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Intracranial Pressure and Neuromonitoring in Brain Injury

Proceedings of the Tenth International ICP Symposium, Williamsburg, Virginia, May 25–29, 1997

Edited by
A. Marmarou, R. Bullock,
C. Avezaat, A. Baethmann,
D. Becker, M. Brock, J. Hoff,
H. Nagai, H.-J. Reulen,
G. Teasdale

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Anthony Marmarou, Ph.D.
Medical College of Virginia, Richmond, Virginia, U.S.A.

Ross Bullock, M.D., Ph.D.
Medical College of Virginia, Richmond, Virginia, U.S.A.

Cees Avezaat, M.D.
University Hospital Rotterdam, Rotterdam, The Netherlands

Alexander Baethmann, M.D., Ph.D.
University of Munich, Munich, Germany

Donald Becker, M.D.
UCLA School of Medicine, Los Angeles, California, U.S.A.

Mario Brock, M.D.
University of Berlin, Berlin, Germany

Julian Hoff, M.D., Ph.D.
University of Michigan, Ann Arbor, Michigan, U.S.A.

Hajime Nagai, M.D.
Nagoya City University, Nagoya, Japan

Hans-J. Reulen, M.D.
Ludwig Maximilians University, Munich, Germany

Graham Teasdale, M.D.
Institute of Neurological Sciences, Glasgow, U.K.

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This volume is dedicated to the memory of our dear friend and colleague

J. Douglas Miller, M.D., Ph.D.
1937–1995
Professor of Neurosurgery
University of Edinburgh

Preface

The first international symposium on intracranial pressure was held in Hannover Germany in 1972, and 8 symposia have been held since that time in all parts of the world. This volume provides a summary of the tenth symposium which was held in Williamsburg, Virginia, and marked the 25th anniversary of our initial meeting. In these past 25 years, significant strides have been made in understanding the cause and effects of raised intracranial pressure, and this symposium represented a milestone in our quest for knowledge to help improve patient outcome. It is here that we expanded the scope of our meeting to include additional forms of neuromonitoring to provide a broader view of the pathophysiologic changes occurring in injured or diseased brain. Important contributions were made in experimental and clinical studies of brain tissue oxygen, neurochemical measures utilizing microdialysis, jugular oximetry, near infrared spectroscopy, cerebral blood flow and magnetic resonance spectroscopy to name a few. These other monitoring modalities were welcomed at our ICP symposium and it is natural that results of these additional probes into the brain are discussed in concert with the first brain probe, intracranial pressure.

The Williamsburg symposium attracted 417 scientists from all parts of the world and 298 abstracts were accepted for presentation at the meeting. A total of 182 manuscripts were submitted and of these, 107 manuscripts were selected for expanded publication. The remainder of the abstracts (191) are also published in this volume. The top six categories containing most abstracts are: Pathophysiology of ICP, Hydrocephalus, Traumatic Brain Injury, Management of ICP and CPP, Brain Oxygen Monitoring and Neuromonitoring in the ICU. Combined, these topics accounted for 65% of the abstracts. The symposium also scheduled several workshops, which allowed the veteran scientists more time to discuss their research and recommend new areas of investigation to the younger investigators. These workshops were fully attended by the participants and expanded our knowledge base. In addition, a special satellite meeting of "Neurochemical Monitoring in the Intensive Care Unit" was held following the ICP symposium, which attracted more scientists to present their most recent findings and to complement our general theme of neuromonitoring. These manuscripts are contained in a separate volume.

We were also fortunate during the opening ceremony to hear videotaped introductory comments by Professor Lundberg, who is doing well and enjoying retirement on the farm of his parents in Lund, Sweden. Professor Lundberg commented on the fact that the ICP symposia are an odd phenomenon in the jungle of medical associations, since there is no permanent organization, no president, no staff, no formal membership, no society, no written rules, etc. etc. How is it possible, he asked, that such a loosely built association has been kept living during 25 years, prospering and developing in to an almost indispensable ingredient of scientific neurosurgery? We found the answer in Williamsburg where the number of new investigators represented a large percentage of participants. The ICP symposia for the past 25 years have welcomed these young scientists to the field and have provided a fertile ground to learn, grow and eventually become the seasoned investigators that brain research so desperately needs.

The scientific works presented in this volume document the current state of the art in ICP research and the field of neuromonitoring. We look forward to continued progress at our next symposium to be held in Cambridge, England, in the year 2000. Finally, we wish to acknowledge the competent collaboration of R. Petri-Wieder of Springer-Verlag, Vienna in the production of this volume.

Anthony Marmarou
on behalf of the Advisory Board

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Cerebral Hemodynamic Changes during Sustained Hypocapnia in Severe Head Injury: Can Hyperventilation Cause Cerebral Ischemia?

A. Ausina[3], **M. Báguena**[3], **M. Nadal**[1], **S. Manrique**[1], **A. Ferrer**[1], **J. Sahuquillo**[2], and **A. Garnacho**[3]

Departments of [3]Intensive Care Unit, [2]Neurosurgery, and [1]Anesthesiology, Vall d'Hebron University Hospitals, Barcelona, Spain

Summary

Hyperventilation (HV) is routinely used in the management of increased intracranial pressure (ICP) in severe head injury. However, this treatment continues to be controversial because it has been reported that long-lasting reduced cerebral blood flow (CBF) due to profound sustained hypocapnia may contribute to the development or deterioration of ischemic lesions. Our goal in this study was to analyze the effects of sustained hyperventilation on cerebral hemodynamics (CBF, ICP) and metabolism (arterio jugular differences of lactates = AVDL). Co_2-reactivity and CBF was estimated using $AVDO_2$ (arteriojugular differences of oxygen content). Global cerebral ischemia and increased anaerobic metabolism were considered according to $AVDO_2$ and AVDL respectively. Thirty-three patients with severe and moderate head injury and increased ICP were included. Within 72 hours after accident, patients were hyperventilated for a period of 4 hours. During this time jugular oxygen saturation (SjO_2), arterial oxygen saturation (SaO_2), ICP, mean arterial blood pressure (MABP), $AVDO_2$ and AVDL were recorded.

In our study, most patients preserved CO_2-reactivity (88.2%). In these cases HV was very effective in lowering ICP. Our findings showed that this reduction was due to a CBF decrease. According to basal $AVDO_2$ twenty-five patients (75.7%) were considered as hyperemic and eight (24.2%) as not hyperemic. Global ischemia and increased anaerobic metabolism were detected in one case in the non-hyperemic group. According to $AVDO_2$ and AVDL, no adverse effects were found during four hours of HV in hyperemic patients. Nevertheless, $AVDO_2$ and AVDL are global measurements and might not detect regional ischemia surrounding focal lesions such as contusions and haematomas. We suggest that monitoring of $AVDO_2$ or other haemometabolic variables should be mandatory when sustained HV is used in the management of head injury patients.

Keywords: Cerebral ischemia; head injury; sustained hypocapnia.

Introduction

Autoregulation and CO_2-reactivity can be impaired independently of each other in many brain insults, the so called "dissociated vasoparalysis". In most patients with severe head injury and increased intracranial pressure (ICP), autoregulation is impaired in the first days, although CO_2-reactivity is usually preserved. This fact has many clinical implications. In these patients, uncontrollable intracranial hypertension is the most frequent cause of death. Vascular mechanisms have been classically considered in some type of lesions (swelling) as the most important etiopathogenic factor. Hyperventilation (HV) has been routinely used for many years with a demonstrated effectiveness for decreasing ICP. However, this treatment continues to be controversial because it has been reported that long-lasting diminished cerebral blood flow (CBF) due to profound sustained hypocapnia may contribute to the development or deterioration of ischemic lesions. Our goal in this study was to analyze the effects of HV in cerebral hemodynamics and metabolism of severe head injury.

Material and Methods

In this prospective study 33 consecutive patients with severe and moderate head injury (GSC ≤ 12) and increased ICP (>20 mmHg) were included. Those patients with pulmonary disorders which did not allow modifications of the ventilation parameters were excluded. The protocol used in our study was reviewed and approved by the Ethics committee of the Vall d'Hebron University Hospitals.

Study Protocol

ICP, SjO_2 and MABP were continuously monitored in all patients with a GCS score below or equal to eight. Within 72 hours after accident, patients were hyperventilated for a period of four hours. First arterial and jugular samples were extracted to establish baseline values. Then minute ventilation was increased to de-

crease basal arterial pCO_2 and this change was maintained for a period of four hours. Continuous capnography was used to prevent significant variations of arterial pCO_2. During this time arterial and jugular samples were extracted at 30 minutes, 1 hour, 2 hours and 4 hours to determine $AVDO_2$ and arterial pCO_2. ICP and MABP were also recorded. AVDL were measured before hyperventilation and at 30 minutes and 4 hours after induced hypocapnia.

CO_2-reactivity was tested in all patients according to previously reported methodology [13]. Intact CO_2-reactivity was considered when changes in estimated CBF were greater than 1%. $AVDO_2$ were calculated by using the following equation: $AVDO_2 = 1.34 \times Hb \times [(SaO_2 - SjO_2)/100]$. $AVDO_2$ at one hour, two hours and four hours were corrected for spontaneous changes in pCO_2 according to the pCO_2 at 30 minutes.

Expressed as 100%, the percent change of CBF ($1/AVDO_2$) relative to the baseline value was calculated according to the following equation:

$CBF\% = 100 - [(1/AVDO_{2B} - 1/AVDO_{2HV})/(1/AVDO_{2B}) \times 100]$, where $AVDO_{2B}$ are the basal $AVDO_2$ and $AVDO_{2HV}$ the $AVDO_2$ at 30 minutes, one hour, two hours or four hours of HV.

Assuming a normal range of $AVDO_2$ of 1.7–3.8 μmol/ml [9], $AVDO_2 < 1.7$ μmol/ml was considered as brain hyperemia and $AVDO_2 > 3.8$ μmol/ml as suggestive of brain ischemia. Increased anaerobic metabolism was considered when ADVL > –0.42 μmol/ml [8].

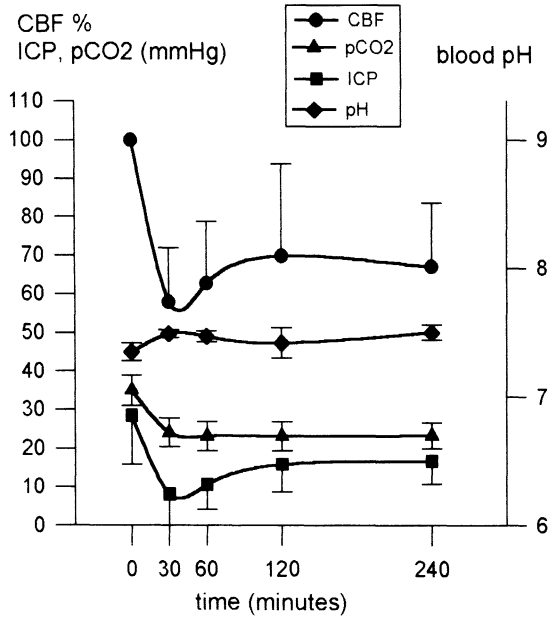

Fig. 1. Induced ICP, CBF, pCO_2 and blood pH changes during the hyperventilation period

Statistical Analysis

Statistical analysis was carried out using the BMDP package. Mean ± SD was used to summarize variables. The level of statistical significance was established at 0.05.

Results

Mean age in our group was 31.6 ± 14.4 years. Twenty-six patients were male (81.3%) and six female (18.7%). Initial GSC was 6.0 ± 3.3. The study was carried out 58 ± 4.2 hours after accident. According to CT scan findings and based on Marshall's classification, fourteen patients had a type II injury, ten a type III, four a type V and three a type VI. In our study most patients preserved CO_2-reactivity (88.2%). We did not use data from the three patients with abolished CO_2-reactivity for analysis. The main variables recorded during the test are summarized in Table 1.

Hyperventilation acutely decreased arterial pCO_2, ICP and CBF. The decrease was most marked during the first hour and showed a mild tendency to return to baseline values during the following hour. After the second hour there were no significant changes (Fig. 1).

According to the basal $AVDO_2$ twenty-eight patients (93.3%) were considered as hyperemic. In the hyperemic group, no patient developed cerebral ischemia according to AV DO_2 and AVDL. In the non hyperemic group only one patient developed cerebral ischemia and increased cerebral metabolism at 30 minutes of HV (Fig. 2). HV was immediately stopped and the patient was later diagnosed as having vasospasm.

Outcome was assessed according to the Glasgow Outcome Scale at 6 months. 39.3% of patients had a bad outcome: 4 died, 2 were in a persistent vegetative state and 7 were severely disabled and 60.6%

Table 1. *Summary of Main Recorded Variables During Hyperventilation Period*

	BASAL	30 min	1 hour	2 hours	4 hours
pCO_2 (mmHg)	34.8 ± 3.9	24.1 ± 3.7	23.2 ± 3.8	23.3 ± 3.8	23.1 ± 3.3
pH blood	7.35 ± 0.07	7.49 ± 0.03	7.47 ± 0.04	7.42 ± 0.12	7.50 ± 0.06
ICP (mmHg)	27.7 ± 12.9	7.8 ± 11.0	10.2 ± 6.4	15.3 ± 7.7	16.2 ± 6.5
CPP (mmHg)	53.1 ± 13.1	76.9 ± 11.0	76.5 ± 9.9	75.2 ± 11.1	74.4 ± 10.7
CBF%	100	57.9 ± 13.9	62.7 ± 16.1	69.8 ± 23.9	67.0 ± 16.5
$AVDO_2$ (μmol/ml)	1.21 ± 0.4	2.2 ± 0.7	2.0 ± 0.6	1.8 ± 0.5	1.8 ± 0.6
AVDL (μmol/ml)	0.01 ± 0.27	–0.09 ± 0.26			–0.01 ± 0.06

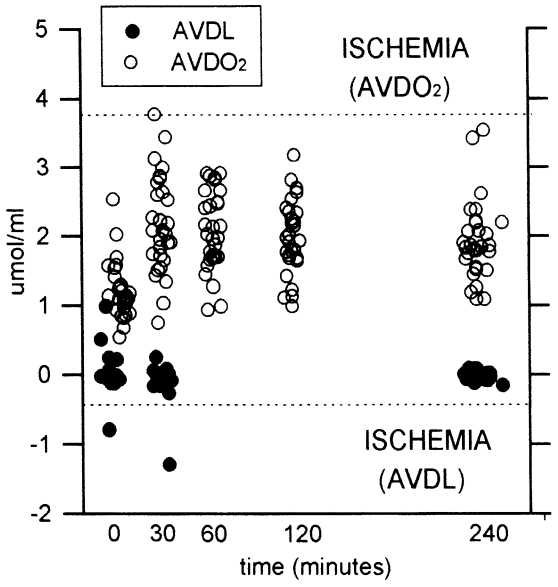

Fig. 2. $AVDO_2$ and AVDl during the hyperventilation period. The limits of ischemia are marked by dotted lines

had a good outcome: 9 good recovery, 11 moderate disability.

Discussion

Hyperemia

$AVDO_2$ showed a hyperemic CBF pattern in most of our patients (93.3%). This percent is higher than in other series published in the literature [6,11]. This could be for three reasons: 1) Most of the patients (72.7%) in our series had a diffuse head injury (types II and III and Marshall's classification). 2) The length of time from the accident to admittance to our study was in most cases more than 24 hours. A trend toward normal to elevated CBF unrelated to a decreased $CMRO_2$ after the first hours of accident has been described by some authors [11]. 3) An inclusion criteria in our study was the presence of elevated ICP and hyperemia has been associated with a high occurrence of intracranial hypertension in diffuse injuries [11].

CO_2-Reactivity

CO_2-reactivity was preserved in most of our patients. This corresponds to findings in other studies [7,11]. HV was very effective in lowering ICP during four hours in these cases. The clinical implication is that many patients with head injury and increased ICP could benefit from HV during at least four hours as a therapeutic method.

Hemodynamic Changes

HV decreased CBF and ICP significantly in our patients. Our findings showed that ICP reduction was related to a CBF decrease. The highest decrease of CBF and ICP was during the first hour with a slight tendency to return to baseline values during the second hour. However, during the following two hours CBF and ICP continued to be significantly reduced to around 40% of basal values. No tendency to lose CBF response to HV was noticed after the first two hours. A tolerance to HV effects, which begins around 6 hours and is complete within 30 hours, has been described [2]. This coincides with studies of CSF adaptation in animal experiments [10]. However, there are fewer studies on the effects of sustained hyperventilation in patients with head injury. Cold [4] proposed that in these patients CSF pH adaptation could be delayed. In our study HV was used during only four hours and we cannot predict its effect after this time.

Arterial pH increased during the first 30 minutes after induced hypocapnia. This coincided with the initial fall of CBF and ICP. Blood pH increase was then maintained without significant variation throughout the four hours. This suggests that the increase in arterial pH was responsible for initial changes found in CBF and ICP probably mediated by changes in CSF pH. Further changes in CBF cannot be explained by blood pH variations. They may be due to changes in CSF pH as being reported in other studies [12].

Ischemia

Since Adams and Graham [1] described the high incidence of postmortem ischemic brain damage, many authors have pointed out the possibility of development or deterioration of ischemic lesions due to HV. Muizelaar [10] found a poor outcome in his group of hyperventilated patients, and Cold [3] described a CBF decrease close to ischemic threshold caused by acute HV.

According to our $AVDO_2$ and AVDL results, only one patient in the non hyperemic group showed ischemia. Our data may suggest that in this hyperemic period patients would benefit from HV. This agrees with Obrist *et al.*(11) who found no adverse effects of HV in hyperemic patients. However, it should be emphasized that in our study regional ischemia may not be detected as $AVDO_2$ are an

estimate of global CBF. Moreover, blood lactates may not represent lactates in CSF after several hours of HV. CSF lactates have been found to be more related to high ICP and outcome than blood lactates [5]. Further studies of lactates in CSF are necessary to confirm our data.

Acknowledgements

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Correspondence: Alicia Ausina Aguilar, M.D., c/Homero 45–49, entlo 2, esc. A., 08023 Barcelona, Spain.

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Use of Vasopressors to Raise Cerebral Perfusion Pressure in Head Injured Patients

A. Biestro[1], **E. Barrios**[1], **J. Baraibar**[1], **C. Puppo**[1], **D. Lupano**[1], **M. Cancela**[1], **B. Borovich**[2], and **J. Pouso**[3]

[1] Intensive Care Unit and [2] Department of Neurosurgery, Hospital de Clinicas, and [3] Satistical Consultant, Hospital Militar, Montevideo, Uruguay

Summary

Cerebral ischemia due to low cerebral perfusion pressure (CPP) is the most important secondary effect of severe head injury. There is consensus regarding the maintenance of this pressure at levels above 70 mm Hg. One way to elevate CPP is by increasing mean arterial pressure (MAP). In this study, the authors attain this target by using adrenergic vasopressors investigating the effectiveness of dopamine, noradrenaline and methoxamine in 16 severe head injured patients. The results were: a) the increase of MAP effectively increased CPP without changes in intracranial pressure (ICP) and cerebral extraction of oxygen (CEO_2); b) noradrenaline at a dose of 0.5 mg to 5 mg/h was effective and safe and might be considered the drug of choice; c) dopamine was not as effective at a high dose of 10 to 42.5 µg/kg/min; d) methoxamine given as a bolus was an effective way to control sudden decreases in MAP. It made the patients more responsive to dopamine. No important undesirable reactions occurred during the study.

Keywords: Cerebral perfusion pressure; head injured; vasopressors.

Introduction

Cerebral ischemia due to low cerebral perfusion pressure (CPP) is one of the most important secondary events affecting outcome following severe head injury [9,18]. In this setting, increasing CPP can help to avoid diffuse and regional ischemia.

The optimal value of CPP following head injury, has not been established by prospective randomized controlled clinical trials (Class 1 data). Until new evidence becomes available, it is recommended to mantain CPP above 70 mm Hg [10,13] or even higher (20,21), with an intracranial pressure (ICP) under 20–25 mm Hg.

One of the ways to increase CPP is by raising mean arterial pressure (MAP) and in order to attain this, it is standard practice to use adrenergic vasopressor drugs. Nodradrenaline and dopamine administered by infusion – two adrenergic cathecolamine drugs- are by far the most used vasopressors [4,15]. On the other hand, methoxamine – an adrenergic non cathecolamine alfa 1 agonist drug – commonly used in bolus, has not been studied in this setting, and could be an interesting option.

The aim of this work was to investigate the difference in effectiveness of these three drugs, their side effects and the possible repercussion of their use on ICP.

Materials and Methods

Our study focused on 16 patients, 15 males and 1 female, ranging in age from 23 to 60 (mean = 38.8 ± 12.9). These patients were admitted to the Intensive Care Unit (ICU) of the University Hospital de Clínicas, Montevideo, Uruguay, over a period of 13 months, from August 1995 to September 1996.

ACT of the head was performed at admission in all cases and for control whenever the clinical condition of the patient demanded. Twelve patients were operated upon for mass lesions, two of them twice. CT findings and clinical characteristics are presented in Table 1. All patients underwent monitoring of intra-arterial blood pressure, intracranial pressure, jugular bulb oxigen saturation (SjO_2) and arterial oxygen saturation (SaO_2). ICP was monitored with a subdural catheter in the 12 surgical cases and with a subdural screw in the 4 non-surgical ones. The sensors were connected directly to external transducers [3]. They were zeroed at the same level of the arterial transducer at the external auditory meatus. The accuracy of the ICP records was assured, applying the Mc Graw methodology for subdural hydraulic measurements [26]. $Sj0_2$ was monitored through a jugular bulb catheter, inserted retrogradely in the jugular vein on the right side [12]. X-ray verification of the correct catheter position was obtained in all patients before sampling jugular blood [2]. Intermittent samples of arterial and jugular bulb oxygen saturation were obtained simultaneously.

Table 1. *Clinical Characteristics of 16 Patients with Severe Head Injury*[a]

Case number	Age (years)/sex	Cause of injury	GCSs	Fixed and dilated pupil(s)	*CT* classification	
					Marshall	Lobato
1	25, M	Motorcycle accident	5	Yes	II	DAI + BC
2	32, F	Gunshot wound	7	No		(SH operated)
3	47, M	Fall	9	No	EML	SH + HS
4	28, M	Assault	6	No	II	UC
5	35, M	Motorcycle accident	9	No	EML[a]	SH + HS + UC
6	26, M	?	3	Yes	EML	SH + SAH
7	43, M	Motor vehicle accident	8	No	II	DAI + UC
8	25, M	Motor vehicle accident	3	No	EML[a]	EH + UC
9	53, M	?	7	No	EML	SH + BC
10	56, M	Motorcycle accident	11	No	EML	SH + BC
11	60, M	Pedestrian	6	No	II	SH + BC
12	25, M	Assault	3	Yes	EML	EHB
13	48, M	Motor vehicle accident	5	No	EML	SH + BC
14	50, M	Motor vehicle accident	8	No	EML	SH + BC
15	47, M	?	8	No	EML	UC
16	23, M	Motorcycle accident	5	Yes	EML	UC + DAI

GCSs Glasgow Coma Scale score on admission; *CT classification* classification based on computerized tomography, according to Marshall H *et al.* [16], and Lobato H *et al.* [15]. *EML* evacuated mass lesion; *EML*[a] evacuated twice; *DAI* diffuse axonal injury; *BC* bilateral contusions; *SH* subdural hematoma; *HS* hemispheric swelling, *UC* unilateral contusion; *SAH* subarachnoid haemorrhage; *EH* extradural hematoma; *EHB* extradural hematoma bilateral.

CPP was calculated according to the formula CPP = Mean Arterial Pressure (MAP) – Mean Intracranial Pressure (MICP). Cerebral Extraction of Oxigen (CEO_2) was calculated according to the formula $CEO_2 = SaO_2 - SjO_2$. The normal range for CEO_2 is 24%–42% [8].

Two patients underwent hemodynamic monitoring with a Swan Ganz catheter (cases 5,11).

After achieving adequate intravascular volume expansion, vasopressors were applied, and the dose was adjusted to raise MAP in order to reach a CPP above 70 mm Hg. Drugs were given in the following hourly sequence: 1) dopamine infusion (dopamine 1); 2) noradrenaline infusion; 3) methoxamine boluses; 4) dopamine infusion post-methoxamine (dopa 2). No direct treatment to lower ICP was attempted and, the ventilatory pattern was not changed during this trial period with vasopressors.

The infusion rate of dopamine and noradrenaline, the number of bolus of methoxamine and their respective dose was recorded every 15 minutes for 45 minutes. Simultaneously, ICP, MAP and CPP were measured or calculated. CEO_2 was obtained at 15 and 45 minutes. The mean values of vasopressors dose, ICP, MAP, CPP and CEO_2 were analyzed (Table 2), and the result was compared by one-way analysis of variance (ANOVA). The Newmans Keuls method was used to identify significant differences among the different groups of "means".

In order to continue the statistical analysis, the whole group was divided into two: 1) group A, 7 patients, measured from basal conditions. In this group, basal values of ICP, MAP, CPP and $CE0_2$ were compared with the mean values obtained with each vasopressor; 2) group B, 7 patients as well. They were so ill that they were already receiving dopamine before enrolling into this protocol. In this group, it was considered unethical to withdraw the vasopressors. The values obtained with dopamine in this group were considered as baseline values and consequently compared with those obtained under the other 3 situations. Two remaining cases (patients 13, 16) were not statistically analyzed because they were already under nodradrenaline on admission to the ICU. Kruskal-Wallis test for the two groups was applied to them for comparisons.

The level of statistical significance was established at 0.05.

Results

An ANOVA test for comparing mean of ICP, MAP, CPP and CEO_2 of the entire group of patients in the five respective situations (basal, dopamine 1, noradrenaline, methoxamine and dopamine 2 post methoxamine) showed significant differences among means of MAP and means of CPP ($p = 0.008$). For means of ICP and CEO_2 no significant differences were detected ($p = 0.8$ and 0.6 respectively) (see Table 3).

The Neuman-Keuls test detected significant differences ($p = 0.05$) between two clusters: mean CPP with methoxamine and dopamine 2 (post methoxamine) on one side and mean CPP basal, with dopamine 1 and with noradrenaline, on the other.

According to the Kruskal Wallis test in the group A there was a significant increase of MAP and CPP with noradrenaline, methoxamine and dopamine 2 (post methoxamine) (Fig. 1) while in the group B a significant increase in MAP and CPP was noted with noradrenaline and dopamine 2 (post methoxamine) (Fig. 2).

As side effects: dopamine clearly induced or facilitated polyuria in cases 2, 9 and 10. Noradrenaline did not show undesirable effects. Its hypertensive response was mild in four (cases 1, 4, 7, 11). Methoxamine showed transitory bradycardia in

Table 2. *Basal Data, Vasopressor Dose, ICP, CPP and CEO_2 of 16 Severe Head Injured Patients*

Case	Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
B	ICP	16	16	8	21			22			14				27		
	CPP	64	64	60	60			65			68				64		
	CEO2	36	21	57	25.5			25			13.5				23		
D1	dose1	11.5	10	10	10	36	20	10	42.5	15	10	24	37		10	12	
	ICP	13.6	17	9	14	19	16.5	24	20	26	10.5	21	37.5		20	243	
	CPP	83	57.5	91.5	81	71	44.5	66.5	69	59	59.5	62	43		66.5	73	
	CEO2	29.5	18	35	19	19	26	26		20.5	24.5	28.5	27.5		25	28.5	
N	dose2	0.6	0.5	1	0.5	0.5	1.6	0.5	2.0	1.5	0.5	0.9	2.5	0.5	0.5	0.5	5
	ICP	15	18	11	17	21	20.5	23	23.5	12.5	13.5	20	32	61.5	21.5	24.5	14
	CPP	78	63	97	80.5	81.5	81	65.5	117	79.5	69	63	53.5	43.5	85	85.5	76
	CEO2	34	24	34	19	14	18.5	25		27	25.5	36.5	23.5	35.5	27.5	29.5	11.5
Mtx	dose/n	40/2	60/3	60/3	60/3	60/3		60/3	120/3	120/3	60/3		120/3	60/3	20/1	60/3	40/2
	ICP	8.5	18	11.5	11.5	19		22	22.5	12.5	16		26	51	18	32	12
	CPP	106.5	77	99	104	88		73.5	93.5	59.5	71.5		68.5	59	120	98.5	54
	CEO2	38	18	33	22.5	19		23		28	15		30	33.5		27.5	14.4
D2	dose1	11.5	8.3	8	10	34.5		10	42.5		10		37	10		12.4	20
	ICP	8.5	17.5	10.5	15	27.5		23.5	22		18.5		30.5	49.5		33	14
	CPP	130.5	72	69	107	93.5		103.5	78		73.5		69.5	68		95	70.5
	CEO2	28	18	39	19	9		18			15.5		28.5	33.5		27.5	11

B basal data, *D1* dopamine, *N* noradrenaline, *Mtx* methoxamine, *D2* dopamine postmethoxamine, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *CEO_2* cerebral extraction of oxygen, *dose1* µg/kg/min, *dose2* mg/h, *dose/n* total dose of methoxamine / total amount of bolus.

Table 3. *Mean Data of ICP, MAP, CPP and CEO_2 of 16 Head Injured Patients in Basal Condition and after Vasopressor Trial*

	Basal	Dopamine 1	Norad.	Methox.	Dopamine 2	ANOVA p Value
Doses (mean)	–	18.4 µg/kg/min	1.2 mg/h	67 mg	17.8 µg/kg/min	–
Doses (ranks)	–	10.0–42.5	0.5–5.0	20–120	8–42.5	–
ICP (mean)	17.7	19.4	21.8	20.0	22.5	ns
MAP (mean)	81.4	85.7	97.9	103.7	108.4	$p < 0.05$
CPP (mean)	63.6	66.2	76.1	83.7	85.9	$p < 0.05$
CEO2 (mean)	28.7	25.1	25.6	25.1	22.4	ns

ICP intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *CEO_2* cerebral extraction of oxygen, *ns* not significant.

four (cases 1, 3, 9, 14). Two of them required atropina, one was an atrio-ventricular block. In two patients there was a paradoxical hypotensive effect (cases 9 and 16 of group B) after repeated bolus. In other two cases (cases 2 and 15) it clearly caused olyguria.

Discussion

In the management of severe head injury it was determined that it was not only necessary to lower ICP but simultaneously also increase MAP in order to obtain an adequate increase of CPP. The increase in MAP has the theoretical danger of an unwanted increase in ICP due to surpassing of the upper limit of autoregulation or by defective autoregulation. Both mechanisms might induce a "pressure passive" vasodilatation and transcapillary fluid filtration at the defective autoregulation areas [1]. Although probable, this has not been demonstrated in clinical B studies.

The present study, as well as previous ones, [5,6,7,20,22] showed that within certain limits it is safe to increase MAP. In our study, without knowledge of autoregulation stage of the patients, the increase of MAP with adrenergic vasopressors in a significant value of 20–27 mm Hg resulted in a significant increase of CPP of 15–22 mm Hg without changes in ICP, and CEO2 [24].

Rosner [21] has indicated a CPP mean of 113 mm Hg as a turning point. After that, his patients started to increase ICP. In our study, some patients even reached a CPP of 125 mm Hg after a bolus of methoxamine without increasing of the ICP.

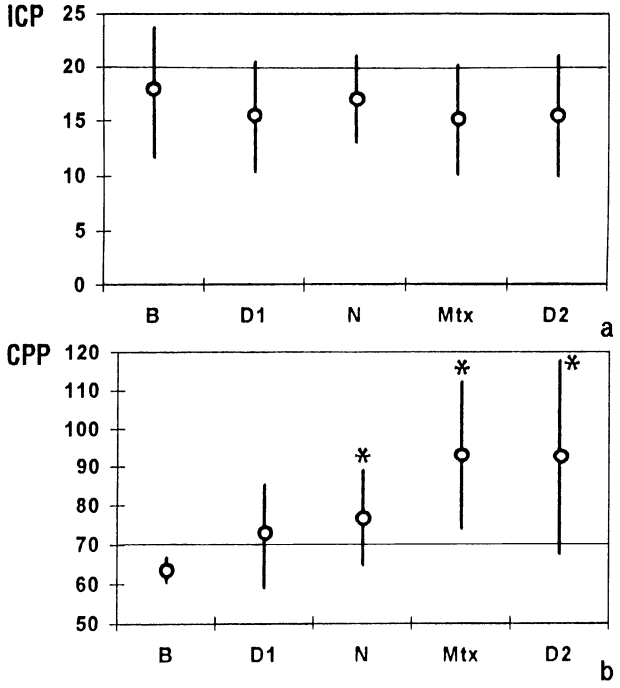

Fig. 1. Patients of Group A (in basal conditions) (a) Response of intracranial pressure after administration of different vasopressors: there were no significant differences. (b) Response of cerebral perfusion pressure after administration of different vasopressors: there were significant differences with noradrenaline, methoxamine and dopamine postmethoxamine. *Significance $p < 0.05$ relative to basal condition. *B* basal, *D1* dopamine initial, *N* noradrenaline, *Mtx* methoxamine, *D2* dopamine postmethoxamine

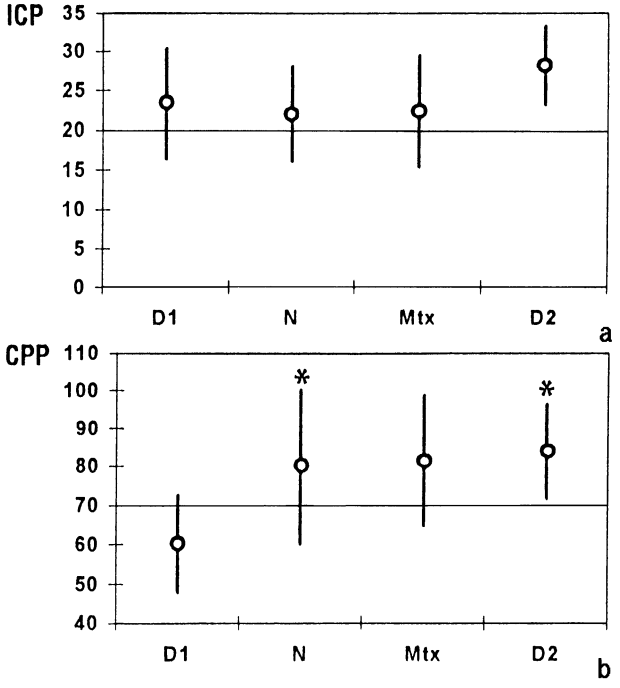

Fig. 2. Patients of group B (after initial treatment with dopamine). (a) Response of intracranial pressure to differents vasopressors: there were no significant differences. (b) Response of cerebral perfusion pressure to differents vasopressors: there were significant differences with noradrenaline and dopamine 2. *Significance $p < 0.05$ relative to dopamine 1. *D1* dopamine initial, *N* noradrenalina, *Mtx* methoxamine, *D2* dopamine postmethoxamine

A better knowledge of this upper limit would allow a higher CPP ceiling and thus act to increase regional cerebral blood flows optimizing the ischemia treatment.

A second point of discussion is to know which of the adrenergic drugs used is the most suitable for CPP optinization.

In the present study, dopamine ($\alpha 1$, $\beta 1$, $\beta 2$, D1 and D2 agonist) was not as effective even at a high dose, perhaps due to its vasodilatatory ($\beta 2$, D1) and polyurique effect (D1, D2), [25] both decreasing its vasopressor power. However, we did not reach megadoses of dopamine (60µg/kg/min) as other authors did. Noradrenaline ($\alpha 1$, $\alpha 2$, $\beta 1$ agonist) at a dose of 0.5 mg–5 mg/h was effective and reliable without untoward effects. It might be considered the drug of choice even though the response was not the expected one in a few cases. Perhaps this was due to a subclinical cardiac insufficiency as a result of potent vasoconstriction increasing afterload.

Methoxamine, a strong $\alpha 1$ agonist [14] has the advantage of a sustained effect even after a single bolus injection that can also be repeated. It is an effective means to control sudden decreases of CPP due to arterial hypotension which is very common during the care of these patients in the ICU. Increasing the velocity of infusion of another vasopressor might not be sufficiently rapid to correct sudden hypotension. However, careful attention should be paid, using this drug because in some cases repeated boluses of methoxamine could generate hypotension probably by an increased afterload and also by adenosine liberation [11]. We did not find a relationship between this paradoxical hypotension and the presence of bradycardia.

An interesting effect of methoxamine seen in the present study was an improvement of the perfomance of dopamine (dopamine 2 post methoxamine), perhaps through a counter effect on the vasodilatation and polyuria induced by it. Dopamine in turn improves the cardiac perfomance under methoxamine. Recently, noradrenaline bolus has been studied as well in human beings (1–4µg/kg) [23]. However, its short action and the cumbersome preparation of "microbolus" makes it unsuitable.

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Correspondence: Alberto Biestro, M.D., Avda. Halia 3190/803, CP 11.600, Montevideo, Uruguay.

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Effects on Intracranial Pressure of Fentanyl in Severe Head Injured Patients

M. de Nadal[1], **A. Ausina**[1], **J. Sahuquillo**[2], **S. Pedraza**[3], **A. Garnacho**[4], and **V. A. Gancedo**[1]

Departments of [1] Anesthesiology, [2] Neurosurgery, [3] Neuroradiology, and [4] Neurotraumathology Intensive Care Unit, Vall d'Hebron University Hospitals, Barcelona, Spain

Summary

Despite opioids are routinely used for analgesia in head injured patients, the effects of such drugs on ICP and cerebral hemodynamics remain controversial. Cerebrovascular autoregulation (CAR) could be an important factor in the ICP increases reported after opiod administration. In order to describe the effects on intracranial pressure of fentanyl and correlated such efects with autoregulation status, we studied 30 consecutive severe head injury patients who received fentanyl (2μg/kg) intravenously over one minute. Prior to study, CAR was assessed. Monitoring included MAP, HR, SaO_2, $ETCO_2$, SjO_2 and ICP. Changes in cerebral blood flow (CBF) were estimated from relative changes in $AVDO_2$. Patients mean GCS was 5.7 ± 1.7 (mean ± STD) and mean ICP on admission was 23.8 ± 16.3 mmHg. Fentanyl caused significant increases in ICP and decreases in MAP and CPP, but CBF remained unchanged when estimated by $AVDO_2$. In patients with preserved CAR (34.5%), opiod-induced ICP increase was greater (but not statistically significant) than in those with impaired CAR (65.5%). We conclude than fentanyl moderately increased ICP and decreased MAP and CPP. Our data suggests that in patients with preserved CAR, potent opioids could cause greater increases of ICP, probably due to activation of the vasodilatadory cascade.

Keywords: CBF; fentanyl; head injury; opoids.

Introduction

Synthetic opioids are routinely used for analgesia in severe head-injured patients as part of the management of increased intracranial pressure (ICP). However, the cerebrovascular effects of opioids remain controversial. Studies in laboratory animals and humans have shown increases, decreases or no change in cerebral blood flow (CBF) and/or ICP after opioid administration. Most of these studies found a concomitant decrease in mean arterial pressure (MABP) and recently, it has been suggested that systemic hypotension could in fact be responsible for the increases in ICP observed after the administration of potent opioids such as fentanyl or sufentanil [2,11]. In patients with low intracranial compliance and intact autoregulation, reduced MABP would be expected to result in vasodilation, increased blood volume and thus increased ICP. Cerebrovascular autoregulation (CAR), which is impaired in at least 50% of severe head injured patients [5,7], could be an important factor in the ICP increases reported after opioid administration. In order to investigate the role of CAR in opioid-induced cerebral hemodynamic changes, we studied the effect of fentanyl upon ICP and CBF in patients with severe head injury and high ICP in whom the status of autoregulatory mechanisms were previously assessed.

Materials and Methods

After institutional approval, 30 consecutively admitted patients with severe head injury (post-resuscitation Glasgow coma scale score ≤8) and a diffuse brain lesion were included in this study.

All patients underwent monitoring of blood pressure and central venous pressure. Heart rate was measured from a standard ECG lead and mean arterial blood pressure (MABP) was calculated. Arterial oxygen saturation (SaO_2) from a pulse oxymeter and end-tidal CO_2 ($ETCO_2$) by capnography were continuosly monitored. A frontal intraparenchymatous Camino transducer (Camino Laboratories, San Diego, CA) was used to monitor ICP. Continuous jugular venous oxygen saturation (SjO_2) monitoring was regularly performed. From these variables, cerebral perfussion pressure (CPP) and cerebral arteriojugular venous oxygen content difference ($AVDO_2$) were calculated for estimation of CBF. All $AVDO_2$ values were corrected for changes in pCO_2. The methodology used to test both autoregulation and CO_2 reactivity has been previously described [7].

Patients received fentanyl (2μg/kg) intravenously over one minute. Prior to infusion, MABP, HR, ICP, CVP, T, $EtCO_2$, SaO_2 and SjO_2 were recorded and CPP calculated. At time 0 (T_0), the study drug was infused, and all the above measurements were

repeated at T_2, T_5, T_{10}, T_{15}, T_{20}, T_{25}, T_{30}, T_{40}, T_{50} and T_{60}. Arterial and jugular blood samples were collected at T_0, T_5, and T_{60} for $AVDO_2$ measurements.

The mean values obtained for each of the measured and calculated variable were analyzed within groups by repeated-measures ANOVA. Differences between groups were tested by two way ANOVA. For all analysis, statistical significance was inferred when $p < 0.05$.

Results

Mean age of our group (23 male/7 female) was 30.2 ± 13.2 (mean ± STD), GCS was of 5.7 ± 1.7 and mean ICP on admission was of 23.8 ± 16.3. Hemodynamic instability forced the exclusion of one patient during the first day of study. Of the 29 left, 19 (65.5%) showed impaired/abolished autoregulation and 10 (34.5%) had preserved autoregulation. Cerebrovascular response to CO_2 was preserved in all cases ($CO_2R > 1\%$). Blood gases, pH, temperature and CVP were unchanged by opioid administration.

Fentanyl induced significant decreases in MABP (of 4.5 ± 0.1 mmHg) and increases in ICP (of 2.8 ± 1.1 mmHg) at 2 and 5 minutes postadministration of the drug (Fig. 1). While ICP returned to baseline levels after 30 minutes, MABP was persistently lower than preinfusion values at 1 hour. The fall in MABP and the increase of ICP resulted in a transient but important fall in CPP (of 5.3 ± 1.1 mmHg). A small decrease of $AVDO_2$ (from 1.55 ± 0.5 to 1.44 ± 0.6 μmol/ml) was observed at 5 minutes (Fig. 1) but this decrease was not statistically significant. Estimated CBF increased by 14% at 5 minutes after administration, returning at 1 hour to baseline levels. When patients were classified in function of their autoregulation status (Fig. 2), no significant changes in ICP were found between groups after fentanyl administration, although patients with preserved CAR seemed to experience a major rise in ICP in comparison with the group with impaired/abolished CAR (4.8 vs 2.3 mmHg).

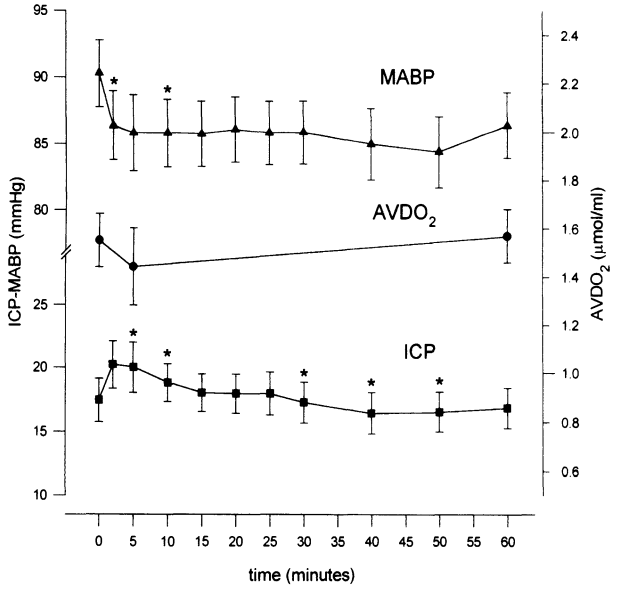

Fig. 1. Fentanyl-induced changes in ICP, MAPB and $AVDO_2$. MABP at 5 and 10 minutes was significantly lower than baseline value, while ICP was significantly higher at 5, 10, 30, 40, and 50 minutes ($p < 0.05$). The decrease in $AVDO_2$ did not reach statistical significance. Results are presented as mean ± SEM

Discussion

Several studies in humans [1,3,8,10] have reported increases in ICP or CBF after the administration of synthetic opioids such as fentanyl, sufentanil and alfentanil. By contrast, Werner [11] observed no change in ICP in patients with mantained MABP but a significant increase in patients with decreased MABP, whereas CBF velocity as an index of flow did not change regardless of changes in MABP. When systemic hypotension was blunted by the administration of phenylephrine, another study [2] found that changes in cerebrospinal fluid pressure were minimized. Both authors concluded that opioid-induced ICP elevations could be related to autoregulatory vasodilation secondary to systemic hypotension rather than increases in CBF.

According to Obrist *et al.* [5], about half the patients with severe head injury have a variable degree

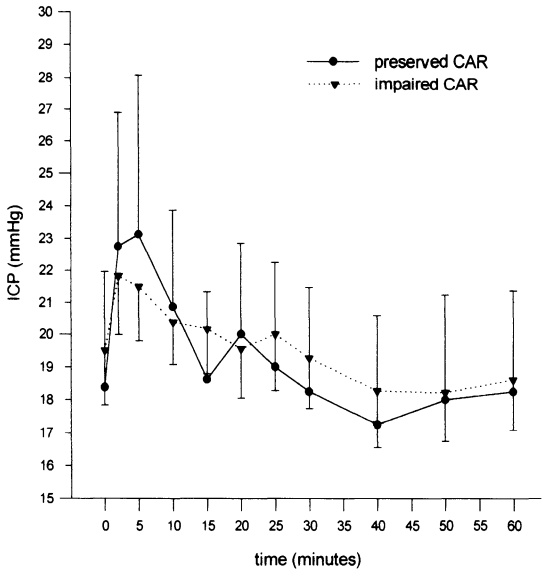

Fig. 2. Autoregulation status and ICP changes after fentanyl. *CAR* cerebral autoregulation. No statistical differences were found between patients with preserved CAR and impaired CAR. Results are presented as mean ± SEM

of autoregulation impairment. A recent study by our group [7] found that 57% of the patients with a diffuse injury had impaired/abolished autoregulation. In the present study, our initial hypothesis was that ICP would only increase in the intact-autoregulation group and would follow MABP or remain unchanged in the impaired-autoregulation group. Although ICP elevation was greater in patients with preserved autoregulation, both groups showed ICP increases after fentanyl administration.

Besides changes in systemic hemodynamic variables, intrinsic properties such as direct cerebrovasodilation or changes in cerebral metabolism could also explain ICP increases after fentanyl administration. Different types of opioid receptor binding have been demonstrated on cerebral microvessels [6], and some endogenous agonists have been proved to cause pial artery dilatation [9]. However, little is known concerning the effects of synthetic opioids on cerebral circulation in the injured human brain. On the other hand, opioids may affect cerebral metabolism ($CMRO_2$) which could indirectly induce cerebral vasodilation or constriction. Conflicting results regarding this point may be due to background anesthetic technique. Moreover, it has been observed that some anesthetic agents can alter the cerebrovascular effects of opioids. Although opioids do not uncouple CBF to $CMRO_2$, Milde [4] found a small decrease in $CMRO_2$ and a 14% increase in CBF after fentanyl administration in dogs which received no other anesthetic drug.

In conclusion, fentanyl moderately increases ICP and decreases MABP and CPP in patients with severe head injury. No differences were found in the ICP response between patients with preserved and impaired autoregulation, suggesting that other mechanisms related to intrinsic properties of opioids may be implicated in the ICP increase observed after the administration of such drugs.

Acknowledgement

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Correspondence: M. de Nadal, M.D., Unidad de Neurotraumatología, Hospital de Traumatología, Hospitals Vall d'Hebron, Paseo Vall d'Hebron 119–129, 08035 Barcelona, Spain.

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The Possible Role of CSF Hydrodynamic Parameters Following in Management of SAH Patients

M. Heinsoo, J. Eelmäe, M. Kuklane, T. Tomberg, A. Tikk, and **T. Asser**

Department of Neurology and Neurosurgery, University of Tartu, Estonia

Summary

It is suggested that reduced intracranial compliance may be present even when measured ICP is normal and may precede clinical deterioration. Our findings reflect a decompensation of hydrodynamic parameters more pronounced 4–7 postictal days, when compliance is reduced not only in patients with poor clinical condition, but also in patients with Hunt-Hess grade I–III. Increased CSF outflow resistance in the first few days is not surprising; it is thought to be due to the blockage of flow of CSF through the basal subarachnoid cisterns and clogging of the arachnoid villi with erythrocytes and fibrin. Enlargement of ventricles seen on CT scan at the same time suggests the development of acute hydrocephalus. During the first days after SAH, our data reflects evidence of ventricular enlargement in patients presenting with both poor and better clinical condition. We conclude that the monitoring of ICP and dynamic measuring of CSF hydrodynamic parameters is important for longer than the generally accepted few days for selected cases after SAH.

Keywords: CSF dynamics; Hydrocephalus; SAH.

Introduction

Increase of ICP plays a determinate role in the development of secondary brain damage following subarachnoid hemorrhage (SAH) and may be caused by hemorrhage itself, edema formation and disturbance of CSF dynamics [1]. ICP response after SAH and following pathophysiological changes probably depends principally on the volume of hemorrhage. A study in 52 patients in acute stage after SAH (monitoring of ICP for a mean of 8 days after ictus) showed that mean intracranial pressure rose as clinical grade worsened [5]. On the other hand, it is known that before ICP rises, there is possibly some compensation of intracranial system dysequilibrium which depends upon the compliance of the intracranial system. Reduced intracranial compliance may be present even when measured ICP is normal [6].

Hydrocephalus and vasospasm are well-recognized sequelae of SAH from ruptured intracranial aneurysms and additionally affect intracranial balance [2].

Following the time course of CSF hydrodynamic parameters in the acute stage of SAH is the aim of this investigation.

Methods

In 32 aneurysmatic SAH patients ICP was monitored through a ventricular catheter using Bell-Howell external transducer. Serial measurements of pressure-volume index (PVI), compliance (C), elastance (E) and resistance to CSF absorption R were performed using repeated bolus-infusion tests.

Clinical features of each case were documented using Hunt and Hess grading scale.

Dynamic CT scanning was performed in the case of negative change in neurological status during postictal period. For estimation of ventricular size dynamics, Evans ratio and bicaudate index were calculated.

Results

In days 1–3 after SAH, mean ICP in patients with Hunt-Hess grade I–III was as low as 4.7 mm Hg compared to 13.9 mm Hg the same time in patients with Hunt-Hess grade IV–V. During the next few days ICP showed a tendency to increase and reached its maximum in both groups by the end of the first week after ictus (Table 1).

C in patients with Hunt-Hess grade IV–V indicated worsening in the intracranial compliance at the end of first week after ictus (Table 1). R reached its

Table 1. *CSF Hydrodynamic Parameters Dynamics after SAH.* Mean values (SD)

Days after SAH	ICP in patients with Hunt-Hess grade I–III	ICP in patients with Hunt-Hess grade IV–V	C in patients with Hunt-Hess grade I–III	C in patients with Hunt-Hess grade IV–V	R in patients with Hunt-Hess grade I–III	R in patiens with Hunt-Hess grade IV–V
2–3	4.7 (3.9)	13.9 (14.3)	0.42 (0.1)	0.65 (0.6)	3.3 (0)	6.3 (7.5)
4–5	12.8 (10.8)	17.1 (4.3)	0.58 (0.4)	0.29 (0.1)	24.7 (36.1)	16.5 (10.9)
6–7	15.5 (10.7)	15.0 (12.8)	0.58 (0.4)	0.21 (0.07)	4.2 (4.0)	21.0 (9.6)
8–9	12.2 (8.7)	4.0 (4.2)	0.95 (0.4)	0.48 (0.2)	6.1 (4.6)	6.6 (7.9)
10–11	9.8 (8.3)	16.2 (5.8)	0.38 (0.19)	1.05 (0)	5.2 (3.9)	8.4 (0)
12–20	12.8 (5.2)	2.1 (1.4)	0.38 (0.19)	1.39 (0.35)	18.4 (19.3)	6.7 (3.6)

ICP N = <15 mm Hg; Compliance (C) N = 0.2–0.6 ml/mm Hg; CSF outflow resistance (R) N = <10 mm Hg/ml/min.

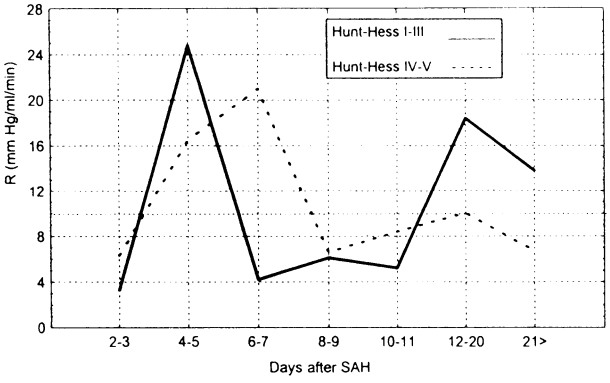

Fig. 1. Dynamics of CSF outflow resistance (R) in Hunt-Hess I–III and IV–V groups

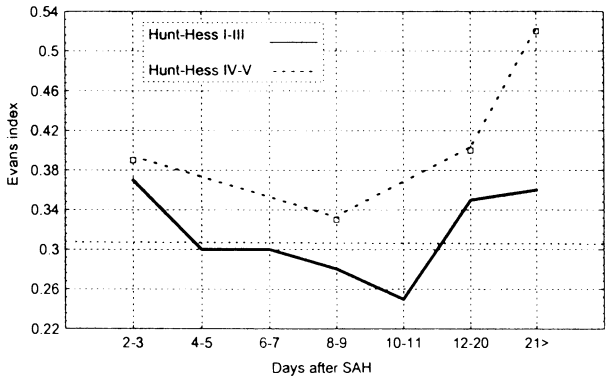

Fig. 2. Dynamics of EVANS ratio in Hunt-Hess I–III and IV–V groups

maximum at 4–7 days after SAH and then showed a tendency to decrease in both patients groups. The second peak of increased CSF outflow resistance appeared in the days 12–20 after SAH (Fig. 1). Calculated Evans ratio indicated ventricular enlargement most evident in days 2–3 and twelve or more days after ictus (Fig. 2).

Discussion

Raised ICP has been found in several studies of patients with ruptured intracranial aneurysm, and it is higher in patients with worse clinical condition. [5]. Also in our study, highest values of ICP were measured in patients with Hunt-Hess grade IV–V, most evident in days 4–7 after ictus. In the same time decreased values of compliance appeared, which indicates brain edema formation. Also vasospasm, which may develop at any time in the acute stage of aneurysmatic SAH has highest incidense in days 5–7 after rupture [8] and may be one cause of CSF hydrodynamic parameters dysequilibrium.

Hydrocephalus may occur during both the early phase (10–30% of patients with SAH) and in 10–15% of patients in the long-term phase after SAH, as demonstrated on a CT or MRI scan [7]. Increased CSF outflow resistance in the first days is not surprising; it is thought to be due to the blockage of flow of CSF through the basal subarachnoid cisterns and clogging of the arachnoid villi with erythrocytes and fibrin [4]. Our data are reflecting, in the first days after SAH, evidence of ventricular enlargement in patients with both, better and poorer clinical condition.

During the long-term phase after SAH, one cause of hydrocephalus is scarring of the arachnoid granules and disturbances in CSF absorption. The treatment for chronic hydrocephalus after SAH is placement of a permanent ventricular shunt [7]. In our study 6.2% of patients required delayed shunting due to clinical deterioration.

Table 2. *Ventricular Size (Evans ratio) Dynamics after SAH.* Mean values (SD)

Days after SAH	Mean Evans ratio (SD) in patients with Hunt-Hess grade I–III	Mean Evans ratio (SD) in patients with Hunt-Hess grade IV–V
2–3	0.37 (0.07)	0.39 (0.03)
8–9	0.28 (0.11)	0.33 (0.08)
12–20	0.35 (0.1)	0.40 (0)

Evans ratio by normal ventricular size = 0.1–0.2; in the case of cerebral edema <=0.1 and hydrocephalus >=0.3.

Monitoring of ICP and CSF hydrodynamic parameters helps the neurointensivist achieve or approach normal ICP, improve intracranial compliance and maintain adequate cerebral perfusion pressures [6]. In long-term phase after SAH, measuring intracranial hydrodynamic parameters may be a helpful tool to decide whether hydrocephalus is caused due to cerebral atrophic processes following ischemic damage or due to disturbed CSF resorption [9,10].

We conclude that monitoring of ICP and dynamic measuring of CSF hydrodynamic parameters is important for longer than the generally accepted few days for selected cases after SAH.

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Correspondence: Jaan Eelmäe, Department of Neurosurgery, University of Tartu, 2L. Puusepp St., EE 2400, Tartu, Estonia.

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Decompressive Craniectomy in Patients with Uncontrollable Intracranial Hypertension

E. Kunze, J. Meixensberger, M. Janka, N. Sörensen, and **K. Roosen**

Department of Neurosurgery, University of Würzburg, Federal Republic of Germany

Summary

There has been controversial discussion about the benefits of decompressive craniectomy in patients with critically raised intracranial pressure (ICP) after severe head injury. The aim of this retrospective study was to analyze the results of secondary decompressive craniectomy in patients with uncontrollable raised ICP after maximum aggressive medical treatment. The data of 28 patients (mean age 22 years, range 8–44 years) with severe head injury and posttraumatic cerebral edema were analyzed retrospectively. Surgery was not indicated in patients with vast primary lesions, hypoxia, ischemic infarction, brainstem injuries and central herniation. The outcome was classified according to the Glascow Outcome Scale (GOS) after one year. The decompressive crainectomy was performed an average of 68 hours after trauma, and ICP (<25 mm Hg) decreased always while cerebral perfusion pressure (CPP > 75 mm Hg) improved as well as cerebral blood flow and microcirculation to normal values. 15 patients (56%) had a good outcome after one year (GOS 4 + 5).

5 patients (18%) were severely disabled, 4 patients (14%) remained in vegetative state and 3 patients (11%) died. Decompressive craniectomy should be kept in mind as the last therapeutic step, especially in young patients with head injury and raised ICP, which is not controllable with conservative methods.

Keywords: Decompressive craniectomy; head injury; uncontrollable raised ICP.

Introduction

Decompressive craniectomy in patients with critically raised intracranial pressure after severe head injury is still a subject of controversial discussion [1–10]. In 1905 Harvey Cushing established the principle of decompressive craniectomy as a treatment for increased ICP [1]. Although first systematic studies of Venes and Cooper in 1975 and 1976 demonstrated good outcome, this fact did not influence further strategy [7]. The aim of this retrospective study was to analyze the results of secondary decompressive craniectomy in patients with uncontrollable raised ICP after maximum conservative treatment.

Material and Methods

The data of 28 patients (mean age 22 years, range 8–44 years) with a severe head injury and posttraumatic cerebral edema were analyzed retrospectively. If the maximal conservative therapy with head elevation (head over body with 30–45°) and midline kept head, moderate hyperventilation, osmodiuretics, barbiturate and THAM, CSF drainage failed to lower ICP, uni- or bilateral decompressive craniectomy from frontal to the temporoparietal region (minimal diameter >8 cm) was performed. The decompressive effect obviously depends on the volume gained by craniectomy [9]. Considering the mechanisms of herniation, decompression should be extended far enough to the bottom of the middle fossa to relieve pressure caused by mediobasal herniation, the parietal extension should reach the midline to avoid compression of the bridging veins. Incision of the dura was performed as large as possible. At the end of the study, duraplasty was performed in nearly every case. When a patient showed a hemispheric edema, a unilateral craniectomy was done; in case of general brain swelling, bilateral decompression was performed.

Surgery was not indicated in patients with vast primary lesions, hypoxia, ischemic infarction, brainstem injuries, central herniation and primary unisocoria.

The outcome was classified according to Glascow Outcome Scale (GOS) one year after trauma. The calottal defect was covered, after clinical recovery, either with the sterilized bone graft or with plastic material for protective and cosmetic reasons.

Results

Thirteen of the 28 patients show an initial GCS from 3–6, 2 patients of these had shock and resuscitation was done to six patients who were classified with GCS from 7 to 8. Three patients had an initial score of 9–12 (1 patient had a shock). Twenty-four of the

28 patients show a severe closed head injury, and 4 patients show a CSF leak.

Twenty-four of the patients had one or more contusions, unilateral or bilateral. Ten of these patients had a small epidural or subdural haematoma without mass effect and no evidence of herniation. Twelve patients showed an initial midline shift. Seventeen of the 28 patients got a unilateral craniectomy, 11 patients were bilaterally decompressed because of generalized brain edema. To estimate the efficiency and the prognosis of these patients, the Glascow Outcome Score after one year was used.

Decompressive craniectomy was performed in the mean time of 68 hours following the trauma. In detail: 3 patients were decompressed in the first 24 hours, 9 patients in the first 48 hours, 8 patients within 3 days and the rest of 8 patients were decompressed up to day 6.

Table 1 compares pre- and postoperative values of ICP and CPP: in terms of ICP, we found preoperative values of 41.7 mm Hg (standard deviation of the mean of 10.1 mm Hg) and postoperative values of 20.6 mm Hg (standard deviation of the mean of 15.3 mm Hg) CPP changed to values of 78.9 (sdm of 7.2 mm Hg) 24 hours after decompression (Fig. 1).

16 patients (57%) had a good outcome after one year (GOS 4,5), 5 patients (18%) were severely disabled (GOS 3), 4 patients (14%) remained in vegetative state while 3 patients (11%) died (Table 1).

The bad outcome of the patients (GOS 1,2) was caused by different factors. One patient with GOS 2 showed postoperatively demarcated brainstem ischemia, another patient developed a MCA-infarct without mass effect, one a global edema and the fourth patient with an GOS 2 after one year showed progredient demarcations of his multiple contusions.

Reasons for death were caused by raised intracranial pressure and consecutive herniation in one patient; two other patients had a cardiac arrest during follow-up period.

Regarding the age in comparison to the GOS, one finds significantly better outcome in younger patients: 80% of the patients under 30 years had a final GOS of 4 or 5, while just 80% of the older patients got 2 or less in the mean (Fig. 2).

Discussion

Decompression of the brain by turning the closed cavity of the skull into an open one is a traditional neurosurgical concept. It has been applied in several conditions of uncontrollable raised ICP. Indications include head injury, cerebellar infarction and massive stroke [1–10]. But there is still a controversial discussion about decompression in trauma surgery, although it has been reported in rather large numbers of patients in the last decades. Still, today, the

Table 1. *Initial Glasgow Coma-Score (GCS) and Postoperative Glasgow Outcome Score (GOS) after One Year*

Primary GCS	n	Shock	Resocitation
3–6	13/28	2	2
7–8	6/28	1	–
9–12	3/28	1	–
13–15	6/28	–	–
GOS	n	%	
4/5	16	57	
3	5	18	
2	4	14	
1	3	11	

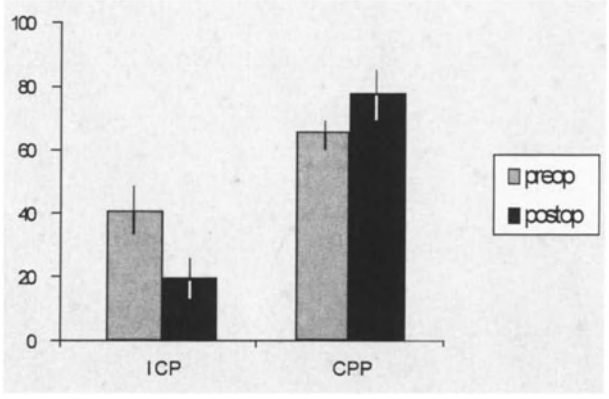

Fig. 1. ICP/CPP pre- and postoperatively

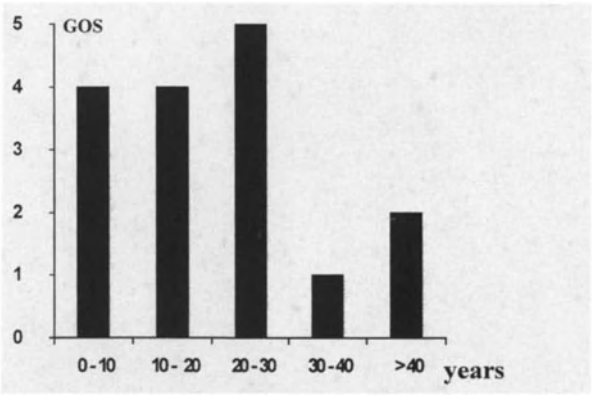

Fig. 2. Outcome depending on patient age

only indication that seems to be widely accepted is cerebella infarction with consecutive deterioration.

