Hyperventilation in Craniotomy for Brain Tumor

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The effect of the method of pulmonary ventilation on cerebrospinal fluid pressure (CSF), brain tension, and blood gas changes was investigated in 20 patients undergoing craniotomy for brain tumor. Five different methods of ventilation were successively employed in the same patient during halothane/oxygen anesthesia. Assisted ventilation gave the highest values for CSF pressure (average = 238 mm. of water). Intermittent positive pressure breathing caused a moderate fall in CSF pressure (mean = 212 mm. of water). Positive-negative pressure breathing at minute volumes equal to or less than 15 liters per minute resulted in the lowest values for CSF pressure (mean = 115 mm. of water), and clinically was associated with a slack brain. When a minute ventilation volume greater than 15 liters per minute was employed, CSF preessure tended to rise (mean = 179 mm. of water), while the brain became tight and congested. This occurred in spite of respiratory alkalosis and a negative phase during expiration. Large ventilatory volumes were also associated with a progressive increase in cerebral arterial-venous oxygen difference and fall in oxygen saturation of blood sampled from the sagittal sinus. The data indicate that brain tension and CSF pressure can be modified by varying the method of ventilation under halothane/oxygen anesthesia.

ESSENTIAL to the proper conduct of operations for brain tumor is the control of brain mass. Drainage of cerebrospinal fluid from the spinal subarachnoid space and ventricles, intravenous administration of hypertonic solutions, urea, and mannitol, hypothermia, and induced hypotension have all, singly or in combination, assisted in the attainment of this objective. Ideally, however, procedures that are immediately controllable are preferred. Specifically, it is a distinct advantage to employ techniques which can be instituted, terminated, and reinstituted at will during the operative procedure with predictable results. Pulmonary hyperventilation seems to possess these attributes when properly employed. Recent reports, however, have cast some doubt on its efficacy [1, 2]; and in our experience, the desired effects were not achieved at all times. For this reason, the present study was undertaken to define the optimal ventilatory pattern that would attain effective reduction in brain volume. Five methods of ventilation were evaluated in each patient during craniotomy for brain tumor. The findings obtained constitute the basis of this report.

Methods

Twenty patients were studied. Their ages ranged from 20 to 65 years. After receiving atropine sulphate 0.4 mg. hypodermically preoperatively, anesthesia was induced with thiopental (150–250 mg.), succinylcholine (40–60 mg.) and following ventilation with oxygen, intubation of the trachea was accomplished. Halothane and oxygen were administered through a Copper Kettle (Foregger) vaporizer in a partial rebreathing system. During the steady state of anesthesia, the concentration of halothane in oxygen was kept between 1.5 and 2.0 per cent. A large bore plastic catheter was introduced into the cephalic or the basilic vein. In patients No. 9, 10, 12, a number 14 gauge 24-inch long radio-opaque polyethylene catheter was inserted into an antecubital vein, advanced well within the thoracic inlet, and connected to a water manometer. The position of the catheter was

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ascertained by the fluctuation of the meniscus with each respiratory cycle during measurements. A malleable needle was placed in the lumbar spinal subarachnoid space (L3-L4). This was connected to a water manometer for registration of the cerebrospinal fluid pressure with the level of the right atrium as the zero point. Cerebrospinal fluid pressures were recorded before changes in position and before changes in pattern of ventilation. Control pressure measurements before anesthesia were not obtained.

The lungs of each patient were ventilated according to 5 respiratory patterns: spontaneous, assisted, intermittent positive pressure, positive-negative pressure I (PNPB I = minute volume equal to or less than 15 liters per minute), and positive-negative pressure II (PNPB II = minute volume greater than 15 liters per minute). Each breathing pattern period lasted 20 minutes with the exception of the spontaneous pattern which was limited to 10 minutes. Controlled respiration was carried out with a timed-cycled pressure generator ventilator (Jefferson) after the patient had been paralyzed with either succinylcholine or *d*-tubocurarine. During controlled ventilation (IPPB-PNPB I and PNPB II) patients were respired at a rate of 16 breaths per minute with a phasing of 1 to 1.5 inspiratory:expiratory ratio. Airway pressures were measured at the level of the carina by means of a wide bore polyethylene catheter of 32 cm. in length and 0.3 cm., inside diameter, and connected to an aneroid manometer. The values were read in centimeters of water. The catheter was introduced through the endotracheal tube and advanced 1 cm. beyond the distal end of the tube. To counteract the effect of increased airway pressure and to enhance cerebral ve-

