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Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury

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Object. Hyperventilation therapy, blood pressure augmentation, and metabolic suppression therapy are often used to reduce intracranial pressure (ICP) and improve cerebral perfusion pressure (CPP) in intubated head-injured patients. In this study, as part of routine vasoreactivity testing, these three therapies were assessed in their effectiveness in reducing ICP.

Methods. Thirty-three patients with a mean age of 33 ± 13 years and a median Glasgow Coma Scale (GCS) score of 7 underwent a total of 70 vasoreactivity testing sessions from postinjury Days 0 to 13. After an initial ^{133}Xe cerebral blood flow (CBF) assessment, transcranial Doppler ultrasonography recordings of the middle cerebral arteries were obtained to assess blood flow velocity changes resulting from transient hyperventilation (57 studies in 27 patients), phenylephrine-induced hypertension (55 studies in 26 patients), and propofol-induced metabolic suppression (43 studies in 21 patients). Changes in ICP, mean arterial blood pressure (MABP), CPP, $PaCO_2$, and jugular venous oxygen saturation ($SjvO_2$) were recorded. With hyperventilation therapy, patients experienced a mean decrease in $PaCO_2$ from 35 ± 5 to 27 ± 5 mm Hg and in ICP from 20 ± 11 to 13 ± 8 mm Hg ($p < 0.001$). In no patient who underwent hyperventilation therapy did $SjvO_2$ fall below 55%. With induced hypertension, MABP in patients increased by 14 ± 5 mm Hg and ICP increased from 16 ± 9 to 19 ± 9 mm Hg ($p = 0.001$). With the aid of metabolic suppression, MABP remained stable and ICP decreased from 20 ± 10 to 16 ± 11 mm Hg ($p < 0.001$). A decrease in ICP of more than 20% below the baseline value was observed in 77.2, 5.5, and 48.8% of hyperventilation, induced-hypertension, and metabolic suppression tests, respectively ($p < 0.001$ for all comparisons). Predictors of an effective reduction in ICP included a high $PaCO_2$ for hyperventilation, a high study GCS score for induced hypertension, and a high $PaCO_2$ and a high CBF for metabolic suppression.

Conclusions. Of the three modalities tested to reduce ICP, hyperventilation therapy was the most consistently effective, metabolic suppression therapy was variably effective, and induced hypertension was generally ineffective and in some instances significantly raised ICP. The results of this study suggest that hyperventilation may be used more aggressively to control ICP in head-injured patients, provided it is performed in conjunction with monitoring of $SjvO_2$.

Key Words • hyperventilation therapy • induced-hypertension therapy • pressure autoregulation • metabolic suppression therapy • propofol • transcranial Doppler ultrasonography • traumatic brain injury • vasoreactivity

For the past three decades, commonly used therapies for the reduction of ICP in a patient who has incurred head injury have included hyperventilation, ventricular drainage of cerebrospinal fluid, osmotherapy with mannitol, and metabolic suppression therapy.[6,11,12,19,21,32,41] More recently, maintenance of an adequate CPP, so-called CPP therapy, as described by Rosner and colleagues[46,47] has also been used as a means of improving or stabilizing ICP. Of these five therapies, hyperventilation, metabolic suppression, and CPP therapy remain the most controversial. Their relative effectiveness and the factors that may lead to a greater improvement in ICP or CPP with each of these therapies have not been well defined. Furthermore, each of these treatments has potential deleterious effects for brain-injured patients. Results from some studies indicate that excessive hyperventilation has been associated with reduced

Abbreviations used in this paper: AVDglu = arteriovenous difference for glucose; $AVDO_2$ = arteriovenous difference for oxygen; CBF = cerebral blood flow; CBV = cerebral blood volume; CMRglu = cerebral metabolic rate for glucose; $CMRO_2$ = cerebral metabolic rate for O_2; CPP = cerebral perfusion pressure; eCVR = estimated cerebrovascular resistance; EEG = electroencephalography; $ETCO_2$ = end-tidal carbon dioxide; GCS = Glasgow Coma Scale; ICP = intracranial pressure; MABP = mean arterial blood pressure; MCA = middle cerebral artery; OR = odds ratio; PAI = pressure autoregulation index; $SjvO_2$ = jugular venous O_2 saturation; TCD = transcranial Doppler; UCLA = University of California at Los Angeles; V_{MCA} = velocity of blood flow through the MCA; %Δ = percentage change.

$SjvO_2$ and brain tissue oxygenation and poorer long-term outcome after severe head injury.[36,51,61] Use of metabolic suppression therapy with high-dose pentobarbital or propofol may also be associated with serious systemic complications.[15,56,62] Aggressive CPP therapy with intravascular volume expansion and vasopressor agents can lead to pulmonary edema and end-organ ischemia.[22,43]

With these issues in mind, we endeavored to determine the relative efficacy of hyperventilation, CPP, and metabolic suppression therapies in improving ICP in intubated head-injured patients. Assessment of these three treatment modalities was performed during bedside vasoreactivity testing for CO_2 reactivity, pressure autoregulation, and metabolic suppression reactivity by using TCD ultrasonography. An additional goal of this study was to identify factors that were predictive of an effective reduction in ICP.

Clinical Material and Methods

Patient Enrollment and Ethical Considerations

Transcranial Doppler ultrasonography and ^{133}Xe CBF monitoring are routinely used in the acute care of moderately and severely head-injured patients at UCLA and Harbor-UCLA Medical Centers. The vasoreactivity test battery described later was initiated to help optimize management of ICP and CPP, and was subsequently formalized into a prospective study in which the testing frequency was increased and additional metabolic data from jugular bulb catheters were collected. This report includes data from 28 patients who were recently described in terms of their responses to serial vasoreactivity testing.[29] Five additional patients have since been enrolled in the current study and their data are included in this report. Of the total cohort of 33 patients, the last 23 were prospectively enrolled in the vasoreactivity study and the first 10 patients were tested for clinical indications. The institutional review boards of both the UCLA and Harbor-UCLA Medical Centers approved our research protocol.

