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 133Xe 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 26 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, PaCO2, and jugular venous oxygen saturation (SjvO2) were recorded. With hyperventilation therapy, patients experienced a mean decrease in PaCO2 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 did SjvO2 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 PaCO2 for hyperventilation, a high study GCS score for induced hypertension, and a high PaCO2 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 SjvO2.

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. More recently, maintenance of an adequate CPP, so-called CPP therapy, as described by Rosner and colleagues 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 cerebral blood flow; CBV = cerebral blood volume; CMRglu = cerebral metabolic rate for glucose; CMRO2 = cerebral metabolic rate for O2; CPP = cerebral perfusion pressure; eCVR = estimated cerebrovascular resistance; EEG = electroencephalography; ETCO2 = 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; SjvO2 = jugular venous O2 saturation; TCD = transcranial Doppler; UCLA = University of California at Los Angeles; Vmca = velocity of blood flow through the MCA; %Δ = percentage change.
SjvO₂ and brain tissue oxygenation and poorer long-term outcome after severe head injury. Use of metabolic suppression therapy with high-dose pentobarbital or propofol may also be associated with serious systemic complications. Aggressive CPP therapy with intravascular volume expansion and vasopressor agents can lead to pulmonary edema and end-organ ischemia.

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 CO₂ 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 ¹³³Xe 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 CPP and ICP, 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. 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 score of 3 to 12, and who required mechanical ventilation 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” 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 SjvO₂ and determination of AVDO₂ 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. 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 ¹³³Xe 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 CMR₀₂. Normal values for these parameters are as follows: CMRglu = 3.58 ± 0.29 ml/100 g/min and CMR₀₂ = 5.58 ± 1.07 mg/100 g/min.

**Physiological Monitoring.** Prior to and during each vasoreactivity test, MABP, ICP, CPP, and SjvO₂ were recorded. These values were used to determine the absolute and relative changes in ICP, CPP, and SjvO₂ 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 CO₂ Reactivity.** Increasing the ventilatory rate lowered PaCO₂, with a goal of decreasing ETCO₂ by 6 to 8 mm Hg. Blood gas analysis data obtained before and during hyperventilation confirmed the change. Average V̇MCO₂ was determined prior to and minute by minute after the change in PaCO₂. An initial blood gas sample was taken concurrently with the baseline TCD ultrasonography recording to determine actual PaCO₂. Mean arterial blood pressure was maintained at a constant level during the CO₂ reactivity testing by titrating a phenylephrine infusion as needed. Relative CO₂ reactivity was defined as the %Δ in V̇MCO₂ per mm Hg PaCO₂. Normal CO₂ reactivity was defined as 3.7 ± 0.5% ΔV̇MCO₂ per mm Hg PaCO₂. Global ischemia was defined as an SjvO₂ level less than 30%.

**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
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Autoregulation was calculated by measuring the change in eCVR (defined as MABP/V_MCA). 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 = (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. Studies were initiated at a baseline end-tidal PaCO2 value of 32 mm Hg. Baseline and final values obtained using TCD ultrasonography were adjusted by multiplying the raw values by the patient’s CO2 reactivity and the difference between the baseline PaCO2 and the standard value of 34 mm Hg.

Metabolic Suppression Vasoreactivity. Propofol, an ultra–short acting, sedative/anesthetic/nonanalgesic drug was used to induce EEG burst suppression. 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. 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 CO2-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 PaCO2 value of 34 mm Hg, based on the patient’s CO2 reactivity for that day. Patients whose baseline MABP was lower than 80 mm Hg had metabolic suppression reactivity testing postponed or canceled.

Values of A/V (AVDglu) and AVDVO2 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 CMRO2 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 (CMRO2/CMRGlu) was also determined at each test. An abnormally low metabolic ratio (CMRO2/CMRGlu < 0.6) indicates that cerebral glucose use is high relative to O2 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, SvO2, PaCO2, ETCO2, jugular venous CO2, CMRO2, AVDVO2, CMRGlu, and AVDglu as well as the derived values for CO2 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.