TABLE 1. Data during Various Respiratory Patterns in 20 Patients

Data	Spontaneous Respiration	Assisted Respiration	Intermittent Positive Pressure Breathing	Positive Negative Pressure Breathing I (mv = 15 lpm)	Positive Negative Pressure Breathing II (mv = 15 lpm)
$Paco_2$					
N	14	17	18	20	16
$\bar{X}$	39.3	29.8	25.2	20.4	19.9
Pao_2					
N	7	15	16	16	14
$\bar{X}$	96.2	343.7	382.6	413.5	419.9
Arterial pH					
N	14	17	18	20	16
$\bar{X}$	7.38	7.47	7.55	7.62	7.63
CSF px					
N	17	19	19	20	16
$\bar{X}$	231	238	212	115	179
Minute volume					
N	14	17	18	20	16
$\bar{X}$	6.36	9.52	13.76	12.89	19.49
Airway pressure					
N	12	18	18	18	16
Peak insp. px					
$\bar{X}$	−2	+13.7	+13.1	+11.1	+14.5
Peak exp. px					
$\bar{X}$	+1	+ 1.7	0	− 8	− 8.2

N = number of observations; $\bar{X}$ = mean values; Peak insp. px = Peak inspiratory pressure; Peak exp. px = Peak expiratory pressure; CSF px = Cerebrospinal fluid pressure.

Mean of $Paco_2$ in mm. Hg, Pao_2 in mm. Hg, arterial pH, CSF px in mm. H_2O, minute volume in liters per minute and tracheal airway pressures in cm. H_2O.

nous drainage all patients were placed in a 25 to 35 degree head-up tilt.

Samples of arterial blood were drawn intermittently in heparinized syringes via a needle placed in the radial or brachial artery. The syringes were capped, iced, and measurements made in duplicate within 60 minutes. The *p*H, P_{CO_2}, and P_{O_2} were determined by means of an Instrumentation Laboratory electrode system. The electrodes were calibrated before and after each determination with previously analyzed gases and 7.384 buffer as supplied by the Instrumentation Laboratory.

Body temperature was measured intermittently through the nose into the nasopharynx. This reading reflects closely brain temperature.[3] The mean nasopharyngeal temperature was 35.9° C.

In order to ascertain to what degree prolonged hyperventilation would affect cerebral oxygenation and blood flow, simultaneous arterial and sagittal sinus samples of blood were drawn in 5 unselected patients 30 and 60 minutes after the start of hyperventilation by positive-negative pressure breathing and following craniotomy. Blood was drawn from the sagittal sinus in preference to the internal jugular vein since it more accurately reflects cerebral venous oxygen saturation.[4, 5] In addition to the determination of arterial *p*H, P_{CO_2}, and P_{O_2}, the samples were analyzed for oxygen saturation and content using the manometric method of Van Slyke and Neil. Oxygen saturation was derived from the oxygen capacity and content, cognizance being given to dissolved oxygen, temperature, and barometric pressure. Control blood studies from the sagittal sinus were not available in this type of patient.

Intravenous infusions were limited to Ringer's solution (60–80 gtts./minute) and blood when necessary.

Data were transformed to logarithms for statistical analysis. The Tukey-Kramer method for multiple tests adjusted for multiple variances was used in order to make any and all comparisons among several means.[6] In addition, the observations of the operating surgeon were recorded. Particular note was made of scalp, bone, and epidural bleeding, the relative tension of the unopened dura, bulging or recession of the exposed brain, and degree of capillary ooze from the incised brain surface.