Inclusion and Exclusion Criteria

Eligible patients included those aged 16 years or older, who had sustained a closed or penetrating traumatic brain injury with a postresuscitation (or delayed deterioration) GCS[58] score of 3 to 12, and who required mechanical ventilation therapy and ICP monitoring. Patients were exempted from the study when they were extubated or were able to follow commands. Patients did not receive mannitol, or have changes in sedative doses or vasopressor therapy for at least 1 hour prior to beginning the study. Patients were studied only if they were incapable of following commands and had stable cardiovascular and pulmonary systems.

Patient Management

All patients were admitted to the intensive care unit after initial stabilization or after emergency craniotomy for evacuation of an intracranial hematoma. Patient management was in concordance with the "Guidelines for the Management of Severe Head Injury"[3,4] and included a stepwise algorithm for maintaining an ICP lower than 20 mm Hg and a CPP higher than 70 mm Hg. A jugular bulb catheter was in place during 79% of all vasoreactivity testing sessions to allow monitoring of $SjvO_2$ and determination of $AVDO_2$ and AVDglu.

Patient Demographics

This study included 33 acutely head injured patients, five women and 28 men, with a mean age of 33 ± 13 years and a median postresuscitation GCS score of 7 (range 3–14); 73% of patients had a postresuscitation GCS score of 8 or lower. The mechanisms of injury included 11 motor vehicle accidents, eight falls, seven pedestrians struck by motor vehicles, two motorcycle accidents, two bicycle accidents, two gunshot wounds, and one assault. Of these patients, 48.4% underwent a craniotomy for evacuation of an epidural hematoma (two cases), a subdural hematoma (seven cases), an intracerebral hematoma or a contusion (four cases), or a combination of these lesions (three cases).

Transcranial Doppler Ultrasonography Vasoreactivity Battery

As previously described, serial vasoreactivity testing was performed during postinjury Days 0 to 13 over a 2- to 3-hour period.[29] As many as five testing sessions were conducted during the acute postinjury period. Bilateral TCD ultrasonography of the MCA was performed using an apparatus (Nicolet Neuroguard; Fremont, CA) with bilateral 2-MHz ultrasonography transducers fixed to a headband to prevent motion artifact and to allow for extended monitoring. A ^{133}Xe CBF study was performed and arterial and jugular bulb venous samples were obtained at the beginning of each test battery to allow calculation of CMRglu and $CMRO_2$.[28,40] Normal values for these parameters are as follows: $CMRO_2$ = 3.58 ± 0.29 ml/100 g/min and CMRglu = 5.58 ± 1.07 mg/100 g/min.

Physiological Monitoring. Prior to and during each vasoreactivity test, MABP, ICP, CPP, and $SjvO_2$ were recorded. These values were used to determine the absolute and relative changes in ICP, CPP, and $SjvO_2$ resulting from hyperventilation therapy, induced hypertension, or metabolic suppression therapy. Electroencephalography studies were performed using an eight-channel longitudinal montage with scalp electrodes. Burst suppression was defined as EEG burst activity with intervening periods of 4 to 8 seconds of electrical silence.

Hyperventilation for Assessing CO_2 Reactivity. Increasing the ventilatory rate lowered $PaCO_2$, with a goal of decreasing $ETCO_2$ by 6 to 8 mm Hg. Blood gas analysis data obtained before and during hyperventilation confirmed the change. Average V_{MCA} was determined prior to and 15 minutes after the change in $PaCO_2$. An initial blood gas sample was taken concurrently with the baseline TCD ultrasonography recording to determine actual $PaCO_2$. Mean arterial blood pressure was maintained at a constant level during the CO_2 reactivity testing by titrating a phenylephrine infusion as needed. Relative CO_2 reactivity was defined as the %Δ in V_{MCA} per mm Hg $PaCO_2$.[26] Normal CO_2 reactivity was defined as 3.7 ± 0.5% ΔV_{MCA} per mm Hg $PaCO_2$.[27] Global ischemia was defined as an $SjvO_2$ level less than 50%.

Induced Hypertension for Assessing Pressure Autoregulation and CPP Therapy. A titratable phenylephrine infusion was used to elevate MABP by 10 to 15 mm Hg. The %Δ in ICP per mm Hg increase in MABP was calculated. Pressure

autoregulation was calculated by measuring the change in eCVR (defined as MABP/V_{MCA}).[59] Autoregulatory capacity is the %Δ in eCVR to the %Δ in MABP from baseline MABP (1, baseline value) to the higher MABP (2, ending value), that is, %ΔeCVR/%ΔMABP, where %ΔeCVR = (eCVR2 − eCVR1)/eCVR1 and %ΔMABP = (MABP2 − MABP1)/MABP1. Thus, autoregulation is expressed as a percentage of normal: 100% indicates full capacity, 0% indicates a completely pressure-passive cerebrovasculature, and negative values indicate a paradoxical decrease in eCVR to an increase in blood pressure. An autoregulatory capacity of less than 70% was defined as abnormal.[59] Studies were initiated at a baseline end-tidal $PaCO_2$ value of 32 to 36 mm Hg. Baseline and final values obtained using TCD ultrasonography were adjusted by multiplying the raw values by the patient's CO_2 reactivity and the difference between the end-tidal $PaCO_2$ and the standard value of 34 mm Hg.[40]