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, CO2 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 PaCO2 was 35 ± 5 mm Hg and decreased by a mean of 8 ± 5 mm Hg. In all tested variations, the correlation between ETCO2 and PaCO2 was statistically significant but poor (baseline: ETCO2 compared with PaCO2, r = 0.59, p < 0.001; hyperventilation, r = 0.52, p < 0.001; ΔETCO2 compared with ΔPaCO2, 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
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 SjvO₂ from 73 ± 8% to 67 ± 8% (p < 0.001). No change in SjvO₂ was recorded in one third of all studies. In none of the studies did SjvO₂ decrease below 55%, and in only eight (24.2%) of 33 did SjvO₂ 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); SjvO₂ 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 MABP was 104 ± 12 mm Hg and on average increased by 10 ± 10 mm Hg (p = 0.001). 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 CMRO₂ 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 CMRO₂ 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 SjvO₂ 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 value. The likelihood of hyperventilation or metabolic suppression 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 PaCO₂ was predictive of the degree of reduction in ICP. The higher the baseline PaCO₂, 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
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**TABLE 3**
Results of induced-hypertension therapy tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Studies</th>
<th>Baseline*</th>
<th>Hypertension*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>55</td>
<td>104 ± 12</td>
<td>118 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>55</td>
<td>88 ± 15</td>
<td>100 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>55</td>
<td>16 ± 9</td>
<td>19 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>*SvO₂ (%)</td>
<td>55</td>
<td>71 ± 27</td>
<td>76 ± 29</td>
<td>0.002</td>
</tr>
<tr>
<td>SjvO₂ (%)</td>
<td>37</td>
<td>72 ± 7</td>
<td>74 ± 9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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.

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 CO₂ reactivity on the day of the study also did not correlate with the degree of decrease in ICP, although CO₂ reactivity was generally intact (mean value 3.2 ± 1.5 ΔSvO₂/mm Hg PaCO₂) 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 decreased 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 SjvO₂.

**Metabolic Suppression Therapy.** Of all assessed factors, only a high baseline global CBF (OR 1.1, p = 0.01) and a high baseline PaCO₂ (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 PaCO₂ 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 = 0.0098) 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).

**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 4**
Results of metabolic suppression therapy tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Studies</th>
<th>Baseline*</th>
<th>Burst Suppression*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̅O₂ (cm/sec)</td>
<td>43</td>
<td>73 ± 38</td>
<td>61 ± 36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>43</td>
<td>39.8 ± 13.8</td>
<td>33.5 ± 12.9†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>43</td>
<td>20 ± 10</td>
<td>16 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMRglu (mg/100 g/min)</td>
<td>34</td>
<td>3.7 ± 2.6</td>
<td>2.3 ± 1.5</td>
<td>0.003</td>
</tr>
<tr>
<td>jugular-venous PaCO₂</td>
<td>43</td>
<td>38.8 ± 5.4</td>
<td>37.3 ± 8.1</td>
<td>0.08</td>
</tr>
<tr>
<td>MABP (mm Hg)§</td>
<td>43</td>
<td>107 ± 12</td>
<td>107 ± 12</td>
<td>0.56</td>
</tr>
<tr>
<td>metabolic ratio (ml/mg)</td>
<td>34</td>
<td>0.64 ± 0.61</td>
<td>0.82 ± 0.78</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* 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 %ΔSvO₂ from baseline.

**TABLE 5**
Odds ratios for ICP decrease greater than 20% from the baseline value and 95% CI*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperventilation compared w/ induced hypertension</td>
<td>65.3</td>
<td>22.0–193.9</td>
</tr>
<tr>
<td>metabolic suppression compared w/ induced hypertension</td>
<td>17.5</td>
<td>6.0–51.4</td>
</tr>
<tr>
<td>hyperventilation compared w/ metabolic suppression</td>
<td>3.7</td>
<td>1.7–8.2</td>
</tr>
</tbody>
</table>

