An additional therapeutic effect of adequate hyperventilation in severe acute brain trauma: normalization of cerebral glucose uptake

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In a total of 309 frequent serial studies, arteriojugular differences in glucose and oxygen levels were concurrently evaluated in 33 adult patients who were experiencing the most acute phase of severe brain trauma.

Hyperventilation therapy was optimized to maintain both normalized intracranial pressure and cerebral extraction of oxygen. Under these circumstances, global cerebral glucose extraction was found to be closest to normal during profound optimized hyperventilation, with PaCO₂ levels below 25 mm Hg. In contrast, during normocapnia global cerebral glucose extraction dropped below normal range, indicating impairment of cerebral glucose uptake.

Findings from this study show that in severe acute brain injury, optimized hyperventilation exerts an additional metabolic effect with respect to cerebral glucose uptake.

KEY WORDS • head injury • coma • intracranial pressure • arteriojugular oxygen difference • arteriojugular glucose difference • optimized hyperventilation

Additional physiological effects of hypocapnia were investigated in relation to cerebral glucose uptake. Studies were conducted in light of the management of posttraumatic intracranial hypertension, primarily by means of optimized hyperventilation.

Clinical Material and Methods

Patient Selection

Thirty-three comatose adults with severe acute brain trauma were prospectively evaluated. The patients ranged in age from 16 to 76 years (median 32 years) and their Glasgow Coma Scale scores ranged from 4 to 8 (mean 6). All patients who were evaluated remained comatose for at least 24 hours.

On admission to the hospital, computerized tomography (CT) scans of each patient’s head revealed predominantly diffuse brain swelling, determined by small lateral ventricles and effacement or obliteration of the basilar cisterns. In 21 patients (64%), the brain swelling was associated with hemorrhagic contusions; in seven patients (21%), it was also associated with an acute subdural hematoma. The latter was removed as soon as possible after CT scans were obtained.
Exclusion Criteria

Patients were excluded from the study if they presented with clinical signs of impending or actual brain death on admission to the Intensive Care Unit (ICU). These signs were associated with one or more of the following events: initially unmanageable intracranial hypertension; a cranial CT scan that disclosed midline shift greater than 1.5 cm; or evidence of prolonged and profound arterial hypotension and/or hypoxemic hypoxia prior to ICU admission. Patients were also excluded from the study if they presented with CT evidence of preserved cerebrospinal fluid (CSF) spaces, as in the case of a normal scan, or if the condition was diagnosed as pure diffuse axonal injury without associated brain swelling.

Monitoring and Management

Posttraumatic intracranial hypertension was a requirement for entry into the study. Intracranial hypertension was indicated when spontaneous and sustained intracranial pressure (ICP) elevations reached 20 mm Hg or greater over a period of 10 or more minutes despite ongoing sedation and mild hyperventilation.

Once in the ICU, patients were positioned and maintained at a head tilt of approximately 30°. Routine continuous monitoring was instituted for electrocardiogram, pulse oximetry, body temperature, systemic arterial pressure, and ICP. The latter was recorded from the subarachnoid space in all patients. Additional intermittent monitoring was adopted for arterial and jugular bulb oxyhemoglobin saturation, carbon dioxide tension, and glucose concentration.

The jugular bulb was catheterized percutaneously with standard 16- or 19-gauge intracatheters at the level of the cricoid cartilage without turning or lowering the patient’s head. The tip of the catheter was properly positioned inside the right jugular bulb in a manner previously demonstrated.16 Arteriojugular monitoring was initiated between 3 and 8 hours postinjury in 21 cases (64%) and between 8 and 36 hours in the remaining cases.

Central venous lines were placed in all patients to guide normovolemic fluid management. For patients who required more careful systemic hemodynamic monitoring, central venous lines were replaced by Swan Ganz catheters. Patients routinely received 5% dextrose in normal saline solution administered intravenously. This was replaced by total parenteral nutrition after the first 48 to 72 hours. Occasional episodes of transient hypovolemia were managed by prompt, sometimes vigorous, volume expansion with normal saline solution and/or 5% albumin. Vasodilting agents were required in only three patients because of barbiturate (Nembutal) administration for ICP control after termination of the studies.