Metabolic Suppression Vasoreactivity. Propofol, an ultra–short acting, sedative/anesthetic/nonanalgesic drug was used to induce EEG burst suppression.[1,18,29,39] The use of propofol is advantageous in vasoreactivity testing, because at high doses it does not impair pressure autoregulation or CO_2 reactivity in healthy individuals.[34,57,59]

As described previously, a loading dose of propofol (1 mg/kg) was administered over 10 minutes, followed by an infusion starting at 100 μg/kg/min and increasing every 5 minutes by 10-μg/kg/min increments, until adequate EEG burst suppression (4–8 seconds) had been maintained for 5 minutes.[29] The maximum propofol infusion rate was 220 μg/kg/min. The V_{MCA}, ICP, MABP, and CPP were monitored continuously from their baseline values until EEG burst suppression was achieved. Metabolic reactivity was defined as %Δ in V_{MCA} between these two recordings. Normal metabolic reactivity was defined as a decrease in CO_2-corrected V_{MCA} of 30% or more. A phenylephrine infusion was titrated to maintain MABP at a constant baseline level. Baseline and final values obtained using TCD ultrasonography were corrected to a $PaCO_2$ value of 34 mm Hg, based on the patient's CO_2 reactivity for that day. Patients whose baseline MABP was lower than 80 mm Hg had metabolic suppression reactivity testing postponed or canceled.

Values of AVDglu and $AVDO_2$ were also recorded at baseline and during EEG burst suppression. Because only one baseline ^{133}Xe CBF study was performed at each testing session, the propofol-induced change in $CMRO_2$ and CMRglu was estimated by multiplying the baseline CBF by the %Δ in V_{MCA}, from its baseline value (prior to initiating propofol administration) to its final value (during burst suppression). The metabolic ratio[13] ($CMRO_2$/CMRglu) was also determined at each test. An abnormally low metabolic ratio ($CMRO_2$/CMRglu < 0.6) indicates that cerebral glucose use is high relative to O_2 metabolism.

Predictors of Successful ICP Reduction

The following factors were analyzed according to their predictive value in determining the effectiveness of ICP reduction during hyperventilation, induced hypertension, and metabolic suppression: patient age and sex, GCS score on admission, GCS score prior to study, global CBF prior to study, and postinjury day. At baseline and after manipulation, the following parameters were also recorded: ICP, MABP, CPP, $SjvO_2$, $PaCO_2$, $ETCO_2$, jugular venous CO_2, $CMRO_2$, $AVDO_2$, CMRglu, and AVDglu as well as the derived values for CO_2 reactivity, PAI, and metabolic suppression reactivity. Predictors were considered to be significant if they were associated with a decrease in ICP of 20% or more.

TABLE 1

Results of global vasoreactivity tests

Subject of Test	No. of Studies	Parameter	Mean ± SD*	Abnormal (%)†
baseline CBF	55	global CBF (ml/100 g/min)	39 ± 13‡	
hyperventilation	57	CO_2 reactivity (mm Hg)	3.2 ± 1.5	12.5
induced hypertension	55	pressure autoregulation (%)	64 ± 70	55.4
metabolic suppression	43	metabolic reactivity (%)	16 ± 11	88.4

* SD = standard deviation.

† Percent of studies with abnormal vasoreactivity. Normal CO_2 reactivity is defined as 3.7 ± 0.5%/mm Hg $PaCO_2$; normal pressure autoregulation is defined as a PAI greater than 70%; and normal metabolic suppression is defined as a decrease in CO_2-corrected V_{MCA} of 30% or more after the patient has undergone administration of high-dose propofol, according to Lee, et al.

‡ Of the baseline ^{133}Xe CBF studies, data from one study (1.8%) demonstrated global ischemia, which was defined as global CBF lower than 20 ml/100 g/min, and data from 10 studies (18%) showed absolute hyperemia, which was defined as global CBF higher than 55 ml/100 g/min, according to Kelly, et al., 1996, and Obrist, et al.

Statistical Analysis

In this study, we report the results of individual vasoreactivity tests; however, intraindividual correlation must be considered when correlations are calculated between parameters. The change in ICP was stratified quantitatively and qualitatively. The odds of achieving this goal were calculated for each of the tested modalities. To define predictors of success for a given therapy, mixed-effects logistic regression analysis was performed and the Pearson correlation coefficient was calculated. For all statistical tests, a difference was defined as significant when the probability value was less than 0.05.

Results

Table 1 shows the results of the global tests for baseline CBF, CO_2 reactivity, pressure autoregulation, and metabolic suppression reactivity.

Hyperventilation Therapy

Table 2 and Fig. 1 show the results of 57 hyperventilation tests performed in 27 patients. The mean baseline $PaCO_2$ was 35 ± 5 mm Hg and decreased by a mean of 8 ± 5 mm Hg. In all tested variations, the correlation between $ETCO_2$ and $PaCO_2$ was statistically significant but poor (baseline: $ETCO_2$ compared with $PaCO_2$, $r = 0.59$, $p < 0.001$; hyperventilation, $r = 0.52$, $p < 0.001$; $\Delta ETCO_2$ compared with $\Delta PaCO_2$, $r = 0.37$, $p = 0.008$). The mean baseline ICP was 20 ± 11 mm Hg and the mean ending ICP was 13 ± 8 mm Hg ($p < 0.001$). A decrease in ICP occurred in 96.5% of

TABLE 2

Results of hyperventilation therapy tests

Parameter	No. of Studies	Baseline*	Hyperventilation*	p Value†
end-tidal $PaCO_2$ (mm Hg)	57	33.4 ± 4.8	25.9 ± 4.2	<0.001
$PaCO_2$ (mm Hg)	48	34.5 ± 4.6	27.3 ± 4.5	<0.001
ICP (mm Hg)	57	20 ± 11	13 ± 8	<0.001
$SjvO_2$ (%)	33	73 ± 8	67 ± 8‡	<0.001
V_{MCA} (cm/sec)	57	111 ± 45	86 ± 37	<0.001
MABP (mm Hg)	54	106 ± 13	104 ± 12	0.11

* Values are expressed as the means ± SD.

