Cerebral tissue PO$_2$ and SjvO$_2$ changes during moderate hyperventilation in patients with severe traumatic brain injury

ROBERTO IMBERTI, M.D., GUIDO BELLINZONA, M.D., AND MARTIN LANGER, M.D.

Servizio di Anestesia e Rianimazione II, IRCCS Policlinico San Matteo, Pavia, Italy

Object. The aim of this study was to investigate the effects of moderate hyperventilation on intracranial pressure (ICP), jugular venous oxygen saturation ([SjvO$_2$], an index of global cerebral perfusion), and brain tissue PO$_2$ (an index of local cerebral perfusion).

Methods. Ninety-four tests consisting of 20-minute periods of moderate hyperventilation (27–32 mm Hg) were performed on different days in 36 patients with severe traumatic brain injury (Glasgow Coma Scale score \(\leq 8\)). Moderate hyperventilation resulted in a significant reduction in average ICP, but in seven tests performed in five patients it was ineffective. The response of SjvO$_2$ and brain tissue PO$_2$ to CO$_2$ changes was widely variable and unpredictable. After 20 minutes of moderate hyperventilation in most tests (79.8%), both SjvO$_2$ and brain tissue PO$_2$ values remained above the lower limits of normality (50% and 10 mm Hg, respectively). In contrast, in 15 tests performed in six patients (16.6% of the studied population) brain tissue PO$_2$ decreased below 10 mm Hg although the corresponding SjvO$_2$ values were greater than 50%. The reduction of brain tissue PO$_2$ below 10 mm Hg was favored by the low prehyperventilation values (10 tests), higher CO$_2$ reactivity, and, possibly, by lower prehyperventilation values of cerebral perfusion pressure. In five of those 15 tests, the prehyperventilation values of SjvO$_2$ were greater than 70%, a condition of relative hyperemia. The SjvO$_2$ decreased below 50% in four tests; the corresponding brain tissue PO$_2$ values were less than 10 mm Hg in three of those tests, whereas in the fourth, the jugular venous O$_2$ desaturation was not detected by brain tissue PO$_2$.

The analysis of the simultaneous relative changes (prehyperventilation – posthyperventilation) of SjvO$_2$ and brain tissue PO$_2$ showed that in most tests (75.5%) there was a reduction of both SjvO$_2$ and brain tissue PO$_2$. In two tests moderate hyperventilation resulted in an increase of both SjvO$_2$, and brain tissue PO$_2$. In the remaining 17 tests a redistribution of the cerebral blood flow was observed, leading to changes in SjvO$_2$ and brain tissue PO$_2$ in opposite directions.

Conclusions. Hyperventilation, even if moderate, can frequently result in harmful local reductions of cerebral perfusion that cannot be detected by measuring SjvO$_2$. Therefore, hyperventilation should be used with caution and should not be considered safe. This study confirms that SjvO$_2$ and brain tissue PO$_2$ are two parameters that provide complementary information on brain oxygenation that is useful to reduce the risk of secondary damage. Changes in SjvO$_2$ and brain tissue PO$_2$ in opposite directions indicate that data obtained from brain tissue PO$_2$ monitoring cannot be extrapolated to evaluate the global cerebral perfusion.

Key Words • hyperventilation • brain tissue partial pressure of oxygen • jugular venous oxygen saturation • cerebral oxygen metabolism • intracranial pressure

Although the safety and utility of hyperventilation in the treatment of intracranial hypertension is still the subject of debate, recent surveys of critical care management of comatose, head-injured patients in the United States have shown that it is a commonly used treatment.

Hyperventilation can reduce ICP in patients with severe TBI and intracranial hypertension, but it can produce excessive arterial vasoconstriction that could result in cerebral ischemia. Whereas it is widely recognized that aggressive hyperventilation (PaCO$_2$ < 25 mm Hg) can be associated with marked reduction in CBF and cerebral energy failure, which may provoke or exacerbate cerebral ischemia, moderate hyperventilation is commonly regarded as devoid of risks. Monitoring of SjvO$_2$ has been used to reduce the risk of secondary damage and to guide hyperventilation.