The protocol for controlling ICP levels below 20 mm Hg has been described elsewhere.3 In the present series, no patient underwent ventricular catheterization, thus CSF drainage was not adopted for ICP control. After the studies were completed, supplementary barbiturate therapy was required in only five cases and decompressive craniotomy in two. Induced hypothermia was not adopted.

For the most part, the underlying therapeutic regimen was a combination of periodic sedation, paralysis, and bolus injections of 25% mannitol, which supplemented sustained optimized hyperventilation. Hyperventilation consisted of upward or downward titration of PaCO2, used to maintain simultaneously normalized ICP and global cerebral extraction of oxygen (CEO2)3,4,6–12 (arteriojugular oxyhemoglobin saturation difference).

Although CEO2 was modulated by decreasing or increasing PaCO2,3,11 and by administering 25% mannitol in a fast intravenous bolus, if necessary,11 no specific management strategy was adopted to control cerebral glucose uptake. Arteriojugular glucose measurements were evaluated for observational purposes only because, although several studies have focused on the management of CEO2,3,8,10,11 no study has been reported that addresses the management of cerebral extraction of glucose (CEG) in severe acute brain trauma.

Optimized hyperventilation for ICP control was gradually made more pronounced as problems with ICP became more prominent. Conversely, in cases in which normal and stable ICP values could be sustained for at least 18 hours, patients were gradually allowed to become normocapnic. The average duration of ICP and arteriojugular monitoring was 6 days. No complications resulted from this prolonged internal jugular catheterization.

Data Collection and Analysis

A total of 309 simultaneous, multivariate physiological studies were completed with a mean of 9.5 studies per patient. Studies were performed on each patient at approximately 12-hour intervals over an average period of 4.5 days. Measurements were obtained and evaluated for ICP; cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure and ICP; PaCO2; CEO2; arteriojugular glucose concentration difference; and body temperature.

To fine tune the measurements of arteriojugular glucose concentration, over 3300 repeated blood glucose determinations were performed immediately after paired blood sampling (average of 5.5 arterial and jugular measurements per sample) and their mean values were assessed. Glucose concentration was measured in whole blood, using a polarographic analyzer with a glucose oxidase device. Blood samples were maintained on ice throughout the repeated measurements. Good measurement stability was found, with only four studies deleted from the analysis because their standard deviation of the repeated glucose measurements exceeded 10% of the mean values.

On the basis of data provided by Gibbs, et al.,15 from the largest known series of spontaneously breathing volunteers, we assessed raw data and calculated the normal range for CEO2. At first, a normal range of 31.6% ± 7.8% (mean ± 2 standard deviations) was proposed.16 Subsequently, a small correction of 2% was made to account for frequent increases in arterial oxyhemoglobin saturation during mechanical ventilation of patients in the ICU. This corrected normal range is approximately 24% to 42%.3,4,17 The normal range for arteriojugular glucose concentration difference is 6.5 to 13 mg percent18 and requires no corrections for mechanical ventilation.

* Glucose–Lactate analyzer, Model 2300, manufactured by Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.
These normal ranges are based on physiological values previously found to lie within an approximately normal statistical distribution. On the basis of these ranges, metabolic coupling or uncoupling was evaluated between global cerebral oxygen and glucose uptake; normal coupling was identified when both arteriojugular measurements lay within their respective normal ranges, and uncoupling was identified when that was not the case.

Based on ICP requirements for optimized hyperventilation, studies were conducted during three ventilatory phases: Phase N, normocapnia; Phase M, moderate hyperventilation (PaCO₂ in the range of 25 to 30 mm Hg); and Phase P, profound hyperventilation (PaCO₂ below 25 mm Hg). All of the patients had multivariate physiological measurements taken as they progressed through the three ventilatory phases. For statistical purposes, each patient’s multiple measurements were first averaged to a single value within ventilatory phases so that they could be evaluated as independent parameters.