* 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 hypertension compared with metabolic suppression, p = 0.0045). Abbreviation: CI = confidence interval.
Hyperventilation therapy has been used for almost three decades as a means of treating intracranial hypertension. It is widely assumed that the hyperventilation-induced decrease in PaCO₂ causes arteriolar vasoconstriction, although the exact mechanism remains somewhat ill-defined. The observation in this study that hyperventilation caused a greater reduction in ICP at higher a baseline PaCO₂ may be explained by a nonlinear response of the cerebral arterioles to decreasing CO₂. In fact, Rosenberg 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,” authors state that hyperventilation below a PaCO₂ 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. Results of more recent studies demonstrate that the risk of “aggressive hyperventilation” to a PaCO₂ of less than 25 mm Hg has probably been overstated given that global ischemia (defined as an SjvO₂ < 55%) has been rarely reported.

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 CO₂ reactivity around the contusions.

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 SjvO₂ monitoring. 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. Given that the vasoconstrictor effect of hyperventilation on pial arterioles diminishes after 24 hours, sustained hyperventilation should be avoided if ICP is normal. Hyperventilation during the first 6 to 12 hours postinjury when CBF is lowest should also be induced with caution. Interestingly, however, results of a recent study indicate that hyperventilation to a PaCO₂ of a mean 29 mm Hg during the period from 8
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Induced-Hypertension Therapy

Based on the theory of Lundberg's plateau and B-waves, Rosner and colleagues 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 consequentially CBV and ICP decrease. 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. 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. 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.

Metabolic Suppression Therapy

Shapiro, et al., 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. Results of a recent metaanalysis showed no benefit in outcome from the administration of barbiturates and emphasized the dangers of barbiturate-induced hypotension. 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, whereas data from another indicate that the long-term administration of high-dose propofol can be associated with serious side effects.

Messeter, et al., reported that intact CO2 reactivity was necessary to reduce ICP successfully with the aid of metabolic suppression therapy. In the present study, in 87.5% of test sessions, CO2 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. 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 CO2 production. Because of preserved CO2 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 PaCO2 and CBF. The metabolic effects of propofol were, on average, decreases in CBF, CMRO2, and CMRglu by a mean 16, 11, and 18%, respectively, reductions less than those observed in normal animals. 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. 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 in CBF, CMRO2, and CMRglu.

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, CO2 reactivity remained relatively intact, autoregulation was variably impaired, and metabolic suppression reactivity was severely impaired. In the present study, the resilience of CO2 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 PaCO2 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, potential dangers of excessive CPP and the greater importance of ICP in determining outcome have been demonstrated in more recent studies. In the recent study by Robertson, et al., of 189 severely head injured patients, those maintained with a CPP above 70 mm Hg and a PaCO2 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 PaCO2 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
primary therapy
  mild hyperventilation (PaCO2, 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 (PaCO2, 25–30 mm Hg), maintaining
  SjvO2 ≥60%
  reduction of MABP (reducing or stopping infusion of vasopressor
  agents), maintaining SjvO2 ≥60%
  tertiary therapy
  metabolic suppression w/ high-dose barbiturate agents or propofol

* The use of SjvO2 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 oc-
  curred by maintaining CPP above 60 mm Hg. 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 rea-
  sonable 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, al-
  though this effect may be transient.

To maximize the utility and minimize the risks of hy-
  perventilation, induced hypertension, and metabolic sup-
  pression therapies, SjvO2 monitoring is recommended for
  head-injured patients at risk for intracranial hypertension.
  Insertion of jugular bulb catheters is a relatively safe proce-
  dure in the hands of experienced intensivists and neurosur-
  geons. With such monitoring, ICP treatment alternatives
  include judicious use of aggressive hyperventilation, blood
  pressure reduction or augmentation, and metabolic suppres-
  sion therapy, with a goal of maintaining a normal SjvO2 in
  the range of 60 to 70% (Table 6).

