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Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial

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✓ There is still controversy over whether or not patients should be hyperventilated after traumatic brain injury, and a randomized trial has never been conducted. The theoretical advantages of hyperventilation are cerebral vasoconstriction for intracranial pressure (ICP) control and reversal of brain and cerebrospinal fluid (CSF) acidosis. Possible disadvantages include cerebral vasoconstriction to such an extent that cerebral ischemia ensues, and only a short-lived effect on CSF pH with a loss of HCO_3^- buffer from CSF. The latter disadvantage might be overcome by the addition of the buffer tromethamine (THAM), which has shown some promise in experimental and clinical use. Accordingly, a trial was performed with patients randomly assigned to receive normal ventilation ($PaCO_2$ 35 ± 2 mm Hg (mean ± standard deviation): control group), hyperventilation ($PaCO_2$ 25 ± 2 mm Hg: HV group), or hyperventilation plus THAM ($PaCO_2$ 25 ± 2 mm Hg: HV + THAM group). Stratification into subgroups of patients with motor scores of 1–3 and 4–5 took place. Outcome was assessed according to the Glasgow Outcome Scale at 3, 6, and 12 months. There were 41 patients in the control group, 36 in the HV group, and 36 in the HV + THAM group. The mean Glasgow Coma Scale score for each group was 5.7 ± 1.7, 5.6 ± 1.7, and 5.9 ± 1.7, respectively; this score and other indicators of severity of injury were not significantly different. A 100% follow-up review was obtained. At 3 and 6 months after injury the number of patients with a favorable outcome (good or moderately disabled) was significantly ($p < 0.05$) lower in the hyperventilated patients than in the control and HV + THAM groups. This occurred only in patients with a motor score of 4–5. At 12 months posttrauma this difference was not significant ($p = 0.13$). Biochemical data indicated that hyperventilation could not sustain alkalinization in the CSF, although THAM could. Accordingly, cerebral blood flow (CBF) was lower in the HV + THAM group than in the control and HV groups, but neither CBF nor arteriovenous difference of oxygen data indicated the occurrence of cerebral ischemia in any of the three groups. Although mean ICP could be kept well below 25 mm Hg in all three groups, the course of ICP was most stable in the HV + THAM group. It is concluded that prophylactic hyperventilation is deleterious in head-injured patients with motor scores of 4–5. When sustained hyperventilation becomes necessary for ICP control, its deleterious effect may be overcome by the addition of THAM.

Key Words • **head injury** • **hyperventilation** • **tromethamine** • **outcome** • **cerebral blood flow** • **intracranial pressure**

In 1981, Jennett and Teasdale[15] wrote: "There is general agreement that spontaneous hyperventilation and hypocapnia are common in severely head injured patients, but there is still considerable debate about the usefulness of inducing controlled hyperventilation." Nevertheless, generous use of hyperventilation to obtain a $PaCO_2$ of 20 to 30 mm Hg during the first few days after severe head injury is advocated in a number of texts on traumatic coma.[2,3,13,19,26] Although it is usually not explicitly stated, this is based on two premises. First, it is well known that elevated intracranial pressure (ICP) adversely affects outcome;[17] thus, it is hoped that outcome can be improved by reducing ICP through the cerebral vasoconstrictory effect of hyperventilation. Second, cerebral lactic acidosis is often found after severe head injury and is correlated with poor outcome.[6–8] As CO_2 freely passes the blood-brain barrier, hyperventilation should diminish cerebral CO_2, thereby increasing pH and counteracting acidosis.

Several points can be raised, however, against the

prophylactic use of hyperventilation. Foremost, its use has never been compared to normoventilation in a randomized clinical trial and, despite its theoretical advantages, it might have unsuspected deleterious side effects, further compounding the management problem. Moreover, it has been argued that hyperventilation might turn borderline cerebral ischemia (sometimes present after severe head injury) into frank ischemia with ensuing neuronal death.[23] In addition, it has been shown that the effect of hyperventilation on cerebrospinal fluid (CSF) pH and arteriolar diameter is only short-lived and possibly counterproductive after 24 hours.[22] As this latter problem is caused by the depletion of bicarbonate buffer in the CSF, it might be overcome by the addition of an agent such as tromethamine (THAM). This agent is a weak base and buffer that crosses the blood-brain barrier more slowly and has shown some promise after brain injury in experimental and clinical applications.[1,9,24,27,31] Accordingly, a randomized study was designed to compare the effects upon outcome in severely head-injured patients of normoventilation, hyperventilation, or hyperventilation plus THAM. Although the endpoint of outcome renders this study (in terms of Schwartz and Lellouch[28]) "pragmatic," it was also designed to give an explanation for possible effects on outcome of each of the treatment modalities.

