Does Hyperventilation Improve Operating Condition During Supratentorial Craniotomy? A Multicenter Randomized Crossover Trial

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BACKGROUND: Hyperventilation has been an integral, but poorly validated part of neuroanesthetic practice. We conducted a two-period, crossover, randomized trial to evaluate surgeon-assessed brain bulk and measured intracranial pressure (ICP) in patients undergoing craniotomy for removal of supratentorial brain tumors during moderate hypocapnia or normocapnia.

METHODS: Two-hundred and seventy-five adult patients with supratentorial brain tumors were randomized to one of two treatment sequences: hyperventilation (arterial carbon dioxide tension, $Paco_2$ = 25 ± 2 mm Hg) followed by normoventilation ($Paco_2$ = 37 ± 2 mm Hg) or normoventilation followed by hyperventilation. Ventilation and end-tidal CO_2 tension were kept constant for 20 min. Patients were also randomly assigned to receive a propofol infusion or isoflurane anesthesia. At the end of each study period, subdural ICP was measured and the neurosurgeon, blinded to the treatment group, was asked to rate the brain bulk using a four-point scale.

RESULTS: Using a generalized estimation equation model, we found that hyperventilation decreased the risk of increased brain bulk by 45%, P = 0.004, 95% confidence intervals 22% to 61%, and the number needed to treat was 8. The mean (±SD) ICP during hyperventilation, 12.3 ± 8.1 mm Hg, was lower than that during normoventilation, 16.2 ± 9.6 mm Hg, $P < 0.001$. Anesthetic regimen did not affect brain bulk assessment or ICP.

CONCLUSIONS: In patients with supratentorial brain tumors, intraoperative hyperventilation improves surgeon-assessed brain bulk which was associated with a decrease in ICP.

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Hyperventilation has been an integral part of neuroanesthesia for the past 50 yr.[1] Although more recent guidelines discourage the use of long-term hyperventilation in severe head injury, hyperventilation of some degree is still commonly provided to facilitate intracranial surgery.[1–3] This is due to the perceived advantage of brain relaxation and a lack of apparent serious deleterious effects associated with mild-to-moderate hyperventilation.[1] In this regard, it is generally believed that cerebral blood volume and intracranial pressure (ICP) are decreased when arterial carbon dioxide tension ($Paco_2$) is decreased during deliberate hyperventilation. These decreases, in turn, should decrease brain bulk and perhaps lessen the need for a potentially harmful retraction of the brain.

Studies have confirmed the effectiveness of hyperventilation in reducing increased ICP.[4–10] However, most of the data were derived from head-injured patients in the intensive care setting, and therefore may not be applicable to the elective intraoperative setting. Several other studies have evaluated the effects of hyperventilation on ICP and operating conditions, but the results were confounded by the choice of anesthetic regimens, absence of a control or comparable group, or inadequate power.[11–16] Therefore, we conducted a randomized, crossover trial to evaluate the efficacy of moderate hyperventilation in patients undergoing craniotomy for excision of supratentorial brain tumors during isoflurane or propofol anesthesia.

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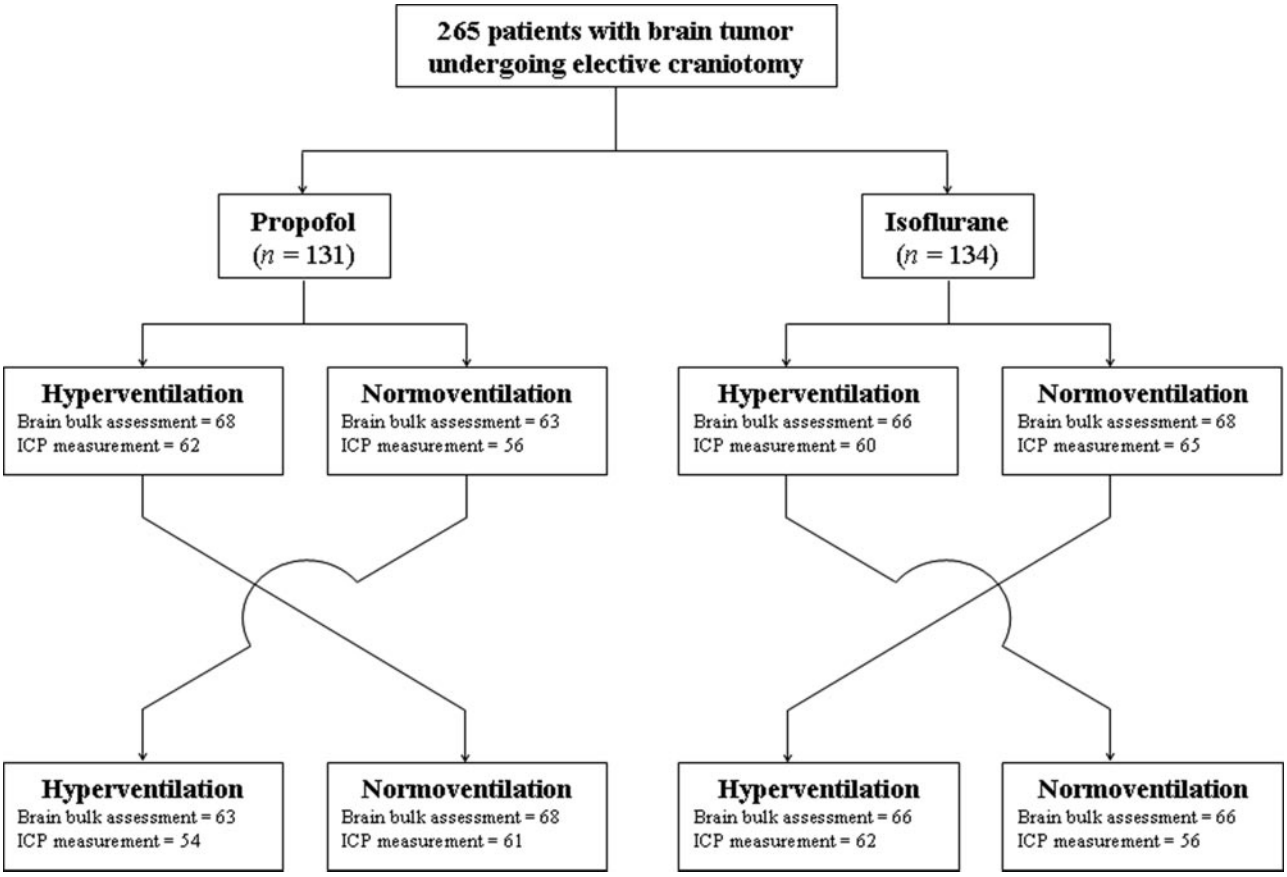

