiable differences in patient characteristics inadvertently caused by sampling error. The relative distributions by sex and age were approximately the same in all groups, as were the distributions of vascular lesions (in Groups I and II). Of the 48 patients studied, 12 (25 per cent) had vascular lesions. Of the 17 patients of Groups I and II in whom CSFP's increased after the introduction of halothane, 5 (29 per cent) had vascular lesions. As suggested in both figure 1 and table 2, the large increases in pressure in Group I tended to occur in patients with higher initial (pre-halothane) CSFP's, but this did not occur consistently. The degrees of hypocapnia achieved were similar in all groups, and none of the CSFP changes could be related to changes in

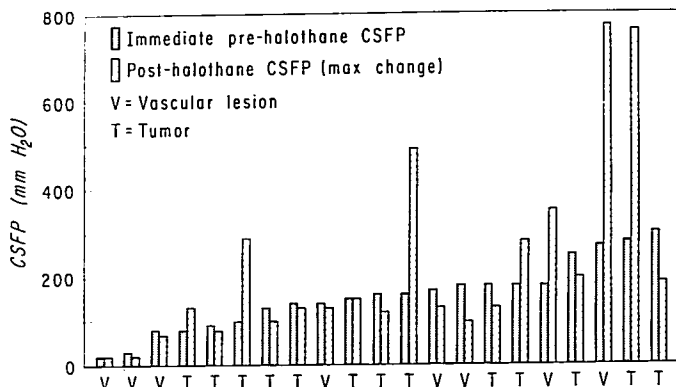


FIG. 1. Effect of halothane on CSFP when administered simultaneously with the onset of hyperventilation (Group I). In this and figures 2 and 3, each patient is represented by a paired bar indicating pre-halothane (or pre-Innovar) CSFP (solid bar) and the post-halothane (or post-Innovar) value at the time of maximal change in CSFP (hatched bar). Values are presented in sequence of increasing pre-halothane CSFP. Thirteen of these patients were operated on for discrete intracranial mass lesions (T) and the remainder, for vascular lesions (V). Large pressure increases after the use of halothane were observed in both types of patient. There was no relationship between pre-halothane CSFP and magnitude (or direction) of change in CSFP after halothane.

central venous pressure or mean arterial pressure (tables 1 and 2).

The temporal characteristics of the CSFP increases in Group I were similar in relation to the time of halothane introduction (fig. 4). The onset was always between 1 and 5 minutes after administration of halothane; peak pressure was achieved between 5 and 11 minutes; return to prehalothane pressures occurred between 10 and 31 minutes. The small pressure increases that occurred in Group II followed a similar pattern. As also shown in figure 4, brief increases in CSFP were commonly observed prior to halothane use and during induction in response to various stimuli (for example, application of the face mask, endotracheal intubation, and positioning). Such pressure increases were seen in all three groups, and at times were striking (table 3). Without exception, these CSFP increases were of brief duration (1 to 2 minutes), unpredictable, and easily explained after the fact. Neither the frequency nor the magnitude of CSFP increases at induction was greater in the patients who subsequently showed in-

creases after halothane use than in those who did not.

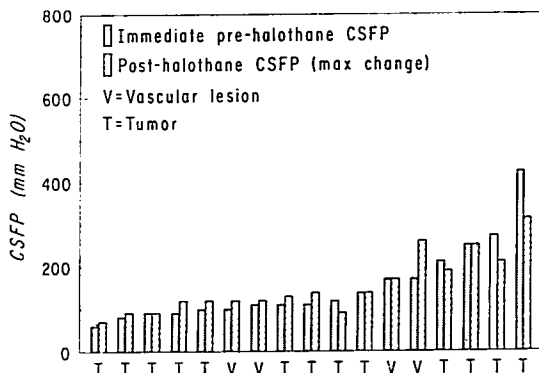
None of the 48 patients died, and no recognized complications resulted from the CSFP increases or from the subarachnoid punctures.

### Discussion

Our results support certain conclusions concerning the effect of halothane on CSFP in patients with intracranial vascular or mass lesions. As previously reported, halothane may cause large increases in CSFP, whereas Innovar will not.<sup>6</sup> Contrary to previous reports, halothane-induced increases in CSFP can be reduced markedly, and probably rendered insignificant, by establishing hypocapnia below 30 mm Hg before beginning the administration of halothane. Finally, the increases in CSFP that occur in response to halothane last only 10 to 30 minutes and are completely reversible despite the continued administration of halothane.