Clinical Material and Methods

The patient population for the present study group consisted of all patients admitted to the Medical College of Virginia, Richmond, aged 3 years or older, with a severe closed head injury who did not follow commands (Glasgow Coma Scale (GCS)[29] score ≤ 8) after aggressive resuscitation, diagnosis, and treatment of acute mass lesions. After obtaining informed written consent from the next of kin or guardian, the patients were first stratified by the motor score part of the GCS (≤ 3 or > 3) and then randomly assigned to one of three groups: normoventilation (control); hyperventilation (HV); or hyperventilation plus THAM (HV + THAM).

Randomization

Using random-number tables, opaque envelopes were filled with a card on which was written either control, HV, or HV + THAM. Each batch of nine envelopes was balanced with respect to the three treatments ("batch-design"), and there were two separate series of envelopes related to the motor score ("stratification"). In each of the two stratified series, envelopes were numbered consecutively, and the indicated treatment assigned to eligible patients in that order. For each patient, the trial period commenced on opening of the envelope, irrespective of whether the goals of randomization were met or not ("intent to treat").

By adjusting the respiratory rate and volume of the ventilator, $PaCO_2$ was kept at 30 to 35 mm Hg in the control group and at 24 to 28 mm Hg in both the HV and the HV + THAM groups. The HV + THAM group received THAM in an initial bolus followed by intravenous infusion for 5 days.

Calculation of THAM Dose

The THAM was administered intravenously as a 0.3-M solution. Dosage was calculated based on the amount of THAM required to raise arterial pH to 7.6, which was calculated according to the following relationship: THAM (ml) = body weight (kg) × base deficit. For example, if a patient had an initial plasma bicarbonate concentration of 22 mEq with a $PaCO_2$ of 35 mm Hg and a pH of 7.4, increasing pH to 7.6 would require 32 mEq/liter if $PaCO_2$ remains constant. This results in an additional base requirement of 10 mEq/liter. Thus, in a 70-kg man, 700 ml of 0.3-M THAM (70 kg × 10) is required. The initial dose was administered over 2 hours and was followed by a constant infusion of 0.3-M THAM at a rate of 1 ml/kg/hr for a period of 5 days.

Clinical Management

All patients were intubated and artificially ventilated. When necessary, Pavulon (pancuronium bromide) a paralyzing agent, was administered. Arterial pO_2 was maintained above 80 mm Hg by increasing positive end-expiratory pressure from 0 to 20 cm H_2O and increasing the fraction of inhaled O_2 from 30% to 100% as necessary.

Attempts were made to keep serum electrolytes and glucose levels normal, while hematocrit was kept between 30% and 40%. Fluid administration was ample and was adjusted in all groups to maintain a pulmonary artery wedge pressure of 10 to 15 mm Hg. Intracranial pressure was monitored by ventricular catheter or subarachnoid bolt and, after exclusion of treatable causes for elevated ICP such as low PaO_2, low blood pressure, or mass lesions, attempts were made to keep ICP below 25 mm Hg by various measures used in the following sequence: 1) skeletal muscle paralysis with Pavulon and sedation with morphine; 2) drainage of CSF; 3) intravenously administered mannitol; 4) hyperventilation to the amount of $PaCO_2$ necessary to control ICP; and 5) barbiturate coma. It should be noted here that more aggressive hyperventilation was used only when the other methods had failed to control ICP.

Physiological Data Monitoring and Acquisition

The ICP, blood pressure from an intra-arterial line, pulmonary artery wedge pressure, heart rate, and end-tidal CO_2 were measured continuously. The signals for these parameters were routed from the bedside monitor to a dedicated computer located in the intensive care unit (ICU). The ICP and systolic, diastolic, and mean arterial blood pressure values were measured at 30-second intervals and were averaged hourly to provide mean values based on 120 pressure measurements.

TABLE 1

*Demographic and prognostic data on admission**

Factor	Control Group	HV Group	HV + THAM Group
no. of cases	41	36	36
sex (% male)	70	75	61
age (yrs)	32 ± 18	28 ± 15	34 ± 19
median age (yrs)	27	26	25
absent pupillary response	37%	42%	33%
GCS score	5.7 ± 1.7	5.6 ± 1.7	5.9 ± 1.7
motor score 1–3	49%	53%	42%
shift > 5 mm on CT	30%	32%	22%
obliterated perimesencephalic cistern	49%	53%	41%
elevated ICP on admission (>20 mm Hg)	14%	14%	5%
hypoxia (PaO_2 < 60 mm Hg)	28%	22%	26%
arterial hypotension (BP < 90 mm Hg)	2.3%	2.8%	0

* HV = hyperventilation; GCS = Glasgow Coma Scale;[14] CT = computerized tomography; ICP = intracranial pressure; BP = systolic blood pressure. Means are given ± standard deviation.