Figure 1. Study design and trial profile.

Our null hypothesis was that neither ICP nor surgeon-assessed brain bulk was altered by deliberate hyperventilation and that the effect was independent of the anesthetic used.

METHODS

This was a prospective, multicenter, randomized factorial trial with a two-period, two treatment crossover design (Fig. 1). Patients were randomly assigned to one of the following two treatment sequences: hyperventilation ($Paco_2$ = 25 ± 2 mm Hg) followed by normoventilation ($Paco_2$ = 37 ± 2 mm Hg) or *vice versa*. Treatment sequence was stratified by site, using permuted blocks, according to a computer-generated random number. To determine the effect of anesthetic regimen on hyperventilation, patients were also randomized to receive either isoflurane or propofol infusion as the primary anesthetic.

The study was performed between July 2001 and June 2003 at four institutions (London Health Sciences Centre, Canada; Prince of Wales Hospital, Hong Kong; All India Institute of Medical Sciences, Delhi, India; and National Institute of Mental Health and Neurosciences, Bangalore, India). Eligible patients were between 18 and 75 yr of age, ASA physical status I–III, and scheduled for elective craniotomy for excision of a supratentorial tumor. We excluded patients who were neurologically unstable or if the attending neurosurgeon considered the mass effect too great to allow safe participation in the study. Patients with severe cardiorespiratory or other severe systemic disorders were also excluded. The protocol was approved by the IRBs of the respective institutions. Written informed consent was obtained from all patients or their guardians.

Preoperative medications, including corticosteroids (received by all) and anticonvulsants, were prescribed according to local practices at the discretion of the attending neurosurgeons and anesthesiologists. All patients were fasted for at least 6 h before surgery. In the operating room, patients received standard monitoring that included invasive and noninvasive arterial blood pressure, continuous electrocardiogram, pulse oximetry, esophageal temperature, urine output, and end-tidal CO_2 and anesthetic concentrations. Temperature was kept between 35°C and 37°C using warming blankets.

Anesthesia was induced with fentanyl 3–5 μg/kg and propofol 1–2 mg/kg. Vecuronium or rocuronium was administered to facilitate tracheal intubation. Anesthesia was then maintained with isoflurane or propofol infusion as per group assignment. The dosage was adjusted according to clinical judgment but with the intent that at bone flap removal the propofol infusion would be at a rate of 100–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or the isoflurane at an end-tidal concentration of 0.9–1.1 vol%. The lungs were mechanically ventilated with an air/oxygen mixture at an inspiratory oxygen concentration

of 0.4. Nitrous oxide was not used in either group. All patients were placed in the supine position with a head-up tilt of no more than 10°. In appropriate cases, the neck was rotated by up to 45°.

After removal of the bone flap and exposure of dura, a 20-gauge plastic cannula was inserted into the subdural space along the surface of the brain. This was connected to a calibrated pressure transducer via a length of polyethylene high pressure tubing filled with normal saline. The transducer was placed at ear or nose level. The cannula was positioned so that respiratory and arterial blood pressure fluctuations could be identified.[15,16] During the study, subdural ICP was continuously recorded. An arterial blood sample was obtained for blood gas analysis. $Paco_2$ was measured at 37°C and corrected to patient's esophageal temperature. This was used to determine the difference between arterial and end-tidal carbon dioxide tension ($P_{a\text{-}ET}CO_2$).[17] Lung ventilation was then adjusted by varying tidal volume and respiratory rate to achieve the desired end-tidal CO_2 tension ($P_{ET}CO_2$). Airway pressure was kept below 22 cm H_2O. Positive end-expiratory pressure was not applied.

