Does Acute Hyperventilation Provoke Cerebral Oligaemia in Comatose Patients After Acute Head Injury?

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Summary

In 27 comatose patients with acute head injury, 45 paired studies of regional cerebral blood flow (rCBF) were performed before and after hyperventilation. In total 676 regions were studied, and rCBF was calculated as initial slope index using the intracarotid washout technique of 133 Xe. The tests were applied from one day to three weeks after the acute trauma.

In total hyperventilation from $PaCO_2$ averaging 4.8 to 3.5 kPa increased the frequency of regions with oligaemia defined CBF < 20 ml/100 g/min from 5 to 16%. Before hyperventilation oligaemia was observed in 11 of 45 studies (9 of 27 patients); after hyperventilation the frequency increased to 21 studies (15 patients). The frequency of severe oligaemia (CBF < 15 ml) increased from 0.1 to 3% of all regions, or from 2 to 8 of all studies (from 2 to 9 patients). The increased frequency of oligaemia after hyperventilation was correlated to a poor outcome (dementia, vegetative survival or death), where it was observed in 21% of all regions, in 16 of 26 studies and 11 of 15 patients, whereas the frequency in patients with a good recovery was found to be 7% of all regions and observed in 5 of 19 studies (4 of 12 patients). The high frequency of oligaemia after hyperventilation was associated to a low hemispheric CBF before hyperventilation, but not to the level of $PaCO_2$, the level of intracranial pressure, cerebral perfusion pressure or CSF-pH or lactate.

These findings strongly suggest that acute hyperventilation might be controversial as it provokes a decrease in rCBF close to ischaemic threshold, especially in patients with reduced rCBF prior to acute hyperventilation. Furthermore, it suggest that rCBF < 20 ml indicate a poor outcome.

Keywords: Acute head injury; CO_2 reactivity; cerebral blood flow; cerebral ischaemia; ischaemic threshold; hyperventilation; intracranial pressure.

Introduction

In the acute phase after severe head injury a relative or absolute luxury perfusion might occur. This state can be revealed either by measurements of cerebral blood flow (CBF), or by measuring the arteriovenous difference of oxygen content (AVDO 2)[5, 8, 9, 26]. A relative or absolute hyperaemia or luxury perfusion is associated with a preserved or often augmented reactivity of CBF to changes in $PaCO_2$ (high CO_2 reactivity)[5, 6, 9]. Generally hyperperfusion is observed in relatively young victims[6, 26], it is associated with a high intracranial pressure[26], and it might occur regionally, hemispheric or globally[6, 9, 26].

Theoretically hyperventilation might induce dangerous decrease in CBF below ischaemic threshold which has been defined recently[3, 4, 32]. If the CO_2 reactivity is high as in cases of hyperperfusion or luxury perfusion, the risks of severe oligaemia or ischaemia might be present. On the other hand these risks also might be present if the CBF is reduced prior to an acute decrease in $PaCO_2$, although the CO_2 reactivity in this situation generally is low.

In recent studies of the effect of acute hyperventilation on rCBF, ischaemic thresholds were not defined[5, 8]. rCBF was measured with the intracarotid washout technique of 133 Xe, a technique which at low rCBF give reliable results, because activity in the external carotid regions does not play an important role, and restactivity easely can be corrigated.

In order to investigate if hyperventilation in the acute phase of head injury decreases rCBF below or brings it close to the ischaemic threshold, these old studies were re-analyzed. Although the investigations were performed before CT scannings were available, it seems reasonable to re-evaluate the results, because the intraarterial 133 Xenon technique, now obsolete because of complications, gives more reliable results at low cerebral blood flow as compared with the intravenous and the inhalation method used nowadays.