Two mechanisms may explain halothane-induced increases in CSFP. Originally, Marx *et al.*,<sup>7</sup> after comparing the percentage changes

FIG. 2. Effect of halothane on CSFP when administered 10 minutes after the onset of hyperventilation (Group II). Only small increases in pressure were observed in some patients after the use of halothane. The largest increase (90 mm H<sub>2</sub>O) occurred in a patient with a vascular lesion. There was no relationship between pre-halothane CSFP and CSFP increases after halothane.



in central venous pressure and CSFP, concluded that the effect of halothane on CSFP was ultimately the result of myocardial depression. However, in our study and in the study by Jennett *et al.*,<sup>4</sup> no significant change in central venous pressure occurred during halothane-induced CSFP increases. The current recognition that halothane has a cerebrovasodilating effect provides a more likely basis for the effects on CSFP. It is now well-documented that halothane, in the absence of changes in mean arterial pressure and  $P_{aCO_2}$ , increases cerebral blood flow,<sup>8,9</sup> and that there is a direct relationship among cerebral blood flow, cerebral blood volume, and CSFP.<sup>10-12</sup>

Because cerebral vessels remain responsive to change in  $P_{aCO_2}$  during halothane anesthesia,<sup>13</sup> the critical question is whether halothane-induced increases in CSFP can be rendered harmless by the addition of hypocapnia to levels that will predictably and sufficiently decrease cerebral blood flow and cerebral blood volume. In our patients, the simultaneous initiation of hyperventilation and introduction of halothane did not always prevent large (although transient) increases in CSFP, whereas the prior induction of hypocapnia consistently prevented such increases. This observation contrasts with that of the McDowall group, who reported that prior induction of hypocapnia was ineffective in preventing large increases in CSFP. The basis for such divergent results is not entirely clear. However, com-

parison of our protocol of study with that of Jennett and associates<sup>4</sup> reveals one striking difference. Jennett *et al.* intended to produce  $P_{aCO_2}$  levels of 35 to 45 mm Hg. Inadvertent hypothermia (commonly to below 35 C) necessitated correction of their blood-gas measurements such that, in many instances, corrected  $P_{aCO_2}$  values were below 35 mm Hg and hence were "hypocapnic." However, at temperatures other than 37 C "normal"  $P_{aCO_2}$  is not known.

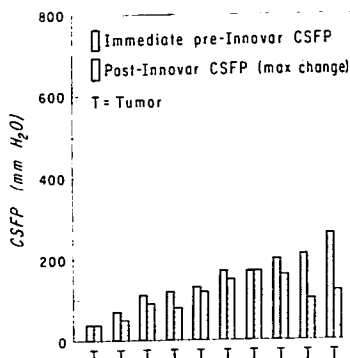


FIG. 3. Effect of Innovar on CSFP when administered simultaneously with the onset of hyperventilation (Group III). No increases in CSFP occurred. In eight patients, CSFP decreased. The greatest decreases occurred in patients with the highest pre-Innovar CSFP's.

TABLE 1. Cerebrospinal Fluid Pressures, Central Venous Pressures, Mean Arterial Pressures, and  $P_{aCO_2}$ 's (Mean  $\pm$  SE) of 48 Patients

	Condition	Number of Patients	Awake CSFP (mm Hg)	Postinduction						
				Initial Values (Before Halothane or Innovar)			Values at Maximal $\Delta$ CSFP (After Halothane or Innovar)			
				CSFP (mm Hg)	CVP (mm Hg)	MAP (mm Hg)	CSFP (mm Hg)	CVP (mm Hg)	MAP (mm Hg)	Preop. 10 Minutes after Hyperventilation (mm Hg)
Group I	Halothane; hypocapnia	21	175 $\pm$ 20	156 $\pm$ 17	3 $\pm$ 1	96 $\pm$ 4	221 $\pm$ 46	4 $\pm$ 1	88 $\pm$ 4	26 $\pm$ 1
Group II	Hypocapnia; halothane	17	172 $\pm$ 19	152 $\pm$ 22	5 $\pm$ 1	88 $\pm$ 7	155 $\pm$ 17	5 $\pm$ 1	80 $\pm$ 7	20 $\pm$ 1
Group III	Innovar; hypocapnia	10	169 $\pm$ 33	148 $\pm$ 21	8 $\pm$ 2	89 $\pm$ 5	110* $\pm$ 15	8 $\pm$ 3	81 $\pm$ 5	26 $\pm$ 1

\* Significantly different from awake CSFP.

† Significantly different from initial postinduction CSFP.