Ventilation and $P_{ET}CO_2$ were kept constant for at least 20 min, which is long enough for stabilization of any vascular responses to the change in $Paco_2$. At the end of the equilibration period, we performed the period 1 assessment. Another arterial blood sample was obtained to confirm that the targeted $Paco_2$ was achieved. The mean subdural ICP was recorded at end-expiratory phase. The neurosurgeon, unaware of the anesthetic and ventilatory management provided, was then asked to score the brain bulk according to a four-point scale as previously described[15,16]: 1 = excellent with no swelling; 2 = minimal swelling, acceptable; 3 = swollen but no treatment required; and 4 = swollen, needing treatment. After this assessment, ventilation was changed according to group assignment for period 2 assessment. Another 20 min of equilibration was allowed and measurements were repeated. The study ended at this point, the subdural cannula was then removed and surgery proceeded as normal. During the entire study period, anesthetic delivery was kept constant. Specific or routine interventions for brain swelling such as a change in body position or diuretic therapy with mannitol or furosemide were not administered until the study had ended. However, for ethical reasons, interventions could be made after period 1 assessment if requested by the surgeon and the patient then withdrew from the study. The primary end-point was surgeon-assessed brain bulk. The secondary end-point was subdural ICP.

An estimate of the sample size was calculated for a 5% absolute difference between groups (with an odds ratio ≥ 1.5) in the proportion of patients with brain swelling (i.e., patients with grades 3 and 4 brain bulk assessment). Accordingly, a two-period crossover study with a type I error of 0.05 and a type II error of 0.1 would require 125 patients per group with two-sided significance testing. We planned to include 260 patients in this study. With this sample size, a difference in ICP of 4 mm Hg can be detected with >90% power.

Data were analyzed based on the treatment allocation, rather than the actual $Paco_2$ values measured (intention-to-treat). The treatment (hyperventilation versus normoventilation), period (period 1 versus period 2), and carryover (treatment × period interaction) effects were calculated using the method proposed by Hills and Armitage.[18] A carryover effect occurs when the first intervention influences the second intervention, i.e., period 1 influences period 2. We also performed a multivariate analysis using a generalized estimation equation (GEE) approach.[19] Brain bulk assessment was modeled according to a multinomial distribution and a cumulative logit function. The data on subdural ICP were skewed, therefore square root transformation was applied to all analyses and an identity link function was specified. The SAS procedure PROC GENMOD (Release 8.02. SAS Institute, Cary, NC) was used to fit the GEE models. The GEE model considers the intra-correlation between measurements during the two study periods and is adjusted for the period effect and carryover effect. A number of models were created using a combination of prespecified covariates. The following factors were examined: patient's age, gender, size, location and type of tumor, type and dosage of anesthetics, hemodynamic and ventilatory variables, surgeon, center, and preoperative drug therapy. The final model was selected based on quasi-likelihood criterion.[20]

An analysis of variance model was used to compare the differences in ICP among the various grades of brain bulk assessment. Multiple comparisons were adjusted by Dunn-Sidak procedure. We also determined the threshold ICP value that was associated with brain swelling during assessment using the receiver operating characteristics method.

RESULTS

Two hundred sixty-five patients completed the study as one patient withdrew before randomization. Of these, 134 patients received hyperventilation for the first period followed by normoventilation for the second period, and 131 patients received normoventilation for the first period, followed by hyperventilation (Fig. 1) for the second period. Twenty-eight experienced surgeons participated. There were technical difficulties with subdural ICP recordings in 22 patients during period 1. This was primarily due to dense arachnoid adhesions that prevented smooth insertion of the cannula. In another 10 patients, ICP waveforms were considered unreliable during period 2. Subdural ICP was not recorded in these patients. Brain bulk assessment was completed in all patients.

Table 1. Baseline Characteristics

	Hyperventilation → normoventilation		Normoventilation → hyperventilation		
	Propofol	Isoflurane	Propofol	Isoflurane	*P*
Number of patients	68	66	63	68	
Gender: male	39 (57%)	40 (61%)	36 (57%)	39 (57%)	0.83
Age (yr)	47 ± 14	48 ± 17	46 ± 13	43 ± 12	0.09
Weight (kg)	64 ± 16	67 ± 21	68 ± 24	64 ± 16	0.96
Height (cm)	166 ± 9	167 ± 9	163 ± 18	166 ± 8	0.25
Radiologic abnormalities					
Maximum lesion diameter (cm)	5 ± 2	5 ± 2	5 ± 2	4 ± 2	0.15
Midline shift (mm)	5 ± 5	5 ± 6	3 ± 4	3 ± 4	0.06
Significant oedema on the scan	59 (86%)	52 (81%)	53 (84%)	55 (81%)	0.59
Site of lesion					0.56
Frontal	31 (47%)	27 (41%)	34 (54%)	20 (30%)	
Parietal	15 (22%)	15 (23%)	17 (27%)	19 (28%)	
Temporal	19 (28%)	18 (27%)	9 (14%)	26 (39%)	
Occipital	2 (3%)	6 (9%)	3 (5%)	2 (3%)	
Pathology					0.10
Glioblastoma	6 (10%)	10 (16%)	3 (5%)	2 (3%)	
Glioma	31(49%)	23 (37%)	29 (52%)	35 (57%)	
Meningoma	18 (29%)	22 (36%)	17 (30%)	19 (32%)	
Others	8 (12%)	7 (11%)	7 (13%)	5 (8%)	
At the beginning of procedure					
Induction dose of propofol used (mg)	124 ± 38	128 ± 43	130 ± 44	129 ± 45	0.53
Total dose of fentanyl dose (μg)	223 ± 82	228 ± 69	228 ± 74	224 ± 89	0.93
Use of muscle relaxant					
Rocuronium					
No. of patients (%)	49 (71%)	46 (70%)	46 (73%)	53 (78%)	0.72
Dose (mg)	57 ± 27	51 ± 20	56 ± 23	57 ± 22	0.19
Vecuronium (mg)					
No. of patients (%)	20 (29%)	20 (30%)	17 (27%)	15 (22%)	0.72
Dose (mg)	6.4 ± 1.4	5.9 ± 2.6	6.5 ± 1.3	6.1 ± 1.3	0.71
Total dose of lidocaine used for scalp block (mg)	78 ± 31	69 ± 35	70 ± 33	73 ± 30	0.59

Values are mean ± standard deviation or number (%).