However, in our opinion decompressive craniectomy should be taken into consideration in patients with uncontrollable raised ICP to avoid irreversible brain damage after failed conservative treatment.

The benefit of this surgical procedure depends considerably on a careful indication and preferably on young head injured patients.

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Correspondence: Ekkehard Kunze, M.D., Neurochirurgische Klinik und Poliklinik, Universität Würzburg, Josef-Schneider-Straße 11, D-97080 Würzburg, Federal Republic of Germany.

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A Comparison of the Effects of Norepinephrine, Epinephrine, and Dopamine on Cerebral Blood Flow and Oxygen Utilisation

J. A. Myburgh, R. N. Upton, C. Grant, and **A. Martinez**

Department of Anaesthesia and Intensive Care, University of Adelaide, Australia

Summary

The concomitant effects of infusions of catecholamines on cerebral blood flow (CBF), intracranial pressure (ICP), arterio-venous oxygen content difference ($AVDO_2$), and cerebral oxygen utilization (COU) were prospectively studied in an intact cerebral autoregulatory model.

Epinephrine, norepinephrine and dopamine were infused at doses used in clinical practice in awake, chronically catheterized sheep (n = 5). Mean arterial pressure (MAP), CBF and ICP were measured continuously, COU was expressed as $\delta CBF \times AVDO_2$.

All 3 drugs significantly increased MAP in a dose dependent manner. Norepinephrine and epinephrine had no significant effects on ICP, CBF, $AVDO_2$ or COU at infusions of 0–60 μg/min. Infusions of dopamine from 0–60 μg/kg/min resulted in statistically significant increases in ICP (+34.5 ± 3.7 to +97.2 ± 6.8) and CBF (+13.3 ± 3.2 to +52.6 ± 24.3) (% change baseline ± SEM, 95% CI, ANOVA), reduction in $AVDO_2$ (3.54 ± 0.2. to 2.69 ± 0.2 mg%) and a biphasic response in COU. In the intact physiological model, induced hypertension by epinephrine and norepinephrine is not associated with global changes in CBF, ICP or COU which remain constant. At equivalent doses, dopamine causes cerebral hyperaemia, increased ICP and increased global cerebral oxygen utilization.

Keywords: $AVDO_2$; Dopamine; Epinephrine; Norepinephrine; Oxygen utilisation.

Introduction

Augmentation of cerebral perfusion in patients with disturbed autoregulation is now advocated to prevent cerebral hypoperfusion, particularly in traumatic head injury and subarachnoid haemorrhage. This is primarily achieved with fluid based strategies to achieve a euvolaemic state and supplemented with inotropic or vasopressor agents.

The aim of this study was to analyze the concomitant effects of infusions of norepinephrine, epinephrine and dopamine on cerebral blood flow (CBF), intracranial pressure (ICP), difference in arterio-venous oxygen content ($AVDO_2$) and cerebral oxygen utilisation (COU) using infusion rates commonly used in clinical practice.

Ethical approval for this study was obtained from the University of Adelaide Animal Ethics Committee and animals were handled in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Materials and Methods

A two stage preparation was used in 5 adult female merino sheep (approximately 50 kg weight). Under general anaesthesia, the carotid artery and internal jugular vein were exposed. Vascular catheters were then inserted using the Seldinger technique under image intensification into the aortic root, right atrium and superior vena cava for measurement of systemic pressures, blood sampling and administration of drug [3]. A craniotomy was then performed and an ultrasonic Doppler transducer (Tritonics Medical instruments, Iowa) placed on the dorsal sagittal sinus to measure CBF using previously published methods [4]. A blood sampling catheter was placed in the sagittal sinus "downstream" of the probe [1]. An intraparenchymal strain gauge catheter (Codman Microsensor) placed through the same craniotomy to measure ICP. The craniotomy was closed and all intravascular catheters secured and connected to a continuous heparinized flushing system. A period of 7–10 days elapsed between insertion and measurements to allow a fibrous scar to develop around the flowmeter and the sagittal sinus. This ensures minimal movement between the two and a constant angle between the ultrasonic beam and the direction of blood flow. Changes in vessel diameter in response to anticipated changes in perfusion pressure caused by infused pressors or changes in posture are therefore minimized [4].

On day of measurement, the awake animal was placed in a supportive sling. Each animal acted as its own control. In random order, the animal received ramped infusions of the three catecholamines. Epinephrine and norepinephrine were infused at rates at 10, 20, 40, 60 μg/min in 5 minute periods; dopamine at the rates at μg/kg/min. These concentrations were delivered at the

equivalent ml/hr. Changes in CBF and ICP were recorded using a continuous computerised acquisition system sampling at 1 Hz and expressed as relative change in frequency shift from baseline; absolute changes in MAP were recorded in mm Hg also sampling at 1 Hz. Blood samples were taken intermittently in 5 minute intervals from the aortic root and sagittal sinus to measure $AVDO_2$; COU was expressed as $\delta CBF \times AVDO_2$.

Measurements were made continuously for a baseline period of ten minutes, during the ramped infusion and post infusion until parameters returned to baseline values.

On completion of the study, the animal was returned to a holding area with free access to food and water.

Results

As expected, all three drugs produced a significant increase in MAP with prompt return to baseline values on cessation of the infusion. There were variable effects on ICP by the three agents (Fig. 1). Norepinephrine did not increase ICP, while epinephrine produced a modest dose dependent increase in ICP at doses greater 40μg/min. Dopamine produced a significant increase in ICP at doses greater than 20μg/kg/min (+78.6 ± 13.1 to +97.2 ± 6.8% change baseline ± SEM). On cessation of the infusions, ICP returned to baseline values with 5–10 minutes.

The effects of the infusions on CBF and $AVDO_2$ are shown in Fig. 2. No significant change in CBF from baseline occurred with norepinephrine or epinephrine over the range of infusion and into the post infusion period. Dopamine produced a statistically significant rise in CBF when the infusion rate exceeded 40μg/kg/min (+13.3 ± 3.2 to +52.6 ± 24.3% change baseline ± SEM, 95% CI, ANOVA). On cessation of infusion, cerebral blood flow returned to baseline levels within 5–10 minutes.

No significant change in $AVDO_2$ and COU from baseline occurred with norepinephrine or epinephrine over the rang of infusion and into the post infusion period. Dopamine produced a significant reduction in $AVDO_2$ when dose exceeded 20μg/kg/min. At similar doses, global COU had a biphasic response: there was an initial decrease when dose exceeded 20μg/kg/min followed by an increase that approached baseline levels at 60μg/kg/min (Table 1).

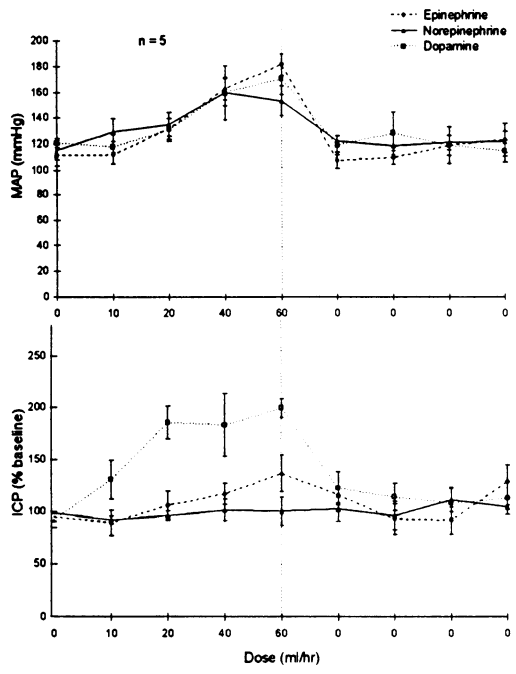

Fig. 1. Effect of catecholamine infusions on MAP (top panel) and ICP (lower panel). All catecholamines produced a dose dependent increase in MAP. Dopamine increased ICP from baseline at dose >20μg/kg/min. Values are displayed and mean ± SEM

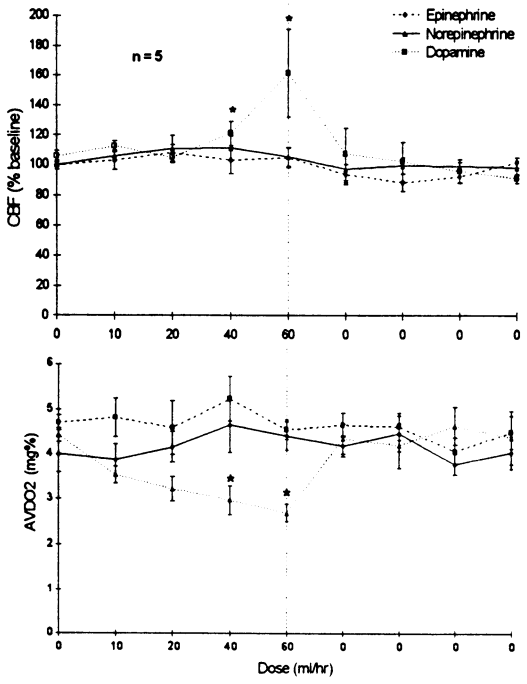

Fig. 2. Effect of catecholamine infusions on CBF (top panel) and $AVDO_2$ (lower panel). Dopamine produced a dose dependent significant increase in CBF (95%CI, ANOVA) which was associated with a reduction in $AVDO_2$. Norepinephrine and epinephrine did not alter CBF or $AVDO_2$

Table 1. *Effect of Dopamine Infusion*

Dopamine (μg/kg/min)	CBF (% change baseline)	$AVDO_2$ (mg%)	COU
10	+13.3 ± 3.2	3.54 ± 0.2	391.8 ± 31.5
20	+6.8 ± 3.4	3.21 ± 0.3	338.5 ± 36.3
40	+21.0 ± 6.7	2.97 ± 0.3	351.1 ± 40.0
60	+52.6 ± 24.3	2.69 ± 0.2	407.4 ± 70.0

On cessation of infusion, $AVDO_2$ and COU returned to baseline levels within 5–10 minutes.

Discussion

There is conflicting opinion both about the drug of choice to achieve a desired cerebral perfusion pressure and the effects that these agents may have on cerebrovascular dynamics in patients with normal or impaired autoregulation. There is a paucity of controlled data both in animal studies and in clinical trials addressing these issues. This is the first controlled animal study analysing the effects of exogenous catecholamine infusions using a continuous measurement of CBF in an intact cerebral autoregulatory model. Norepinephrine, epinephrine and dopamine augmented MAP to an equivalent degree. While the effects of the infusions on ICP was variable, with dopamine producing a significant increase in ICP from baseline, the effects on ICP must be taken in the context of effect on cerebral perfusion pressure (CPP). The absolute changes in ICP were not associated with reductions in CPP in the presence of induced systemic hypertension which is not unexpected in a model with intact cerebral autoregulation.

Dopamine produced a significant increase in CBF which was associated with a reduction in $AVDO_2$ in the presence of compensated cerebral metabolism. In an awake, intact cerebral autoregulatory model, these findings implicate cerebral hyperaemia as the predominant for elevation in ICP and reduced $AVDO_2$. The mechanism whereby dopamine produces a central cerebrovascular effect that is quite distinct from norepinephrine and epinephrine at equivalent doses is unclear. All infusions were associated with equivalent systemic effects across a dose range that stimulates β and α receptor populations [2]. As catecholamines do not cross the intact blood brain barrier, the absence of significant cerebrovascular effects by norepinephrine and epinephrine would suggest that dopamine was acting via a non-adrenergic mechanism or that uptake across the blood barrier was occurring with resultant effects on CBF and oxygen extraction; however, these two postulated mechanisms remain speculative. No reduction in CBF was identified by any of the three catecholamines which would suggest that selective cerebral vasoconstriction at high doses does not occur in the intact brain. In conclusion, in the intact cerebral autoregulatory model, induced hypertension by epinephrine and norepinephrine is not associated with changes in CBF, ICP or COU which remains constant. At equivalent doses, dopamine causes cerebral hyperaemia, increased ICP and increased global cerebral oxygen utilisation.

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Correspondence: John A. Myburgh, MBB Ch, DA(SA), Intensive Care Unit, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000.

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Comparative Effects of Hypothermia, Barbiturate, and Osmotherapy for Cerebral Oxygen Metabolism, Intracranial Pressure, and Cerebral Perfusion Pressure in Patients with Severe Head Injury

I. Nara, T. Shiogai, M. Hara, and **I. Saito**

Department of Neurosurgery, Kyorin University School of Medicine, Tokyo, Japan

Summary

In order to select the optimal neurointensive treatment for patients with severe head injury and intracranial hypertension, the effects of hypothermia (HT), barbiturates (BT), and osmotic agents (OT) on focal and diffuse cerebral oxygen metabolism were evaluated by means of continuous monitoring of bifrontal regional oxygen saturation (rSO_2), jugular bulb oxygen saturation (SjO_2), jugular bulb temperature (Tjb), intracranial pressure (ICP), and cerebral perfusion pressure (CPP).

Patients and Methods: Cerebral oxygen metabolism in SjO_2 and rSO_2, ICP, CPP, and Tjb were continuously monitored in severe head injury patients with Glasgow Coma Scale <8, ages 10–62: 13 with focal and 10 with diffuse injuries. The effects of BT (n = 6), HT (n = 9), and OT (n = 8) on these parameters (ICP/CPP, SjO_2, and rSO_2) were compared. Evaluations were performed in terms of: a) Percentage of abnormal values based on normal control values; ICP < 20 mm Hg, CPP > 60 mm Hg, SjO_2 55–75%, and rSO_2 60–80% were calculated. b) Effects of pentobarbital dose (mg/kg/h) for the parameters compared among <1.0, 1.1–2.0, 2.1–3.0, and >3.1. c) Effects of Tjb (°C) on parameters compared among hyperthermia (>38°C), normothermia (36–37.9°C), mild hypothermia (34–35.9°C) and moderate hypothermia (<33.9°C).

Results: a) Abnormal data differed significantly among the three treatment groups. rSO_2 showing ischemia on the affected side was more marked in BT than in HT or OT. b) ICP decreases and CPP increases correlated significantly with the pentobarbital dose. c) ICP decreases and CPP increases correlated significantly with decreased Tjb.

Conclusion: The therapeutic effects of hypothermia, barbiturates, and osmotherapy on cerebral oxygen metabolism and ICP/CPP are different according to the underlying pathological lesions of patients with severe head injury.

Keywords: Barbiturate; head injury; hypothermia; osmotherapy; oxygen metabolism.

Introduction

Secondary brain damage accompanying increased intracranial pressure (ICP), which includes transtentorial herniation and cerebral ischemia, as well as primary brain damage due to severe head injury, are important factors that greatly influence outcome [2]. Among the neurointensive treatment procedures for increased ICP, the effects of hyperventilation and osmotherapy (OT) using diuretics or hyperosmolar agents have long been known [6,21]. The effects of barbiturate therapy (BT), not only on ICP but also on cerebral blood flow (CBF) and metabolism, have also been assessed experimentally [12,19] and clinically [15,16,19]. The effects of hypothermia (HT), for protecting and resuscitating the brain upon sustaining damage accompanying severe head injury and cerebral ischemia, have been experimentally elucidated in recent years as well [7,18]. HT has been applied clinically to severe head injury patients, and the influence of HT on cerebral oxygen metabolism including the arteriovenous oxygen-content difference ($AVDO_2$) and cerebral metabolic rate of oxygen ($CMRO_2$), as well as ICP, cerebral perfusion pressure (CPP) and CBF are also being assessed [3,20]. Every previous evaluation of cerebral oxygen metabolism, however, is fragmentary, and this parameter has not been evaluated with time in severe head injury patients, whose condition may change abruptly in neurointensive care settings. In contrast to this situation, monitoring of regional oxygen saturation (rSO_2) by near-infrared spectroscopy and jugular bulb venous oxygen saturation (SjO_2) has allowed the continuous evaluation of cerebral oxygen metabolism, and this methodology has been applied to neurointensive treatment [14,17].

The purpose of this study was to determine the effects of various neurointensive treatments, on oxy-

gen metabolism at focal regions in the brain as well as the global brain. In addition, ICP and CPP of severe head injury patients were assessed by continuously monitoring rSO_2 of the frontal lobe on the affected and non-affected sides, SjO_2 and jugular venous blood temperature (Tjb).

Subjects and Methods

The subjects were 23 patients with severe head injuries (13 focal and 10 diffuse injuries), who showed a Glasgow Coma Scale (GCS) of 8 or lower on admission. All patients received hyperventilation and OT by the administration of 10% Glycerol or 20% Mannitol (800 ml/day). HT was carried out in 9, BT in 6, and OT in 8 patients [including 3 patients given hypertonic saline solution therapy]. Table 1 shows background factors of the subjects: age, type of brain injury, GCS on admission, and the outcome 3 months after injury. Regional SO_2 was determined simultaneously in the frontal region on the affected and non-affected sides, which had been evaluated by computed tomography, by means of two devices of INVOS-3100 (Somanetics Inc.), or TOS96 (Tostec Inc.). SjO_2 and Tjb were also measured by a jugular bulb catheter (Opticath, Abott Co.). In addition, ICP and CPP were also monitored in 19 patients. Monitoring data was stored in a computer. The randomized data collected at the same time point every 20–30 minutes were extracted, and analyzed.

The data were evaluated according to the following three items:

a) *Assessment of the effects of various neurointensive treatments procedures.* Twenty data points each were extracted every 10 minutes. According to changes in each parameter, abnormal value was determinated by the following criteria; >20 mm Hg, CPP < 60 mm Hg, SjO_2 < 55% or rSO_2 < 60% as showing ischemic abnormal, and SjO_2 > 75% or rSO_2 > 80% as showing hyperemic abnormal [16,20]. The effects of the treatments were assessed on the basis of the frequency of abnormal values.

b) *Comparison of BT effects according to pentobarbital dose administered.* Data were obtained from each patient every 20–30 minutes, and the effects of BT were classified into 4 groups according to the pentobarbital dose: <1.0 mg/kg/h for the small dose group, 1.1 to 2.0 mg/kg/h and 2/1–3.0 mg/kg/h for the moderate dose groups, and >3.1 mg/kg/h for the large dose group. Changes in each parameter were compared among the 4 groups.

c) *Comparison of HT effects.* HT effects were classified into 4 groups according to Tjb: >38°C for hyperthermia, 36–37.9°C for normothermia, 34–35.9°C or mild hypothermia, and <33.9°C or moderate hypothermia. Changes in each parameter were compared among the 4 groups.

Table 1. *Background Factors of the Three Treatment Groups*

Groups	BT	HT	OT	p value
n	6	9	8	
Age	27 ± 15	49 ± 14	42 ± 14	ns[a]
(range)	(10–54)	(25–62)	(17–59)	
Type of injury				ns[b]
focal	4	4	5	
diffuse	2	5	3	
GCS	4 ± 2	4 ± 2	6 ± 2	ns[a]
GOS				$p < 0.005$[b]
GR (%)	0 (0)	4 (44)	2 (25)	
MD (%)	2 (33)	4 (44)	1 (12.5)	
SD (%)	1 (17)	0 (0)	1 (12.5)	
VS (%)	1 (17)	0 (0)	2 (25)	
D (%)	2 (33)	1 (11)	2 (25)	

[a] ANOVA, [b] $\chi^{2\text{-test}}$. *BT* barbiturate therapy, *HT* hypothermia, *OT* osmotherapy, *GCS* Glasgow coma scale, *GOS* Glasgow outcome scale, *GR* good recovery, *MD* moderate disability, *SD* severe disability, *VS* vegetative, *D* dead, *ns* not significant.

Results

a) *Frequencies of abnormal values for each parameter during each neurointensive treatment (Table 2).* The frequencies of abnormal ICP values were significantly ($p < 0.0001$) higher in the BT group than in the OT and HT groups. The frequency of an abnormal CPP value was significantly ($p < 0.0001$) lower in the BT and OT groups than in the HT group. With regard to the frequency of abnormal SjO_2 values, ischemic abnormal (SjO_2 < 55%) tended to be low in the OT group while that hyperemic abnormal (SjO_2 > 75%) tended to be low in the BT groups. The frequency of ischemic abnormal rSO_2 (<60%) on the non-affected side was 100% (all treatment groups), and this parameter tended to be high in the BT group. The frequency of ischemic abnormal rSO_2 (<60%) on the affected side was significantly ($p < 0.0001$) elevated in the BT group, while the frequency of hyperemic abnormal rSO_2 (>80%) was low in the BT and OT groups ($p < 0.0001$). There were thus distinct differences among the treatment groups.

b) *Relationship between pentobarbital dose and each parameter (Table 3).* ICP was significantly ($p < 0.05$) decreased and CPP tended to be elevated as the pentobarbital dose increase. No distinct tendency was identified for either SjO_2 or rSO_2.

c) *Relationship between Tjb and each parameter (Table 4).* ICP tended to be decreased, CPP to be elevated, with the decline in Tjb. However, there were no marked differences in SjO_2 or rSO_2 among the groups. $PetCO_2$ tended to decrease at moderate and severe hypothermia.

Discussion

Neurointensive treatments, such as OT, BT and HT, are used in conjunction with surgical treatment in order to prevent secondary brain injuries due to cerebral ischemia and cerebral herniation, which are as-

Table 2. *Frequencies of Abnormal Values for Each Parameter in the Three Neurointensive Treatment Groups*

		Frequency of abnormal value (%)			
		BT (n = 120)	HT (n = 180)	OT (n = 160)	p value[a]
ICP (mm Hg)		83 (69)	66 (36)	24 (30, n = 80)	$p < 0.0001$
CPP (mm Hg)		28 (23)	70 (39)	26 (32, n = 80)	$p < 0.0001$
SjO_2 (%)	<55%	14 (12)	35 (19)	16 (10)	$p < 0.0001$
	>75%	10 (8)	28 (16)	29 (18)	$p < 0.0001$
Affected side rSO_2 (%)	<60%	42 (35)	15 (8)	9 (7)	$p < 0.0001$
	>80%	18 (15)	57 (31)	21 (13)	$p < 0.0001$
Non-affected side rSO_2 (%)	<60%	31 (26)	34 (19)	34 (21)	$p < 0.0001$
	>80%	4 (3)	18 (10)	9 (6)	$p < 0.0001$

[a] $\chi^{2\text{-test}}$. *ICP* intracranial pressure, *CPP* cerebral purfusion pressure, SjO_2 jugular bulb venous oxygen saturation, rSO_2 regional oxygen saturation.

Table 3. *Effects of Pentobarbital Doses on ICP, CPP, SjO_2, rSO_2, and $PetCO_2$*

Pentbarbital (mg/kg/h)	≧3.1 n = 30	2.1–3.0 n = 30	1.1–2.0 n = 50	≦1.0 n = 50	p value (ANOVA)
ICP (mm Hg)	10 ± 7	24 ± 14	33 ± 5	37 ± 8	$p < 0.05$
CPP (mm Hg)	103 ± 15	86 ± 22	82 ± 13	68 ± 12	ns
SjO_2 (%)	67 ± 6	69 ± 8	67 ± 8	62 ± 9	ns
Affected side rSO_2 (%)	64 ± 2	62 ± 8	69 ± 10	69 ± 10	ns
Non-affected side rSO_2 (%)	73 ± 15	73 ± 19	66 ± 18	59 ± 12	ns
$PetCO_2$ (mm Hg)	22 ± 2	23 ± 6	25 ± 5	25 ± 1	ns

Values are expressed as means ± standard deviation, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, SjO_2 jugular bulb venous oxygen saturation, rSO_2 regional oxygen saturation, $PetCO_2$ end-tidal CO_2 partial pressure, *ns* not significant.

Table 4. *Effects of Tjb on ICP, CPP, SjO_2, rSO_2, and $PetCO_2$*

Tjb (°C)	≧38.0 n = 49	37.9–36.0 n = 80	35.9–34.0 n = 90	≦33.9 n = 81	p value (ANOVA)
ICP (mm Hg)	18 ± 5	20 ± 15	15 ± 9	12 ± 8	$p < 0.05$
CPP (mm Hg)	81 ± 19	78 ± 17	88 ± 17	91 ± 18	$p < 0.05$
SjO_2 (%)	67 ± 8	69 ± 7	71 ± 10	68 ± 8	ns
Affected side rSO_2 (%)	73 ± 8	72 ± 8	70 ± 8	70 ± 9	ns
Non-affected side rSO_2 (%)	69 ± 2	69 ± 3	68 ± 7	67 ± 7	ns
$PetCO_2$ (mm Hg)	31 ± 8	33 ± 7	28 ± 6	25 ± 7	ns

Values are expressed as means ± standard deviation, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, SjO_2 jugular bulb venous oxygen saturation, rSO_2 regional oxygen saturation, $PetCO_2$ end-tidal CO_2 partial pressure, *ns* not significant.

sociated with or secondary to increased ICP, systemic hypotension and hypoxia, as well as primary brain injury due to head injury. Not only monitoring of CPP but also monitoring of cerebral oxygen metabolism by determination of SjO_2 and rSO_2 have been applied to such treatments with reference to cerebral ischemia based on ICP regulation [14,17].

In this series, with regard to the frequency of abnormal values obtained during each neurointensive treatment, the frequency of abnormal ICP values was significantly higher in the BT group than in the HT and OT groups. The ICP decrease was, however, dependent on the pentobarbital dose. The frequency of abnormal CPP values was significantly reduced in the BT group, further demonstrating the marked effects of BT. BT is known to induce decreases in cerebral blood flow volume and ICP, which are mediated by the decreased CBF accompanying cardiac

suppression and decreases in venous pressure, blood pressure reflex and sympathetic activity [8]. However BT has also been recognized as being ineffective for increased ICP in some patients with severe head injuries [13].

The effects of HT, in terms of protecting and resuscitating the brain which has sustained damage accompanying severe head injury and cerebral ischemia, have been experimentally clarified in recent years [7,18]. As to the effects of HT in patients with severe head injuries, HT is known to improve CPP as a result of the decrease in ICP [10,20]. In the present series as well, CPP tended to be elevated as Tjb fell, but the frequency of abnormal CPP values was highest in the HT group.

BT has also been investigated experimentally for its effects not only on ICP but also on CBF and metabolism [12,19], as well as in clinical cases receiving neurointensive treatment [15,16,19]. HT effects on cerebral oxygen metabolism involving CBF to ICP/CPP, $AVDO_2$ and $CMRO_2$ are also being investigated [3,20]. It has been experimentally demonstrated, by the determination of $CMRO_2$, that cerebral oxygen consumption decreases as body temperature falls [7]. The decrease in cerebral oxygen consumption is considered to be effective for preventing secondary brain damage, such as cerebral ischemia accompanying decreased CBF after head injury. With regard to frequency of abnormal SjO_2 values, the frequency of $SjO_2 < 55\%$ tended to be higher in the HT group while that of $SjO_2 > 75\%$ tended to be higher in OT than in the other groups. There was thus a difference in the effect of each neurointensive treatment on oxygen metabolism of the global brain.

Concerning the frequency of abnormal rSO_2 on the non-affected side, all treatment groups tended to show rSO_2 lower than 60%. On the affected side, the frequency of $rSO_2 < 60\%$ was high in the BT group, whereas the frequency of $rSO_2 > 80\%$ tended to be high in the HT group. Based on the changes in rSO_2, the presence of abnormalities in regional cerebral oxygen metabolism, particularly on the affected side, were estimated. There was thus a difference in the regional cerebral oxygen metabolism response among the treatment groups. A certain investigator was apprehensive as to the reliability of rSO_2 values determined in severe head injury patients [20], but rSO_2 reportedly does not change even under hypothermic anesthesia [1]. The changes in pentobarbital dose and Tjb showed no marked differences in terms of cerebral oxygen metabolism among the groups. However, the influence of $PetCO_2$ can not be neglected that $PetCO_2$ was decreased as Tjb fell in the HT group.

In any event, selection of individual or combined use of neurointensive treatment procedures on the basis of monitoring not only ICP/CPP but also CBF and cerebral oxygen metabolism is considered to be important.

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Correspondence: Issei Nara, M.D., Department of Neurosurgery, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181, Japan.

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Incidence of Intracranial Hypertension after Severe Head Injury: A Prospective Study Using the Traumatic Coma Data Bank Classification

M. A. Poca[1], **J. Sahuquillo**[1], **M. Báguena**[2], **S. Pedraza**[3], **R. M. Gracia**[2], and **E. Rubio**[1]

Departments of Neurosurgery[1], Neurotraumatology Intensive Care Unit[2], and Neuroradiology[3], Vall d'Hebron University Hospitals, Barcelona, Spain

Summary

Intracranial hypertension (ICH) is a frequent finding in patients with a severe head injury. High intracranial pressure (ICP) has been associated with certain computerized tomography (CT) abnormalities. The classification proposed by Marshall *et al.* based on CT scan findings, uses the status of the mesencephalic cisterns, the degree of midline shift, and the presence or absence of focal lesions to categorize the patients into different prognostic groups. Our aim in this study was to analyze the ICP evolution pattern in the different groups of lesions of this classification.

Patients and methods: We present the results of a prospective study in 94 patients with severe head injury, in whom ICP was monitored for at least 6 hours. ICP evolution was classified into three different categories: 1) ICP always < 20 mm Hg, 2) Intracranial hypertension at some time during monitoring, but controlled by medical or surgical treatment, 3) Uncontrollable ICP. The ICP pattern was correlated with the final CT diagnostic category.

Conclusions: 3 patients had a normal CT scan, and none of them presented intracranial hypertension. In diffuse injury type II, the ICP evolution may be quite different. Patients with bilateral brain swelling (Diffuse Injury III) have a high risk of increased ICP (63.2%). Although in our study the frequency of Diffuse Injury IV was low, all patients in this category had a refractory ICP. In the category of evacuated mass lesions, two thirds of the patients presented an intracranial hypertension. In one third, ICP was refractory to treatment. 85% of patients with a non-evacuated mass lesion showed an increased ICP.

Keywords: Computerized tomography; head injury; ICP monitoring; intracranial hypertension.

In patients with severe head injury, the initial CT scan allows us to classify patients into different diagnostic categories. At present, the Traumatic Coma Data Bank classification is the most widely accepted and used. According to the status of the mesencephalic cisterns, degree of midline shift and presence or absence of high or mixed density lesions >25 cc, this classification differentiates between 4 categories of diffuse injury and 2 types of focal injury [6]. Different studies have shown a direct relationship between these categories and outcome [5]. Our aim in this study is to analyze the evolution pattern of intracranial pressure (ICP) in the different groups of this classification.

Patients and Methods

Between January 1993 and December 1995, a prospective study was carried out in 94 patients with severe head injury (post-resuscitation Glasgow coma scale score ≤8). In each patient, the following information was prospectively determined: initial GCS score, pupillary examination, demographic characteristics, mechanism of injury, and preadmission hypoxia or shock. In all cases, we collected information about sequential CT scan findings, ICP evolution and outcome.

Head Injury Classification

In all patients, a CT scan was performed after admission to our center. Patients were included in the different categories proposed by Marshall *et al.* [6]. According to this classification, patients were included into one of the following categories: *Diffuse injury I*: no visible intracranial pathology seen on CT scan; *Diffuse injury II* cisterns are present with midline shift 0–5 mm and/or high or mixed-density lesions ≤25 cc; *Diffuse injury III*: cisterns compressed or absent with midline shift 0–5 mm and/or high or mixed-density lesions ≤25 cc; *Diffuse injury IV*: midline shift >5 mm without high or mixed-density lesion >25 cc; *Evacuated mass lesion*: any lesion surgically evacuated; *Nonevacuated mass lesion*: high or mixed-density lesion >25 cc not surgically evacuated. In each patient at least one control CT scan was performed during the first week after injury. If these control CT scans showed significant changes in the lesions, patients were recategorized accordingly.

Table 1. *Clinical Data*

	Uncomplicated[a] diffuse injury	Complicated[b] diffuse injury	Evacuated mass lesion	Nonevacuated mass lesion
n	37	21	23	13
Age*	26.5 ± 1.4	28.3 ± 8	31.7 ± 1.1	40 ± 21.1
GCS*	5.6 ± 0.2	5 ± 2.1	5.9 ± 0.7	4.8 ± 1.6
Puplis* (ab.)	29.7%	40%	45.5%	23.1%
Hypoxia*	18.9%	25%	4.5%	–
Hypotension*	5.4%	20%	22.7%	7.7%

[a]For statistical analysis, diffuse injuries type I and type II were reclassified under the category "uncomplicated diffuse injury". [b]Diffuse injury type III and type IV were also reclassified under the category "complicated diffuse injury". *P > 0.05.

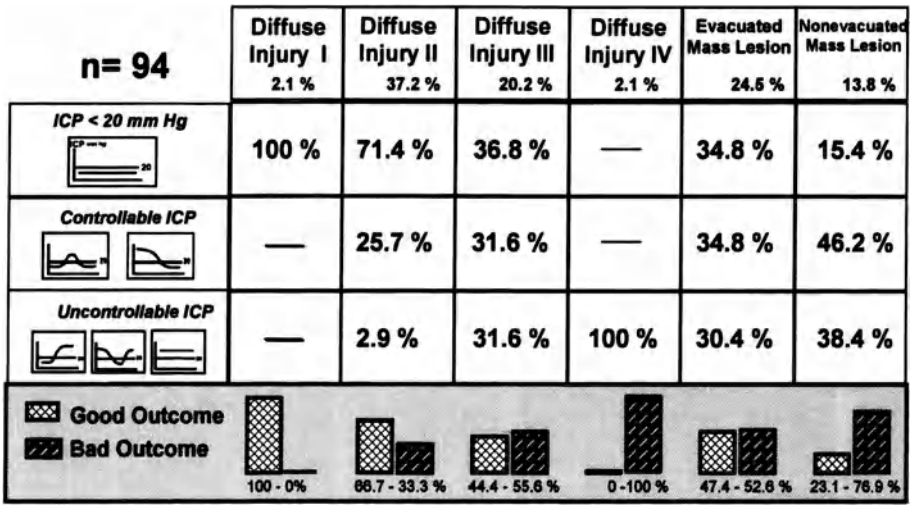

Fig. 1. Incidence of intracranial hypertension, ICP evolution and outcome in each final diagnostic category

ICP Monitoring

In every patient, brain tissue pressure was monitored for at least 6 hours (CAMINO ICP monitor). A modification of Marshall's ICP patterns was used to describe the patient's ICP evolution [4]. ICP evolution was summarized into three categories: 1) ICP always < 20 mm Hg, 2) Intracranial hypertension at some time during monitoring, controllable by medical or surgical treatment, and 3) Uncontrollable ICP. In those patients who developed high ICP, the time when ICP rose was recorded and all possible related factors screened. The ICP pattern was correlated with the initial and final CT diagnostic categories.

Outcome

Outcome was evaluated at six months of injury and assessed using the dichotomized Glasgow Outcome Scale (GOS): *good outcome* (patients with good recovery and moderate disability) and *bad outcome* (patients severely disabled, vegetative or dead).

Results

Figure 1 shows the ICP evolution and outcome for each diagnostic category. Table 1 summarizes the clinical information for the study group. Patients' age, Glasgow score, pupillary response, hypoxia and hypotension recorded on admission were not significantly different for each intracranial diagnostic category.

Discussion

Intracranial hypertension (ICH) is a frequent finding in patients with a severe head injury. In a prospective study Narayan *et al.* reported that the incidence of ICH in patients with an abnormal CT scan was between 53–63% [7]. However, ICH may also be present in patients with a severe head injury and a normal CT as well as in some patients with a moderate or even mild head injury. Different authors have demonstrated the correlation between high ICP and a bad outcome in severe head injured patients. The classification proposed by Marshall *et al.* based on CT scan findings, uses the status of the mesencephalic cisterns, the degree of midline shift, and the presence or absence of focal lesions to categorize the patients

into different prognostic groups. Below, we present and discuss our ICP findings in 94 patients classified according the different groups proposed by Marshall's classification [6].

Diffuse Injury Type I

In our study, the initial CT scan was normal in only three patients. None of these patients presented intracranial hypertension at any time during monitoring. In one of the three cases, the control CT scan showed a new lesion (small cerebral contusion) and the patient was reclassified in the category of diffuse injury type 2. Our findings correspond with those published by Lobato *et al.*, who reported that one in every three severely head injured patients with a normal CT scan at admission presents new lesions in the control CT scans [3]. Although high ICP was not present in our patients, it has been shown that between 10–15% of patients with a severe head injury and a normal initial CT scan will present an intracranial hypertension during their evolution [2,7]. The guidelines to severe head injury management recommend that ICP monitoring is appropriate in this type of patients if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing and systolic blood pressure below 90 mm Hg [1].

Diffuse Injury Type II

Small brain contusions are the most frequent findings in patients with a head injury. In our study, 35 patients showed a diffuse injury type II in the admission CT scan. Three of these patients showed an obliteration of the perimesencephalic cisterns in the control CT scan and were recategorized into diffuse injury type III. One patient presented a new lesion >25 cc, which was not evacuated (final diagnostic category: nonevacuated mass lesion). Four additional patients, initially in other diagnostic categories, were included in the diffuse injury type II group. Thus, the analysis of the ICP evolution in this diagnostic category has been carried out in 35 patients. In diffuse injury type II, a variety of pathological processes may be present: patients with only a small lesion, patients with multiple lesions and cases with or without midline shift (≤5 mm). Given this context, the ICP evolution may be quite different. Ten of the 35 patients (28.6%) presented intracranial hypertension. In nine of theses cases, the ICP was normal at the beginning, exceeded 20 mm Hg during the patients' evolution and was finally controlled by medical treatment. All these 9 patients presented a moderate intracranial hypertension (mean ICP between 20 and 30 mm Hg). Intracranial hypertension was uncontrollable in only one patient in this diagnostic category. We did not find any significant differences between patients with normal ICP and patients with intracranial hypertension, although 5 of the 10 patients with high ICP presented a midline shift in the CT scan. 26% of the patients with a diffuse injury type II showed a bad outcome.

Diffuse Injury Type III

Patients with brain swelling presented high ICP in 63.2% of cases. In one third of all the patients in this category, ICP was uncontrollable from the initial reading and all these patients died. 58% of the patients with brain swelling presented a bad outcome. These findings suggest a very strong relationship between the appearance of perimesencephalic cisterns in the CT scan, frequency of intracranial hypertension and bad outcome. In this group of patients, hyperemia may be the main cause of high ICP. In these patients, we need to incorporate multimodality monitoring and use very aggressive treatment to improve their outcome.

Diffuse Injury Type IV

Only 6 patients showed a midline shift above 5 mm without focal lesions >25 cc. These patients presented high ICP from the first hours of monitoring. Four patients, showed an improvement in the midline shift in serial CT scans and were reclassified. The 2 remaining patients with midline shift >5 mm presented an uncontrollable ICP. Four of the 6 patients in this diagnostic category presented a bad outcome. All these 4 patients presented abnormal motor response and abnormal pupillary findings at admission and in all cases the unilateral brain swelling was accompanied by a small subdural hematoma. However, the remaining 2 patients with a diffuse injury type IV presented a good recovery. These 2 patients had normal motor response and normal pupils at admission and the serial CT scans showed a correction in the midline shift. These last 2 patients who were reclassified into diffuse injury type II, presented a moderate intracranial hypertension (mean ICP between 20 and 40 mm Hg) and ICP was finally controlled by medical

treatment. Our findings coincide with those of Marshall *et al.* According to these authors' results, although the frequency of diffuse head injury with midline shift is relatively low, its high mortality rate suggests that these patients may represent a target group for testing innovative therapies [6].

Evacuated Mass Lesion

This diagnostic category includes a heterogeneous group of patients. The biggest problem related to this category, is that the patients' prognosis may vary, according to the nature of the evacuated mass lesion (epidural, subdural or intracerebral hematomas or brain contusion). 65.2% of patients in this diagnostic category presented intracranial hypertension. Mean ICP differed greatly between patients. In 30.4% of cases, intracranial hypertension was uncontrollable and all these patients had a bad outcome. The high incidence of intracranial hypertension after surgery suggests that ICP monitoring may also be necessary in some patients with moderate or mild head injury who need surgical treatment.

Nonevacuated Mass Lesion

Thirteen patients presented at admission or in control CT scans an acute subdural hematoma or several brain contusions >25cc which were not evacuated. Surgical treatment was not carried out due to the patients' clinical condition or the location and multiplicity of the lesions. In 11 of these patients, high ICP values were recorded in the first hours after sensor implantation. In 5 of these 11 cases, intracranial hypertension could not to be controlled. Only 2 patients presented ICP values below 20mmHg during the total recording time. The ICP evolution in this category confirms that the presence of lesions with a volume above 25cc are strongly predictive of intracranial hypertension. In this context, high ICP may be difficult to control without surgical treatment.

Acknowledgments

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Correspondence: M. A. Poca, M.D., Angels 12, 3-2, 08001 Barcelona, Spain.

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Treatment of Elevated Intracranial Pressure by Infusions of 10% Saline in Severely Head Injured Patients

C. Schatzmann, H. E. Heissler, K. König, P. Klinge-Xhemajli, E. Rickels, M. Mühling, M. Börschel, and **M. Samii**

Neurochirurgische Klinik, Medizinische Hochschule Hannover, Federal Republic of Germany

Summary

The management of intracranial pressure (ICP) is a factor in outcome of patients with head trauma. However, recent studies have revealed that the current strategies, which have been applied to control ICP for adequate cerebral perfusion, are unsatisfactory. Against this background, the efficacy of short-term infusions of hypertonic saline on ICP was investigated.

In severely head injured (SHI) patients, hypertonic saline (100 ml 10% NaCl) was administered when standard agents (mannitol, sorbitol, THAM) failed in reducing ICP. To evaluate the pressure reduction after saline infusions the resulting ICP relaxations were analysed statistically in respect to the parameters amplitude, duration and dynamic behaviour of the ICP responses.

In 42 randomized relaxations, the relative ICP decrease was 43% [28%–58%] (median [interquartile range]). The corresponding pressure drop was 18 mm Hg [15–27 mm Hg]. Relaxations lasted for 93 min [64–126 min] and a relative ICP minimum was reached 26 min [12–33 min] after infusion. In the individual cases the temporal course of the parameters amplitude and decline interval depict a tendency toward lower and higher values, respectively, under conditions of a generally increasing ICP.

As expected, the infusion of hypertonic saline reduces ICP in patients suffering from SHI. The pressure drop, duration and dynamic behaviour are suspected to depend both on the pressure level to reduce and concomitant medications.

Keywords: Elevated intracranial pressure; head injured patients; hypertonic saline.

Introduction

For the effective treatment of elevated intracranial pressure (ICP) criteria represent a challenge despite numerous strategies to this day. Use of hypertonic agents is a basic element of this therapy. Administration of hypertonic solutions which have mainly found use in emergency medicine for small-volume-resuscitation has seen more frequent use [5]. From animal experiments first, results about the effects of hypertonic saline on intracranial pressure were available [1,2,4,7,8]; however, clinical use has hardly been documented [3,6,9]. In the present study the efficacy of infusions of hypertonic saline in severly head injured patients was assessed.

Patients and Methods

Six patients (4 male, 2 female) were treated in the order of their appearance in the intensive care unit. With the exception of one patient (SAH, Hunt-Hess 5) all patients suffered from trauma and severe head injury. The mean age of patients was 40 years (range 16–73 years) and the median score of Glasgow Coma Scale was 6 (range 3–7) at the time of admission. All patients were subjected to a standardized treatment protocol for raised ICP, i.e. therapy was initiated when either the ICP exceeds 25 mm Hg or cerebral perfusion pressure (CPP) drops below 70 mm Hg. If the efficacy of standard intracranial pressure relaxing agents (mannitol, THAM, sorbitol) was exhausted, 100 ml of hypertonic saline (10%) was administered intravenously over 5 minutes. Infusions were omitted when renal failure was known or plasma sodium and plasma osmolality were higher than 150 mmol/l and 325 mOsmol/l, respectively.

The traces of 42 relaxations were observed and recorded in the context of the multisensory monitoring. The vital parameters such as mean arterial pressure (MAP), intracranial pressure (ICP), jugular oxymetry ($SvjO_2$), and brain tissue oxygenation (tpO_2) were monitored for at least 60 minutes after saline administration with a sample rate of 15 seconds. Perfusion pressure was calculated as the difference of MAP and ICP. Unless otherwise noted the data is given as means ± the standard deviation.

Results

The initial ICP was 52 ± 16 mm Hg and the saline-induced minimum ICP was 30 ± 14 mm Hg. The resulting pressure decrease was −22 ± 13 mm Hg, i.e. −43 ± 17% from baseline values. This was reached after 24 ± 15 minutes. The ICP-lowering lasted 101 ± 59 (n = 27) minutes. In 74% (n = 31) of relaxations

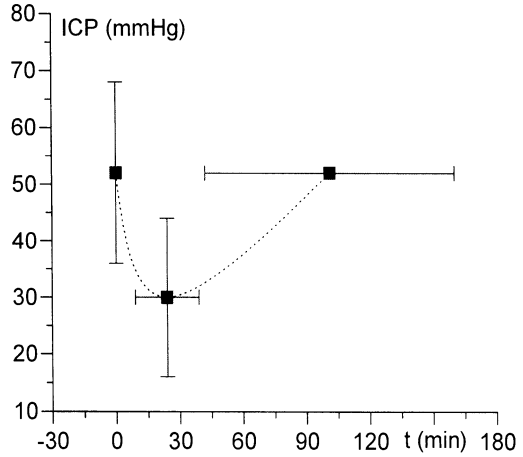

Fig. 1. Efficacy of 10% NaCl administration. Intracranial pressure (52 ± 16 mm Hg) baseline values at t = 0, maximum ICP decrease (30 ± 14 mm Hg) at 24 ± 15 minutes and recovery of ICP to baseline at 101 ± 59 minutes. Splines approximates the basic bahaviour of transient ICP relaxation due to hypertonic saline infusions

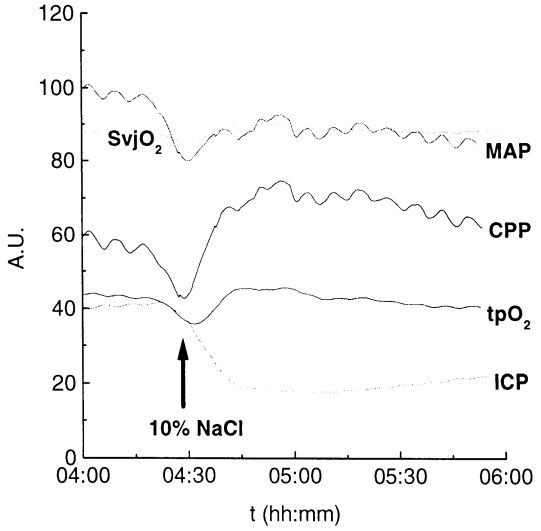

Fig. 2. Sample intracranial pressure relaxation epoch. Time series of mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), jugular bulb oxygenation ($SvjO_2$), and brain tissue oxygen pressure (tpO_2) before, during and after administration of 10% saline (arrow) in a severely head injured patient. All pressure have unit mm Hg; $SvjO_2$ is given in percent

ICP remained under the baseline values for 1 hour at least. The efficacy of saline infusions was observed to fade by the frequency of administration in the individual case.

Discussion

As expected, infusions of hypertonic saline decreases intracranial pressure sufficiently, and with its well-known stabilizing influence on circulation [1], a beneficial effect on cerebral perfusion could be expected. However, one patient who is not included in the data presented did not respond to hypertonic saline infusion. The pharmacodynamics on intracranial pressure varied markedly, i.e. after an initial decrease, the intracranial pressure remained stable at a low level or was restored within an hour to baseline pressure. In some case an overshoot could be observed which is likely due to a progressively increasing ICP through-out the patient's course.

Fisher *et al.* [3] described the use of 3% saline in 18 children. The responses at 30 and 120 minutes after administration led to an increase in CPP of 10 and 3 mm Hg, respectively. Furthermore, six of 18 patients did not respond to saline infusions. Horn *et al.* [6] observed 23 relaxations in 8 patients treated with 7.5% saline that showed maximum ICP decrease of 19 ± 7 mm Hg at 95 ± 54 minutes post administration. Pressure relaxations lasted for 162 ± 45 minutes. In 2 patients and two administration of 28.5% saline Worthley *et al.* [9] lowered intracranial pressure by 40 and 50 mm Hg for 24 and 12 hours, respectively. Obviously a clear coherence exists between pressure relaxation, and duration of ICP lowering with concentration. Time to maximum ICP decrease appears reciprocal to concentration.

In our patients, no adverse side effects have been observed by the administration of hypertonic saline and we therefore consider 10% saline infusions a reasonable completion in treatment protocol for raised ICP.

Acknowledgement

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Correspondence: Christiane Schatzmann, M.D., Neurochirurgische Klinik, Medizinische Hochschule Hannover, D-30623 Hannover, Federal Republic of Germany.

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Pharmacokinetics of Serum Glycerol and Changes of ICP: Comparison of Gastric and Duodenal Administration

H. Takagi, H. Tsuyusaki, M. Endo, and **T. Kitahara**

Department of Neurosurgery, Yamato City Hospital, and Department of Pharmacy and Critical Care Medicine, Kitasato University School of Medicine, Japan

Summary

To investigate the more effective route of oral administration of glycerol to decrease the raised ICP, two different routes were employed in the clinical practice. The one was through a Naso-Gastric tube, and the other was through an Entero-Duodenal tube. Pharmacokinetics of glycerol in relation to the decrease of ICP, and the changes of other parameters which could influence the serum osmotic pressure were sequentially monitored for initial 30 minutes.

In the group of Entero-Duodenal route, the time to reach to the maximum glycerol concentration (Tmax) was faster, the maximum concentration of glycerol (Cmas) was higher, and ICP reduction rate was greater than these in the group of Naso-Gastric route.

Other parameters (Na, K, BUN and Glucose) showed no significant difference between the two routes.

It can be concluded that the Entero-Duodenal administration of glycerol is the more effective route to decrease the raised ICP, when it is administered orally.

Keywords: Changes of ICP; duodenal administration; serum glycerol.

Introduction

Glycerol is one of the hypertonic agents which has been used to decrease the raised ICP. One of the benefits of glycerol is that it can be administered venously or orally [1,3].

The potential to decrease the ICP is reported that both routes of administration have almost the same effect to decrease the raised ICP [1]. In our institute, oral administration of glycerol has been employed either through a Naso-Gastric tube or an Entero-Duodenal tube.

To investigate which route of glycerol administration is more effective to control the raised ICP, pharmacokinetics of glycerol in relation to the decrease of ICP and other parameters which influence the serum osmotic pressure were sequentially monitored and the changes of these parameters were compared between the two different routes.

Materials and Methods

Nine severe head injured patients with increased ICP (29.6 mm Hg), which was continuously monitored by subdural balloon method were subjected for this study. 50% of glycerol (0.5 g/Kg) was administered in one minute through a Naso-Gastric tube in 4 patient and through an Entero-Duodenal tube in 5 patients. Serum glycerol concentration was sequentially measured (1, 3, 5, 10, 15, 30 minutes) by the enzymatic method using Glycerol-Lypid Test (Berlinger-Manheim) [2] and at the same time intervals, serum osmotic pressure, Na, K, Cl, Cr, BUN and Glucose were measured. The pharmacokinetics of glycerol were calculated and analyzed by compartment method assisted by MULTI computer program.

Results

In all nine cases, after glycerol administration, the time course of serum glycerol concentration showed a rapid elevation and reached to a maximum concentration of serum glycerol within 10 minutes accompanied by the rapid elevation of serum osmotic pressure.

The time course of ICP showed an immediate response to decrease and reached to a maximum reduction within 30 minutes (Fig. 1).

If we made a grouping of nine cases according the different route of glycerol administration, the time course of serum glycerol concentration, serum osmotic pressure and ICP took different time courses between Naso-Gastric and Entero-Duodenal glycerol administration (Fig. 2a–c).

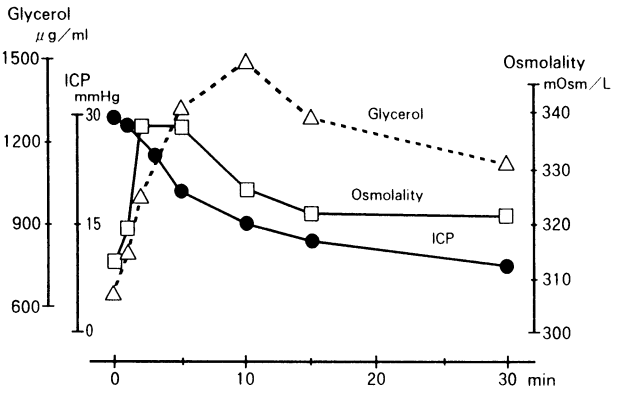

Fig. 1. Time course of serum glycerol concentration, serum osmotic pressure and ICP in all nine cases after glycerol administration

The pharmacokinetic parameters of serum glycerol and the changes of ICP showed that, through an Entero-Duodenal route, the time to reach to the maximum concentration of glycerol was faster (Tmax _6.8), the maximum glycerol concentration was higher (Cmax _1529), and the reduction rate of ICP was greater than these parameters through a Naso-Gastric route. Although, statistical analysis of these data showed that the maximum reduction of ICP for 30 minutes was significant, however Tmax and Cmax were not significant between the two different glycerol administration routes (Table 1).

Time course of other parameters such as Na, K, Cl, Cr, BUN and Glucose showed no significant changes between the two different glycerol administration routes.

Discussion

Glycerol is a water soluble, tri-alcochol chemical, hypertonic agent, rapidly absorbed from gastrointestinal tract, elevates serum osmotic pressure resulting to decrease the raised ICP [1]. The driving force to decrease the ICP seemed to be created within a few minutes after the administration of glycerol to the gastrointestinal tract [1,3].

Our results show that if we take the route of Entero-Duodenal glycerol administration, the maximum serum glycerol concentration is reached faster and higher, and also a greater reduction of ICP can be obtained than through a route of Naso-Gastric administration. Although, Tmax and Cmax between the two routes were not statistical significant in spite of the significant ICP reduction within 30 minutes. This may be due to the large distribution of standard

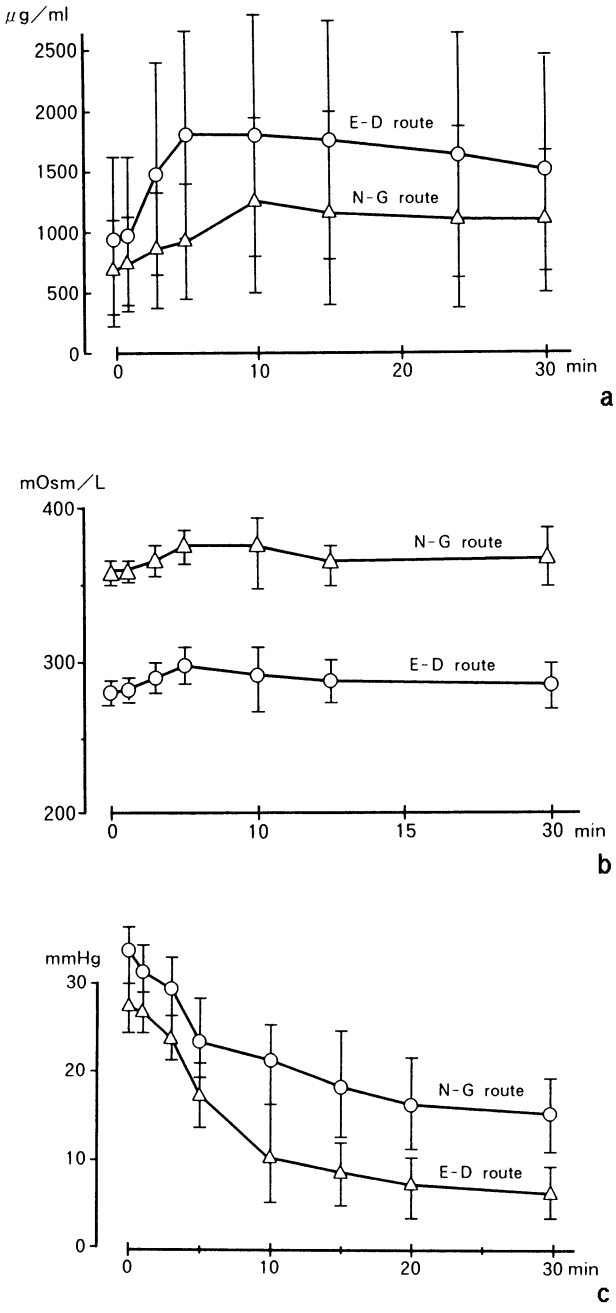

Fig. 2. Time course of serum glycerol concentration (a), serum osmotic pressure (b) and ICP (c) through a Naso-Gastric (N-G) and an Entero-Duodenal (E-D) route

deviation, especially in a group of Naso-Gastric glycerol administration in the clinical practice.

The basic concept of the action to decrease the ICP of hypertonic solution, demonstrated by intravenous administration of mannitol [4], may be applied to the oral glycerol administration as well. The most effective way of administration of hypertonic solution is a bolus administration. However, intravenous bolus administration of glycerol have a possible side effects – volume over load in patients with heart failure and hemolysis that may cause renal failure.

Table 1. *Pharmacokinetic Parameters after Glycerol Administration*

Route of administration	Parameters			Changes of ICP	
	Tmax	Cmax	Ka		
Naso-Gastric (4)	7.6 ± 5.2	1376 ± 897	1.267 ± 0.95	10.7 ± 4.5	*
Entero-Duodenal (5)	6.8 ± 0.7	1529 ± 820	0.608 ± 0.07	17.0 ± 6.2	

Tmax (min): time to reach to the naximum glycerol concentration
Cmax (μg/ml): maximum glycerol concentration
Ka: absorption rate constant
ICP (mm Hg): maximum reduction of ICP for 30 minutes
(mean ± SD, p. = 0.05, * significant)

Fifty percent of oral glycerol contains no Na, 0.5 g/kg is a relatively small amount compared to the 10% intravenous glycerol solution which contains 0.9% Na, 5% fructose, can be administered safely as a bolus through Entero-Duodenal route without disturbing the serum electrolytes balance and clinical condition.

Conclusion

If glycerol is administered orally, a study of pharmacokinetics of serum glycerol combined with sequential changes of other serum parameters to decrease the raised ICP, demonstrated that the Entero-Duodenal administration is a more effective route of glycerol administration. The driving force to decrease the raised ICP was created within a few minutes after the administration of glycerol through this route. Clinical benefits of the oral administration of glycerol were discussed.

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Correspondence: H. Takagi, M.D., Department of Neurosurgery, Yamato City Hospital, Fukaminishi 8-3-6, Yamato City, Kanagawa 241, Japan.

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External Lumbar Drainage in Uncontrollable Intracranial Pressure in Adults with Severe Head Injury: A Report of 7 Cases

R. B. Willemse and **S. M. Egeler-Peerdeman**

Department of Neurosurgery, University Hospital Vrije Universiteit, Amsterdam, The Netherlands

Summary

The retrospective results of external lumbar drainage in 7 adult patients with severe closed head injury and intracranial pressure (ICP) refractory to aggressive management strategies are presented. All patients had Glasgow Coma Scale (GCS) scores of 8 or less within 24 hours after admission and were treated by a staircase protocol including sedation, ventricular drainage, hyperventilation and mannitol. In three cases barbiturate drugs and an artificially induced hypothermia were used. Four patients required surgical evacuation of mass lesions. Three patients made a good functional recovery, 2 were severely disabled and 2 patients died. In none of the patients clinical signs of cerebral herniation occurred. We recommend additional external lumbar drainage in adults with severe head injury unresponsive to agressive ICP control with open basilar cisterns and absent focal mass lesions on computerized-tomography scan before drainage.

Keywords: Adults; head injury; intracranial hypertension; lumbar drain.

Introduction

Patients who sustain severe closed head injury frequently develop increased intracranial pressure (ICP) and, therefore, require ICP monitoring [1,3,10]. In the absence of focal mass lesions, which require prompt surgical evacuation, management strategies are aimed at ICP control in adjunction with control of cerebral perfusion pressure (CPP). High intensity treatment of ICP consists of sedation, paralysis, hyperventilation, ventricular drainage, mannitol and barbiturates in a staircase approach [8]. Some institutions also use artificially induced hypothermia. Raised ICP refractory to high intensity treatment is generally associated with a poor outcome [10,14]. Second-tier therapies such as decompressive craniectomies [5] have been described, and neuroprotective agents acting upon excitatory neurotransmitters are currently under investigation. Recently, however, controlled lumbar drainage has been described as another potentially useful treatment for pediatric patients with severe head injury and raised ICP despite maximum management strategies [2,7]. In this preliminary paper we report our experience with this treatment modality in a small group of seven adult patients with head injury in which agressive ICP and CPP control failed or became ineffective.

Materials and Methods

The patient group consisted of 7 patients, four males and three females, aged 21–35 years (mean 26 years) with severe head injury. All patients had a Glasgow Coma Scale (GCS) score of 8 or less within 24 hours after admission and underwent a ventriculostomy. In the presence of focal mass lesions prompt surgical evacuation was instituted. All patients were treated by sedation, intermittent hyperventilation, ventricular drainage and mannitol to lower ICP and vasopressor agents to maintain adequate CPP. Three patients had an artificially induced moderate hypothermia (down to 32°C) and received a barbiturate coma titrated to burst suppression. Lumbar drainage was only instituted in the absence of focal mass lesions and with discernible basilar cisterns on computerized-tomography (CT) scan. Drainage height was set to 5–15 cm above Monro. The follow-up period was at least 6 months after injury using the Glasgow Coma Outcome (GOS) scale.

Results

On admission 6 of the 7 patients had a GCS score less than 8 and one patient deteriorated to a GCS score of 5 within 24 hours after admission due to an epidural hematoma. Two patients sustained injuries in a traffic accident, five patients fell. Four of the seven

patients showed absent pupillary reactions on admission, but had normal light reactions after treatment. Two patients had diffuse edema and contusions, four patients required surgery for mass lesions and one patient had a small subdural hematoma (<1 cm) which was not evacuated.

Prior to lumbar drainage, all patients had discernible basilar cisterns on the CT-scan and ICPs above 25 mmHg despite aggressive ICP management strategies. Three patients had an artificially induced hypothermia down to 32–33°C and received barbiturate drugs. Two patients developed progressive brain edema in conjunction with sepsis and died. In none of the patients clinical signs of cerebral herniation occurred 24 hours post-drain placement. After six months 3 of the 5 survivors had a good outcome and two patients were severely disabled. Clinical features, cause of injury, GCS and pupillary reactions on admission, CT-findings, surgical interventions, ICP before and after drainage (1, 4 and 12 hours) and Glasgow Outcome Scale (GOS) categories are summarized in Table 1.

Discussion

Raised ICP is a common phenomenon after severe head injury and may indicate brain damage and limitation of cerebral blood flow, producing further brain dysfunction and damage [11]. In the treatment of head injury, agressive monitoring and treatment of elevated ICP clearly improves the patients outcome [10,14]. However, despite maximum management strategies a number of patients develop uncontrolled intracranial hypertension which is associated with a high mortality [3].