These data were then analyzed for each patient group using a relational data base (INGRES) for descriptive statistics.

In addition to the routine monitoring of ICP, a complete assessment of ICP dynamics which included pressure-volume index, outflow resistance, and formation and absorption rates of CSF was performed at baseline (before randomization) and then every 12 hours until ICP monitoring was discontinued.[18,20] Other variables that were monitored intermittently for the purpose of the study were $PaCO_2$ every 4 to 6 hours, arteriovenous oxygen difference ($AVDO_2$) every 4 to 6 hours, multimodality evoked potentials at baseline and then every 24 hours, cerebral blood flow (CBF), and cerebral metabolic rate of oxygen ($CMRO_2$) and autoregulation at baseline and 24 hours and 72 to 96 hours after randomization, levels of lactate and pH in blood and CSF every 12 hours, and THAM levels in blood daily. Autoregulation and CBF were measured with standard intravenous ^{133}Xe techniques as described earlier,[21] yielding CBF_{15} (equivalent to height over area method) in ml/100 gm/min. These data were entered manually into the ICU computer by data-entry personnel dedicated to this project.

Outcome Measurement and Monitoring of Study Progress

Outcome was assessed by a single evaluator (J.D.W.) using the Glasgow Outcome Scale (GOS)[14] at 3 months (± 2 weeks), 6 months (± 1 month), and 12 months (± 2 months). It should be noted that this evaluator was not blinded as to the treatment given, although at the time of outcome evaluation these data were not available for him to review. Study progress was monitored by our statistician (S.C.C.), who performed a statistical analysis of outcome every 3 months. He was instructed to notify the Institutional Review Board if a beneficial or deleterious effect were to become evident, in which case the investigators would be notified and the trial stopped. Thus, when the outcome at 3 and 6 months postinjury in the HV group was determined to be significantly ($p < 0.05$) worse, the study was stopped, although our goal was to compare outcome in the three groups at 12 months. The difference in outcomes among the three groups was analyzed using the logistic regression which relates the probability of outcome categories to covariables and treatment groups.[12] The covariables used were age and admission motor scores, two important prognostic indicators.[4] The interaction effect of the treatment group and the motor score and that of group and age were also considered so as to examine whether possible differences between the groups depended on certain motor scores or age ("post-stratification").

Results

A total of 113 patients were studied: 41 in the control group, 36 in the HV group, and 36 in the HV + THAM group. The somewhat larger number of patients in the control group is due to the fact that early in the study, patients for whom informed consent to participate could not be obtained immediately were assigned to control, without drawing an envelope. As soon as we became aware of this protocol violation it was stopped, but we could not determine in retrospect which patients were properly entered into the study and which were not, as there were signed informed consent forms in all of the charts.

Demographic, Blood, and CSF Data

Table 1 shows the demographic data and some prognostic factors[4,30] in each of the three groups. Although none of the differences between the three groups was statistically significant, the impression remains that the severity of injury in the HV + THAM group was slightly less than that in the control and HV groups. When studying Table 1 one should keep in mind, however, that many factors such as pupillary responses and midline shift on computerized tomography scans or the absence of perimesencephalic cisterns and the presence of high ICP may be interdependent and thus the same pathophysiological factor is represented more than once in the table.

Table 2 shows $PaCO_2$ and related data in arterial blood and CSF. It should be noted that $PaCO_2$ and other values in arterial blood were obtained in all patients still alive on a particular day. The CSF analysis was from a smaller number of patients because CSF sampling was limited. Nevertheless, CSF data were obtained from sufficient patients (20 in the control group, 29 in the HV group, and 28 in the HV + THAM

TABLE 2

*Arterial and cerebrospinal fluid (CSF) pH, CO_2, and HCO_3^- in the three treatment groups over 5 days**