After the procedure described above, multivariate changes that occurred among the three ventilatory phases were assessed by analysis of variance (ANOVA). For arteriojugular measurements of oxygen and glucose, the absolute differences between the ventilatory phases were assessed by t-test. The z-scores were used to assess the relative differences in these two variables within the ventilatory phases. The summary data resulting from these procedures are presented as the means ± standard deviation with a p value of less than 0.05 considered to be significant. Outcome at 6 months postinjury was assessed according to the Glasgow Outcome Scale. Institutional Review Board approval of all testing was obtained.

**Results**

**Postinjury Outcome**

At 6 months postinjury, 23 of the patients evaluated (70%) had achieved good recovery or mild or moderate disability and resumed independent life activities; five patients (15%) had severe disability, although fully conscious; one patient (3%) was in a prolonged vegetative state; and four patients (12%) had died, only one of whose death was a result of unmanageable intracranial hypertension.

**Physiological Findings**

Table 1 shows the distribution of physiological differences across the three ventilatory phases as assessed by ANOVA. As seen, higher ICP levels were associated with lower levels of PaCO₂ (according to the treatment protocol). Cerebral perfusion pressure, however, remained normal, with no significant differences among ventilatory phases. A similar lack of differences was found for body temperature. In contrast to values for CEO₂, which lie well within the normal range across ventilatory phases, values for arteriojugular glucose difference fell significantly below normal during normocapnia. Values for CEG came closest to normal during profound optimized hyperventilation.

With regard to absolute physiological differences, analysis by t-test showed no significant differences for CEO₂ or for arteriojugular glucose difference when compared between conditions of profound and moderate hyperventilation. However, significant differences were found for these variables when compared between conditions of profound hyperventilation and normocapnia (p < 0.03 for CEO₂; p < 0.0001 for arteriojugular glucose difference). The same was true between conditions of moderate hyperventilation and normocapnia (p < 0.02 for cerebral extraction of oxygen; p < 0.03 for arteriojugular glucose difference). Figure 1 illustrates these findings as well as other patterns of arteriojugular differences in relation to their respective normal ranges.

With regard to the relative physiological differences that appear within ventilatory phases, z-scores were significantly different for CEO₂ compared to arteriojugular glucose difference (p < 0.001); that is, CEO₂ was relatively higher than CEG in all three ventilatory phases. The best metabolic coupling, signified by the smallest relative difference between cerebral oxygen and glucose uptake, was found during profound optimized hyperventilation (Fig. 2).

**Discussion**

**Interpretation of the Present Findings**

Adequate interpretation of physiological changes during the three distinct ventilatory phases requires a basic understanding that in patients with posttraumatic brain swelling, phasic changes in cerebral blood flow (CBF) may occur very frequently. In a previous study in which frequent serial measurements of CBF were conducted throughout the acute phase, Zane, et al., identified a phase of cerebral hyperemia that occurred during an average 3-day period following a brief phase of reduced CBF. This pattern represented phasic hemodynamic changes in the overall population of severely head injured patients.
In patients with severe posttraumatic brain swelling, however, the time period related to decreased CEO2 (relative cerebral hyperperfusion) and associated intracranial hypertension may last longer than it does in the overall population of severely head injured patients. Further, although the appearance of elevated ICP in the very early hours following injury may or may not be associated with relative cerebral hypoperfusion (increased CEO2), the overall tendency for patients with posttraumatic brain swelling is to develop cerebral luxury perfusion soon afterward.