Material and Method

In 27 unconscious patients (Glasgow coma scale < 6 at admission), 45 studies of rCBF were performed before and after an acute

decrease in $PaCO_2$. The median age was 23 years (range 9–67). 15 studies were performed within two days of trauma, 16 studies between the third day and one week, eight studies in the second week and six studies in the third week. In 15 patients the CO_2 reactivity was tested repeatedly (2–3 studies), with intervals of 2–4 days in 2 patients, and one week or above in 9 patients.

In 21 patients angiographic studies revealed a space-occupying lesion. These patients were operated upon, and cortical lesions (contusion, subdural haematoma, laceration) were observed during operation. In 11 of these patients neurological examination revealed impairments of the brain stem reflexes (oculocephalic, vestibular and pupillary reflexes), while the brain-stem reflexes were unaffected in 10 patients. In 6 patients the angiographic studies did not reveal any space-occupying lesions, and exploration through burr holes did not reveal any localized haematoma or severe brain contusion.

Controlled ventilation was used throughout the study (Servo ventilator 900 A), the aims of the respirator treatment being moderate hypocapnia with $PaCO_2$ ranging from 4.0–5.4 kPa and PaO_2 above 9.3 kPa. Chlorpromazine, meperidine and diazepam were used in small doses for sedation, neuromuscular blockers were never used. In 23 patients and 35 studies intraventricular pressure (IVP) was recorded continuously by the method of Lundberg[21]. In 31 of the studies ventricular fluid was withdrawn about one hour prior to the CBF measurements and determined for lactate[22] and pH.

If IVP increased above 25 mmHg in the ward the following procedures were initiated: Tracheal suction, supplementary sedation with diazepam, meperidine or chlorpromazine, osmotic therapy with mannitol in doses of 0.5 g/kg, injection of frusomide, drainage of ventricular fluid and decompression by craniotomy if a localized space-occupying lesion was unveiled by angiography.

The rCBF was measured by the intracarotid 133 Xe washout technique with a 16-channel Cerebrograph[5, 9]. The CBF studies were performed over the most severely injured hemisphere (the site of the mass lesion) in patients where a space-occupying lesion was present. The calculation of CBF was based on the initial slope index as defined by Olesen et al. (1971)[27], using regression analysis of the first-minute semilogarithimically displayed clearance curve. In regions with initial slope index below 20 ml stochastic analyses were applied as well. The partition coefficient for grey matter was used for calculation of the initial slope index, and the average partition coefficient for the calculation of stochastic flow. The partition coefficients were corrected for haemoglobin and remaining activity[17]. The hemispheric flow was calculated as the average of the 16 rCBF values.

The setting of the ventilator was not changed six hours prior to the CBF studies. 15 minutes after the first Xenon injection (3 mCi), the pulmonary ventilation was increased by 20–30%, resulting in a 0.5–1.0% decrease in end-tidal CO_2. When the end-tidal CO_2 was stabilized about 10 minutes after the change in respirator setting, the rCBF was repeated. IVP and mean arterial blood pressure (MABP) were continuously recorded by Statham transducers, and recorded. During the rCBF studies the patients were sedated with meperidine in doses of 10–25 mg, and chlorpromazine in doses of 5–10 mg. Muscular relaxation was obtained with pancuronium in small doses.

According to a follow-up study performed from 6 months to one year after the trauma, the patients were devided into two groups. Group I: good recovery or slight mental impairment (19 studies in 12 patients). Group II: Dementia present, vegetative survival and patients who died without regaining consciousnesss (26 studies in 15 patients).

The rCBF studies were classified as follows: Moderate oligaemia defined as $15 \leq rCBF < 20 \, ml/100 \, g/min$. Severe oligaemia as $rCBF < 15 \, ml$. In regions with initial slope index $< 20 \, ml$ stochastic analysis of CBF using the mean partition coefficient was applied and corresponding values of initial slope index and stochastic flow were compared. The mean values in these regions were 16.4 and 16.2 respectively, initial slope index ranged from 10–19 ml and stochastic values from 9–23 ml. The coefficient of variation was 10.3%. The low correlation coefficient indicates that only the results of initial slope index are presented.