Factor	Group	Baseline	Day 2	Day 3	Day 4	Day 5
arterial pH	control	7.45 ± 0.07	7.48 ± 0.06	7.47 ± 0.06	7.45 ± 0.10	7.46 ± 0.06
	HV	7.44 ± 0.08	7.56 ± 0.07	7.51 ± 0.07	7.49 ± 0.07	7.49 ± 0.07
	HV + THAM	7.42 ± 0.09	7.56 ± 0.05	7.53 ± 0.05	7.51 ± 0.06	7.51 ± 0.07
arterial pCO_2 (mm Hg)	control	31 ± 7	31 ± 6	32 ± 6	31 ± 7	32 ± 7
	HV	30 ± 6	26 ± 5	26 ± 5	27 ± 6	28 ± 6
	HV + THAM	32 ± 6	24 ± 4	25 ± 4	26 ± 5	26 ± 5
arterial HCO_3^- (mm Hg)	control	21.2 ± 2.7	22.8 ± 2.8	22.6 ± 3.1	22.2 ± 4.3	22.2 ± 2.7
	HV	19.9 ± 2.8	20.4 ± 3.0	20.5 ± 2.5	20.6 ± 2.8	20.7 ± 2.4
	HV + THAM	21.4 ± 3.6	21.2 ± 2.8	20.3 ± 2.5	20.7 ± 2.8	20.5 ± 2.4
CSF pH	control	7.31 ± 0.12	7.36 ± 0.05	7.36 ± 0.07	7.29 ± 0.09	7.29 ± 0.13
	HV	7.31 ± 0.03	7.37 ± 0.06	7.34 ± 0.05	7.33 ± 0.04	7.26 ± 0.09
	HV + THAM	7.33 ± 0.08	7.38 ± 0.05	7.38 ± 0.05	7.37 ± 0.05	7.35 ± 0.06
CSF pCO_2 (mm Hg)	control	33 ± 5	32 ± 5	30 ± 7	35 ± 8	37 ± 11
	HV	38 ± 5	30 ± 4	33 ± 5	32 ± 5	38 ± 4
	HV + THAM	38 ± 8	32 ± 5	31 ± 5	33 ± 4	34 ± 5
CSF HCO_3^- (mmol/liter)	control	17.9 ± 1.9	19.0 ± 4.1	20.3 ± 6.0	17.7 ± 1.9	18.8 ± 6.2
	HV	18.9 ± 1.8	16.7 ± 2.3	16.8 ± 1.5	18.3 ± 5.4	15.8 ± 2.4
	HV + THAM	19.5 ± 2.8	18.3 ± 1.6	17.6 ± 1.9	17.8 ± 2.1	17.8 ± 1.2

* HV = hyperventilation. All values are means ± standard deviations.

group) that we feel they are representative for the three groups. The baseline $PaCO_2$ values were similar among the three groups and efforts to maintain $PaCO_2$ within the prespecified range were successful.

The results showed that THAM was somewhat more successful than hyperventilation in maintaining a slight alkalosis in arterial blood, but pH in the HV group was also higher than in the control group. On the other hand, hyperventilation did not result in a sustained increased pH in CSF as compared to normoventilation, but THAM clearly had the expected effect on CSF pH. Moveover, hyperventilation resulted in a small decrease in CSF HCO_3^-, which led to some loss of pH buffer capacity of CSF.

Outcome

Table 3 shows the outcome data, classified into the stratifications, for the three groups at 3, 6, and 12 months, respectively. A 100% follow-up review was obtained. At 12 months, data were missing for one patient each in the control and HV groups, but when seen more than 2 years after injury both patients were in the same outcome category as they were at 6 months, so that outcome was assigned to them at 12 months.

TABLE 3

*Outcome at 3, 6, and 12 months, stratified for motor scores 1–3 and 4–5 in the three treatment groups**

Motor Score	Group	Total Cases	3 Months			6 Months			12 Months		
			G/MD	SD/V	D	G/MD	SD/V	D	G/MD	SD/V	D
no. of cases											
1–3	control	20	1	9	10	3	6	11	4	5	11
	HV	19	1	11	7	4	8	7	4	8	7
	HV + THAM	15	1	8	6	1	8	6	3	4	8
4–5	control	21	10	9	2	12	7	2	12	6	3
	HV	17	3†	13	1	4†	12	1	7	8	2
	HV + THAM	21	9	9	3	12	6	3	14	4	3
% of cases											
1–3	control		5	45	50	15	30	55	20	25	55
	HV		5	58	37	21	42	37	21	42	37
	HV + THAM		7	53	40	7	53	40	20	27	53
4–5	control		48	43	10	57	33	10	57	30	15
	HV		18†	77	6	24†	71	6	44	47	12
	HV + THAM		43	43	14	57	29	14	67	19	14

* Outcome assessed according to the Glasgow Outcome Scale:[14] G = good; MD = moderate disability; SD = severe disability; V = vegetative state; D = death.