TABLE 2. Cerebrospinal Fluid Pressures, Central Venous Pressures, Mean Arterial Pressures, and  $P_{aCO_2}$ 's (Mean  $\pm$  SE) of the 17 Patients with Postinduction Increases in CSFP

	Condition	Number of Patients	Awake CSFP (mm Hg)	Postinduction							Mean $P_{aCO_2}$ after Hyposp. ventilation (mm Hg)
				Initial Values (Before Halothane)				Values at Maximal $\Delta$ CSFP (After Halothane)			
				CSFP (mm Hg)	CVP (mm Hg)	MAP (mm Hg)	CSFP (mm Hg)	CVP (mm Hg)	MAP (mm Hg)		
Group I	Halothane; hypocapnia	7	204 $\pm$ 38	179 $\pm$ 29	3 $\pm$ 1	101 $\pm$ 7	438* $\pm$ 63	4 $\pm$ 1	91 $\pm$ 11	28 $\pm$ 2	
	Hypocapnia; halothane	10	140 $\pm$ 21	112† $\pm$ 12	5 $\pm$ 1	92 $\pm$ 10	138† $\pm$ 18	6 $\pm$ 1	91 $\pm$ 11	27 $\pm$ 1	

\* Significantly different from awake CSFP.

† Significantly different from initial postinduction CSFP.

‡ Significantly different from Group I value.

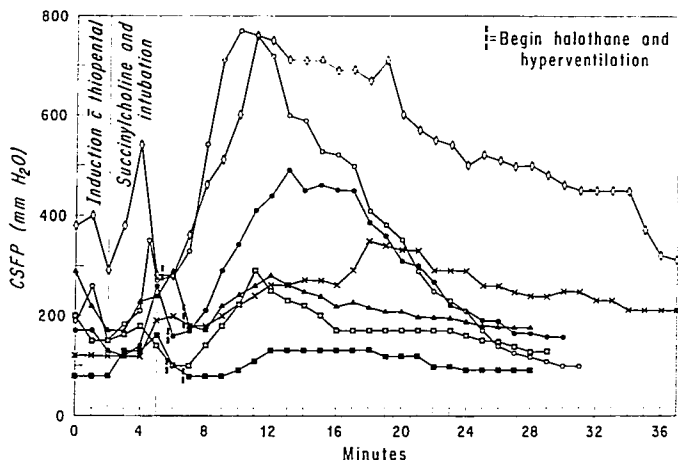


FIG. 4. CSFP changes in the seven patients of Group I who had halothane-induced CSFP increases. CSFP is plotted individually from prior to induction of anesthesia with thiopental to the time of return of CSFP to pre-halothane levels. During induction of anesthesia, variable brief CSFP increases occurred in response to placement of the face mask (zero time), administration of succinylcholine, and endotracheal intubation. With simultaneous administration of halothane and onset of hyperventilation, CSFP increased during a 5-minute period and then spontaneously returned to pre-halothane levels within 30 minutes.

and therefore the  $\text{CO}_2$  tension at which the cerebral vascular resistance is "normal" is not known. Thus, those patients of Jennett and associates' study who were considered hypocapnic because of hypothermia perhaps were not hypocapnic as regards the response of the cerebral vessels.

Another apparent difference relates to patient selection, inasmuch as Jennett *et al.*<sup>4</sup> studied only patients with space-occupying lesions (neoplasms, abscesses, and hematomas), whereas we included patients with vascular lesions (recently-ruptured aneurysms) in whom neurologic deficits were present. However, our results indicate that vascular lesions which produce deficits of the central nervous system have a potential equal to that of space-occupying lesions for developing excessive increases in CSFP during halothane anesthesia. We conclude that the edema resulting from a vascular insult to the brain is space-occupying in its own right or, alternatively, that normal

autoregulation of the cerebral vasculature in these patients is somehow altered.

In our study the time intervals between introduction of halothane, onset of pressure increase, achievement of peak pressures, and return toward control were similar to those found by McDowall *et al.*<sup>1</sup> in normal dogs. In all of our patients with halothane-induced pressure increases, the pressures returned spontaneously to control levels between 10 and 31 minutes after halothane was introduced despite continued administration. In Jennett and associates' study,<sup>4</sup> halothane was administered for only 10 minutes, and, therefore, spontaneous return of CSFP to control levels was not observed. McDowall and associates<sup>1</sup> suggested explanation for their observation in the dog was that cerebral blood flow and volume may have subsequently decreased after an initial vasodilation because they observed that cerebral venous pressure decreased in parallel with CSFP. An alternative explana-

TABLE 3. Increases in Cerebrospinal Fluid Pressure during Induction of Anesthesia among 48 Patients

Increases (mm H <sub>2</sub> O)	Number of Patients
0-10	7
10-100	16
100-200	11
200-300	6
300-400	2
400-500	3
500-600	3
	—
	TOTAL 48

tion might be that a slowly-compensating decrease in CSF volume occurs in response to the sudden increase in cerebral blood flow and CSFP.