Baseline Characteristics

Overall, 195 patients (73%) had brain tumors >3 cm in diameter with associated mass effect (Table 1). The most common lesions were gliomas and meningomas and they were located primarily in the anterior and middle cranial fossae. The distribution of lesion pathology or their locations were not different between groups.

At the beginning of the procedure, similar amounts of propofol, fentanyl, muscle relaxant, and lidocaine infiltration were used between groups (Table 1). The mean (±SD) $Paco_2$ during hyperventilation was 26 ± 2 mm Hg. The mean $Paco_2$ during normoventilation was 38 ± 3 mm Hg (Table 2). The overall $P_{a\text{-}ET}CO_2$ was 4 ± 3 mm Hg. In patients randomized to receive isoflurane (n = 134), anesthetic delivery was stabilized at an end-tidal concentration of 0.93 ± 0.18 vol%. Patients in the propofol group (n = 131) received a constant infusion of 119 ± 35 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There were no changes in the anesthetic doses over the course of the measurements. Core temperature, arterial and airway pressures did not differ between groups.

Brain Bulk Assessment

Based on a crossover analysis,[18] hyperventilation significantly decreased the number of patients with brain swelling, including those patients with grades 3 and 4 brain bulk assessments, compared with the bulk brain assessment during normoventilation (116 [43.8%] vs 153 [57.7%]; odds ratio = 0.55 [95% CI: 0.39–0.78]; P = 0.004) (Fig. 2). The absolute reduction in the incidence of brain swelling was 13.9% (95% CI: 5.5–22.4). The number-needed-to-treat was 8 (95% CI: 4.5–18.1). There was no carryover effect (P = 0.07) and the order of treatment (period effect) did not affect the results (P = 0.20). The benefit of hyperventilation was unaffected after adjustment for surgeon, center, preoperative drug therapy, patient characteristics (age, gender), mass effect, and the type and doses of anesthetic administered (adjusted odds ratio = 0.52 [95% CI: 0.31–0.86], P = 0.011). Based on our GEE model, the other predictors for brain swelling were midline shift and edema in the preoperative scan (Table 3). However, the type of anesthetic had no measurable effect on brain bulk assessment.

ICP

Hyperventilation decreased subdural ICP by an average of 3.7 mm Hg (95% CI: 2.9–4.6 mm Hg; P < 0.001) (Fig. 3). Our crossover analysis confirmed an absence of period effect (P = 0.09), but we found a significant carryover effect (P = 0.04). Nevertheless, the treatment effect was largely unchanged in an

Table 2. Conditions During Brain Bulk Assessment and Intracranial Pressure Measurement

	Hyperventilation → normoventilation		Normoventilation → hyperventilation		
	Propofol	Isoflurane	Propofol	Isoflurane	*P*
Rate of propofol infusion ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					0.64
Period 1	120 ± 31	—	118 ± 40	—	
Period 2	119 ± 31	—	119 ± 39	—	
End-tidal isoflurane concentration (vol%)					0.19
Period 1	—	0.93 ± 0.20	—	0.93 ± 0.16	
Period 2	—	0.92 ± 0.19	—	0.93 ± 0.17	
Arterial carbon dioxide tension (mm Hg)					<0.001
Period 1	26 ± 3	26 ± 2	38 ± 2	38 ± 2	
Period 2	37 ± 3	38 ± 2	27 ± 3	27 ± 3	
Arterial-to-end-tidal carbon dioxide tension gradient (mm Hg)					0.60
Period 1	5 ± 2	4 ± 2	4 ± 3	3 ± 4	
Period 2	4 ± 3	4 ± 3	5 ± 3	4 ± 3	
Airway pressure (mm Hg)					0.22
Period 1	21 ± 4	20 ± 4	18 ± 4	18 ± 4	
Period 2	18 ± 5	17 ± 5	20 ± 5	20 ± 5	
Mean arterial blood pressure (mm Hg)	0.12				
Period 1	89 ± 16	86 ± 14	85 ± 14	80 ± 13	
Period 2	87 ± 14	85 ± 17	87 ± 14	79 ± 12	
Temperature (°C)					0.18
Period 1	36 ± 0.6	36 ± 0.7	36 ± 0.5	36 ± 0.6	
Period 2	36 ± 0.6	36 ± 0.6	36 ± 0.7	36 ± 0.7	

Values are mean ± standard deviation.