† Significantly different from control, $p < 0.05$, multiple logistic regression technique.

TABLE 4

*Mean CBF, $AVDO_2$, and $CMRO_2$ in patients with measurements at baseline, and at 24 and 72 hours postrandomization**

Group	Time of Study	CBF_{15} (ml/100 gm/min)	$AVDO_2$ (vol%)	$CMRO_2$ ml/100 gm/min	$PaCO_2$ (mm Hg)
control	baseline	36 ± 13	5.5 ± 2.3	1.8 ± 0.8	32 ± 5
(20 cases)	24 hrs	35 ± 13	4.0 ± 1.6†	1.4 ± 0.6†	32 ± 5
	72 hrs	41 ± 13	3.9 ± 1.9†	1.4 ± 0.7	31 ± 6
HV	baseline	34 ± 10	4.8 ± 1.8	1.6 ± 0.8	33 ± 5
(21 cases)	24 hrs	36 ± 11	4.2 ± 1.3	1.6 ± 0.6	25 ± 3†
	72 hrs	32 ± 7	3.8 ± 1.7†	1.3 ± 0.7	25 ± 4†
HV + THAM	baseline	37 ± 11	5.2 ± 1.8	1.8 ± 0.8	35 ± 5
(26 cases)	24 hrs	28 ± 7†	5.5 ± 2.1	1.6 ± 0.6	25 ± 3†
	72 hrs	27 ± 9†	4.7 ± 1.3	1.6 ± 0.8	25 ± 4†

* CBF_{15} = mean cerebral blood flow in the fast- and slow-clearing compartments; $AVDO_2$ = arteriovenous oxygen difference; $CMRO_2$ = cerebral metabolic rate of oxygen; HV = hyperventilation. Values are means ± standard deviations.

† Different from baseline values, $p < 0.05$ (paired Student's t-test).

The analysis of outcomes at 3 months showed that patients in the HV group fared worse than the corresponding control group ($p < 0.03$). The data revealed that the group difference was in the patients with a motor score of 4 or 5 but not in those with a motor score of 3 or less. This finding was reflected in the outcome pattern, indicating that the deleterious effect of hyperventilation was noted primarily in the good and moderately disabled outcome categories with no significant difference in mortality. The deleterious effect of hyperventilation as indexed by the GOS assessment was also evident at 6 months, although the difference between the two groups was somewhat less pronounced than at 3 months ($p < 0.05$, Table 3). Similarly, the interaction effect of treatment group and motor score was again found to be significant ($p < 0.02$), indicating that the detrimental effect of hyperventilation was limited to patients with relatively better prognosis at admission. Although by 12 months there were still fewer patients with favorable outcome in the HV group than in the control group, this difference was no longer statistically significant ($p < 0.15$ in motor scores 4 and 5, Table 3). One interesting result was that the mortality rate in the control group was actually higher than in the HV group. For example, at 12 months, 34% of the control group had died versus 25% in the HV group; however, the difference was not significant, although the power of determining such a difference in the mortality rate as significant is less than 10% because of the relatively small sample size. As for the difference between the HV + THAM-treated group and the control group, no significant differences in outcome were found at any of the three time points.

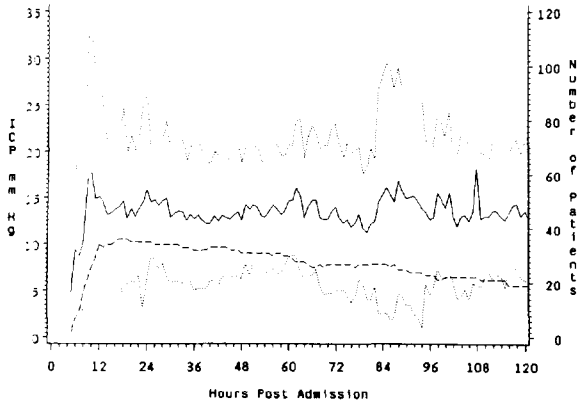

FIG. 1. Temporal course of intracranial pressure (ICP) for the control group, averaged from 30-second sampled data. The *broken line* indicates the number of patients contributing to the average. The *fine broken lines* above and below the mean ICP indicate ± 1 standard deviation.