In fact, owing to continuous monitoring of CEO2, it has become clear that global cerebral luxury perfusion (decreased CEO2) may be an unequivocal contributor to the development of severe intracranial hypertension. This association previously had been identified by Obrist, et al., in the overall population of head injured patients by means of combined measurements of CBF and oxygen metabolism. Although that study was limited by a lack of continuous measurements, our two studies involving online hemodynamic–metabolic monitoring confirmed the clinical relevance of posttraumatic cerebral luxury perfusion. In these two studies, despite the frequent occurrence of life-threatening increases in ICP, prompt therapeutic interventions (including profound hyperventilation) were associated with extremely favorable outcome figures.

The present findings reveal that higher ICP levels were associated with lower PCO2 values (according to the protocol for hypocapnic optimization). However, during profound optimized hypocapnia, CEO2 was therapeutically normalized and did not significantly differ from that occurring during moderate hypocapnia. This finding provides clear evidence that profound optimized hypocapnia was properly adjusted to offset more pronounced cerebral luxury perfusion and its associated higher levels of ICP. Had profound hypocapnia been adopted without measurements of CEO2, adequate normalization of this parameter would not be possible.

Also relevant, during profound optimized hypocapnia, CEG was close to normal rather than abnormally increased. This finding also supports the physiological adequacy of profound optimized hypocapnia, in light of phasic changes in cerebral hemodynamics and ICP. During the most pronounced problems with ICP, profound optimized hypocapnia not only was a contributor to ICP control (sometimes supplemented by other therapies), but did not result in ischemic cerebral anaerobiosis. This is clear because the latter would be reflected by abnormally increased, not normalized, CEO2 and CEG.

With respect to CPP the present findings also disclose that, without the need for iatrogenic hypervolemia and arterial hypertension, aggressive, optimized, and combined therapeutic normalization of ICP and CEO2 results in adequate levels of CPP as well. This is clear from the
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lack of statistically significant differences in normal CPP across the three ventilatory phases.

Hyperventilation Versus Other Therapies

Among the most currently adopted therapeutic modalities for the management of acute posttraumatic brain swelling and associated intracranial hypertension, hyperventilation stands out as a single multivariate strategy. Hyperventilation produces several simultaneous physiological effects: restoration of impaired pressure autoregulation; increase in cerebral oxygen metabolism, in terms of CMRO₂; resolution of global cerebral luxury perfusion and associated ICP problems; improvement or maintenance of adequate systemic hemodynamics; normalization in the sense of an increase of cerebral glucose uptake (present findings).

In contrast, other therapies have had fewer clinically relevant effects. Among those are improved control of intracranial hypertension by barbiturate therapy; satisfactory and temporary ICP response to mannitol; and increases in CBF and oxygenation by mannitol.

In light of recent ongoing attempts to manage severely head injured patients using experimental drugs, the possibility arises that some of these therapies may be found to have at least the same multiple positive effects identified for hyperventilation. In fact, insofar as normalization of cerebral glucose uptake represents a step for optimization of cerebral aerobic metabolism, the present findings associated with profound optimized hypocapnia appear to be relevant. To the best of our knowledge, similar results have not been previously reported.

Thus, we can state for the first time that, in addition to contributing to a sustained normalization of elevated ICP, optimized hypocapnia has a dual cerebral metabolic effect: it simultaneously allows adequate coupling between global CBF and CMRO₂ (expressed by normalization of CEO₂), and contributes to the optimization of global cerebral glucose uptake in relation to cerebral oxygen metabolism.

Global Arteriojugular Measurements

A relative concern about global arteriojugular monitoring is that regional cerebral ischemia is not detectable by this technique. However, in one of our earlier reports on regional (r)CBF and global cerebral oxygen extraction in acute brain trauma, an excellent inverse relationship was found to exist between mean regional flow values and those of global cerebral oxygen extraction. Furthermore, in response to hypocapnia at PaCO₂ levels below 25 mm Hg, Öbrist and coworkers have found that the rCBF map becomes more homogeneous than at higher PCO₂ levels. This occurs because hyperemic foci are hyperreactive to PCO₂ manipulations, in contrast to areas of reduced CBF.