Clinically, the potential hazard of a sudden increase in intracranial pressure in the patient with a space-occupying lesion cannot be ignored, whether caused by induction of anesthesia or by administration of a volatile anesthetic. Fortunately, neither our patients nor the patients studied by McDowall's group<sup>1</sup> suffered any apparent ill effects as a result of the transient increases in pressure. The capacity to compensate for sudden changes in intracranial volume is necessarily decreased and possibly exhausted in patients with space-occupying lesions. If an increase in pressure occurs while the skull is unopened, the risk of internal herniation of the brain is increased. A further source of complication from increased intracranial pressure is a decrease in perfusion pressure, enhanced by a simultaneous decrease in arterial pressure that may accompany general anesthesia. Although in humans there is no established "critical" perfusion pressure below which autoregulation ceases to function (this certainly must vary with age and extent of cerebrovascular disease), Zvetnow and associates<sup>14</sup> demonstrated biochemical evidence of hypoxia in dogs when perfusion pressure was reduced to between 50 and 60 mm Hg for prolonged periods. Jennett and associates<sup>4</sup> correctly pointed out that this experimental evidence should not be hastily compared to the clinical situation with halothane, because it is presumably the increase in blood flow itself that is causing the increase

in CSFP. If this reduces cerebral blood flow, then the pressure will necessarily decrease and, to a point, the system might be self-regulating. With the skull open, the major hazards of increased intracranial pressure are external herniation of the brain, increased bleeding, and difficult or impossible operating conditions.

The occurrence of sudden CSFP increases in response to halothane administration, observed in this study, was not predictable and was apparently unrelated to preanesthetic CSFP levels. Such unpredictability is probably explained by the fact that CSFP changes little with a gradual increase in the volume of one of the intracranial compartments so long as compensatory decreases in the volumes of the other two compartments are possible. Thus, measurement of awake CSFP would not be expected to reflect approaching decompensation. However, when compensatory mechanisms are exhausted, even small increases in intracranial volume cause large increases in pressure. Presumably, the seven patients in Group I who showed halothane-induced CSFP increases were approaching decompensation, whereas the other patients in the group were not. That prior hyperventilation predictably decreases or abolishes halothane-induced CSFP increases suggests that a reduction in cerebral blood volume sufficient to balance the subsequent increase in volume produced by halothane occurs in response to hypocapnia.

The CSFP increases observed during induction of anesthesia, although of brief duration, were common in our patients and, on occasion, of striking magnitude. This is not a new observation; it was discussed in 1954 by Stephen *et al.*<sup>15</sup> Although our study was designed to examine a question of current concern regarding the effect of halothane on intracranial pressure in neurosurgical patients, our observations clearly demonstrated the equal, or perhaps greater, importance of other factors critical in the management of these patients. The long-recognized principles in neuroanesthesia of smooth induction, adequate relaxation, proper positioning, and adequate anesthetic depth are indeed valid and will remain so regardless of the anesthetic selected for maintenance.

Innovar is effective in preventing increases in intracranial pressure during maintenance of anesthesia, and currently is considered by many to be the best anesthetic for patients with space-occupying lesions. At the same time, halothane has lost favor and is commonly believed to be contraindicated for such patients. It is our conclusion that, if hypocapnia is established initially, halothane is not contraindicated in patients with intracranial mass lesions, and in some circumstances it may be the most appropriate anesthetic available.

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### Respiration

**NEBULIZATION IN PULMONARY DISEASE** Ultrasonically nebulized mist, with a median particle diameter of  $5.0 \pm 1.6 \mu\text{m}$  and a mist density of about 50 mg H<sub>2</sub>O/l air, was administered by mist tent for 15 minutes to 20 normal children, 20 children with cystic fibrosis, and 20 children with bronchial asthma. No child was given any bronchodilator drug or showed any acute exacerbation of pulmonary disease on the day of testing. Half of each group inhaled orally and half, nasally. Maximum expiratory flow volume curves were made using a wedge spirometer; airway resistance and thoracic gas volume were measured by body plethysmography. Forced expiratory flow (FEV), maximum ex-

piratory flow ( $\dot{V}_{\text{max}}$ ), expiratory flow at 25 and 50 per cent of vital capacity ( $\dot{V}_{25}$  and  $\dot{V}_{50}$ ) and specific airway resistance ( $\text{sR}_{\text{aw}}$ ) were calculated. The normal children showed a slight but significant decrease in  $\text{sR}_{\text{aw}}$  when breathing mist nasally. Children with cystic fibrosis showed no significant change in any measurement after inhalation of mist. Asthmatic children showed a significant increase in  $\text{sR}_{\text{aw}}$  and significant decreases in all flow measurements and in forced vital capacity. The last measurement suggested air trapping. (Barker, R., and Levison, H.: *Effects of Ultrasonically Nebulized Distilled Water on Airway Dynamics in Children with Cystic Fibrosis and Asthma, Pediatrics* 80: 396-400, 1972.)