Statistical Analysis

Mean values and SD were calculated. The Wilcoxon test was applied for paired data, and the Mann-Whitney test for unpaired data. The Chi square test with Yates correction was used for differences between frequencies. A P value less than 0.05 was considered significant.

Results

The median age and range of ages in group 1 was 21 years (9–47), and in group 2 24 years (14–67), $P = 0.294$. The median age and range in patients with regional oligaemia was 29 years (15–63), and in patients without regional oligaemia 17 years (9–67), $P = 0.053$.

In total, acute hyperventilation from $PaCO_2$ averaging 4.8 to 3.5 kPa increased the frequency of regions with oligaemia defined as CBF $< 20 \, ml$ form 5 to 16% in 676 regional studies. Before hyperventilation oligaemia was observed in 11 of 45 studies (9 of 27 patients), whereas oligaemia was observed in 21 studies

Table 1. *Number of Regions, Number of Studies and Patients with Regional Cerebral Blood Flow (rCBF) Measured as Initial Slope Index Below 20 ml Before and After an Acute Decrease in $PaCO_2$. Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are indicated as mean values and SD*

	$PaCO_2$ kPa	ICP kPa	CPP kPa	Number of regions with rCBF $< 20 \, ml$ in % of 676 regions	Number of studies with rCBF $< 20 \, ml$	Number of patients with rCBF $< 20 \, ml$
Before hyperventilation	4.8 ± 0.7	2.6 ± 0.8	10.1 ± 2.0	5.3%	10 of 45	8 of 27
After hyperventilation	3.6 ± 0.7	1.9 ± 0.6	10.1 ± 1.3	16.1%*	21 of 45*	15 of 27

* Statistical difference (P < 0.05).

CBF Initial
Mean CBF 27.8 ml
MABP   13.3 kPa
PaCO$_2$ 5.3 kPa

CBF Initial
Mean CBF 21.7 ml
MABP   11.7kPa
ICP   2.3 kPa
CPP   9.4 kPa
PaCO$_2$ 4.9 kPa

CBF Initial
(Hyperventilation)
Mean CBF 18.6 ml
MABP   12.7 kPa
PaCO$_2$ 3.5 kPa

CBF Initial
(Hyperventilation)
Mean CBF 18.2 ml
MABP   11.3 kPa
ICP   1.3 kPa
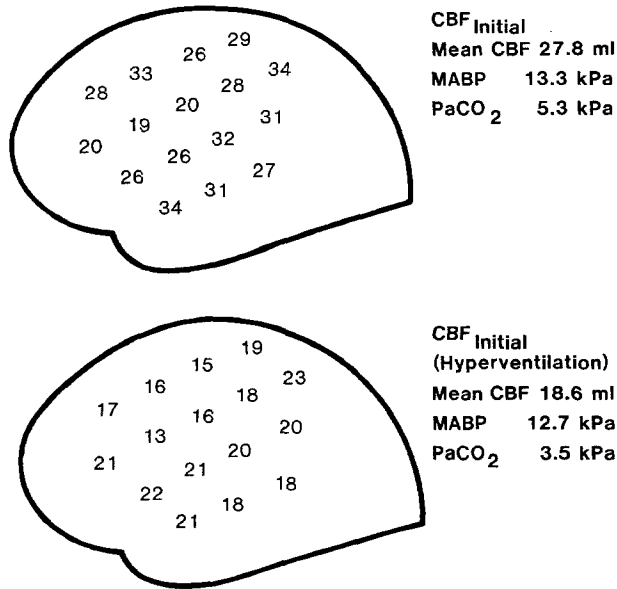CPP   10.0 kPa
PaCO$_2$ 3.7 kPa