Recently, Cruz showed that the outcome of patients with severe TBI can be improved by manipulating PaCO$_2$ upward or downward (range 20–30 mm Hg) to normalize simultaneously ICP, CPP, and cerebral extraction of O$_2$ (optimized hyperventilation). Nevertheless, because SjvO$_2$ is an index of global cerebral perfusion, regional ischemia may not be excluded even when SjvO$_2$ values are in the range of normality. Regional changes in cerebral perfusion can be evaluated using methods that examine local CBF and metabolism, including xenon CT, xenon-133, single-photon emission CT, and positron emission tomography.

Abbreviations used in this paper: CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CT = computerized tomography; ICP = intracranial pressure; MABP = mean arterial blood pressure; SD = standard deviation; SjvO$_2$ = jugular venous oxygen saturation; TBI = traumatic brain injury.
patients. Values represent the mean ± SD. *p < 0.01 compared with prehyperventilation.

In this study we investigated the effects of short-term moderate hyperventilation on ICP, CPP, SjvO₂, and brain tissue PO₂ in patients with severe TBI.

Clinical Material and Methods

Patient Characteristics and Experimental Design

The effects of moderate hyperventilation on ICP, SjvO₂, and brain tissue PO₂ were investigated in 36 patients whose ages ranged from 16 to 75 years and who had severe closed TBI (Glasgow Coma Scale36 scores ≤ 8 after resuscitation). The injury types were classified as follows:21 diffuse injury Type II in seven patients; diffuse injury Type III in nine; diffuse injury Type IV in 13 (two of these patients underwent decompressive craniotomy); and evacuated intracranial mass in seven. All patients underwent intubation and ventilation. The PaCO₂ levels before the tests ranged from 34 to 38 mm Hg. All patients underwent standard therapy, which included early evacuation of any intracranial mass, sedation with infused fentanyl and/or propofol, and mannitol administration (final osmolality 305–315 mOsm) if ICP was greater than 20 mm Hg. Attempts were made to keep CPP values above 60 mm Hg, possibly 70 mm Hg, if necessary, also by increasing MABP by volemic expansion with albumin and/or infusion of dopamine or norepinephrine.

Tests of moderate hyperventilation, defined as levels of PaCO₂ ranging between 32 and 27 mm Hg, were performed when ICP was above 20 mm Hg. Moderate hyperventilation was achieved by maintaining a constant tidal volume and increasing the ventilatory rate to cause a decrease in PaCO₂. If patients were treated with mannitol, hyperventilation was performed at least 2 hours after mannitol infusion to exclude the acute osmotic effects. All hyperventilation tests were performed on different days, between the 2nd and the 5th day after TBI; every patient underwent two or three tests that lasted 20 minutes each. After the 20-minute hyperventilation tests were completed, the ventilatory rate was gradually returned to the prettrial rate. For the purpose of evaluating the effects of hyperventilation on ICP, SjvO₂, and brain tissue PO₂ we chose a short period because brain-injured patients may have unstable blood pressure and ICP and they may also have spontaneous variations of ventilation. To obviate this last variable, all patients underwent drug-induced paralysis during the periods of hyperventilation (it is not our policy to paralyze brain-injured patients for long periods unless it is strictly necessary).

The ICP was monitored using an intraparenchymal fiberoptic catheter (Camino Laboratories, San Diego, CA), and brain tissue PO₂ by using a Clark-type electrode (Licox GMS, Kiel, Germany) that was inserted 1 to 1.5 cm behind the catheter used to measure ICP in an uninjured area of the cerebral white matter confirmed on CT scans. The ICP, MABP, CPP, brain tissue PO₂, and end-tidal CO₂ were monitored continuously and the data were transmitted to a dedicated bedside personal computer equipped with adapted software (LabVIEW; National Instruments, Austin, TX). The arterial transducer was raised to the level of the patient’s ear.

The SjvO₂ was evaluated by intermittent blood sampling and, in a few patients, also continuously with a fiberoptic catheter (Abbott Laboratories, Chicago, IL). Blood samples were collected for evaluation of SjvO₂ and for performance of arterial blood gas analysis just before and after the 20-minute period of hyperventilation and they were assessed using a gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark).

The limits of normality for SjvO₂ were considered to be 50 to 75%, and the lower limit of normality for brain tissue PO₂ was considered to be 10 mm Hg. Because the PaO₂ can influence brain tissue PO₂ and SjvO₂,10,16 the fraction of inspired O₂ was adjusted to obtain PaO₂ values ranging between 100 and 150 mm Hg. Hemoglobin levels were maintained above 10 g/dl.

Informed consent for invasive cerebral monitoring was obtained from the patients’ next of kin.