To fine tune an assessment of regional cerebral ischemia, however, it is our impression that studies involving positron emission tomography would be the most suitable. In addition to measuring rCBF, this technique allows quantification of regional cerebral oxygen extraction. The latter provides more information than CBF alone (irrespective of the technique) because it describes the balance between blood flow and oxygen consumption. Unfortunately, to the best of our knowledge, a truly regional technique for bedside assessment of CEO₂ is not yet available.

In the present series, no patient evaluated developed signs of regional cerebral infarction-ischemia on follow-up CT scans. Whether more subtle ischemic changes developed (not assessable by CT scans) remains a subject for future studies. This fascinating question will hopefully be clarified when an adequate technique becomes available for bedside assessment of truly (multi-) regional cerebral ischemia. This technique would add substantially to others, such as in the case of near-infrared spectroscopy or microdialysis probes, which only allow focal measurements.

Cerebral Extraction of Oxygen

The present work involved a comparative analysis of CEO₂ and arteriojugular glucose concentration difference. Cerebral extraction of oxygen was chosen as a focus instead of arteriojugular oxygen content difference because the latter is only a reliable parameter of cerebral oxygen metabolism under nonanemic conditions. Cerebral extraction of oxygen, however, is a stable parameter under anemic or nonanemic conditions. In fact, statistically significant differences between these two variables have been found under conditions of both profound and moderate acute anemia. Because acute anemia was found in 30 patients (90.9%) in the present series, CEO₂ was a more appropriate option for physiological assessment.

Clinical Implications

In addition to the combined effects described above, prolonged optimized hyperventilation appears to shorten substantially the duration of monitoring and management involved with severely brain injured patients in the ICU. In fact, in previous studies of patients with severe posttraumatic brain swelling who were subjected to prolonged optimized hypocapnia, the average duration of ICP monitoring and management was close to 1 week. This is in sharp contrast with the 2 to 3 weeks reported by Rosner and Daughton, used for an overall population of severely head injured patients for whom hyperventilation was not instituted.

Also relevant is the fact that optimized hyperventilation is based on easy physiological ventilatory manipulations. This is in contrast to mannitol, whose limitations regarding serum osmolality prove significant in some cases, or barbiturate therapy, whose frequent arterial hypotensive effects require aggressive, careful surveillance of systemic and cerebral hemodynamics, sometimes for prolonged periods of time.

An additional feature of prolonged optimized hypocapnia is that, as previously reported, its effects on humans can be observed well beyond the initial 24 hours postinjury, on Days 2 and 3 after trauma. This contrasts with the effects of hypocapnia observed at the pial arteriolar level, in the nontraumatized rabbit brain. These findings from normal animal experimentation have been extrapolated to human brain trauma and contraindicate hyperventilation after 24 hours, for its presumed loss of effectiveness.

In this latter study by Muizelaar and colleagues, however, frequent serial studies of CBF and its relation to ICP...
and optimized hypocapnia were not reported; instead, only overall data on CBF and oxygen metabolism were presented. In light of our findings on continuous monitoring of CEO₂ and ICP, frequent serial measurements of CBF, and the present series, a different interpretation of the physiological findings must be considered. This is because, rather than interpreting cerebrovascular CO₂ reactivity based entirely on changes in CSF pH, the natural history of posttraumatic cerebral luxury perfusion now appears to play a distinct role; whether or not it is related to pH changes, cerebral hyperemia tends to develop, to become severe, and to resolve.

Under these circumstances, it is apparent that a constant PCO₂ level throughout the acute phase will not therapeutically match the natural history of phasic changes in CBF in patients with severe acute brain trauma. In the present work, however, adequate therapeutic phasic changes in PCO₂ resulted in simultaneous, multivariate optimization of ICP, CPP, CEG, and CEO₂. Simultaneous normalization of ICP and CEO₂, by means of optimized hypocapnia, has also been found not to result in cerebral ischemia, assessed by frequent measurements of cerebral lactate production.

Can Hyperventilation Be Harmful?