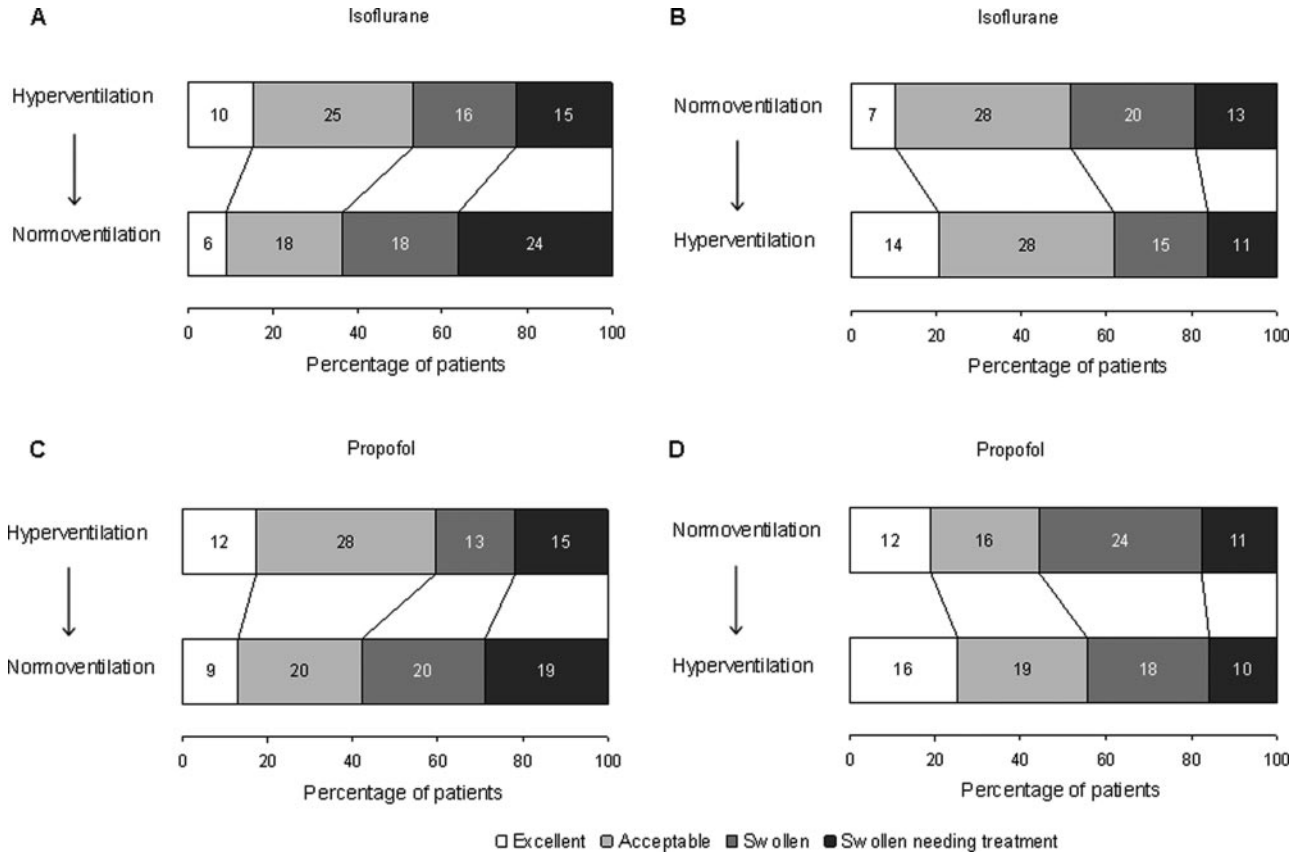

Figure 2. Changes in brain bulk assessment in patients who initially received hyperventilation and then crossed over to normoventilation (left panels, A and C) or *vice versa* (right panels, B and D) during isoflurane (upper panels, A and B) or propofol anesthesia (lower panels, C and D). The numbers in the boxes are the actual number of patients with the specific brain bulk assessment.

analysis adjusted for the carryover effect, period effect, age, gender, mass effect, and anesthetic. The adjusted difference in ICP between hyperventilation and normoventilation was 5 mm Hg; 95% CI: 3.1–7.2 mm Hg; $P < 0.001$. Using the GEE model, size of the lesion and midline shift on preoperative scans also

Table 3. Effect of Patient Characteristics, Anesthetic Delivery, and Ventilatory Strategy on Intraoperative Brain Swelling

	Brain swelling†	Acceptable or excellent brain condition	Odd ratios	*P*
Number of patients				
Period 1	127	138	—	—
Period 2	135	130	—	—
Age (yr) (n = 265)	46.1 ± 13.3	45.7 ± 15.0		
Gender (n = 265)				0.88
Male	79 (29.8)	74 (27.9)	1.00 (0.98–1.02)	
Female*	53 (20.0)	59 (22.3)		
Preoperative scan (n = 265)				
Maximum lesion diameter (cm)	5.3 ± 1.7	4.9 ± 1.9	1.00 (0.96–1.04)	0.90
Midline shift (mm)	5.9 ± 5.3	2.6 ± 3.9	1.18 (1.10–1.27)	0.02
Significant edema on the scan no. (%)				0.02
Yes	112 (42)	97 (36)	3.03 (1.14–8.07)	
No*	7 (2.6)	34 (12.8)		
Anesthetic delivery (n = 265)				
Isoflurane no. (%)	70 (26.4)	64 (24.2)	0.91 (0.50–1.65)	0.76
End-tidal concentration—period 1 (vol%)	0.91 ± 0.17	0.94 ± 0.19		
End-tidal concentration—period 2 (vol%)	0.93 ± 0.24	0.98 ± 0.18		
Propofol* no. (%)	63 (23.8)	68 (25.7)		
Infusion rate—period 1 ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	122 ± 38	117 ± 33		
Infusion rate—period 2 ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	120 ± 35	118 ± 36		
Ventilatory management				
Hyperventilation			0.52 (0.31–0.86)	0.01
Period 1	59 (22.3)	75 (28.3)		
Period 2	54 (20.4)	77 (29.1)		
Normoventilation*				
Period 1	68 (25.7)	63 (23.8)		
Period 2	81 (30.6)	53 (20.0)		

Values are mean ± standard deviation or number (%).