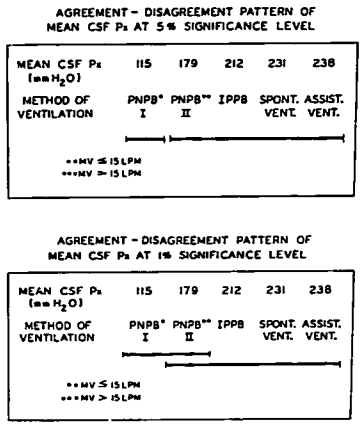

FIG. 1. Methods of ventilation arranged in order of increasing mean cerebrospinal fluid pressure. The 5 per cent level is an accepted value of statistical significance in clinical investigation.

Results

The data are summarized in table 1. In figure 1 the methods of ventilation are arranged in order of increasing mean cerebrospinal fluid pressure. Any two methods listed above the same line are considered to be the same within a sampling error; those not, differ at the stated level of significance. Analysis was carried out at the 5 and 1 per cent levels of significance.

PNPB I (minute volume equal to or less than 15 liters per minute) differed significantly from all other methods of ventilation at the 5 per cent level of significance. At this level the other four methods were similar within sampling error. The analysis at the 1 per cent level of significance, a more strict criterion with greater statistical significance, was used to determine the degree of difference between PNPB I and PNPB II. At the 1 per cent level of significance, PNPB I did not differ from PNPB II, but differed significantly from the other methods of ventilation.

TABLE 2. Correlation between Blood Gas Analysis and Clinical Observations after 30 and 60 Minutes of Hyperventilation

Patients	Art. P_{O_2}	Art. P_{CO_2}	Art. pH	Art. O_2 Cont. (vol. %)	Venous (S) Cont. (vol. %)	A-V O_2 Cont. (vol. %)	Ven. Sat. (S) (%)	Ventilation Volume (liters per minute)	Clinical Observations
#9	284	14.8	7.63	22.05	6.53	15.52	42.2	MV = 19	BP = 80/60 CSF = 350 mm. H_2O C. V. Px = 120 mm. H_2O Epidural bleeding Relaxed brain
	333*	14.2*	7.67*	22.30*	7.24*	15.06*	46.08*	MV = 24	
#10	494	25.7	7.56	21.70	12.01	9.69	69.5	MV = 19.2	BP = 70/40 CSF Px = 170 mm. H_2O C. V. Px = 90 mm. H_2O Tight brain Epidural bleeding
#11	578	18.8	7.63	15.42	8.50	6.92	52.2	MV = 16	BP = 90/60 CSF Px = 180 mm. H_2O Relaxed brain
#12	550	21.8	7.59	13.25	6.57	6.50	31.9	MV = 16	BP = 90/60 CSF Px = 90–100 mm. H_2O C. V. Px = 85 mm. H_2O Epidural bleeding
	567*	15.9*	7.67*	13.48*	6.27*	7.21*	35.2*	MV = 16	
#13	305	24.5	7.49	16.95	10.94	6.01	57.3	MV = 12	BP = 80/60 CSF Px = 120 mm. H_2O Slack brain
	284*	24.0*	7.50*	17.69*	11.40*	6.29*	59.6*	MV = 14	

* Samples retaken after one hour of hyperventilation.

BP = Arterial blood pressure; CSF Px = Cerebrospinal fluid pressure; C. V. Px. = Central venous pressure in mm. H_2O; S = Sagittal sinus.

Body tilt up 25 to 30 degrees; halothane 1.5 per cent/O_2; positive negative pressure breathing.