In concordance with Baldwin *et al.* [2] lumbar drainage was only instituted in the presence of discernible basilar cisterns. Why some patients with uncontrollable ICP still have discernible basilar cisterns on CT-scan is unclear. The presence of cerebrospinal fluid (CSF) in the basilar cisterns on CT-scan in conjunction with increased ICP might reflect a CSF-circulation disorder. Possibly, in closed head injury, compression of the aquaduct in combination with CSF-formation in the choroid plexus of the fourth ventricle can lead to accumulation of CSF in the spinal and basilar compartments. Especially, if there is an additional absorption disorder due to the presence of blood in the CSF spaces and secondary compression of the superior sagittal sinus in the presence of increased ICP [13]. Consequently, ventricular CSF drainage alone is insufficient to divert all CSF and lower ICP. Lumbar drainage of accumulated CSF in the spinal and basilar compartments could therefore lead to a lowering of ICP.

To date, the use of lumbar drainage in uncontrollable intracranial hypertension has only been described in pediatric head injury [2,7]. Levy *et al.* [7] hypothesized mechanisms comparable to pseudotumor cerebri as an explanation for the effects of lumbar drainage. However, the pathophysiology of diffuse pediatric head injury is still a matter of debate. Bruce *et al.* [4], emphasized the hyperemic nature of this condition, however, more recent reports indicate mechanisms comparable to those in adult head injury [12,15]. Therefore, the management of uncontrolled ICP in adults with closed head injury with lumbar drainage might be as valuable as in pediatric head injury patients.

To our knowledge this is the first report about lumbar drainage in adults with uncontrollable ICP. Five of the seven patients had a lasting decrease in ICP after lumbar drainage and survived. Whether the outcome would be worse if these patients were not treated by lumbar drainage is unclear. However, the presence of increased ICP can induce secondary

Table 1. *Patient Data*

Case No.	Age (yrs)/ sex	Cause of injury	GCS (admission)	Pupillary reaction	Lesion	Surgery	Barbiturates	Drain placed (day)	ICP (pre-/post) (mmHg)	GOS
1	27/M	fall	1-2-1	–/–	contusions	no	no	3	27/9-5-4	severe
2	24/M	fall	3-4-1	+/+	EDH	yes, 3×	no	2	34/21-18-26	good
3	21/F	bike vs. car	4-6-4	+/+	EDH	yes	no	7	32/7-7-13	good
4	26/M	fall	1-3-1	–/–	contusions	no	no	8	43/10-9-23	severe
5	24/F	fall	1-2-1	+/+	SDH	no	yes	1	30/14-11-18	good
6	26/F	ped. vs. car	1-2-1	–/–	SDH	yes	yes	2	25/36-4-15	dead
7	35/M	fall	1-2-1	–/–	SDH/EDH	yes, 2×	yes	3	50/11-21-50	dead

M male; *F* female; *ped.* pedestrian; + reactive; – non-reactive; *EDH* epidural hematoma; *SDH* subdural hematoma.

brain damage, which might have been avoided by lumbar drainage. Two patients died due to progressive brain edema which could not be avoided by barbiturates, hypothermia or lumbar drainage. In none of the patients clinical signs of cerebral herniation occurred within 24 hours post-drain placement.

The possible hazard of lumbar puncture, induction of transtentorial or tonsillar herniation, is not supported by evidence. A large clinical series and review of early reports have indicated that the incidence of cerebral herniation after lumbar CSF drainage in patients with elevated ICP was less than 1.2% [6]. Herniation occurs only in the presence of some degree of obstruction of normal CSF pathways between the cranial and spinal subarachnoid spaces. Therefore, the presence of discernible basilar cisterns is an important factor when considering lumbar drainage in the presence of increased ICP.

Since the introduction of the ventricular catheter to monitor ICP and drainage of CSF, the controversial use of lumbar puncture lost its importance in the management of increased ICP. However the results give the impression that lumbar drainage might be useful in the management of raised ICP and consequently in the reduction of the extent of secondary brain damage in selected patients. Further investigations are justified to elucidate the potential value of this treatment.

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Correspondence: Ronald B. Willemse, M.D., Department of Neurosurgery, University Hospital Vrije Universiteit, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.

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ICP-CBF Trauma Bolt, Laboratory Evaluation

J. Brennan, P. Tompkins, F. A. Stevens, and **L. P. Carter**

Health Sciences Center, The University of Oklahoma, Oklahoma City

Summary

Thermal diffusion flowmetry is a continuous quantitative technique of measuring regional cerebral blood flow utilizing a silastic strip probe placed through a craniotomy or craniectomy in the operating room. A new bolt like application of this technology is now available for commercial use and is especially designed for bedside placement in trauma patients. This new trauma bolt is tested in juvenile pigs who are subjected to episodes of hypercapnea to increase cerebral blood flow, and records significant changes in blood flow. Another feature of the trauma bolt is a second port for the placement of an intracranial pressure (ICP) monitor. Placement of the probe and ICP monitor were easier than with the silastic probe and had relatively little complication.

Keywords: CBF trauma bolt; cerebral blood flow; thermal diffusion.

Introduction

The use of thermal diffusion to determine blood flow in a tissue was first described in 1933. Brawley [2] utilized a Peltier stack with a thermal differential placed upon the cortical surface to determine cerebral blood flow (CBF). This probe has undergone many modifications and currently utilizes a silastic strip with two gold plates to create and measure thermal differentials. The differential is then correlated to a quantitative blood flow using a determined tissue constant for human brain. This probe (Flowtronics, Phoenix, AZ) is commercially available and requires a burrhole created in the operating room for passage of the silastic probe under the skull with a tunneled exit wound under the scalp, for later removal.

In an attempt to create a thermal diffusion flowmetry (TDF) probe that could be placed in the emergency room or intensive care unit a new bolt like probe has been created and is currently available commercially. This bolt utilizes a smaller circular probe on the end of a piston which is passed through a skull secured bolt and can be adjusted for proper placement on the cortical surface. The burr hole required measures 11 cm. in diameter which can be created with a twist drill. An added feature of the trauma bolt probe is the ability to pass an intracranial pressure (ICP) monitor through a separate port.

This new trauma bolt was tested in our laboratory to determine ease of placement and reactivity of the CBF and ICP recordings after a hypercapnic challenge.

Materials and Methods

Juvenile pigs (weighing 5–10 kg) were sedated with Ketamine (10 mg/kg, intramuscular) and then anesthetized with isoflurane (3% in 100% O_2 induction, 0.25–1.0% in 60:40 N_2O:O_2, maintenance). Attention was then turned towards establishing venous and arterial access via the femoral artery and vein. The animal was then turned and placed in a stabilized head holder. A rectal temperature probe was placed and a feedback controlled warming blanket was used to maintain body temperature at 37.5°C. The scalp was divided in an anterior to posterior fashion and dissected laterally exposing the bony skull surface. A Hudson-Brace hand drill was then used to create bilateral burr holes in the parietal regions. The dura mater was then carefully reflected and cauterized in a cruciform fashion to expose the cortical surface. Measurements to determine the skull thickness and depth to the cortical surface were made for proper placement of the probe surface.

The trauma bolt with the piston set flush to the bolt sleeve's cortical surface is then screwed to the appropriate depth so as not to penetrate the cortical tissue. The probe is then attached to the monitor and the specific calibration programmed. The piston is then advanced utilizing the micrometer scale on the side to determine the depth of the probe surface. The CBF recording is monitored during the advancement of the piston and after an adequate CBF measurement is determined the confidence of the contact is determined. This confidence factor is a ratio of the temperature recorded at both gold plates after the heating element is turned off. This also allows determination of the cortical temperature and

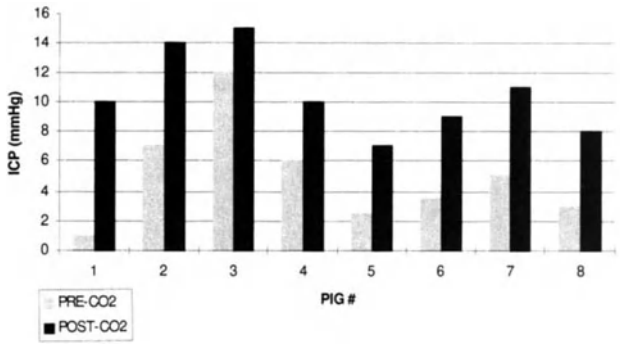

Fig. 1. ICP change pre- and post-CO_2 challenge

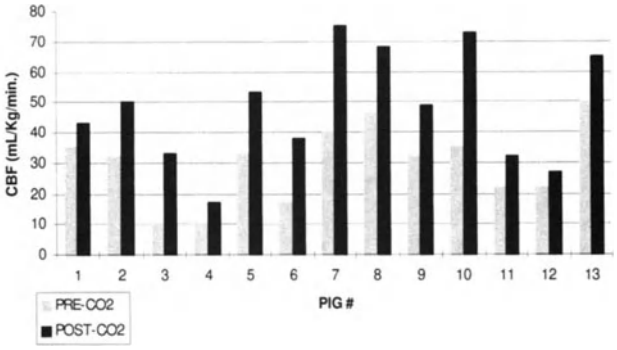

Fig. 2. CBF change pre- and post-CO_2 challenge

assures normothermia. The ICP monitor is then passed to a predetermined length so that no more than one centimeter is exposed past the probe surface.

The animal is allowed to stabilize for 30 minutes while baseline data is collected. The animal is then allowed to become hypercapnic by decreasing the ventilation. Arterial blood gas (ABG) determinations are determined before, during and after the CO_2 challenges to assure adequate increases in pCO_2. The CBF and ICP changes were recorded for 13 and 8 pigs respectively. Following the testing the animals were sacrificed with an intravenous bolus of KCl and dead brain values were recorded. The CBF values were corrected for the dead brain values.

Results

Prior to the development of the trauma bolt a silastic probe was utilized; however, this required an operating room for craniectomy and tunneling of the probe. We found that the bolt probe was easier to place than the silastic probes. Contact with the cortical surface could be assured using the micrometer scale provided on the piston after the appropriate measurements for skull thickness and depth to cortical surface were recorded. Use of the probe in the clinical setting is underway and ease of placement at the bedside should be determined.

As indicated in figures 1 and 2 CBF and ICP both increased significantly in response to CO_2 challenge ($p = 0.003$ for CBF, $p = 0.001$ for ICP). Average CBF measured 29.5 +/– 3.5 pre and 47.9 +/– 5.1 post challenge (ml/100gm/min, AVG +/– SEM, n = 13, corrected for dead brain value). Average ICP measured 5.0 +/– 1.2 pre and 10.5 +/– 1.0 post challenge (mmHg, AVG +/– SEM, n = 8).

Intraparenchymal placement of the ICP probe through the second port did not significantly affect the CBF values unless a major vessel was injured during placement. Of note, the cortical surface vascular anatomy of the pig was much more abundant than that of the human, and clinical use of this probe type should pose less of a difficulty than use in the laboratory setting.

Conclusions

The trauma bolt is easy to place and allows ready access in monitoring both ICP and CBF in the trauma patient. Precise placement of the probe along the cortical surface is easily observed. This bolt is currently available commercially and should improve the ease of continuously monitoring CBF and ICP in the trauma patient. Use of the trauma bolt in other neurosurgical settings such as vascular procedures will require further study.

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Correspondence: James Brennan, M.D., The University of Oklahoma, Health Sciences Center, 711 Stanton L. Young Blvd., Suite 206, Oklahoma City, Oklahoma 73104, U.S.A.

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Bilateral ICP Monitoring: Its Importance in Detecting the Severity of Secondary Insults

I. R. Chambers, P. J. Kane[1], D. F. Signorini[2], A. Jenkins[3], and A. D. Mendelow[3]

Regional Medical Physics Department, Newcastle General Hospital, [1]Department of Neurosurgery, Middlesbrough General Hospital, [2]Department of Clinical Neurosciences, University of Edinburgh, and [3]Department of Surgery (Neurosurgery), University of Newcastle-upon-Tyne, U.K.

Summary

The aim of head injury management is to prevent secondary insults to the damaged brain. Raised intracranial pressure and low cerebral perfusion pressure are two secondary insults which are important determinants of outcome following severe head injury (SHI). Traditionally ICP is measured in the right frontal region in an attempt to minimise the effects and complications of transducer placement. This assumes that the brain acts like a fluid and that ICP is transmitted equally throughout the intracranial space. Experimental studies suggest that this is not the case: expanding mass lesions are associated with the development of ICP gradients. Ten patients with SHI who had an unilateral mass lesion confirmed on CT were studied. All had bilateral placement of intraparenchymal Camino ICP transducers in the frontal regions. Data from both transducers were recorded every two minutes and stored electronically. The volume of the mass lesion was calculated from the CT scan.

Significant and lasting ICP gradients between hemispheres were found in all patients with an acute subdural haematoma (greater than 10 mmHg for longer than 10 minutes). Such differences were not found in patients with intracerebral haematoma or contusions. We would advocate that ICP is recorded IPSILATERAL to the lesion in patients with SHI due to acute subdural haematoma.

Keywords: Bilateral ICP monitoring; secondary insults.

Introduction

It is widely accepted that monitoring intracranial pressure (ICP) and cerebral perfusion pressure (CPP) provides valuable information in the management of patients with severe head injury. They provide information on the status of cerebral haemodynamics and are useful in detecting and hence mitigating secondary insults to the damaged brain. In patients who are being monitored for a non-evacuated mass lesion (intracerebral or subdural) there may be ICP gradients within the brain. Previous studies have produced conflicting evidence as to the magnitude of these gradients. Recent experimental work has shown that expanding masses can produce significant and lasting ICP gradients. If ICP gradients do exist then the traditional placement of the ICP transducers in the right frontal regions (our usual practice) may lead to an underestimate of ICP values when there is a contralateral lesion.

Methods

Ten patients with SHI who had documented unilateral mass lesions were studied. In each patient bilateral frontal intraparenchymal Camino ICP transducers were inserted. ICP and CPP data were recorded continuously every two minutes and stored electronically. Monitoring continued whilst clinically indicated. At the end of the recording period the atmospheric pressure reading of each transducer was recorded to ensure that the readings were not biased by drift. Medical and nursing staff were blinded to the second ICP trace so as not to alter normal practice. In this study a detailed analysis of the first six hours of recording from each patient has been undertaken. The volume on the intracranial mass lesion was quantified from the CT data. The CT images were converted into digital format using a back-lit scanner and these were analysed using a software program written in Delphi. The area of the mass lesion on each contiguous slice was outlined with a polygon. As the CT slices were 1 cm apart, a very good approximation of the volume of the mass lesion can be calculated. The study was approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority and the University of Newcastle upon Tyne. Consent was obtained before entry into the study.

Results

There was a wide range in the ICP levels of the patients which reached a maximum of 84 mmHg in the six hour period. The maximum zero offset

Table 1. *Study Population*

Injury type	Number of cases	Volume range
Contusions	5	12–17 ml
ICH	2	26–29 ml
SDH	3	9–13 ml

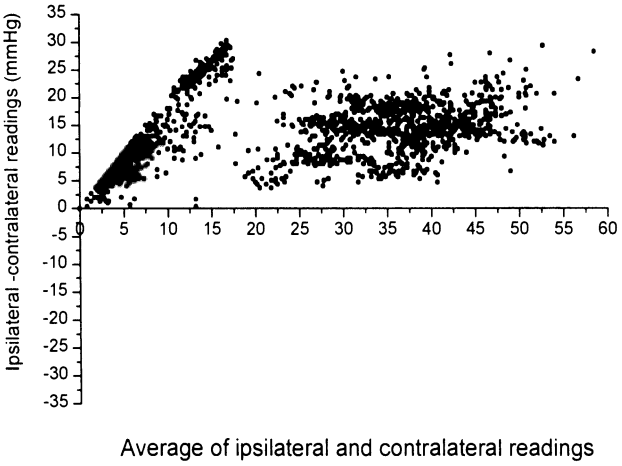

Fig. 1. Recordings from patients with subdural haematoma

measured upon removal of the ICP catheters was 2 mmHg. The recordings could be divided into two groups: those who had sustained differences (>10 minutes) of over 10 mmHg (group 1) and those in which the readings remained within 10 mmHg (group 2). The patients in group one all had a non-evacuated subdural haematoma whilst the patients in group two had contusions [5] or an intracerebral haematoma [2] (Table 1).

The volumes of the abnormalities were similar, yet there was a sustained difference (>1 hr) in the readings between the ipsilateral and contralateral sides when a subdural haematoma was present.

The recordings from those with subdural haematomas showed a positive difference between the ipsilateral and contralateral recordings which ranged up to 30 mmHg (Fig. 1). In contrast, the recordings from patients with intracerebral haematoma or contusions showed a close agreement between the two measurement sites with most of the readings contained in a band with −10 to +10 mmHg (Fig. 2).

Discussion

The data suggests that there may be differences in the levels of ICP which are obtained from each

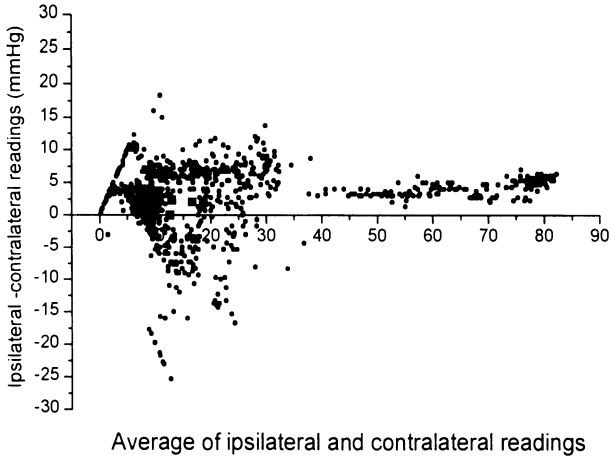

Fig. 2. Recordings from patients with contusions or ICH

hemisphere in patients with an unrelieved subdural haematoma. ICP values were higher ipsilateral to the clot. Similar differences were not found in patients with intracerebral haematomas or cerebral contusion which were of similar size. These observations are the subject of further investigation.

With a greater emphasis on the detection and prevention of secondary insults, it is important to recognize that these differences exist between the hemispheres. There may also be more localized pressure gradients which have yet to be determined. Our data would suggest that in patients with SHI and an acute subdural haematoma that ICP is most accurately measured on the side of the clot.

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Correspondence: I. R. Chambers, Regional Medical Physics Department, Newcastle General Hospital, Newcastle-upon-Tyne, U.K.

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Clinical Evaluation of the Codman Microsensor Intracranial Pressure Monitoring System

H. M. Fernandes[1], **K. Bingham**[2], **I. R. Chambers**[2], and **A. D. Mendelow**

[1] Department of Neurosurgery, University of Newcastle-upon-Tyne and [2] Regional Medical Physics Department, Newcastle General Hospital, U.K.

Summary

Introduction: The use of the Camino fibre-optic subdural device for measuring Intracranial Pressure (ICP) in patients, has been shown to correlate well with recordings from the "gold standard" intraventricular fluid filled catheter [1]. Following this work, its use has become standard in the clinical monitoring of patients. More recently, laboratory studies have demonstrated accuracy, acceptable drift and high fidelity for the new Codman Microsensor ICP Transducer, a miniature strain gauge mounted on a flexible nylon catheter [3]. Its performance in patients, however, has yet to be fully assessed, in comparative studies.

Methods: Eight patients (5 head injured, 3 with an Intracerebral haematoma) had a Codman Microsensor inserted. A Camino Transducer was fitted immediately adjacent to it. A computerised system was used to continuously record both ICP readings.

Results: In total 140,323 recordings were made over a wide range of ICP values. Study periods ranged from 0.5 to 116 hours. In one patient the Codman transducer tracing failed after several days, probably due to fracture of electrical cable close to the interface box. The readings from the two ICP transducers were compared on Time Series, logistic regression and Altman-Bland plots.

Drift of the ICP recorded by the Codman microsensor, was noted in 2 patients, 1 in positive direction (maximum 30 mmHg), 1 negative (max. 20 mmHg). In both cases the Camino ICP recording was relatively stable. In 24% of the recordings the Codman microsensor recorded ICP as 5 or more mm Hg greater than the Camino, this difference was 10 mm Hg or greater in 9% of recordings. Conversely the Camino recording was 5 mm Hg or more, than the Codman, in 5% of all recordings, and 10 mm Hg or more in 3%.

Conclusion: These differences could in the majority of cases (excepting the negative drift) be explained by a constant offset of the Codman transducer, as described previously [6]. Further examination of this device is required.

Keywords: ICP transducer; microsensor; subdural.

Introduction

Continuous Intracranial Pressure (ICP) measurement now forms part of the standard management of many patients with all types of intracranial disease. The most accurate method of measurement, by placement of an intraventricular catheter [5] is now rarely used, not only because of its invasive nature and risk of infection but because of the development of a series of devices that can be used in the intraparenchymally/subdural space and inserted conveniently at the bedside. The use of the Camino fibre-optic device for measuring ICP has been shown to correlate well with recording from this "gold standard" intraventricular fluid filled catheter [1]. Following this work, its use has become standard as the sole ICP device in the clinical monitoring of patients. More recently a further device suitable for use intraparenchymally/ in the subdural space has become available; the Codman MicroSensor ICP Transducer, consisting of a miniature strain gauge mounted on a flexible nylon catheter. Laboratory studies have demonstrated acceptable drift and high fidelity of the microsensor [2,3], but its performance in patients over prolonged periods has yet to be fully assessed. This study was designed to achieve this by comparing *in vivo* recordings from adjacent Codman and Camino devices.

Method

Eight patients were included in the study, in all of whom continuous ICP recording was clinically indicated. Five patients had sustained a head injury and 3 patients had Intracerebral Haematomas (ICH).

Under local anaesthetic, by the bedside, a Camino device was inserted in the normal manner using the OLM screw fixation. Immediately adjacent, through a similar twist drill hole, a Codman

MicroSensor was inserted. This was held in place with a scalp suture. A computerised system was used to record paired readings from the two transducers at 10 second intervals for the duration of ICP monitoring of each patient.

Results

In total 140,323 measurements were obtained with ICP values from 0–80 mm Hg. The recording periods ranged from 3 hours to 5 days (average 2 days). No clinical complications occurred in the insertion of either device and there were no cases of infection.

Two of the transducers failed, one Codman and one Camino. The Codman failed after several days and was thought to be caused by a fracture of the electrical cable at the interface connector. In a different patient the Camino tracing failed after the patient pulled at the fibreoptic cable.

The paired ICP readings from each patient were compared using time series, linear regression and Altman-Bland plots. The analysis has shown that there were large discrepancies between the two pressure readings on a number of occasions.

The recordings from one patient showed a good agreement between the pressure readings from the two devices, with most of the readings differing by less than 2 mm Hg. However, in 4 patients the Codman MicroSensor recorder a positive bias relative to the Camino for the duration of the monitoring. The offset was constant for each patient, but varied from 2 to 8 mm Hg between patients. In another patient the Codman reading appeared fairly stable, whilst the Camino recording drifted in a negative fashion (maximum deviation 15 mm Hg). In the last two other patients the Codman device appeared to drift, one in a positive direction (max. 30 mm Hg see Fig. 1), and the other in a negative direction (max. 15 mm Hg see Fig. 2). In both cases the Camino appeared relatively stable, hence a large discrepancy in the level of ICP measured, for the majority of the duration of recording.

Discussion

Insertion of a ventricular catheter, the most accurate compartment in which to measure ICP, may be difficult because of compression of the lateral ventricular system. It should also be avoided because of the potential risk to the intervening brain parenchyma and the risk of infection. Thus in many neurosurgical units clinical decisions are influenced by the ICP recordings obtained from a single intraparenchymal/sub-dural device. Insertion of these devices is convenient. It can be performed safely by the bedside, under local anaesthetic by junior members of the team. However insertion through a twist drill hole usually employed is "blind" in the sense that one is unsure of the actual position of the tip. Recordings may therefore be from brain parenchyma or from the

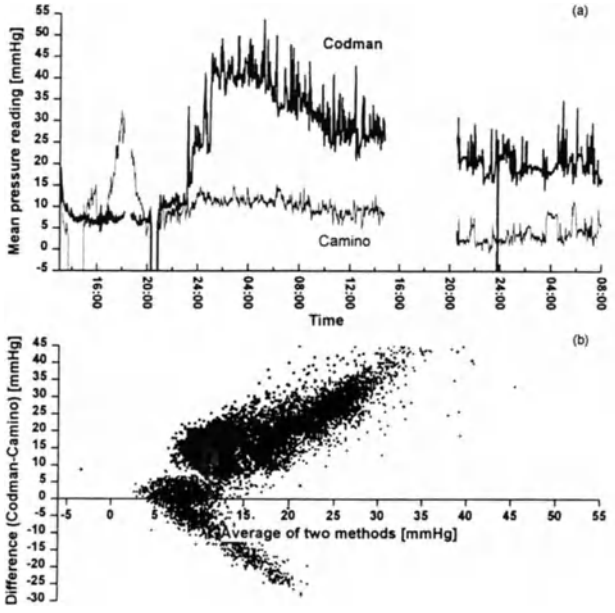

Fig. 1. (a) Time Series and (b) Altman-Bland plot showing positive drift of Codman compared to relatively stable Camino device

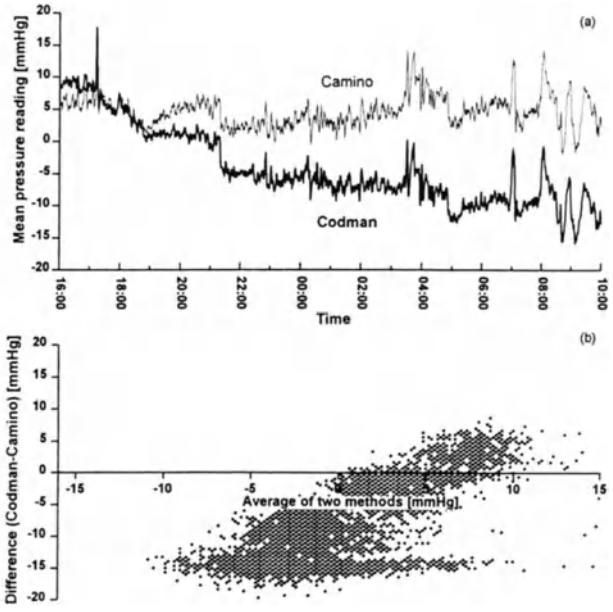

Fig. 2. (a) Time series and (b) Altman-Bland plot showing negative drift of Codman MicroSensor

subdural space, although in clinical practice this is hardly relevant. We felt, therefore, that the direct comparison of the Codman MicroSensor to the Camino, that has been in use in our Unit for many years, would enable us to make an accurate judgment of the reliability and accuracy of the Codman MicroSensor in clinical use. The bolt fixation device of the Codman MicroSensor was avoided because we felt that the diameter of the drill hole (about 6mm) was too large to be safely used by the bedside. The device was thus inserted through a twist drill hole (diameter about 2mm) and sutured to the scalp.

Overall although the two traces tended to show good agreement in terms of the timings of ICP changes, there was often considerable offset between the measurements from the two devices. In 24% of the recordings the Codman Microsensor recorded ICP as 5 or more mmHg greater than the Camino, this difference was 10mmHg or more in 9% of recordings. Conversely the Camino recording was 5mmHg or more, than the Codman, in 5% of all recordings, and 10% or more in 3%. On average, the Codman read higher than the Camino by 6mmHg. However, the continuous monitoring of the two pressures did show that the differences between them may vary with time. This may explain results described previously [6].

The cause of the discrepancies described is unclear. Although the position of the measuring part of the sensors is not precisely known there is a good correlation between measurement of ICP in the subdural space and brain parenchyma [4]. If clinical decisions are made on the basis of absolute ICP values, it appears that the management of these patients may differ when different devices are used to monitor ICP. A further investigation is planned to compare in vivo and in vitro performance of each pair of transducers under test.

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Correspondence: Helen M. Fernandes, M.D., Ward 31, North Wing, Newcastle General Hospital, Westgate Road, Newcastle-upon-Tyne NE4 6BE, U.K.

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Cerebral Monitoring Devices: Analysis of Complications

L. L. Guyot, C. Dowling, F. G. Diaz, and **D. B. Michael**

Departments of Neurological Surgery, Anatomy and Cell Biology, Wayne State University School of Medicine and Detroit Receiving Hospital, Detroit, MI, U.S.A.

Summary

The use of indwelling cerebral monitoring devices (ICMDs) is common in the intensive care of neurosurgical patients. ICMDs are used to measure and treat intracranial pressure (ICP), temperature, blood flow and the microchemical environment. Intracranial hemorrhage (ICH) and infection are risks of ICMD use [4]. This study presents ICMD use at Detroit Receiving Hospital (DRH) from July 1993- March 1997. Analysis of complications associated with ICMD placement will test the hypothesis that complication rate depends upon type of ICMD used. A log of all patients having ICMDs at DRH has been kept since 1993. This log was used to identify complications of ICMD placement. Each case was reviewed and the following data obtained: diagnosis, patient age, initial Glasgow Coma Score, Glasgow Outcome Score, type of ICMD, number of ICMDs per patient, duration of implant and complication. Descriptive and non-parametric statistics were used to compare samples of interest. The following number of ICMDs were placed: 274 ventriculostomies, 229 Camino® intra parenchymal ICP monitors, and 33 other ICMDs. Complications in these 536 cases include 21 infections, 15 ICHs, 1 granuloma and 1 persistent cerebrospinal fluid leak. Complication was analyzed as a function of ICMD type using Chi-Square test for independence. The rate of infection and ICH was significantly higher in the ventriculostomy group ($p = 0.0001$). These results support the hypothesis that complications of ICMD use are due to the type of device implanted. The determinants of ICMD complication is undoubtedly multifactorial. The clinician must consider the complication rate related to a particular ICMD among other factors when choosing to place an ICMD.

Keywords: Complications; infection; Glasgow Coma Score.

Introduction

Indwelling cerebral monitoring devices (ICMD's) in the form of ventricular puncture were first described by Guillaume and Janny in 1951. Their use became routine after Lundberg's publication in 1961 that described their accuracy in reading normal and abnormal intracranial pressure waves [3]. In the 1970's, subarachnoid screws, subdural and epidural monitors were described and commonly used, when appropriate, in the place of ventricular puncture. The use of ICMD's has become commonplace in the intensive care of neurologically injured and at risk patients [5]. ICMDs may be used to monitor and treat elevated intracranial pressure. Other ICMDs monitor cerebral temperature, oxygen concentration, blood flow or the microchemical environment.

Recent studies suggest that management of traumatic brain injury based on cerebral perfusion pressures may be superior to management based on intracranial pressure alone [1]. Aggressive monitoring and management of cerebral perfusion requires continuous monitoring of intracranial pressure. ICMD's have been described as safe [2] and causing rare patient morbidity [3].

It is important for clinicians to realize the relative risks of each type of monitor placed. This study presents ICMD use at Detroit Receiving Hospital (DRH) from July 1993-March 1997. Analysis of complications associated with ICMD placement will test the hypothesis that complication rate depends upon the type of ICMD used.

Materials and Methods

A log of all patients having ICMD's at DRH has been kept since 1993. This log was used to identify complications of ICMD placement. Each case was reviewed and the following data obtained: diagnosis, patient age, initial Glasgow Coma Score (GCS), Glasgow Outcome Score (GOS), type of ICMD, number of ICMD's per patient, duration of implant and complication. The following number of ICMD's were placed: 274 ventriculostomies, 229 Camino® intraparenchymal ICP monitors and 33 other ICMDs. This last category includes combination Camino® bolt-ventriculostomies and a three way Camino® bolt which also includes a Licox tissue oximeter and a Vasomedics laser doppler.

Results

Complications in these 536 cases include 21 infections, 15 intracranial hematomas, 1 granuloma and 1 persistent cerebrospinal leak. Complications in the ventriculostomy group were as follows: 20 infections (7.29%); 9 hematomas (3.28%); and 4 malfunction due to position (1.45%). Total complications for the ventriculostomy group was 12.04%. The complications in the Camino® group consisted of 2 intracranial hematomas (0.87%) and 1 scalp granuloma. There have been no complications associated with other types of ICMDs to date (Fig. 1). Two complications were thought to contribute to patients' deaths, both hematomas in the ventriculostomy group (see Fig. 2). The overall mortality for ICMD in this series is 0.38%.

Complication was analyzed as a function of ICMD type using the Chi-Square test for independence. The total rate of complications ($p = 0.0001$) and infections ($p = 0.008$) were significantly higher in the ventriculostomy group, thus supporting our hypothesis that complication rate depends on the type of ICMD placed. The rate of intracerebral hemorrhage was not significantly different between the ventriculostomy and Camino® group ($p = 0.108$).

Non-parametric statistical analysis was used to examine the data from the ventriculostomy patients with ICMD complications. Mean GCS (9.04), GOS (2.62) and duration (11.93 days) of ICMD were compared by complication using the Mann-Whitney test. Mean GOS (2.62) was significantly associated with complication ($p = 0.018$), while no such association was found between complication and GCS or duration.

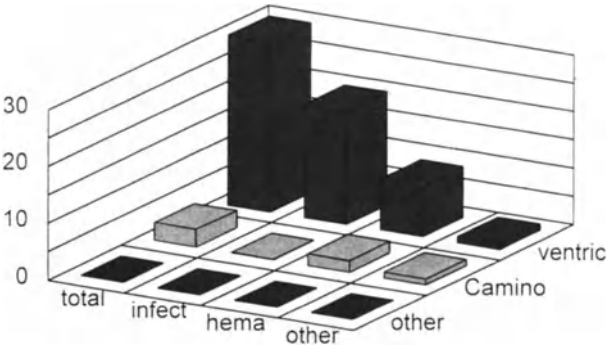

Fig. 1. ICMD complications Total ventric vs Camino $p = 0.0001$; infect ventric vs Camino $p = 0.0008$

Discussion

Our results support the hypothesis that complication rate depends on the type of ICMD placed. Ventriculostomy had a significantly higher number of total complications and infections when compared to the Camino® group. There was no such difference

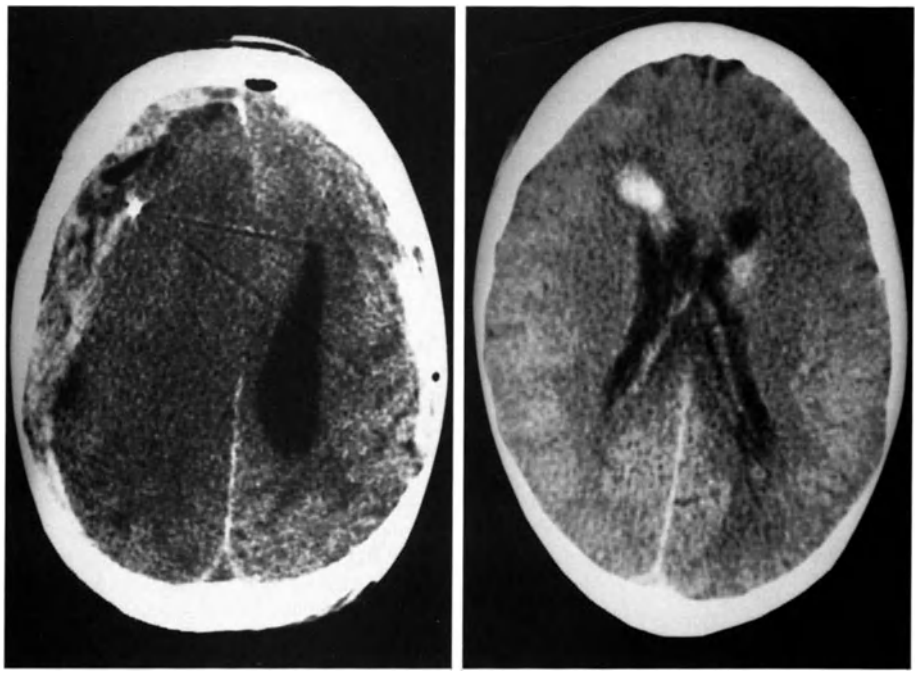

Fig. 2. CT scan images of 2 ventriculostomy patients with intracranial hemorrhage complications

for hemorrhage between the ventriculostomy and Camino® groups. The fact that insertion of both devices requires dural puncture may explain hemorrhage rates which are not significantly different.

The analysis of the ventriculostomy group complications suggests an association between complication and GOS, rather than presenting GCS or duration of implant. It is possible that the complication was one of the factors determining GOS. Further analysis of factors determining complication and outcome would require more data regarding the non complication groups for both ventriculostomy and other ICMDs as a control. Such studies are in progress in our institution.

There is no clear standard of care regarding whether to employ an ICMD or which type of device should be used to manage the head injured patient [1]. When it is possible to place a ventriculostomy in a patient with suspected elevated intracranial pressure (ICP) this is preferred, as the device may be used to measure and treat ICP with ventricular drainage.

The clinician must weigh the risks and the benefits of any ICMD prior to placement. If there are no compelling reasons for ventricular drainage, an ICMD with a lower complication rate should be used (e.g. post craniotomy). This study serves to provide clinicians with information comparing different types of ICMD's and their complications. Further study may ultimately demonstrate the impact of ICMD complication and patient outcome.

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Correspondence: Daniel B. Michael, MD, PhD, Department of Neurological Surgery, 6E UHC, 4201 St. Antoine, Detroit, MI, U.S.A.

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Comparison of Percutaneous Ventriculostomies and Intraparenchymal Monitor: A Retrospective Evaluation of 156 Patients

S. H. Khan, I. U. Kureshi, T. Mulgrew, S. Y. Ho, and **H. C. Onyiuke**

Department of Neurosurgery Head Injury Program, Hartford Hospital, University of Connecticut School of Medicine, Hartford, CT, U.S.A.

Summary

Intraventricular catheters (IVC) and Intraparenchymal fiberoptic catheters (IPC) are the prevalent methods of intracranial pressure (ICP) monitoring. This study assesses the complications caused by either method. Previous studies have shown a higher complication rate with IVC. In 156 consecutive patients, with IVC (n = 104) or IPC (n = 52) insertion, the demographics, Glasgow coma score (GCS), ICP, duration of monitoring, changes in monitoring device, complications and computerized tomography findings, were recorded. The patients were categorized into severe (GCS 3–8), moderate (GCS 9–12) and mild (GCS 13–15) groups. A retrospective, comparative analysis of both techniques was conducted, using Kruskal-Wallis one way analysis of variance with chi square approximation and Mann-Whitney U tests.

The use of IPC at 86.5% predominated in patients with GCS 3–8, while IVC at 81.4% and 92% prevailed in GCS groups 9–12 and 13–15, respectively (p = 0.000). 43.2% IVC were used for 10+ days and 25.9% for 1–3 days, while 80% of IPC were used for less than 6 days (p = 0.000). The complication rate for IVC and IPC was 25% vs 4.4% (p = 0.000). The infection rate was 4.4% and 0.6% (p = 0.1) while, inadvertent removal 4.4% vs 1.2% (p = 0.4), respectively. Malpositions occurred only with IVC (20.1%). All documented complications were without untoward clinical sequelae. We conclude that, IVC remains comparable to IPCs in complications.

Keywords: Complications; percutaneous ICP monitoring; ventriculostomies.

Introduction

ICP monitoring plays an integral part in management of patients with various neurosurgical disorders in a neurosurgical intensive care unit (NICU). The prevalent methods of ICP monitoring and management include, IVC [4,9], which utilizes an external fluid-filled transducer system, and the Camino IPC, consisting of a fiberoptic catheter tipped transducer system [11]. The center where this study was conducted, uses both these methods. Hence, the complications ensuing from either, were compared under uniform circumstances.

Material and Methods

At a level 1 trauma center, of 156 consecutive patients, 104 underwent IVC (Codman & Shurtleff, Inc., Randolph, MA) and 52 IPC (Camino, Neurocare™, Inc., San Diego, CA) insertion. The demographics, GCS, ICP, CT findings, duration of monitoring, any changes in monitoring device and complications were evaluated. The patients were categorized into severe (GCS 3–8), moderate (GCS 9–12) and mild (GCS 13–15) groups, respectively. The cohort was further classified to one of the following five diagnostic groups: Spontaneous Subarachnoid hemorrhage (SAH), closed head injury (CHI), Brain Tumors, Gun shot wounds and miscellaneous (intracerebral hemorrhage, cerebellar hemorrhage, cerebellar infarct, brainstem hemorrhage, granulomatous angitis).

The treatment rendered for raised ICP comprised of the following: sedation, paralytics, hyperventilation, diuretics, cerebrospinal fluid (CSF) drainage and barbiturate coma. The following complications were reviewed: infection, validated by positive catheter tip or CSF culture [10], hemorrhage due to monitor insertion, malposition of monitor, and inadvertent removal. Hemorrhage and malposition were confirmed by CT scans. A retrospective, comparative analysis of the two techniques was conducted, using Kruskal-Wallis one way analysis of variance with chi square approximation and Mann-Whitney U tests.

Results

In the selected cohort, we found the use of IVC and IPC to be 66% and 33%, respectively. Overall, the age ranged from 10–87 years (mean = 49.17 years, median = 50 years). However, there was an age difference noted in the two groups, so that the age means of the IVC and IPC groups were 56.3 and 34.8, respectively (p = 0.000). Amongst the 156 patients,

104 were in GCS 3–8, 27 in 9–12 and 25 in 13–15 (Fig. 1).

The use of IPC at 86.5% predominated in patients with GCS 3–8, while IVC at 81.4% and 92% prevailed in GCS groups 9–12 and 13–15, respectively ($p = 0.000$). Overall, IVC were changed 62 times and IPC 11 times, respectively. Spontaneous subarachnoid hemorrhage (SAH) was the commonest diagnosis in the IVC group (n = 49); whereas closed head injury (n = 46) comprised the majority of IPC ($p = 0.001$). While, 25.9% IVC remained inserted for less than 3 days and 43.2% for more than 10 days, 42.3% of IPC were used for less than 3 days and only 3.8% for more than 10 days. Eighty percent of IPC were used for less than 6 days ($p = 0.000$).

As can be seen from Fig. 2, complications were encountered in 46 cases (29.4%). The IVC group had 25% (n = 39), whereas the remaining 4.4% (n = 7) occurred with IPC ($p = 0.000$). The infection rate was 5.1% (8 cases); 4.4% (n = 7) with IVC and 0.6% (n = 1) in the IPC group ($p = 0.1$), respectively. Coagulase negative staphylococci were the most common etiological organisms encountered (n = 4), followed by S. aureus (n = 2) and 1 case each of Kl. Pneumoniae, Enterobacter aerogenes and Enterobacter cloacae, respectively. In the infected IVC group, a positive blood culture had preceded the CSF infection by 2 days, while a concomitant urine culture was positive in another case. Two types of hemorrhages were found to be associated with catheter insertion i.e., intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH). IVH constituted 0.9% (n = 1) of the IVC group, whereas ICH comprised 1.9% each of the IVH (n = 2) and IPC (n = 1) groups, respectively. There were 21 cases of malpositions, all confined to IVC (20.1%); eight occurred in the third ventricle (7.6%) 4 ended in the thalamus (3.8%), 2 in brainstem (1.9%), while 1 each (0.9%) in the foramen of Munro, suprasellar cistern, internal capsule, midbrain, interpeduncular cistern, frontal lobe and temporal lobe, respectively. The incidence of inadvertent removal was 5.7% (n = 9), which included 4.4% (n = 7) in IVC and 1.2% (n = 2) in the IPC group ($p = 0.4$). Replacement for complication such as mechanical failure or drift was documented in 2.5% cases, of which 0.64% (n = 1) was performed in IVC and 1.9% (n = 3) in IPC.

Discussion

IVC is the accepted "gold standard" for ICP monitoring, with the added advantage of direct control on ICP by CSF drainage, as well as, the ability to administer pharmacological agents via this route. However, they come with an established risk of infection and hemorrhage [9,13], which thus far are complications infrequent with IPCs. Fibroptic IPC have a comparable accuracy and reliability, with a reading difference of 2–4 mm Hg from the IVC [6,12,14]. IVC also need frequent calibration and the requisite fluid-filled column is prone to trapping air bubbles, which in turn may dampen the waveform [2,3]. IPCs are not flawed in this manner, since they comprise of a fiberoptic catheter tip, pressure-sensitive, transducer

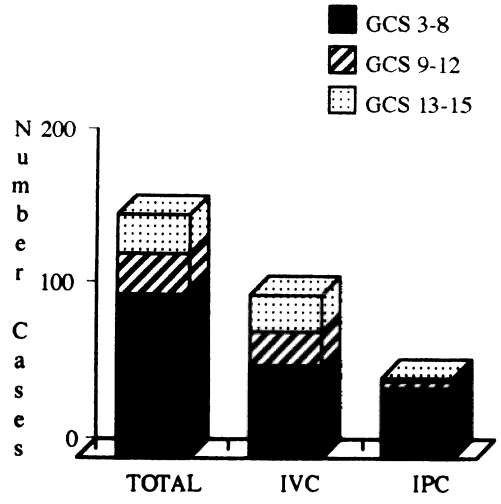

Fig. 1. Distribution of cases into GCS groups at initial presentation. *IVC* intraventricular catheter, *IPC* intraparenchymal catheter, *GCS* Glasgow coma scale

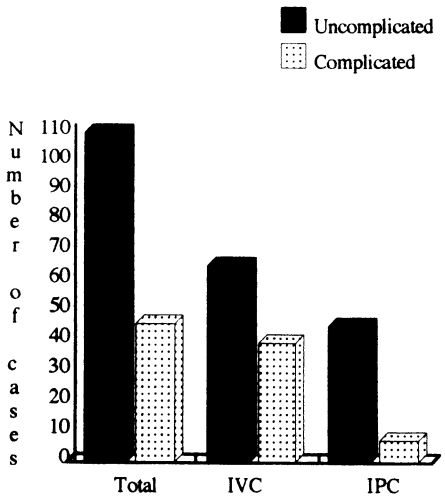

Fig. 2. Comparison of complications between intraventricular and intraparenchymal catheters. *IVC* intraventricular catheter, *IPC* intraparenchymal catheter

which has proven to be consistently reliable. However, IPCs are fragile and the delicate fiberoptic system is more likely to fail, in face of the unavoidable mechanical insults in the ICU setup [15]. This may well account for 1.9% of our IPC vs 0.64% of IVC requiring replacement.

The difference between duration of monitoring in IVC and IPC, arises from the prevalence of a particular diagnostic category in either group. The fact that a majority of IPC are discontinued within a week, points to their role in short term ICP monitoring in the absence of a reliable neurological examination. Whereas, the use of nearly half the IVC beyond 10 days indicates their utility as an interventional measure in monitoring and managing ICP. This extended use of IVC is also due to the patients who have become dependent on external CSF drainage and a significant proportion of these will go on to require a shunting procedure.

The infection rate for IVC is cited from 0% up to 40% [4,7] compared to 0.5% to 1.7% for IPC [12,15]. Our infection rate of 4.4% for IVC and 0.6% for IPC, is comparable with other studies. It is worthy of note that a majority of our catheters (91%) were inserted in an ICU setting, where a better control of the surroundings appears to contribute to our favorably low infection rate. A review of literature points to numerous factors responsible for ventricular infection, e.g., poor technique at the time of insertion, prolonged duration of catheterization, opening of the fluid-filled system to air, system manipulation such as withdrawing CSF or injecting drugs, ICP > 20 mm Hg, extraneous procedures at the ventriculostomy site e.g., dressing changes, concurrent cranial surgery, presence of intracerebral or intraventricular hemorrhage, associated injuries like, open intracranial wounds or skull fractures and breakdown in the system in the form of CSF leaks [1,2,8,10,13]. Percutaneous tunneling of IVC may contribute to a diminished rate of infection [6,4]. The IPC fibreoptic system is a closed one, requiring calibration only once, just prior to insertion. Hence, it avoids all the pitfalls noted above. None of the complications from either system led to an untoward clinical outcome.

A review of the gathered data indicates that the pattern of use of IVC and IPC in our study was similar to that in other trauma centers [5], with the former being used predominantly, followed by the latter. This study also pointed to a pattern of monitor usage, where IVC are inserted more in the presence of SAH, while IPC are favored in CHI. Based on the data, our conclusion is that IVC remain comparable to IPC in complications. IPC, due to their inability to facilitate CSF drainage, are indicated and useful in a subset of patients, rather than universally.

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Correspondence: H. C. Onyiuke, M.D., Department of Neurosurgery, S-607, Head Injury Program, Hartford Hospital, 80 Seymour street, Hartford, CT 06102-5037, U.S.A.

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Anterior Fontanelle Pressure Recording with the Rotterdam Transducer: Variation of Normal Parameters with Age

N. Massager[1], **J.-L. Wayenberg**[2], **D. Vermeylen**[3], and **J. Brotchi**[1]

[1]Departments of Neurosurgery, [3]Neonatal Intensive Care Unit, University Hospital Erasme, [2]Department of Paediatrics, Hôpital Fançais Free University of Brussels, Brussels, Belgium

Summary

Using a reliable non-invasive technique for ICP monitoring, we realized 93 continuous anterior fontanelle pressure (AFP) recordings in 86 healthy infants aged from 29 to 85 post-conceptional (PC) weeks. For each recording, we calculated the mean and extremes values of AFP, cerebral pulse amplitude, and pressure waves rate and amplitude. We observed the occurrence of plateau-waves of relatively low amplitude and duration in most infants aged of more than 49 PC weeks. We postulate that PW represents a physiological phenomenon which is amplified under pathological conditions. All AFP parameters are correlated to PC age and vary during early infancy according to an ascending sigmoidal relation (this variation may be explained by a connection between several cranio-cerebral characteristics of the young infant). We conclude that the interpretation of AFP recordings must take into account [1] PC age rather than postnatal age, [2] variation of AFP parameters with age, and [3] occurrence of physiological plateau-waves.

Keywords: Anterior fontanelle pressure; infants; non-invasive technique.

Introduction

ICP monitoring in neonates and young infants may be useful in many clinical situations; at this age, increased ICP may induce brain lesions and have deleterious effects on cerebral development. However, little is known about the evolution of ICP parameters in normal infants during the first months of life. Until recently, evaluation of the ICP characteristics in normal infants was not possible because of the need for invasive procedures. Since the past decade, a new generation of transfontanellar devices allows reliable non-invasive ICP monitoring through the open anterior fontanelle [1,14]. Using the Rotterdam Transducer, we realized continuous anterior fontanelle pressure (AFP) recordings in healthy infants of various ages in order to analyse the physiological evolution of ICP parameters and pressure waves in early infancy.

Materials and Methods

We studied 86 healthy infants aged from 29 to 85 postconceptional (PC) weeks (18 prematures, 38 neonates and 37 infants). Informed consent was obtained from all parents. All patients had normal neurological history and examination at the time of monitoring, and their psychomotor development remained normal afterwards. We realized 93 one-night continuous AFP monitorings by means of the Rotterdam Transducer, a transfontanellar device that has previously been proved to record reliable information about ICP [14]. The principles and technical details of the device have been extensively described by de Jong and co-workers [1]. For each recording, and after exclusion of awakening periods and motion-induced artefacts, we analyzed mean and max AFP, mean and max cerebral pulse amplitude (CPA), max B-wave (BW) amplitude, plateau-wave (PW) rate, mean and max PW amplitude and duration. We defined BW as cyclic 2–4 per min waves, and PW as sustained spontaneous AFP increases lasting at least 2 min and reaching at least 2 mm Hg above the baseline. We divided our population in 4 groups according to infant's PC age. All AFP variables were correlated to patient's age in order to establish charts of the evolution of AFP and pressure wave parameters. The relationship between AFP parameters and infant's age was tested by Spearman's regression coefficient (Rs). The extent of the graphical relationship of AFP values with age was evaluated by Pearson's correlation coefficient (R^2) in order to determine the most accurate trendline (linear, logarithmic or sigmoidal).

Results

The values of AFP parameters for each age group are summarized in Table 1. One hundred fifty-nine PW were observed in 24 patients (extremes: 2–19 PW per recording). PW were never observed in infants

Table 1. *Values of AFP and Pressure Waves Variables in the Three Age Groups and Statistical Analysis*

Age group (weeks)	No. of patients	Mean AFP	Max. AFP	Mean CPA	Max. CPA	Max. B-W amplitude	Mean P-W amplitude	Max. P-W amplitude	Mean P-W duration	Max. P-W duration	P-W rate
Results											
29–36	18	2.95 (1.57)	4.18 (1.04)	0.70 (0.32)	0.91 (0.56)	1.06 (0.76)	–	–	–	–	–
36–44	38	5.63 (1.67)	7.92 (1.84)	0.95 (0.43)	1.58 (0.99)	1.83 (0.75)	–	–	–	–	–
45–65	28	7.33 (1.57)	10.11 (2.19)	2.46 (0.95)	4.14 (1.39)	3.30 (1.05)	12.98 (9.53)	18.41 (13.52)	4.33 (3.09)	7.18 (5.09)	9.35 (9.23)
66–85	9	10.69 (1.86)	13.01 (2.66)	3.91 (1.21)	5.89 (1.87)	6.56 (2.24)	30.00 (8.23)	45.56 (13.35)	9.50 (2.86)	15.78 (4.94)	25.83 (7.97)
Satistical analysis											
Sigmoidal progression											
Pearson's correlation coefficient (R^2)		0.82	0.80	0.86	0.84	0.85	0.83	0.86	0.74	0.73	0.68
Correlation with age											
Spearman's regression coefficient (Rs)		0.76	0.72	0.86	0.81	0.84	0.82	0.84	0.73	0.70	0.66

( ) standard deviation; *AFP* arterior fontanellar pressure; *CPA* cerebral pulse amplitude; *BW* B-wave; *PW* plateau-wave.

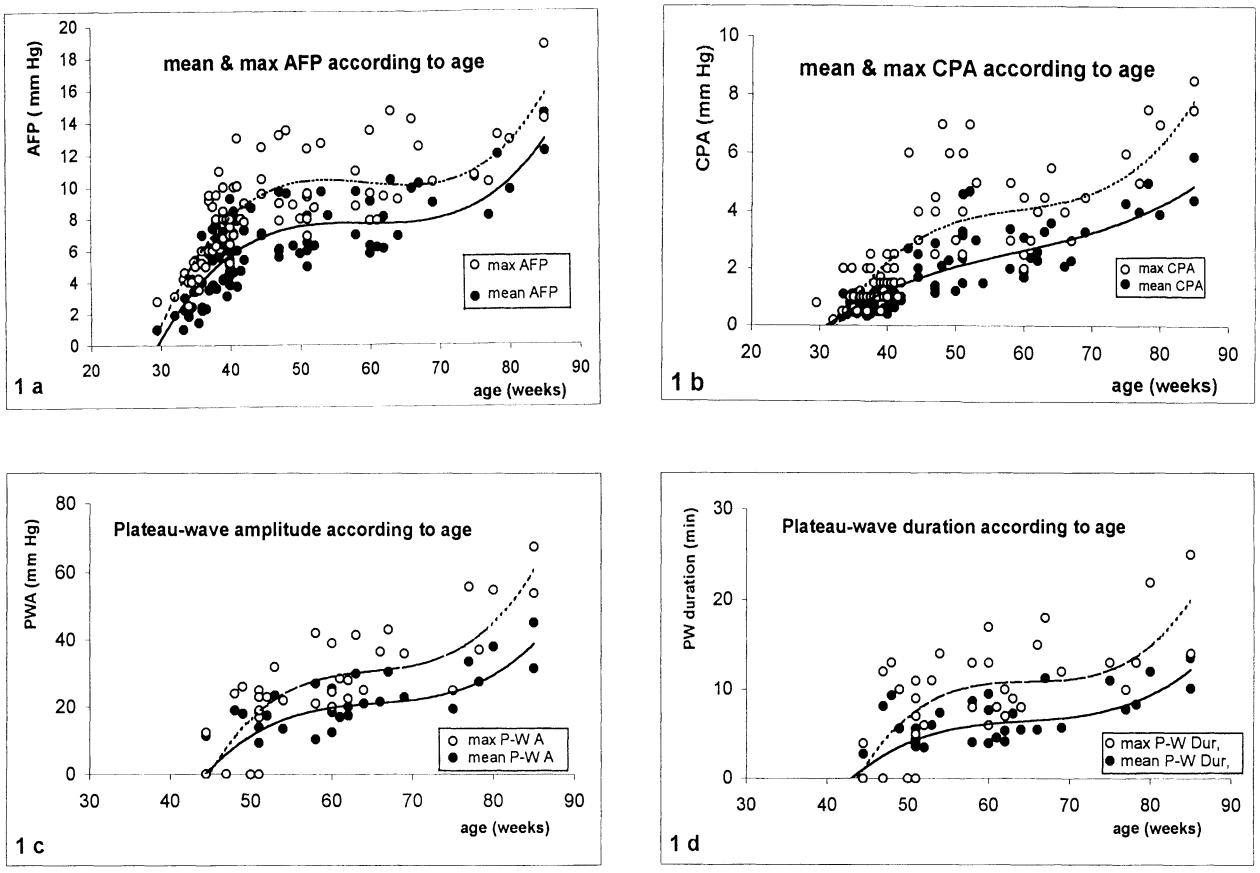

Fig. 1. Evolution of some AFP and pressure waves values with infants' post-conceptional age: (a) mean and max AFP; (b) mean and max CPA; (c) mean and max PW amplitude; (d) mean and max PW duration

aged less than 49 PC weeks. All AFP and pressure waves variables are increased in older infants; these variables were plotted on two-dimensional charts in order to analyze their evolution according to age during the first year of life. Except for PW rate which follows a linear progression, all AFP variables increased with age according to a sigmoidal progression (Fig. 1a–d). AFP parameters increase rapidly between (roughly) the 30th and 50th postconceptional week, after which they progressively stabilize; around the 70th week, variables of AFP recordings start again to increase until closure of the anterior

fontanelle. The correlation between AFP parameters and infants' PC age is very good (Rs ranged from 0.66 to 0.86); Pearson's correlation coefficient of the sigmoidal progression of variables with age ranged from 0.68 to 0.86 (Table 1).

Discussion

In his original publication, Lundberg [5] introduced the concept of "Plateau-waves" as acute elevations of ICP rapidly rising to 50–100 mm Hg and lasting from 5 to more than 20 min before returning to the baseline level. The origin and clinical significance of PW are still debated. Using a reliable non-invasive technique for ICP monitoring in young infants, we observed that PW of relatively low amplitude and duration may be found in AFP monitoring of normal infants aged more than 49 PC weeks. Several authors have already reported the occurrence of PW in ICP monitoring of young infants with neurological diseases [7,9]. PW were also observed in ICP recordings of normal monkeys [3], as well as in infants with craniostenosis or arrested hydrocephalus and normal baseline ICP [2,12]. Some authors have postulated that PW actually constitutes a physiological phenomenon which is amplified (in terms of duration and amplitude) under pathological conditions because of a decrease in cerebral compliance or of cerebrovascular dysfunction [8,11]. Our data seem to confirm this hypothesis.

A progressive increase of ICP with age in preterm and full-term babies has already been reported by both non-invasive and invasive techniques [10,14]; nevertheless, the evolution of ICP and other parameters of ICP monitoring (cerebral pulse amplitude and pressure waves (during early infancy has, to our knowledge, never been extensively studied. By means of a non-invasive device, we found that all variables of the ICP monitoring (including pressure waves) increase gradually with age following a sigmoidal curve. Schematically, AFP parameters increase rapidly during the first 3 months after birth; they reach a plateau during the next 3 months; they further increase after this time until fontanelle closure. The reasons for this evolution are unknown. Some cranio-cerebral characteristics of the young infant probably play a role on this progression, such as progressive closure of sutures and fontanels, head growth rate, variations of cerebral compliance [6], capacities of modulation of cerebrospinal fluid absorption and CSF flow, and maturation of the brain stem and their control mechanisms [4]. Our study demonstrates that infants' post-conceptional age has to be taken into account for an accurate interpretation of AFP recordings.

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Correspondence: Nicolas Massager, M.D., Department of Neurosurgery, University Hospital Erasme Route de Lennik 808, 1070 Brussels, Belgium.

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Interhemispheric Pressure Gradients in Severe Head Trauma in Humans

Th. Mindermann and **O. Gratzl**

Neurological Surgery, University Hospitals Basel, Basel, Switzerland

Summary

Interhemispheric pressure gradients may occur following severe head trauma in patients even in the absence of intracranial space occupying lesions. A higher ICP of the contralateral hemisphere may escape routine unilateral ICP monitoring. Clinical signs and CT scans do not seem to predict reliably a lateralized ICP. According to our data with a limited number of patients, interhemispheric pressure gradients seem to occur in the initial posttraumatic phase in some patients, and they seem to resolve following adequate ICP treatment after several hours. Therefore, simultaneous bilateral ICP measurement may be warranted in the initial posttraumatic phase.

Keywords: Head trauma; interhemispheric pressure gradients.

Introduction

Considerable pressure gradients have been observed between the various intracranial compartments in animal experiments and in humans following trauma or surgery [1,2,4]. Yet, they are believed to be of no clinical significance [3]. To evaluate their occurrence and extent we measured intracranial pressure (ICP) bifrontally in patients with severe head trauma.

Materials and Methods

Patients admitted with severe head trauma and a Glasgow Coma Score (GCS) ≤9 were entered into the study if they had no space occupying lesions that would warrant surgery and if coagulation parameters were within normal limits. First, we tried to determine if computer tomography (CT) or clinical signs (dilated pupil, focal neurological deficit) would indicate an interhemispheric pressure gradient and which hemisphere might have a higher ICP. The results were recorded on the protocol before commencement of bilateral ICP measurement. Then, we calibrated and introduced intraparenchymal stain-gauge microsensors (Codman/Johnson & Johnson Professional, Inc., Randolph, MA) bifrontally through paramedian, precoronal burr holes and measured ICP and mean arterial pressure (MAP) continuously. For data acquisition and recording we used MacLab/4e, Chart 3.5 (ADInstruments Pty Ltd, Castle Hill, Australia), and a Powerbook 540c (Apple Computer, Inc., Cupertino, CA). Elevated ICP was treated stepwise according to our clinical standards (positioning, hyperventilation, mannitol, barbiturates, and ventricular drainage). Treatment was aimed at the higher ICP reading. Whenever possible, cerebral perfusion pressure (CPP) was kept ≥60 mm Hg and ICP ≤20 mm Hg. Data are reported as mean ± standard deviation.

Results

Six patients were entered into the study. Their mean age was 26.7 ± 21.6 years, n = 6 and their admission GCS was 5.7 ± 2.5, n = 6. There were no side effects or complications of the bilateral ICP measurement. Patient characteristics are listed in Table 1. The position of the intraparenchymal probes is shown in Fig. 1 (patient 6). Mean recording time was 76.6 ± 84.2 hours, n = 6. In patient 6, only the first 38 hours of the 99-hour recording were evaluated because cables of the probes may have been switched after the first 38 hours on the intensive care unit. Three of the six patients (patients 1, 2, and 3) had interhemispheric pressure gradients of 6–10 mm Hg from the beginning of continuous monitoring equalizing gradually thereafter over a time course of 6–7 hours. As an example, the recording of patient 1 is shown in part in Fig. 2. In two of the three patients with interhemisperic pressure gradients (patients 1 and 3), clinical findings or CT scans indicated a higher ICP on the wrong side. In two of six patients (patients 2 and 6), emergency room interpretation of clinical and radiological findings (pre-monitoring) were unequivocal and correlated with ICP readings in regard to the presence or absence of interhemispheric pressure gradients or in predicting the lateralization of ICP correctly.