† Probability values were calculated using the paired t-test for dependent variables, but their calculation did not take into account the presence of other contributing factors.

‡ An $SjvO_2$ less than 55% did not occur in any of these studies. An $SjvO_2$ less than 60% occurred in 24.2% of (8 of 33) studies.

the studies, a decrease of more than 20% occurred in 77.2% of the tests, and the mean ICP decrease was 37 ± 21%. A jugular venous catheter was used in 33 (58%) of 57 studies. Hyperventilation was associated with a mean decrease in $SjvO_2$ from 73 ± 8% to 67 ± 8% ($p < 0.001$). No change in $SjvO_2$ was recorded in one third of all studies. In none of the studies did $SjvO_2$ decrease below 55%, and in only eight (24.2%) of 33 did $SjvO_2$ decrease below 60%.

Induced-Hypertension Therapy

Table 3 and Fig. 1 show the results of 55 induced-hypertension tests performed in 26 patients. The mean baseline MABP was 104 ± 12 mm Hg and on average increased by 14 ± 5 mm Hg ($p < 0.001$). The mean baseline ICP was 16 ± 9 mm Hg and the mean ending ICP was 19 ± 9 mm Hg ($p = 0.002$). Intracranial pressure increased by a mean of 17 ± 40% ($p = 0.001$), and CPP by a mean of 14 ± 9% ($p < 0.001$); $SjvO_2$ had a mean increase from 72 ± 7 to 74 ± 9% ($p < 0.001$). In only three studies (5.5%) did ICP decrease more than 20% from its baseline value, whereas in 35 studies (63.6%) ICP changed no more than 20%, and in 17 studies (30.9%) ICP increased more than 20%.

Metabolic Suppression Therapy

Table 4 and Fig. 1 show the results of 43 metabolic suppression tests performed in 21 patients. The mean baseline and ending MABP were 107 ± 12 mm Hg and 107 ± 12 mm Hg, respectively. The mean baseline ICP was 20 ± 10 mm Hg and the mean ending ICP was 16 ± 11 mm Hg ($p = 0.001$). A decrease of more than 20% occurred in 48.8% of the studies, and the mean ICP decrease was 21 ± 28%. At baseline, both $CMRO_2$ and CMRglu were subnormal, with values of 1.4 ± 0.8 ml/100 g/min and 3.7 ± 2.6 mg/100 g/min, respectively. Metabolic suppression therapy caused a further decrease in $CMRO_2$ and CMRglu of 11 ± 53% ($p = 0.003$) and 18 ± 55% ($p = 0.003$), respectively; estimated CBF was reduced by 16 ± 11% ($p < 0.001$) and $SjvO_2$ increased from 72 ± 8 to 75 ± 8% ($p = 0.003$).

Relative Effectiveness of Hyperventilation, Induced Hypertension, and Metabolic Suppression Therapies

Table 5 lists the ORs among hyperventilation, induced hypertension, and metabolic suppression for the likelihood of an ICP reduction of greater than 20% from its baseline

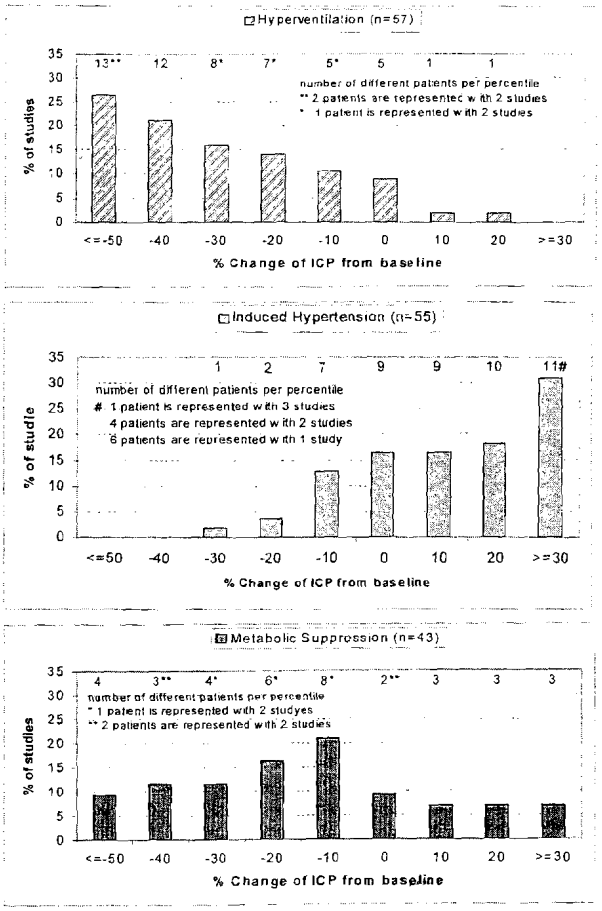

FIG. 1. Graphs demonstrating the %Δ in ICP from baseline for each test of hyperventilation (a), induced hypertension (b), and metabolic suppression (c). Each test was then categorized into a percentile range, and in each graph, the percentile categories total 100%. This graphic display shows the consistent effectiveness of hyperventilation therapy, the consistent ineffectiveness of induced hypertension, and the variable effectiveness of propofol-induced metabolic suppression in reducing ICP. N = number of studies.

value. The likelihood of hyperventilation or metabolic suppression therapy being effective in decreasing ICP was much higher than that for induced hypertension therapy. Across postinjury days, hyperventilation and metabolic suppression showed relative consistency in the degree of effectiveness to reduce ICP. In contrast, induced hypertension increased ICP by as much as 50% in seven (19%) of 37 studies during postinjury Days 0 to 3, but had only minimal effect on ICP on postinjury Days 6 to 13.