For each respiratory pattern the mean values for cerebrospinal fluid pressure (in mm. of water) were plotted against the arterial P_{CO_2} (in mm. of mercury) in order to determine the correlation between ventilation, arterial P_{CO_2}, and cerebrospinal fluid pressure. During spontaneous respiration, cerebrospinal fluid pressure remained high (mean = 231 mm. of water). Assisted respiration was associated with the highest values for cerebrospinal fluid pressure (mean = 238 mm. of water) in spite of a low Pa_{CO_2}. Intermittent positive pressure breathing resulted in lower cerebrospinal fluid pressure with a clustering of values around 200 mm. of water (mean = 212). In all three methods of ventilation, no correlation was found between cerebrospinal fluid pressure and the observed P_{CO_2}. Positive-negative pressure breathing I (MV $\leq$ 15 liters per minute) gave the lowest values for cerebrospinal fluid pressure (mean = 115 mm. of water). The average minute volume was 12.8 liters per minute. When patients were respired with positive-negative pressure breathing II (MV greater than 15 liters per minute), cerebrospinal fluid pressure tended to rise (mean = 179 mm. of water). Since the only variant was the respiratory pattern, the lack of correlation between cerebrospinal fluid pressure and the observed Pa_{CO_2} indicates that the pattern of ventilation may alter cerebrospinal fluid pressure.

The methods of ventilation were changed at random during surgery, and the clinical effects were observed and evaluated by the surgeon who did not know which type of ventilatory pattern was being used at that time. The following observations were made: assisted ventilation was often associated with increased bleeding either from the scalp or bone

when compared with intermittent positive pressure breathing or positive-negative pressure breathing I; when employed from the time of trephination, assisted ventilation resulted in significant bone oozing, epidural bleeding, and a tight dura to the point that it was necessary to change the method of ventilation in order to modify these conditions. A persistent residual positive pressure was also noted during the expiratory phase (mean = + 1.7 cm. of water).

Optimal operative conditions were produced when patients were ventilated with PNPB I (MV $\leq$ 15 liters per minute). Here conditions of the brain varied from moderate to marked relaxation with an absence of epidural bleeding or bone oozing.

In table 2 the relation among blood gas values, ventilation, and clinical observation is detailed. When the minute volume was greater than 15 liters per minute, there was epidural bleeding and brain swelling. In these patients there was a moderate to marked respiratory alkalosis. In 3 patients the monitored central venous pressure, though increasing from a control range of 35 to 45 mm. of water, remained within its upper limits (table 2). In 2 patients the sagittal sinus oxygen saturation fell below 50 per cent. In figure 2, an attempt was made to correlate ventilatory volume and cerebral arterio-venous oxygen differences. Although limited to only 8 observations, minute volumes greater than 16 liters per minute seemed to be associated with a steep rise in the cerebral arterio-venous oxygen difference. Clinically, these were associated with a congested and bulging brain.

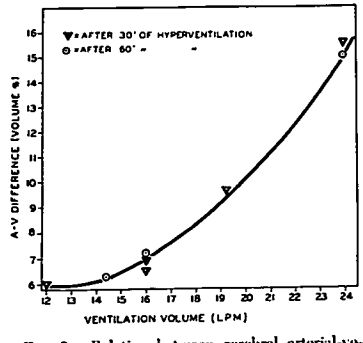

FIG. 2. Relation between cerebral arterial-venous oxygen content and ventilation volume in 5 patients. Blood samples were withdrawn at 30 and 60 minutes after hyperventilation.

Discussion

Methods for reducing brain mass act by modifying one or more of the following components: cerebrospinal fluid volume and pressure, content of the intracellular and extracellular fluid, and intravascular volume.[7] Techniques of hyperventilation are presumably effective primarily because of reduction of volume in the intravascular compartment resulting from hypocapnic vasoconstriction. On the other hand increase in volume in the intravascular compartment may occur as a result of dilatation of cerebral vasculature (arteries and capillaries) or dilatation of cerebral veins as a result of a decrease in the velocity of flow or impaired venous drainage. Since the venous system contains approximately two thirds of the total cerebral blood volume,[8] it can be expected that alterations here may play a role in determining the effect of any measure in reducing brain mass.