* Reference group for categorical variables.

† Brain swelling group includes patients with brain bulk assessments of 3 or 4.

predicted changes in ICP (Table 4). There was no difference in ICP between the patients receiving propofol and those receiving isoflurane.

Relationship Between ICP and Brain Bulk Assessment

The mean (±SD) subdural ICP in grade 1 and 2 patients (favorable brain conditions), 6 ± 5 mm Hg, was significantly different from that in grade 3 and 4 patients (i.e., those with brain swelling), 24 ± 9 mm Hg, $P < 0.001$ (Fig. 4). Although ICP differed significantly between each grade of brain bulk assessment, there was substantial overlap of the ranges. Nevertheless, surgeons generally reported grade 3 (brain swelling but no treatment needed) when ICP >13 mm Hg (sensitivity and specificity ranges, 74%–84% and 66%–79%, respectively) and grade 4 (swollen needing treatment) when ICP >16 mm Hg (sensitivity and specificity ranges, 75%–81% and 64%–76%, respectively). Anesthetics and hyperventilation did not affect the relationship between ICP and brain bulk assessment (P = 0.88 and 0.21, respectively).

DISCUSSION

In this prospective, randomized, crossover study, operating conditions were improved with moderate hyperventilation ($Paco_2$ 27 ± 2 mm Hg) during craniotomy for excision of supratentorial brain tumors. In a large, heterogeneous group of patients, our data demonstrate that hyperventilation decreased ICP by 24% (5 mm Hg) and decreased the risk of brain swelling by 14% compared with normoventilation ($Paco_2$ 37.7 ± 2.6 mm Hg). In contrast, choice of anesthetic regimen had no measurable effect on surgeon-assessed operating conditions or ICP.

Furness is generally credited with the first clinical description in 1957 of controlled ventilation in neurosurgery.[21] Contemporary use of hyperventilation has been supported by numerous studies showing a decrease in cerebral blood flow and ICP with hypocapnia in animals and patients with and without intracranial pathology.[1,22–26] Collectively, such studies confirmed that cerebral blood flow, the associated blood volume and ICP are decreased in both neoplastic and normal brain during hyperventilation. However, none of these studies included a formal evaluation of operating conditions.

Petersen et al.[16] evaluated ICP, cerebral hemodynamics, and operating conditions in 117 patients undergoing craniotomy for removal of supratentorial brain tumors. Patients were randomized to receive propofol-fentanyl (n = 41), isoflurane-fentanyl (n = 38), or sevoflurane-fentanyl (n = 38) anesthesia. Although it was not the primary aim, measurements were also made during normoventilation ($Paco_2$ 34.5–36.0 mm Hg) and hyperventilation ($Paco_2$ 28.5–30.8 mm Hg). Their data also demonstrated a