Predictors of ICP Reduction

Hyperventilation Therapy. Hyperventilation therapy was associated with a reduction in ICP in all but two studies. Only the baseline value of $PaCO_2$ was predictive of the degree of reduction in ICP. The higher the baseline $PaCO_2$, the more pronounced was the percentage decrease in ICP (corrected for intrapatient Pearson correlation coefficient, $r = -0.49$, $p < 0.001$; Fig. 2). A baseline ICP greater than 20 mm Hg was present in 21 (36.8%) of 57 studies. Of those 21 studies, ICP was reduced to less than 20 mm Hg in

TABLE 3

Results of induced-hypertension therapy tests

Parameter	No. of Studies	Baseline*	Hypertension*	p Value†
MABP (mm Hg)	55	104 ± 12	118 ± 12	<0.001
CPP (mm Hg)	55	88 ± 15	100 ± 16	<0.001
ICP (mm Hg)	55	16 ± 9	19 ± 9	0.001
V_{MCA} (cm/sec)	55	71 ± 27	76 ± 29	0.002
$SjvO_2$ (%)	37	72 ± 7	74 ± 9	<0.001

* Values are expressed as the means ± SD.

† Probability values were calculated using the paired t-test for dependent variables, but their calculation did not take into account the presence of other contributing factors.

11 (52.4%). In 10 studies in which ICP remained above 20 mm Hg after hyperventilation therapy, baseline ICP was, on average, very high with a mean value of 37 ± 11 mm Hg. With hyperventilation therapy, there was no correlation between percentage change in ICP and postinjury day. The calculated CO_2 reactivity on the day of the study also did not correlate with the degree of decrease in ICP, although CO_2 reactivity was generally intact (mean value 3.2 ± 1.5 ΔV_{MCA}/mm Hg $PaCO_2$) and abnormal values were observed in only 12.5% of the studies.

Induced-Hypertension Therapy. Of all assessed factors, only the patient's GCS score prior to initiating the study correlated inversely with a reduction in ICP. In patients with a study GCS score of 3 or 4, ICP increased from a mean of 21 ± 11 mm Hg to a mean of 24 ± 11 mm Hg. In patients with a study GCS score of 5 to 8, ICP generally remained stable (16 ± 9 mm Hg to 17 ± 9 mm Hg), and only in moderately head injured patients (GCS Score 9 or 10) did ICP decrease from a mean of 14 ± 8 mm Hg to a mean of 11 ± 5 mm Hg. The differences between the severe (GCS Scores 3–8) and less severe groups (GCS Score 9 or 10) were statistically significant (Fig. 3). Regarding the state of pressure autoregulation, of the three studies in which a decrease in ICP of more than 20% occurred with the use of induced hypertension therapy, all three were conducted in patients with intact pressure autoregulation on the same test day, with a mean PAI of 122%. Overall, however, the PAI did not correlate with the change in ICP (Pearson correlation coefficient, r = 0.09; p = 0.5). The baseline CPP also did not correlate with the change in ICP (r = 0.04, p = 0.8), and there was no correlation between the change in CPP and that in $SjvO_2$.

Metabolic Suppression Therapy. Of all assessed factors, only a high baseline global CBF (OR 1.1, p = 0.01) and a high baseline $PaCO_2$ (OR 1.3, p < 0.01) were predictive of successful ICP reduction by metabolic suppression (sensitivity and specificity 75%). In studies in which ICP decreased more than 20% compared with those in which ICP decreased less than 20%, baseline global CBF was higher (46 ± 16 ml/100 g/min compared with 34 ± 8 ml/100 g/min, p = 0.04) and baseline $PaCO_2$ was higher (35 ± 5 mm Hg compared with 31 ± 4 mm Hg; p = 0.005, logistic regression analysis). A baseline ICP value greater than 20 mm Hg was demonstrated in 15 (34.8%) of 43 studies. Of these 15 studies, ICP was found to decrease to less than 20 mm Hg in four (26.6%). In the 11 studies in which ICP remained above 20 mm Hg despite the administration of high-dose propofol, mean baseline ICP was higher (33 ± 10 mm Hg compared with 24 ± 2 mm Hg, p = 0.098) and the average decrease in ICP was less (8.7 ± 19.8% compared with 31.6 ± 14.4%; p = 0.06) than in studies in which ICP decreased below 20 mm Hg. Patients in 34 of 43 tests had reliable metabolic data. In studies of patients with relative hyperglycolysis (metabolic ratio < 0.6), a reduction in ICP was less than that in studies of patients with a normal metabolic ratio (−11.3 ± 25.5% compared with −31.3 ± 31.2%, p = 0.055).