Fig. 1. rCBF before and after hyperventilation in a 63-year-old man studied on the fifth day after trauma. The changes in rCBF, PaCO$_2$ and mean arterial blood pressure are presented. As indicated hyperventilation provoked decrease in rCBF below the oligaemic threshold defined as rCBF < 20 ml
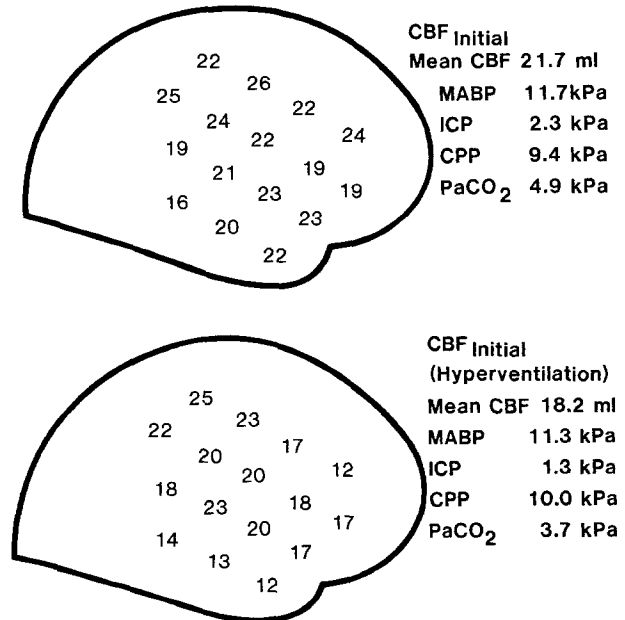
Fig. 2. rCBF before and after hyperventilation in a 19-year-old male, studied on the second day after trauma. The changes in PaCO$_2$, rCBF, ICP, mean arterial blood pressure (MABP) and cerebral perfusion pressure (CPP) are presented. As indicated hyperventilation provoked severe oligaemia (rCBF < 15 ml) in four regions

(15 patients) after hyperventilation (Table 1). In the 11 studies (9 patients) where oligemia was observed before hyperventilation, a further decrease in PaCO$_2$ aggravated the tendency to oligemia. The frequency of severe oligemia (CBF < 15 ml) increased from 0.1 to 3% of all 276 regions, and was observed in 9 patients against 2 before hyperventilation.

Case 1

On Fig. 1 a typical example is shown. The patient, a 63 year old male, with a subdural haematoma evacuated on the first day after the trauma, was investigated on the fifth day. At that time Glasgow coma score was 8, and the brain stem reflexes were normal. Mean CBF before hyperventilation averaged 27.8 ml, at a PaCO$_2$ of 5.3 kPa, and oligaemia was only observed in one region. After hyperventi-

Table 2. *The Frequency of Regions with Moderate Oligaemia (15 ml $\leq$ rCBF < 20 ml), and Severe Oligaemia (rCBR < 15 ml) Before and After Hyperventilation in Two Groups of Patients.* In group 1 (good recovery or slight mental impairment), 19 studies on 12 patients were performed. In group 2 (dementia, vegetative survival and death), 26 studies on 15 patients were performed. The mean values of PaCO$_2$, intracranial pressure (ICP) and cerebral perfusion pressure (CPP) before and after hyperventilation are indicated by mean values and SD

		PaCO$_2$ kPa	ICP kPA	CPP kPa	Number of regions with moderate oligaemia (15 $\leq$ rCBF < 20 ml) in % of total no. of regions	Severe oligaemia (rCBF < 15 ml) in % of total no. of regions	Number of studies with rCBF < 20 ml	Number of patients with rCBF < 20 ml
Group I: Good recovery or slight mental impairments.	Before hyperventilation	4.8 ± 1.1	2.8 ± 0.7	9.6 ± 2.0	0	0	0 of 19	0 of 12
	After hyperventilation	3.6 ± 0.9*	2.0 ± 0.5*	9.6 ± 1.7 *	6.3%*	1.0%	5 of 19	* 4 of 12
Group II: Dementia, vegetative survival and death.	Before hyperventilation	4.7 ± 0.7	2.5 ± 1.0	10.5 ± 2.0	8.5%	* 0%	10 of 26	* 8 of 15
	After hyperventilation	3.5 ± 0.6*	1.7 ± 0.7*	10.5 ± 1.4	16.7%*	4.1%*	16 of 26	11 of 15

* Statistical difference within and between groups (P < 0.05).