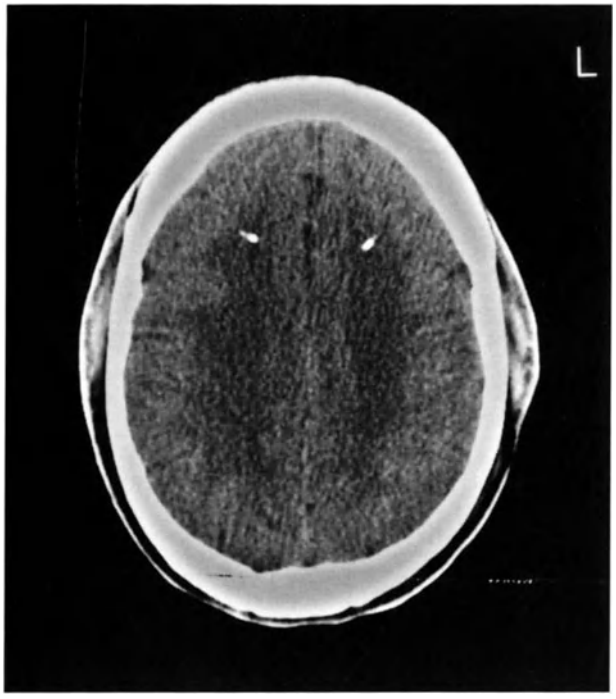

Fig. 1. CT scan showing the intraparenchymal position of the tips of the bifrontal ICP probes in patient 6

Discussion

Our data rely on a limited number of patients. Yet, our observations question the paradigm of an evenly distributed ICP. Interhemispheric pressure gradients seem possible in some patients after head trauma, even in the absence of space occupying lesions. In two-thirds of our patients, we were not able to determine who might have pressure gradients or which hemisphere might be affected most by raised ICP based on clinical and CT findings only.

In the light of these observations, the case of patient 1 is of particular interest. Clinical signs did not indicate the presence of an interhemispheric pressure gradient. The CT scan was interpreted as a slightly pronounced edema of the right hemisphere. ICP monitoring revealed a differential ICP with an elevated left hemispheric pressure. ICP readings were ≤20 mm Hg over the right hemisphere in the initial phase and >20 mm Hg over the left hemisphere at the same time (see Fig. 2). The right hemispheric pressure would warrant close observation, whereas

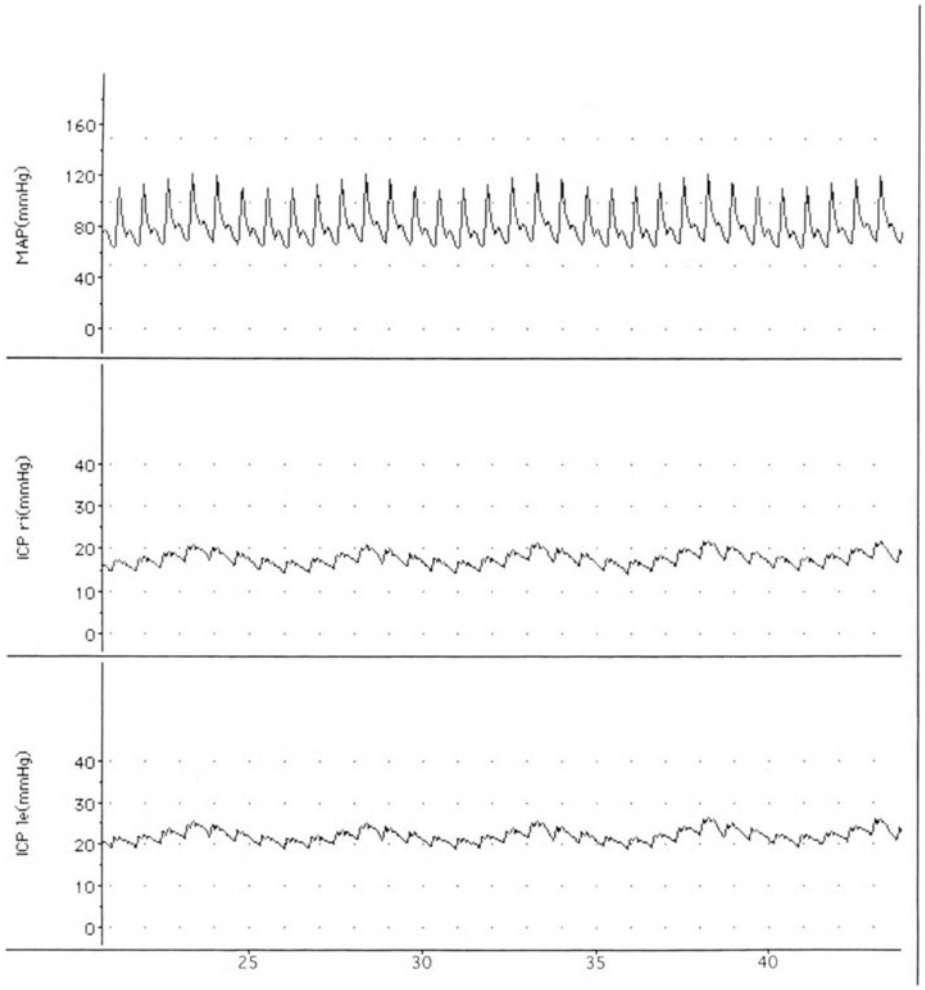

Fig. 2. Simultaneous recording of MAP and bilateral ICP within the first 6 hours after commencement of monitoring in patient 1. For the shown data, MAP is 81.07 ± 13.65 mm Hg. right hemispheric ICP is 17.66 ± 1.58 mm Hg, and left hemispheric ICP is 22.17 ± 1.55 mm Hg. Both ICPs have a tendency to rise

Table 1. *Patient Characteristics*

Patient no.	Gender	Age (years)	Trauma	GCS	Clinical signs	CT	ICP monitoring	ICP gradient (mm Hg)
1	M	34	gunshot	5	no gradient	ri > le	5 days	le > ri (6)
2	F	7	bicycle	8	ri > le	ri > le	10 hours	ri > le (7)
3	M	66	bicycle	3	ri > le	no gradient	30 minutes	le > ri (10)
4	M	25	work	3	le > ri	ri > le	17 hours	no gradient
5	M	10	bicycle	6	le > ri	le > ri	9 days	no gradient
6	M	18	car	9	no gradient	no gradient	4 days (first 38 h evaluated)	no gradient

the left hemispheric pressure would warrant a stepping up of specific ICP therapy. Under routine conditions with unilateral, right sided ICP monitoring, this pressure gradient would have gone unnoticed. The clearly elevated ICP of the left hemisphere may have been treated less than optimally and the range of CPP may have been chosen inadequately for the dominant hemisphere. The question arises if, under such conditions, an initially lateralized higher ICP of the contralateral side remaining undetected may eventually lead to a more severe brain edema and consequently to more severe secondary brain damage caused by a delay of detection and treatment.

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Correspondence: Thomas Mindermann, M.D., Neurosurgery, University Hospitals Basel, 4031 Basel, Switzerland.

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An Avoidable Methodological Failure in Intracranial Pressure Monitoring Using Fiberoptic or Solid State Devices

A. Raabe, R. Stöckel, D. Hohrein, and **J. Schöche**

Department of Neurosurgery, University of Leipzig, Leipzig, Federal Republic of Germany

Summary

Failure of intraventricular pressure (IVP) measurement in case of catheter blockage is believed to be eliminated by using intraventricular microtransducers. We report about an avoidable methodological error, which may affect the reliability of IVP measurement with these devices.

Intraventricular fiberoptic or solid state devices were implanted in 43 patients considered to be at risk for catheter occlusion. Two different types were used: devices where the transducer is placed inside the ventriculostomy catheter (Type A), and devices where the transducer is integrated in the external surface of the catheter (Type B).

Of the 15 patients treated with Type A devices, no reliable pressure recording could be obtained in three patients where ventricular puncture was not successful. In four cases of the remaining 12 patients, periods of erroneous pressure readings were revealed. After opening of CSF drainage, all Type A devices failed to reflect real IVP. In patients treated with Type B devices, no erroneous pressure recording could be identified, irrespective if CSF drainage was performed or not.

Transducers, which are simply placed inside the ventriculostomy catheter require fluid coupling. They may fail, either during CSF drainage or when the catheter is blocked or placed within the parenchyma.

Keywords: Catheter occlusion; failure; fiberoptic; intracranial pressure; intraventricular pressure; microtransducers; solid state device.

Introduction

Intraventricular pressure (IVP) measurement is considered to be the gold standard in intracranial pressure (ICP) monitoring, against which all other systems are compared. However, standard ventriculostomy catheters measuring IVP by fluid coupled external transducers have certain limitations both in clinical practice and experimental work. They may fail in case of progressive mass lesion and compressed ventricles, in situations of catheter blockage or when the catheter is dislodged and placed within the brain parenchyma.

To overcome these problems, technological improvements led to development of fiberoptic and solid state transducers with direct pressure measurement. These techniques were developed primarily for intraparenchymal, subdural or extradural pressure measurement, in which fluid coupling is not possible or does not give correct results. In intraparenchymal location, these microtransducers have made clinical ICP monitoring simpler, safer and more accurate [2,3,5].

These technologies were also transferred to IVP measurement and kits combined with ventricular catheters are commercially available for clinical use. In one type, coded Type A, the pressure transducer is simply placed inside a ventriculostomy catheter. However, with this technique the pressure of the intraluminal fluid seems to be measured and fluid coupling to the extraluminal intraventricular CSF should be necessary to reflect real IVP. In a different type of device, coded Type B, the transducer is an integrated part of the external surface of the ventriculostomy catheter and has direct contact to the extraluminal CSF or brain tissue. This study reports about our experience with comparatively priced Type A and Type B devices.

Material and Methods

43 patients of different intracranial diseases fulfilled the criteria of 1) being scheduled for ventriculostomy and ICP monitoring according to their management protocol and 2) based on computerised tomography scans, being at risk to develop blockage of the ventriculostomy catheter either due to large intraventricular clots

or due to slit ventricles. Twenty-nine patients presented with severe head injury, 7 with subarachnoidal haemorrhage and 7 with intracerebral haemorrhage.

In all these cases, intraventricular fiberoptic or solid state transducers were implanted to avoid erroneous IVP measurements reported with fluid filled external transducers [1]. Intraventricular pressure was measured with a Camino Ventricular pressure monitoring kit (Camino Laboratories, San Diego, California) in twelve cases, with a Sensodyn transducer (Draeger Medical Electronics, Best, The Netherlands) in three cases, with a Neurovent catheter (Raumedic, Rehau AG, Rehau, Germany) in twenty-five cases, and with a Ventcontrol catheter (Draeger Medical Electronics, Best, The Netherlands) in three cases (total = 43). The duration of intraventricular pressure monitoring ranged from 12 hours to 21 days (mean 5 days).

The Camino and the Sensodyn set-up includes positioning of a separate transducer catheter inside the ventriculostomy catheter (Type A devices). The Neurovent catheter and the Ventcontrol catheter are Type B devices and their transducer is an integrated part of the external surface of the tip of these catheters (Fig. 1).

Results

In three cases, where access to the ventricular system with Type A devices was not possible, no accurate pressure monitoring could be established. With Type B catheters, in all of the five cases with failed ventricular puncture, an accurate and reliable IVP measurement could be obtained for the remainder of the monitoring time.

In the first hours after insertion, accurate IVP measurements were observed in all cases with both Type A and Type B devices with correct intraventricular catheter position. Secondary failure of IVP measurement for more than 10 minutes occurred in 4 of 12 cases where Type A devices were used. Of Type B devices, all IVP recordings were correct at the time of pressure monitoring irrespective the presence or absence of CSF drainage.

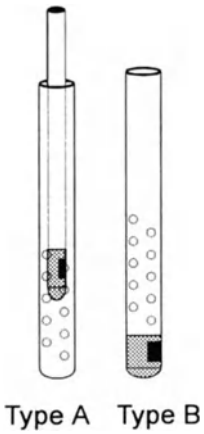

Fig. 1. Drawing of the two different types of intraventricular catheters using fiberoptic or solid state transducers for pressure monitoring. In Type A devices, an additional pressure transducer is positioned inside the ventriculostomy catheter. In Type B devices the pressure transducer is an integrated part of the external surface of the ventriculostomy catheter

After opening of CSF drainage, with all recordings with Type A devices, the recorded pressure decreased to exactly the hydrostatic difference pressure between the intraventricular transducer and the distal end of the drainage tube. In no case was real IVP reflected. With Type B devices, accuracy of measurement was not affected by opening of CSF drainage. The change in the amplitude of the IVP pulse wave and its configuration reflected the physiological behaviour during outflow of CSF.

In all periods with erroneous IVP measurements with Type A devices, false low pressures were revealed. 50% of these periods were characterized by maintenance of pulsations with decreased pulse pressure amplitude. In 16% of these periods, a nearly normal pulse pressure amplitude was seen. Identification was only possible by using graphs of long time recording and scatterplots of IVP pulse pressure amplitude.

Discussion

Until now, there is no report in the literature about failure of IVP measurement when fiberoptic or solid state transducers are used. Using Type A devices, we found in our study in the group of patients with compressed ventricles or large intraventricular blood clots, evidence of periods of erroneous measurement in 33% of cases. No Type A device reflected real IVP, when CSF drainage was performed to treat for elevated IVP or when ventricular puncture failed and the catheter was left in the brain parenchyma. All periods of erroneous pressure recording with Type A devices, lasting by our definition from 10 minutes to permanent failure, showed a decrease in mean pressure and an overproportional decline in pulse pressure amplitude.

This type of failure is unknown, when microtransducers are used for intraparenchymal pressure measurement, because they measure pressure in direct contact with the brain or CSF. If the same technology was used in IVP measurement, as it applies to Type B devices, accurate measurement was observed all the time, including situations of occluded or dislodged ventriculostomy catheter, open ventricular drainage or failure of ventricular puncture [4].

Our figures demonstrate that transducers placed inside the ventriculostomy catheter require fluid coupling for accurate IVP measurement. Thus they may fail, when the ventriculostomy catheter is blocked or placed within the parenchyma. It is of clinical importance to emphasise the faulty low pressure readings, which might not clearly be identified as erroneous data and may lead to inadequate treatment decisions. In patients at risk for secondary failure of IVP measurement due to catheter occlusion or dislodgement, catheters with an integrated external surface pressure transducer (Type B) should be used.

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Correspondence: Andreas Raabe, M.D., Department of Neurosurgery, University of Leipzig, Johannisallee 34, D-04103 Leipzig, Federal Republic of Germany.

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Influence of Hyperventilation on Brain Tissue-PO_2, PCO_2, and pH in Patients with Intracranial Hypertension

G.-H. Schneider, A. S. Sarrafzadeh, K. L. Kiening, T. F. Bardt, A. W. Unterberg, and **W. R. Lanksch**

Department of Neurosurgery, Rudolf Virchow Medical Center, Humboldt University, Berlin, Federal Republic of Germany

Summary

A harmful effect of prolonged hyperventilation on outcome has been shown in comatose patients after severe head injury. The purpose of this study was to assess the acute effect of moderate hyperventilation for treatment of intracranial hypertension (ICP < 20 mmHg) on invasively measured brain tissue-PO_2 ($PtiO_2$), PCO_2 ($PtiCO_2$) and pH (tipH) in severely head injured patients.

15 severely head injured patients (GCS ≤ 8) were prospectively studied. Intracranial pressure (ICP), mean arterial blood pressure (MABP), cerebral perfusion pressure (CPP), endtidal CO_2 ($ETCO_2$), $PtiO_2$, $PtiCO_2$ and tipH (Paratrend or Licox microsensors) were continuously recorded using multimodal monitoring. Following a baseline period of 15 minutes, patients were hyperventilated for 10 minutes. Arterial blood gas analysis was done before, during and after hyperventilation. At least three hyperventilation maneuvers were performed per patient. For statistical analysis the Friedman test was used.

Hyperventilation (p_aCO_2: 32.4 ± 0.6 to 27.7 ± 0.5 mmHg) significantly reduced ICP from 25.3 ± 1.5 to 14.2 ± 1.9 mmHg ($p < 0.01$). As a consequence, CPP increased by 9.6 ± 3.4 mmHg to 76.8 ± 3.2 mmHg. Brain tissue PCO_2 decreased from 37.5 ± 1.3 to 34.6 ± 1.2 while tipH increased from 7.13 to 7.16. In all patients, hyperventilation led to a reduction of brain tissue PO_2 ($PtiO_2$ / Licox: 24.6 ± 1.4 to 21.9 ± 1.7 mmHg, n.s.; $PtiO_2$ / Paratrend: 35.8 ± 4.3 to 31.9 ± 4.0 mmHg, n.s.). In one case hyperventilation even had to be stopped after 7 min because the drop in brain tissue PO_2 below 10 mmHg signalized imminent hypoxia.

As well known, hyperventilation improves CPP due to a reduction in ICP. However, this does not ameliorate cerebral oxygenation as demonstrated by the decrease in $PtiO_2$. This underlines that hyperventilation should only be used with caution in the treatment of intracranial hypertension.

Keywords: Brain tissue PO_2; hyperventilation; intracranial hypertension; PCO_2 and pH.

Introduction

Hyperventilation has traditionally been used in the treatment of intracranial hypertension [1,2]. There is general agreement that hyperventilation leads to an effective reduction of raised intracranial pressure (ICP) by a reduction of cerebral blood volume through cerebral vasoconstriction [1,3,4]. As CO_2 freely diffuses over the blood-brain barrier a theoretical advantage of hyperventilation may also be an attenuation of posttraumatic cerebral lactic acidosis [5] which is correlated with poor outcome. Despite all this potentially beneficial influence, the general use of hyperventilation for treatment of raised ICP has been controversially discussed during the last years [6–9]. The effect of hyperventilation on alkalization of cerebrospinal fluid pH and arteriolar diameter was only short-lived in rabbits and may possibly be counteractive after 24 hrs [7]. In a randomized clinical trial Muizelaar *et al.* [6] reported that prophylactic prolonged hyperventilation may be deleterious to the outcome of severely head injured patients.

Hyperventilation induced cerebral vasoconstriction to such an extent that cerebral ischemia may result could be a possible cause for adverse effects of hyperventilation. Since new methods for continuous monitoring of cerebral oxygenation and pH have recently evolved it was the aim of this study to assess the acute influence of hyperventilation on invasively measured brain tissue-PO_2 ($PtiO_2$), PCO_2 ($PtiCO_2$) and pH (tipH).

Materials and Methods

Fifteen patients who sustained a severe head injury between March 1996 and March 1997 with a postresuscitation Glasgow Coma Score of ≤8 were admitted to the study. The mean age of these patients was 33.5 ± 3.2 yrs, ranging from 18 to 52 yrs. There

were 6 female and 9 male patients. Patients were managed according to international standards which included aggressive treatment of raised intracranial pressure and evacuation of intracranial mass where necessary.

Intracranial pressure was measured using a frontally placed Camino (Camino Laboratories, San Diego, USA; n = 9) or Codman (Johnson & Johnson Professional, Raynham, USA; n = 6) device. Brain tissue PO_2 as a parameter of cerebral oxygenation was monitored with a Licox (GSM, FRG) or Paratrend (Diametrics Medical, UK) microsensor (10) which was also introduced via a frontal burr hole. In 7 patients both systems were used, while in 4 patients either Licox or Paratrend was inserted. Care was taken not to place the PO_2 probes within a contused brain area but in supposedly vital and reactive brain tissue. Besides the amperometric PO_2 sensor the Paratrend device also comprises probe areas enabling continuous measurement of brain tissue-PCO_2, pH and temperature. Insertion of invasive probes was usually accomplished within 12 to 48 hrs following head injury. Additionally, mean arterial blood pressure, cerebral perfusion pressure and endtidal CO_2 were recorded. All data were stored for analysis using a multimodal monitoring system.

Hyperventilation studies were done on day 1 to day 10 post trauma (median: 5). Hyperventilation is aimed at a decline of about 5 mmHg of endtidal CO_2. Following a baseline period of 15 minutes, hyperventilation lasted for 10 minutes and patients were monitored for an additional 10 minutes after the end of hyperventilation. At least three such hyperventilation maneuvers were performed per patient with a minimal interval of 1 day. Arterial blood gas analysis was done before, during and after hyperventilation.

Results were checked for statistically significant differences by use of the Friedman test.

Results

As expected, moderate hyperventilation from an arterial PCO_2 of 32.4 ± 0.6 to 27.7 ± 0.5 mmHg significantly reduced intracranial pressure (all patients: 25.3 ± 1.5 to 14.2 ± 1.9 mmHg, $p < 0.01$; for Licox probe see Fig. 1a). As mean arterial blood pressure did not change significantly, this in turn caused an improvement of cerebral perfusion pressure by 9.6 ± 3.4 mmHg to 76.8 ± 3.2 mmHg. In all patients, moderate hyperventilation led to a decrease in brain tissue PO_2 which was sometimes pronounced ($PtiO_2$/Licox: from 24.6 ± 1.4 to 21.9 ± 1.7 mmHg, n.s., Fig. 1a; $PtiO_2$/Paratrend: from 35.8 ± 4.3 to 31.9 ± 4.0 mmHg, n.s., Fig. 1b). Brain tissue PCO_2 in patients monitored with the Paratrend sensor was also found to be decreased by the hyperventilation maneuver (from 37.5 ± 1.3 to 34.6 ± 1.2 mmHg, Fig. 1b). In accordance to alkalization of blood, hyperventilation caused a slight rise in brain tissue pH from 7.13 to 7.16 (n.s.). After the end of hyperventilation brain tissue PCO_2 slowly started to increase again with brain tissue PO_2 following but not reaching baseline within the next 10 minutes observation period (Fig. 1). In one case hyperventilation led to a drastic decline in brain

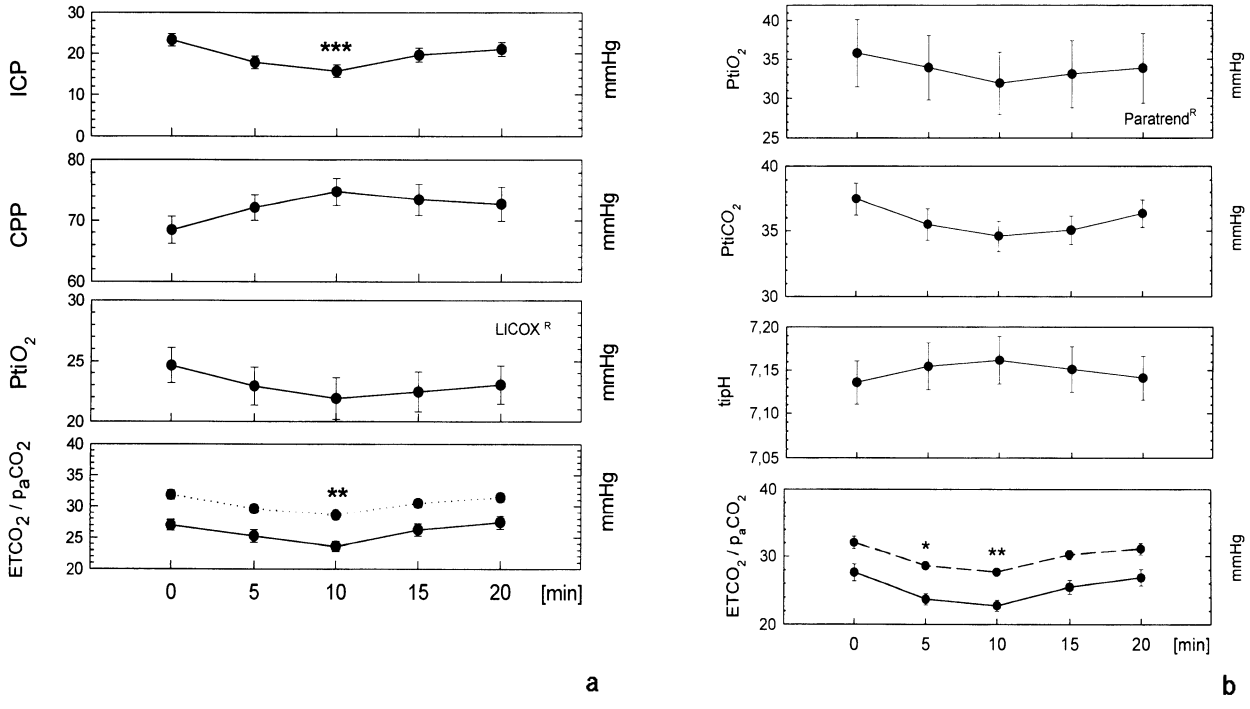

Fig. 1. Effect of a 10 minute maneuver of moderate hyperventilation on (a) intracranial pressure (ICP), cerebral perfusion pressure (CPP) and brain tissue PO_2 ($PtiO_2$) as measured by Licox probe (11 patients). (b) brain tissue PO_2 ($PtiO_2$), PCO_2 ($PtiCO_2$) and pH (tipH) as measured by Paratrend sensor (11 patients). p_aCO_2 = arterial PO_2; $ETCO_2$ = endtidal CO_2. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

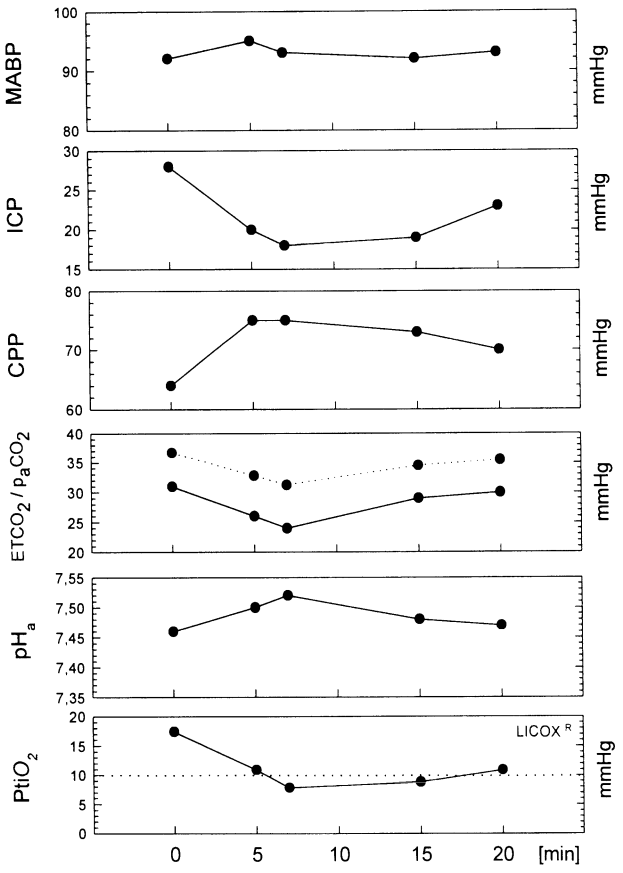

Fig. 2. Registration of one hyperventilation maneuver. In this patient hyperventilation led to a severe drop of $PtiO_2$ below 10mmHg causing imminent cerebral hypoxia. The maneuver, therefore, had to be stopped after 7 minutes. *MABP* mean arterial blood pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, p_aCO_2 arterial PO_2, $ETCO_2$ endtidal CO_2, pH_a arterial pH, $PtiO_2$ brain tissue PO_2 (Licox probe)

oxygenation as measured by $PtiO_2$ and the maneuver had to be stopped after 7 minutes because brain tissue PO_2 had dropped below the critical threshold of cerebral hypoxia (Fig. 2).

Discussion

This study again proves that hyperventilation due to vasoconstriction and reduction in cerebral blood volume is capable of effectively reducing raised intracranial pressure. This, in turn, leads to an improvement in CPP which would favor hyperventilation, since the importance of a sufficient CPP has more and more evolved during the last decade [11]. On the other hand, there have been several reports lately, that the use of hyperventilation may be disadvantageous or even harmful for some patients [6–9,12]. Muizelaar *et al.* [6] showed a deterioration in 3 and 6 month outcome in patients with a motor score of 4–5; however, he could not pinpoint the possible cause for this to ischemia because he found no evidence of ischemia in intermittent measurements of cerebral blood flow (CBF). Since the hyperventilation induced change in cerebral blood flow was reported to be more pronounced than the change in cerebral blood volume [9] therapeutic hyperventilation could still more impair CBF than reduce ICP. In accordance, in this study acute moderate hyperventilation led to a reduction in brain tissue pO_2 despite the beneficial effects on ICP and CPP. This has to be taken into account when considering the risk of hypoxic/ischemic phases in the early posttraumatic period [12] and the increased vulnerability of traumatized brain to ischemia [13]. The obviously higher $PtiO_2$ values measured by Paratrend as compared to Licox may be explained by a slightly different insertion technique which led to a closer placement of the Paratrend PO_2 sensor towards cerebral grey matter. Given the ongoing controversy over whether or not patients should be hyperventilated it was reasonable to employ new techniques of measuring $PtiO_2$, $PtiCO_2$ and tipH. Though hyperventilation caused a slight alkalization of brain tissue no amelioration of cerebral oxygenation could be obtained. In most patients the decrease in $PtiO_2$ was not as pronounced. The case, however, in which $PtiO_2$ dropped below the ischemic threshold illustrates that hyperventilation induced vasoconstriction may be dangerous. Taken together, these findings suggest that hyperventilation in the treatment of intracranial hypertension should only be used with caution and alertness to potentially adverse effects and whenever possible under monitoring of cerebral oxygenation.

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Correspondence: Gerd-Helge Schneider, M.D., Department of Neurosurgery, Rudolf Virchow Medical Center, Humboldt University Berlin, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Noninvasive Measurement of Pulsatile Intracranial Pressure Using Ultrasound

T. Ueno[1], **R. E. Ballard**[1], **L. M. Shuer**[2], **J. H. Cantrell**[3], **W. T. Yost**[3], and **A. R. Hargens**[1]

[1] Gravitational Research Branch (239-11), NASA Ames Research Center, [2] Department of Neurosurgery, Stanford University Medical Center, and [3] Nondestructive Evaluation Sciences Branch, NASA Langley Research Center, Moffett Field, CA, U.S.A.

Summary

The present study was designed to validate our noninvasive ultrasonic technique (pulse phase locked loop: PPLL) for measuring intracranial pressure (ICP) waveforms. The technique is based upon detecting skull movements which are known to occur in conjunction with altered intracranial pressure. In bench model studies, PPLL output was highly correlated with changes in the distance between a transducer and a reflecting target ($R^2 = 0.977$). In cadaver studies, transcranial distance was measured while pulsations of ICP (amplitudes of zero to 10 mm Hg) were generated by rhythmic injections of saline. Frequency analyses (fast Fourier transformation) clearly demonstrate the correspondence between the PPLL output and ICP pulse cycles. Although theoretically there is a slight possibility that changes in the PPLL output are caused by changes in the ultrasonic velocity of brain tissue, the decreased amplitudes of the PPLL output as the external compression of the head was increased indicates that the PPLL output represents substantial skull movement associated with altered ICP. In conclusion, the ultrasound device has sufficient sensitivity to detect transcranial pulsations which occur in association with the cardiac cycle. Our technique makes it possible to analyze ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular circulation.

Keywords: Cerebrovascular circulation; intracranial pressure; noninvasive measurement.

Introduction

Elevated intracranial pressure (ICP) is used as a sign of neurological deterioration in the management of patients with head trauma, cerebrovascular diseases, and brain tumors [6]. Conventional methods for ICP monitoring require surgical procedures which are accompanied by increased risk of infection. For this reason, candidates for ICP monitoring are currently only patients with severe neurological conditions. A noninvasive technique could make it possible to monitor ICP more easily and repeatedly in patients with a variety of neurosurgical conditions, thus aiding clinical management and reducing the mortality and morbidity related to neurological diseases.

We have developed a new ultrasonic device to measure ICP waveforms. Although mean ICP is commonly used for ICP monitoring, the analysis of ICP waveforms is also important because the waveforms contain information on intracranial compliance and cerebrovascular tonus, which cannot be estimated from mean ICP [1]. Our technique [8], the principle of which is called pulsed phase-locked loop (PPLL) method, is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers [2–5,7] have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. The present study was designed to validate our noninvasive technique for the measurement of ICP waveforms.

Technique

The ultrasound technique [8] we utilized to detect skull pulsation is based upon a modification of the pulsed phase-lock loop design, which makes it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. Sensitivity of the device is on the order of 0.1 μm. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity,

reflects off the inner surface of the opposite side of the skull, and is received by the same transducer. The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 ms.

The details of PPLL are described elsewhere [8,9]. Briefly, if path length is changed by Δl, the frequency shift (Δf) of the ultrasound which is made to maintain the 90° phase difference between the output of the device and the received signal can be expressed as $\Delta l/l = -\Delta f/f$ (see Appendix). This is the fundamental PPLL technique. In order to provide continuous monitoring, we modified the PPLL circuit to integrate error signals of the phase shift from normal 90° phase difference (PPLL output). Theoretically, integration of the error signals also correlates with altered path length (Δl).

Methods

Bench Test

A specially constructed aluminum cylinder was used to examine the PPLL output characteristics. Two pressure-resistant tubes were connected to the cylinder filled with saline. The other ends of the two tubes were connected to a plastic syringe and a fiber-optic, transducer-tipped catheter (Camino Laboratories, San Diego) which measures fluid pressure, respectively. An ultrasonic transducer was placed on the top of the cylinder. Pressure pulsations were generated at a frequency of 1 Hz by pumping the syringe while its amplitudes were changed randomly. Changes in distance were calculated from changes in ultrasound frequency.

Cadaver Study

The correlation between the PPLL output and ICP were evaluated in two fresh cadavera (age 85 and 90) which were less than 48 hours postmortem. In supine position, a catheter was inserted to the frontal horn of the right lateral ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate the PPLL output with ICP directly, a fiber-optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. In the first experiment (cadaver A), we recorded the PPLL output while generating ICP pulsations and thereafter increased the circumference pressure around the head in steps of 10 mm Hg (0–40 mm Hg) by inflating the pressure cuff. In the second experiment (cadaver B), we recorded the pulsatile PPLL output by infusing saline of different temperatures into the ventricle (4°C and 20°C).

Data Analysis

The amplitudes were calculated based upon the fundamental harmonic of the data using 256 point-fast Fourier transformation (sampling rate: 50 Hz) to avoid distortion caused by other frequency waves.

Results

Bench Test

Our model experiments demonstrated that changes in the PPLL output correlated with changes in the distance to a high degree (Fig. 1). Theoretically, the distance calculated from the ultrasound frequency can be obtained independently of PPLL output. In the results, PPLL output is expressed as:

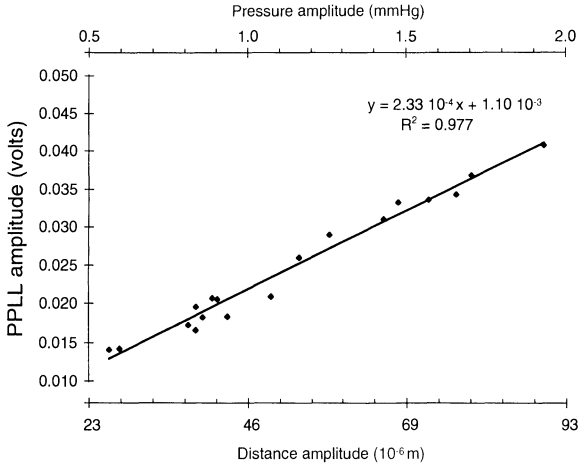

Fig. 1. The relation of the PPLL output to the pressure inside the cylinder and the distance between the transducer and the bottom of the tank is shown, where x = distance (μm) and y = PPLL output (voltage)

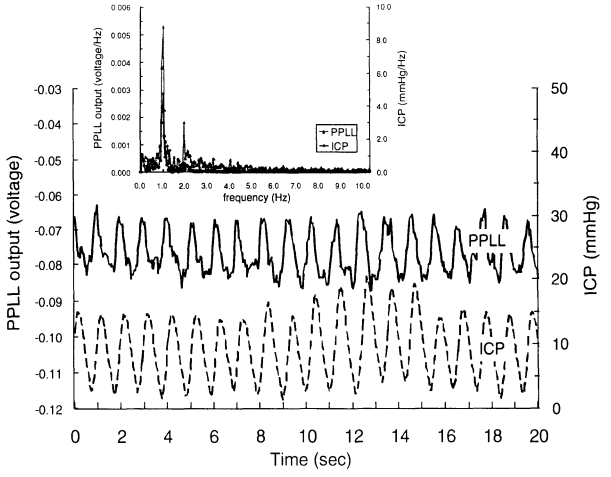

Fig. 2. Typical waveforms in the PPLL output and directly measured ICP are shown as solid and dash lines, respectively. The results of frequency analysis (fast Fourier transformation) are provided in the top inset

$$\Delta \text{int}\ (\text{voltage}) = 2.33 \cdot 10^{-4}\, \Delta l\ (\mu\text{m}) \qquad (1)$$

Where Δint and Δl are the changes in PPLL outputs and distance, respectively.

Cadaver Study

The PPLL output closely followed the pulsatile component of ICP (Fig. 2). The results of fast Fourier transformation are provided in the top insert, showing the coincidence between the PPLL output and ICP pulse cycles. In the results of the first experiment, the ratio of PPLL amplitude to ICP amplitude significantly decreased along with increased external compression around the head:

$$y = -1.0 \cdot 10^{-5} x + 0.0008,\ R^2 = 0.87\ (p = 0.020)$$

where x = circumferencial compression (mm Hg) and y = ratio of PPLL amplitude to ICP amplitude (voltage/mm Hg). In the second experiment, the correlation between the PPLL and ICP amplitudes was expressed as the same equation in both saline temperatures:

$$y = 3.0 \cdot 10^{-4} x + 0.0011 \qquad (2)$$

where x = ICP amplitude (mm Hg) and y = PPLL amplitude (voltage).

Discussion

The results demonstrate that our PPLL device can clearly detect changes in the integrated phase shifts of the transmitted ultrasound (PPLL outputs) in association with alterations in ICP. As shown in the Appendix, the observed phase shift can be caused by changes in the distance between the transducer and the opposite side of the skull and also by changes in the ultrasound velocity in the cranium. However, we believe that changes in the PPLL output observed in the present cadaveric study represent small but detectable skull movements associated with alterations in ICP.

Infusion of saline into the ventricle could change the temperature inside the cranium, resulting in altered sound velocity. As another possible factor, changes in the density of the brain tissue due to altered ICP could affect ultrasound velocity. In the cadaver study, however, no significant difference was observed in the amplitudes of PPLL when different temperature saline was infused into the ventricle. Also, increased circumference pressure around the head decreased PPLL amplitudes. This observation cannot be explained by changes in ultrasound velocity. This study may be the first report to measure skull movements noninvasively in association with alterations in ICP.

According to the Eq. 2, the ratio of PPLL amplitude to ICP amplitude is expressed as:

$$\Delta \text{int}/\Delta \text{ICP} = 3.0 \cdot 10^{-4} (\text{voltage}/\text{mm Hg}) \qquad (3)$$

Using equations 1 (shown in the Results) and 3, the skull elastance, defined as ΔICP/ΔI, is approximately 1.6 mm Hg/μm ($= 2.33 \cdot 10^{-4}/(3.0 \cdot 10^{-4}) \cdot 2$). Heisey and Adams [3] demonstrated that skull elastance in adult cats is 4.5 mm Hg/μm by invasively measuring the skull movement across the sagittal suture with strain gauge. The difference between our data and theirs might be due to the difference in skull elastance between cat and human. Also, we measured skull movements transversely, while they measured the movement only across the sagittal suture. This difference in the site of measurement may affect changes in the distance obtained.

In conclusion, our technique allows analysis of ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular tonus in general clinical settings.

Acknowledgements

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Appendix

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

$$n\Delta\lambda = \Delta l\ (\Delta\lambda:\ \text{changes in wavelength},\ \Delta l:\ \text{changes in distance})$$

where $n = l/\lambda$ (l: initial distance between a transducer and a target, λ: initial wavelength).

Therefore, $\frac{\Delta\lambda}{\lambda} = \frac{\Delta l}{l}$

Also, $\Delta\lambda = \frac{\partial\lambda}{\partial v}\Delta v + \frac{\partial\lambda}{\partial f}\Delta f$ where Δv is changes in ultrasound velocity, and $f = v/\lambda$.

Solving these equations, we obtain $\frac{\Delta f}{f} = \frac{\Delta v}{v} - \frac{\Delta l}{l}$

If changes in sound velocity are negligible, the above equation is finally expressed as $\frac{\Delta f}{f} = -\frac{\Delta l}{l}$

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Correspondence: Alan R. Hargens, Ph.D., Gravitational Research Branch (239-11), NASA Ames Research Center, Moffett Field, CA 94035-1000, U.S.A.

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Non-Invasive Measurement of Intracranial Pressure in Neonates and Infants: Experience with the Rotterdam Teletransducer

J.-L. Wayenberg

Department of Paediatrics, Hôpital Français – Reine Elisabeth, Brussels, Belgium

Summary

On the basis of an experience of more than 400 recordings, we demonstrate the usefulness of the anterior fontanelle pressure monitoring (AFP) in several clinical conditions. Main indications for AFP monitoring are the evaluation and the differential diagnosis of neonatal encephalopathy and the assessment of infants with enlarged ventricular spaces, ventriculo-peritoneal derivation or increased head growth rate. Further technical progress is needed to permit AFP recordings in infants with small anterior fontanelle and to reduce the time necessary for the AFP measurement and interpretation procedure. We conclude that it is technically possible and clinically helpful to obtain accurate information about ICP and changes in cerebral compliance in a wide range of clinical conditions without the use of invasive techniques.

Keywords: Encephalopathies; infants; neonates; teletransducer.

Introduction

Because increased ICP has deleterious effects on the developing brain, ICP monitoring may be beneficial in many conditions such as head injury, hydrocephalus and post-asphyxial, infectious, metabolic and toxic encephalopathies. In infants with an open fontanelle, it is possible to measure ICP non invasively and accurately by means of the Rotterdam Teletransducer [2,9]. Our aim is to report our clinical experience of more than 400 recordings of the anterior fontanelle pressure (AFP).

Material and Methods

Patients

Healthy infants. AFP was measured on 93 occasions in 86 healthy children, including prematures, term neonates and infants aged from 1 to 12 months. Neurological evolution and psycho-motor development were normal in all cases.

Hypoxic-ischemic encephalopathy. We studied 87 continuous AFP recordings performed on 46 full-term neonates who experienced birth asphyxia, defined by the presence of foetal distress and/or depression at birth, associated with metabolic acidosis at 30 min of life (arterial base deficit > 10 mEq/l). Neonatal evolution was favourable in 26 patients; 20 developed signs of moderate or severe post-hypoxic-ischemic encephalopathy (HIE) as defined by Finer *et al.* [4].

Hydrocephalus. We studied 42 patients with hydrocephalus (98 continuous AFP recordings). According to their clinical condition and cerebral imaging results, patients were divided into a vacuo hydrocephalus (AVH, n = 10), progressive hydrocephalus (PRH, n = 24), well functioning derivation (n = 11) and shunt dysfunction (n = 4).

Increasing head growth rate and external hydrocephalus. Thirty patients aged from 1 to 10 months were evaluated because of an asymptomatic increase in their head growth rate. Cerebral imaging and 12-months follow-up were obtained in all cases.

Other conditions. AFP was also measured on 114 occasions in 58 patients with various conditions such as subdural haematoma (6 patients) and hygroma (n = 2), metabolic diseases (5 patients), CNS infections (n = 3), neonatal subarachnoidal hemorrhage (n = 4), congenital syndromes (Down, Marfan, foetal-alcohol) and in neonates with respiratory distress (n = 10).

Anterior Fontanelle Pressure Measurements

The Rotterdam Teletransducer was developed at the department of experimental neurosurgery of Erasmus University, Rotterdam. Technical details and measurement procedure are extensively described elsewhere [2]. AFP was measured in dorsal horizontal position and care was taken to avoid neck flexion.

Analysis of AFP Traces and Statistics

We studied both basal AFP variables, AFP and pulse pressure amplitude (PPA), and pressure waves, only when the infant was quiet or sleeping. Mean AFP and mean PPA are calculated as the average of points taken every five minutes, excluding movement artefacts and pressure waves. Pressure waves are defined as spontaneous AFP increases, and classified according to their morphology into plateau waves (PW), representing sustained AFP increases, and B-like waves (BW), representing sharp-pointed 0.02–0.05 Hz AFP increases. For each recording, we measure the duration and the amplitude of each PW, the mean AFP occurring

during PW, the BW maximal amplitude, and calculate the PW and BW rates (total duration of PW or BW divided by total interpretable recording time). AFP variables were considered as abnormal if exceeding the 90th percentile of normal age-related values. Wilcoxon, Mann-Whitney and Chi-square tests are used for statistical analysis. Correlations are tested by Spearman correlation test.

Results

AFP Recordings in Normal Infants

Normal values of AFP, PPA and pressure waves variables are now available at various ages. Each AFP variable changes with post-conceptional age and with sleep stages. Detailed data are presented elsewhere [8].

Hypoxic-Ischemic Encephalopathy

In patients with moderate/severe HIE, significant changes in AFP variables were noted as compared with patients with normal neonatal evolution or mild HIE (Fig. 1): while mean AFP increases between the 12th and the 72nd hour of life, PPA is already increased at birth and remains elevated during the first days of life. Among patients with moderate/severe HIE, three died, all had increased AFP. Among survivors from moderate/severe HIE, the AFP variables are significantly higher in patients with abnormal neurological examination at discharge than in those with normal examination ($p < 0.05$); increase of the AFP above 15 mmHg is associated with subsequent neurodevelopmental handicap in the 12 patients available for follow-up ($p < 0.05$).

Hydrocephalus

In patients with AVH, all AFP variables are in the normal range; mean AFP did not exceed the 50th

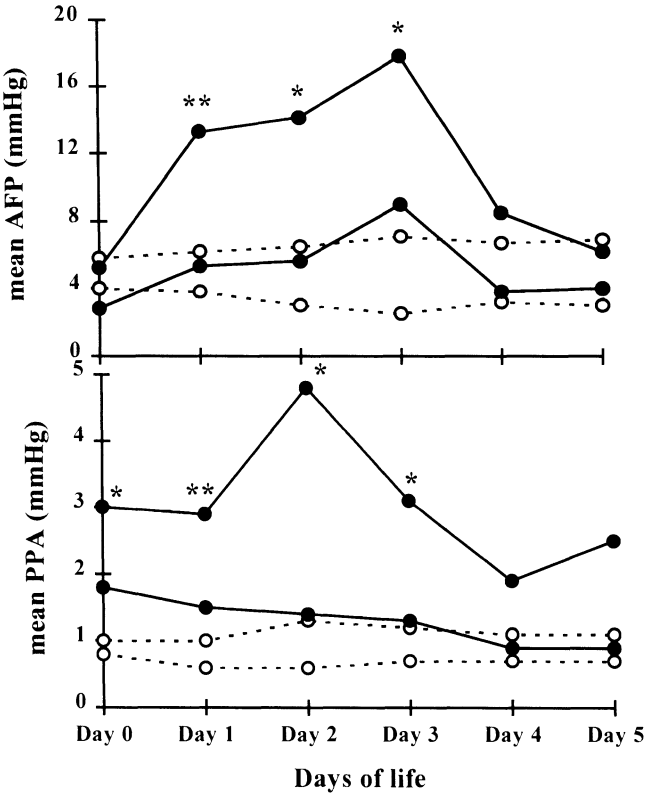

Fig. 1. Evolution of max. AFP and mean PPA after birth asphyxia. Open circles: mean ± standard-deviation of patients with normal neurological evolution or mild HIE. Closed circles: mean ± standard-deviation of patients with moderate or severe HIE. *$p < 0.05$, **$p < 0.01$

percentile normal value. Compared with both normal infants and patients with AVH, a significant increase of all AFP variables except one (mean AFP) is observed in PRH patients. Mean AFP is increased in only one half of the patients; in all cases but one, the PPA, the PW and BW amplitude and/or the PW rate are above normal values, mainly during active sleep. A PW rate greater than 25% is the most reliable criteria for the diagnosis of PRH. The diagnostic value of AFP monitoring in the presence of ventricu-

Table 1. *Clinical Value of AFP Monitoring*

Clinical condition	χ^2	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Hypoxic-ischemic encephalopathy:					
– prediction of neurodevelopmental outcome in survivors of moderate or severe HIE	<0.05	100%	71%	71%	100%
Hydrocephalus:					
– differentiation between progressive and stable ventricular enlargement	<0.0001	96%	100%	100%	91%
– assessment of shunt function	<0.001	100%	100%	100%	100%
Increased head growth rate:					
– prediction of the need for neurosurgical procedure	<0.001	100%	88%	63%	100%

lar enlargement is presented in Table 1. AFP traces are relatively flat in well-functioning shunts; in contrast, pressure waves of an amplitude higher than 4 mmHg and a BW rate greater than 25% are observed in all four patients with shunt dysfunction.

Increasing Head Growth Rate

Eight recordings were classified as abnormal; basal AFP was increased in four; in the other four PW amplitude, PW duration, PW rate and/or BW amplitude were increased only. Cerebral imaging showed subdural collection in 4 cases, ventricular enlargement in another 3, and in the last case enlargement of both subarachnoidal spaces and ventricles. Five out of the 8 patients of this group further developed neurological deficits and/or increase of the ventricular size in the following months, and required neurosurgical procedures. Twenty-two AFP recordings were classified as normal; cerebral imaging was normal in 10 cases; enlarged subarachnoidal spaces and normal ventricles were noted in the other 12. All patients of this group remained asymptomatic and further normalised head growth rate; none required neurosurgical procedure. Table 1 presents the clinical value of AFP monitoring for the evaluation of the need for neurosurgical procedure in this situation.

Other Conditions

Increases of AFP, PPA and pressure waves variables are observed in patients with subdural haematomas, CNS infections and metabolic diseases with cerebral edema. In contrast, normal range AFP is noted in neonatal subarachnoidal hemorrhage, metabolic diseases without cerebral edema and congenital syndromes. In non-intubated term patients with respiratory distress, PPA is significantly increased when compared to normal term neonates ($p < 0.05$). In ventilated prematures, mean AFP and PPA are correlated with peak inspiratory pressure ($r_s = 0.9$, $p < 0.05$). An increase of positive end-expiratory pressure from 0 to 5 cm H_2O induces an 1–2 mmHg increase of mean AFP.

Discussion

Increased ICP is of particular importance in the developing brain because of its association in infantile hydrocephalus with delayed myelination and reduction in neurodevelopmental testing scores [5,6]. Therefore it is useful to obtain this information, preferably by means of a non-invasive procedure. In our experience, accurate continuous information about changes in ICP and cerebral compliance may be obtained in wide range of clinical conditions by means of the Rotterdam Transducer. A significant increase of the AFP variables is observed in most patients with <<active>> cerebral diseases such as progressive hydrocephalus, subdural haematoma and cerebral edema due to birth asphyxia, metabolic disorders or infection.

Our results confirm and complete the observations of other investigators, obtained by means of invasive methods [3,7]. After severe birth asphyxia, AFP monitoring shows the typical ICP pattern secondary to progressive cerebral edema while the early increase in PPA reflects the increase in cerebral blood flow noted in Doppler studies [1]. As reported by Levene, increased AFP is associated with worse neurological prognosis [7]. In neurologically distressed neonates, increased AFP observed on patients with severe birth asphyxia, meningitis or hyperammonaemia contrasted with normal AFP observed in patients with congenital syndromes, subarachnoidal hemorrhage, metabolic disease without cerebral edema and intoxications by substances taken by the mother. In hydrocephalus AFP monitoring is of great value to differentiate progressive from stable ventricular enlargement and to check shunt function. As basal mean AFP is within the normal range in about half of the cases, amplitude and rate of the pressure waves must be analyzed during continuous recordings and compared to changing with post-conceptional age and sleep stage normal values [8–10]. However, AFP monitoring must sometimes be repeated in very slowly progressive cases. In patients with increased head growth rate AFP monitoring help us in the evaluation of the need for extensive explorations or neurosurgical procedures.

Thus AFP monitoring allows us to explore and understand changes in cerebral compliance occurring in a large number of indications, such as increased ventricular size, increased head growth rate, CNS disease of the newborn, neonatal ventilation, intracranial hemorrhage and space-occupying lesions, CNS infections and metabolic diseases. Unfortunately a wider use of the Rotterdam Teletransducer is limited by the need for sufficient fontanelle size (11×11 mm) and by the time necessary to install and calibrate the device and to interpret the recordings. Further

progress in automation of the installation procedure and in computerisation of the AFP recordings are needed.

Acknowledgements

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Correspondence: Jean-Louis Wayenberg, M.D., Department of Paediatrics, Hôpital Français – Reine Elisabeth, 180, avenue V. Goffin, B-1080 Brussels, Belgium.

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Continuous Monitoring of Cerebrovascular Pressure-Reactivity in Head Injury

M. Czosnyka, P. Smielewski, P. Kirkpatrick, S. Piechnik, R. Laing, and **J. D. Pickard**

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Summary

Objective: Cerebrovascular vasomotor reactivity reflects changes in smooth muscle tone in the arterial wall in response to changes in transmural pressure or concentration of carbon dioxide in blood. We have investigated whether slow waves in ABP and ICP may be used to derive an index which reflects reactivity of vessels to changes in arterial blood pressure.

Method: A method for the continuous monitoring of the association between slow spontaneous waves in ICP and AP has been adopted in a group of 98 head injured patients. ABP, ICP and transcranial Doppler blood flow velocity (FV) in the middle cerebral artery was recorded daily (20 to 120 minutes time periods). A Pressure-Reactivity Index (PRx) was calculated as a moving correlation coefficient between 40 consecutive samples of values for ICP and ABP averaged over 5 seconds. A moving correlation coefficient between spontaneous fluctuations of mean FV and CPP (Mx), which was previously reported to describe cerebral blood flow autoregulation, was also calculated.

In an additional 25 patients, PRx was calculated and recorded continuously along with mean ICP, ABP and parameters describing ICP waveform.

Results: A positive PRx correlated with high ICP ($r = 0.366$; $p < 0.001$), low admission GCS ($r = 0.29$; $p < 0.01$), and poor outcome at 6 months after injury ($r = 0.48$; $p < 0.00001$). During the first two days following injury, PRx was positive ($p < 0.05$) in patients with unfavourable outcome. The correlation between PRx and Mx ($r = 0.63$) was highly significant ($p < 0.000001$).

Continuous recordings demonstrated that PRx was able to indicate individual thresholds of vascular reactivity for CPP, ICP, and ventilation parameters.

Conclusion: Computer analysis of slow waves in ABP and ICP is able to provide a continuous index of cerebrovascular reactivity to changes in arterial pressure, which is of prognostic significance.

Keywords: Head injury; pressure reactivity; Pressure-Reactivity Index (PRx); vasomotor reactivity.

Introduction

Cerebrovascular reactivity to changes in arterial blood pressure describes the ability of vascular smooth muscle to change basal tone in response to variation in transmural pressure. When the cerebral autoregulatory reserve nears exhaustion, cerebral blood flow becomes unstable. However, vessels may still show responses to a further reduction in perfusion pressure of changes in concentration of carbon dioxide [3,6]. Vascular responses continue to occur outside the range of a stable cerebral blood flow, i.e. outside the limits of cerebral autoregulation [6]. Slow fluctuations in ABP, lasting from 30 seconds to a few minutes, is almost always present in ventilated patients [5–8], and the rate of change observed is usually sufficient to provoke a noticeable vasomotor response [1,4]. Theoretically, if cerebrovascular reactivity to pressure changes is intact, an increase in ABP should produce vasoconstriction, a decrease in cerebral blood volume, and a decrease in ICP, provided the brain compliance is low [11]. If vessels remain non-reactive, an increase in ABP should cause an increase in the cerebral blood volume, and hence ICP.

Our aim was to study the correlation between slow wave changes in ICP and ABP using a simplified Pressure-Reactivity Index (PRx). We have investigated the relationship of this index to intracranial hypertension, and to changes in mean ABP in patients with a severe head injury. We summarized our previous study on correlation between PRx and the severity of injury, outcome, and cerebral perfusion pressure. We also explored a value of PRx as an on-line index of changes in cerebrovascular reactivity in long-time monitoring of head injured patients.

Material and Methods

A hundred and seven head injured patients with a mean Glasgow Coma Score of 6 (range 3 to 13) admitted to Addenbrooke's Hospital were included in the study. There were 27 females and 55 males with age ranging from 6 to 75 years (mean age 36 years).

The patients were paralyzed, sedated and ventilated to achieve mild hypocapnia (3.5–4.5 kPa). Intractranial hypertension (ICP > 25 mm Hg) was managed with boluses of mannitol (200 ml of 20%, over a period of 20 min) and cerebral perfusion pressure was maintained at 60 mmHg or above, using plasma expansion (alternating colloid and normal saline infusions) and ionotropic support if necessary (dopamine 2–15 µg/kg per minute). Arterial pressure was monitored directly from the radial or dorsalis pedis artery (System 8,000, S&W Vickers Ltd, Sidcup, UK). Intracranial pressure was monitored continuously using an intraparenchymal fibre-optic transducer (Camino Direct Pressure Monitor, Camino Laboratories, San Diego, CA). Transcranial Doppler investigations were performed daily for a period of between 20 and 120 minutes from the day of admission until discharge from the intensive care unit (PCDop 842 Doppler Ultrasound Unit, Scimed, Bristol, UK).

Analogue outputs from all monitored were processed through an analogue-to-digital converter digitized (DT 2814, Data Translation, Marlboro, USA) and data collected on a portable IBM AT laptop computer (Amstrad ALT 386 SX, UK). Data was sampled, digitized and stored on the hard disk using specific software for the waveform recording (W. Zabolotny, Wrasaw University of Technology, Poland) and then processed using software developed in-house (ICMR, M.C.).

Time averaged values of ICP, ABP, CPP, (CPP = ICP-ABP), and the MCA blood flow velocity (FV) were calculated using waveform time-integration for 6 second intervals. Pearson's moving correlation coefficients for 40 consecutive samples of averaged ICP and ABP, defined as the Pressure-Reactivity Index (PRx), was computed for every 6 second epoch. In 25 patients, we used PRx for long-term patient monitoring and collected one minute moving-averaged values together with other monitored modalities.

Results

Correlation with Clinical Findings (N = 82 Patients)

Spearman rank correlation coefficients between averaged (for each patient) values of PRx, ICP, CPP, admission GCS, outcome, and TCD-derived index of autoregulation (Mx) are presented in Table 1. Disturbed pressure-reactivity (i.e. positive PRx) correlated with lower admission GCS, poorer outcome, greater ICP, and disturbed TCD-derived index of autoregulation.

From the analysis of PRx versus outcome, a critical value for averaged (over whole period of intensive care monitoring) PRx appears to be +0.2, above which chance of an unfavourable outcome was 81% (n = 27 cases). All patients with a PRx of less than –0.2 had a favourable outcome (n = 8 cases).

Long-Term monitoring of PRx (N = 25 Patients)

Index of cerebrovascular reactivity was monitored continuously in 25 severly head injured patients. In all cases negative correlation between changes in CPP and PRx with time was observed (average R^2 = 0.65). On average PRx started to rise when CPP decreased below 67 mm Hg; however, an obvious breakpoint could not always be demonstrated. Moreover, if detectable, it was case- and time-dependent. Patients who had a complicated post-injury period showed frequent changes in PRx from negative to

Table 1. *Spearman Rank Correlation Coefficients and Their Significance Levels Calculated between the Analysed Parameters*

	GOS	GCS	CPP	ICP	ABP	PRx
GCS	–0.425					
	$p < 0.0001$					
CPP	–0.0628	0.167				
	$p < 0.57$	$p < 0.14$				
ICP	0.21	–0.063	–0.66			
	$p < 0.058$	$p < 0.58$	$p < 0.0000$			
ABP	0.18	0.11	0.543	0.202		
	$p < 0.14$	$p < 0.34$	$p < 0.0000$	$p < 0.07$		
PRx	0.484	–0.29	–0.19	0.36	0.0127	
	$p < 0.0000$	$p < 0.0095$	$p < 0.09$	$p < 0.001$	$p < 0.25$	
Mx	0.42	–0.34	–0.32	0.455	0.046	0.65
	$p < 0.0002$	$p < 0.002$	$p < 0.004$	$p < 0.0000$	$p < 0.68$	$p < 0.0000$

GCS admission Glasgow Coma Scale, *GOS* Glasgow Outcome Score, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *ABP* arterial blood pressure, *PRx* pressure reactivity index, *Mx TCD*-derived index of autoregulation.

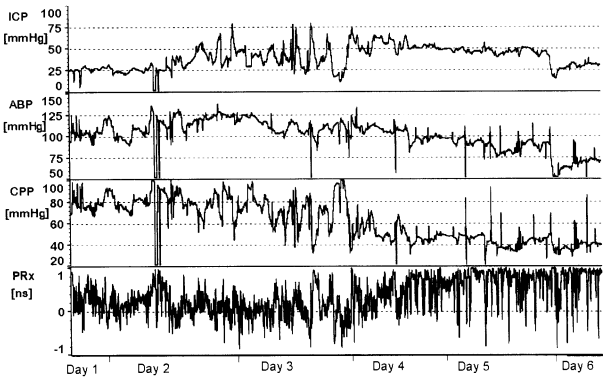

Fig. 1. Example of long-term monitoring (6 days) of ICP and ABP and on-line analysis of the PRx index in patient after severe head injury (GCS = 4). Patient died on Day 6. PRx indicated diminishing cerebrovascular reactivity on day 4 after injury

positive values. If PRx persisted above 0.2 for more than 4–6 hours, this was usually associated with fatal complications due to refractory intracranial hypertension (Fig. 1).

Rise of PRx in one case showed a negative association with jugular bulb oximetry (Fig. 2). During first three days, PRx was rather negative with short periods of positive values when short-term increases in ICP were detected. Started from the day 4, a more persistent increase in ICP was recorded. The jugular bulb was catheterized, showing a value of SJO_2 above 70%. Around the midday a long period of arterial hypotension, with SJO_2 decreasing below 55% was noted. Starting from this moment PRx became persistantly positive, and ICP had a tendency to increase. All this ended with a brain-stem herniation on day 5.

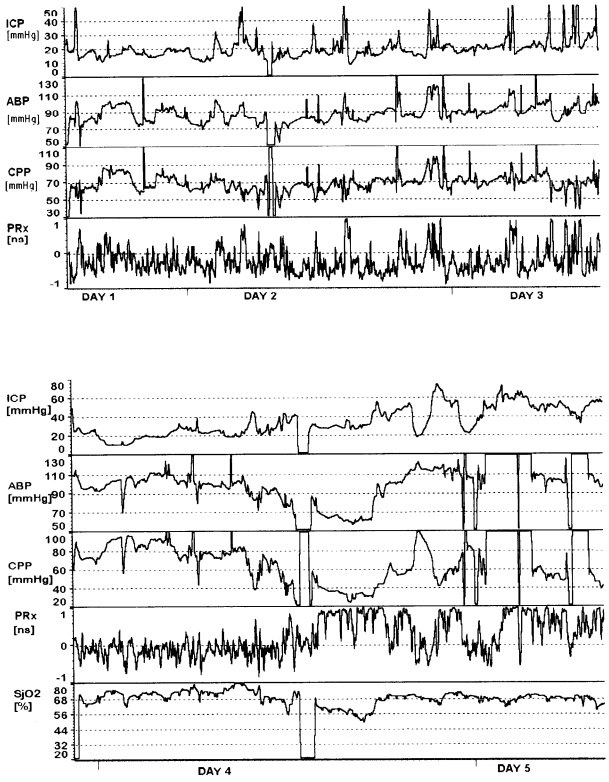

Fig. 2. Five days monitoring of ICP, ABP and SJO_2 (starting from day 3) following severe head injury (GCS = 3). PRx indicated an averaged good reactivity during first 3 days. On the Day 4 a decrease in SJO_2 below 55% was recorded, associated with a decrease in CPP. PRx became positive permanently, indicating severity of this secondary brain insult

Discussion

The association between slow waves in ABP and ICP has been previously used as an index of the state of cerebral pressure-autoregulation [7,9,12]. In our patients, a significant correlation was found between PRx and ICP, outcome, GCS, and a TCD-derived index of autoregulation (Mx). Moreover, we demonstrated that PRx reacted dynamically to decreases in CPP, during which cerebral autoregulation (according to FV criteria) was compromised (Figs. 1 and 2). We propose that PRx can be used to reflect global cerebrovascular reactivity to changes in arterial blood pressure.

Continuous analysis of PRx does not demand expensive ICP transducers which have good frequency response and low zero drift. Because the time-response of interest ranges from 30 sec to 2 min, virtually any type of ICP transducer, (either epidural or subdural) can be used. An internal "biological oscillator" [5] which provokes vasomotor-derived fluctuations in ABP would need to be present to allow full analysis of PRx. Although sometimes attenuated, the vasomotor activity in ABP and ICP is usually present, and can be analyzed using computer-supported methods of digital signal detection.