Cerebral Blood Flow, $AVDO_2$ and $CMRO_2$

Mean values and standard deviations for CBF, $AVDO_2$, and $CMRO_2$ are shown in Table 4. Because the particularly interesting feature of these data was their development from baseline (just before randomization) over the ensuing few days, we included only those patients who had all measurements at the three time points. Thus, a few patients could not be included because the jugular catheter was not in place for $AVDO_2$ measurements at all times, a few patients did not have baseline CBF measurements, and a few patients did not have follow-up CBF measurements because of equipment failure or lack of ^{133}Xe; the most common reason for exclusion was the death of patients before their (last) follow-up measurement. This introduced some bias toward including only survivors but occurred equally in all three groups, making the intergroup differences still valid. It is obvious that baseline CBF, $AVDO_2$, and $CMRO_2$ were not substantially different in the three groups. After 24 and 72 hours, CBF in the control and HV groups had not changed significantly; however, in the HV + THAM group, CBF remained 25% lower than baseline CBF, reflecting the fact that only in the HV + THAM group was CSF alkalosis sustained. Although $CMRO_2$ tended to diminish over time, this was statistically significant only in the control group at 24 hours. In the HV + THAM group, the decrease in $CMRO_2$ is matched by CBF changes, with $AVDO_2$ remaining the same. The $AVDO_2$ decreased significantly at 72 hours in the HV group and at 24 and 72 hours in the control group.

Intracranial Pressure

The temporal course of mean ICP and standard deviation for each patient group is shown over 5 days in Figs. 1 to 3. The number of patients comprising the mean ICP value for each patient group is also shown. All patients entered into the study were monitored, and the reduction of patient numbers in the plots reflects

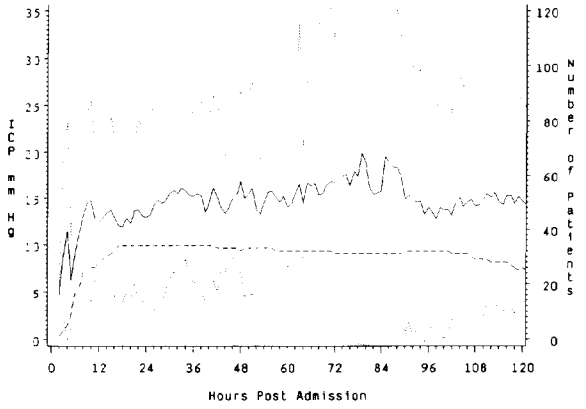

FIG. 2. Temporal course of intracranial pressure (ICP) for the hyperventilation group, averaged from 30-second sampled data. The *broken line* indicates the number of patients contributing to the average. The *fine broken lines* above and below the mean ICP indicate ± 1 standard deviation. Note the high variability beginning at 60 hours postinjury.

those patients who died during the first 5 days postinjury.

The hourly ICP average was below the treatment threshold of 25 mm Hg for all groups during the 5-day period of observation. No significant differences in hourly mean values were observed. Although differences are small, patients treated with HV + THAM exhibited the most stable ICP course with minimal variability compared to patients randomly assigned to the control and HV groups. This was more evident beyond 2 days postinjury, where standard deviations of ICP for both the control and HV groups increased. The maximum variation of ICP was observed after 60 hours postinjury in patients in the HV group (Fig. 2).

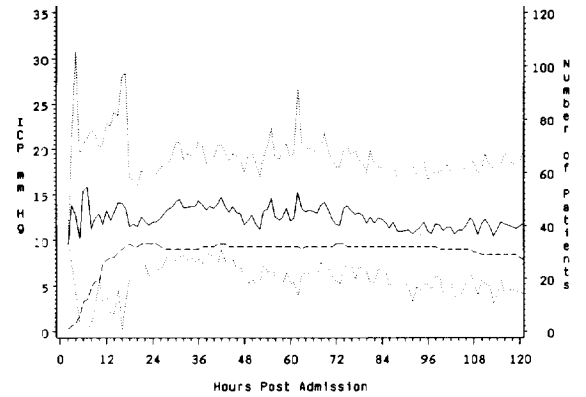

FIG. 3. Temporal course of intracranial pressure (ICP) for the group treated with hyperventilation plus THAM, averaged from 30-second sampled data. The *broken line* indicates the number of patients contributing to the average. The *fine broken lines* above and below the mean ICP indicate ± 1 standard deviation. Note that THAM administration, although not affecting the mean pressure level, reduces the variability of ICP.