The present methodology sharply differs from that of a randomized clinical trial, in which adverse effects of hyperventilation were addressed by Muizelaar, et al. Two major methodological differences exist between the studies: 1) in the present series, all of the patients (100%) presented with ICP values of 20 mm Hg or greater for arteriojugular monitoring and optimized hypocapnia to be clinically indicated. In the series by Muizelaar, et al., however, only 14% of the patients initially had high ICP (see Table 1 of that study). Nevertheless, approximately two-thirds of those patients were immediately started on hyperventilation, according to the randomization protocol. 2) Patients were not consecutively admitted into our study. Optimized hypocapnia was indicated on the basis of combined findings of diffuse brain swelling found on CT scan, ICP, and CEO₂. According to our methodology, some patients underwent temporary upward manipulations of PCO₂ whenever CEO₂ was increased. Conversely, the combination of decreased CEO₂ and elevated ICP indicated to us the need for more profound optimized hypocapnia. In the series by Muizelaar, et al., on the other hand, consecutively admitted patients were selected to be or not to be hyperventilated for several days, and at constant PCO₂ levels. Such selection was based entirely on randomization, and not on the criteria adopted in our work.

In one of our previous studies on CBF and metabolism and their relation to posttraumatic intracranial hypertension, we had stressed that hypocapnia in patients with reduced blood flow resulted in increased global cerebral oxygen extraction, a finding that was suggestive, although not necessarily indicative, of cerebral ischemia. In the same study, we emphasized that patients with reduced CBF differed significantly from those with hyperemia; the former tended to have normal levels of ICP, whereas the latter more frequently presented with intracranial hypertension. It is, therefore, somewhat surprising that a randomized clinical trial conducted in the manner described after potential side effects of hyperventilation in patients with normal ICP had been addressed.

Outcome

The present outcome figures are not representative of the overall population of severely head injured patients. As stated in the Methods section, patients in our study were selected on the basis of the appearance of decreased CSF spaces on CT scan and concurrent high ICP levels. In contrast, in studies evaluating the outcome of consecutively admitted comatose patients, monitoring and management were not described in relation to the type of lesion appearing on CT scans. In addition, in the study by Muizelaar, et al., only 14% of consecutively admitted comatose patients were found to have intracranial hypertension in the most acute phase, and in the study undertaken by Rosner and Daughton, information was not provided on the incidence of initial intracranial hypertension.

In another recent study in which hyperventilation was not adopted, Marion, et al., reported a lack of statistically significant outcome differences in patients randomized to be or not to be treated with moderate hypothermia. Once again, information was not provided about stratification of patients based on the type of lesion seen on the CT scan and incidence of acute intracranial hypertension. In a similar manner, in another study by Muizelaar, et al., hyperventilation was only adopted for "the shortest interval possible." Although differences in outcome were evaluated in relation to the administration of an experimental drug, no stratification was shown with respect to lesion type or levels of intracranial pressure.

From the above discussion, it is apparent that comparisons of outcome between our present series and those of others should take into account a number of factors: 1) in consecutively admitted comatose patients, the overall incidence of acute intracranial hypertension is lower than in our series; 2) monitoring and management strategies differ between investigators; and 3) outcome may be related to the type of lesion appearing on the CT scan.

Future Prospects

Of particular importance in this study, as well as in previous reports, is the notion of optimized hyperventilation. This therapeutic strategy allows simultaneous maintenance of normalized ICP and CEO₂. The latter, in turn, represents an adequate therapeutic match between CMRO₂ and blood flow. In addition, prolonged optimized hypocapnia is now associated with normalization of cerebral glucose uptake and, therefore, cerebral aerobic metabolism. Thus, a sustained (PCO₂-related) normalization of these physiological interrelationships appears to represent a logical underlying therapeutic modality, upon which other therapies could be subsequently adopted in a comprehensive fashion. Optimized hyperventilation represents an outgrowth of conventional hyperventilation, in which PCO₂ manipulations have been traditionally based on ICP alone, without concomitant data on CEO₂.

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