We suggest that PRx may be monitored independently of CPP and ICP to provide a measure of cerebrovascular self-protection. It is important to emphasize that PRx may be helpful in identifying either transient phenomena (associated with cerebrovascular derangement as in Fig. 2), or used as a measure of the "steady state" of the cerebrovascular reserve. If used for this purposes its value should be averaged over a minimum of 2 hours. A value above +0.2 reflects a poor state of cerebrovascular pressure-reactivity, while a value below –0.2 demonstrates excellent reactivity.

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Correspondence: Dr. Marek Czosnyka, Academic Neurosurgical Unit, P.O. Box 167 Addenbrooke's Hospital, Cambridge CB2 2QQ, U.K.

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Real-Time Multiparametric Monitoring of the Injured Human Cerebral Cortex – a New Approach

A. Mayevsky[1], **T. Manor**[1], **S. Meilin**[1], **A. Doron**[2], and **G. E. Ouaknine**[2]

[1] Department of Life Sciences, Bar-Ilan University, Ramat-Gan, [2] Department of Neurosurgery, Tel-Aviv Med. Center, Tel-Aviv, Israel

Summary

Intracranial pressure (ICP) is currently the main parameter monitored following severe head injury or during the post operative period in neurosurgical patients. The normal cerebral cortex depends upon a continuous supply of O_2, and direct coupling exists between adequate cerebral blood flow (O_2 supply) and ion homeostasis as well as electrical activities. We have developed a new "Brain Function Analyzer – BFA" which enabled monitoring of the following parameters continuously in real time from the surface of the cortex: ICP; tissue blood flow & volume; intramitochondrial NADH redox state; DC steady potential; electrocorticography; tissue temperature. The probes were assembled in a Brain Function Multiprobe (BFM) which was connected to the brain via the burr hole procedure used for ICP monitoring. Measurements were performed in 18 comatose patients after severe head injury (GCS ≤ 8) who were monitored in the ICU for 48–72 hours. The basic concept of the multiparametric monitoring approach was proven to be practical in neurosurgical patients. Clear correlations were recorded between hemodynamic, metabolic, ionic and electrical activities under various treatments administered to the patients or after pathological events. Responses similar to cortical spreading depression and ischemic depolarization were recorded from a severely head injured patient.

Keywords: Brain Function Analyzer; ion homeostasis; multiparametric monitoring.

Introduction

Severe head injuries may result in a high mortality rate or in the development of irreversible brain damage in another part of the brain [5]. One way to improve the outcome of such patients is to begin treatment as soon as possible after hospitalization. The aim of treatment given to the head-injured patient is to reduce irreversible damage as much as possible. Therefore, early diagnosis of the origin of the damage or the initial functioning status of the brain may significantly improve the prognosis.

The main monitoring approach currently used in head injury is the measurement of intracranial pressure (ICP) after drilling a small hole in the skull and inserting the connecting tube to the pressure monitor [4,8]. When the ICP exceeds a critical level (15–20 mm Hg) the patient is treated by different means in order to decrease the ICP level and improve the perfusion pressure of the brain. The most common treatments are injection of a hyperosmolar solution such as mannitol, decreasing the blood pCO_2 or even barbiturate injection. Since the population of head-injured patients is heterogenic, the responses to the same treatment may be different in various patients or during various phases in the same patient. The definition of the status of the brain after a traumatic event is therefore of great significance when choosing the kind and duration of treatment.

At least two responses of CBF are possible in head injured patients [11], a decrease in blood flow – ischemia [1] or an increase in CBF – hyperemia – which is not utilized for the metabolic purposes of the tissue. It is currently not possible to determine the actual situation scientifically or practically in real time. Therefore, more than one treatment is commonly employed simultaneously, i.e., injection of a hyperosmolar solution together with hyperventilation. With this approach the effects on the patient and on the outcome are not always clear.

Furthermore, the focus of ICP monitoring has shifted toward cerebral perfusion pressure (CPP) monitoring [2]. Other real-time techniques used in the ICUs for brain evaluation are the EEG and the EP [9] or regional CBF measured by Laser Doppler or thermal diffusion flowmetry [10].

Various imaging techniques, i.e., CT, MRI, PET, have been developed during the past 2–3 decades and have been applied to the study of the human brain. These techniques offer the advantage of noninvasiveness as well as supplying 3-dimensional information. However, they cannot provide information on various brain functions such as ionic homeostasis or mitochondrial respiratory-metabolic activity. Information on extracellular ion concentrations or respiratory function of the mitochondria has so far been derived only from experimental animals. Confirmation of these functions by direct measurements from the human brain under clinical situations has yet to be obtained.

During the past 20 years we have developed and applied a multiparametric monitoring system for studying the brain of various animal models. We have recently modified and adapted these techniques for monitoring the human brain following severe head injury. The aims of the present report are to demonstrate the feasibility of using this multiparametric monitoring system.

Methods

The technique used in this application (Multiparametric assembly) integrated multiparametric monitoring of the main indicators representing various brain functions in real time [7]. The monitoring assembly which was placed on the cortex (after opening of the dura matter) includes an ICP probe and was connected to the skull using the same principle. The following parameters were measured simultaneously in real time:

1. Tissue blood flow (using laser Doppler flowmeter)
2. Intramitochondrial redox state (NADH fluorometry)
3. Extracellular K^+ level (surface minielectrode)
4. Direct current (DC) steady potential (Ag/AgCl electrode)
5. Intracranial pressure (using a Camino probe)
6. Electrocorticography (bipolar cortical electrodes)
7. Tissue temperature (surface thermistor)

All probes were connected to the appropriate amplifiers and the signals were calibrated, stored and displayed on a 16 channel computerized acquisition and storage system as described in detail [6]. Informed consent was obtained in accordance with the IRB of the Tel-Aviv Medical Center.

The MPA was sterilized before usage according to standard gas sterilization procedures. After admission of the patient to the ICU and his stabilization, the following activities were performed:

1. An 8–9 mm diameter hole was carefully drilled in the frontal area. After cleaning the exposed area of bone residue, the dura matter was cut to enable direct contact between the MPA and the brain.
2. The MPA holder was screwed into the skull to a predetermined depth, thus avoiding any undue pressure on the brain.
3. The MPA was introduced into the holder and fastened into position.

Immediately after connection of the MPA, the various parameters were recorded and the baseline which served as a reference for the rest of the monitoring period was established.

Results

During the initial phase of the study we were able to monitor 20 patients. The development of the technique was part of this study. In order to present the potential use of this technology for head injured patients 2 typical events are presented, which have to-date never been reported to occur in the human cerebral cortex. Fig. 1 shows a recording (about 1 hour) obtained from a comatose patient, who was treated with mannitol. Before treatment ICP gradually increased and as a result CBF and NADH indicated some signs of ischemia. The mannitol treatment led to hypotension and to an improvement in the energy balance (increased CBF and oxidation of NADH). The extracellular K^+ level was apparently also affected by this treatment (decrease). The spontaneous spreading depression (SD) seen in the recording was part of a repetition of more than 40 cycles developed in this patient.

The responses to SD were very similar to those recorded in rats, including a transient metabolic deficiency as indicated by a decrease in CBF and an increase in NADH. The second unique recording was obtained a few hours before the declaration of brain death (after more than 60 hours of monitoring). A gradual increase in ICP was recorded while the CBF was stable or even showed a slight increase (Fig. 2). The ECoG was flat for at least 4–5 hours prior to the presented recording and the NADH trace included unstable signals at this stage (not shown). Due to the missing real time data on blood pressure in this patient, it is difficult to correlate the general hemodynamic and local CBF or other parameters measured from the brain. After reaching a very high ICP level

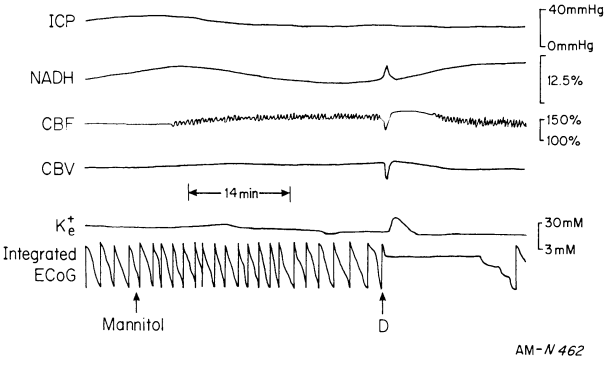

Fig. 1. Effects of IV infusion of mannitol on brain hemodynamic, metabolic and ionic activities in a head injured patient. *ICP* intracranial pressure; *R* 366 nm reflectance; *CBF*, *CBV* cerebral blood flow and volume; K_e^+ extracellular potassium; *D* spontaneous depolarization developed repeatedly every 30 minutes

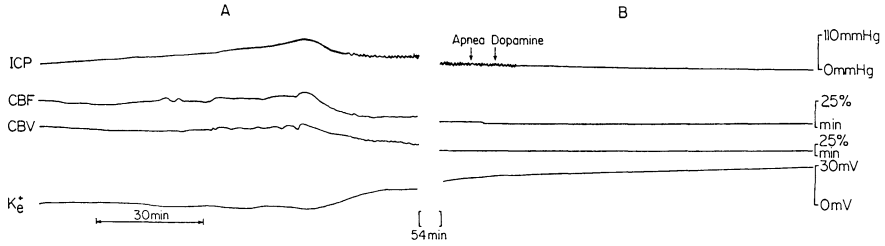

Fig. 2. Terminal depolarization recorded in a head injured patient several hours before determination of brain death was performed. Abbreviations as in Fig. 1

(about 100 mm Hg), a rapid decrease in CBF together with a large increase in extracellular K^+ was noted. One hour later dopamine and apnea tests were performed to diagnose the status of brain stem functions. Those tests together with the depolarization response suggested that a possible brain death event occurred. The final verification of this finding was performed 6 hours later.

Discussion

The introduction of multiparametric monitoring devices is a natural trend after long years of brain monitoring (in the head injured patients) with single or dual parameter instruments [8–11]. Indeed, few attempts have been made to increase the number of monitored parameters. Kirkpatrick *et al.* [3] have shown that the multimodality monitoring system used provided a useful tool for assessing the brain of comatose patients. In their approach, only hemodynamic parameters from the brain tissue were recorded (ICP, CBF). In our approach we combined a set of parameters representing hemodynamic, metabolic, ionic and electrical activities measured simultaneously in severely head injured patients.

Even in less severe neurological disorders such as stroke, the need for new monitoring techniques is still very significant. Wiebers *et al.* [12] made the following very lucid statement on the issue of human brain monitoring:

"Ultimately, however, the answers to many of our questions regarding the underlying pathophysiology and treatment of stroke do not lie with continued attempts to model the human situation perfectly in animals, but rather with development of techniques to enable the study of more basic metabolism, pathophysiology and anatomical imaging detail in living humans".

The results presented in this study suggest that it is feasible and practical to monitor the human brain under various pathophysiological conditions. The development and implementation of the surface probes organized in the multiprobe assembly (MPA) for animal studies [7] has made it relatively simple to modify the system and adapt it to clinical situations. Indeed, in a preliminary study (7) we showed a clear correlation between CBF and NADH redox state under partial ischemia induced in the human brain during neurosurgical procedures. The discovery of human spreading depression using the MPA (6) and the various responses to it suggest that basic mechanisms of brain pathophysiological processes may be similar in the animal and human brain. It is well documented that during the SD wave, which basically includes a propagation of depolarization through the entire hemisphere, a large increase in O_2 consumption occurs due to the stimulation of the ion pumps [7]. This increased demand for O_2 is compensated by a large increase in CBF.

When SD is induced under normal conditions, complete coupling occurs between the increase in O_2 consumption and the large increase in CBF. If the O_2 supply is limited (ischemia, hypoxia) the responses of the brain to SD will be different.

The combination of the NADH probe with the CBF probe used in the present study indicated that the reversed NADH response (an increase instead of a decrease) is due to the limitation in CBF compensation as indicated by the initial decreased CBF response (Fig. 1).

Acknowledgements

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Correspondence: A. Mayevsky, M.D., Department of Life Science, Bar-Ilan University, 52 900 Ramat-Gan, Israel.

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Continuous Intracranial Multimodality Monitoring Comparing Local Cerebral Blood Flow, Cerebral Perfusion Pressure, and Microvascular Resistance

J. I. Miller, M. W. Chou, A. Capocelli, P. Bolognese, J. Pan, and **T. H. Milhorat**

Department of Neurological Surgery, State University of New York, Health Science Center at Brooklyn, U.S.A.

Summary

Maintaining cerebral perfusion pressure (CPP) above 70 mm Hg is currently a mainstay of neurosurgical critical care. Shalmon, *et al.* recently showed poor correlation between CPP and regional cerebral blood flow (CBF) [1]. To study the relationship between CPP and CBF, at a microvascular level, we retrospectively analyzed multimodality digital data from 12 neurosurgical critical care patients in whom a combined intracranial pressure (ICP) – laser Doppler flowmetry (LDF) probe (Camino, San Diego) had been placed. Over the entire interval of continuous monitoring for all patients, 97% of local CBF data was at ischemic levels below a CPP of 70 mm Hg. For CPP above 70 mm Hg, local CBF data had considerable dispersion ranging from ischemic (71%), to normal (19%), and hyperemic (10%) levels. Elevated jugular bulb oxyhemoglobin saturation levels (SjO_2) complemented intervals of hyperemia. Autoregulation was impaired or absent in all monitored patients. We conclude that with disrupted autoregulation, CPP above 70 mm Hg does not necessarily insure adequate levels of cerebral perfusion. Restoration and maintenance of adequate cerebral perfusion should be performed under the guidance of direct CBF monitoring.

Keywords: Cerebral blood flow; microvascular resistance; multimodality monitoring.

Introduction

In the absence of direct cerebral blood flow (CBF) monitoring during critical care, cerebral perfusion pressure (CPP) has been used to assess the pressure gradient of blood across brain. The mainstay of therapy in the neurosurgical ICU is to maintain cerebral perfusion pressure (CPP) above a clinical ischemic threshold of 70 mm Hg. The recent availability of continuous CBF monitoring devices suitable for clinical settings enable us to investigate the hypothesis that CPP is an adequate indirect assessment of CBF.

Methods

An integrated parenchymal pressure and LDF probe (Camino Laboratories, San Diego, CA) was inserted at the bedside with rigid fixation through a conventional subarachnoid screw in 12 neurosurgical critical care patients for continuous monitoring of ICP and local CBF. The most affected side of cerebral injury was monitored on the basis of neuroimaging. Arbitrary units of local CBF were converted to absolute units (ml/100 g/min) using quantitative autoradiographic data from an animal model [2]. Multimodality monitoring included: systemic arterial pressure; central venous or pulmonary arterial pressure; cardiac output; SjO_2 on the most affected side of cerebral injury; pulse oximetry; end-tidal CO_2; and computed CPP and cerebrovascular resistance (CVR). Transcranial Doppler velocimetry (TCD), autoregulation, and CO_2 vasoreactivity were assessed daily [3]. A sampling frequency of 64 Hz was used for each parameter over 24 hour intervals of monitoring. Mean values of CPP and local CBF were computed for every minute in each patient over the entire interval of monitoring. This clinical protocol was approved for human subjects by the Institutional Review Board of the State University of new York Health Science Center at Brooklyn.

Results

A total of 12 patients with a mean age of 34 years (range 3 to 60 years) were monitored for an average of 5 days (range 2 to 10 days). Pathology included 8 patients with subarachnoid hemorrhage (SAH), Hunt & Hess grades II through V, and 4 with severe head injury, Glasgow Coma Scores 4 through 7. Six of the 12 patients had continuous SjO_2 monitoring, of which 4 had severe head injury and 2 had SAH. The patients with SAH had elevated SjO_2 (≥80%) coupled with increased TCD velocities and hyperemic levels of local CBF. Autoregulation was tested (n = 33) and found to be absent in all patients

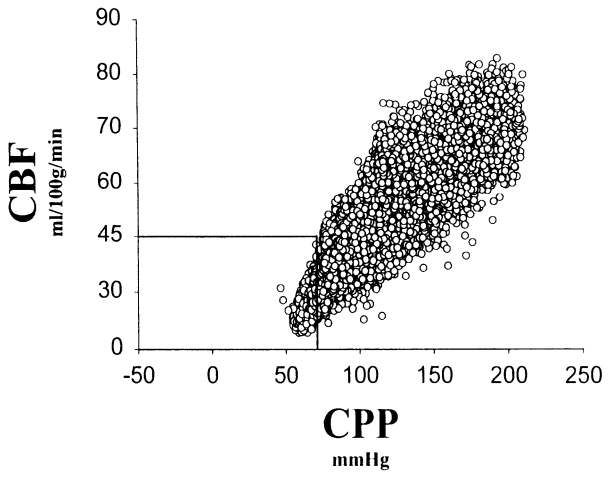

Fig. 1. Scatter-plot demonstrating a loss of autoregulation with close correlation between instantaneous signals of local CBF and CPP over 15 minutes (r = 0.87 and p < 0.001). Note that below a CPP of 70 mm Hg, there are ischemic levels of local CBF

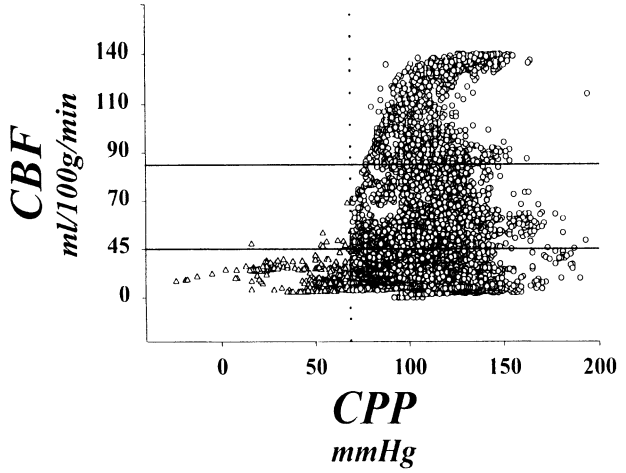

Fig. 2. Scatter-plot comparing CPP to local CBF for all patients over the entire interval of monitoring. Each data point is the mean of 1 minute of continuous monitoring per patient. The normal range is indicated from 45 to 80 ml/100 gm/min. Hyperemic values are above this range and ischemic values are below. Note the triangular data points (CPP < 70 mm Hg) and circular data points (CPP > 70 mm Hg)

(Fig. 1). Out of 34 evaluations, CO_2 vasoreactivity was present in 24 and lost in 10.

A scatter-plot compared mean CPP and local CBF (n = 28,798 points) on all patients over the entire interval of monitoring (Fig. 2). For CPP below 70 mm Hg, 97% of local CBF data points fell within the ischemic range. For CPP above 70 mm Hg, local CBF data had considerable dispersion ranging from ischemic (71%), to normal (19%), and hyperemic (10%) levels. A chi-square test (χ^2) performed on this data indicated that the distribution was not random ($\chi^2 = 1139.30$; $p < 0.001$; $\alpha = 0.05$). Poor correlation was noted between CPP and CBF: for CPP < 70 mm Hg, r = +0.149 and p < 0.01; for CPP ≥ 70 mm Hg, r = +0.299, p < 0.01; and for all CPP data, r = +0.337, p < 0.01.

Discussion

This small series was biased towards severe cerebral injury as demonstrated by the absence of autoregulation in all patients. Our results are similar to the findings of Shalmon *et al.* in that CPP has poor correlation with an assessment of CBF. For CPP < 70 mm Hg, local CBF was consistently ischemic, but correlation remained poor. For CPP > 70 mm Hg, all levels o local CBF were found, including hyperemia. Disparity between CPP and local CBF may be related to microvascular resistance which will affect flow rates, despite adequate CPP.

Increased SjO_2 in two SAH patients supports the presence of hyperemia. For patients with SAH or head injury, it is important to distinguish hyperemia from vasospasm in the presence of elevated TCD velocities [3–5]. With appropriate monitoring, hypertensive therapy can be avoided during periods of hyperemia.

In the presence of disrupted autoregulation, manipulation of CPP aimed at restoration and maintenance of adequate cerebral perfusion should be performed under the guidance of direct CBF monitoring.

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Correspondence: John I. Miller, M.D., FACS, Department of Neurological Surgery, State University of New York, Health Science Center at Brooklyn, B7-510, Box 1189, 450 Clarkson Avenue, Brooklyn, NY 11203, U.S.A.

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Significance of Multimodal Cerebral Monitoring under Moderate Therapeutic Hypothermia for Severe Head Injury

T. Nakamura, S. Nagao, N. Kawai, Y. Honma, and **H. Kuyama**

Department of Neurological Surgery, Kagawa Medical University, Kagawa, Japan

Summary

The therapeutic significance of moderate hypothermia and cerebral monitorings was assessed in the 10 patients with severe head injury. Cooling was begun as soon as possible after admission, using water blankets under general anesthesia. Jugular venous or tympanic temperature of patients was maintained at 32°C for 3 to 5 days, then rewarming at the rate of 1°C a day was started. The intracranial pressure was controllable less than 20 mm Hg under hypothermia. Moderate hypothermia reduced the jugular venous lactate (33.5%) as well as the cerebral blood flow velocity at M1 portion of middle cerebral artery (CBFV-M1) measured by transcranial Doppler (7.2%), while increase of the the jugular venous oxygen saturation (SjO_2) (17.9%) was observed in a majority of the patients. Our results demonstrated that moderate therapeutic hypothermia significantly reduced cerebral circulation and metabolism. Measurement of SjO_2 and CBFV-M1 seems to be useful for estimation of cerebral circulation and metabolism in therapeutic hypothermia.

Keywords: Cerebral blood flow velocity; jugular venous oxygen saturation; moderate hypothermia; severe head injury; SjO_2; transcranial Doppler.

Introduction

Moderate or hypothermia has been shown to decrease neuronal death in rodent after global forebrain ischemia [2,5], and furthermore to reduce neuronal loss after experimental traumatic brain injury [3,4]. Recently several clinical studies have demonstrated that moderate or mild hypothermia is effective for severe head injury [6,9]. The present study aims to define the relation of intracranial pressure (ICP), jugular venous oxygen saturation (SjO_2), cerebral blood flow velocity at M1 portion of middle cerebral artery (CBFV-M1), and other cerebral monitorings in patients with severe head injury during moderate therapeutic hypothermia.

Materials and Methods

Patients

Between February, 1995 and October, 1996, 10 patients who suffered severe head injury admitted to the Kagawa Medical University Hospital with subsequent Glasgow Coma Scale (GCS) of less than 8 or predicted brain swelling on admission were considered for this study. There were 2 female and 8 male with a mean age of 29.8 years (range of 4 to 67 years). Summary of patients is presented in Table 1.

Managements

All patients were initially managed with intubation and ventilatory support. Computerized tomography (CT) of the head was obtained as soon as possible. If necessary, surgical procedures were performed for hematomas and contusion. Eight of 10 patients underwent craniotomy, and one was a burr hole. Cooling was begun immediately, using water blankets under general anesthesia. Jugular venous or tympanic temperature was used for temperature measurements during this treatment. Temperature was maintained at 32°C for 3 to 5 days, and then rewarmed at the rate of 1°C a day. To prevent shivering during hypothermia, systemic neuromuscular paralytic medication was administered.

Monitorings

Epidural or subdural sensors were placed in 3 patients to use for continuous measurement of ICP. Mean arterial blood pressure (MAP) was measured through radial or femoral artery catheter. Cerebral perfusion pressure (CPP) was calculated by difference between MAP and ICP. To monitor jugular venous temperature, jugular venous lactate and SjO_2, fiberoptic catheter was inserted percutaneously into the internal jugular bulb in 8 patients. Nine patients were investigated with daily CBFV-M1 measured by transcranial Doppler.

Table 1. *Summary of the Patients*

Case no.	Age (yr)	Sex	GCS (on admission)	Operation	Outcome (GOS)
1	12	M	8	craniotomy	MD
2	67	M	5	craniotomy	SD
3	16	F	3		D
4	16	M	14	craniotomy	GR
5	17	M	7	craniotomy	GR
6	10	M	7	burr hole	GR
7	52	M	5	craniotomy	MD
8	57	F	5	craniotomy	VS
9	4	M	5	craniotomy	SD
10	47	M	5	craniotomy	GR

GCS Glasgow Coma Scale, *GOS* Glasgow Outcome Scale, *GR* good recovery, *MD* moderate disability, *SD* severe disability, *VS* vegitative state, *D* death, *M* male, *F* female.

Results

Intracranial Pressure and Cerebral Perfusion Pressure

The ICP was maintained below 20 mm Hg during this treatment in 3 patients. The CPP was reduced by cooling (17.2%) and contrary increased by rewarming (29.3%). Although the jugular venous temperature and the ICP showed a poor correlation ($r = 0.439$, $p < 0.01$), the jugular venous temperature and the CPP showed a good correlation ($r = 0.733$, $p < 0.01$).

Jugular Venous Oxygen Saturation, Jugular Venous Lactate and Cerebral Blood Flow Velocity

The mean SjO_2 was increased by cooling (24.1%) and decreased by rewarming (12.2%). On the other hand, the jugular venous lactate was decreased by cooling (33.5%) and increased by rewarming (33.5%). The mean value of CBFV-M1 was decreased by cooling (7.5%) and increased by rewarming (42.4%). The jugular venous temperature and SjO_2 showed a good correlation ($r = -0.849$, $p < 0.01$) as well as the jugular venous temperature and CBFV-M1 ($r = 0.898$, $p < 0.01$).

Cerebral Perfusion Pressure and Cerebral Blood Flow Velocity

Fig. 1 demonstrates the correlation of CPP and CBFV-M1 in 2 patients. The CPP and the CBFV-M1 showed a good correlation.

Patients Outcome

The outcome of the patients according to Glasgow Outcome Scale is shown in Table 1. Four out of 10 patients obtained good recovery (GR), 2 showed moderately disabled (MD), 2 patients survived severely disabled, 1 was vegetative state, and 1 died of

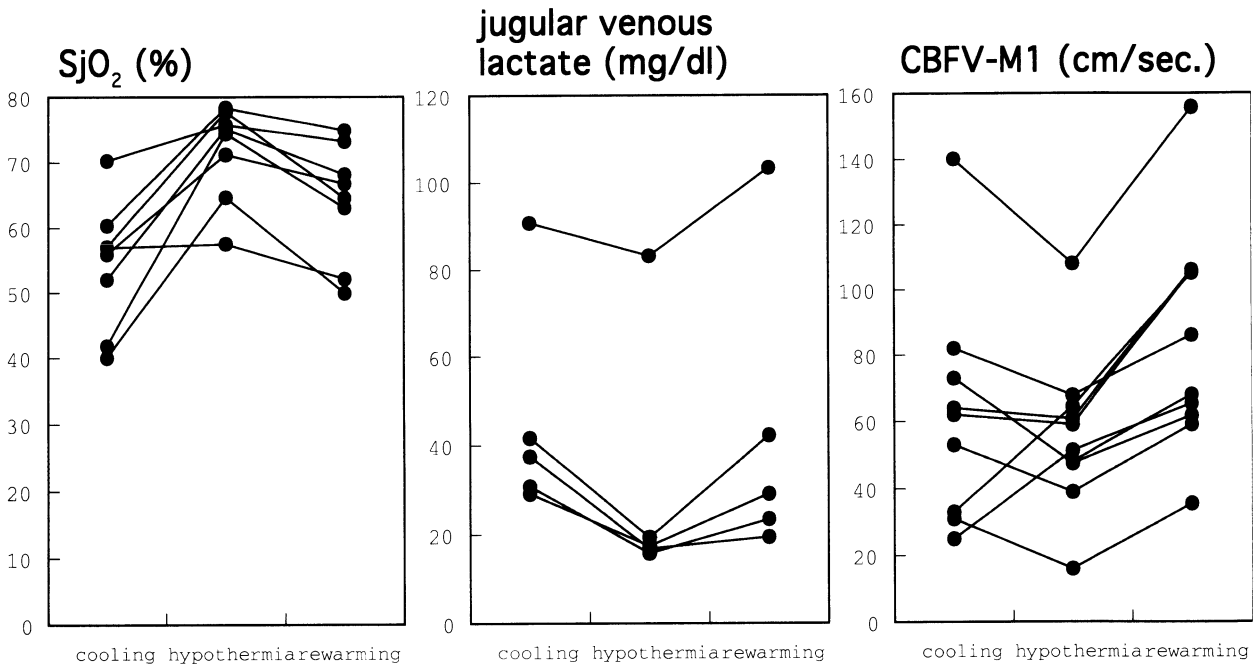

Fig. 1. Changes in cerebral blood flow velocity at M1 portion of middle cerebral artery (CBFV-M1) (left), jugular venous oxygen saturation (SjO_2) (middle) and jugular venous lactate (right)

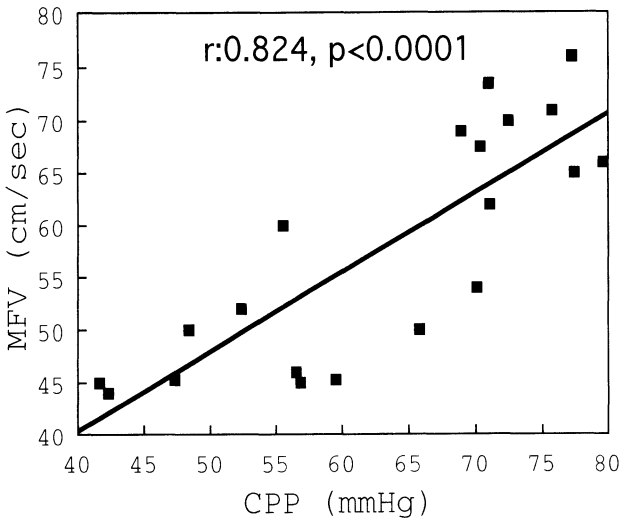

Fig. 2. Correlation of cerebral perfusion pressure (CPP) and cerebral blood flow velocity at M1 portion of middle cerebral artery (CBFV-M1). *r* correlation coefficient, *p* p-value

primary brain stem injury. Therefore, 6 patients were good outcome (GR, MD).

Discussion

In experimental studies, both CBF and cerebral metabolic rate for oxygen ($CMRO_2$) decreased 6.7% a 1°C reduction in body temperature of normal dogs (8). Hypothermia at 30°C was associated with a 50% reduction in $CMRO_2$ [7]. But, in clinical cases, systemic complications including cardiac and pulmonary abnormalities have been associated with conventional hypothermia (less than 30°C). Recently, clinical studies reported that moderate hypothermia (32°C) significantly reduced ICP (40%) [6] and CBF (26%), and Mild hypothermia (34°C) significantly reduced ICP (10.4mmHg) and increased CPP (14.0mmHg) [9].

In our study, undergoing moderate hypothermia, the measurement of CBFV-M1 and CPP showed a good correlation. Frequently, there was a disturbance of autoregulation on CBF after severe head injury. The changes in CBFV-M1, therefore, are similar to changes in CBF [1]. Thus measurement of CBFV-M1 is useful to know whether cerebral circulation or cerebral metabolism results in changes of SjO_2 predominantly. It was assumed that the decrease of CBFV-M1 during hypothermia stage might be caused by reduction of cerebral circulation and MAP. The increase of the SjO_2 and the decrease of the jugular venous lactate were most probably associated with marked reduction of cerebral metabolism.

It was shown in the present study that moderate therapeutic hypothermia significantly reduced cerebral circulation and metabolism. The measurement of SjO_2 and CBFV-M1 seems to be useful for estimation of cerebral circulation and metabolism in therapeutic hypothermia. These observations lead us to conclude that hypothermia had protective effects on cerebral metabolism in low CPP level and resulted in good outcome in severe head injury.

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Correspondence: Takehiro Nakamura, M.D., Department of Neurological Surgery, Kagawa Medical University, 1750-1 Ikenobe, Miki-cho Kita-gun, Kagawa 761-07, Japan.

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Brain-Stem Auditory Evoked Potential Monitoring in Experimental Diffuse Brain Injury

S. K. Rosahl, M. U. Schuhmann, S. Thomas, T. Brinker, and **M. Samii**

Department of Neurosurgery, Nordstadt Hospital, Hannover, Federal Republic of Germany

Summary

The time course of brain-stem auditory evoked potential (BAEP) changes was investigated using an impact-acceleration trauma model in 23 spontaneously breathing rats. Intracranial pressure (ICP), arterial blood pressure and respiratory rate were monitored. The experiments were terminated at four hours after trauma. No significant changes in intracranial pressure (ICP) occurred following the impact. After a short increase, blood pressure returned to baseline values within 5 min. Transient apnea was not followed by prolonged respiratory depression. Diffuse closed head injury (CHI) did not result in general, unidirectional changes of peak latencies or amplitudes of auditory evoked responses. Most BAEP changes developed slowly reaching a maximum at 1 to 4 hours after the injury. In the absence of ICP changes, this pattern reflects secondary ischemia in sensitive brain-stem areas rather than direct traumatic lesions or hypoxia due to respiratory depression.

Keywords: Brain-stem auditory evoked potentials; brain injury; rat; hypoxia; respiratory depression.

Introduction

The impact-acceleration model, introduced by Marmarou and colleagues [3,5] has contributed substantially to the understanding of the mechanisms of diffuse closed head injury. It has been demonstrated that secondary injury, such as hypoxia and hypotension may cause prolonged breakdown of the blood-brain barrier, deleterious edema and increase of ICP [1,4].

The major cause of death due to impact in non-ventilated animals has been attributed to respiratory depression. Mortality rate has been reported to increase from 10% to 50% with the same impact level when the animal was allowed to breathe spontaneously [5].

In severely injured rats with no artificial ventilation, transient respiratory depression following weight-drop impact was paralleled by a temporary brain-stem physiological dysfunction indicated by inconsistency of wave IV of the BAEP [12].

We assumed that secondary insult due to respiratory depression would also be reflected in changes of BAEP components. The study was conducted to investigate primary and secondary BAEP changes following experimental diffuse brain injury in spontaneously breathing rats.

Materials and Methods

Twenty-three adult Lewis rats, weighing between 320 and 400 g, were anesthetized using an initial intramuscular dose of 100 mg/kg ketamine and 10 mg/kg xylazine. Intravenous ketamine (40 mg/kg/h) maintained an adequate depth of anesthesia during the entire experimental period. Body temperature was monitored continuously and kept within normal range. Arterial blood pressure was recorded from a catheter in the femoral artery. After a midline scalp incision, the skin and periosteum were reflected. A plastic canula was inserted subfrontally through a 1 mm-burrhole into the subdural space and connected to a Statham pressure transducer. To prevent skull fractures, a round stainless steel disk was fixed to the dry skull using cyano acrylate.

Four subcutaneous needle electrodes were placed over the left and right posterior convexity of the skull (+), nose (–) and neck (ground). A dosage of 2 ml/kg Evans blue dye was injected immediately before trauma induction. The animal was positioned on a foam bed under a hollow plexiglass tube, and a metal weight of 500 g was dropped from a height of 1.5 m onto the center of the metal helmet. Overall mortality rate was 22%. Surviving animals were sacrificed for histological examination after 4 hours.

BAEP in response to 100 dB SPL condensation clicks (duration 100 μs) delivered monaurally through NICOLET TIP-10 tubal insert earphones were recorded immediately preceding and at 5 min, 1 h, 2 h, 3 h, and 4 h after trauma in surviving animals. A tube

length of 26cm resulted in an air conduction time of 75ms for the stimulus to arrive at the tympanon. This delay was subtracted from BAEP latencies off-line. Stimulus repetition rate was 10Hz. The non-stimulated ear was masked by 80dB (SPL) white noise. 1,024 sweeps of 10ms duration were averaged per run. Electrophysiological responses were differentially amplified with filters set at 20 to 10,000Hz, digitized and subjected to off-line statistical analysis using the SPSS+ statistical package.

Results

No skull fractures were detected following the trauma. Convulsions developed in 80% of cases. Transient apnea up to 20 seconds occurred in all 18 surviving animals. Mean respiratory rate was 109.8 ± 11.8bpm at 1 hour and 105.3 ± 19.4 at 4 hours following the injury and was not changed significantly in comparison to baseline values (113.0 ± 8.1bpm). Arterial blood pressure increased to a maximum of 200mmHg immediately after CHI. Following a short period of hypotension, systolic pressure returned to baseline values of 80–100mmHg within 5 min after trauma and remained constant for the rest of the experiment. ICP ranged between 5–7mmHg and did not show any significant changes throughout the recording period in all animals. No macroscopical supra- or infratentorial focal brain lesions were found in survivors. On histological examination small disseminated hemorrhages and neuronal damage was seen predominantly in the cerebral cortex bilaterally. No extravasation of Evans blue dye could be detected.

A marginal significant decrease of wave II amplitude (1.35μV to 0.98μV; t = 2.1, p = 0.04; Fig. 2) occurred at 5min after the impact and recovered completely at 1 hour. No other statistically significant changes of mean BAEP amplitudes or latencies ipsilateral to the side of acoustic stimulation occurred in the immediate post-traumatic period. Latency of wave II gradually increased reaching a maximum at 3 hours after trauma (0.73ms to 0.81ms; t = 4.0, p = 0.0001) with a tendency to return towards pre-trauma values. Amplitude of wave III also progressively increased up to a maximum at 3 hours after the impact (0.49 to 1.01; t = 2.6, p = 0.01) and declined afterwards.

Two components showed significant, slowly progressive changes with no tendency to recover within 4 hours after the injury. Amplitude of wave I gradually declined to 60% of pre-trauma values (t = 3.73, p = 0.001). Latency of wave V increased from 2.19ms before the trauma to 2.28ms at 4 hours after the impact (t = 2.64, p = 0.01).

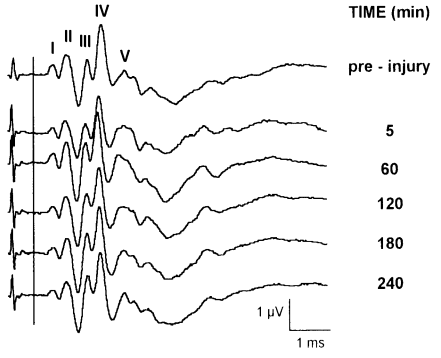

Fig. 1. Example of brain-stem auditory evoked potentials (BAEP) recorded immediately preceding and 5min, 60min, 120min, 180min and 240min following diffuse head injury. The vertical line indicates the time of arrival of the stimulus at the tympanon. Roman numerals denote reference-positive BAEP peaks

Discussion

In contrast to fluid-percussion injury the impact-acceleration model in spontaneously breathing rats does not produce a transient unidirectional increase in BAEP peak latencies or general depression of amplitudes [6,10,12]. This supports the notion of Marmarou et al. (1994) that the weight-drop impact results in disseminated brain damage without massive hypertensive surge or excessive brain-stem damage. It also confirms the data of van den Brink *et al.* (1993) demonstrating generally intact BAEP following diffuse head injury utilizing the same model. Convulsions, transient disinhibition of somatosensory evoked potentials as observed in an earlier investigation of our group [11], cortical paroxysmal EEG discharges and histological pattern all indicate a cortical predominance of primary lesions [3,5].

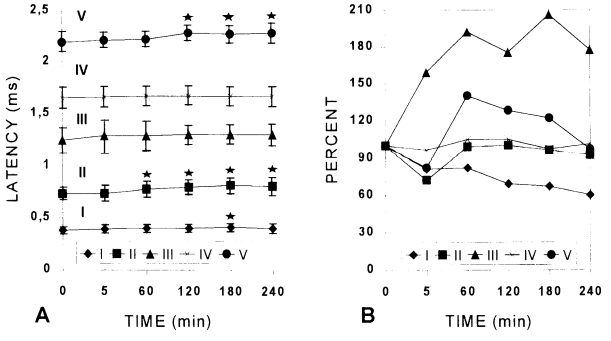

Fig. 2. Time course of peak latencies (A, mean ± standard deviation) and percent changes in amplitude (B) of brain-stem auditory evoked potentials (BAEP) following diffuse head injury

The significant loss of wave II amplitude immediately following injury may be attributed to a direct mechanical stretching of the eighth nerve at its entry zone into the cochlear nucleus [2,9]. All other BAEP changes developed more slowly, gradually reaching a maximum at 1 to 4 hours after the primary injury. The time course of the underlying pathophysiological mechanism should parallel these changes. In the absence of both prolonged respiratory distress and ICP changes, this mechanism may well be consistent with a temporary reduction in cerebral blood flow that has been reported by Piper *et al.* (1995) using the same model. This hypothesis is further supported by reductions in cerebral blood volume [4] and increase of the pressure-volume-index [8] following impact acceleration trauma. It is concluded that the impact-acceleration model does not primarily produce brain-stem injury. However, physiological brain-stem function may be secondarily affected by processes involving longer time constants.

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Correspondence: Steffen K. Rosahl, M.D., Department of Neurosurgery, Nordstadt Hospital, Haltenhoffstr. 41, D-30165 Hannover, Federal Republic of Germany.

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Complications and Safety Associated with ICP Monitoring: A Study of 542 Patients

S. Rossi[1], **F. Buzzi**[2], **A. Paparella**[2], **P. Mainini**[3], and **N. Stocchetti**[1]

[1]Neuro Intensive Care Unit, Ospedale Maggiore Policlinico IRCCS, Milano, [2]Department Anesthesia and ICU, and [3]Division of Neurosurgery, Parma Hospital, Parma, Italy

Summary

In our institution ICP was monitored in patients with GCS ≤ 8 and abnormal CT scan: 362 severely head injured and 180 subarachnoid hemorrhage. Mean duration of monitoring was 103.6 hours (SD 74.96). Among 542 patients, 440 showed at least one episode of ICP above the threshold of 20 mm Hg. Among 362 head injured patients only 71 (19.3%) had an ICP lower than 20 mm Hg. In the remaining 289 (81.7%) at least one episode ≥20 mm Hg was measured. In 13 cases (2.2%) a ventricular infection has been diagnosed. In 1 case an intraparenchimal hemorrhage related to the presence of the catheter was detected.

Elevated risk of HICP and low incidence of complications have been shown in this series.

Keywords: Complications; ICP monitoring; safety.

Introduction

Intracranial hypertension (HICP) has been recognized as one of the most important factors affecting mortality and morbidity in head injury and in other neurosurgical pathologies [7,8,19]. Nevertheless recent reports suggest that only in 30% of American Neuro-ICU, ICP monitoring is currently performed in head injured patients [1].

In Parma Hospital ICP monitoring has been extensively adopted in the last decade, both in the management of head injured patients and in the postoperative surveillance of patients suffering from subarachnoid hemorrhage (SAH) admitted with an Hunt and Hess grade of 4 and 5 [3]. We reviewed our experience in ICP monitoring in order to assess the rate of HICP and to quantify potential complications.

Methods

The analysis involved 542 patients admitted to the Intensive Care of Parma Hospital between 1988 and 1993. Indications for ICP monitoring were: 1) Head injury with GCS ≤ 8 and a CT scan showing masses and/or signs of increased intracranial content (compressed or absent perimesencephalic cisterns); 2) Management of patients with subarachnoid hemorrhage at risk of developing HICP. The placement of a ventricular catheter was considered the first choice. Subdural catheters were used when ventricles were not detectable on the CT scan or when the surgeon failed to place a ventriculostomy. The catheters were placed in the operating room under sterile condition, tunneled for few centimeters under the scalp, secured on the skin and covered with a sterile dressing. No antibiotic was prophylactically used.

In selected patients, mainly head injured, when ventriculostomy was present, twice a day after sterile preparation, pressure-volume tests were performed as described elsewhere. ICP values equal or greater than 20 mm Hg and lasting more than 5 minutes were considered pathological. The worst value of ICP detected during the whole period of monitoring was choosen to classify each patient. A grading was then performed by subdividing ICP raises: ICP < 20 mm Hg, ICP between 20 and 30 mm Hg, between 31 and 40 mm Hg, and greater than 40 mm Hg respectively.

Infections and hemorrhages related to the catheter insertion were recorded in a separate form. Meningeal infection was diagnosed according to criteria described elsewhere [5]. CSF samples were collected from catheters immediately before their removal at the end of monitoring or in case the duration of monitoring exceeded 72 hours, on the fourth day, then every two days. In patients with subdural catheters, a lumbar puncture was performed in case a meningeal infection was suspected.

Outcome at six month was assessed by phone interview and was classified by using a simplified version of the Glasgow Outcome Scale as follows: good recovery and moderate disability (GR-MD), severe disability and persistent vegetative state (SD-VS), death.

Results

ICP monitoring was performed in 362 severely head injured patients and in 180 subarachnoid hemorrhage patients. Head injured patients were classified according to the main lesion detected on the CT scan as follows: epidural hematoma 62 (17.1%), subdural

Table 1. *The Number of Patients (SAH and Head Injured), the Mean Age and Ranges, Percentage of Male and Mean GCS on Admission are Represented. Besides the rates of patients in whom the ICP monitoring started less than six hours after insult in head injury and after admission in SAH, and lasted more than seven days are shown*

	Number	Mean age (ranges)	Male	Mean GCS adm	% ICP started <6 hours from insult	% ICP monitoring >7 days
Brain injury	362	35.6 (2–83)	76.8%	5	65%	15%
SAH	180	51.4 (17–76)	54%	7	74%	23%

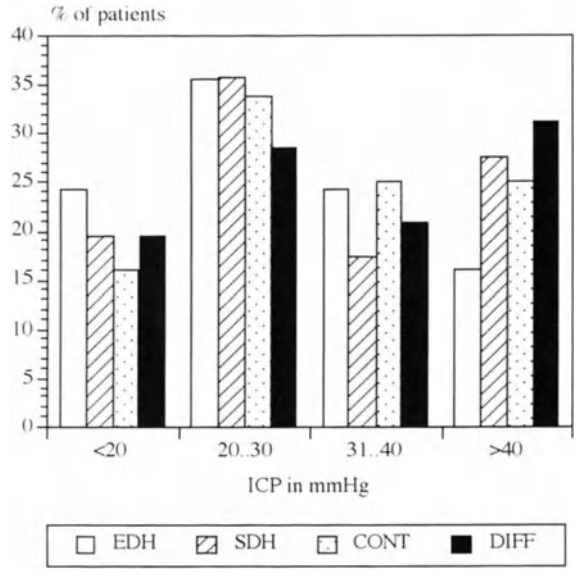

Fig. 1. Rates of HICP in the different classes of head injury are represented. EDH stands for epidural hematoma, SDH for subdural hematoma, CONT for cerebral contusions and DIFF for diffuse damge. The differences are not significant

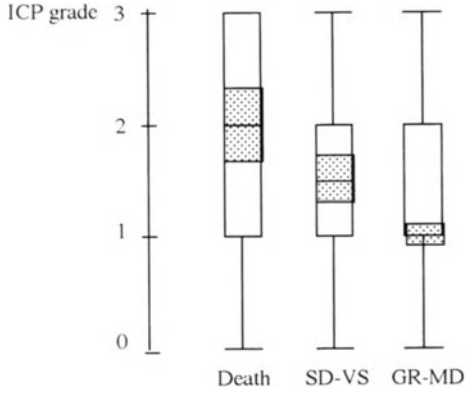

Fig. 2. Relationships between HICP and outcome are shown. HICP is subdivided in 4 grades: 0 (ICP < 20 mm Hg), 1 (ICP between 20 and 30 mm Hg), 2 (ICP between 31 and 40 mm Hg), and 3 (ICP > 40 mm Hg). Median, confidence intervals, middle half of the data between 25th and 75th percentiles, and ranges are summarized in the boxplot. ($p < 0.001$)

hematoma 109 (30.1%), cerebral contusions 124 (33.5%), diffuse damage 67 (18.5%). 248 catheters (43%) were placed into the subdural space, 330 (57%) into the ventricles.

Main data regarding patients' characteristics and timing of catheters insertion and removal are reported in Table 1.

ICP monitoring started 10.64 (sd = 25.56, range 0–288) hours after the insult; mean duration of monitoring was 103.668 (sd = 74.96, range 1–672) hours.

Pressure-volume tests and intracranial dynamics were performed in 127 head injured patients through a ventricular catheter following the procedure described in the previous section.

Head Injured Patients

Among 362 head injured patients only 71 (19.3%) had an ICP lower than 20 mm Hg. In the remaining 289 (81.7%) at least one episode ≥20 mm Hg was measured at some point during the monitoring. Of them 91 patients (25.4%) had an ICP greater than 40 mm Hg. Figure 1 summarizes the rate of HICP in different classes of head injured patients classified based upon the main lesion detected on CT scan.

Outcome at six months could be assessed in 375 head injured patients. Figure 2 shows the relationships between HICP grade and outcome.

Subarachnoid Hemorrhage

Among 180 SAH patients, 47 (26.1%) did not develop HICP, 41 (22.7%) had an ICP between 20 and 30 mm Hg, 42 (23.3%) between 31 and 40, while 50 patients (27.77%) had an ICP greater than 40 mm Hg.

Complications

In 13 cases (2.24%) a ventricular infection has been diagnosed. In 1 case an intraparenchimal hemorrhage

related to the presence of the catheter was detected. There were no deaths related to complications.

Discussion

Despite the variety of underlying lesions, a high incidence of intracranial hypertension was found in our group study.

In SAH, values greater than 30mmHg were detected in more than 50% of the patients. The cause of the high incidence of HICP in this subset of patients is probably due to the fact that only the most severe cases (Hunt and Hess 4 and 5 grade), were admitted to ICU.

In head injured patients the rate of intracranial hypertension was even more elevated: 81% of them showed ICP ≥ 20mmHg. This rate is higher than reported elsewhere [4,6,11]. This high percentage may reflect the criteria followed for identifying patients eligible for ICP monitoring. Our criteria were, in fact, stricter than the Narayan's criteria. On the other hand, we considered as pathological rise of ICP, values greater than 20mmHg lasting at least 5 minutes. This way the incidental occurrence of HICP has been excluded, and the rate discovered underlines a real intracranial disturbance. That probably plays a role in determining the final results as shown by the relationship between the degree of HICP and the occurrence of bad outcome.

The number of infections diagnosed in the group was lower than the rate of infections described in the literature [2,5,11,12]. A scrupulous policy was adopted in order to prevent CNS infections due to the presence of ICP catheter. The duration of monitoring exceeded 7 days only in 15% of head injury and 23% of SAH, besides no antibiotics were used prophylactically. Moreover, all the catheters were placed in the O.R. instead of in the intensive care unit. Clearly this procedure is time and resources consuming, however the benefit in terms of low rate of infections is probably greater than the costs incurred with O.R. placement of the catheters. In conclusion: due to the high incidence of HICP and the strong impact of the latter on outcome, we believe that comatose patients with positive CT scan are those who can greatly benefit from this monitoring. Even with frequent manipulations of the system for drainage and measurement of pressure volume index (PVI), the rate of complications is low.

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Correspondence: Dr. Sandra Rossi, Terapia Intensiva Neurochirurgica, Pad. Beretta Neuro, Ospedale Maggiore Policlinico IRCCS, Via F. Sforza, 35,1-20122 Milano, Italy.

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Morphological and Hemodynamic Evaluations by Means of Transcranial Power Doppler Imaging in Patients with Severe Head Injury

T. Shiogai, K. Nagayama, G. Damrinjap, K. Saruta, M. Hara, and **I. Saito**

Department of Neurosurgery, Kyorin University School of Medicine, Tokyo, Japan

Summary

The following conditions of 17 patients with severe head injury (ages 9–76; mean 37: 12 focal and 5 diffuse injuries) were evaluated during acute phase (1–14 days after injury, mean 5) by transcranial power Doppler imaging (PDI), a new color Doppler ultrasound technique: a) morphological changes via temporal window, b) hemodynamic changes in major intracranial/cervical arteries based on measured angle-corrected time-averaged mean (TAM)/peak velocities and vessel diameter (Va), and calculated pulsatility indices (PI), vessel area (Va), and flow volume (Vf = TAM × Va). a) 1) Major trunks of intracranial vessels and circle of Willis and pathological changes in frontal/temporal lobes and midbrain were finely visualized. 2) Contusional hemorrhage and cerebral contusion demonstrated irregular hyper- and hypo-echoic lesions, respectively. 3) Delayed epidural hematoma showed a hyper-echoic band. b) 1) Decreased velocities, significant PI increase, and Va increase tendency were observed in intracranial arteries. 2) Increased velocities with Vf increase but no Va decrease indicated hyperemia rather than vasospasm. 3) Va in the intracranial vessels, however, tended to increase PDI appears useful in evaluating real-time and simultaneous morphological and hemodynamic information in pathogenesis and neurointensive care of patients with severe head injury.

Keywords: Severe head injury; sonography; transcranial power Doppler.

Introduction

No method which can simultaneously evaluate hemodynamic and morphological changes and repeat non-invasively at bedside has been introduced for neurointensive care of patients with severe head injury Doppler color flow imaging (CFI) or color-coded realtime sonography (2) or color-coded duplex sonography [17] has been used transcranially to visualize changes in intracranial brain parenchyma and major vessels in the basal brain. In addition, evaluation of blood flow volume (Vf) through measurement of vessel diameter (Vd) and flow velocity of the extracranial vessels using CFI also has been made [15,16].

There have been no reports elsewhere of such study involving measurement of Vf in the intracranial arteries In this respect, our previous study utilizing CFI pointed out problems derived from reliability of Vd measurement and calculated vessel area (Va) due to poor visualization of vessel contour [18]. To overcome this, we have introduced power Doppler imaging (PDI) because it is supperior to CFI with respect to visualization of intracranial vessels [7,19].

The objective of this study was to clarify the significance of transcranial PDI in morphological and hemodynamic evaluations of patients with severe head injury on the basis of Vd measurement and Vf estimation.

Subjects and Method

The subjects were 17 comatose patients (ages, 9–76; mean, 37) with severe head injury (12 focal and 5 diffuse injuries) and 11 normal controls (ages 21–61; mean, 34). Table 1 lists age and sex of patients, diagnosis, days after injury up to PDI, Glasgow coma scale scores (GCS), and results of simultaneously measured jugular bulb oxygen saturation (SjO_2), end-tidal CO_2 partial pressure ($PetCO_2$), Intracranial pressure (ICP), cerebral perfusion pressure (CPP), jugular bulb venous blood temperature (Tjb), treatments, and Glasgow outcome scale at one month after injury.

PDI (Ultramark 9 HDI, ATL) was performed using a 2–3 MHz phased-array probe for intracranial arteries and cervical internal carotid artery (ICA) and a 5–10 MHz linear-array probe for com-

Table 1. *Demographics of 17 Patients with Severe Head Injury**

Case	Age	Sex	Diagnosis	Days after injury	GCS	SjO_2	$PetCO_2$	ICP	CPP	Tjb	Treatment	GOS
AK	76	F	ASDH (L)/CC	7	5	59	36			37.4	HT/DC (L)	VS
BK	17	M	DBI/TSAH	2	5	71	23	10	110	35.6	HT	SD
DT	54	M	AEDH (R)/CC (RT)	4	5	54	27			37.9	DC (R)	MD
FM	39	M	CH (LF)	14	9						HLS/DC (L)	MD
HM	29	F	DBI	3	8							GR
KS	25	M	DBI	1	5	85	35	20	71	37.1	HT	MD
KA	22	M	AEDH (L)	2	4	65	23			33.9	BT/HT/DC (L)	SD
KM	55	M	ASDH (R)/CH	3	3	64		13	105	34.1	HT/DC (R)	MD
KY	76	F	ASDH (R)	2	3						DC (R)	BD
MS	29	M	CC (LFT)	5	5	78		16	101	36.1	HLS/HT/DC (L)	D
				8	3	87	17	23	110	35.7	HLS/HT/DC (L)	D
OY	17	M	ASDH (R)/CC/TSAH	5	3	60		22	44	34.2	BT/HT/DC (R)	GR
				12	8						BT/HT/DC (R)	GR
SM	22	F	DBI	5	4	63	30	10	60	35.9	HT	GR
SA	9	M	DBI	5	9						HT	GR
SH	9	F	ASDH (L)	5	6	82	39	11	97	35.4	HT/DC (L)	GR
UY	69	F	AEDH (L)/CC (LT)	1	9						DC (L)	MD
WM	44	F	ASDH (R)	1	3	80	16	49	46	33.3	HT/DC (R)	D
YA	39	M	ASDH (L)	4	6	60	22	8	90	37.9	HT/DC (L)	MD
Mean	37			5	5	70	27	18	83	35.7		
SD	21			3	2	11	8	11	25	1.48		

* *ASDH* acute subdural hematoma, *CC* cerebral contusion, *DBI* diffuse brain injury, *TSAH* traumatic subdural hematoma, *AEDH* acute epidural hematoma, *CH* contusional hemorrhage, *L* left, *R* right, *T* temporal lobe, *F* frontal lobe; *M* Male, *F* female; *GCS* Glasgow coma score, SjO_2 jugular bulb oxygen saturation (%), $PetCO_2$ end-tidal CO_2 partial pressure (mmHg), *ICP* intracranial pressure (mmHg), *CPP* cerebral perfusion pressure (mmHg), *Tjb* jugular bulb venous temperature (°C), *GOS* Glasgow outcome scale; *HT* hypothermia, *DC* decompressive craniotomy, *BT* barbiturate therapy, *HLS* hypertonic lactate saline.

mon carotid artery (CCA). PDI was evaluated in terms of a) morphological changes via the temporal window, and b) hemodynamic changes via the temporal window in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA); via the foramen magnum window in the vertebral artery (VA) and basilar artery, and using the cervical approach in the ICA and CCA. Hemodynamic evaluations were comparing the results of patients with those of controls on the basis of measured angle-corrected time-averaged mean velocity (TAM) and time-averaged peak velocity (TAP) on the Doppler spectrogram, Vd on the PDI, and calculated pulsatility index (PI), resistance index (RI), Va, and flow volume (Vf = TAM × Va). Such utilized parameters as wall filter (WF), pulse repetition frequency (PRF), and color gain (CG) also were evaluated.

Results

1. Morphological Evaluations

Major trunks of intracranial vessels, including the MCA, ACA, PCA, and circle of Willis, and cerebral parenchyma such as the frontal and temporal lobes and midbrain were finely visualized via the temporal window, especially in cases of craniotomy. Contusional hemorrhage in the frontal lobe with shifted midline structures was clearly identified as an irregular hyper-echoic lesion with shifted anterior cerebral arteries (Fig. 1). Cerebral contusion demonstrated hypo-echoic lesions Delayed epidural hematoma could be identified as a hyper-echoic band (Fig. 2).

2. Hemodynamic Evaluations

a. Analysis of normal controls (Table 2)

Via the temporal window, both MCA were detectable in all but one case. Contrarily, only 12 ACAs were detectable in 9 cases and only 8 PCAs in 6 cases. Furthermore, vessel imaging was not sufficiently clear for measuring Vd of one MCA and PCA each. In imaging via the foramen magnum window, vessel contours were detectable in all cases of VA, with the exception of a unilateral side alone in 2 cases, and of the basilar artery in 5 cases. Measured TAM, TAP, and Vd, calculated PI, RI, Va and Vf, and utilized WF, PRF, and CG are summarized in Table 2.

b. Analysis of patients with severe head injury (Table 3)

Concerning measured TAM and TAP in the extracranial arteries, CCA tended to increase; however, ICA and VA tended to decrease. With respect to TAM and TAP in the intracranial arteries, there

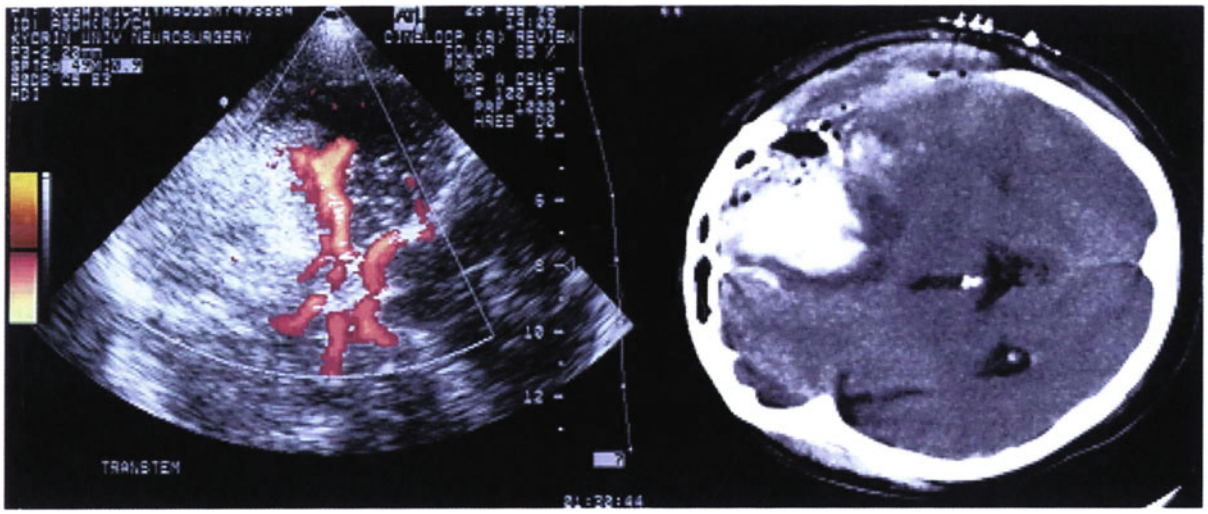

Fig. 1. Fifty five-year-old patient with right acute subdural hematoma is postoperatively examined three days after injury. Hyper-echoic lesion in right frontal lobe shown by PDI (left) corresponds with CT scan (right). PDI visualizes shifted anterior cerebral arteries

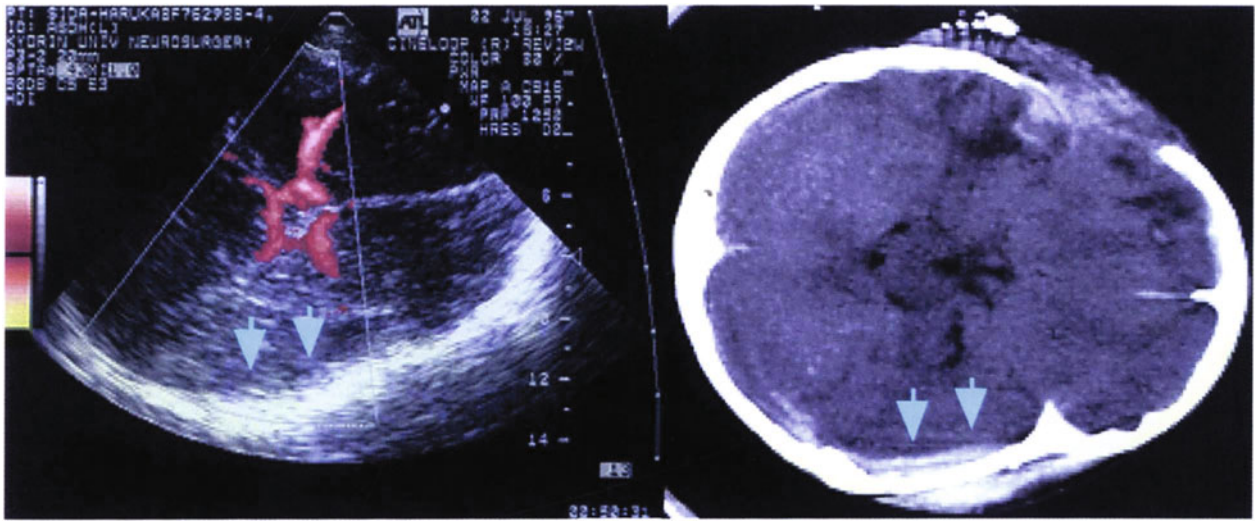

Fig. 2. Five days after decompressive craniotomy for left acute subdural hematoma of 9-year-old girl, delayed epidural hematoma in the contralateral side indicated by green arrows is visualized as a hyper-echoic band in PDI, corresponding with CT

were tendencies to decrease in the PCA and to increase in the MCA, despite their remaining unchanged in the BA and ACA.