Discussion

This study shows that prophylactic use of sustained hyperventilation for a period of 5 days retards recovery from severe head injury, with outcome being statistically significantly worse at 3 and 6 months but not at 12 months. With somewhat fewer patients dying in the HV group, one might argue that those severely injured patients who do not die become vegetative or severely disabled and so increase the number of patients with that outcome in the HV group. It should be emphasized, however, that it is the increased number of patients with admission motor scores of 4 and 5 with a favorable outcome in the control and HV + THAM groups as compared to the HV group that is statistically significantly different, not a decreased number of patients with poor outcome. The use of THAM seems to counteract the deleterious effect of prolonged hyperventilation and, therefore, its use would be beneficial when sustained hyperventilation is required for ICP control.

Methodological Considerations

The present paper describes a randomized, but not blinded or placebo-controlled, clinical trial. Although it would have been possible to give a placebo for the THAM, it was elected not to do this. It is not possible to keep the treating physicians blinded as to whether the patients were hyperventilated or not, so a THAM placebo would have blinded us only between HV and HV + THAM, but the control group would have remained recognizable. Unfortunately, a protocol violation occurred early in the study when patients for whom consent to participate could not be obtained within 12 hours were assigned to the control group without drawing an envelope. This was done by the admitting residents and as soon as the investigators became aware of this practice it was stopped. Probably four extra patients were entered in the control group, slightly biasing the control group patients to be entered early in the study. To assess whether this affected outcome, we compared entry characteristics and outcome at 3, 6, and 12 months in the first 23 and last 18 control group patients, but no differences were found.

Even though the patients were stratified according to motor score, and none of the differences in admission characteristics was statistically significant, the impression remains that the patients in the HV + THAM group were somewhat less severely injured than those in the control and HV groups. There is no explanation for this phenomenon other than "chance," nor is a fix possible: "poststratification" with regard to all of the factors listed in Table 1 would make the groups far too small for meaningful comparison. It should be kept in mind, however, that the clinically most important differences in outcome were found between the control and HV groups, which were well balanced in respect to prognostic factors at admission. Thus, although some caution must be exercised when interpreting the outcome results, we believe that the data unequivocally

show that prophylactic hyperventilation is not beneficial after severe head injury.

Previous Studies of Hyperventilation

Heretofore, no randomized study of the effect of sustained hyperventilation has been reported. In a retrospective study of 251 head-injured patients, Gordon and Rossanda[11] observed a reduction in mortality rate from 32.1% to 9.2% in 51 patients hyperventilated to a $PaCO_2$ of 25 to 30 torr for a period of 6 hours to 41 days. However, hyperventilation treatment did not increase the percentage of patients with good outcome. Few details of case selection are given and the ICP profiles of both groups were not reported. These workers considered that hyperventilation might attain its beneficial effect as a result of correction of CSF acidosis. Based upon these findings, it was later suggested that the use of hyperventilation would contribute to reducing the mortality rate due to severe head injury.[10,25] However, in a randomized study on the use of hyperventilation in stroke no beneficial effect was found.[5]

Mechanisms of Action

There are two important questions raised by the present findings. What factors account for the comparatively poor outcome in the hyperventilation group at 3 and 6 and even at 12 months postinjury and what are the mechanisms by which THAM seemingly protects against the deleterious effect of hyperventilation? Three factors that are possibly affected by hyperventilation and/or THAM and will be considered are: cerebral ischemia, cerebral metabolic factors, and ICP.

Cerebral Ischemia. It is well known that acute hyperventilation, through its effect on extracellular pH, produces vasoconstriction, reducing cerebral blood volume and CBF.[22,23] Therefore, one might question if hyperventilation reduces CBF to ischemic levels and thus affects outcome.

Cerebral metabolic rate of oxygen is defined as $CMRO_2 = CBF \times AVDO_2$; thus, $CMRO_2$ will remain constant with a 50% reduction in CBF, compensated for by a 100% increase in $AVDO_2$. Under normal circumstances, a doubling in $AVDO_2$ results in total extraction of O_2, so additional decreases in CBF cannot be compensated for further and $CMRO_2$ will fail. Thus, ischemia can be defined by looking both at CBF and at $AVDO_2$.[23] It should be borne in mind, however, that CBF and $AVDO_2$ as reported in this paper represent very global values and may not reflect large differences that might exist from one small area to another, even though there is no clear evidence that such differences indeed exist.[21,23] With this limitation of the method in mind, Obrist, *et al.*,[23] showed that after head injury acute hyperventilation can lead to dangerously low CBF, accompanied by high values of $AVDO_2$, such that additional decreases in CBF cannot be compensated for by further increases of $AVDO_2$, with ensuing lowering of $CMRO_2$. As judged by the global CBF measurements, such was not the case in the present series. All of the mean hemispheric CBF values measured within 12 hours and subsequently for 3 days were well above the ischemic range as defined by the criteria of Obrist, *et al.*