Statistical Analysis

Data are expressed as the mean ± SD. The ICP, CPP, MABP, PaO₂, PaCO₂ changes, SjvO₂-CO₂ reactivity, and brain tissue PO₂-CO₂ reactivity were analyzed using the Student paired and unpaired t-tests as required, with a probability value less than 0.05 as the criterion of significance.

Results

Accuracy and Safety of ICP and Brain Tissue PO₂ Measurements

Ninety-four tests of moderate hyperventilation were performed in 36 patients. The period for which the catheters used for blood sampling remained in place ranged from 4 to 9 days. Insertion of catheters to measure ICP and brain
tissue PO2 was not associated with bleeding or infection, as was documented by CT scans and cultures of the catheter tip and smears of the bolt. One rupture of the brain tissue PO2 catheter cable occurred during nursing care of the patient. At the end of monitoring the zero drift of the intraparenchymal fiberoptic ICP catheter was $-8 \pm 8$ mm Hg, the zero drift of the brain tissue PO2 catheter was $0.5 \pm 1.5$ mm Hg and its sensitivity drift was $4.5 \pm 3.7\%$. Altogether these findings confirm that ICP and brain tissue PO2 monitoring using intraparenchymal catheters is reliable and generally safe, although not devoid of risks.

**Effects of Moderate Hyperventilation on PaO2, MABP, ICP, and CPP**

The mean PaCO2 level before hyperventilation was $36.2 \pm 1.3$ mm Hg, and after 20 minutes it was $29.4 \pm 1.1$ mm Hg ($p < 0.001$), whereas PaO2 did not change significantly ($p > 0.2$). Before moderate hyperventilation, ICP values were higher than 21 mm Hg in all cases (range 22–39 mm Hg). Moderate hyperventilation resulted in a significant reduction of ICP, which was evident after 10 minutes and continued throughout the period of observation (Fig. 1). The average ICP decreased from $29.3 \pm 3.9$ mm Hg to $18.1 \pm 3$ mm Hg after 10 minutes and to $18 \pm 4.2$ mm Hg after 20 minutes. The MABP decreased significantly ($p < 0.05$) but slightly after 10 and 20 minutes. As a result, CPP increased significantly (Fig. 1). In seven tests (7.4%) performed in five patients, however, moderate hyperventilation was ineffective in reducing ICP.

**Effects of Moderate Hyperventilation on SjvO2 and Brain Tissue PO2**

The analysis of the prehyperventilation values of SjvO2 and brain tissue PO2 measured simultaneously showed that in most tests (81%) SjvO2 was between 57% and 75% and brain tissue PO2 was greater than 10 mm Hg, whereas in 18 tests SjvO2 was greater than 75% and brain tissue PO2 was greater than 10 mm Hg (Fig. 2A). Notwithstanding that the catheters measuring brain tissue PO2 were positioned in uninjured areas, as confirmed on CT scans, in 15 tests performed in eight patients prehyperventilation brain tissue PO2 values were relatively low, ranging between 11 and 15 mm Hg, although the corresponding SjvO2 values were between 61.3% and 77.4%. In those tests, the baseline average of PaO2 was not different from that of the remaining tests.

The response of SjvO2 and brain tissue PO2 to CO2 changes was unpredictable, and it varied widely. The relative SjvO2-CO2 reactivity (% change in SjvO2/absolute value in PaCO2) ranged between $-9.4$ and 2.7, and the relative brain tissue PO2-CO2 reactivity (% change in brain tissue PO2/absolute change in PaCO2) ranged between $-8.7$ and 7.9.

As is shown in Fig. 2B, after 20 minutes of moderate hyperventilation, in most tests (79.8%) both SjvO2 and brain tissue PO2 values remained above the lower limits of normality (50% and 10 mm Hg, respectively). The SjvO2 decreased below 50% in four tests; the corresponding values of brain tissue PO2 were less than 10 mm Hg in three of those tests, whereas in one test the jugular venous O2 desaturation was not associated with a low brain tissue PO2 value. In 15 tests performed in six patients (16.6% of the entire population studied), brain tissue PO2 decreased below 10 mm Hg, although the corresponding SjvO2 values were greater than 50%. This last finding indicates that harmful local changes in CPP induced by moderate hyperventilation may not be detected with SjvO2 monitoring. The reduction of brain tissue PO2 below 10 mm Hg was independent of prehyperventilation values of PaO2, ICP, MABP, and PaCO2 changes, whereas it was favored by the low prehyperventilation values (10 tests), by the much higher CO2 reactivity than in the remaining tests, and possibly by the...
lower prehyperventilation values of CPP (Table 1). In five of those 15 tests, the prehyperventilation values of SjvO₂ were greater than 70% (range 70–75%). Figure 3 shows an illustrative case.