In comparison with controls, Va increased in all vessels The increases were particularly significant in the intracranial MCA and PCA. Consequently, derived Vf of the CCA significantly increased primarily due to the increase in flow velocities. Contrarily, derived Vf increases in the intracranial MCA, ACA, and PCA mainly were due to increase in Va. Vf increase was not apparent, however, in the ICA and VA CG for VA utilized low, but WF and PRF showed no significant differences.

Discussion

1. Morphological Evaluation Using Transcranial CFI and PDI

Transcranial CFI or color-coded real-time sonography has been used to visualize pathological changes in the intracranial parenchyma of adult and the major trunks of intracranial vessels in the basal brain [2]. Its usefulness in identification of pathological change in cerebral parenchyma, especially visualization of cerebral hematoma, has been reported in conjunction with not only cerebrovascular lesions but also head injuries [17]. The image quality of

Table 2. *Control Values in 11 Normal Control Subjects**

	CCA	ICA	MCA	ACA	VA	BA	PCA
n	19	22	32	12	20	5	8
TAM (cm/s)	20 ± 5	34 ± 7	60 ± 15	56 ± 28	32 ± 10	37 ± 8	44 ± 14
n	19	22	32	12	20	5	8
TAP (cm/s)	34 ± 5	58 ± 16	90 ± 18	88 ± 46	48 ± 15	59 ± 15	66 ± 16
n	19	22	32	11	18	5	7
Vessel diameter (cm)	0.60 ± 0.23	0.48 ± 0.25	0.39 ± 0.25	0.42 ± 0.28	0.42 ± 0.28	0.42 ± 0.34	0.32 ± 0.20
n	19	22	32	11	18	5	7
Vessel area (cm2)	0.28 ± 0.04	0.18 ± 0.05	0.12 ± 0.05	0.14 ± 0.06	0.14 ± 0.06	0.14 ± 0.09	0.08 ± 0.03
n	19	22	32	11	18	5	7
Flow volume (ml/min)	325 ± 103	369 ± 162	434 ± 212	429 ± 193	273 ± 171	344 ± 307	170 ± 57
n	19	22	32	12	20	5	7
PI	1.47 ± 0.31	0.8 ± 0.22	0.71 ± 0.14	0.77 ± 0.10	0.71 ± 0.15	0.71 ± 0.1	0.67 ± 0.17
n	19	22	32	12	20	5	7
RI	0.70 ± 0.05	0.51 ± 0.07	0.49 ± 0.06	0.53 ± 0.04	0.50 ± 0.06	0.51 ± 0.06	0.56 ± 0.08
n	12	22	32	12	20	5	8
Wall filter (Hz)	200	100	100	100	100	100	100
n	12	22	32	12	20	5	8
PRF (Hz)	3500	450	450	450	450	450	450
n	12	22	32	12	20	5	8
Color gain (%)	70 ± 10	69 ± 8	85	85	85 ± 1	85	85

* *n* number of vessels, *CCA* common carotid artery, *ICA* cervical internal carotid artery, *MCA* middle cerebral aretry, *ACA* anterior cerebral artery, *VA* vertebral artery, *BA* basilar artery, *PCA* posterior cerbral aretry, *TAM* time-averaged mean velocity, *TAP* time-averaged peak velocity, *PI* pulsatility index, *RI* resistance index, *PRF* pulse repetition frequency.

brain parenchyma utilizing the CFI B-mode is not, however, necessarily better than that of CT. This is because CFI aims at transcranial visualization and employs ultrasound frequencies as low as 2 to 3 MHz. It is considered to improve the quality of image resolution utilizing a slightly higher frequency probe, in cases of bone flap removal or burr holes operation [1].

In visualizing the intracranial vessel contours, conventional CFI could not demonstrate high resolution images [2]. Whereas the CFI viscualizes Doppler mean frequency, the recently developed PDI delineates the integrated Doppler power itself and features angle independence, no aliasing, and a low signal-to-noise ratio resulting in a wide dynamic range [13]. In fact, its superiority in the visualization of intracranial vessels [7,19] has been reported. Consequently, PDI was adopted in this series.

2. *Measurement of Blood Flow Volume*

Ultrasonographic measurement of Vf in the cerebral vessels has been introduced in clinical settings, mainly in the CCA [10]. Lately, using CFI, attempts have been made to measure Vf experimentally in the peripheral small artery [20] and clinically in the cervical ICA and VA [15,16], and the reproducibility of the obtained data was confirmed [16].

There have been no reports elsewhere of such study involving measurement of Vf in the intracranial arteries. Our pervious report of study utilizing CFI pointed out problems arising from reliability of Vd measurement and calculated Va due to poor visualization of vessel contour [18]. Under these circumstances, we employed PDI which features high resolution of vessel contour for this study.

With respect to intracranial vessels of normal subjects, MCA and ACA Vd in our series were 0.39 ± 0.25 cm and 0.42 ± 0.28 cm, respectively. Direct postmortem measurements of intraluminal Vd in MCA and ACA were 0.21 ± 0.038 (or 0.21 ± 0.041) cm and 0.161 ± 0.037 (or 0.163 ± 0.039) cm, respectively [11]. Taking postmortem vessel shrinkage into consideration might result in underestimation of Vd in cadaver studies [11], whereas our PDI measurements of intracranial Vd probably are overestimations. Furthermore, measurements may be unreproducible due to overlapping of vessels, especially in A1 and A2 portions of the ACAs and anterior communicating artery.

In the extracranial arteries, Vd in the cervical ICA and VA measured by CFI using a 7 MHz linear-array probe demonstrated 0.48 ± 0.07 cm and 0.34 ± 0.06 cm, respectively [15]. Our PDI data using a 2–3 MHz phased-array probe result of 0.48 ± 0.25 cm in the ICA was almost the same, while the result of

Table 3. *Values of 17 Patients with Severe Head injury**

		TAM(L)	TMA(R)	TAP(L)	TAP(R)	Va(L)	Va(R)	Vf(L)	Vf(R)	PI(L)	PI(R)	RI(L)	RI(R)	WF(L)	WF(R)	PRF(L)	PRF(R)	CG(L)	CG(R)
CCA	n	14	13	14	13	14	13	14	13	14	13	14	13	14	13	14	13	14	13
	mean	25.61	22.45	46.95	41.27	0.30	0.31	460	421	1.59	1.62	0.74	0.73	126	138	1350	1369	69	70
	SD	9.40	5.45	21.16	16.86	0.03	0.06	170	137	0.52	0.45	0.12	0.07	48	49	893	924	12	11
	p value	<0.05	ns	<0.01	ns	ns	ns	<0.01	<0.05	ns	ns	ns	ns	nc	nc	nc	nc	ns	ns
ICA	n	16	15	16	15	16	15	16	15	16	15	16	15	16	14	16	14	16	14
	mean	27.3	27.6	50.5	47.9	0.25	0.22	458	367	1.08	1.08	0.61	0.60	125	121	994	993	72	69
	SD	11.4	14.2	21.6	23.7	0.11	0.09	364	240	0.40	0.58	0.11	0.13	43	41	155	166	9	9
	p value	<0.05	ns	ns	ns	<0.01	ns	ns	ns	<0.01	<0.05	<0.01	<0.05	nc	nc	nc	nc	ns	ns
VA	n	15	15	15	15	14	15	14	15	15	15	15	15	15	15	15	15	15	15
	mean	23.35	28.18	47.48	46.35	0.22	0.16	278	243	1.03	0.95	0.59	0.58	127	127	993	993	80	80
	SD	6.91	14.64	25.30	29.55	0.14	0.06	132	108	0.51	0.18	0.11	0.07	44	44	160	160	5	5
	p value	<0.01	ns	ns	ns	<0.05	ns	ns	ns	<0.01	<0.01	<0.01	<0.01	nc	nc	nc	nc	<0.01	<0.01
MCA	n	16	17	16	17	16	17	16	17	16	17	16	17	16	18	16	18	16	17
	mean	59.4	57.2	95.6	96.5	0.23	0.23	807	713	0.90	0.97	0.58	0.57	113	117	1085	894	82	82
	SD	31.9	29.1	45.2	40.2	0.11	0.14	561	563	0.22	0.47	0.08	0.09	33	37	739	301	2	2
	p value	ns	ns	ns	ns	<0.01	<0.01	<0.05	ns	<0.01	<0.05	<0.01	<0.01	nc	nc	nc	nc	nc	nc
ACA	n	14	14	14	14	14	13	14	13	14	14	14	14	14	14	14	14	14	14
	mean	52.0	54.8	85.9	85.2	0.21	0.21	598	673	0.91	1.01	0.58	0.64	114	107	982	1271	83	83
	SD	25.0	32.5	29.5	43.1	0.12	0.11	353	354	0.27	0.38	0.12	0.21	35	26	257	1416	2	3
	p value	ns	ns	ns	ns	ns	ns	<0.05	ns	ns	<0.05	ns	ns	nc	nc	nc	nc	nc	nc
PCA	n	12	15	12	15	12	14	12	14	12	15	12	15	12	15	12	15	15	15
	mean	31.2	31.3	59.9	58.8	0.20	0.23	403	463	0.88	1.20	0.56	0.60	108	120	979	953	993	81
	SD	10.0	17.5	17.8	26.7	0.13	0.10	394	421	0.24	1.05	0.09	0.14	28	40	277	284	160	3
	p value	<0.05	ns	ns	ns	<0.05	<0.01	ns	ns	ns	<0.05	ns	ns	nc	nc	nc	nc	nc	nc
BA	n	6		6		6		6		6		6		6		6		6	
	mean	40.33		63.40		0.22		696		0.91		0.58		133		983		82	
	SD	22.58		37.09		0.17		860		0.15		0.04		47		253		4	
	p value	ns		ns		ns		ns		<0.05		<0.05		nc		nc		nc	

* *TAM* time-averaged mean velocity, *TAP* time-averaged peak velocity, *Va* vessel area, *Vf* volume flow, *PI* pulsatility index, *RI* resistance index, *WF* wall filter, *PRF* pulse repetition frequency, *CG* color gain; p-values are based on the data in comparison with controls (Student t-test).

0.42 ± 0.28 cm in the VA was greater than Schöning's data [15]. Experimental CFI data using a 7 MHz linear-array probe in the anterior tibial artery of newborn lambs also indicated overestimation of Vd by 10–27% [20].

These overestimations and wide variability of Vd in the intracranial arteries in our PDI study probably were affected by depth from probe to vessels and the resolvigng power of vessel contours using a 2–3 MHz low frequency phased-array probe. Measurement of Vd also is affected by WF, PRF [6], and Reynolds number [5]. Further studies including reduction of random errors [4] are essential.

It is known that 10 to 15% higher flow velocity values were obtained on the basis of angle correction using CFI in comparison with conventional transcranial Doppler [14]. Flow velocity values in the MCA and ACA measured in this series also tend to be higher.

3. Hemodynamic Evaluation in Patients with Severe Head Injury

The flow velocities measured in this series showed a decreasing tendency for the ICA, VA, and PCA and an increasing tendency for the MCA. In evaluating the flow velocity increase of intracranial arteries, it is necessary to distinguish between cerebral vasospasm or hyperemia, utilizing SjO2 monitoring [3] or quantitative cerebral blood flow measurements based on intravenous ^{133}Xe [9] and single photon emission CT [12], and the risk of cerebral ischemia due to vasospasm has been pointed out.

The increasing tendency in the flow velocity meaured for the MCA in this series is suspected of vessel contraction due to vasospasm. Because flow velocity in the ICA showed a decreasing tendency, it is considered that there is also a decreasing tendency in the cerebral blood volume [8]. It is not always easy in this series to demonstrate Vd decrease due to vasospasm In fact, an inconsistency was observed that Vd increase resulted in calculated Vf increase. This inconsistency, encountered in evaluation of normal cases, is attributable to Vd measurement. Further study will be required for improved reliability in this respect.

PI and RI, on the other hand, showed significant increases except those for the CCA. This is considered in relation to hyperventilation therapy for increased ICP used in this series, and the increase in peripheral resistance due to cerebral parenchymal lesions.

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Correspondence: Toshiyuki Shiogai, M.D., Ph.D., Department of Neurosurgery, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181, Japan.

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The Effect of Experimental Spinal Cord Edema on the Spinal Evoked Potential

K. Tanaka, A. Kim, H. Naruse, and **A. Hakuba**

Department of Neurosurgery, Osaka City University Medical School, Osaka, Japan

Summary

Experimental spinal cord edema was successfully produced in the cat intumescentia cervicalis by the infusion method of Marmarou. The water content around the infusion site significantly increased to 75.9% from the normal value of 69.8% of white matter in the lateral column, with the infusion of 20 µl of autoserum. The edema was observed for a length of ca.20 mm, spreading mainly longitudinally in the lateral column. The spinal evoked potential was measured four times on the course of infusion and the N1 peak latency at the end of infusion did not show any significant difference compared to the value before infusion. This model may contribute to basic understanding of pathophysiology of spinal cord edema by changing the nature and the volume of infusate, and the location of infusion, according to the experimental purpose.

Keywords: Spinal cord edema; spinal cord trauma; spinal evoked potential.

Introduction

Although spinal cord trauma and intramedullary spinal cord tumor are often encountered in the clinical setting, there are only a few reports of experimental spinal cord lesions [1,2,9]. The infusion method of producing experimental cerebral edema is a well-known method by which a fairly reproducible edema can be produced in the brain parenchyma [4,7,8]. Experimental spinal cord edema was produced in the cat intumescentia cervicalis by this infusion method, and the distribution of water along the spinal cord axis and its effect on spinal evoked potentials were studied.

Materials and Methods

Adult cats were anesthetized with an intraperitoneal injection of pentobarbital sodium (40 mg/kg), intubated and mechanically ventilated and maintained on 1:3 gas mixture of O_2 and N_2O. The head was fixed on a stereotactic apparatus and laminectomy from C1 through C7 was performed. A 30-gauge needle, which was connected with the polyethylene tubing to the 1 ml syringe mounted on a variable speed infusion pump, was inserted into the right lateral column of the intumescentia cervicalis at the level between C5 and C6 vertebrae. The point of needle insertion was at the right 1/6th of the width of spinal cord. A total amount of 20 µl of autoserum was infused at a rate of 10 µl/hr. The in-line pressure was measured by a pressure transducer via a three-way stopcock which was placed in the infusion line.

Three cats were used for the measurement of water distribution along the spinal cord axis from the infusion point. In this group, immediately after 20 µl of autoserum was infused, the cats were sacrificed by intravenous injection of KCl, and the total length of the cervical and upper thoracic spinal cord was removed. Thirteen axial slices with 3 mm thickness of the spinal cord, such that the central slice contains the infusion point, were obtained. Two samples from the lateral column and one sample from the central gray matter were obtained from each half of the spinal cord in every slice, and the water content was measured by specific gravity method. In order to measure the water content by specific gravity method, the specific gravities of the solid components (SPGRs) of white matter and gray matter of the spinal cord must be known [3]. The values of 1.12197 and 1.19535 were used respectively, for the SPGRs of the spinal cord white matter and gray matter, which have been obtained in the other series of experiments in our laboratory.

Five cats were used for the measurement of the spinal cord evoked potentials. The stimulation electrodes were inserted between toes of forelimbs bilaterally, and the spinal evoked potential was recorded by monopolar lead with the silver ball electrodes, which were placed over the bilateral dorsal column at the level of C1 vertebra. The stimulation was performed by a train of square waves, 1/sec, with a duration of 0.5 msec, with 130% of the intensity which elicited forelimb movement. Routinely 100 responses were processed by an averaging computer. The spinal evoked potential was recorded intermittently at post-insertion of the infusion needle, and at the times when the accumulated volume of autoserum reached 5 µl, 10 µl, 15 µl, 20 µl. The recording was performed in four different ways: the left forelimb stimulation and the left dorsal column recording, the left forelimb stimulation and the right dorsal column recording, the right side stimulation and

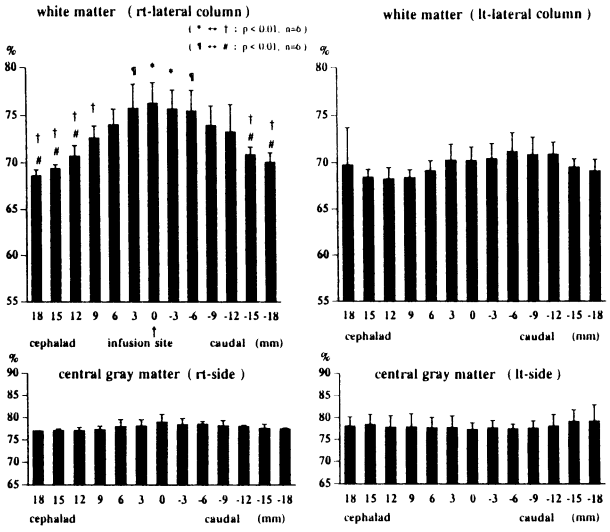

Fig. 1. Water distribution along the cervical spinal cord axis. Numerals in the X-axis represent the distance from the site of infusion. The positive number is used for cephalad direction and the negative number is used for caudal direction. The water content was measured in four locations in each axial plane, rt- & lt-lateral column, rt- & lt- central gray matter. The significant increase was observed only in four slices around the infusion site in the rt-lateral column. The mean % water content in these edematous slices reached 75.85 ± 2.03% (mean ± SD) whereas the mean value of all slices in the lt-lateral column (contra-lateral side) was 69.80 ± 1.78

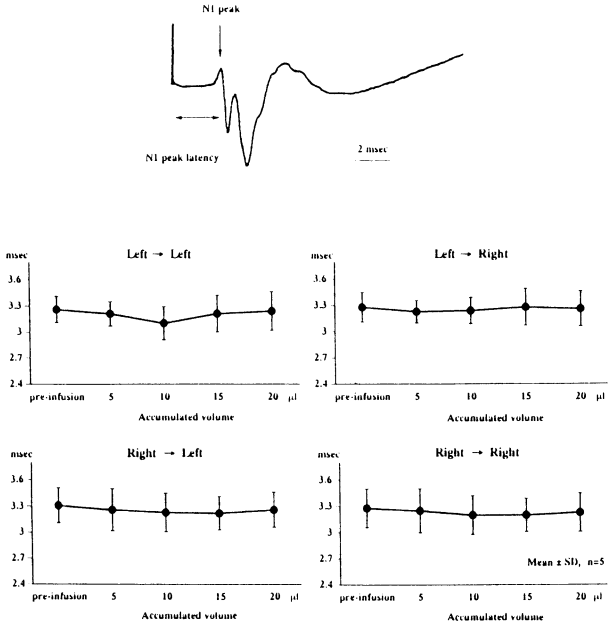

Fig. 2. The changes in the N1 peak latency of spinal evoked potentials in the course of infusion. Numerals in the abscissa represent the accumulated volume of autoserum in the right lateral column. The abbreviation like "Left → Right" means that the recording was done on the right dorsal column at the level of C1 by stimulation of left forelimb. The N1 peak latency at the infusion was terminated (accumulated volume: 20μl) and did not show any significant/difference compared to the value before infusion in four manners of recordings

the left side recording, the right side stimulation and the right side recording.

Results

The water content was measured in four locations in each slice, the lateral column of the right side where the infusion of autoserum was performed, the lateral column of the left side, the central gray matter bilaterally (Fig. 1). The significant increase of the water content was observed only in four central slices around the infusion point in the right lateral column compared to the remote slices ($p < 0.001$). The mean value of these four slices reached 75.85 ± 2.03% (mean ± SD, n = 24). There were not any significantly increased slices in other locations. The values of the lateral column and the central gray matter of the left-side, contralateral to the infusion side, were 69.80 ± 1.78% (mean ± SD, n = 70) and 77.88 ± 1.84% (mean ± SD, n = 33), respectively. The pressure rise in the infusion line while the infusion pump was motorized was 5.0 ± 0.8 mm Hg and the tissue pressure after termination of infusion was 4.3 ± 1.1 mm Hg.

In order to examine the effect of edema on transmission of impulse through the posterior column and the lateral column, the peak latency of the first negative deflection of spinal evoked potential, which is the conduction time from the site of stimulation to the level of C1 vertebra, was focused. To avoid redundant description, the manner of stimulation and recording was expressed in a short form, such that when the recording was performed over the left posterior column by stimulation of right forelimb, it was arbitrarily designated as "right-left" recording. The peak latencies of N1 in the left-left, left-right, right-left, and in the right-right recordings before the infusion pump was motorized were 3.26 ± 0.15, 3.28 ± 0.17, 3.31 ± 0.20, 3.28 ± 0.22 msec, respectively, and 3.24 ± 0.22, 3.26 ± 0.20, 3.26 ± 0.20, 3.26 ± 0.20, 3.23 ± 0.22 msec at the accumulated volume of infusate reached 20μl (Fig. 2). There were not any significant delays in conduction time through any tracts.

Discussion

The method of producing brain edema by infusion has been reported elsewhere [4,7,8]. When it is applied to the spinal cord, we have to consider that the volume which will accommodate infusate is very

small because of its size, then the total amount of infusion must be limited to a small amount, the needle which is used must be very thin and the speed of infusion must be very slow in order to minimize tissue injury. We have solved these problems by using 30-gauge needle, and infusing 20μl at a speed of 10μl/hr.

The preliminary report of the histological aspect of this model has been presented at the Tenth International Brain Edema Symposium. The extracellular space was markedly distended and filled with electron-dense material. These features were similar to the findings which were seen in the infusion type of brain edema [6,8]. The water content of four slices around the infusion needle significantly increased in the lateral column (Fig. 1). Including the skirts of this peak (three slices), the distribution of edema seemed to extend for ca.100mm in both directions from the infusion site. Although a slight infiltration of Evans' blue was observed in the adjacent border of the central gray matter in the previous study [5], no significant increase of water content was detected in the central gray matter in the infused side.

The spinal evoked potential was recorded in four manners; left-left, left-right, right-left, right-right (refer to the *results* for these abbreviations). In order to investigate whether there is any effect of edema on the conduction time, the first negative deflection of the spinal evoked potential, the N1 peak latency, was focused on. Although the other type of experiment must be designed to define through which tract the impulse is conveyed in each recording. When they are compared in each animal the N1 peak latency in the left-left recording is shorter than in the left-right recording (4/5 cats), and the right-right recording is shorter than the right-left recording (4/5 cats). We presume that the impulse seemed to be conveyed through posterior column in the left-left, and in the right-right recordings, and it seemed to be conveyed through lateral column in the left-right, and in the right-left recordings. Taking these assumptions into consideration, N1 peak latency in the left-right recording must be greatly affected by infusion in the rt-lateral column. Not only in the left-right recording, N1 peak latency did not change in any other recordings. This magnitude of edema, 6% increase in water content, did not affect conduction of impulse. These results coincide with the results which were reported in the previous study that there was not any delay in the conduction of SEP in the infusion type of brain edema [7]. The edema per se seemed to be a benign event even in the spinal cord.

In a few experimental works concerning experimental spinal cord injury, injury was produced by freezing or weight dropping technique [1,2,9]. In these models, there inevitably exist tissue necrosis, which in turn causes secondary damage to the spinal cord. Tissue necrosis was not observed in this experiment. The spinal cord edema model presented here may contribute to basic understanding of pathophysiology of spinal cord edema by changing the volume and the nature of infusate, and the location, according to the experimental purpose.

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Correspondence: Kiyoaki Tanaka, M.D., Department of Neurosurgery, Osaka City University Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545, Japan.

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Blood Brain Barrier Permeability and Acute Inflammation in Two Models of Traumatic Brain Injury in the Immature Rat: A Preliminary Report

P. D. Adelson, M. J. Whalen, P. M. Kochanek, P. Robichaud, and **T. M. Carlos**

Department of Neurosurgery and Anesthesiology/Critical Care Medicine, Children's Hospital of Pittsburgh and The Safar Center for Resuscitation Research and the Dept of Medicine, University of Pittsburgh, Pittsburgh, PA, U.S.A.

Summary

We sought to investigate the course and magnitude of blood brain barrier (BBB) permeability following focal and diffuse traumatic brain injury (TBI) in immature rats and examine the time course of markers of acute inflammation (neutrophil accumulation and E-selectin [E-sel] expression) following these two types of injury. We measured BBB permeability using IV injection Evans Blue (EB) and the extent of inflammation using immunohistochemical techniques identifiying neutrophils (monoclonal antibody RP-3) and the endothelial adhesion molecule, E- selectin. Male Sprague-Dawley immature (17 day-old) rats (30–45 g, n = 80) were subjected to a controlled cortical impact (CCI: 2 mm, 4 m/s), a closed head diffuse injury (DI: 150 g/2 m) or a corresponding sham procedure (with or without craniotomy). EB was injected IV at 30 min before sacrifice, which occurred at 1 h, 4 h, or 24 h after injury. BBB permeability was observed in both the CCI and DI rats at 1 h after injury which largely resolved by 24 h. In the CCI, EB extravasation was seen within and around the contusion. In DI, diffuse BBB permeability was seen. DI was not associated with acute inflammation since there was neither neutrophil accumulation nor E-selectin expression. The CCI rats though had 5.1 ± 2.2 neutrophils/hpf and 3.0 ± 0.4 endothelial cells/hpf expressing E- selectin (mean ± SEM) (both $p < 0.05$ vs sham and DI). These data suggest that BBB breakdown occurs in the immature rat after both focal and diffuse TBI. This early BBB permeability was not associated with acute inflammation in DI but was in CCI. These data also suggest that contusion is a key factor in the development of a tradtional acute inflammatory response after TBI in the immature rat.

Keywords: Acute inflammation; blood brain barrier; immature rat.

Introduction

Little is known of the pathophysiological processes that occur and are unique in children after traumatic brain injury (TBI). Clinically, children are considered to respond to severe TBI by exhibiting diffuse cerebral swelling more commonly than adults. The development of diffuse swelling is associated with increased mortality and disability. Why children more commonly develop diffuse swelling compared to adults is not well understood and the etiology of this diffuse swelling remains to be determined. Cerebrovascular failure with hyperemia [3], breakdown of the blood brain barrier (BBB) with edema [2], and cytotoxic edema [7] have been suggested as key events in the evolution of this pathophysiological response.

Enhanced BBB permeability has been reported to occur after many different types of experimental acute cerebral injury. Fluid percussion [6,11], CCI [8,10], and diffuse impact-acceleration [2] TBI as well as other types of cerebral insults such as hypoxia-ischemia, and radiation cerebritis in the adult rat are accompanied by varying degrees and durations of increased BBB permeability. The etiologies of the loss of BBB integrity has been attributed to direct mechanical disruption, or to specific mechanisms such as inflammation [11] or excitotoxicity [9]. There are presently no animal studies addressing either the acute response of the BBB or the relationship between permeability of the BBB and inflammation following experimental diffuse TBI in the developing brain. In this preliminary study, we sought to increase understanding of the response of the immature brain to diffuse impact acceleration [1], and to compare that response to that observed after focal CCI in the immature rat, by determining the extent of BBB permeability and its relationship to acute posttraumatic inflammation.

Material and Methods

Four experimental groups were used for this study. Male Sprague-Dawley immature (17 day-old) rats (35–50 g, n = 80) were subjected to either a diffuse or focal TBI. Diffuse injury was produced using a previously described closed head impact acceleration model (DI: 150 g/2 m) [1]. Focal contusion was produced using a newly developed modification of CCI (1.5 mm, 4 m/s) in the immature rat. Corresponding sham procedures (without [S-DI] or with [S-CCI] craniotomy) were also used. Two types of sham procedures were used since in previous studies of BBB integrity in adult experimental preparations, there was a measureable increase in BBB permeability from craniotomy alone. Craniotomy is needed for the production of the injury in the CCI but not in the diffuse TBI model.

BBB permeability was determined by using an intravenous (IV) injection of Evans Blue (EB) at specific times after the injury and the rats were sacrificed 30 min later at 1 h, 4 h, and 24 h. The brains were perfused transcardially with saline, removed and quick frozen at –70°C. Brains were bisected coronally through either the contusion or a comparable location (for the DI rats) and BBB permeability was initially qualitatively assessed in these sections. Each of the anterior brain segments were then weighed and the EB was extracted using a standard volume of N-n-dimethyl formamide for 5 d. The absorbance of the solutions was calculated at a wavelength of 620 nm and expressed as absorbance units/g of tissue ×1,000.

The extent of inflammation was determined using standard immunohistochemical techniques in serial coronal brain sections (20 μm) obtained from the posterior half of the remaining brain using MoAb RP-3 (which identifies rat neutrophils) and a MoAb against E-selectin (an endothelial adhesion molecule induced by IL-1β and TNFα). The number of stained cells were quantified by counting 22–28 randomly selected high power (100 X) fields (hpf).

Statistical analysis was performed by comparing injury and sham groups using Student t-test and analysis of variance (ANOVA) with post-hoc comparisons where appropriate. Statistical significance was defined by a p value <0.05.

Results

BBB permeability was observed in both the CCI and DI rats compared to sham injured controls. Permeability was maximal at 1 h after injury but had almost completely resolved by 24 h (see Table 1). In the CCI, EB extravasation was seen for the most part within and around the contusion though there was minimal BBB permeability diffusely in the ipsilateral hemisphere. In DI, there was diffuse BBB permeability, this was fairly equal between hemispheres but was greater on the dorsal compared to the ventral surface of the brain. Moreover, the BBB permeability at 1 h after injury was greater in the CCI than in the DI.

S-DI, S-CCI and DI were not associated with acute inflammation since there were neither neutrophils nor E-sel expression in any of the high power fields, although S-CCI had an occasionally staining positive cell beneath the craniotomy site. The CCI rats though had increased numbers of postitive stained cells for both markers, particularly around the site of contusion ($p < 0.05$ vs S-CCI, S-DI, and DI (see Table 2).

Discussion

This preliminary report represents the first data to show that there is BBB permeability in the immature rat after both experimental focal and diffuse TBI. This breakdown in the BBB was noted to be maximal at 1 h in both types of injury and was shown to largely resolve by 24 h. This is similar to previous work in adult animals following diffuse impact acceleration injury [2] and fluid percussion injury [26] where the BBB permability was also transient and lasted no more than 30–60 min depending on the severity of injury. In previous work on focal injury, BBB permeability was observed up to 10 h after injury [5]. Age-related differences or differences in severity of injury may have been the source for this discrepancy in BBB permeability. As assessed with our paradigm (eg) between 1 h and 24 h, BBB permeability was also found to be greater after CCI than after DI. This is particularly true if one considers regional permeability in and around the contusion (which was not quantified in this initial study). This suggests greater local vascular injury in contusion than in DI.

Table 1. *Blood Brain Barrier Permeability (Absorbance units/gram of tissue)*

	1 hour	4 hour	24 hour
S-DI	17.7 +/– 0.09	33.3 +/– 9.2	23.7 +/– 4.3
DI	54 +/– 7.5	34.8 +/– 4.2	29.3 +/– 8.4
S-CCI	34.3 +/– 10.3	29.7 +/– 6.5	23.3 +/– 3.5
CCI	135.6 +/– 78.8	50.8 +/– 8.0	24.6 +/– 1.7

S-DI sham without craniotomy; *DI* diffuse injury; *S-CCI* sham with craniotomy; *CCI* focal injury.

Table 2. *Acute Inflammation (Number of stained cells/hpf) (mean ± SEM)*

	1 hour	4 hour	24 hour
S-DI- RP-3	0	0	0
E- Sel	0	0	0
DI- PR-3	0	0	0
E- Sel	0	0	0
S-CCI- RP-3	0	0	0.3 +/– 0.3
E- Sel	0	0.1 +/– 0.1	0
CCI- RP-3	0.1 +/– 0.1	6.4 +/– 1.5	18.0 +/– 6.4
E- Sel	0	8.2 +/– 2.0	8.4 +/– 2.3

BBB permeability was not necessarily associated with acute inflammation. In both our models of TBI in the immature rat, early acute BBB permeability is present whether or not there is acute inflammation; no cellular markers of inflammation were noted in DI although there was significant inflammation noted after focal injury (CCI). In a previous report of BBB permeability after fluid percussion TBI in adult rats, neutrophil accumulation occurred where there was concomittant BBB damage [11]. These data suggest that a contusion produced by our model of CCI is a key factor in the triggering of an acute inflammatory response after focal TBI. We speculate that this response is a result of either severe vascular disruption in CCI, or the elaboration of chemotaxin in the necrotic contusion zone. As a result, the importance of contusion to the development of a traditional cellular inflammatory response may not be limited to the immature since this is a key feature of contusion in adult rats [4]. Also, because BBB permeability is increased in the diffuse impact acceleration model in the adult rat as early as 60 min after injury [2], evaluation of earlier timepoints in the immature rat may be warranted.

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Correspondence: P. David Adelson, M.D., Deptartment of Neurosurgery, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213–2583, U.S.A.

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Prospective Analysis of Patient Management in Severe Head Injury

A. Baethmann[1], **D. Lehr**[1], **A. Wirth**[1], and **Study Group**[2]

[1] Institute for Surgical Research, Klinikum Großhadern, Ludwig-Maximillans-University, Munich, Federal Republic of Germany
[2] H.-J. Reulen, H.-J. Steiger, W. Stummer, D. Hölzel: Klinikum Großhadern, Ludwig-Maximilians-University Munich, Ch. Lackner, J. Assal, A. Belg, M. Schrödel, N. Müller, P. Ueblacker, A. Chlistalla, G. Schneider: ANR, Ludwig-Maximilians-University Munich, L. Schweiberer, H.-G. Dietz: Department Surgery, Ludwig-Maximilians-University Munich, A. Trappe, W.-E. Göbel: Dept. Neurosurgery, Technical University of Munich, H. Jaksche, V. Messner: Dept. Neurosurgery, Trauma Hospital Murnau, Th. Grumme, P. Wenger, H. Müller: Dept. Neurosurgery, Klinikum Augsburg, E. Stolpe, J. Döffinger: Dept. Surgery, City Hospital Munich-Harlaching, Ch. Lumenta, W. Gerstner: Dept Neurosurgery, City Hospital Munich-Bogenhausen, G. Prokscha, D. Sackerer, F. Höfner, T. Eisenstein: Dept. Neurosurgery and Surgery, City Hospital Munich-Schwabing, G. Lenz, A. Preisz, F. Rothmeier, U. Kirmayer, M. Böhme, W. Horak, Th. Weeß: Dept. Anesthesiology, Klinikum Ingolstadt, Federal Republic of Germany

Summary

Severe head injury with and without peripheral trauma is the most frequent cause of death and of severe disability up to 45 years. Outcome is determined by two major factors, the extent and nature of the irreversible primary brain damage, and the evolving secondary sequelae, which contrary to the former are responsive in principle to therapeutic intervention. An improvement of outcome from severe head injury can be expected only from an increased efficiency of the measures to prevent secondary brain damage. A research consortium "Neurotrauma" was formed by the University of Munich in collaboration with almost all city hospitals in Munich, Augsburg, Murnau, Ingolstadt, Vogtareuth and Southern Bavaria, providing care for neurotrauma patients. These hospitals together with the associated organizations carry out a system analysis on the management, logistics, organization, patient referral, etc. In severe head injury. Data acquisition is e.g. also concerned with outcome-relevant time periods of emergency care measures in the pre-clinical phase until hospital admission, conclusion of diagnostic procedures, and of the initial clinical care. Current results and experiences with establishment of this comprehensive research organization are presented, where no less than 31 hospitals. Institutions and organizations, and a study group of more than 40 physicians, students and statisticians are collaborating.

Emerging data appear to be suitable to further improve pertinent aspects of the patient management as a basis to lower the incidence of secondary brain damage from severe head injury.

Keywords: Clinical management; neurotrauma; research consortium; severe head injury.

Introduction

Severe head injury is the most important cause of mortality and disability in an age range of up to 40–45 years. In Germany, approximately 10,000 accident- and other victims are dying per annum as a consequence of severe head injury. Assuming a case mortality of 35% [1] it can be concluded that the incidence of cases with severe head injury approached 30,000 per year. It is suspected that early insults to the brain, in the prehospital phase, make major contributions to the development of secondary brain damage and a raised intracranial pressure. The outcome depends on two factors, the nature and severity of the primary injury of the brain at the moment of the traumatic impact, and the various manifestations of secondary brain damage [2,3]. Progress in improving outcome in severe head injury requires a more efficient inhibition of the development of secondary brain damage – the various forms of primary injury from trauma are by definition refractory to any treatment. They should be avoided by the measures of prevention.

In essence, the treatment of head injury comprises many components, such as organization and logistics of the prehospital management at the scene, referral and admission of the patient to a suitable hospitable, as well as the subsequent diagnostic and therapeutic procedures including rehabilitation. This requires a highly developed communication system, organization, logistics, and management of the prehospital rescue service, availability and sufficient density of neurotrauma centers, well trained medical and

paramedical personnel – each of which is essential in raising the efficiency of services involved in the patient management and care.

Purpose of Current Study

A system Analysis was designed and initiated to assess all major components of the head injury management commencing at the scene of an accident. A Study Group was established as an objective of the Research Consortium "Neurotrauma" Munich, supported by the Federal; Department of Education, Research and Science [7]. The System Analysis is expected to provide data on the efficiency of the current management, including logistics and organization of patient care in the prehospital and early clinical phase. The analysis includes the dispatch of emergency services, time intervals relevant to outcome, as well as the patient's state at the scene, during transport, and after hospital admission, also the occurrence and nature of complications.

In a currently concluded first study phase, data were prospectively collected – quasi on-line – by an independent team of assistants, i.e. medical students trained as paramedics. The documentation assistants arrive at the scene of an accident together with the rescue team, most often by helicopter. The prospective data collection is continued during transport and after admission of the patient to the hospital. The specifically designed protocol was established by members of the Study Group, particularly emergency physicians and neurosurgeons.

An endpoint of the Phase-1 study was to obtain information on the current state of preclinical care and the early clinical management. The following aspects were considered to be of specific interest:

- Number and distribution of neurotrauma hospitals in the catchment area
- Allocation and transfer of patients to and from general trauma hospitals to neurosurgical units
- Type of emergency vehicle (ambulance car, helicopter)
- Monitoring and care of the patient at the scene, during transport, and after hospital admission
- Time periods and intervals relevant to outcome ("time management"), e.g. the promptness of recognition and correction of life-threatening complications
- Frequency and nature of life-threatening complications at the scene, during transport, and during the early clinical phase, e.g. hypoxia, hypercapnia, or arterial hypotension.

Outcome was assessed by the Glasgow Outcome Score [4].

Design and Methods

The catchment area contains large and small cities and rural areas in Southern Bavaria, Munich was included as big city with a large number of high intensity level hospitals. The city of Augsburg (population ca. 120,000) is a typical smaller sized community which, however, has a large medical center (Zentralkllnikum) providing also intensive care in all disciplines, including general trauma surgery, and neurosurgery. The cities of Murnau, Ingolstadt, and Vogtareuth are covered as smaller communities, yet also having modern, high level hospitals serving Southern Bavaria and beyond. The total catchment area covers approximately one third of the Bavarian population, Altogether. 14 hospitals (general trauma, neurosurgical, etc.) are taking part, also the institute of Surgical Research and the institute of Medical information, Biometrics, and Epidemiology of the University of Munich. An important issue is the involvement of specific organizations in the region. One organization of our university (Arbeitsgameinschaft f. Notfallmedizin und Rettungswesen – ANR) is assigned with research on emergency medicine and rescue services, others are in charge of the rescue helicopters "Christoph 1" based at the Community Hospital Munich-Harlaching or "Christoph 32" based at the Medical Center of Ingoistadt. Moreover, the Bavarian Red Cross is taking part, the various dispatch centers for emergency services, e.g. in Munich, Rosenheim, Erding, Forstenfaidbruck, Wellheim, Augsburg, Krumbach, Kempten and Ingolstadt, and, finally, the headquarters of the Munich fire brigade.

There are no specific instructions about the management for the rescue services or the primary or secondary care hospitals, as it is a point of this study to assess and analyse the status quo. The only exception is the sampling of arterial blood at the scene of an accident by the rescue team, which is performed, if possible before the patient is intubated, ventilated, and given oxygen [5]. Care is taken, of course, that the blood sampling is not interfering with the routine emergency care for the patient. The blood gases are analyzed to gather information on the actual respiratory state of the patient. Data so far obtained in 45 cases indicate that most patients from whom blood was sampled prior to intubation and, thus, were spontaneously breathing, to have a subnormal to hypoxic arterial PO_2 (i.e. < 80–86 mmHg), whereas the arterial PCO_2 most often was in the normal range. Other features documented at the scene are the GCS blood pressure, respiratory rate, and visible complications, injuries and, of course, management procedures.

The recording of time intervals was using as a reference the time of the incoming call to the dispatch center. Times of interest include when the rescue team arrives at the place of an accident, when the patient is intubated, when transport starts, or when the patient is admitted to the hospital. The time of CT-diagnosis and of surgical or intensive care interventions was also recorded.

A patient is finally recruited as having a severe head injury, if the Glasgow Coma Score on the scene is 8 points or below, i.e. before intubation or sedation, or if the GCS deteriorates to 8 points or below within 24 hrs. However, assessment of the GCS most often is complicated by management procedures on the scene, particularly by the intubation and analgo-sedation, Under these circumstances, the diagnosis of severe head injury is established by respective CT-findings, e.g. utilizing the classification of L. F. Marshall *et al.* [6].

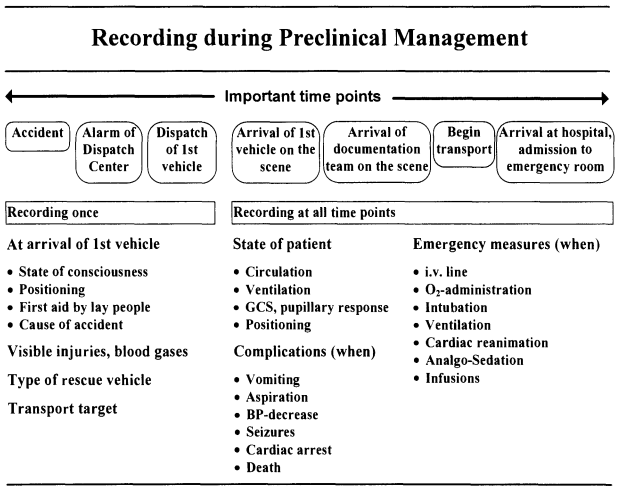

Fig. 1.

Present State of Date Collection

At approximately two years after start of the Phase-1 study, 148 patients have been recruited, 77 cases were included as the diagnosis of severe head injury was confirmed, 72 cases were excluded, either since severe head injury was not confirmed, or the patients died within 24 hrs. In 75% of cases the rescue team arrived at the site of an accident within less than 15 min after the call was received at the dispatch center, intubation was done within 40 min, admission to hospital within 70 min, cranial CT-scan within 120 min, and the acute clinical procedures were completed within 3.5 hrs. The majority of patients (79%) were transported by helicopter together with an emergency physician.

Although the number of patients so far recruited is limited, our experience shows the extraordinary requirements to ensure that all information is collected prospectively, partly even at an on-line basis providing for a maximum level of data quality. The well trained research assistants must be available on a stand-by basis at the home-port of the rescue vehicle (most often a helicopter), during a whole period of duty, i.e. from morning until night in order to arrive at a patient with severe head injury as soon as possible after an accident. For organizational reasons, we were focusing our study on the helicopters "Christoph 1" in Munich, or "Christoph 32" in ingolstadt. This markedly improved the chances that among the many missions of these vehicles patients with severe head injury meeting our inclusion criteria are available for documentation. Of course ground based vehicles are also transporting patients with severe head injury, but their large number on duty and missions in our catchment area renders the probability rather low that a given case will be a patient with severe head injury.

Important issues have been recognized in the present study. One is maintenance of the quality of data. A critical moment, for example, is the transition of the responsibilities after a patient is admitted to the hospital, when documentation must be continued by a physician of the admitting clinic. Another problem is that a patient is prematurely discharged from the hospital, raising the possibility that the documentation is interrupted. The Phase-1 study on the preclinical and early clinical management in patients with severe head injury was concluded in October/November 1997. Thereafter, the system analysis will be carried out as a Phase-2 study on an epidemiological population-based level in the catchment area.

Acknowledgements

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Correspondence: Alexander Baethmann, M.D., Ph.D., Institute for Surgical Research, Klinikum Großhadern, Ludwig-Maximilians-University Munich, Marchioninistr. 15, D-81366 München, Germany.

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Effects of Cerebral Perfusion Pressure on Brain Tissue PO_2 in Patients with Severe Head Injury

P. Bruzzone[1], **R. Dionigi**[1], **G. Bellinzona**[1], **R. Imberti**[1], and **N. Stocchetti**[2]

[1] Servizio di Anestesia e Rianimazione, IRCCS Policlinico S. Matteo, Pavia, and [2] Servizio di Anestesia e Rianimazione, IRCCS Ospedale Maggiore di Milano, Italy

Summary

Ischemia causes secondary brain damage after severe head injury (SHI). Cerebral perfusion is commonly estimated by monitoring CPP, but the adequacy of cerebral oxygenation requires further measurements, such as jugular oxygen saturation or, more recently, $PtiO_2$ monitoring. In 7 patients with severe head injury, ICP, MAP, CPP, SjO_2 and $PtiO_2$ were monitored for a mean time of 9.0 ± 2.2 days. Most of the data were in a "normal" range. Focusing on values under the thresholds of 60 mm Hg for CPP and 20 mm Hg for $PtiO_2$, we found a relationship between CPP and $PtiO_2$. Looking at the $PtiO_2$ time-course, we observed a quite constant increasing trend during the first 48 hours of monitoring, then the values remained relatively constant within a normal range. Our data show that decreases of $PtiO_2$ are not uncommon after severe head injury and therefore it seems that monitoring of $PtiO_2$ in SHI may be useful in order to minimize secondary insults.

Keywords: Brain tissue PO_2; cerebral perfusion pressure; CPP; ICP; jugular oxygen saturation; severe head injury.

Introduction

Adequacy of cerebral perfusion is commonly assessed by monitoring Cerebral Perfusion Pressure (CPP), calculated as the difference between Mean Arterial Pressure (MAP) and Intracranial Pressure (ICP). Any modification in ICP or MAP which causes a reduction of CPP below the autoregulation threshold can lead to a critical reduction of cerebral blood flow (CBF). Reduction in CBF is of paramount importance in head injured patients because ischemia is the common mechanism of secondary brain damage and it has been proved that ischemia severely affects the final outcome.

In recent years the relationships between CBF and oxygen consumption have been studied by looking at Jugular Oxygen Saturation (SjO_2). The evaluation of SjO_2 has many limits: 1) the optimal catheter location, especially when the patient has a diffuse brain injury, is still debated [5,6]; 2) the catheter position can be infuenced by head movements and it has frequent dislocations; and 3) when an optical catheter is used, measurements are often unreliable due to artifacts.

The monitoring of $PtiO_2$ is a more recent technique based on the measurement of oxygen tension in tissue and fluid through a polarographic Clark type electrode. $PtiO_2$ monitoring has some advantages over other established methods such as SjO_2 monitoring: 1) recalibration is not necessary; and 2) once inserted, it allows valid and stable mesurement lasting hours and even days. Of course there are limitations: first of all the technique explores small portions of the brain tissue (about 17 mm^2). Moreover, it is unknown if the probe induces a microvascular compression [2] when positioned, and, if this is the case, whether this could affect the readings.

Normal or hypoxic thresholds have not been clearly defined: in head injured patients such as in experimental situations, the reported values for normality are above 20 mm Hg [3,7,8]. Clinically, a value of 10 mm Hg is generally reported as hypoxic threshold; at this value of $PtiO_2$, other signs of inadequate oxygenation have been observed, such as SjO_2 less than 50% and a CPP less than 60 mm Hg.

The aim of this study was to evaluate the frequency and the clinical meaning of low (less than 20 mm Hg) and very low (less than 11 mm Hg) values of $PtiO_2$ in

patients suffering of severe head injury and possible pathophysiological causes.

Materials and Methods

We investigated 7 patients (6 male) with severe head injury (GCS ⇐ 8). The mean age was 35 ± 20 and the mean GCS on admission was 6.2 ± 1.5 (median 5). All patients were intubated and ventilated after GCS valutation and underwent cerebral CT scan after admission in ICU (Table 1). All patients were sedated with continuous infusion of Propofol (100–200 mg/hour) and Fentanyl (0.05–0.1 mg/hour) and paralyzed, according to clinical needs, with Vecuronium. MAP was maintained between 90–110 mm Hg and increased ICP was treated optimizing sedation, applying moderate hyperventilation ($PaCO_2$ 32–35 mm Hg) and infusing mannitol and eventually barbiturates. Electrocardiogram (ECG), body temperature, peripheric arterial O_2 saturation (SpO_2) and end-tidal CO_2 ($etCO_2$) were monitored. ICP, MAP, CPP, SjO_2 and $PtiO_2$ were continuously monitored and recorded. Data were collected at 1 minute intervals starting between 6 and 24 hours after the trauma (mean value 13.0 ± 6.7 hours). Data collection lasted 9.0 ± 2.2 days.

ICP was measured using a fiberoptic intraparenchymal device (Camino Laboratories, San Diego, CA); $PtiO_2$ was monitored using a flexible Clark-type catheter (LICOX System: GMS, Kiel, Germany). The device was placed into the non-lesioned frontal white matter, usually 1–1.5 cm behind the ICP probe using an introducer and a special bolt screwed in a second hole. $PtiO_2$ values were continuously corrected according to actual body core temperature. No pre-insertion calibration of the catheter was made setting the specific factors provided by the manufacturer.

SjO_2 monitoring was performed using a 8G catheter (lengh 20 centimeters) percutaneously inserted in jugular bulb; only in one patient SjO_2 was monitored in continuous using a No. 4 French fiberoptic catheter (Opticath U425C, Oximetric System; Abbott Laboratories, N. Chicago, IL). CPP was continuously calculated as the difference between MAP and ICP.

Analog signals of all parameters were digitalized using a multimodal computer system (LabVIEW, National Instruments, Austin, TX) and were stored at 1 minute intervals as mean values of the last 60 sec. All artifacts and technical errors were checked and excluded.

Results

Overall, we collected data regarding 83337 minutes; after filtering, we recorded reliable $PtiO_2$ data for 67664 mins (81.19%) and suitable CPP data for 68742 mins (82.48%); both parameters were reliably and simultaneously recorded for 62936 mins (75.5%).

$PtiO_2$ was below 20 mm Hg for 19033 mins (28.12%) and below 11 mm Hg for 2714 mins (4%) (Fig. 1). CPP was less than 60 mm Hg for 11886 mins

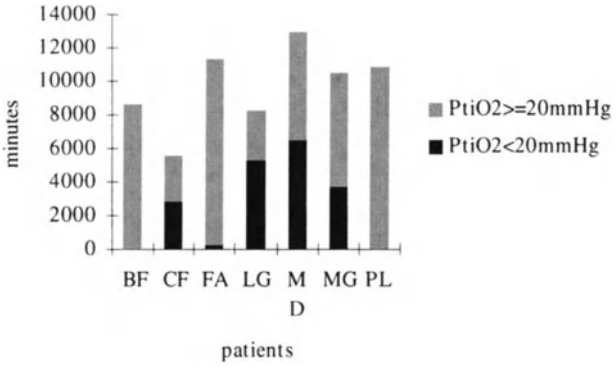

Fig. 1. Number of $PtiO_2$ data collected in each patient olivided according to the threshold of 20 mm Hg

Table 1. *CT-Scan Results and Neurosurgical Approach*

Patients	CT-scan results	Neurosurgical approach
B.F.	– Left temporal and parietal contusions – Omolateral edema	None
C.F.	– Left frontal contusions – Right temporal and occipital contusions	None
F.A.	– Right epidural hematoma – Right subdural temporal hematoma – Diffuse edema	Immediate
L.G.	– Left subdural hematoma – Left contusions	Immediate
M.D.	– Right temporal contusions – Shift >5 mm – Diffuse edema	Delayed
M.G.	– Right talamic contusion – Diffuse edema	None
P.L.	– Right temporal contusions – Bilateral frontal contusions – Left internal capsula contusion – Left parietal contusions – Diffuse edema	Delayed

Table 2. *Distribution of CPP and $PtiO_2$ (Number of Data Collected)*

	$PtiO_2$		
CPP	≤11 mm Hg	12–19 mm Hg	≥20 mm Hg
<60 mm Hg	1,451 (2.3%)	4,943 (7.8%)	3,541 (5.6%)
≥60 mm Hg	899 (1.4%)	11,946 (19.0%)	40,707 (64.7%)

(17.29%). CPP and $PtiO_2$ were simultaneaously in the pathological range for 4943 mins (7.8%). CPP was closely related to $PtiO_2$ when the lower limit of autoregulation was exceeded (<60 mm Hg), whereas when CPP was greater than 60 mm Hg this relationship was no longer evident (Table 2).

Jugular bulb saturation was recorded by intermittent samples for a total of 128 determinations. In only 20 determinations (15.6%) SjO_2 was less than 55%. Interestingly, a strong relationship between SjO_2 and $PtiO_2$ was found. Desaturation was, in fact, detected when $PtiO_2$ was lower than 20 mm Hg. In one case, SjO_2 had been monitored continuously and the trend of jugular saturation and $PtiO_2$ were similar, confirming that reduction in oxygenation were reflected by both measurements.

We also evaluated the time course of $PtiO_2$, starting from the third hour of monitoring (the first two hours were excluded for allowing stabilization of the probe). $PtiO_2$ increased during the first 48 hours the lower value being recorded during the first day of monitoring.

Each $PtiO_2$ and ICP catheter were checked at the end of monitoring. $PtiO_2$ probes were tested for sensivity and for zero value at the end of monitoring. Sensitivity drift was $-4.5 \pm 3.2\%$ and zero drift was 0.5 ± 1.3 mm Hg. Mean drift of ICP intraparenchmal device was 0.8 ± 2.9 mm Hg. No catheter-related infections or intracranial bleeding were observed.

Each patient survived; the mean GCS at discharge from the ICU was 9.0 ± 1.8. At six months follow-up, 3 cases showed moderate disability and 4 suffered severe disability. The mean length of stay in ICU was 24.5 ± 6.4 days.

Discussion

The aim of our study was to verify the incidence and, possibly, the mechanisms of pathological values of $PtiO_2$. Our hypothesis was that values less than 20 mm Hg (or even lower <11 mm Hg) were signs of compromized cerebral oxygenation. Low values of $PtiO_2$ were observed in more than 28% of measured points. Low values of $PtiO_2$ were more common during the phase immeadiately following trauma. This may be in agreement with the incidence of jugular desaturation and low CBF already reported during the first two days after injury [4]. As for the mechanisms leading to reduced $PtiO_2$, the close relashionship between CPP and $PtiO_2$ suggest that tissue oxygenation is mainly a function of perfusion.

The optimal level of CPP is still debated; some authors [1] consider above 60 mm Hg appropriate for CBF and cerebral oxygenation; other propose a higher [4] level. In our data the threshold for $PtiO_2$ (and SjO_2) falls corresponds to a CPP of 60 mm Hg.

SjO_2 was considered as an index of cerebral extraction because arterial saturation was constantly greater than 97%. Only few episodes of jugular desaturation (SjO_2 <55%) were detected. Our data suggest that measurement of severe head injuries brain tissue tension of oxygen adds substantially to monitoring.

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Correspondence: Paola Bruzzone, M.D., Servizio di Anestesia e Rianimazione, IRCCS Policlinico S. Matteo, Piazza Golgi 23, 27100 Pavia, Italy.

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Neuroprotective Properties of Aptiganel HCL (Cerestat®) following Controlled Cortical Impact Injury

S.-N. Kroppenstedt, G.-H. Schneider, U.-W. Thomale, and **A. W. Unterberg**

Department of Neurosurgery, Virchow Medical Center, Humboldt University, Berlin, Federal Republic of Germany

Summary

Recent studies revealed a neuroprotective effect of the non-competitive NMDA receptor antagonist Aptiganel HCL (Cerestat® CNS 1102) in focal cerebral ischemia. This study investigates the influence of Cerestat on contusion volume, post-traumatic brain edema and intracranial pressure (ICP) following Controlled Cortical Impact Injury (CCII). In rats (n = 54) CCII was applied to the left hemisphere using a pneumatic impactor. Cerestat (2 mg/kg i.v.) or vehicle was injected 15 min after injury animals were sacrificed 24 hours later. Contusion volume was measured planimetrically (n = 18). Hemispheric swelling and water content were determined gravimetrically (n = 20). ICP, mean arterial blood pressure (MABP) and cerebral perfusion pressure (CPP) were monitored for 30 min before sacrifice (n = 16). Cerestat reduced contusion volume from 77.3 ± 5.8 mm^3 to 66.8 ± 3.9 mm^3 ($p < 0.05$). Hemispheric swelling was also diminished from 11.1 ± 0.8% to 8.2 ± 1.4% as soon was water content (Cerestat 82.30 ± 0.18% vs. control: 82.78 ± 0.12%, $p < 0.05$). ICP was decreased by treatment from 31.7 ± 3.5 mmHg to 26.3 ± 2.2 mm Hg and CPP was significantly improved (82.1 ± 4.4 mm Hg vs 57.7 ± 4.8 mm Hg; $p < 0.05$) 24 hours after injury. Cerestat administration was associated with decrease contusion volume, less hemispheric swelling, a lower ICP and increased CPP.

Keywords: Aptiganel HCL; cortical impact injury; N-methyl-D-aspartate (NMDA).

Introduction

Secondary or delayed brain damage is a major characteristic of traumatic brain injury (TBI). Recent investigations have identified that the release of the excitatory amino acid glutamate has a major role in the pathophysiological mechanisms of delayed brain tissue damage [4].

Glutamate binds to various excitatory amino acids (EAA) receptors. Since activation of the ionotropic N-methyl-D-aspartate (NMDA) receptor leads to an influx of Ca^{2+} and Na^{+} and an efflux of K^{+} [3] this receptor is presumed to play a key role in the glutamate-mediated excitotoxicity. The consequent increase in intracellular Ca^{2+} causes metabolic disturbances within the cell initiating a cascade of autodestructive responses.

Cerestat® (CNS 1102, aptiganel hydrochloride) is a recently developed high affinity non-competitive NMDA-receptor antagonist binding within the ion channel. Neuroprotective effects of Cerestat have been demonstrated after focal cerebral ischemia [7] and phase III trials of Cerestat for have been in patients with and traumatic brain injury.

So far, there are no reports on the effects of this substance in models of TBI. Thus, this study investigates the effects of Cerestat on contusion volume, brain edema and ICP induced by Controlled Cortical Impact Injury [2].

Material and Methods

For the study, 54 male Sprague-Dawley rats weighing 270–330 g were used. Under inhalation anesthesia (2% isoflurane in a 2:1 gas mixture of N_2O/O_2, and spontaneous breathing) a craniotomy was performed over the left temporo-parietal region leaving the dura intact. Using a computer controlled pneumatic impactor [2] with a convex tip surface (diameter 5 mm), a standard CCII was applied to the cortex (velocity 7 m/s; deformation depth: 2 mm). Rectal temperature was maintained at 37°C. Mean arterial blood pressure (MABP) was monitored throughout the experiment. Arterial blood gases (pH, pCO_2, pO_2) were analyzed 5 minutes before trauma. Cerestat® (CNS 1102, aptiganel HCL, Cambridge NeuroScience, Cambridge, MA.) was administered in a single intravenous dose of 2 mg/kg body weight 15 min after impact. In the control group an identical volume of vehicle was given. 24 hours after injury animals were sacrificed and the brains were removed

for specific investigations. Animals were randomly assigned to one of the following groups.

In groups A1 (Cerestat, n = 10) and A2 (vehicle, n = 8) the contusion volume was determined. After perfusion fixation with 4% paraformaldehyde, coronal sections – 10 µm thick – were prepared at intervals of 400 µm and stained with hematoxylin and eosin (H.E.). The area of contusion was measured by computerized planimetry and the volume of contusion was assessed by multiplying with section interval.

Groups B1 (Cerestat, n = 10) and B2 (vehicle, n = 10) were used to investigate hemispheric swelling and water content. Following sacrifice, hemispheric swelling was determined gravimetrically after meticulous seperation of hemispheres using a microscope. Thereafter hemispheres were dryed at 100°C for 24 hours. Cerebral water content was then calculated as the difference between hemispheric wet- and dry weight.

In groups C1 (Cerestat, n = 8) and C2 (vehicle, n = 8) ICP, MABP and CPP were monitored for 30 minutes before the animals were sacrificed to determine hemispheric swelling and water content. For ICP measurements a Codman ICP-probe was inserted 6 mm into the right hemisphere through a burr hole. In this series, ICP was correlated with hemispheric swelling and water content of the traumatized hemisphere determined after sacrifice.

Results

Arterial blood gases were within normal range and MAPB (control: 94.6 ± 4.3 mm Hg vs. Cerestat: 94.2 ± 7.4 mm Hg) showed no significant differences between groups before cortical contusion.

Cerestat reduced posttraumatic contusion volume by 13.6% from 77.3 ± 2.1 mm^3 in controls to 66.8 ± 3.9 mm^3 in Cerestat treated animals (p = 0.044, Table 1).

Hemispheric swelling was also significantly diminished from 11.1 ± 0.8% in controls to 7.6 ± 1.4% in the Cerestat group (p = 0.049), representing a reduction by 31.5% (Table 1).

CCII lead to a significant increase in water content in the traumatized hemispheres in both the Cerestat and the control group (p < 0.001), but water content in Cerestat treated rats (82.31 ± 0.18%) was significantly lower than in control animals (82.78 ± 0.12%, p = 0.046, Table 1). Non-lesioned hemispheres did not differ in water content (81.32 ± 0.06% in controls vs Cerestat: 81.39 ± 0.07%, p = 0.436).

24 hours after injury, Cerestat treatment decreased ICP from 32.0 ± 2.7 mm Hg to 25.5 ± 2.4 mm Hg, p = 0.096. The MABP was significantly higher in the treatment group (107.8 ± 3.6 mm Hg) in comparison to the control group (89.9 ± 2.4 mm Hg; p < 0.001) resulting in a significantly higher CPP (Cerestat: 82.6 ± 4.2 mm Hg vs vehicle 57.3 ± 4.7 mm Hg; p < 0.001; Table 1).

Significant correlations were found between ICP and posttraumatic hemispheric swelling (p < 0.001) as well as ICP and posttraumatic water content of the injured hemisphere (p < 0.001; Fig. 1).

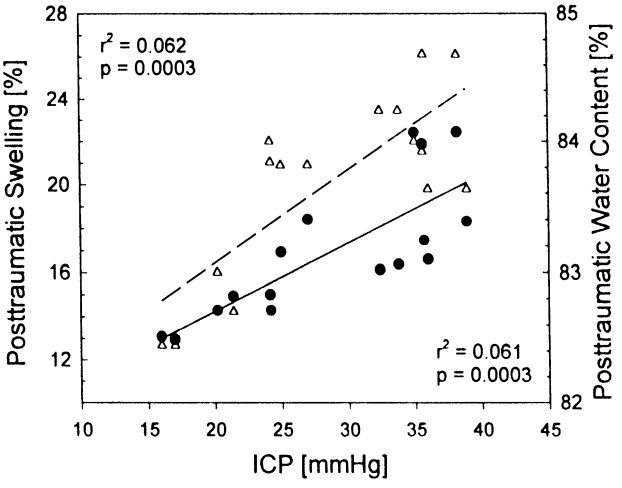

Fig. 1. Linear regression analyses of intracranial pressure (ICP) and posttraumatic hemispheric swelling (△) and ICP and posttraumatic water content (●) of the traumatized hemisphere

Table 1. *Posttraumatic Contusion Volume, Hemispheric Swelling and Water Content at 24 Hours Following Controlled Cortical Impact Injury (CCII). Mean intracranial pressure (ICP), mean arterial blood pressure (MABP) and cerebral perfusion pressure (CCP) were monitored for 30 minutes at 24 hours after CCII*

	Vehicle	Cerestat	p-value
Contusion volume [mm^3]	77.3 ± 2.1	66.8 ± 3.9	0.044
Hemispheric swelling [%]	11.1 ± 0.8	7.6 ± 1.4	0.049
Water content [%] non-traumatized Hemisphere	81.32 ± 0.06	81.39 ± 0.07	0.436
Water content [%] traumatized Hemisphere	82.78 ± 0.06	82.31 ± 0.18	0.046
ICP [mm Hg]	32.0 ± 2.7	25.5 ± 2.4	0.096
MABP [mm Hg]	89.9 ± 2.4	107.8 ± 3.6	0.001
CPP [mm Hg]	57.3 ± 4.7	82.6 ± 4.2	0.001

Discussion

In head injury, hypoxia and ischemia are important secondary cerebral insults but unlike stroke, are additional causes of brain damage, such as contusion, haematoma or diffuse axonal injury. Thus, for compounds being considered for clinical trials in head injury, anti-ischemic efficacy alone is not sufficient and neuroprotection should also be demonstrated in models of trauma [1]. After focal cerebral ischemia Cerestat reduces the volume of infarcted tissue by 70% [4] but so far, there are no reports on the effects of this substance in models of traumatic brain injury.