Conclusions

In this study we compared three commonly used meth-
  ods of ICP control, namely hyperventilation therapy, in-
  duced hypertension, and metabolic suppression therapy. Hy-
  perventilation was consistently effective, induced hyper-
  tension was consistently ineffective, and metabolic suppres-
  sion therapy was variably effective. These findings support
  the more frequent use of hyperventilation in controlling in-
  tracranial hypertension after head injury, provided that ap-
  propriate monitoring of SjvO2 is performed.

References

  propofol anesthesia in humans studied with positron emission to-
  mography. Anesthesiology 82:393–403, 1995
2. Allen CH, Ward JD: An evidence-based approach to management of
4. Anonymous: The use of hyperventilation in the acute management of
  severe traumatic brain injury. Brain Trauma Foundation. J
5. Artru AA, Shapiro Y, Bowdle TA: Electroencephalogram, cere-
  bral metabolic, and vascular responses to propofol anesthesia in
  head injury with early diagnosis and intensive management. J
  Neurosurg 47:491–502, 1977
  glucose metabolism and level of consciousness during the period of
  metabolic depression following human traumatic brain injury. J
  Neurotrauma 17:389–401, 2000
8. Bouma GI, Muizelaar JP: Cerebral blood flow, cerebral blood vol-
  ume, and cerebrovascular reactivity after severe head injury. J
9. Bouma GI, Muizelaar JP: Cerebral blood flow in severe clinical head
  tion of regional cerebral blood flow in severely head-injured pa-
  tients using xenon-enhanced computerized tomography. J Neu-
  rosurg 77:360–368, 1992
11. Bricolo AP, Glick RP: Barbiturate effects on acute experimental
  fects of mannitol following experimental head injury. J Neu-
  rosurg 50:423–432, 1979
  metabolism in man during halotane anesthesia. Effects of PaCO2,
  on some aspects of carbohydrate utilization. Anesthesiology 25:
  186–191, 1964
  ic effects of pentobarbital coma in head-injured patients. J Neu-
  rosurg 35:927–936, 1999
  infusion and cardiac failure in adult head-injured patients. Lancet
  357:117–118, 2001
  cerebral autoregulation in head-injured patients. Stroke 27:
  1829–1834, 1996
17. Diringer MN, Yundt K, Videen TO: No reduction in cerebral me-
  tabolism as a result of early moderate hyperventilation following
18. Doyle PW, Matta BF: Burst suppression or isoelectric encepha-
  logram for cerebral protection: evidence from metabolic suppres-
19. Eisenberg HM, Frankowski RF, Contant CF, et al: High-dose bar-
  biturate control of elevated intracranial pressure in patients with
  flow and intraventricular pressure in acute head injuries. J Neu-
  rosurg Psychiatry 37:1378–1388, 1974
  severe head injury. Neurochirurgia 20:35–47, 1977
  and cerebral perfusion pressure: influence on neurological deteri-
  oration and outcome in severe head injury. The Executive Com-
  mittee of the International Selfotel Trial. J Neurosurg 92:1–6,
  2000
  of moderate and severe head injury: a randomized, prospective

TABLE 6
Stepwise algorithm to treat elevated ICP

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Management</th>
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<tr>
<td>Primary therapy</td>
<td>mild hyperventilation (PaCO2, 30–35 mm Hg)</td>
</tr>
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</table>
| Penventilation             | induced hypertension, metabolic sup-
| (w/o jugular bulb catheter | pression                              |
| in place)                  | bolus mannitol therapy (25 g intravenous |
|                            | bolus every 6 hrs as needed)            |
| Elevation of MABP         | vasopressor agent to increase CPP      |
| (additional secondary     | reduction of MABP (reducing or stopping |
| therapies (w/ jugular      | infusion of vasopressor                |
| bulb catheter in place)   | agents)                                 |
| Moderate hyperventilation | PaCO2, 25–30 mm Hg, maintaining         |
| (w/o jugular bulb         | SjvO2 ≥60%                              |
| catheter in place)         | reduction of MABP (reducing or stopping |
|                           | infusion of vasopressor agents)         |
| Tertiary therapy          | metabolic suppression w/ high-dose      |
|                           | barbiturate agents or propofol          |

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