In spontaneous respiration the increase in intrathoracic volume caused by the expansion of the chest and descent of the diaphragm creates an intrathoracic pressure negative to the atmospheric. Air flows into the lungs and venous return is augmented since blood also flows into the great veins of the thorax. All methods of artificial respiration, including assisted, IPPB, and PNPB, result in a reversal of the normal negative pressure existing during inhalation. The positive pressure results in a decreased venous return. Compensation occurs by reflex vasoconstriction and increase in venous pressure; venous return is maintained.[9] Any pattern of ventilation which causes an increase in central venous pressure sufficient to reflect in a rise in jugular pressure will result in increased brain mass and negate any beneficial effect produced by hypocapnia. Our studies have shown that the method of ventilation has a direct effect upon brain mass during general anesthesia.

Spontaneous Respiration. One of the significant findings of the present investigation was that spontaneous respiration in the presence of a normal CO_2 excretion resulted in elevated cerebrospinal fluid pressure. Since the tracheal airway pressure changes were not significantly increased (−2; +1), one could assume a normal central venous pressure. The only other factor which could explain the rise in cerebrospinal fluid pressure would be dilatation of the cerebral vascular bed by the anesthetic. In support of this, Sondergaard found elevation of cerebrospinal fluid pressure up to 250 mm. of water during halothane anesthesia without a corresponding rise in CO_2.[10] Alexander *et al.* demonstrated that during halothane/O_2 anesthesia at Pa_{CO_2} of 30 to 45 mm. of mercury, cerebral vascular resistance was reduced resulting in increased cerebral blood flow.[11] During halothane anesthesia for neurosurgery, unless arterial P_{CO_2} is effectively reduced by hyperventilation below normal, the cerebral vascular compartment will increase leading to a tight brain.

Assisted Ventilation. The importance of the method of ventilation in achieving hyperventilation is shown when respiration was assisted. It becomes difficult to explain the tight and congested brain in spite of a mild respiratory alkalosis. One could infer that arterial P_{CO_2} was not lowered to a level where cerebral hypocapnic vasoconstriction is predominant. This method of hyperventilation, furthermore, resulted in a persistent increase in airway pressure during the expiratory phase (mean = + 1.7 cm. of water). These findings suggest that assisted respiration is the poorest respiratory pattern to reduce the cerebral vascular compartment, since the residual airway pressure during expiration could lead to a continuous positive pressure pattern of breathing. This will undoubtedly cause greater elevation of venous pressure than the other methods of hyperventilation employed in our study.

IPPB. Hyperventilation by intermittent positive pressure also was ineffective. Our findings confirm the work of Ueyama *et al.* on the ineffectiveness of hyperventilation by IPPB in reducing brain tension, since this method caused increases in central venous pressure and internal jugular pressure.[2] (Those studies were carried out in dogs during pentobarbital anesthesia and in the supine position.) All of our patients here were in moderate respiratory alkalosis and, therefore, any vasodilating effect of halothane on cerebral vessels could be excluded.[12] The head up tilt of 25 to 35 degrees would be expected to vitiate the effect of increased airway pressure on cerebral venous vessels. Our results seem to disprove this. While the peak airway pressure used in our patients was within the limits of that recommended,[13] the pattern in which this pressure was applied could partially account for our poor results with hyperventilation by IPPB.

Moderate increase in airway pressure does not seem to affect brain tension adversely. Supporting this, one report showed that in patients hyperventilated by IPPB via an Engstrom ventilator and anesthetized with halothane and N_2O/O_2, a moderate increase in airway pressure had no apparent effect on cerebral ventricular fluid pressure. The authors attributed this to the low mean pressure produced by this type of ventilator.[14]

According to Mapleson, a "flow generator" ventilator will produce a flow pattern with peak pressure reached in mid-expiration. The peak pressure in the alveoli lasts only a fraction of a second. This will result in a low mean pressure in the lungs. In our studies, a "pressure generator" ventilator whose main function is to deliver a volume at a constant pressure throughout the inspiratory phase was used. The drawback of this is a tendency to produce a "plateau" resulting in a high mean pressure in the lungs.[15] Hyperventilation by IPPB failed to reduce the cerebral vascular compartment probably because the ventilatory pattern resulted in a high mean pressure in the lungs.