One might argue that the effect of hyperventilation on vessel caliber and thus on CBF is only short-lived.[22] Therefore, a CBF measurement 24 hours after the beginning of hyperventilation would miss possible ischemia during the first 4 to 12 hours of hyperventilation. This does not seem likely because $AVDO_2$ measurements, which were performed much more frequently than CBF measurements, yielded only one value above 9 vol%, the level which Obrist, *et al.*,[23] have described as a threshold for the advent of ischemia. Thus, although the possibility exists that deep brain regions may be ischemic, we conclude from available CBF and $AVDO_2$ data that global measurements of CBF showed that cerebral circulation was able to meet oxidative demands of the brain. Even in the HV + THAM group (in which alkalinization of the CSF occurred, mean CBF was lower than in the control and HV groups, and vasoconstriction was sustained), neither CBF nor $AVDO_2$ data indicate the presence of global cerebral ischemia from measurements obtained within 12 hours of admission up to 96 hours later.

Cerebral Metabolic Factors. Although it seems that the cerebral circulation was sufficient to meet oxidative demands, it is difficult to assess by these data whether or not the total energy requirement of the brain was met. For this purpose, laboratory experiments were conducted to study the changes in brain metabolism that occur when injured brain is hyperventilated.[31] In fact, the design of the clinical trial was duplicated in the laboratory and bioenergetics were evaluated using magnetic resonance spectroscopy in mechanically injured animals treated with: 1) sustained hyperventilation; 2) a combination of THAM and hyperventilation; or 3) THAM alone. The highest lactate production was associated with animals treated with sustained hyperventilation. Lactate production was ameliorated in the THAM-treated group and this was the first experimental evidence showing a direct metabolic effect of the buffer THAM upon brain tissue. The second piece of evidence was suggested by minimal recovery of oxidative stores, as indexed by the ratio of phosphocreatinine to inorganic phosphate (PCr/P_i), associated with those animals treated with sustained hyperventilation following injury. Third, brain edema was reduced with THAM treatment compared with untreated controls. Finally, PCr/P_i ratios of hyperventilated animals treated with THAM returned to control levels. Taken in concert, these findings provide supporting evidence for the deleterious effect of sustained hyperventilation observed in the clinical setting and the normalization of this effect in patients treated with THAM.

Factors Influencing Intracranial Pressure. Another possible explanation for the deleterious effect of

hyperventilation is that prophylactic hypocapnia prematurely compromises mechanisms available for volume compensation, and this leads to a later rise in ICP.[22] Our data showed that the mean hourly ICP course for the HV and HV + THAM groups was not significantly different when compared to that of the control group. Moreover, mannitol administration for ICP control was necessary in an average of 36% of control patients, 25% of HV patients, and 24% of HV + THAM patients during each of the first 5 days, with the total average amount of mannitol per day not being different in the control and HV groups (64 and 45 ml, respectively), but significantly higher in the control group than in the HV + THAM group (30 ml). Barbiturate administration became necessary for ICP control in six patients in each of the three groups (15% of the control group, 17% of the HV group, and 17% of the HV + THAM group). This is not surprising in view of the findings of Muizelaar, *et al.*,[22] as to the effect of chronic hyperventilation upon pial arteriolar caliber in rabbits. Their studies showed that, under conditions of prolonged hyperventilation, pH in blood remains elevated but pH in CSF returns to baseline within 24 hours. The data in this study, shown in Table 2, show a similar pattern. Cerebral arteriolar diameter in experimental animals was found to be decreased shortly after institution of hyperventilation, but returned to baseline within 24 hours and increased slightly over baseline after that period. Moreover, with the loss of bicarbonate buffer from CSF during prolonged hyperventilation, the blood vessels became hypersensitive to changes in $PaCO_2$. Similar findings in unanesthetized rabbits were reported earlier by Levasseur, *et al.*[16] In the present study, mean ICP levels were not different, the vessel hypersensitivity to $PaCO_2$ changes during chronic hyperventilation might explain the increased variability in ICP observed in the hyperventilation patient group approximately 60 hours postinjury (corresponding to 40 hours postrandomization) as shown in Fig. 2. It has been shown that the percentage of time during which ICP exceeds 20 mm Hg is deleterious.[17] We therefore believe that the ICP variability and the higher ICP levels reached in the hyperventilated patients comprise one factor that might account for the less favorable outcome.

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