Table 3. *Hemispheric Cerebral Blood Flow (mean CBF), $PaCO_2$, Cerebral Perfusion Pressure (CPP), Intracranial Pressure (ICP) Before and After Hyperventilation in Patients With and Without Regional Oligaemia Defined as rCBF < 20 ml. CSF-pH and CSF-lactate are also indicated. All patients recovered or showed moderate disability (Group 1). Mean values and SD are indicated*

		Mean hemispheric CBF ml/100 g/min	$PaCO_2$ kPa	ICP kPa	CPP kPa	Ventricular fluid lactate mmol/l	Ventricular fluid pH
Patients without oligaemia (rCBF > 20 ml)	Before hyperventilation	43.2 ± 8.2	5.0 ± 0.7	2.4 ± 0.5	10.6 ± 2.2	2.8 ± 1.2	7.365 ± 0.069
	After hyperventilation	32.7 ± 5.6*	3.8 ± 0.7*	1.7 ± 0.5*	11.0 ± 1.9		
Patients with oligaemia (rCBF < 20 ml)	Before hyperventilation	33.2 ± 3.9	4.7 ± 1.5	3.2 ± 1.0	8.9 ± 1.8	1.6 ± 0.8	7.303 ± 0.006
	After hyperventilation	22.7 ± 2.2*	3.5 ± 1.2*	2.4 ± 0.5*	8.4 ± 1.2		

* Statistical difference within and between groups (P < 0.05).

Table 4. *Hemispheric Cerebral Blood Flow (mean CBF), $PaCO_2$, Cerebral Perfusion Pressure (CPP), Intracranial Pressure (ICP) Before and After Hyperventilation in Patients With and Without Regional Oligaemia. Defined as rCBF < 20 ml. CSF-pH and CSF-lactate are also indicated. All patients were in group 2 (dementia, vegetative survival and death). Mean values and SD are indicated*

		Mean hemispheric CBF ml/100 g/min	$PaCO_2$ kPa	ICP kPa	CPP kPa	Ventricular fluid lactate mmol/l	Ventricular fluid pH
Patients without oligaemia (rCBF > 20 ml)	Before hyperventilation	40.2 ± 9.7	4.7 ± 0.8	3.1 ± 1.2	10.3 ± 2.1	3.1 ± 1.0	7.317 ± 0.029
	After hyperventilation	32.7 ± 8.2*	3.5 ± 0.6*	1.9 ± 0.7*	10.5 ± 1.2		
Patients with oligaemia (rCBF < 20 ml)	Before hyperventilation	25.3 ± 4.5	4.6 ± 0.6	1.8 ± 0.9	10.7 ± 2.0	3.1 ± 1.1	7.311 ± 0.020
	After hyperventilation	20.8 ± 3.0*	3.4 ± 0.6*	1.4 ± 0.7*	10.5 ± 1.6		

* Statistical difference within and between groups (P < 0.05).

lation to 3.5 kPa, the mean CBF was found to be 18.6 ml, moderate oligaemia (15 < CBF < 20 ml) was observed in 8 regions, and severe oligaemia (CBF < 15 ml) in one region. Mean arterial blood pressures were 100 mmHg before and 95 mmHg after hyperventilation. At follow-up study 6 months after the injury, the patient was demented, unable to take care of himself.