Hyperventilation by PNPB I. The addition of a negative pressure during the expiratory phase has been shown to lower the mean airway pressure.[16] Our data as shown in table 1 indicate that positive-negative pressure breathing employing a minute volume of 15 or less liters per minute is the most satisfactory pattern for reducing brain mass in patients undergoing craniotomy for brain tumor. This supports the view of others that a negative

pressure during expiration is necessary to counteract the compensatory rise in venous pressure.[13, 17, 18]

Several facts are worth noting in this regard. The internal jugular vein is a valveless, collapsible structure, and any change in the intrathoracic vascular pressure is transmitted to the cranial vessels, thereby influencing cerebral outflow. This is more distinct during positive pressure breathing than when the intrathoracic pressure pattern is reversed. On the other hand, because of the flow/pressure relation in a collapsible vascular system, a mechanism that augments cerebral venous outflow will result in a fall of internal jugular pressure. This can be obtained by the addition of a negative phase during expiration and postural drainage.[19]

Ressel showed that cerebral ventricular fluid pressure in dogs was lower only when positive-negative pressure breathing was used.[20] In recent experiments with a displacement transducer, Galloon demonstrated that positive-negative pressure breathing produced a better reduction in brain tension than any other method of ventilation.[21] Our results showed that this method of hyperventilation effectively reduced brain mass and cerebrospinal fluid pressure.

Hyperventilation by PNPB II. Other evidence substantiating the relation between the method of ventilation and brain mass is the adverse effect on brain tension obtained when large ventilatory volumes are used (tables 1, 2). The steep rise in cerebral arterio-venous oxygen difference (fig. 2), and the low saturation of cerebral venous blood that is observed in some patients during this pattern of hyperventilation are findings suggestive of a severe fall in cerebral blood flow.[22, 23] One would expect a reduced cerebral vascular compartment from the resulting hypocapnic vasoconstriction. This apparently did not occur since the brain appeared tight and congested. The possibility that the congested brain could be an indirect manifestation of cerebral hypoxia from the reduced blood flow can be excluded on the basis of the findings of Cohen *et al.* They demonstrated: (1) the brain's ability to extract sufficient oxygen from the perfusing blood over a wide range of cerebral blood flows; (2) a depression of cerebral oxygen consumption by 15 per cent, presumably from the lowered body temperature (in our patients the mean nasopharyngeal temperature was 35.9° C.); (3) the lack of excess lactate accumulation when cerebral blood flow was lowered during hypocarbia.[12]

Although we have no definite proof, it is conceivable that at least 2 mechanisms might have been responsible for the altered cerebral hemodynamics. One was an increase in airway pressure (from +11.0 to 14.5 peak inspiratory pressure) leading to a rise in cerebral venous pressure. Yet, central venous pressure, although monitored in only 3 patients, remained within normal limits. The other mechanism was a lower perfusion pressure (perfusion pressure = mean arterial pressure minus mean jugular pressure) leading to cerebral vasodilatation in the presence of marked arterial hypocapnia.[24] The fall in perfusion pressure could have been caused here by the arterial hypotension resulting from the combination of halothane anesthesia and head up tilt. These data demonstrate that large ventilatory volumes, despite a negative pressure during expiration and marked respiratory alkalosis, can be responsible for a tight congested brain.

From our investigation it is evident that the choice of the method of hyperventilation and the degree of respiratory alkalosis will determine the effectiveness of the hypocapnic vasoconstriction in reducing the cerebral vascular compartment. This study emphasizes the hazard of assisted respiration in neurosurgery. The inadvertent rise in airway pressure during expiration can be significant enough to offset the beneficial effects of hypocapnic vasoconstriction and result in an enlarged cerebral vascular bed.