TABLE 4

Results of metabolic suppression therapy tests

Parameter	No. of Studies	Baseline*	Burst Suppression*	p Value†
V_{MCA} (cm/sec)	43	73 ± 38	61 ± 36	<0.001
CBF (ml/100 g/min)	43	39.8 ± 13.8	33.5 ± 12.9‡	<0.001
ICP (mm Hg)	43	20 ± 10	16 ± 11	<0.001
CMRglu (mg/100 g/min)	34	3.7 ± 2.6	2.3 ± 1.5	0.003
$CMRO_2$ (ml/100 g/min)	43	1.4 ± 0.8	1.2 ± 0.7	0.003
$SjvO_2$ (%)	43	72 ± 8	75 ± 8	0.003
$PaCO_2$ (mm Hg)	43	33.0 ± 5.1	32.1 ± 5.4	0.02
jugular-venous $PaCO_2$ (mm Hg)	43	38.8 ± 5.4	37.3 ± 8.1	0.08
MABP (mm Hg)§	43	107 ± 12	107 ± 12	0.56
metabolic ratio (ml/mg)	34	0.64 ± 0.61	0.82 ± 0.78	0.21

* Values are expressed as the means ± SD.

† Probability values were calculated using the paired t-test for dependent variables, but their calculation did not take into account the presence of other contributing factors.

‡ The CBF during burst suppression was calculated based on the $\%\Delta V_{MCA}$ from baseline.

§ A relatively constant MABP was maintained using a titratable phenylephrine infusion as needed.

Discussion

Overview of Findings

The purpose of this study was to define the relative effectiveness of three commonly used therapies to reduce ICP, namely hyperventilation, induced hypertension, and metabolic suppression. Overall, ICP was reduced in 96.5, 34.6, and 79.1% of studies with hyperventilation, induced hyper-

TABLE 5

*Odds ratios for ICP decrease greater than 20% from the baseline value and 95% CI**

Comparison	OR	95% CI
hyperventilation compared w/ induced hypertension	65.3	22.0–193.9
metabolic suppression compared w/ induced hypertension	17.5	6.0–51.4
hyperventilation compared w/ metabolic suppression	3.7	1.7–8.2

* An ICP reduction of greater than 20% from baseline was observed in 77.2, 5.5, and 48.8% of studies for hyperventilation, induced hypertension, and metabolic suppression, respectively (hyperventilation compared with induced hypertension, p < 0.001; metabolic suppression compared with induced hypertension, p < 0.001; induced hyperventilation compared with metabolic suppression, p = 0.0045). Abbreviation: CI = confidence interval.

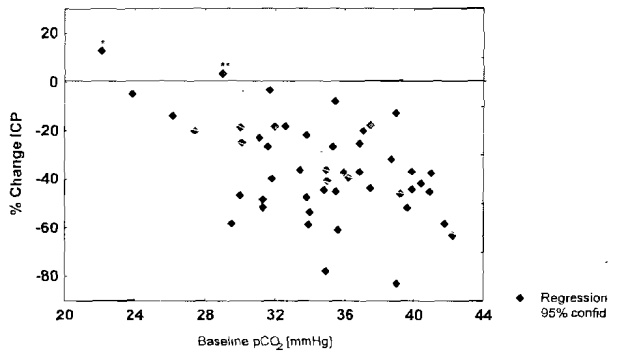

FIG. 2. Graph demonstrating a strong correlation between the baseline $PaCO_2$ and the %Δ in ICP with hyperventilation therapy. At a high baseline $PaCO_2$, hyperventilation is more effective. *This patient's ICP increased from 23 to 26 mm Hg while his $SjvO_2$ remained unchanged. The CBF at baseline was 30 ml/100 g/min. **This patient's ICP remained unchanged at 11 mm Hg, his baseline $SjvO_2$ was 62%, and his CBF was 37 ml/100 g/min. Confid. = confidence interval.

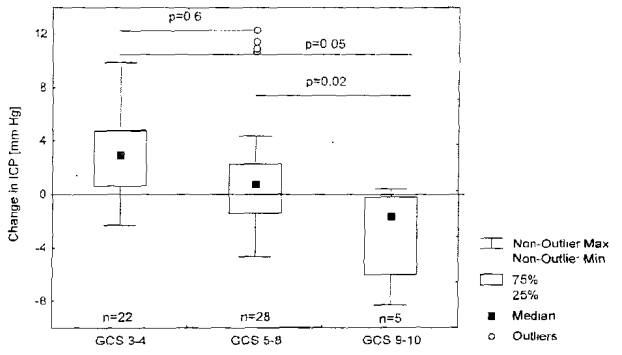

FIG. 3. Graph showing the ICP response to induced hypertension relative to the patient's GCS score at the time of the study. A higher study GCS score was associated with a greater likelihood of a decrease in ICP.

tension, and metabolic suppression therapies, respectively, and effective ICP reduction, defined as a decrease of more than 20%, was seen in 77.2, 5.5, and 48.8% of studies, respectively. Interestingly, in 31% of studies, induced hypertension resulted in an increase in ICP of more than 20% from its baseline value. Induced hypertension was useful in decreasing ICP only in patients with relatively higher study GCS scores. Metabolic suppression was most effective in lowering ICP when baseline global CBF, $PaCO_2$, and $CMRO_2$ were relatively elevated. Hyperventilation therapy was most effective when baseline $PaCO_2$ was higher. The clinical significance and pathophysiological implications of these findings are discussed later.

Methodological Issues

The nature of this study carries with it a selection bias for comatose head-injured patients with relative cardiopulmonary stability. When patients were capable of following commands, they were exempted from the study. Likewise, when they experienced hemodynamic or pulmonary instability, or when ICP was extremely labile, vasoreactivity tests were postponed. Nonetheless, the patients studied represent a fairly typical spectrum of severely and some moderately head injured patients. Regarding data analysis, the decision to present the data by individual study response as opposed to individual patient response was based on the fact that ICP treatment in head-injured patients often changes on a day-to-day, and sometimes an hour-to-hour, basis. Nonetheless, in repeated tests in individual patients an intraindividual correlation must be assumed. The statistical evaluation incorporated a methodology that corrected for this intraindividual correlation. Finally, the transient nature of these therapeutic manipulations makes conclusions regarding their long-term impact difficult to determine. For example, in this study we did not specifically address how long the beneficial ICP effects of hyperventilation may last.