Figure 2C presents the relative simultaneous changes (prehyperventilation — posthyperventilation) of SjvO₂ and brain tissue PO₂ after 20 minutes of moderate hyperventilation. The response to moderate hyperventilation was variable; in most tests (75.5%) there was a reduction of both SjvO₂ and brain tissue PO₂, whereas in 17 tests there was a reduction of SjvO₂ associated with an increase in brain tissue PO₂, and in four tests there was an increase in SjvO₂ associated with a reduction in brain tissue PO₂. These last findings indicated a redistribution of the CBF leading either to an increase in local perfusion (“inverse” steal) or to a local reduction in cerebral perfusion (steal). Finally, in two tests moderate hyperventilation resulted in an increase in both SjvO₂ and brain tissue PO₂. The correlation between SjvO₂ and brain tissue PO₂ changes was weak and nonsignificant ($r^2 = 0.045$).

Altogether these findings indicate that these two parameters reflect different aspects of cerebral oxygenation and give complementary information on cerebral oxygenation/perfusion.

**Discussion**

**Normocapnic Ventilation and Global and Local Oxygenation/Perfusion**

Although the brain tissue PO₂ catheters were positioned in uninjured areas of the brain, in 15 tests performed in eight patients, prehyperventilation brain tissue PO₂ values were relatively low, ranging between 11 and 15 mm Hg, although the corresponding SjvO₂ values were between 61.3 and 77.4% (Fig. 2A). These findings indicate that despite normocapnic ventilation, severe TBI can induce areas of low perfusion that can last for a few days after injury.

**Intracranial Hypertension, Moderate Hyperventilation, and Cerebral Oxygenation**

Studies performed in the last 20 years have shown that patients with intracranial hypertension have a worse outcome.20,22,26,28 Hyperventilation is generally effective in reducing intracranial hypertension, but the reduction of ICP, which is caused by vasoconstriction of cerebral arteries, occurs at the expense of CBF and may induce harmful episodes of hypoperfusion. In particular, contusions and the surrounding parenchyma, in which vasoreactivity may be three times greater than normal, are particularly vulnerable, especially if hyperventilation is aggressive.23

Monitoring of SjvO₂, although not exempt from limits and criticisms (the most important being its inability to detect episodes of regional hypoperfusion and the differences existing between the two jugular veins),12,32,35 has been used to guide hyperventilation and, more generally, in the treatment of TBI, in the attempt to prevent secondary damage.4,5,10,12,14,32,33 Our study indicates that during moderate hyperventilation jugular venous O₂ desaturations can occur, although this is infrequent (4.2%). In contrast, the risk of local hypoperfusion is higher than the SjvO₂ values would have indicated. After 20 minutes of moderate hyperventilation, favored by relatively low prehyperventilation values of brain tissue PO₂ and high CO₂ reactivity, the brain tissue PO₂ decreased below 10 mm Hg in 15 tests performed in six patients on different days (Fig. 2B). These findings are consistent with the observations of Marion and Bouma17 and Marion, et al.,18 who demonstrated that in patients with severe TBI, CBF and vasoresponsivity to CO₂ changes differ significantly in different areas of the brain. In these conditions, hyperventilation, even if moderate, can further impair local perfusion. Monitoring of brain tissue PO₂ in apparently healthy brain can detect harmful local reductions of CPP, although only in part, because the cerebral volume sampled by the catheter is small and other regions of the brain can develop unnoticed hypoperfusions. This limitation may affect the results, leading to underestimation rather than overestimation of the risk of tissue hypoperfusion during moderate hyperventilation.

There is a general consensus on the use of hyperventilation in patients with TBI and relative hyperemia (CBF in excess of metabolic requirements, SjvO₂ > 70–75%).5,25 As shown in Fig. 3, however, in our study brain tissue PO₂ values lower than 10 mm Hg were recorded in five moderate hyperventilation tests, indicating a possibility of local hypoperfusion, even in hyperemic patients (prehyperventilation SjvO₂ > 70%).