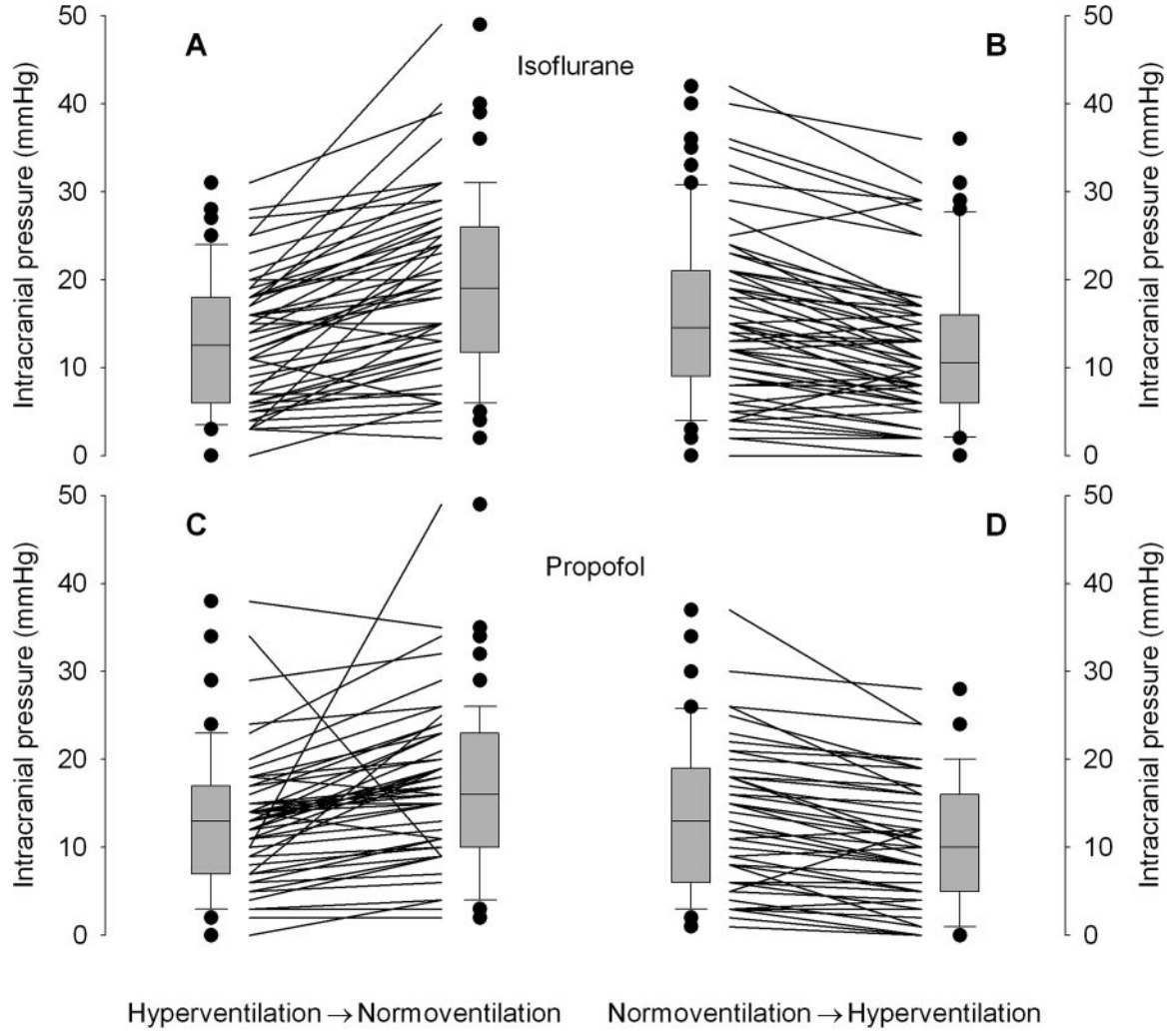

Figure 3. Changes of intracranial pressure in patients who initially received hyperventilation and then crossed over to normoventilation (left panels, A and C) or *vice versa* (right panels, B and D) during isoflurane (upper panels, A and B) or propofol anesthesia (lower panels, C and D). The line within the box is the median value, the ends of the box show the interquartile range, the whiskers represents the 10th and 90th percentiles and the dots represent values outside 10th and 90th percentiles range.

significant decrease in ICP after hyperventilation compared with normoventilation (mean difference 2.9 mm Hg, 95% CI: 1.3–4.5 mm Hg, $P < 0.001$), which is slightly less than our finding. The proportion of patients with moderate or pronounced brain swelling during hyperventilation was also less than that in the normoventilation period (43 [36.8%] vs 64 [54.7%]; odds ratio = 0.48; 95% CI: 0.29–0.81; $P = 0.006$). However, this analysis is potentially biased because ventilatory management was not randomly assigned but applied sequentially from normoventilation to hyperventilation in all patients. Nonetheless, these observations are consistent with our data suggesting that hyperventilation is robust in decreasing ICP and improving surgeon-assessed brain bulk at multiple institutions.

There is some evidence that propofol anesthesia produces more favorable characteristics in cerebral hemodynamics compared with inhalation-based anesthesia. In patients with normal ICP undergoing transphenoidal hypophysectomy, two studies reported no change in lumbar cerebrospinal fluid pressure with propofol but cerebrospinal fluid pressure was increased by 25%–50% after administration of isoflurane, desflurane, and sevoflurane.[27,28] In the study by Petersen et al.,[16] it was also noted that brain swelling was significantly improved with propofol anesthesia compared with isoflurane or sevoflurane. However, patients in that study did not receive equipotent doses of anesthetics. The larger dose of propofol may have accounted for the apparent difference in brain bulk assessment. Furthermore, their patients received isoflurane and sevoflurane 1.5 MAC during the initial phases of the study protocol whereas our protocol did not allow such high doses to be used at any time. Another study in brain tumor patients, like ours, also found no difference in ICP recordings or surgical assessment among propofol-fentanyl, isoflurane-nitrous oxide, or fentanyl-nitrous oxide anesthesia.[15] Our

Table 4. Effect of Patient Characteristics, Anesthetic Delivery, and Ventilatory Strategy on Intracranial Pressure

	Intracranial pressure (mm Hg) median (interquartile range)	Estimated effect (95% CI)	*P*
Number of patients			
Period 1 (n = 243)		—	—
Period 2 (n = 233)		—	—
Age (per 10 yr)		0.02 (−0.10 to 0.10)	0.70
Gender			
Male	13 (10)	−0.16 (−0.45 to 0.13)	0.29
Female*	13 (13)		
Preoperative scan (n = 243)			
Maximum lesion diameter (per cm)	—	0.16 (0.08–0.24)	<0.001
Midline shift (per mm)	—	0.30 (0.17–n0.43)	<0.001
Significant edema on the scan			
Yes	14 (12)	0.17 (−0.25 to 0.58)	0.43
No*	12 (12)		
Anesthetic delivery			
Isoflurane	13 (12)	0.20 (−0.08 to 0.48)	0.17
Propofol*	13 (11)		
Ventilatory management			
Hyperventilation	10 (10)	−0.71 (−1.03 to −0.40)	<0.001
Normoventilation*	13 (10)		

Estimated effect on intracranial pressure is derived from the generalized estimating equation model.

* Reference group for categorical variables.