In the selection of the proper ventilator careful consideration must be given to those factors conducive to a low mean airway pressure.[25] Pressure patterns producing a plateau will result in sustained high mean airway pressure. The magnitude of transmitted venous pressure changes may be significant enough to compromise the effects of hypocarbia on cerebral vascular resistance. This is evidenced by our failure to lower cerebrospinal fluid pres-

sure and brain tension during hyperventilation by IPPB. One should avoid the extremes of respiratory alkalosis, since arterial P_{CO_2} below 20 mm. of mercury could be associated with significant alteration in cerebral hemodynamics leading to a congested brain.

The object of hyperventilation for neurosurgery should be a moderate respiratory alkalosis with the least airway pressure and an augmented cerebral venous outflow. Enhanced cerebral venous outflow in our patients was obtained by: (1) positive-negative pressure breathing at a minute volume range between 9 and 15 liters per minute; (2) proper posture of the head; and (3) postural drainage of 25 to 35 degrees.

Summary

An attempt has been made to define the characteristics of a ventilatory pattern that would be effective in reducing brain tension during craniotomy for brain tumor. In patients anesthetized with halothane/oxygen anesthesia, 5 different respiratory patterns were studied for possible correlation between cerebrospinal fluid pressure, arterial P_{CO_2} changes, brain tension, and method of ventilation. The data presented demonstrate that the only factor which has any statistical correlation with cerebrospinal fluid pressure changes here is the method of ventilation. Spontaneous respiration at near normal P_{CO_2} caused an increase in cerebrospinal fluid pressure and brain mass. Assisted ventilation was the poorest method for reducing brain tension and gave the highest values in cerebrospinal fluid pressure, in spite of a mild respiratory alkalosis. Intermittent positive pressure breathing by means of a "pressure generator" ventilator lowered the cerebrospinal fluid pressure, but failed to reduce brain mass. Positive-negative pressure breathing at minute volumes ranging from 9 to 15 liters per minute (mean = 12.89) resulted in the lowest cerebrospinal fluid pressure and in good operative conditions. Ventilatory volumes greater than 15 liters per minute caused brain bulging and epidural bleeding. This occurred in spite of respiratory alkalosis and a negative phase during expiration. It is concluded that the biochemical effects of hyperventilation play a limited role, and methods that will enhance cerebral venous outflow are of critical importance in reducing brain mass. Because of the pharmacological effects of halothane on the vascular system, our conclusions are applicable to only those situations where this anesthetic is the primary agent.

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Surgery

NATIONAL HALOTHANE STUDY The subcommittee found the evidence insufficient to establish or refute a casual relationship between halothane and postoperative hepatic damage. The number of deaths attributable to massive hepatic necrosis was perhaps one death in 10,000 operations. No data were available on the incidence of hepatic necrosis in patients receiving other anesthetics or on the role of preexisting hepatic disease, viral hepatitis or prolonged operative shock as etiological factors in postoperative hepatic failure. Hepatic necrosis occurred more frequently after operations associated with high death rates. Nineteen, or nearly one fourth, of the cases followed open-heart operation with cardiopulmonary bypass, although these procedures accounted for only 1 per cent of all operations in the study. Halothane, rather than being a dangerous anesthetic, had a record of safety as reflected in an overall mortality of 1.8 per cent, compared to an average for all anesthetic practices of 1.93 per cent. No evidence was found to support the imputed risk of halothane in operations performed on the gallbladder or bile ducts, or in craniotomies. Although attention has been directed to patients who received halothane, the possible effect of other anesthetics should not be overlooked. Cyclopropane was followed by a greater incidence of massive hepatic necrosis than any of the other anesthetics. The disproportionately large total number might well have been related to the selective use of this agent for patients in shock. The possibility that cyclopropane damages the liver cannot be excluded, however. Of special interest and concern were the large differences in postoperative mortality occurring among the participating institutions. These differences among institutions, even after adjustments, remain very much larger than the differences among anesthetics. (*Subcommittee on the National Halothane Study of the Committee of Anesthesia, National Academy of Sciences-National Research Council: Summary of the National Halothane Study. Possible Association Between Halothane Anesthesia and Postoperative Hepatic Necrosis, J.A.M.A. 197: 775 (Sept.) 1966.*)