It has been reported that when brain tissue PO₂ monitoring is performed in undamaged areas of the brain, although the probe measures O₂ tension in only a small volume of tissue, these values can be extrapolated to evaluate global oxygenation/perfusion.2 Our study does not support this opinion. The redistribution of CBF induced by moderate hyperventilation in 17 tests resulted in an increase in brain tissue PO₂ that was associated with reduction of SjvO₂ (upper left quadrant of Fig. 2C). Considering only brain tissue
Cerebral tissue $PO_2$ and SjvO$_2$ changes during moderate hyperventilation

PO$_2$ changes, we would have arrived at the misleading conclusion that moderate hyperventilation globally improved the cerebral oxygenation/perfusion, which was not the case. Moreover, the increase of local perfusion in undamaged areas does not indicate that the redistribution of CBF benefited hyperperfused areas.

Gupta, et al.,$^{13}$ in their study based on progressive hyperventilation in patients with severe TBI, were able to show that when the $O_2$ probe was inserted in areas without focal pathology there was good correlation between SjvO$_2$ and brain tissue PO$_2$ changes ($r^2$ = 0.69), whereas there was no correlation when the $O_2$ probe resided in areas of focal pathology. Although in our study the $O_2$ probe was inserted in uninjured areas of the white matter, the correlation between SjvO$_2$ and brain tissue PO$_2$ changes was not significant (see Results). We have no explanation for this apparent discrepancy except, perhaps, that our correlation is based on a higher number of observations.

**Lower Limit of Normality for Brain Tissue PO$_2$**

As for SjvO$_2$, a crucial point of brain tissue PO$_2$ monitoring is the determination of the ischemic threshold. Experimental studies in animals indicate that the critical values for brain tissue PO$_2$ are between 8 and 10 mm Hg.$^{3,15}$ In cats in which the middle cerebral artery was occluded, the reduction in brain tissue PO$_2$ below 10 mm Hg was associated with a progressive increase in the width of the ischemic area.$^9$ Clinical studies performed using the Licox system indicate that we should consider brain tissue PO$_2$ values critical below 8 to 10 mm Hg.$^{12,16}$ Van Santbrink, et al.,$^{17}$ showed that brain tissue PO$_2$, values of 5 mm Hg or less within 24 hours after trauma correlated negatively with outcome. The lower limit of normality for the Paratrend system is higher.$^8$ In our study, in which we used the Licox system, we have adopted 10 mm Hg as the lower limit of normality for brain tissue PO$_2$. Although we cannot affirm that our patients in whom moderate hyperventilation induced a reduction of brain tissue PO$_2$ below 10 mm Hg would have developed local ischemia, they were at risk of impending ischemia even if SjvO$_2$ values were in the normal range. In such cases, therapeutic strategies other than moderate hyperventilation should be used to reduce ICP and increase CPP.

**Conclusions**

Hyperventilation can be a powerful instrument in the treatment of intracranial hypertension, but, even if moderate, it can frequently result in harmful local reductions in brain tissue PO$_2$ that cannot be detected by SjvO$_2$. Therefore, moderate hyperventilation should be used with caution and should not be considered safe. After moderate hyperventilation, SjvO$_2$ and brain tissue PO$_2$ changes can go in opposite directions. Therefore, brain tissue PO$_2$ monitoring should not be considered an alternative to SjvO$_2$ monitoring. This study confirms that SjvO$_2$ and brain tissue PO$_2$ are two parameters that give complementary information on brain oxygenation that is useful to reduce the risk of secondary damage, and indicates that data obtained from brain tissue PO$_2$ monitoring cannot be extrapolated to evaluate global cerebral perfusion.

**Fig. 3.** Graph showing a harmful reduction of brain tissue PO$_2$ induced by moderate hyperventilation. Although prehyperventilation SjvO$_2$ was 74%, the corresponding brain tissue PO$_2$ value was 15 mm Hg. Moderate hyperventilation increased CPP but further impaired the local oxygenation perfusion. ETCO$_2$ = end-tidal CO$_2$.

**References**


Manuscript received February 12, 2001. Accepted in final form September 19, 2001. Supported by Grant No. 10078/RC98 from IRCCS Policlinico San Matteo, Pavia, Italy.

Address reprint requests to: Roberto Imberti, M.D., Rianimazione II, IRCCS Policlinico San Matteo, 27100 Pavia, Italy. email: r.imberti@smatteo.pv.it.