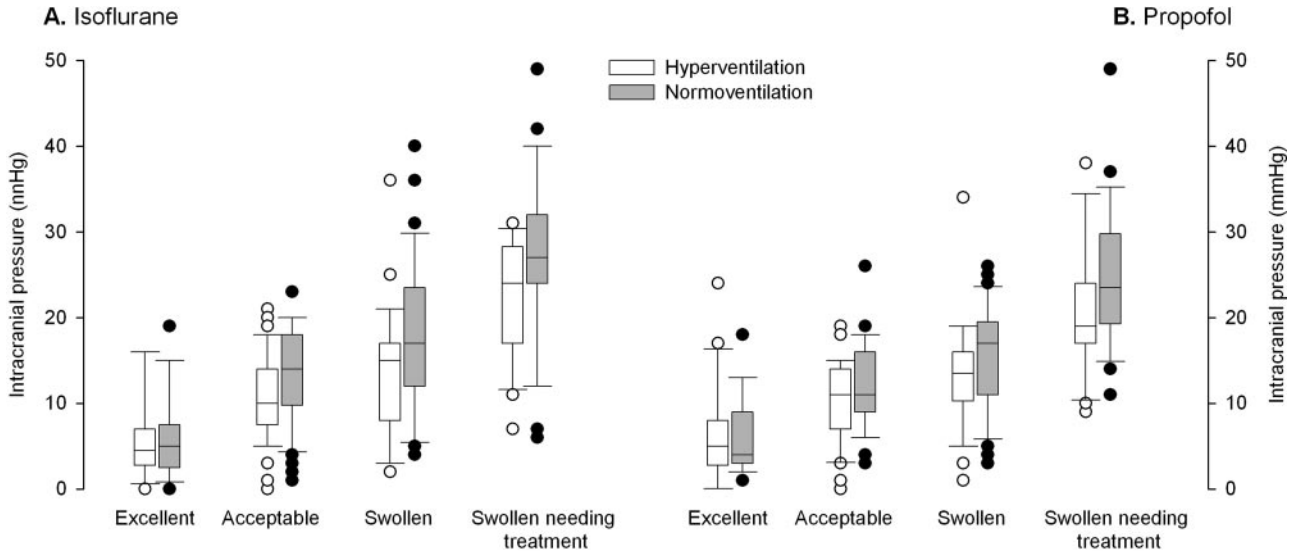

Figure 4. Box plots of intracranial pressure at different brain bulk assessments during hyperventilation or normoventilation in patients receiving either isoflurane (left panel, A) or propofol (right panel, B) anesthesia. The line within the box is the median value, the ends of the box show the interquartile range, the whiskers represents the 10th and 90th percentiles and the dots represent values outside 10th and 90th percentiles range.

patients were at an average isoflurane MAC of 0.85, which may also have decreased the associated cerebral vasodilation making it less apparent in relation to propofol.

Both ICP measurement and the surgeon-assessed brain bulk are important in intracranial surgery. ICP becomes effectively zero when the dural incision is made, after which the surgeon's perception is critical. A direct correlation between these two factors has always been assumed. Our data show that this relationship is the closest when ICP is higher than 15 mm Hg, but others have reported different threshold values ranging from 6 to 17 mm Hg to predict brain swelling.[29–31] This highlights the subjective nature of brain bulk assessment for which other factors such as firmness of the tumor and the amount of bulging relative to the craniotomy size may contribute to overall assessment. Nevertheless, surgeon assessment of operating conditions is what the anesthesiologist must respond to in the operating room. We have therefore used brain bulk assessment as our primary end-point.

Despite the improved operating condition, there is concern that hyperventilation may dispose to cerebral ischemia. In head trauma patients receiving treatment in a critical care unit, brief hyperventilation doubled the volume of severely hypoperfused tissue within the

injured brain.[32] In contrast, relatively little is known about the risk of intraoperative hyperventilation. Studies in brain tumor patients have reported a decrease in jugular venous oxygen saturation ($SjvO_2$) after hyperventilation and during additional hypothermia with up to 50% of patients having $SjvO_2$ <50%.[16,33,34] Although a previous study demonstrated $SjvO_2$ values of 40%–45% were associated with metabolic failure and secondary brain damage in head-injured patients,[35] we are uncertain how the ischemic threshold should be applied during anesthesia. It is possible that inadvertent cerebral ischemia may outweigh the benefits of hyperventilation, and should be the subject of further investigation. In the interim, caution should probably be used and the decision to use hyperventilation made carefully. It is also important to note that in changing to normoventilation, some patients had very large increases in ICP (Fig. 3) and this change too should be done with caution and careful consideration in patients with a closed cranium or before adequate tumor debulking.

We designed the current study as a two-period, crossover trial, allowing each patient to serve as his or her own control.[18] This requires fewer subjects compared with a standard parallel design. However, interpretation of the crossover trial can be complicated by the inherent risk of a carryover effect. In our analysis of the ICP changes, we detected a small residual carryover effect, i.e., the first intervention influencing the second. Although there is no consensus in the literature as how to handle such bias, we believe a multivariate model to adjust for the carryover effect is appropriate because it does not exclude valuable observations.[19]

In conclusion, the ability of moderate hyperventilation to improve surgeon-assessed brain bulk and ICP during craniotomy for removal of supratentorial brain tumors was demonstrated in this study and was independent of anesthetic. Our data support the use of intraoperative hyperventilation as part of the anesthetic technique to improve operating conditions in patients with brain tumors.

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