In the present study, Cerestat given 15 minutes i.v. after TBI, reduced contusion volume by 13.6% and hemispheric swelling by 31.5%. It could be speculated that the neuroprotective effect of Cerestat would be even more pronounced if the drug had been given immediately after or even before trauma. Cerebral tissue microdialysis in the CCII model has demonstrated that interstitial glutamate concentration peaks immediately after the injury [8]. Thus, to achieve a most effective neuroprotection the drug should be applied as early as possible. As shown peviously with the noncompetitive NMDA receptor antagonist MK-801 [6].

The importance of maintaining adequate CPP after severe head injury is well established [9,5]. 24 hours after contusion CPP was increased after treatment with Cerestat by 56.9%, mainly due to the elevation of MABP. Thus, in addition to the NMDA-receptor blocking effect, the hypertensive effect of Cerestat might be responsible for decrease in contusion volume in Cerestat treated animals.

Our data show a reduction of ICP by 20.3% in the treatment group. The ICP decrease could be a result of the MABP elevation causing cerebral vasoconstriction [9] or brain edema reduction. Since there was a significant correlation between ICP and posttraumatic water content as well as hemispheric swelling, the decrease in ICP is most likely due to a reduction in posttraumatic brain edema.

In conclusion, Cerestat exerts various beneficial effects following experimental traumatic brain injury. It decreases contusion volume, hemispheric swelling and ICP and also increases CPP. Thus, this drug appears promising for further clinical trials in brain trauma. Additional studies may clarify the role of blood pressure elevation in the neuroprotective properties of Cerestat.

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Correspondence: Stefan-Nikolaus Kroppenstedt, M.D., Department of Neurosurgery, Humboldt University, Virchow Medical Center, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Relationship of Neuron Specific Enolase and Protein S-100 Concentrations in Systemic and Jugular Venous Serum to Injury Severity and Outcome after Traumatic Brain Injury

E. G. McKeating, P. J. D. Andrews, and **L. Mascia**

Department of Anaesthetics, University of Edinburgh, Western General Hospital, Edinburgh, U.K.

Summary

Neuron specific enolase (NSE) and protein S-100 have previously been described as markers of brain injury. We aimed to discover whether concentrations of either were raised in arterial and jugular venous serum after traumatic brain injury, and whether serum profiles were related to injury severity and neurological outcome. We recruited 22 patients with a traumatic brain injury who were admitted to the intensive care unit. Paired arterial and jugular venous blood samples were taken on admission, and at 24, 48 and 96 hrs after injury. Samples were analysed for NSE and S-100 by RIA. Concentrations of both NSE and S-100 were increased above controls – mean NSE concentration was highest on admission, whilst mean S-100 peaked at 24 hours after injury. There was a small, but significant difference between jugular venous and arterial concentrations of S-100 ($p = 0.022$). High NSE and S-100 concentrations were significantly related to poor neurological outcome ($p = 0.004$ and $p < 0.001$ respectively). Both serum NSE and S-100 may be of some value in helping to predict outcome after a traumatic brain injury.

Keywords: Astroglial specific protein; neuron specific enolase; protein S-100; traumatic brain injury.

Introduction

Prediction of outcome after traumatic brain injury (TBI) is difficult. There has recently been interest in the measurement of neuron specific enolase (NSE), an isoform of the glycolytic enzyme enolase, which is found in neurons and neuroendocrine cells, in the serum and cerebrospinal fluid (CSF) after brain injury [1,3]. Some investigators have claimed that it is a good quantitative marker of neuronal damage. Others have suggested that measurement of serum or CSF concentrations of protein S-100, a protein present predominantly in astroglial cells, is a suitable quantitative marker of severity of brain injury [4]. Our aim was to measure the profiles of NSE and S-100 in both arterial and jugular venous serum after TBI. We hypothesised that serum concentrations would be raised, that jugular venous concentrations would be higher than arterial and that the serum profiles would be related to injury severity and neurological outcome.

Materials and Methods

We investigated the difference between jugular venous (JV) and arterial concentrations of NSE and S-100 in 21 patients with TBI admitted to the intensive care unit. Data of patient characteristics, consisting of sex, age, Injury Severity Score (ISS) and Glasgow Coma Score (GCS) after non-surgical resuscitation were collected on admission (Table 1). If a patient had an Abbreviated Injury Score >1 for a body region other than the head/neck, he/she was classified as having extracranial injuries. If this was not the case then the patient's injury was classified as an isolated head injury. Injury type was classified as either focal or diffuse from the initial CT scan, read by a single neuroradiologist. Patients whose CT scan appeared normal or showed both diffuse and focal injuries were classified as "neither".

Paired arterial and JV blood samples were taken at designated times after brain injury: on admission (median time 8 h 30 min after injury, range 6 h 30 min – 14 h), at 24 hours, 48 hours and 96 hours. These were allowed to clot and spun down in a refrigerated centrifuge. Serum was then immediately frozen at –25 C. Analysis of serum for NSE and S-100 was performed by immunoradiometric assay (AB Sangtec Medical, Bromma, Sweden). A total of 136 samples (68 pairs) were analysed by a single operator. Standards and samples were analysed in duplicate. Standard curves and NSE and S-100 concentrations were calculated by a personal computer interfaced to a gamma-counter. Glasgow Outcome Scores (GOS) at 6 months after injury were obtained from information supplied by the patients' family doctors. The GOS refer to the following: 1 – dead, 2 – vegetative, 3 – severely disabled, 4 – moderate recovery, 5 – good recovery [2]. Statistical analysis was by means of SPSS Base 7.0 for Windows with

Student's t-test, analysis of variance (ANOVA), linear modelling and linear and logistic regression.

Results

Mean JV concentration of NSE was 11.69 mcg/l at all time points (95% CI [9.81–13.59]). This was not significantly different from the mean arterial concentration, which was 11.16 mcg/l (95% CI [9.66–12.67], p = 0.416). Arterial concentrations at each time point, and comparisons with control samples, are shown in Table 2. ANOVA showed there to be no significant differences between concentrations of NSE at different time points (p = 0.131).

Mean JV concentration of S-100 was 1.13 mcg/l (95% CI [0.59–1.66]), which was significantly higher than the mean arterial concentration which was 1.05 mcg/l (95% CI [0.54–1.55], p = 0.022). Table 2 shows mean arterial S-100 concentrations. ANOVA showed there to be no significant differences between concentrations of S-100 at different time points (p = 0.90). Individual patient profiles for NSE and S-100 are shown in Fig. 1.

There was a inverse relationship between both NSE and S-100 concentrations and the GCS, but neither was statistically significant (p = 0.063 and 0.131 respectively). There was a positive relationship between both NSE and S-100 and the ISS. This was statistically significant for NSE (p < 0.001), but not for S-100 (p = 0.155).

Glasgow Outcome Scores were summarised into two categories – the first representing a good outcome (GOS 4–5, n = 12), the second a poor outcome (GOS 1–3, n = 9). There was a significant difference in age between those with good and poor outcome – mean age was 28.5 yrs (95% CI [20.2–36.8]) for "good" and 42.3 yrs (95% CI [30.3–54.3]) for "poor", p = 0.039), however there was no difference in either GCS or ISS between those with good outcome and those with poor outcome (p = 0.237 and 0.652 respectively). There was a significant correlation between

Table 1. *Data of Patient Characteristics*

Sex: male/female	17/4
Age: range	17–69
median	35
Glasgow coma score: range	3–13
median	6
Injury: Isolated head / + extracranial	11/10
CT: Diffuse/focal/neither	7/10/4
Injury severity score: range	9–38
median	25
Glasgow outcome score: range	1–5
median	4

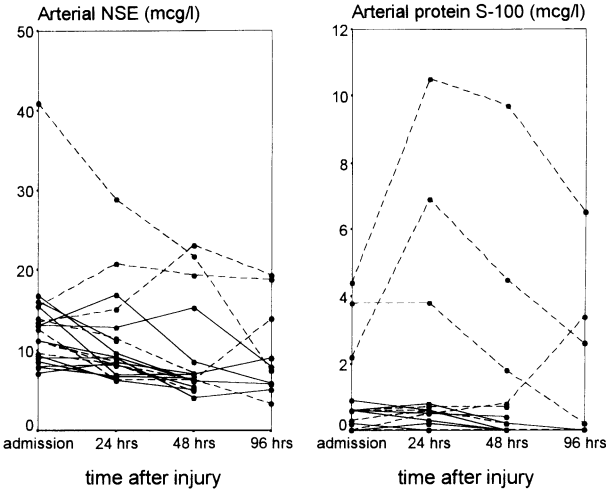

Fig. 1. Patient profiles for arterial NSE and protein S-100. Those patients with poor outcome are shown with broken lines, those with good outcome with solid lines. In those where S-100 was undetectable (<0.2 mcg/ml) the profile lies on the x-axis

Table 2. *Mean Concentrations of NSE and S-100 in Arterial Serum in Volunteer Controls and Patients over a Period up to 96 Hours after Brain Injury. P values are for a two-tailed t-test of patients v controls*

	NSE (mcg/l)			S-100 (mcg/l)		
Time	Mean	95% CI	p value	Mean	95% CI	p value
Controls	6.9	6.3–7.5		ND	–	
Admission	13.7	10.4–17.0	<0.001	0.80	0.24–1.35	–
24 hours	11.2	8.6–13.7	0.003	1.28	0–2.49	–
48 hours	9.5	6.5–12.5	0.096	1.02	0–2.23	–
96 hours	9.2	5.4–13.0	0.220	1.15	0–2.59	–

*ND = not detected (lower limit of detection 0.2 mcg/l).
Patient samples which contained concentrations of S-100 <0.2 mcg/l were assigned a concentration of zero for statistical analysis.

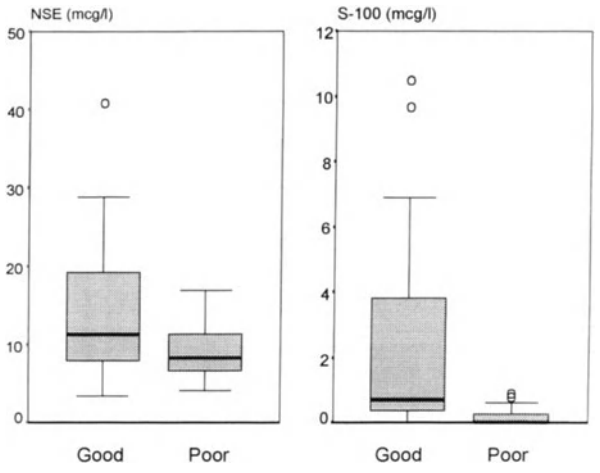

Fig. 2. Boxplots showing median, interquartile range and outliers (o) for arterial concentrations of NSE and S-100 in patients with poor and good outcomes

high serum concentrations of both NSE and S-100 and poor outcome ($p = 0.004$ and $p < 0.001$ respectively), controlling for time (Fig. 2). Patients with poor outcome are shown with dotted lines in Fig. 1. This relationship was still significant if the first three time points only were considered for NSE ($p = 0.014$) and if the first two time points only were considered for S-100 ($p = 0.006$).

There was no significant difference in NSE concentrations between patients with an isolated head injury and those with additional extracranial injuries ($p = 0.813$). However, for S-100, those with an isolated head injury had significantly higher serum concentrations of S-100 than those with additional extracranial injuries – mean 1.91 mcg/l (95% CI 0.75–3.07) v 0.49 mcg/l (95% CI [0.23–0.75]) respectively, $p = 0.024$. Both serum NSE and S-100 were significantly higher in those with a diffuse injury than those with a focal injury (patients classified as "neither" were not included in the analysis) – mean 13.1 mcg/l (95% CI [10.1–16.1]) v 9.5 mcg/l (95% CI [8.1–10.9] for NSE, $p = 0.033$, and 1.20 mcg/l (95% CI [0.58–1.82]) v 0.26 mcg/l (95% CI [0.14–0.38]) for S-100, $p = 0.006$. There was no significant difference in outcome between either those with an isolated head injury and those with additional extracranial injuries ($p = 0.670$) or those with a focal injury and those with a diffuse injury ($p = 0.657$).

Concentrations of S-100 were highly correlated with NSE ($r = 0.619$, $p < 0.001$), and used together in a logistic regression model they were both independently predictive of poor outcome ($p = 0.002$ and 0.027 respectively), even in this small patient population.

Discussion

Concentrations of both NSE and S-100 were increased in JV and arterial serum after TBI. There was a small, but significant, increase of S-100 in JV serum, compared to arterial; surprisingly this was not the case for NSE. Mean NSE levels were highest on admission, whereas mean S-100 levels peaked around 24 h after injury.

This study supports previous work which claimed that serum NSE and protein S-100 concentrations were indicators of severe brain damage. Figure 1 shows that any patient in whom serum arterial S-100, an astroglial specific protein, was found to be above 0.9 mcg/l had a poor neurological outcome. S-100 was undetectable in only 2 patients with poor outcome. It is interesting to note that patients with an isolated head injury had higher arterial concentrations of S-100 than patients with additional extracranial injuries. This may suggest that the brain injury itself was more severe in the group with isolated head injury. Serum concentrations of NSE, an enolase restricted mainly to neurons and neuroectodermal tissue, were also significantly related to outcome, although not as strongly as S-100. These proteins can be regarded as markers of brain damage, and measurement of systemic concentrations of both may help in prediction of outcome.

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Correspondence: E. Grant McKeating, FRCA, Department of Anaesthetics, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, U.K.

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Antioxidant, OPC-14117, Attenuates Edema Formation, and Subsequent Tissue Damage Following Cortical Contusion in Rats

T. Mori[1], **T. Kawamata**[1], **Y. Katayama**[1], **T. Maeda**[1], **N. Aoyama**[1], **T. Kikuchi**[2], and **Y. Uwahodo**[2]

[1] Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, and [2] Third Tokushima Institute of New Drug Research, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan

Summary

Oxygen free radicals contribute to various kinds of tissue injury processes within the central nervous system. It has been suggested that inhibition of free radical formation has the potential to attenuate secondary neural tissue damage involving ischemia or trauma, and antioxidant therapy may offer a promising approach. In the present study, employing a cortical contusion model in the rat, contusion-induced neural damage, was evaluated by investigating edema formation, behavioral activities and histological changes. The effects of the superoxide radical scavenger, OPC-14117, were also tested to determine how free radicals may contribute to such neural damage. The results demonstrated that cerebral contusion induces a progressive decrease in tissue specific gravity representing edema formation, and behavioral deficits in the Morris water maze test and habituation of exploratory activity. Histological examinations revealed necrotic cavity formation in the cortex and selective neuronal death of the hippocampal CA3 region. These changes were significantly attenuated by OPC-14117, which was administered as a single dose immediately following trauma induction. The above results indicate that oxygen free radicals are involved in contusion-induced edema formation, subsequent tissue damage and cognitive deficits. The superoxide radical scavenger, OPC-14117, has a powerful therapeutic potential for preventing secondary cell damage following traumatic brain injury.

Keywords: Antioxidant; cortical contusion; edema formation; lipid peroxidation; OPC-14117.

Introduction

Severe head injury is often complicated by complex secondary or delayed pathophysiological events leading to catastrophic damage to the central nervous system. One of these events is the massive edema formation seen in tissue surrounding cerebral contusions. It is important to elucidate the pathophysiology that underlies contusion-induced edema formation, since one principal goal of treatments for traumatic brain injury is to prevent such secondary damage following injury. Oxygen free radicals may contribute to various kinds of tissue injury processes in the central nervous system. Recent studies have suggested that inhibition of free radicals can improve secondary neural tissue damage in experimental models of ischemia or trauma, and antioxidant therapy appears to have promising possibilities [7,8]. In the present study, in an attempt to clarify whether or not oxygen free radicals contribute to secondary cellular damage following cerebral contusion, we investigated the edema formation, behavioral and histological changes occurring in a rat cortical contusion model, and the effects of the superoxide radical scavenger, OPC-14117, were tested [2,5].

Materials and Methods

Surgical Procedure and Injury Induction

Male Wistar rats (200–250 g) were anesthetized with a gas mixture of 66% nitrous oxide, 33% oxygen and 1% halothane. The head of each animal was secured in a stereotaxic apparatus and an 8-mm diameter craniectomy, centered 3 mm caudal to the bregma, 3 mm lateral to the midline, was performed at the left side of the parietal cranium. The dura was left intact. Cortical contusion was induced with a controlled cortical impact device, as described in detail elsewhere [1]. A 5-mm diameter injury tip, 6 m/sec impact velocity and 3 mm penetration depth were employed for the injury induction. These parameters were chosen in order to provide a moderate level of cortical contusion [1].

Drug Administration

Immediately following the injury induction, the superoxide radical scavenger, OPC-14117, was administered trans-orally (300 mg/kg).

This dose was chosen based on previous experiments in which it had been found to be the most effective [2,5]. Vehicle-administered animals and sham-operated animals were employed as a non-treated control and normal control, respectively.

Behavioral Assessments

Cognitive deficits were assessed by the Morris water maze test (days 6–12 post-injury) [4,8] and habituation of exploratory activity (days 22 and 23 post-injury) [6].

Histological Examinations

After completion of the behavioral testing, the brain was removed and coronal sections of 10 µm in thickness were processed for hematoxylin and eosin (HE) staining. The volume of contusion necrosis and the number of neuronal cells (cells/mm) in the CA3 region were determined with a computerized image analyzing system.

Evaluation of Brain Edema

In a different group of animals, small amounts of brain tissue were sampled from the center of the contusion and from peripheral areas 2.5 mm distant from the center, and the edema formation was evaluated by a tissue specific gravimetric technique [3].

Results

The non-treated/injured rats exhibited significant deficits in their Morris water maze performance and habituation of exploratory activity, as compared to the sham-operated rats, indicating that the cortical contusion had induced cognitive dysfunction (Fig. 1). Administration of OPC-14117, while showing no significant effect, did reveal a tendency to improve the water maze performance. On the other hand, the impairment of habituation of exploratory activity was significantly attenuated by the OPC-14117 treatment ($p < 0.05$). The changes in specific gravity indicated that cerebral contusion induced progressive edema formation in both the central and peripheral areas of the contusion. Such edema formation was significantly attenuated by the examinations OPC-14117 administration especially in the peripheral areas (Fig. 2). The histological examinations revealed contusional necrosis measuring 13.55 ± 5.25 mm^3 in the non-treated/injured animals and 1.91 ± 0.55 mm^3 in the treated/injured animals, implying that OPC-14117 had significantly reduced the size of contusion ($p < 0.01$) (Fig. 3). The cell number of the CA3 region was 120 ± 12.4 cells/mm in the normal control, 73.6 ± 9.86 cells/mm in the non-treated/injured animals, and 111.2 ± 10.2 cells/mm in the treated animals, indicating that cerebral contusion had induced selective neuronal cell death in the CA3 region, and such neuronal death was significantly attenuated by the OPC-14117 administration ($p < 0.01$).

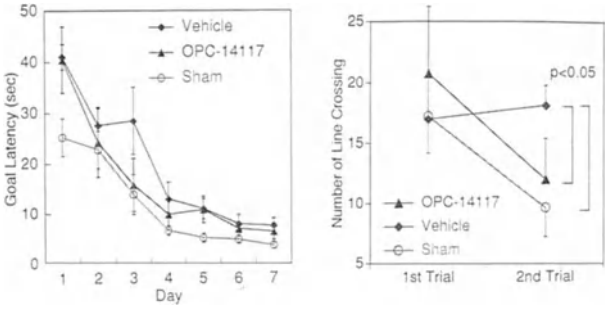

Fig. 1. Cortical contusion induced deficits in Morris water maze performance (left) and habituation of exploratory activity (right), as compared to sham-operated animals. The OPC-14117 treatment, while showing no significant effect, did tend to improve the water maze performance. The impairment of habituation of exploratory activity was significantly attenuated by the OPC-14117 treatment

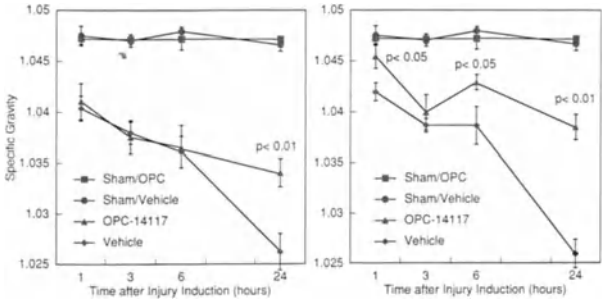

Fig. 2. Changes in specific gravity following contusion demonstrated that cerebral contusion induces progressive edema formation in both the central (left) and peripheral areas (right) of the contusion. Such edema formation was significantly attenuated by OPC-14117 administration. The effects of OPC-14117 were more evident in the peripheral areas than in the center of the contusion, suggesting that superoxide radicals may contribute to edema formation especially in the peripheral areas of the contusion

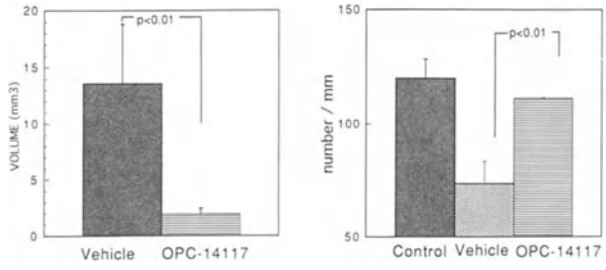

Fig. 3. Histological examinations revealed that OPC-14117 administration significantly attenuated the contusional necrosis volume (left) and pyramidal cell death in the CA3 region (right) following contusion

Discussion

The results of the present study demonstrate that experimental cortical contusion induces significant impairments of cognitive functions and a progressive formation of brain edema, and that OPC-14117 administration immediately after the injury can reduce each of these injury-related deficits, as well as the size of contusional necrosis and selective CA3 neuronal death.

It has been reported that free radicals, such as superoxide, are produced in large amounts following brain injury [7,8]. Oxygen free radicals are highly toxic products of the molecular oxygen of hydrogen peroxide (H_2O_2), which can induce cellular injury by oxidizing lipids, proteins or nucleic acids. Lipid membranes, particularly of the microvasculature, are vulnerable to the action of free radicals because of their high content of phospholipid-containing polyunsaturated fatty acids. This free radical-mediated process may contribute to breakdown of the blood-brain barrier and subsequent edema formation in some pathological conditions [7,9].

Administration of OPC-14117 markedly reduced the size of the cortical necrosis, to approximately one seventh in volume. Since this drug cannot treat the primary injury, such findings indicate that OPC-14117 has a powerful potential to attenuate the secondary cell injury processes following cerebral contusion. The generation of free radicals in injured membranes causes extensive cellular damage by eliciting lipid peroxidation in chain reactions, during which the lipids produce additional free radicals. OPC-14117 may act to terminate these chain reactions by scavenging free radicals before they are able to induce secondary and irreversible neuronal damage. Inhibition of such oxygen radical-mediated destructive events at the earliest moment of the injury process could facilitate lesser formation of brain edema and greater sparing of neuronal cells, so resulting in a more complete behavioral recovery.

Histological examinations also revealed selective neuronal death of the CA3 region, which is remote from the primary site of injury. The CA1 region just beneath the cortical contusion did not display any significant cell loss. The CA3 neuronal death was therefore not induced by the direct force of the controlled cortical impact device. Since the administration of OPC-14117 attenuated the selective neuronal death of the CA3 region, as well as the size of cortical contusion, two explanations for such CA3 neuronal death can be considered: one is that free radical formation directly contributes to the CA3 cell death, and the other is that the CA3 cell death is attributable to the volume of cortical contusion. Further studies are needed to establish the precise mechanisms underlying the selective neuronal death of the CA3 region.

In conclusion, the present results suggest that oxygen free radicals are intimately involved in contusion-induced edema formation and cognitive deficits, and the superoxide radical scavenger, OPC-14117, has a powerful therapeutic potential for preventing secondary cell damage following traumatic brain injury.

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Correspondence: Tatsuro Mori, M.D., Department of Neurological Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173, Japan.

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Failure of Cerebral Autoregulation in an Experimental Diffuse Brain Injury Model

R. Prat, V. Markiv, M. Dujovny, and **M. Misra**

Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, U.S.A.

Summary

The normal cerebral circulation has the ability to maintain a stable cerebral blood flow over a wide range of cerebral perfusion pressures and this is known as cerebral autoregulation. Autoregulation may be impaired in the injured brain. Closed head injury was induced in 28 Sprague-Dawley rats weighing 400–450 g. Four groups were studied: control and groups, head injured by weight drop from one meter height using 350 g, 400 g and 450 g respectively. CBF was monitored using laser-Doppler flowmetry along with monitoring of ICP and arterial blood pressure. If the correlation coefficient between CBF and CPP was >0.85 and CPP was within normal range, loss of autoregulation was hypothesized. Loss of autoregulation was seen in all groups of injured rats during first four hours. A statistically significant difference ($p = 0.041$) was seen in the trequency of loss of autoregulation between injured and control animals. No loss of autoregulation was observed in the control group. In conclusion CBF and CPP provide information about loss of autoregulation in diffuse brain injury. Decrease in CBF and increase of ICP is observed as a result of loss of cerebral autoregulation. Knowledge of loss of autoregulation could help in the management of head injured patients.

Keywords: Autoregulation; cerebral perfusion pressure; diffuse brain injury; intracranial pressure; laser Doppler flowmetry.

Introduction

Around 55% of patients with head injury who are in coma on admission suffer from diffuse brain injury [10,22]. Acute and delayed ischemic events have been reported to be the single most important cause of secondary brain damage. The ability of the normal cerebral circulation to maintain a stable cerebral blood flow over a wide range of cerebral perfusion pressures or mean arterial pressures is referred to as "cerebral autoregulation" [20,25]. This mechanism of cerebral autoregulation may become impaired in the injured brain [3,16,19,25] and can cause immediate or delayed cerebral ischemia, an entity considered the most important cause of secondary brain injury [12,16,20,25]. Several methods have been employed to estimate what is an adequate level of cerebral blood flow. Methods, such as jugular venous oxygen saturation [28], 133 Xenon CT scanning [21], SPECT-PET studies [31], magnetic resonance imaging [20], thermal diffusion flowmetry [4] and transcranial cerebral oximetry [6,13,26], provide either direct or indirect evidence about CBF. We evaluated the value of laster Doppler flowmeter in experimentally head injured rats (2). The purpose of our study was to compare CBF with cerebral perfusion pressure (CPP) as an index of autoregulation in this model.

Material and Methods

Twenty-eight Sprague-Dawley rats weighing 400–450 g were used. They were anesthetized with 50 mg/kg of pentobarbital sodium by intraperitoneal injection. Continuous monitoring of arterial blood pressure was established. The rat was positioned on foam and a closed head injury was induced using the device designed by Marmarou *et al.* [9,21]. The animals were divided into four groups: one group was considered a control; the other three groups were injured with weights of 350 g, 400 g and 450 g, respectively, dropped from a 1 m height. A laser Doppler probe (650 microns) was introduced in the right frontal lobe, and a subdural catheter introduced behind the coronal suture on the right side to measure intracranial pressure. The cerebral blood flow, volume, and velocity were monitored using laser Doppler flowmeter (model BPM2, Vasamedics, ST. Paul, MN, USA). Average values of readings were recorded for each group every five minutes during the first hour and every 15 minutes after that. The ICP was measured with a Camino intracranial measuring unit (Camino laboratories, San Diego, CA, USA), and the arterial pressure was measured using an arterial pressure sensor (Sorenson Transpack, Abbott Laboratories, Chicago, IL, USA). All parameters were observed for a

maximum of eight hours in each rat surviving for the entire experiment (n = 17); otherwise rats were monitored for at least six hours (n = 28). Cerebral perfusion pressure was calculated from mean arterial pressure and intracranial pressure values (CPP = MAP – ICP). We did a correlation study to establish the relationship between cerebral blood flow, a dependent variable, with the independent variable, cerebral perfusion pressure. We considered that periods with a level of correlation greater than 0.85 had a close relationship between cerebral blood flow and cerebral perfusion pressure, implying a possible loss of autoregulation. A correlation coefficient greater than 0.85 was considered the lower limit for close correlation; a significance level of $p < 0.05$ was established.

Results

Evaluation of Autoregulation

We found no periods of high correlation during the first four hours in the control group. Nevertheless, during first four hours of study five periods of high correlation were identified in the 350 g impact group, six periods in the group with an 400 g impact, and eight periods in the group injured with 450 g. The statistical analysis also showed periods with changes in cerebral perfusion pressure and changes in cerebral blood flow, however, these changes did not always indicate a loss of vascular autoregulation. We considered the range of CPP in the control group (mean ± 1SD) as the range in which normal cerebral autoregulation is expected; those periods with high correlation, but CPP out of this range, were not classified as periods loss of cerebral autoregulation. According to these assumptions, three periods of loss of autoregulation were observed during the first four hours in the group injured with 350 g impact, four in the 400 g impact group, and four in the 450 g impact group. In the next four hours, two periods of loss of autoregulation were recorded in both A and B groups with 450 g impact (Fig. 1). We performed a Chi-square analysis and found a statistically significant difference ($p = 0.041$) between the number of periods of loss of autoregulation during the first four hours and loss of autoregulation during the second four hours (Fig. 2). During periods of loss of autoregulation, CBF was consistently lower and ICP higher than the baseline values. Although no significant differences in CBF and ICP were observed, these two additional findings may validate our hypothesis of the detection of periods of autoregulation based on study of the correlation between CBF and CPP.

Discussion

The main aim in the treatment of patients with head injury is prevention of secondary brain damage due to post-traumatic ischemia [16,20,24,25]. A direct relationship between an increase of the ICP and a decrease of cerebral blood flow (CBF) cannot be established because an increase of the main arterial pressure can compensate in these situations. In addition, ischemic levels of CBF may prevail even without a significant increase in ICP. Cerebral perfusion pressure (CPP) can be considered as an indirect parameter of CBF. However, CPP does not always correlate with CBF because cerebral blood flow depends not only on the perfusion pressure but also on vascular resistance [1,3]. The variability of cerebral vascular resistance plays an important role in the maintenance of a constant cerebral blood flow in a wide range of values of CPP [1,19,20,24]. Nevertheless, in the injured brain this function may be impaired transiently for short times and, therefore, a

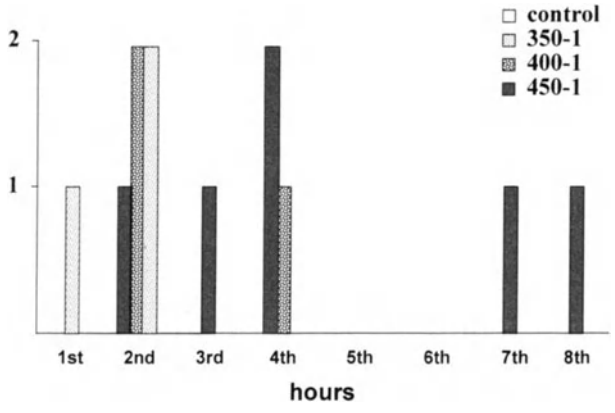

Fig. 1. Number of periods of time with loss of autoregulation in the four groups studied

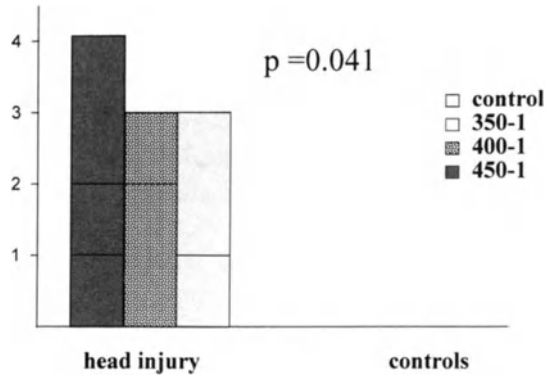

Fig. 2. Number of periods of time with loss of autoregulation in the head injury group (3 groups) compared to the control group during the first four hours (Chi-square = 0.041)

direct and continuous measurement of CBF may be extremely important to detect autoregulation. Under these conditions, treatment that increases CPP in an injured brain may destabilize CBF and by increasing ICP worsen the patient's condition [2,4]. This lead us to evaluate the use of laser Doppler flowmeter to monitor the changes of CBF in a model of diffuse brain injury in rats. Laser Doppler flow studies have been used in the past in both experimental [5,8,14,27,29] and clinical [2,12,16,18] studies. Its limitation is that measurements are from a localized region of monitoring [7,8] and artifacts are easily caused by movement or light [7,8], placement of the probe [2,12], errors in the calibration [2], and statistical analysis [15]. However, laser Doppler flowmetry does provide noninvasive real time and continuous monitoring of CBF.

Evaluation of Autoregulation

The statistical analysis of changes in post-traumatic autoregulation in our study showed evident differences between the head injury group and the control group. There were periods of loss of autoregulation in the head injury group with an increased number of periods of loss of autoregulation observed in the group that suffered the most severe impact; that is, the loss of autoregulation was directly proportional to the severity of injury. Our study detected loss in cerebral autoregulation within a period of one hour, but more frequent acquisition of data could provide information for shorter periods as well [5,16]. Online computerized data acquisition and calculation would be extremely helpful in the detection of these shorter periods of loss of autoregulation. The maximum disruption of autoregulation was seen in our study during the first four hours following injury. However, an important statistical correlation could be demonstrated between CPP and CBF at different periods. Although during certain periods, CPP did not increase or decrease to a level that could induce autoregulatory response, these periods were not considered to have loss of autoregulation [8,17]. Different biochemical changes have been reported using spectroscopy studies that support the possibility of an altered response to trauma during the first hours. Experimental studies have also shown a decrease in pH within 40 minutes after trauma and a reduction in the ratio of phosphocreatine to inorganic phosphate about the fourth hour after injury. This decrease could indicate reduction of CBF or reduced tissue oxygenation [23,30]. Therapeutic implications could be assessed after the detection of periods of loss of autoregulation. The autoregulation is dependent on the threshold of CPP during this period and CPP, in turn, is dependent on MAP and ICP [11]. During loss of autoregulation, an increase in CPP could increase CBF; in addition, an increase in CBF could be associated with an increase in ICP and delayed ischemia. However, if autoregulation is intent, an increase in CPP would decrease ICP, and increase cerebral blood flow [11,20]. Furthermore, careful study of the volume and velocity of changes in CBF could explain the nature of the increase in flow eg due to hyperemic events or vasospasm [2,11].

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Correspondence: Manuel Dujovny, M.D., Department of Neurosurgery (M/C 799), 912 South Wood Street, Chicago, IL 60612, U.S.A.

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Early Cerebral Blood Volume after Severe Traumatic Brain Injury in Patients with early Cerebral Ischemia

M. L. Schröder, J. P. Muizelaar, P. Fatouros, A. J. Kuta, and **S. C. Choi**

Department of Neurosurgery, University Hospital Vrije Universiteit, Amsterdam, The Netherlands

Summary

Recent early cerebral blood flow (CBF) studies on severe head injury have revealed ischemia in a substantial number of patients with a variety of CT diagnoses. However, the underlying derangements causing this early ischemia are unknown, but cerebral blood volume (CBV) measurements might offer some insight into this pathology. Therefore, acute CBF and CBV measurements were performed in 51 adult severely head injured patients within 24 hours after injury. For this purpose the stable Xenon-CT procedure was used for assessment of CBF, and a dynamic CT imaging technique was used for determining CBV. All ischemic patients were found among 35 subjects studied within 4 hours after injury (31%). Based on the occurrence of regional ischemia seven patients with varying anatomical lesions on CT were selected for comparison between CBF and CBV in ischemic and non-ischemic areas. Both CBF ($p < 0.02$) and CBV ($p < 0.02$) exhibited significantly lower values in the ischemic zones. Ten patients showing a subdural hematoma (SDH) were studied preceding surgery and seven were ischemic in at least one lobe or brainstem. Ipsilateral CBF was lower than CBF in the contralateral side ($p < 0.1$). CBV at the ipsilateral side was significantly reduced compared to the contralateral side ($p < 0.05$). Follow-up studies were performed in three ischemic patients and in one borderline ischemic patient immediately after removal of SDH showing a striking increase in both CBF and CBV. In the remaining 26 subjects follow-up studies were obtained between day 2 and day 8 and all patients showed CBF values within the normal range. These data evidently support the suggestion that compromise of the microvasculature is the cause of early ischemia, rather than vasospasm of the larger conductance vessels. This has implications for acute post-traumatic therapeutical strategies and management of the severely head injured patient and may lead to testing of new drugs that are effective in interfering with processes causing this ischemia.

Keywords: Cerebral blood volume; cerebral ischemia; traumatic brain injury.

Introduction

The critical role of ultra-early cerebral ischemia in the pathophysiology of severe head injury becomes increasingly evident [1,12], but its cause remains controversial. At least 30% of severely head injured patients sustain an episode of ischemia in the period immediately following severe head injury [1,12]. Early ischemia, despite adequate perfusion pressure and oxygenation, lasts in most cases for only a few hours [1,12]. Even with reversal of this ischemia, the patients who present with ischemia have a very poor prognosis, the majority of them dying within 48 hours after injury [12]. This confirms that the brain is most vulnerable [4,5] during the early phase. In order to detect ultra-early ischemic events and elucidate the cause of this phenomenon we have performed stable Xenon-CT cerebral blood flow and cerebral blood volume (CBV) measurements in severely head injured patients during the initial and follow-up diagnostic CT scans. A reason to measure CBV is that in case of low CBF, knowledge of CBV allows insight into the cause of low CBF [8]. Previously, we have hypothesized that early ischemia as a consequence of the primary insult is largely caused by vasospasm of the larger conductance vessels [1,8]. However, in this paper we present data to the contrary.

Materials and Methods

Patient Population

We report a series of 51 patients with severe blunt head injury (GCS 8 or less), in whom combined CBF/CBV studies were performed within 24 hours post-injury. The patients' ages ranged from 15 to 82 years. Those known to have been hemodynamically unstable or braindead on their first neurological exam were excluded from this series. The patients were classified according to the lesion on the diagnostic CT-scan. Three patients had epidural hematomas (EDH), but measurements were all performed imme-

diately after removal of this EDH, as was also done in 2 of the 12 patients who had a subdural hematoma (SDH). Twelve patients had intracerebral lesions, 4 had diffuse swelling, and 7 patients had no abnormalities on the initial computed tomography scan (CT). In the NICU all patients were treated according to a standard head injury protocol which is described elsewhere [16].

Determination of CBF and CBV

Following airway and hemodynamic stabilization, all patients underwent a standard emergency CT scan of the brain. This was immediately followed by a stable Xenon-CT CBF and CBV study [2]. Follow-up studies were performed 2 to 8 days after injury. Patients with an EDH or SDH were studied prior to evacuation only if patient's status did not require immediate intervention.

Definition of Ischemia

Ischemia was defined as a CBF lower than 20 ml/100 g/min in at least one entire lobe, in the basal ganglia or in the brainstem [14].

Results

CBF and CBV Measurements

Fifty-nine combined CBF and CBV studies were performed emergently in a series of 51 patients. Ischemia was found in 11 of these 51 studies (22%). However, all 11 patients with ischemia were found among the 35 patients studied between 0.7 and 4 hours after injury, for an incidence of ultra-early ischemia of 31%. Ischemia was more common in patients with SDH and diffuse swelling. Seven patients who exhibited both an ischemic and non-ischemic zone were selected for comparison of CBF and CBV in those areas. These results are presented in Table 2. There was a significant difference between both CBF ($p < 0.02$, Wilcoxon matched signed rank test) and CBV ($p < 0.02$, Wilcoxon matched signed rank test) in the respective areas with the lowest values in the ischemic zones. Follow-up studies were performed in 30 subjects between day 2 and 8 after injury. All patients had CBF values above the ischemic threshold. We then examined CBF and CBV data of 10 patients with a predominant SDH in situ with special attention to the existence of ischemia in one or both hemispheres. Seven of these patients had ischemia in one hemisphere, 4 of whom are presented in table 3 while the remaining 3 had bilateral ischemia excluding them from Table 3. There were 3 patients without ischemia. In all patients a midline shift was present on the initial CT-scan. The temporal and parietal regions were the most frequent sites of the hematomas. This was also the area of the most profound reduction in CBF and CBV. These results are shown in table 3. All measurements in SDH group with ischemia were performed prior to evacuation of the clot. Three patients with ischemia demonstrated marked improvement of CBF and a large increase in CBV immediately after surgery (Table 4).

Table 1. *The Changes Occurring in CBF, CBV, TCD Velocity, and Brain Microscopical Anatomy with Changes in the Cerebral Vasculature*

	CBF	CBV	TCD[a]	BMA[b]
Vasospasm conductance	↓	↑	↑	–
Microcirculatory compression	↓	↓	↓	1
Microcirculatory contraction	↓	↓	↓	2
Microcirculatory plugging	↓	↓	↓	3

[a] Transcranial Doppler; Lindegaard Index, VMCA/VICA [14].
[b] Brain microscopical anatomy. *1* Small extravascular spaces, swelling. *2* Normal extravascular spaces, intravascular aggregates. *3* Cell aggregates in microcirculation.

Table 2. *Comparison of CBF and CBV in Regions with and without Ischemia*

Patient number	Age (yr) /Sex	Intracranial Lesion	GCS Score	PCO2	MABP	Ischemia		No ischemia		Location ischemia
						CBF	CBV	CBF	CBV	
1	30/M	SDH	4	31	116	19	3.9	31	4.5	ipsil. (front, temp, par.)
2	49/F	SDH	4	33	132	9	1.3	21	2.6	ipsil. (front, temp, par.)
3	24/F	SDH	5	31	99	14	3.1	21	4.7	ipsil. (front, temp, par.)
4	15/M	small SDH	6	36	65	9	1.8	30	5.7	frontal lobes
5	17/F	"Normal"	3	24	60	18	1.7	43	3.9	occipital lobes
6	6/M	Swelling	6	37	118	17	3.2	54	8.7	unil. (front, temp.)
7	47/M	Contusion	3	36	92	18	2.6	38	3.9	ipsil. (temp.)
Mean (SD)			4.4 ± 1.3	33 ± 4.5	87 ± 24	15 ± 4.3	2.5 ± 1.0	35 ± 1.9	4.9 ± 1.9	
Normal (SD)								53 ± 13	6.1 ± 0.9	

Values are expressed as means ± standerd deviations.
PCO_2 = mm Hg, MABP = mm Hg, CBF = ml/100 g/min, CBV = ml/100 g.

Table 3. *Ipsi-and Contralateral CBF and CBV Values in Respectively Ischemic and Non-Ischemic Patients with a Subdural Hematoma (SDH)*

Ischemia (n = 4)				No ischemia (n = 3)			
ipsilateral		contralateral		ipsilateral		contralateral	
CBF	CBV	CBF	CBV	CBF	CBV	CBF	CBV
15.9 ± 3.7[a]	3.0 ± 1.1[b]	20.6 ± 4.9	3.9 ± 1.3	39.7 ± 14.5	5.0 ± 1.1	37.0 ± 10.8	4.6 ± 1.0

[a] $p < 0.1$ compared to the contralateral side.
[b] $p < 0.05$ compared to the contralateral side.
CBF = ml/100 g/min, CBV = ml/100 g.

Table 4. *Pre-, and Post-Operative CBF/CBV Data in 3 Ischemic Patients with a SDH*

	PCO_2		MABP		CBF		CBV	
	pre-op.	post-op.	pre-op.	post-op.	pre-op.	post-op.	pre-op.	post-op
Patient A	25	37	91	93	[a]18.0/19.0	[a]75.0/55.0	[a]3.7/3.6	[a]7.5/7.3
Patient B	32	25	111	79	[a]17.9/16.8	[a]33.5/37.4	[a]3.6/3.6	[a]6.1/5.5
Patient C	33	30	120	79	[a]13.9/17.6	[a]42.2/41.0	[a]1.3/2.6	[a]4.5/3.5

[a] Values ipsilateral to SDH.
PCO_2 = mm Hg, MABP = mm Hg, CBF = ml/100 g/min, CBV = ml/100 g.
The pre-operative studies were obtained within 4 hours after injury.
Values are expressed as means ± standard deviations.

Discussion

The incidence and time course of decreased CBF and ischemia is becoming more defined as the first CBF measurements are obtained closer to the time of injury [12,13]. However, the cause of ischemia after severe head injury remains a matter of speculation. By investigating this question by a variety of techniques (Table 1) an answer may be found. In this paper we focus on CBV, but in limited numbers of patients we have ultra-early transcranial Doppler (TCD) data showing that flow velocities are normal or low in relation to the CBF.

Early ischemia lasts mostly from 0–8 hours post injury [1,12] and is, in our opinion, part of the ongoing, primary insult. Early ischemia, accompanied by reduced CBV, apparently occurs in patients with a diversity of CT diagnoses, varying from diffuse swelling to intracranial mass lesions to a "normal" CT-scan. In patients with early pericontusional ischemia we have found marked reduction in CBV which on histological examination was found to be due to microvascular compromise caused by astrocytic swelling and leucocyte plugging [11]. The finding of low CBV in the present series is compatible with these same causes for ischemia as in the patients with contusions. However, it will be much more difficult to obtain histological confirmation as it will not be feasible to take biopsies from patients who do not need intrinsic brain surgery for other reasons.

Therapeutic Implications

Unravelling the mystery of the cause of early ischemia may dramatically change current therapeutic strategies. For instance, if vasospasm of the conductance vessels would be the cause, using either a calcium channel blocker such as Nimodipine or infusion of a magnesium solution, both of which are known to cause relaxation of acutely vasospastic arteries, may be indicated. However, Nimodipine administration to an unselected group of patients with severe head injury has been shown not to improve outcome [17] but it should be kept in mind that this drug was given approximately 8 hours post injury, when low CBF already has spontaneously reversed. The effect on outcome of Nimodipine administered to only those patients with traumatic subarachnoid hemorrhage, is probably related to the prevention of vasospasm on days 4 to 6 [3,7]. Secondly, the blood pressure may need to be raised as the chance of promoting cerebral edema with such a manoeuvre during vasospasm is remote. However, if the microcirculation would be compressed by early cerebral edema [15] a vicious circle of edema, ischemia, more

edema etc. might ensue, requiring measures to "shrink" the brain. It is also possible that the vessels of the microcirculation are contracted during the early post-traumatic phase, e.g. by massive sympathetic discharge or because of lack of intrinsic endothelium derived vasodilators, each requiring administration of specific microvascular vasodilators [9,10]. Finally, segments of the microcirculatory vessels may be plugged with leukocyte aggregates necessitating anti-inflammatory agents (such as indomethacin [6], colchicine, interleukin 1–4) or oxygen radical scavengers (such as PEG-SOD) [9]. Although the precise cause of early ischemia occurring after severe head trauma is unclear, we now can exclude vasospasm as the cause of this type of ischemia. Further investigation is needed, focusing on the clarification of the exact origin of the microvascular compromise which leads to ischemia and decreased CBV.

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Correspondence: Marc L. Schröder, M.D., Ph.D., Department of Neurosurgery, University Hospital Vrije Universiteit, De Boelelaan 1117, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

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Moderate Hypothermia and Brain Temperature in Patients with Severe Middle Cerebral Artery Infarction

S. Schwab[1], **S. Schwarz**[1], **A. Aschoff**[2], **E. Keller**[1], and **W. Hacke**[1]

[1] Departments of Neurology and [2] Neurosurgery, University of Heidelberg, Federal Republic of Germany

Summary

Elevated temperature is known to facilitate neuronal injury after ischemia. After head injury a gradient between temperature and body temperature of up to 3°C degrees higher in the brain has been reported. Hypothermia may limit some of the deleterious metabolic consequences of such increased temperature.

In 20 patients who had suffered severe ischemic stroke in the middle cerebral artery (MCA) territory, intracerebral temperature combined with ICP monitoring was recorded using two different thermocouples, with epidural, and parenchymatous measurements. Mild hypothermia was induced using cooling blankets. Patients were kept at 33°C core temperature for 48 to 72 hours.

In all patients brain temperature exceeded body-core temperature by at least up to 1°C (range 1.0–2.1°C). Systemic cooling was effective and sustained hypothermic (33–34°C) brain temperatures. With mild hypothermia critically elevated ICP values could be controlled. 12 patients survived the hemispheric stroke with a mean Barthel index of 70. Severe side effects of hypothermia were not detected.

After MCA stroke, human intracerebral temperature is higher than central body-core temperature. Mild hypothermia in the treatment of severe cerebral ischemia using cooling blankets is safe and does not lead to severe side effects. Mild hypothermia can help to control critically elevated ICP values in severe space-occupying stroke and may improve clinical outcome in these patients.

Keywords: Hypothermia; middle cerebral artery infarction.

Introduction

In the past 10 years there has been much interest in using modulation of brain temperature to avert the brain damage caused by ischemic injury experimental stroke and other neuronal injuries [7,18]. In several animal models of focal cerebral ischemia, hypothermia reduced infarct volumes up to 90% [2,10,20], and an increase in brain temperature has been shown to have a significantly adverse effect on histopathological findings and outcome after cerebral ischemia [4,5].

Body temperature and brain temperature can differ significantly in neurosurgical patients [13]. To date there are no reports available on brain temperature monitoring in patients with severe ischemic stroke. Even though hypothermia has a potent cerebroprotective effect after experimental focal ischemia, clinical studies modulation of brain temperature after middle cerebral artery (MCA) infarction are lacking. We report our experience of brain temperature monitoring and mild hypothermia therapy in patients with acute severe MCA infarction [8].

Patients and Methods

This study is based on 20 consecutive patients, fourteen men and six women (35 to 64 years of age, with a mean age of 49 ± 12.3 years), who had suffered acute MCA territory stroke and were admitted to the neurocritical care unit for treatment of elevated intracranial pressure (ICP). Inclusion criteria were: clinical and computed tomographic (CT) evidence of acute, large MCA infarction (which consisted of early large parenchymal hypodensity and signs of local brain swelling such as effacement of the sulci and compression of the lateral ventricle); follow-up CT examinations within the first 4 days after stroke showing an increased space-occupying effect; further neurological deterioration after admission to the NCCU; no previous disabling neurological disease; and no terminal illness.

The ICP was monitored in all patients using one of two different types of intraparenchymatous sensor or transducer (Spiegelberg™ pneumatic transducer, Spiegelbert AG, Hamburg, Germany, n = 13; Codman™ microsensor, Johnson & Johnson, Raynham, Massachusetts, USA, n = 7). ICP devices were inserted ipsilaterally to the affected hemisphere in thirteen patients and bilaterally in seven patients. Clinical data were obtained daily from all patients and assessed using the Scandinavian Stroke Scale (SSS) and

Glasgow Coma Scale (GCS) [16,19]. Four weeks after stroke, clinical outcome was assessed using the SSS and Rankin scale (RS) and activities of daily living rated using the Barthel index (BI) [11,14].

Brain temperature was measured with two different temperature sensors. The Spiegelbreg intraparenchymatous ICP probe, which also can be used as an intraventricular ICP device, has a thermistor in the tip of the probe. The accuracy of the temperature measurements is lower than 0.1°C. A Foley temperature catheter for bladder temperature reading with a resolution of 0.1°C was used for monitoring of body core temperature (Mon-a-therm™, Mallinckrodt, St. Louis, Missouri, USA). During all procedures, the patients were sedated and received neuromuscular blockade with atracurium (0.3–0.6 mg/kg i.v.). Monitoring in the neurocritical care unit always consited of continuous monitoring of ICP, electrocardiograms, and blood pressure. Room temperature in the intensive care unit was between 18 and 20°C. In this study, only cooling blankets (Bair Hugger™, Augustine Medical, Saint Prarie; MN, USA) with cool ventilator air fanning the patients body surface were used for external cooling. After the body-core temperature reached 33°C, it was kept between 33° and 34°C for 48 to 72 hours. During the next 12 hours the patient was passively rewarmed to normal temperature values.

Results

Patients

The mean SSS acore on admission was 23.6 ± 6.5 (median 27). Mean GCS on admission was 9 points (range 4–13). Each patient presented with severe hemiparesis and forced eye and head deviation and each had suffered a large middle cerebral artery (MCA) territory stroke. Eight of 20 patients who underwent ICP monitoring died. Each of the twelve survivors was discharged to a rehabilitation programs. The mean SSS score 4 weeks after stroke was 31.3 ± 8.3. The mean Barthel index of the surviving patients was 65 (range 55–80) and the mean Rankin scale 3 points (range 2–4).

The mean interval between onset of symptoms of ischemic stroke and insertion of the monitoring device was 9 hours (range from 4 hours to 24 hours). The average monitoring period varied between 3 and 7 days (mean 4.9 ± 2.5 days). The mean initial ICP was 21.9 ± 10.4 mm Hg (range 13–36 mm Hg). In all patients, ICP values decreased with initiation of hypothermia to mean values of 14.5 ± 4.2 mm Hg. During rewarming ICP values rose continuously to highest measured mean values of 19.4 ± 8.7 mm Hg. Moderate hypothermia was not associated with significant changes in serum amylase, or lipase. However, there was a significant decrease in platelet count over the hypothermia period from a mean of 160 cts/nl to 95 cts/nl. The activated partial-thromboplastin time was slightly higher during hypothermia than before and after hypothermic treatment.

Brain Temperature and Bladder Temperature

In each patients intraparenchymatous brain temperature exceeded body-core temperature, by a mean of 1.5 ± 0.3°C (range 1.0° to 2.1°C). The difference between brain temperature and body-core temperature varied individually and over the measurement period. Hence, the difference between brain and body-core temperature was independent of the measured ICP or cerebral perfusion pressure (CPP). In the seven patients in whom bilateral intraparenchymatous temperature was measured, a significant temperature gradient between the infarcted and contralateral hemispheres was observed. In three patients, in whom bilateral ICP and temperature monitoring was started within the first six hours after the MCA infarction, brain temperatures were up to 0.6°C higher in the infarcted hemisphere than in the contralateral hemisphere. After 12 hours lower temperatures were found in the infarcted hemisphere and subsequently a gradient of 0.6°C to 0.9°C was noted (Figs. 1, 2).

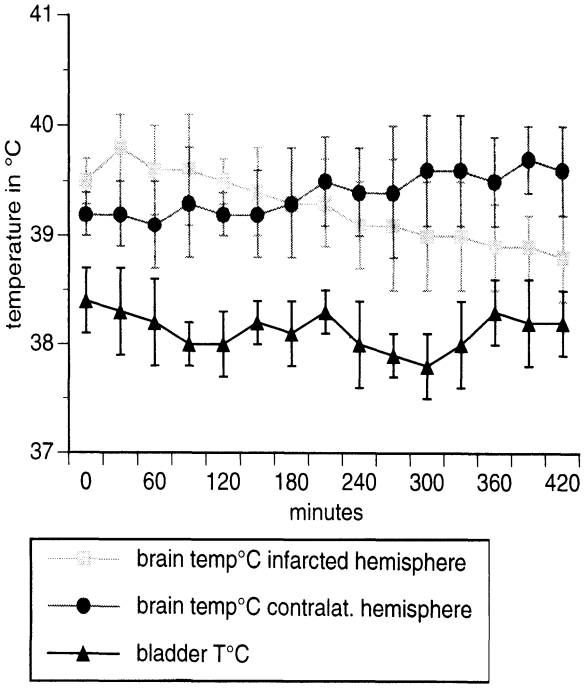

Fig. 1. Bilateral intraparenchymatous temperature monitoring with representative bladder temperatures in patients showing higher temperatures in the infarcted hemisphere within the first hours after stroke. Monitoring began within 6 hours after onset of symptoms. Measurements were taken very 30 minutes

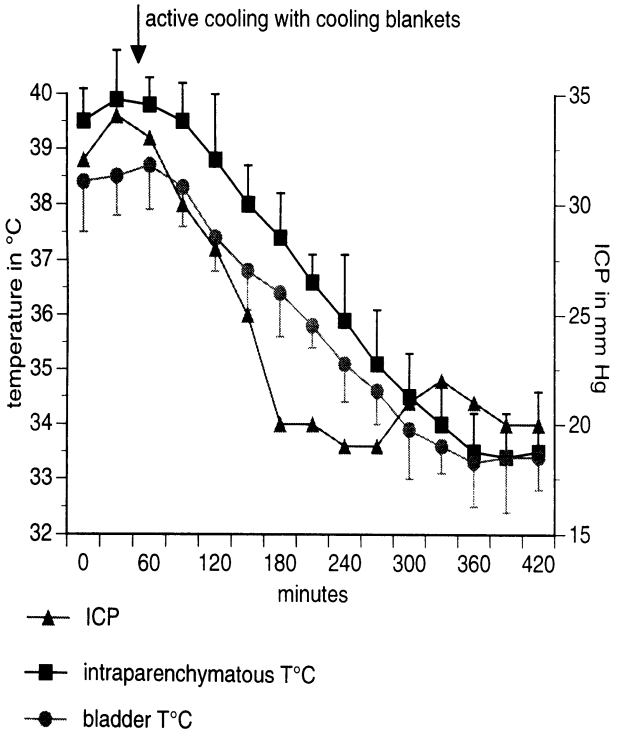

Fig. 2. Temperature measures and ICP course after induction of cooling with cooling blankets and alcohol washing

Discussion

Busto addressed the importance of brain temperature in experimental cerebral ischemic injury [3]. He was able to show a reduction in brain damage depending on the level of brain temperatures during ischemic. In our study, brain temperatures in stroke patients were consistently higher than body-core temperatures. These results comfirm the findings of Mellergard and others, who showed a significant gradient between body-core and brain temperatures in head injured patients [13]. The explanation for this may lie in the high metabolic activity of cerebral tissue with a consequent considerable production of heat [9].

Two recent clinical studies emphasized the importance of body temperature stroke prognosis and severity [1,15]. Reith *et al.* demonstrated lower mortality and better outcome in patients with mild hypothermia on admission. With hyperthermia, outcome was worse. In another study, Azzimondi *et al.* showed that fever in the first 7 days after stroke was an independent predictor of poor outcome [1].

Several studies suggest a beneficial effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury [6,12,17]. Head-injured patients treated with mild hypothermia between 32°C to 34°C core temperature had a significant reduction of ICP and cerebral blood flow compared to normothermic controls. Each of these studies indicated a better outcome with hypothermia brain. In our study, mild hypothermia could be easily and rapidly achieved with cooling blankets and alcohol washing. Side effects of this therapy, such as arrhythmias, predisposition for infection, and hemodynamic instability with profound arterial hypotension, were not seen. Hypothermia led to a significant decrease in ICP and mass effect of postischemic brain edema. Hypothermia might be a potent neuroprotective tool in the therapy of acute cerebral ischemia, especially if body and brain temperatures can be reduced rapidly and easily without major risks or complications.

In conclusion, brain temperature monitoring is safe and provides reliable data. Body-core temperature does not reflect actual brain temperatures in stroke patients and this finding is important to consider in future trials hypothermia as a neuroprotective method in acute cerebral ischemia. Our own preliminary results suggest a beneficial effect of mild hypothermia in the treatment of severe space-occupying MCA infarction. Whether or not early hypothermic treatment, within the first 6 hours after onset of symptoms, has a neuroprotective effect and reduces infarct size needs study in further clinical trials. These studies are currently under way.

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Correspondence: Stefan Schwab, M.D., Neurocritical Care Unit, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Federal Republic of Germany.

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Traumatic Brain Injury in the Developing Rat Pup: Studies of ICP, PVI and Neurological Response

S. Thomas, F. Tabibnia, M. U. Schuhmann, V. H. J. Hans, T. Brinker, and **M. Samii**

Department of Neurosurgery, Nordstadt Hospital, Hannover, Federal Republic of Germany

Summary

Diffuse brain swelling is a common complication in young victims of a seven head injury but, there is a lack of data on relevant models of injury. We produced diffuse brain injury in 21 day old Lewis rat pups (N = 33) by modifying a recently established weight-drop-model. The trauma threshold, neurological response, histological changes, intracranial pressure (ICP), and arterial blood pressure (ABP) were determined. In addition, the pressure-volume-index (PVI) was measured 15 min before, 2 min, and 1 h after brain injury.

In the 1 m/100 g group 4 of 5 rats died, whereas in the 0.5 m/100 g only 4 of 28 died. The PVI increased at 2 min after traumatic brain injury (TBI) but ICP was unchanged, except for a minor increase immediately after injury. Histological studies revealed diffuse neuronal death, predominantly involving the cortex and hippocampus.

The results of the present study indicate that determination of ICP in the developing rat pup during and after diffuse brain injury is possible. A 0.5 m/100 g weight-drop-trauma results in a morphologically severe injury but with low mortality. The increase in PVI can be attributed to a decrease of cerebral perfusion pressure (CPP) after injury. However, the absence of a further increase of ICP after injury in the developing rat indicates that this may not be a primary consequence of injury in paediatric patients.

Keywords: ICP; PVI; rat Pup; traumatic brain injury.

Introduction

Head injury is common in children with an annual incidence of 200/100.000 in the United States (5). The majority of injuries are mild or moderate, and lead to only brief hospital stays. Nevertheless, below 14 years TBI is the most common cause of death. Diffuse cerebral swelling. A feature of paediatric brain injury, and according to the Trauma Coma Data Bank, incidence is twice as frequent in children as adults [2].

Although experimental studies, are necessary to understand the pathophysiological mechanism, only a few experiments have been performed in very young animals [1,8,10].

The aims of the present study were to modify a model of closed diffuse brain injury to produce this type of injury in 21 day old rats and to measure ICP continuously before, during, and after the injury. In addition, intracranial pressure dynamics were determined by measuring the pressure-volume-index before and after the injury and ABP, neurological response and histological findings examinations were studied. In studies previously conducted in adult rats [4,9] no significant changes of ICP were measured following a single TBI produced by the weight-drop-model. It was expected that a single TBI sustained early in life would result in diffuse brain swelling.

Material and Methods

As approved by the Animal Research Committee of the Medical School of Hannover, 21 day old Lewis rat pups were obtained from the in house breeding colony. The pups were nursed by their mother and weaned the day before the experiment. A total of 33 male and female rat pups (39 to 52 g) were divided into different groups. All experiments were performed under general anesthesia (Ketamine 100 mg/kg) without ventilation.

The injury device first described by Marmarou *et al.* [7] in was modified as follows. A brass weight fell free onto a brass helmet glued to the skull of the rat by cyanoacrylate. The weight was guided by a 1 m Plexiglass tube. The animal was placed in prone position on a foam (20 × 20 × 50 cm; spring constant 30/50) held within a wooden frame. The lower end of the tube was placed directly above the helmet. Immediately following the initial impact the box was slid horizontally to prevent a second impact.

In preliminary experiments on cadavers, different height/weight ratios were used and the skull examined for fractures. Thereafter, animals were divided into two groups: 0.5 m/100 g (N = 28) versus 1 m/100 g (N = 5) and mortality and neurological response were determined.

The neurological response was based on two features: duration of apnea and loss of consciousness. Loss of consciousness was defined in terms of absence of a toe-pinch-withdrawal reflex. The reflex was tested every 20 to 30 sec following injury.