Case 2

A 19 years male was admitted after a blunt head injury. At arrival he was unconscious with intermittent pupil size differences and extensor response (Glasgow coma score 4). Carotid arteriography was normal. ICP was continuously recorded (mean level 3.0–4.0 kPa). On the second day after the trauma rCBF measurement was performed (Fig. 2). Mean CBF at $PaCO_2$ 4.9 kPa, ICP 2.3 kPa and CPP 9.4 kPa averaged 21.7 ml/100 g/min, moderate oligaemia was observed in four regions. After hyperventilation to 3.7 kPa (ICP 1.3 kPa, CPP 10.0 kPa) mean CBF was 18.2 ml/100 g/min, moderate and severe oligaemia were observed in five and four regions respectively.

During the next 3 weeks only small clinical improvements were observed. At follow-up study one year later he was demented.

In group I (good recovery or slight mental impairments) moderate oligaemia defined as (15 ml ≤ CBF < 20 ml) was found in 19 of 266 regions (6%), while severe oligaemia (CBF < 15 ml) was observed in only 3 regions (1%). Oligaemia was found in 5 of 19 studies representing 4 of 12 patients. In this group oligaemia was not observed at all before hyperventilation (Table 2).

In group II (dementia, vegetative survival and death), oligaemia was observed in 16 of 26 studies (11 of 15 patients, against 10 of 26 studies (8 of 15 patients) before hyperventilation. In this group the frequency of moderate oligaemia increased from 8.5 to 17% of all

regions and the frequency of severe oligaemia from zero to 5%. No significant difference in ages of the patients was found between the two groups.

The frequency of oligaemia in the two groups were associated with the appearance of low hemispheric mean CBF before hyperventilation, but not to the level of $PaCO_2$ before or after hyperventilation, the level of cerebral perfusion pressure, intracranial pressure, ventricular fluid lactate or pH (Tables 3 and 4).

Discussion

Necrosis of cerebral tissue caused by ischaemia is a frequent finding after brain injury[13]. Thus neuropathological studies of consecutive brains from patients who died as a result of blunt head injury have shown obvious signs of ischaemic brain damage in 91%, localized to the cerebral cortex in 46%, to the hippocampus in 81%, to the cerebellum 26% and to the basal ganglia in 79%[14]. Besides direct impact after the blunt lesion, secondary events like hypotension might give rise to localized necrosis at boundary zones between the major cerebral arteries (watershed lesions)[1]; furthermore neuropathological studies of brain herniation have shown well defined lesions of the parahippocampal and cingulate gyri and infarction in the median occipital cortex[2].

In the acute phase of head injury, studies of regional cerebral blood flow invariably have shown patterns of hyperaemia. These regions of hyperaemia or luxury perfusion[20] have been observed in regions of cerebral contusion[8, 9]. The hyperaemia is provoked by arterial hypertension[7, 9, 10, 28] and disappears after hyperventilation[6, 9, 10, 28]. However, clinical studies with the intracarotid 133 Xe washout method also have revealed regions with reduced rCBF, and it has been observed that regions with reduced rCBF mainly are localized to the territories between the cerebral arteries, and that the reduced hemispheric CBF is correlated with a poor outcome[29, 30].

Until recently, evidence of cerebral ischaemia has been obscured by the lack of definition of ischaemic threshold. However, animal experiments have shown that CBF < 6–8 ml/100 g/min is critical for cellular viability, and below this value membrane failure ensues with a decrease in intracellular ATP and an increase in extracellular potassium[3]. In the interval of 8–16 ml, cellular function and synaptic transmission are abolished, and the term ischaemic penumbra has been applied to rCBF ranging within this interval[4]. In experimental studies of ischaemia as well as human studies performed

during carotid endarterectomy neurological deficits and EEG slowing has been observed at CBF falls below 23 ml[16, 18, 31, 33].