Hyperventilation Therapy

Hyperventilation therapy has been used for almost three decades as a means of treating intracranial hypertension.[48,49] It is widely assumed that the hyperventilation-induced decrease in $PaCO_2$ causes arteriolar vasoconstriction, although the exact mechanism remains somewhat ill defined.[50] The observation in this study that hyperventilation caused a greater reduction in ICP at higher a baseline $PaCO_2$ may be explained by a nonlinear response of the cerebral arterioles to decreasing CO_2. In fact, Rosenberg[44] showed experimentally that profound hypocapnia causes a nonlinear decrease in CBF, thus indicating that a dilated arteriole can constrict significantly, whereas a markedly constricted arteriole may constrict only minimally.

In the "Guidelines for the Management of Severe Head Injury,"[4] authors state that hyperventilation below a $PaCO_2$ of 30 mm Hg should be avoided. This particular guideline is based on data from one randomized prospective trial, however, in which the deleterious effects of aggressive hyperventilation disappeared at 12 months postinjury in patients with GCS motor scores of 4 and 5.[36] Results of more recent studies demonstrate that the risk of "aggressive hyperventilation" to a $PaCO_2$ of less than 25 mm Hg has probably been overstated given that global ischemia (defined as an $SjvO_2 < 55\%$) has been rarely reported.[2,55]

That hyperventilation may also be safe on a local brain level was recently supported by data from a study in which cerebral microdialysis was performed in pericontusional brain during hyperventilation trials in severely head injured patients. Only minor elevations in pericontusional glutamate levels and the lactate/pyruvate ratio occurred during hyperventilation therapy, presumably because of the severe local impairment in CO_2 reactivity around the contusions.[30]

Data from the present study indicate that hyperventilation therapy is a highly effective means of reducing ICP in the majority of head-injured patients, at least transiently, and that it can be performed safely if done in conjunction with $SjvO_2$ monitoring.[43,53] Hypocapnia may be most useful during the posttraumatic hyperemic phase of brain injury, which generally occurs beyond the 1st day postinjury, lasts until postinjury Day 4 or 5, and is often associated with periods of marked intracranial hypertension.[24,25,33] Given that the vasoconstrictor effect of hyperventilation on pial arterioles diminishes after 24 hours,[37] sustained hyperventilation should be avoided if ICP is normal.[36] Hyperventilation during the first 6 to 12 hours postinjury when CBF is lowest should also be induced with caution.[10,33] Interestingly, however, results of a recent study indicate that hyperventilation to a $PaCO_2$ of a mean 29 mm Hg during the period from 8

to 14 hours after severe head injury resulted in no ischemia by $AVDO_2$ measures and no change in $CMRO_2$.[17]

Induced-Hypertension Therapy

Based on the theory of Lundberg's[31] plateau and B-waves, Rosner and colleagues[45,47] developed the concept of CPP management. This concept assumes the presence of a "vasoconstriction/vasodilatory cascade" in which a decrease in blood pressure or CPP results in arteriolar vasodilation, thus increasing CBV, which in turn increases ICP. In contrast, an increase in blood pressure causes an increase in CPP that triggers arteriolar constriction, and consequently CBV and ICP decrease.[47] This theory also assumes that although autoregulation is impaired after injury, at a high enough CPP, autoregulation will become more normal with the resultant beneficial effect on ICP. Data from our recent study of serial vasoreactivity tests indicate, however, that impaired pressure autoregulation occurs in two thirds of these tests despite a baseline CPP higher than 70 mm Hg.[29] Results from other previous studies have also shown that during the 1st week after head injury, autoregulation is impaired in 50 to 80% of patients.[8,9,16,20,27,54] Information from these studies and the present one demonstrate that even though a higher CPP may favorably influence autoregulation, in the majority of severely head injured patients, aggressive blood pressure elevations may exacerbate intracranial hypertension. Although in many instances the ICP increase is only minor, in almost one third of these instances, a greater than 20% ICP increase occurs when MABP is increased a mean of 14 mm Hg. The likelihood of significantly exacerbating ICP appears to be greatest within the first 4 days postinjury. Consequently, the beneficial rise in CPP must be balanced against the risk of worsened intracranial hypertension. One caveat is that the mean baseline MABP in this study was 104 mm Hg, which is already relatively elevated. It is possible that in some instances, these tests were begun at a level of arterial pressure that was already at the upper limit of the normal pressure autoregulation curve, such that further blood pressure elevations resulted in a pressure-passive increase in blood flow and ICP.[27]

Metabolic Suppression Therapy

Shapiro, et al.,[52] introduced metabolic suppression therapy in 1974 to initiate hypothermia in patients with intractable intracranial hypertension. Since then, investigators in numerous studies have addressed the benefits and side effects of high-dose barbiturate medication for severely head injured patients.[14,19,62] Results of a recent metaanalysis showed no benefit in outcome from the administration of barbiturates and emphasized the dangers of barbiturate-induced hypotension.[42] Clinical data on propofol are more limited. Data from one recent prospective study suggest that both sedation and ICP control are beneficial after moderate or severe head injury,[23] whereas data from another indicate that the long-term administration of high-dose propofol can be associated with serious side effects.[15]

Messeter, et al.,[35] reported that intact CO_2 reactivity was necessary to reduce ICP successfully with the aid of metabolic suppression therapy. In the present study, in 87.5% of test sessions, CO_2 reactivity was within normal range, and, on average, propofol-induced burst suppression resulted in a 21% ICP reduction. This finding is notable given that metabolic suppression reactivity was below normal in 88.4% of the tests. Propofol-induced ICP reduction is likely to be related to two possible mechanisms. The first and most well accepted is the ability of propofol to decrease cerebral metabolism. As demonstrated in animal studies, with intact coupling of metabolism and blood flow, CBF and CBV are both decreased, leading to a drop in ICP.[60] Alternatively, when metabolic blood–flow coupling is impaired, as was the case in the majority of patients in this study, administration of high-dose propofol nonetheless causes a global reduction in bodily metabolism and CO_2 production. Because of preserved CO_2 reactivity, this propofol-induced systemic hypocapnia likely leads to vasoconstriction and ICP reduction despite impaired metabolic reactivity.