It is well-known that hypocapnia produces changes in the EEG that are indistinguishable from hypoxic EEG changes[25]; however evidence of reversible cerebral ischaemia elicited by hypocapnia has been documented only at extreme hypocapnic levels below 1.6 kPa in rats and dogs[12, 23], and irreversible signs of ischaemia have never been observed. A safety level of $PaCO_2 > 2.7$ kPa has generally been advocated[11, 15]. It is supposed that the effect of a $PaCO_2$ reduction on cerebral circulation is counteracted by a decrease in cerebrovascular resistance elicited by a decrease in available oxygen supply[34]. It must be stressed that with few exceptions experiments concerning the effect of hyperventilation on cerebral tissue have been performed only in non-injured brains where regulatory mechanisms might be present. In squirrel monkeys subjected to middle cerebral artery occlusion and hypocapnia to 2.7 kPa a significant decrease in cerebral ATP was found as compared with normocapnic animals[24].

In the present study rCBF ranging from 15 to 20 ml were defined as moderate oligaemia and rCBF below 15 ml as severe oligaemia. We found that an acute reduction in $PaCO_2$ augmented the number of regions with moderate and severe oligaemia especially if CBF was reduced prior to hyperventilation. The occurrence of regional oligaemia was associated to a poor outcome. Thus, the results indicate that acute hyperventilation might result in severe oligaemia close to or within ischaemic threshold. The incidence of oligaemia was independent of the level of $PaCO_2$ before and after hyperventilation, the level of intracranial pressure, arterial pressure, ventricular fluid lactate and pH.

The rCBF was measured independently by initial slope index using the partition coefficient of grey matter, and by stochastic analysis using the average partition coefficient. The fair correlation and the relatively small coefficient of variation found between corresponding values, indicate the reliability of both analysis. However, it can be discussed if rCBF below values of 20 and 15 ml/100 g/min referred to as moderate and severe oligaemia, really indicate the presence of moderate and severe ischaemia. Concerning the calculation of rCBF the choice of partition coefficient might influence the results, and the partition coefficients in contused and oedematous cerebral tissue are not known. Another factor of importance is that intraarterially injected 133 Xe does not reach ischaemic areas in measurable amounts, and counts recorded over ischaemic

areas therefore appear to originate from better perfused regions giving rise to an overestimation of rCBF. On the other side, the metabolic depression generally found in the acute phase after severe head injury, might influence and theoretically reduce the ischaemic threshold. Nevertheless, the occurrence of regional oligaemia as defined in this study was associated with a poor outcome, and the results suggest that acute hyperventilation might result in moderate and severe oligaemia close to or within ischaemic thresholds as defined in experimental and clinical studies. Moreover, the low rCBF values after hyperventilation especially are to be observed when CBF is decreased prior to hyperventilation.

Two possible mechanisms might explain the supposed deleterious effects of hypocapnia: The direct vasoconstrictive effect on cerebral vessels elicited by hypocapnia, and the effects of mechanical ventilation, which might depress the systemic circulation and reduce cardiac output and blood pressure. In severely injured patients the cerebral circulation already might be marginal prior to hyperventilation, partly because of increased intracranial pressure secondary to oedema and haemorrhage, partly because of an impending decrease in cerebral perfusion pressure caused by the mechanical ventilation, depressed myocardial function and hypovolaemia. In these situations mechanical hyperventilation might decrease cerebral perfusion pressure, and this decrease is supposed to reduce rCBF below the ischaemic threshold.

The clinical implication of these observations suggests that during the intensive care treatment of patients with severe head injury even short periods of hyperventilation might be harmful especially in patients with reduced CBF. As the incidence of reduced CBF is highest in old victims, and arterial pressure in this group of patients is easily reduced when hyperventilation is applied owing to reduced cardiac reserves, it is suggested that hyperventilation below $PaCO_2$ levels of 30–35 mmHg for more than few minutes should be used with caution, and only when arterial pressure or better cerebral perfusion pressure are carefully monitored. Furthermore, the present study suggests that clinical studies of regional CBF with the intracarotid approach might give valuable information concerning risks of cerebral oligaemia when sustained hyperventilation is used in the intensive care treatment of patients with severe head injury.

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