In this study, predictors of effective ICP reduction with the use of high-dose propofol included a high baseline $PaCO_2$ and CBF. The metabolic effects of propofol were, on average, decreases in CBF, $CMRO_2$, and CMRglu by a mean 16, 11, and 18%, respectively, reductions less than those observed in normal animals.[1,5] This blunted metabolic response is likely related in part to the fact that cerebral oxidative and glucose metabolism are already markedly depressed after head injury.[7,40] Additionally, by maintaining a stable blood pressure during propofol infusion in this study, the hypotensive effect often seen with propofol or pentobarbital was eliminated, thereby reducing the overall decrease seen in CBF, $CMRO_2$, and CMRglu.[14,63]

Clinical Implications

In our recent study in which we assessed acute vasoreactivity changes in patients during the first 2 weeks after moderate or severe head injury, CO_2 reactivity remained relatively intact, autoregulation was variably impaired, and metabolic suppression reactivity was severely impaired.[29] In the present study, the resilience of CO_2 reactivity appears to translate into an effective means of ICP reduction, whereas the high degree of impaired pressure autoregulation translates into the frequent observation of a pressure-passive cerebral vasculature with blood pressure–induced ICP elevations. In contrast, the severe impairment of metabolic suppression vasoreactivity does not necessarily equate with the failure of this therapy in reducing ICP. This seemingly paradoxical observation likely occurs because of propofol-induced bodily hypocapnia and a resultant decrease in ICP. It is reasonable to assume that a similar bodily effect on $PaCO_2$ occurs with the administration of high-dose pentobarbital.

Although the importance of maintaining an adequate CPP after head injury has been stressed during the last decade,[3,47] the potential dangers of excessive CPP and the greater importance of ICP in determining outcome have been demonstrated in more recent studies.[22,43] In the recent study by Robertson, et al.,[43] of 189 severely head injured patients, those maintained with a CPP above 70 mm Hg and a $PaCO_2$ at 35 mm Hg did not have an improved outcome and had a higher complication rate compared with patients maintained with a CPP above 50 mm Hg and treated with hyperventilation therapy to a $PaCO_2$ of 25 to 30 mm Hg for high ICP. Results from a multicenter European pharmacological study of 427 severely head injured patients also demonstrated that an ICP greater than 20 mm Hg was the strongest

TABLE 6

Stepwise algorithm to treat elevated ICP

primary therapy
mild hyperventilation ($PaCO_2$ 30–35 mm Hg)
ventricular CSF drainage
sedation (narcotic agents, benzodiazepines)
neuromuscular blockade
secondary therapy (w/o jugular bulb catheter in place)
bolus mannitol therapy (25-g intravenous bolus every 6 hrs as needed)
elevation of MABP w/ vasopressor agent to increase CPP
additional secondary therapies (w/ jugular bulb catheter in place)*
moderate hyperventilation ($PaCO_2$ 25–30 mm Hg), maintaining $SjvO_2$ ≥60%
reduction of MABP (reducing or stopping infusion of vasopressor agents), maintaining $SjvO_2$ ≥60%
tertiary therapy
metabolic suppression w/ high-dose barbiturate agents or propofol

* The use of $SjvO_2$ monitoring allows for safer use of hyperventilation therapy and blood pressure changes by monitoring for treatment-induced global ischemia.

predictor of poor long-term outcome and that no benefit occurred by maintaining CPP above 60 mm Hg.[22] Data from these two studies in which investigators assessed outcome in relation to CPP and results of the present study in which we assessed the acute impact of blood pressure elevation on ICP indicate that induced hypertension to improve CPP and ICP should be performed with caution. In contrast, given that hyperventilation has been shown to be both safe and effective in reducing ICP in this study and others, its more routine use to levels below 30 mm Hg is probably reasonable during periods of intracranial hypertension beyond the first 6 to 12 hours postinjury. An additional advantage of moderate hyperventilation is that it may help to restore normal pressure autoregulation in head-injured patients, although this effect may be transient.[38]

To maximize the utility and minimize the risks of hyperventilation, induced hypertension, and metabolic suppression therapies, $SjvO_2$ monitoring is recommended for head-injured patients at risk for intracranial hypertension. Insertion of jugular bulb catheters is a relatively safe procedure in the hands of experienced intensivists and neurosurgeons.[64] With such monitoring, ICP treatment alternatives include judicious use of aggressive hyperventilation, blood pressure reduction or augmentation, and metabolic suppression therapy, with a goal of maintaining a normal $SjvO_2$ in the range of 60 to 70% (Table 6).

Conclusions

In this study we compared three commonly used methods of ICP control, namely hyperventilation therapy, induced hypertension, and metabolic suppression therapy. Hyperventilation was consistently effective, induced hypertension was consistently ineffective, and metabolic suppression therapy was variably effective. These findings support the more frequent use of hyperventilation in controlling intracranial hypertension after head injury, provided that appropriate monitoring of $SjvO_2$ is performed.

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