Measurements of ICP and bolus injections for PVI determination (N = 6) were performed using a nylon catheter (I.D. 0.58 mm, O.D. 1.02 mm) placed subdurally through a lateral-frontal burr hole into the anterior fossa. The catheter was connected to a Statham-transducer and ICP was recorded up to one hour after injury. Bolus injections of 0.025–0.05 ml normal saline were performed 15 min before, 2 min, and 1 hour after injury. Pressure-Volume-Index (PVI) was determined according to the method described by Marmarou *et al.*, using the formula PVI = $\Delta V/\log (P_{max}/P_{min})$ [6].

In a separate group, (N = 5) the femoral artery was cannulated with a polyethylene tube (I.D. 0.4 mm, O.D. 0.8 mm) connected to a Statham-transducer. Continuous blood pressure recordings were performed until 30 min after injury.

All brains were processed for hematoxylin-eosin staining using 20 µm coronal sections. A separate group (N = 5) was subjected to histological examination only. Animals were perfused transcardially 3 days after injury and the brains were removed and postfixed in 4%-formalin. Sections were studied under light-microscopy for cell loss and hemorrhage.

All measurements were stored and analyzed using commercially available software (Dasy Lab V.3, Datalog, Mönchengladbach, Germany). Statistical analyis was performed using Wilcoxon signed rank test for paired data. Data are presented as mean ± SD.

Results

A 1 m/100 g injury resulted in death of 4 of 5 animals compared to 4 of 28 in the 0.5 m/100 g group. Therefore, all physiological experiments were performed using a height of 0.5 m and a weight of 100 g. Death occured usually immediately after injury due to ventilatory arrest. In two animals space-occupying subdural hematomas were considered the cause of death.

Surviving animals exhibited a period of apnea, lasting from 10 to 120 sec. Seizures were observed in 65% of all animals involving particularly tail and hind limbs. The loss of the toe-pinch-withdrawal reflex was an inconsistent finding occurying in about 20% and lasting from 10 to 150 sec.

ICP increased immediately following injury from 4.3 ± 1.7 mm Hg to 6.9 ± 2.8 mm Hg ($p < 0.05$). Thereafter, ICP returned to normal values within 10 min.

The PVI increased 2 min after injury from 0.036 ± 0.01 ml to 0.043 ± 0.008 ml with no further increase at one hour (0.042 ± 0.009 ml). However, this increase did not reach statistical significance (Fig. 1).

Blood pressure decreased immediately after injury from 85–95 mm Hg to 65–75 mm Hg, returning to baseline values within 2 min (Fig. 2). The drop of blood pressure resulted in a decrease of CPP even with unchanged ICP.

Gross pathological examination of the surviving animals did not reveal any skull fractures. Subarachnoid hemorrhage overlying both cortices to various extents was observed in 90% of all animals. Histological investigation showed diffuse neuronal cell loss in all cortical areas and in the hippocampus. In addition small perivascular bleedings were detected in the brainstem.

Discussion

The present study indicates that the impact acceleration model can also be applied to the developing rat, and results in a neurological response (seizures), increased PVI, decreased CPP, and diffuse cell loss.

21 day old rat pups were used to satisfy biomechanical and physical requirements. The thickness of the skull had to be sufficient to prevent major skull

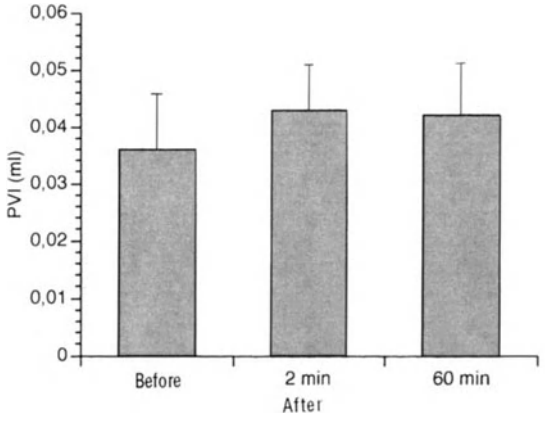

Fig. 1. Pressure-Volume-Index (ml) 15 min before, 2 min, and 60 min following TBI

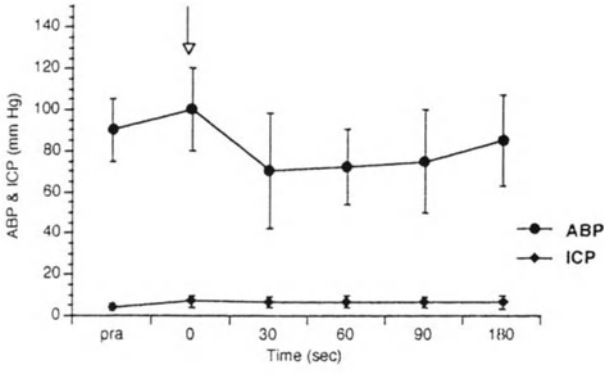

Fig. 2. Mean arterial blood pressure and intracranial pressure (Mean ± SD) before, during, and after injury. ↓ indicates point of injury

fractures and to enable the implantation of a tube for ICP mesurements. A 0.5 m/100 g impact leads to a severe diffuse injury with a moderate mortality in spontaneously breathing young animals. The injury produced by a 1 m/100 g impact is very severe, with a high mortality. These findings are in contrast to results published by Adelson *et al.* [1] using a similar modification of the same model. The differences may be explained by the use of different kinds of foam and anaesthesia.

The slight increase in ICP immediately after injury, with no further alteration, can be explained by transient deformation of the juvenile skull resulting in reduction of the cranial volume. The lack of a longer lasting increase in ICP was unexpected. However, previous results in adult animals are inconclusive. In our own studies we could not detect any significant alterations of ICP [9]. Similar observations were also made by Kita and Marmarou [4] following a single injury without secondary insult. This is in contrast to a significant increase of ICP observed in adult rats within 30 min following a single injury using the same model [3]. The different findings may be explained by slight variations in the trauma device. Another explanation for the lack of an increase of ICP may be the anesthetic agent urea. Ketamin is known to have a neuroprotective effect and therefore it may prevent an increase of ICP. In contrast to findings in adult animals [9] the PVI did not tend to increase progressively following an initial rise. Furthermore, we have studied only the very early period following trauma. Thus, we may have missed changes occuring later, as was shown a delayed outflow resistance of CSF in adult rats [9]. This possibly leads to diffuse brain swelling, if there is no adaequate compensating mechanism in the juvenile brain as indicated by the early cessation of PVI-increase.

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Correspondence: Sebastian Thomas, M.D., Neurochirurgische Klinik, Nordstadt Hospital, Haltenhoffstrasse 41, D-30167 Hannover, Federal Republic of Germany.

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Efficiency of the Glasgow Outcome Scale (GOS)-Score for the Long-Term Follow-Up after Severe Brain Injuries

D. Woischneck and **R. Firsching**

Clinic for Neurosurgery, Otto von Guericke University, Magdeburg, Germany

Summary

The Glasgow Outcome Scale (GOS)-Score is the most widely used instrument for measuring outcome in head injury research. Its reliability is seen controversial because of its simplicity. The study analyzes the correlation between the levels 3 to 5 of recovery to medical data, psychology and quality of life (QOL) 4 to 8 years after the accident. 34 patients, suffered from a severe brain injury (BI) 4 to 8 years ago, were reexamined by a psychological test battery and by evaluating of QOL (using self developed items for private and social activity). Test results and GOS-Scores additionally were correlated to data from the phase of intensive care.

Patients, still alive 4 to 8 years after injury, ranged mainly between the GOS-Scores 3 to 5 of recovery. Consequently, other scores (like Ranchos los Amigos, Barthel Index, GOAT) failed in measuring the outcome after such a long time. Different parameters from the phase of intensive care correlate significantly with the patients GOS-Score: coma length, isolated brain injury versus additional extracranial injury, compression of the basal cisternes on the initial CCT. Different psychological test results and the patients quality of life correlate significantly with the GOS-Scores from 3–5. These correlations could be shown in xy and yx-direction by different mathematical models.

It is concluded, that GOS-levels 3–5 of recovery correlate to the essential medical data from the initial phase after the accident and to a detailed psychological evaluation years after injury.

Keywords: Glasgow Outcome Scale (GOS); severe brain injuries.

Introduction

The Glasgow Outcome Scale (GOS)-Score is the most widely used instrument for outcome measurement in head injury research. Its reliability is seen controversial because of its simplicity. On the other hand, it can be evaluated in a short time and even without personal contact to the patient. To evaluate its efficiency, this study analyses the correlation between the levels 3 to 5 of recovery to psychology and quality of life (QOL) 4 to 8 years after the accident. Additionally, a correlation with medical data material from the phase of intensive care is drawn.

Materials and Methods

Patients, treated for brain injury (BI) between 1986 to 1991 were consecutively investigated 3 to 8 years after the accident.

All patients had a Glasgow Coma Scale (GCS)-score between 3 and 12 when admitted. Additionally, at least one morphological sign of an intracranial injury ("brain injury") had to be visible on the initial computerized tomography (CT). Patients were between 16 and 65 years old at the time of accident. All patients reached the hospital not later than 3 hours after the accident.

From 69 patients, which fullfilled these criteria, 15 (22%) already died during primary intensive care treatment. One additional patient died of unrelated cause. 53 patients survived. 40 of these were followed 3 to 8 years later. 6 of them refused reexamination. 34 (49%) patients underwent a psychological evaluation. The mean age of these 34 patients was 34.3 years at the time of psychological evaluation and 28.4 years at the time of accident. 19 (56%) were male, 15 (44%) female.

The patients were visited at home between August to October 1994. The tests given are listed in Table 1. They are acknowledged to be sensible for the sequelae of brain injury [11].

In the study, which is presented here, 54% of the patients were evaluated as level "5", 38% as level "4" (Table 2).

Quality of Life (QOL) was evaluated using self developed items (Table 3). Firstly, family life, and secondly social activities were evaluated. To address the first issue, abbreviated as private activity (PA), 7 questions were asked, which could be answered with 4 alternatives (1: not done because of sanitary reasons, 4: performed without problems). The final score for PA therefore ranged between 7 and 28 points. The second scale, abbreviated as social activity (SA), contained 5 questions, answered with the same alternatives. Therefore, a total score between 5 and 20 could be reached.

Statistical evaluations were performed with the help of the statistic programm JMP by SAS Institute Inc. (SAS Campus Drive, Cary, NC 27513, USA, 1989–1994). For one way variance analysis, significance was tested by the WILCOXON-test. Logistic regression analysis was performed in order to correlate data of a nominal

Table 1. *Test Battery for Evaluation 4 to 8 Years after Injury. Tests were chosen because of their sensitivity for Disturbances after Brain Injuries*

	LURIA-test	Controlled oral word association-test	Number connection-test, part A and B	REY complex figure-test, copy trial	REY complex figure-test, memory trial
Type	word learning test (free recall)	association-test	complex attention and concentration test	constructive test	constructive test
Instruction	recall 10 unrelated words in high frequency	name words of a given starting letter	draw lines to connect consecutively numbered (A) or numbered and lettered (B) circles on a work sheet	copy a complex standardized figure	reproduct the REY-figure 20 min after Copy trial
Testing functions of:	attention, memory, organisation of recalling memory contents	fluency of word and speech, detecting subclinical forms of aphasias	visual and motoric components of learning	organisation of visual learning	visual memory

Table 2. *Self Developed Items for Evaluating Quality of Life*

Private activity (PA)
7 questions, which could be answered with 4 alternatives final score for PA: 7 and 28 points.

Social activity (SA)
5 questions with 4 alternatives (see PA) final score for SA: 5 and 20 points

Alternatives: 1: not done because of sanitary reasons, 4: performed without problems.

or ordinal character from the clinical phase to continuously distributed results from psychological testing. Significance was assumed, when the whole model test as well as tests for estimated parameters showed p values below 0.005.

Results

1. Late GOS-score and early medical data: Patients, still alive 4 to 8 years after injury, ranged mainly between the GOS-Scores 3 to 5 of recovery (Table 3). Consequently, other scores (like Ranchos los Amigos, Barthel Index, GOAT), which describe states of a more severe disability, failed in measuring the outcome after such a long time.

2. Different parameters from the phase of intensive care correlate significantly with the patients GOS-score. This is exemplarily shown for the coma length by logistic regression analysis (Fig. 1).

Other medical data (Table 4), which are able to differentiate between the GOS-levels 3–5: isolated brain injury versus additional extracranial injury, compression of the basal cisternae on the initial CCT and presence of a cerebral contusion. It is noticed that some of these parameters correlate with the GOS-Score in both mathematical directions.

Table 3. *Glasgow Outcome Scale (GOS-)Score: Results 4 to 8 Years after Brain Injury*

GOS-level	Definition (Jennett, Bond 1975)	Frequency 4–8, years after BI
5	good recovery (resumption of normal life)	58
4	moderate disability (disabled but independent)	34
3	severe disability (conscious but disabled)	8
2	persistent vegetative state (absence of cortical function)	0
1	death (due to brain damage)	–

2. Late GOS-Score and late psychological data (Table 4): Different psychological test results correlate significantly with the levels from 3–5. Exemplarily, this is shown for the brief word learning test due to LURIA (Fig. 2). These correlations between neuropsychology and GOS-Score could be often shown in xy and yx-direction by different mathematical models.

3. Late GOS-Score and late Quality of Life: Parameters, describing the Quality of Life showed significant correlation to the different GOS-levels (Table 4). This was more pronounced for scores on social activities (including his job) than for those concerning the patients condition in the familiar surrounding.

Discussion

Although a GOS-level [10] of 3, 4 or 5 may contain different psychological disturbances, not described by a simple scale, the correlation of the GOS-score to

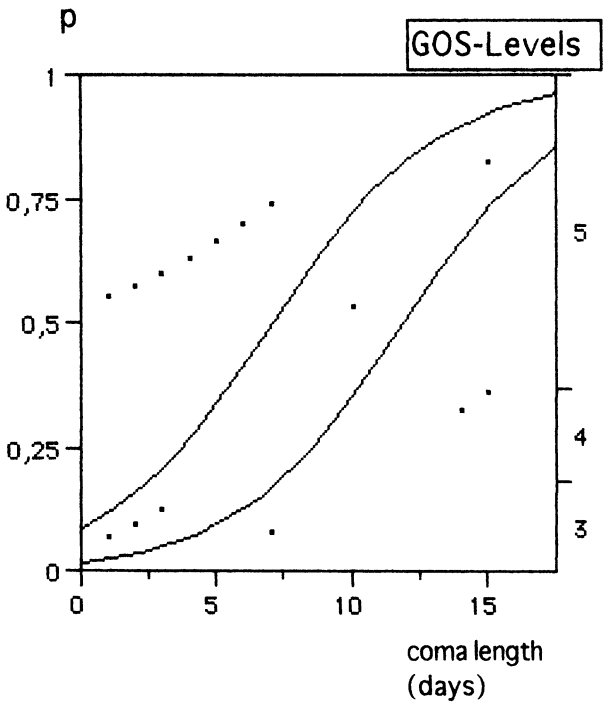

Fig. 1. Correlation between coma length and GOS-Score, evaluated 4 to 8 years after the injury (logistic regression analysis): significant differentiation between th levels 3, 4 and 5 of recovery by coma length

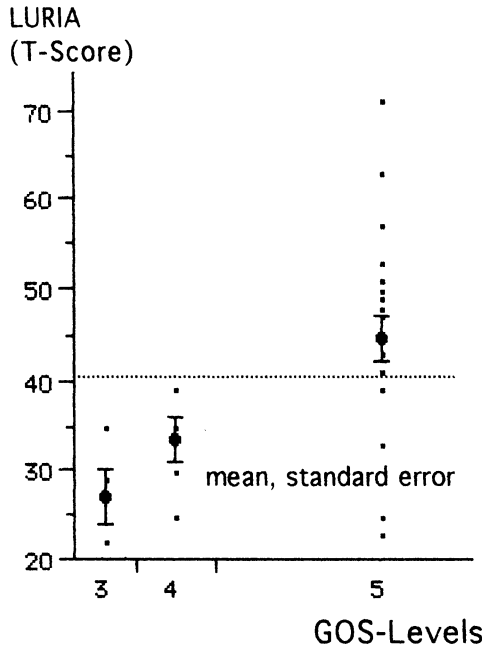

Fig. 2. Correlation of the GOS-Score to the results of a brief word learning test (LURIA): significant differences for all three levels of recovery 4 to 8 years after the accident

Table 4. *Corelation of the GOS-Score 4 to 8 Years after Injury to Medical and Psychologcal Data and to Quality of Life*

Parameter	GOS-level on X-axis	GOS-level on Y-axis
Early medical data		
Cerebral contusion (yes/no)	0.028 (cross table)	not significant (cross table)
Compression of basal cisterns (yes/no)	0.028 (cross table)	0.02 (cross table)
Additional extracranial injury (yes/no)	not significant (cross table)	0.038 (cross table)
Coma length (days)	0.0004 (ANOVA)	0.00032 (logistic regression analysis)
Late psychology		
Controlled Oral Word Association-Test	not significant	0.001
LURIA brief learning-test	0.004	0.003
Number Connection-Test, Part A	not significant	0.0004
Number Connection-Test, Part B	0.02	0.0001
REY Complex Figure-Test, Copy Trial	not significant	0.03
Late Quality of Life		
Private activity	0.00018	0.0001
Social activity	0.00002	0.00002

a complex evaluation of the long term result after a severe BI is evident (Table 4). We conclude, that these 3 levels of recovery correlate to the essential medical data from the initial phase after the accident and to a detailed psychological evaluation years after injury.

The early medical data, found to be in correlation with the GOS-Score, are known as predictors of the squelae of BI: coma length [3,7], compression of the basal cisternae [1,5] and cerbral contusions (13). The importance of the additional extracranial injury (Table 4) cannot be confirmed by literature. In future, correlation of pschological data to parameters from magnetic resonance imaging [8] might lead to other predictors.

The correlation of the GOS-Score to psychological data (Fig. 2, Table 4) is the essential result of his study: it allows to differentiate patients by dividing their complex physical and mental condition into three levels. The test battery, applied in his test, is known to be sensible for BI, comparable to the methos, used in other studies [2,6,9,13].

Measuring Quality of Life in different fields of neurosurgery [4] is still controversial: this study redraws on self developed items, not standardized on a control group. The significant correlation to the GOS-Score, especially to complex social activities (Table 4), therefore, has to be regarded with caution, although it is congruent with the psychological findings.

The study underlines the dominant improtance of the GOS-score for neurorehabilitation and its efficiency for scientific evaluations. Further work has to be done on its correlation to Quality of Life.

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Correspondence: Dieter Woischneck, M.D., Neurochirurgische Klinik, Otto-von-Guericke-Universität, Leipziger Str. 44, D-39120 Magdeburg, Federal Republic of Germany.

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Effects of Lecithinized SOD on Sequential Change in SOD Activity after Cerebral Contusion in Rats

M. Yunoki[1], M. Kawauchi[1], N. Ukita[1], Y. Noguchi[1], S. Nishio[1], Y. Ono[1], S. Asari[1], T. Ohmoto[1], M. Asanuma[2], and N. Ogawa[2]

[1] Department of Neurological Surgery, Okayama University Medical School and [2] Department of Neuroscience, Institute of Molecular and Cellular Medicine, Okayama University Medical School, Okayama, Japan

Summary

To analyze the effect of lecithinized superoxide dismutase (SOD) on superoxide accumulation after traumatic brain injury (TBI) in rats, we studied the SOD activity by NBT-reducing method and the expression of Cu,Zn-SOD mRNA by Northern blot analysis. As determined by the specific gravity method, the administration of lecithinized SOD decreased brain edema in the periphery of the lesion at 6 hr after contusion. SOD activity, without lecithinized SOD administration, increased at the peripheral portion at 30 min after contusion, but decreased to the normal level at 6 hr after TBI. By administration of lecithinized SOD, the increase of SOD activity was preserved until 6 hr after TBI. The expression of Cu,Zn-SOD mRNA increased in the core lesion, peripheral portion, and contralateral hemisphere until 6 hr after TBI, then was suppressed in all three areas by lecithinized SOD. These results support the hypothesis that superoxide anions may play an important role in the development of brain edema after TBI, and that leciyhinized SOD appears to prevent brain edema through a protective effect against superoxide anions.

Keywords: Brain edema; cerebral contusion; SOD.

Introduction

The generation of superoxide anions have been proposed to explain the pathogenesis of brain edema after traumatic brain injury (TBI). However, the therapeutic trial of exogenous superoxide dismutase (SOD) has been limited because of its low cell membrane affinity and rapid metabolism (2). To overcome these disadvantages, the effects of several chemically modified preparations of SOD, including polyethylene glycol-conjugated SOD and pyran SOD, have been investigated, but have not been approved for clinical use due to their insufficient pharmacological potency. Lecithinized SOD, containing a lecithin derivative covalently bound to recombinant human SOD, has recently been shown to have a relatively higher pharmacological potency [2]. In the present study, we examined the effects of lecithinized SOD on water content, SOD activity and Cu,Zn-SOD mRNA expression in rats with TBI.

Materials and Methods

Male Sprague-Dawley rats (250–300 g) were anesthetized with intraperitoneal injection of pentobarbital sodium (50 mg/kg). A burr hole 5 mm in diameter was made in the right parietal bone. The animals were divided into four experimental groups. In the first group, the rats were administered 1 ml of saline intravenously (sham group: n = 5). The second group underwent the same sham-operation, followed by intravenous administration of lecithinized SOD (3000 units/kg; Seikagaku Co., Tokyo, Japan) (sham+SOD group: n = 5) dissolved in 1 ml of saline. In the third group, 1 ml of saline was administered 1 min before traumatic insult. Contusion was made by dropping a 20 g-weight from the height of 30 cm onto the exposed dura (contusion group: n = 5). In the fourth group, lecithinized SOD (3000 units/kg) was injected 1 min before the same traumatic insult (contusion+SOD group: n = 5). Rats were decapitated 30 min and 6 hr after the treatment and the contusion. The brain was dissected into three cortical portions, the injured portion (core), 4 mm anterior to the injured portion (peripheral), and contralateral hemisphere (distal).

At 30 min and 6 hr after TBI, the water content and the SOD activities of each portion were measured using the specific gravity method and NBT-reducind method respectively.

At 6 hr after TBI, the expression of Cu,Zn-SOD mRNA was analyzed using Northern blot analysis. The total RNA was prepared from each portion according to the single-step method of Chomczynski and Sacchi. The probe used for hybridization was a

synthetic 48-mer oligonucleotide with a sequence complementary to bases 372–419 of rat Cu,Zn SOD mRNA. The optical density (O.D.) of detected signals in autoradiograms was analyzed with a computerized image analysis software (Image 1.56, NIH). For quantitative analysis, the ratio for Cu,Zn-SOD mRNA and 18S rRNA was calculated. Data were expressed as the mean ± satandard error of the mean (S.E.M.). Statistical analysis of the data was performed using one-way ANOVA followed by posthoc Duncan's multiple comparison tests. Differences among groups were considered significant if the p value was <0.05.

Results

Water Content

The specific gravity of all cortical regions of sham or sham+SOD group was high and remained at the same level at both time intervals. In the contusion group, the specific gravity of the core lesion diminished at 30 min after TBI, and markedly decreased at 6 hr after TBI. The specific gravity in the peripheral region was also diminished at 6 hr post-TBI, but the decrement was smaller than that in the core lesion. There was no significant change in the water content in the distal portion at both time intervals. Injection of lecithinized SOD (contusion+SOD group) had no effect on contusion-induced rise in water content at both time intervals in the core region, but it significantly reduced the increased water content in the periphery at 6 hr post-TBI (Fig. 1A).

SOD Activity

SOD activity in three examined portions of the sham+SOD group was significantly higher than that of the sham group at 30 min and 6 hr after the operation.

In the core region, contusion resulted in a significant reduction of SOD activity compared with that of the sham group at 30 min after TBI. In contrast, increased SOD activity was observed in the peripheral region of the contusion group at 30 min after TBI. However, this effect was of short duration, it decreased to a level equivalent to that of the sham group at 6 hr. Treatment with lecithinized SOD before contusion (contusion+SOD group) significantly increased SOD activity in the peripheral region not only at 30 min but also at 6 hr after TBI (Fig. 1B).

Cu;Zn-SOD mRNA Expression

Contusion increased Cu,Zn-SOD mRNA expression in the core, peripheral and distal regions at 6 h post-TBI, compared with its levels in sham group. Treatment with lecithinized SOD before contusion suppressed the level of Cu,Zn-SOD mRNA expression at 6 hr to levels equivalent to those observed in the sham group. This was in contrast to pretreatment of sham-operated rats with lecithinized SOD where no change was noted in the expression of Cu,Zn-SOD mRNA (Fig. 1C).

Discussion

In the present study, SOD activity markedly decreased in the core region at 30 min after TBI (Fig. 1B), while Cu,Zn-SOD mRNA expression increased 6 hr after contusion (Fig. 1C). The consequent enlargement of the extracellular space due to blood-brain-barrier (BBB) breakdown may decrease the SOD concentration. Some authors have also reported this subsequent decrease of SOD activity after ischemic brain injury [5], purporting that the damage to mitochondrial function might disturb SOD synthesis, and the accumulation of hydrogen peroxide inactivate SOD irreversibly. Acute inactivation and consumption of SOD occurs due to the severe brain damage, and then its mRNA might compensatory increase to make SOD activity normal.

In contrast to reduced SOD activity in the core region, SOD activity increased in the peripheral region 30 min after contusion injury (Fig. 1B). Furthermore, increases in water content in the peripheral portion were lesser than that in the core portion and gradually progressed (Fig. 1A). The superoxide-induced damage may be moderate enough to allow acute higher intrinsic SOD activity in this region.

Our results also showed the increased Cu,Zn-SOD mRNA expression at the contralateral hemisphere of contusion in spite of lack of change in SOD activity (Fig. 1C). To this effect, bilateral increases in total tissue calcium and calcium flux in both cortical hemisphere has been reported after contusion injury [1]. Cellular calcium influx is also associated with cortical spreading depression [6]. Furthermore, Raghupathi *et al.* have reported the induction of an immediate early gene at the contralateral hemisphere of contusion injury [7]. Therefore, cortical spreading depression may be involved in the increased SODmRNA expression at the contralateral hemisphere.

We also investigated the effects of lecithinized SOD on TBI. The administration of lecithinized SOD suppressed brain edema 6 hr after TBI in the peripheral portion (Fig. 1A). This finding suggests that lecithinized SOD may be serve as an pharmaco-

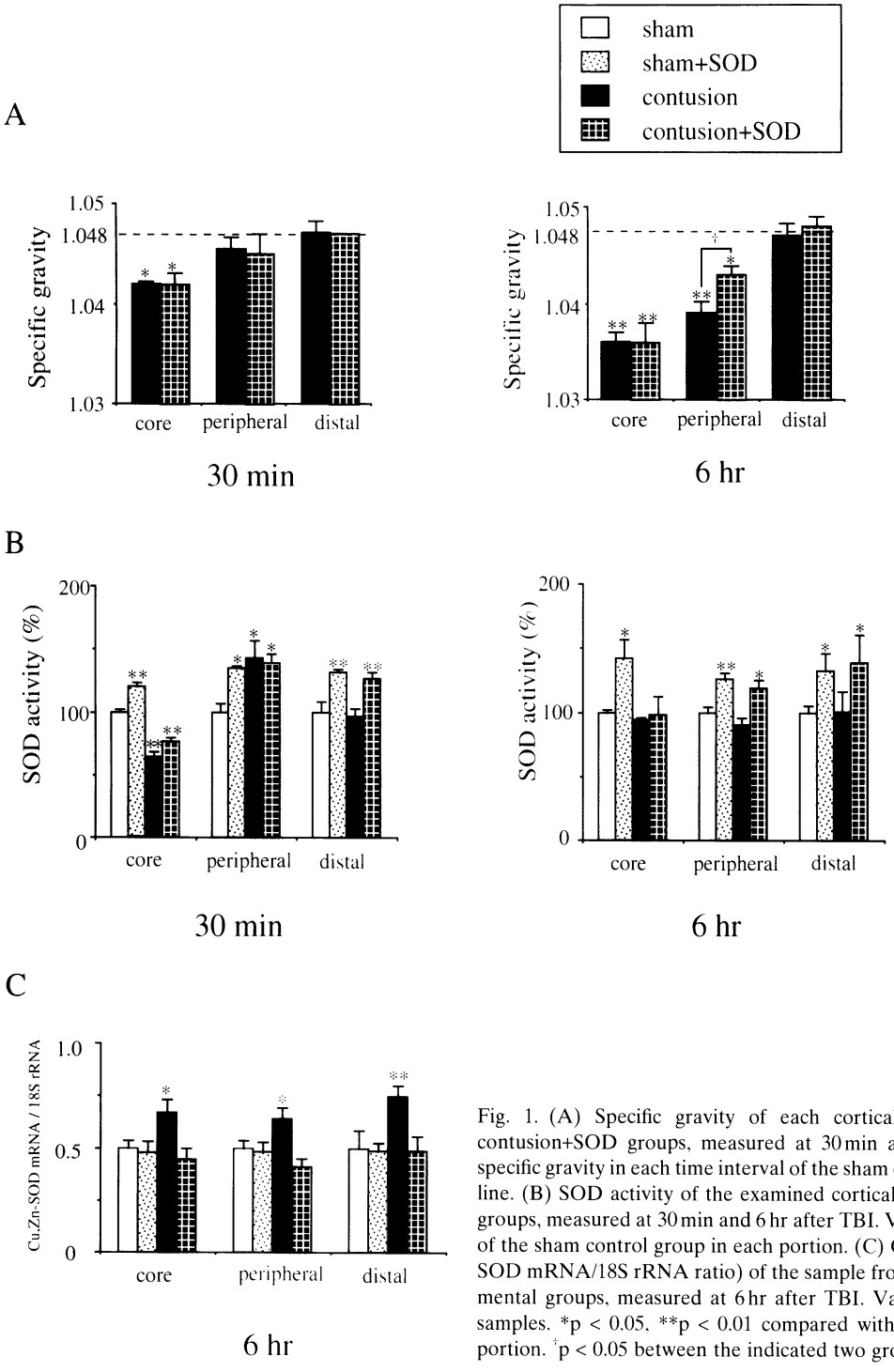

Fig. 1. (A) Specific gravity of each cortical portion in the contusion and contusion+SOD groups, measured at 30 min and 6 hr after TBI. The mean of specific gravity in each time interval of the sham control group is shown as a broken line. (B) SOD activity of the examined cortical portion in the four experimental groups, measured at 30 min and 6 hr after TBI. Values are expressed as percentage of the sham control group in each portion. (C) Cu,Zn-SOD mRNA level (Cu,Zn-SOD mRNA/18S rRNA ratio) of the sample from each portion in the four experimental groups, measured at 6 hr after TBI. Values are the mean ± S.E.M. of 5 samples. *$p < 0.05$, **$p < 0.01$ compared with the sham control group in each portion. †$p < 0.05$ between the indicated two groups

logical treatment for TBI. But in the core portion, lecithinized SOD showed no significant effects on increases in water content after TBI (Fig. 1A). Mikawa *et al.* showed a Cu,Zn-SOD dose-dependent protection against increases in water content after TBI in transgenic mice overexpressing SOD transgenes [4]. Therefore, the dose of injected lecithinized SOD in the present study may be insufficient to protect the increase in water content after TBI in the core portion. Lecithinized SOD administration of more than 3000 units/kg may improve the brain edema in the core.

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Correspondence: Masatoshi Yunoki, M.D., Department of Neurological Surgery, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700, Japan.

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CSF Antibiotic Prophylaxis for Neurosurgical Patients with Ventriculostomy: a Randomised Study

W. S. Poon, S. Ng, and **S. Wai**

Neurosurgical Unit, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Summary

The value of prophylactic antibiotics for patients with ventricular catheter for monitoring and CSF drainage is uncertain. 228 patients were randomised to receive perioperative antibiotics only (Unasyn, Group I) or prolonged antibiotics for the presence of the ventricular catheter (Unasyn and Aztreonam, Group II). The incidence of intracranial and extracranial infection was documented prospectively. Group II patients had a significantly reduced incidence of CSF infection [3/115 (3%) vs 12/113 (11%), p = 0.01] and extracranial infections [23/115 (20%) vs 48/113 (42%), p = 0.002]. CSF pathogens in Group II patients were MRSA and Candida, whereas in Group I, Staphylococci, E coli and Klebsiella. Although prolonged antibiotic prophylaxis significantly reduced the incidence of serious CSF infection as well as extracranial infections, this policy did select resistant or opportunistic pathogens such as Candida and MRSA.

Keywords: Antibiotic prophylaxis; ventriculostomy.

Introduction

The role of prophylactic antibiotics in patients with ventricular catheter for monitoring and CSF drainage is uncertain [2–5], although per-operative antibiotics have been shown in ten randomised trials to significantly reduce infection in clean neurosurgical operations [1]. Bacteria isolated from CSF with ventriculostomy-related infection have been documented as Gram positive cocci in half of the cases, and Gram negative bacilli in the other half [2]. The purpose of this randomised trial is to prove the efficacy of a high dose combination antibiotics regimen against Gram positive cocci and Gram negative bacilli.

Patients and Methods

228 patients who required the insertion of a ventricular catheter for intracranial pressure monitoring or CSF drainage in a 2-year period (October 1993–September 1995) were randomised to receive perioperative antibiotics only (Group I) or prolonged antibiotic prophylaxis covering the period the ventricular catheter was in-situ Group II (intravenous Unasyn 3G and Aztreonam 2G eight-hourly, Group II). The ventricular catheter was inserted into the frontal horn and was subcutaneously tunnelled. The external pressure transducer and a closed drainage system were connected as shown in figure 1 using a commercially available system (EDS II, Codman, USA). The policy of changing the ventricular catheter after 5 days was enforced if prolonged monitoring and CSF drainage were required. The incidence of CSF and extracranial infection was documented prospectively.

Results

The demographic and clinical data of these 228 patients are tabulated in Table 1. Group II patients had a significantly reduced incidence of CSF infection as defined by CSF culture and/or CSF white cell count >50/cumm [3/115 (3%) vs 12/113 (11%), p = 0.01] and extracranial infections [13/115 (20%) vs 48/113 (42%), p = 0.002], whereas cranial wound infection in both groups was uncommon (Table 2). CSF pathogens in Group II patients were MRSA and Candida, whereas in Group I, Staphylococcus aureus and albus, E coli, Klebsiella (Table 3). Ventriculostomy-related infection was associated with the duration of CSF drainage (11 ± 3 vs 4 ± 3, $p < 0.001$). Mortality in both groups was also associated with CSF infection (Table 4).

Discussion and Conclusion

The controversy on the efficacy of CSF antibiotic prophylaxis for ventriculostomy-related sepsis can be summarised as follows:

Table 1. *Demographic and Clinical Data of the Two Groups of Patients*

	Group I	Group II (unasyn+astreonam)
Total number	113	115
Mean age (range)	44 ± 19	46 ± 17
Male (%)	69 (61%)	70 (61%)
Head injury (%)	10 (9%)	12 (10%)
Brain tumour (%)	51 (45%)	53 (46%)
Vascular (%)	33 (29%)	35 (30%)
Req′ CSF drainage (%)	28 (25%)	30 (26%)
Mean duration of catheter	5 ± 4 days	4 ± 3 days
Req′ multiple catheter	20 (18%)	18 (16%)
CSF infection	12 (11%)	3 (3%)

Table 2. *Incidence of Infection in the Two Groups of Patients*

	Group I	Group II (unasyn+aztreonam)	p
Total number of patients	113	115	–
CSF infection (%)	12 (11%)	3 (3%)	0.01
Wound Infection (%)	4 (4%)	3 (3%)	0.7
Extracranial infection (%)	48 (42%)	23 (20%)	0.002

Table 3. *Bacteriology, Duration of CSF Drainage and Clinical Outcome of Patients with Ventriculostomy-Related Infection*

	Patient sex/age	CSF Pathogen	Duration of drainage (days)	Clinical outcome
Group I	F/41	coag-ve staph	11	severe disability
	M/49	coag-ve staph	9	moderate disability
	M/53	staph aureus	7	severe disability
	F/51	staph aureus	10	moderate disability
	F/41	Bacillus sp	11	severe disability
	F/1	E coli	21	good recovery
	M/54	E coli	7	death
	M/38	Klebsiella	10	death
	M/40	Klebsiella	12	death
	M/37	Acinectobacter	14	death
	M/66	Aeromonas hydrophila	10	death
	F/59	Xanthomonas malto.	11	severe disability
Group II	M/37	Candida albican	11	death
	M/42	MRSA	13	severe disability
	M/87	MRSA	14	death

Table 4. *Ventriculostomy-Related Infection was Strongly Associated with a High Mortality*

	Group I	Group II (unasyn+aztreonam)
Number of patients	113	115
Mortality in patients without CSF infection	7/101 (7%)	6/112 (5%)
Mortality in patients with CSF infection	5/12 (41%)	2/3 (66%)
p value	0.002	0.0001

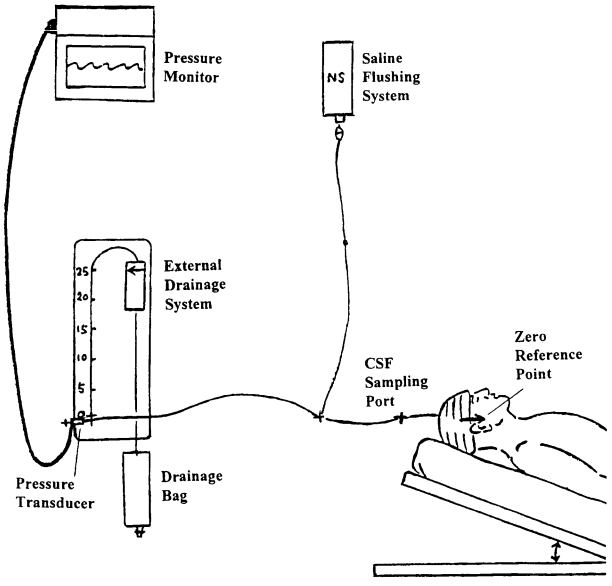

Fig. 1. ICP monitoring

Antibiotic Prophylaxis: Retrospective studies (Wyler 1972, Smith 1976, Winfield 1993) have shown that antibiotics such as cloxacillin could keep CSF infection rate at a low level (4.5%–9%).

Aginist Antibiotic Prophylaxis: The classic prospective epidemiological study on ventriculostomy-related infections (Mayhall 1984) contains data against the use of prophylactic antibiotic: the group of patients on nafcillin had an increased infection rate (13% vs 6%, p = 0.08).

Equivical: Another prospective study (Stenager 1986) generated equivocal results: patients on antibiotic prophylaxis had a modest reduction in infection rate, but the difference did not achieve statistical significance (1/10 (10%) vs 14/77 (18%), p = 0.5).

The present study has two features:

(1) It was a randomised trial comparing Group I, without, and Group II, with prolonged CSF antibiotic prophylaxis.

(2) The choice of antibiotics and their dosage was controlled: we chose high dose Unasyn 3G every eight hours (ampicillin 2G and sulbactam 1G) with good Gram positive cover, and Aztreonam 2G every eight hours, specifically working against Gram negative bacilli such as E coli and Klebsiella. The choice of antibiotics was based on the probability of bacteria isolates causing ventriculostomy-related infection as recorded in the literature [2] and in our hospital laboratory.

This study demonstrated a significant reduction in ventriculostomy-related infection when this high does combination antibiotics regimen was employed (3% vs 11%, p = 0.01). CSF infection Gram negative sepsis in particular, was associated with a high mortality (Table 4). This antibiotic regimen against both Gram positive and Gram negative bacteria was effective in preventing ventriculostomy-related sepsis caused by common pathogens such as Staphylococci, E coli and Klebsilla (Table 3). However, prolonged antibiotic prophylaxis was associated with resistant or opportunistic pathogens such as MRSA and Candida when ventriculostomy-related infection did occur.

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Correspondence: W. S. Poon, M.D., Neurosurgical Unit, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong.

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The Effect of Human Corticotrophin Releasing Factor on the Formation of Post-Traumatic Cerebral Edema

A. Beaumont and **A. Marmarou**

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia, U.S.A.

Summary

Controlled cortical impact is a well validated model of cortical contusion which is known to produce cerebral edema. Corticotrophin Releasing Factor (CRF) is a hypothalamic neuropeptide, which is known to inhibit transendothelial leakage of plasma derived fluid and tissue edema in response to injury. The aim of this study was to determine cerebral edema after controlled cortical impact and then compare the effect of high and low doses of CRF. We evaluated the effect of CRF in rats divided into groups of sham, trauma alone, and trauma treated with CRF at 50 micrograms/kg and 100 micrograms/kg. Animals were sacrificed at 24 hours and water content was determined. We found that CRF was effective in reducing cerebral edema associated with cortical contusion and propose that the action of CRF obviated barrier leakage.

Keywords: Cerebral edema; corticotrophin releasing factor; traumatic brain injury.

Introduction

Formation of cerebral edema following traumatic brain injury is a primary cause of morbidity and mortality. Edema formation may lead to a critical rise in intracranial pressure with concomitant fall in cerebral perfusion pressure, which in turn propagates further cerebral injury. The high mortality in those patients with sustained elevations of ICP and the poor prognosis of those patients who survive is well documented [1]. For this reason it is important clinically to limit edema formation, which can be seen both with diffuse and focal injuries.

Corticotrophin Releasing Factor (CRF) is a 41 amino acid hypothalamic neuropeptide, with a principle role in the hypothalamic-pituitary-adrenal axis. Recently this oligopeptide has been observed to limit edema formation in various models of tissue injury characterised by transendothelial leakage of plasma constituents [2–6], including surgical incision of muscle, cold injury to the cerebral cortex [2], thermal or neurogenic inflammation of the rat pawskin [3], and epinephrine or formaldehyde induced pulmonary edema [4].

Controlled cortical impact is a well-validated model of cortical contusion, which is known to produce cerebral edema. The aim of this study was therefore to assess the ability of human CRF (hCRF) to reduce edema formation following craniocerebral trauma utilising the controlled cortical impact model of cortical contusion.

Methods

A dose escalation study of the effects of hCRF was employed, using doses of 50 µg/kg and 100 µg/kg hCRF. Human CRF was provided by Neurobiological Technologies Ltd, Richmond, Ca. A pH 4.0, 20 mM acetate buffer with 5% mannitol was used as a vehicle for dilution. Drug dilutions were prepared on the morning of use, and stored refrigerated. All diluted drug was discarded after 24 hours. All animals used received human care in compliance with the Guide for the Care & Use of Laboratory Animals" (NIH Publication No. 86–23, 1985).

Adult male Sprague Dawley rats weighing 340–400 g were randomised into one of 4 experimental groups. Group I, Sham trauma (n = 6); Group II, Trauma alone (n = 6); Group III, Trauma with 100 µg/kg Corticotrophin Releasing Factor (CRF) administered post-injury (n = 7) and Group IV, Trauma with 50 µg/kg CRF post-injury (n = 6).

The method of controlled cortical impact has been described in detail elsewhere [7]. Animals were ventilated with a mixture of N_2O (66%), O_2 (33%) and halothane (1.5%). The rats' heads were secured in a stereotactic frame and a 10 mm craniotomy prepared to the right of midline overlying the parietal cortex. Cortical contusion was obtained using a constrained stroke pneumatic impactor which delivered a controlled cortical impact. The impactor was set to deliver a blow at 6 m/s impact velocity to a depth of 3 mm. Immediately after injury the craniotomy site was sealed with the bone flap, gelfoam and rapid drying cyanoacrylic

glue. Drug was administered in four divided doses (25 µg/kg and 12.5 µg/kg each dose, respectively). The first dose was given 30 minutes post-injury, the second at 2 hours post-injury, and the third and fourth doses at two hour intervals after this. The total administered dose of hCRF was 50 µg/kg and 100 µg/kg. Drug was injected subcutaneously into the nuchal region of the animal. Hydration of the animals was maintained using 10 ml of intraperitoneal 0.9% saline.

Edema formation was determined using the method of wet and dry weights. Animals were sacrificed at 24 hours post-injury. Assessment was made of three 3 mm slices centred under the site of injury and divided by hemisphere. The wet weight of these pieces was determined and the tissue incubated to a constant weight in an oven at 95°C, whereupon the dry weight was measured. The mean time for this process was 5 days. From the wet and dry weights of the tissue the cerebral water content was calculated.

Results

The overall mortality rate for animals exposed to cortical contusion was 21.9%, of which only 3.1% (n = 1 animal) died later than the time of the first drug dose. Drug administration could not therefore be observed to significantly affect mortality.

In the right (traumatised) hemisphere, trauma induced increases of 0.97, 1.25 and 0.87% in slices 3, 4 and 5 respectively compared with sham ($p < 0.005$) (Fig. 1a). This effect was attenuated in both CRF treated groups, with a maximal effect seen using 50 µg/kg hCRF, where the water increase over sham was 0.1, 0.25 and 0.18% respectively ($p < 0.01$ cf. trauma). The effect in the 100 µg/kg group was much less marked and not significant. In the left (non-traumatised) hemisphere the effect although present, was less obvious (Fig. 1b). This was in part due to the much smaller increases in cerebral water in this uninjured hemisphere (0–0.4%). Overall it is clear that the 50 µg/kg dose is most effective at reducing edema.

Combining the water contents of these slices for the injured hemisphere, the overall water content in the sham group was 77.59 ± 0.14%. Trauma resulted in a rise in water content to 78.20 ± 0.48% ($p < 0.05$ cf. sham), and administration of 50 µg/kg of hCRF resulted in a reduced water content of 77.62 ± 0.27% ($p < 0.01$ cf. trauma). 100 µg/kg hCRF however did not attenuate the edema formation resulting in a water content of 78.08 ± 0.38% (Fig. 2).

ICP in the untreated injured animals rose from a baseline of 7.9 ± 2.9 mm Hg (mean ± sd), to a peak value of 41.4 ± 15.7 mm Hg in 3.6 ± 1.8 mm Hg minutes after trauma and then declined to a new steady state baseline of 23 ± 6.9 mm Hg, in 24.0 ± 17.4 minutes. ICP in the groups treated with hCRF did not show any significant difference to the untreated group.

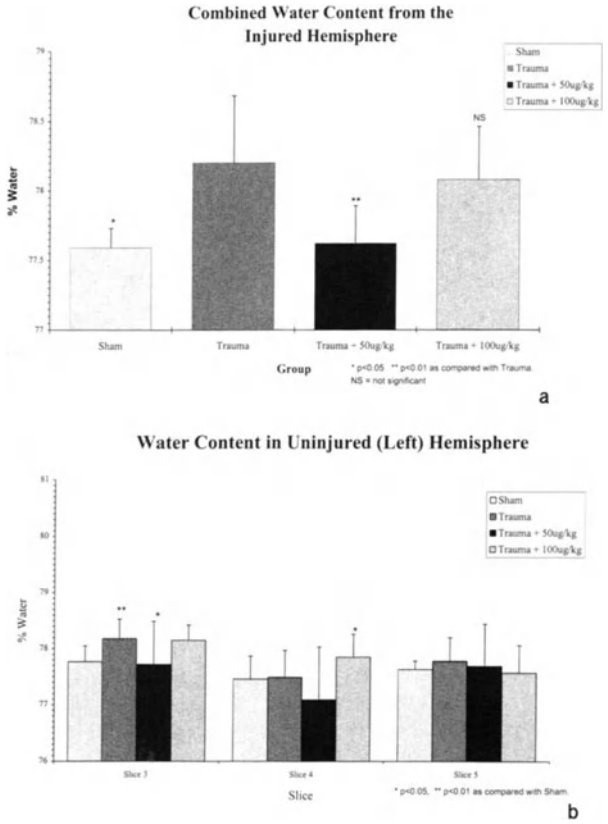

Fig. 1. (a) Graph showing cerebral water content in each slice of brain sampled from the injured hemisphere, in each group of animals. Error bars correspond to standard deviations and significance levels compared to the sham group are as marked. (b) Graph showing cerebral water content in each slice of brain sampled from the non-injured hemisphere, in each group of animals. Error bars correspond to standard deviations and significance levels compared to the sham group are as marked

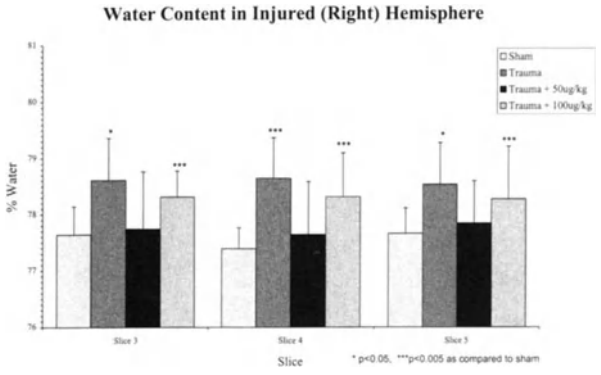

Fig. 2. Graph showing the combined water contents from brain slices taken from the injured hemisphere. Error bars correspond to standard deviations and significance levels compared with the trauma group are as marked

Discussion

Formation of cerebral edema after traumatic brain injury is recognized as a critically important antecedent of morbidity and mortality. For this reason, a large component of current therapeutic practice is aimed at finding ways to limit edema formation. Edema arises following focal cerebral injuries by what is thought to be contusion and blood brain barrier damage.

CRF is a 41 amino acid hypothalamic neuropeptide discovered in 1981 for its principle role in the hypothalamic-pituitary-adrenal axis. In the healthy individual, CRF is produced by the hypothalamus, and in conjunction with arginine vasopressin, it stimulates the production of adrenocorticotrophic hormone (ACTH) in the pituitary gland. ACTH then acts to stimulate production of corticosteroids in the adrenal gland. Recently hCRF has been observed to limit edema formation in various models of tissue injury [2–6], including systemic and cerebral injuries and edema associated with cerebral tumours [8].

CRF has been demonstrated to limit areas of vascular leakage associated with surgical incision of muscle and freezing lesions to the cerebral cortex [2]. Edema formation per se was not measured. The ED_{50} for hCRF in this study was 30μg/kg, however drug administration was completed prior to injury. Other studies have confirmed that CRF is effective in reducing vascular leakage due to thermal and neurogenic injury in the rat pawskin [3–6]. A more recent study has demonstrated that CRF could reduce pulmonary edema caused by intravenous administration of epinephrine [4]. In this particular study the ED_{50} was 3.2μg/kg; considerably lower than see in previous studies. The common feature of these various injuries is vascular leakage, which is known to lead to an increase in extracellular fluid and tissue edema. Although none of these studies considered the tissue water content, one study in particular has examined the water content of brains taken from rats with implanted gliomas using wet weight/dry weight methods and magnetic resonance imaging [8], and found CRF to be effective at reducing the associated vasogenic edema.

Previous studies [9] have demonstrated the formation of edema following cortical contusion which is suggested to be in part due to vascular leakage. Our data clearly shows that hCRF does indeed reduce edema formation following cortical contusion. The optimal dose for this effect appears to be 50μg/kg.

The precise mechanisms by which hCRF limits vascular leakage and edema formation are not yet clear. It is unlikely that the effects are related to a secondary increase of corticosteroid output from the adrenal glands. One study has suggested that the anti-inflammatory action if hCRF is independent of any action on the adrenocortical output of the adrenal glands. This was inferred because hCRF administration systemically does not seem to result in increases in plasma corticosterone and furthermore adrenalectomy with zero levels of corticosterone in the body, do not abolish the antiedematous effect of hCRF, at least as observed with peritumoural edema [8]. It could of course be argued that the effects of hCRF are simply due to its hypotensive effects. This is unlikely since Tjuajev *et al.* in their study took steps to prevent this hypotension, and yet hCRF was still effective [8].

In the absence of a role of corticosterone, the question remains as to the mechanisms of action of hCRF. Two types of receptors for hCRF have been described. CRF-1 is expressed mainly in the brain and pituitary [10] and CRF-2 is expressed in cardiac and skeletal muscle [11]. The nine amino-terminal residues of hCRF activates these receptors, resulting in an increase in cytosolic cAMP and Ca2+ levels [12]. hCRF receptors have not yet been characterised on endothelial cells, but their presence has been inferred from binding of iodinated hCRF which is seen to be near to sites of vascular leakage [2,13].

It is possible that hCRF promotes the repair of intercellular junctions in vascular endothelium by elevating levels of cytosolic secondary messengers. This could occur by either a direct effect on structural repair pathways, or by upregulation of transcription of structural proteins. Alternatively the carboxy-terminus of hCRF has very close homology to portions of intermediate filaments [4]. CRF may modulate the activity of such filaments thus changing cell-cell and cell-matrix adhesions directly. Alternatively, CRF also stimulates other pathways outside the CRF-ACTH-cortisol axis, which include melanocyte stimulating hormone, and endorphins, and its anti-edematous effect may relate, in part, to one of these effects.

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Correspondence: A Marmarou, PhD., Division of Neurosurgery, Medical College of Virginia, Box 980508, Sanger Hall, 1101 E. Marshall St., Richmond, Virginia 23298-0508.

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Monitoring of Brain Tissue PO_2 in Traumatic Brain Injury: Effect of Cerebral Hypoxia on Outcome

T. F. Bardt, A. W. Unterberg, R. Härtl, K. L. Kiening, G. H. Schneider, and **W. R. Lanksch**

Department of Neurosurgery, Virchow Medical Center, Humboldt University, Berlin, Federal Republic of Germany

Summary

This study investigates the effect of hypoxic brain tissue PO_2 on outcome, and examines the incidence of possible causes for cerebral hypoxia.

We studied 35 patients with severe head injury (GCS ≤ 8). Age was 33.2 (±11.3) years. Total time of monitoring of $PtiO_2$, intracranial pressure (ICP), cerebral perfusion pressure (CPP), and endtidal PCO_2 ($ETCO_2$) was 119.3 (±65.7) hours. Data were continuously recorded by a computer system. Outcome was assessed at discharge and after 6 months post injury. 56% of the patients with more than 300 minutes of $PtiO_2$ < 10 mm Hg died, 22% had an unfavourable outcome, 22% had a favourable outcome. Cerebral hypoxia was associated with intracranial hypertension (ICP > 20 mm Hg) in 11.5 (±15.1)%. CPP was compromised below 60 mm Hg in 16.8 (±23.4)%. Hypocarbia ($ETCO_2$ < 28 mm Hg) was present in 48.0% of the time of $PtiO_2$ < 10 mm Hg. No obvious cause for cerebral hypoxia was found in 45% of the data.

These result underscore the association of cerebral hypoxia with poor neurological outcome and stress the meaning of monitoring of $PtiO_2$ as an independent parameter in patients following TBI.

Keywords: Brain tissue PO_2; hypoxia; traumatic brain injury.

Introduction

Continuous monitoring of local brain tissue PO_2 is a promising new methodology that is recently evaluated for the early detection of impending cerebral hypoxia/ischemia [3,5]. Recent studies have suggested that cerebral hypoxia is frequently associated with high compromised cerebral perfusion pressure, and hypocarbia. Purpose of the present study was to examine the association of the possible causes to cerebral hypoxia, and to investigate its effect on outcome in patients following severe head injury.

Materials and Methods

Patient Population and Management

We prospectively studied 35 patients with severe head injury (GCS ≤ 8). Age was 15–55 (33.2 ± 11.3) years. The patients reported in this study were predominantly male (80%). Intracranial diagnosis according to the TCDB classification 6 was a Diffuse Injury II in 28.6%, a Diffuse Injury III in 5.7%, and Evacuated Mass Lesions in 65.7% of the patients. Abnormal pupil reaction was present in 15 (42.9%) patients after admission to the NICU.

Patients were treated to a standardized protocol according to the AANS-guidelines for the management of severe head injury. Space occupying lesions >25 cm^2 were surgically evacuated immediately. Intracranial hypertension, defined as an ICP of >20 mm Hg for over 10 minutes, was treated by head elevation, moderate hyperventilation (arterial PCO_2 30–35 mm Hg) and infusion of boluses of mannitol up to a maximum of 3.5 gm/kg body weight per 24 hours. Barbiturate coma was induced in otherwise uncontrollable intracranial hypertension and guided by a "burst-suppression"-EEG pattern. If this treatment failed, a decompressive craniotomy was performed. Cerebral perfusion pressure was kept over 70 mmHg by reducing elevated ICP and pharmacologically raising mean arterial blood pressure (MABP) with dopamine and noradrenalin.

Brain Tissue PO_2 Monitoring

Patients underwent continuous brain tissue PO_2 ($PtiO_2$) monitoring using the LICOX© (GMS mbH, Kiel, Germany) microcatheter device after informed consent of the patient's relatives. The catheter was placed into the non-lesioned frontal white matter within 8–125 h (mean 52.0 ± 45.3) post-injury. Total time of monitoring was 119.3 (±65.7) hours. Correct position of the catheter's tip in the frontal cerebral white matter was verified by a CCT scan. After monitoring, the $PtiO_2$ catheters were checked for correct PO_2 measurements in room air.

Data Collection and Analysis

Analog signals of MABP, ICP, $ETCO_2$ (Modul M1020A, Hewlett Packard, Waltham, MA), and $PtiO_2$ were continuously digitized at once per minute, displayed and stored on a Windows©-platform running a LabVIEW© (National Instruments, Austin, TX) based software for multimodal data acquisition. Artifact detection was performed off line using a second LabVIEW© program developed for this purpose. Additionally, all data were reviewed off line.

Assessment of Outcome

Neurological outcome was assessed using the Glasgow outcome scale 9 (GOS) at discharge and after six months post trauma. A GOS score of 4–5 (good recovery or moderate disability) was defined as favourable outcome. A GOS score of 2–3 (severe disability or vegetative state) was defined as unfavourable outcome, a GOS score of 1 indicated patient's death.

Results

Brain Tissue Hypoxia

Mean $PtiO_2$ was 22.7 (±9.1) mm Hg in all patients. Incidence of cerebral hypoxia indicated by a $PtiO_2$ < 10 mm Hg was 15.0 (±23.2) hours. 12 patients had no or less than 30 minutes of $PtiO_2$ < 10 mm Hg. In 23 patients more than 30 minutes of reduced cerebral oxygenation were monitored. In patients with no or less than 30 minutes of $PtiO_2$ < 10 mm Hg, $PtiO_2$ was <15 mm Hg in 7.8 (±2.6) hours.

Neurological Outcome

In the acute phase, 31.5% of all patients included into the study died. At discharge, 62.8% were severely disabled or vegetative, and 5.7% had a favourable outcome. After six months post injury, mortality was 37.2%, 17.1% of the patients remained severely disabled or vegetative, and 45.7% had a moderate disability or a good recovery.

Outcome and Cerebral Hypoxia

The incidence of frequent episodes of hypoxic $PtiO_2$ (<10 mm Hg) was associated with a poor neurological outcome. Patients with less than 30 minutes of $PtiO_2$ < 10 mm Hg were predominantly severely disabled or vegetative at discharge (80%), 20% had a favourable outcome, and no patient died in the acute phase. After six months, more than 72.8% of these patients had a favourable outcome, 18.2% had an unfavourable outcome, and 9% died (Fig. 1).

48% of the patients with more than 30 minutes of $PtiO_2$ < 10 mm Hg died in the acute phase, and the other half of these patients had an unfavourable outcome at discharge. After six months, 55.6% of this group were dead, 22.2% remained severely disabled or vegetative and 22.2% achieved a favourable outcome (Fig. 2).

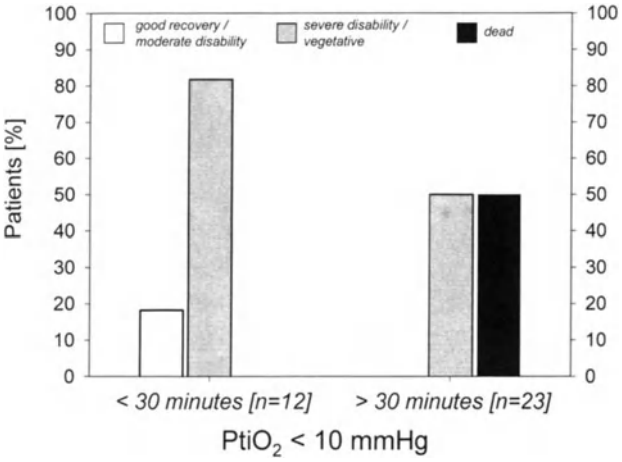

Fig. 1. Outcome at discharge: Patients with less than 30 minutes of cerebral hypoxia were predominantly severely disabled, only few had a favourable outcome. 50% of the patients with more than 30 minutes of $PtiO_2$ < 10 mm Hg died in the acute phase. The other half of these patients was severely disabled

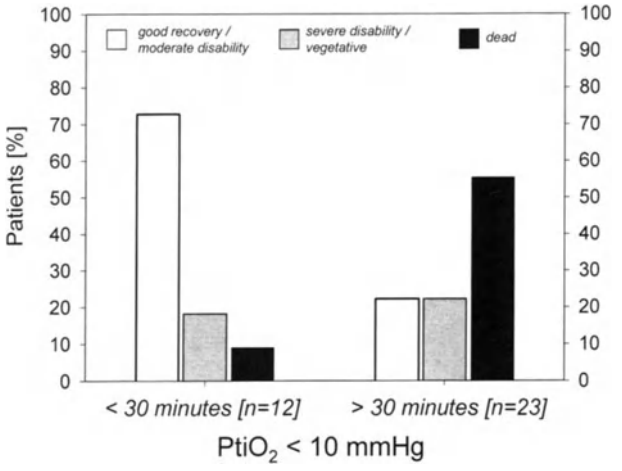

Fig. 2. Outcome six months post trauma; More than 70% of the patients with less than 30 minutes hypoxic brain tissue PO_2 (<10 mm Hg) had a good recovery or a moderate disability. Few remained severely disabled or vegetative. In patients with more than hald an hour of $PtiO_2$ < 10 mm Hg, mortality was 55.6%. More than 20% of this subset of patients achieved a favourable outcome

Relationship of ICP, CPP, and Hypocarbia to Cerebral Hypoxia

Cerebral hypoxia, defined as a $PtiO_2$ < 10 mm Hg was associated with intracranial hypertension (ICP >

20 mmHg) in 11.5 (±15.1)%. CPP was compromised below 60 mmHg in 16.8 (±23.4)%. Hypocarbia ($ETCO_2$ < 28 mmHg) was present in 48.0% of the time of $PtiO_2$ < 10 mmHg. No obvious cause for cerebral hypoxia was found in 45% of the data.

Discussion

In the early 90's, Robertson and coworkers described the contribution of insufficient oxygen saturation for neurological outcome after TBI [2,8]. The incidence of episodes of jugular venous desaturation ($SjvO_2$ < 50% for more than 10 minutes) was significantly associated with a poor outcome. Limitations of this method are that it is unable to detect regional changes in tissue perfusion, and the frequent occurrence of artifacts due to movement of the catheter in the jugular bulb. Sheinberg found up to 50% of critical desaturations of $SjvO_2$ to be incorrect.

As a promising new method, continuous monitoring of local $PtiO_2$ is presently evaluated. The available microcatheters can be placed in those areas of the vulnerable brain, where hypoxia has strictly to be avoided. The probes have a rather quick response time and provide stable measurements even after one week of monitoring.

Therefore, it is not surprising that the incidence of cerebral hypoxia ($PtiO_2$ < 10 mmHg) found in our patients was relatively high. In 27 (83%) of our patients an average of 15.1 (±23.2) hours of $PtiO_2$ < 10 mmHg was recorded, while in only eight patients (23%) no diminished $PtiO_2$ was detected. In contrast, Gopinath *et al.* [2] reported an incidence of 77 desaturation episodes in 45 of 116 patients with TBI with a mean duration of 1.2 hours, while in about 60% of their patients no desaturation episode was recorded. Total time of cerebral hypoxia in our patients was about 10 times higher. This leads to the assumption, that possibly a major part of cerebral hypoxia might not be reflected by $SjvO_2$ but is well documented by monitoring of $PtiO_2$. The incidence of diminished $PtiO_2$ < 10 mmHg was strongly associated with a poor neurological outcome. Our data suggest that even a remarkable short episode of cerebral hypoxia is negatively affecting outcome. Another important result is that about half of the survivors of the subset of patients with more than 30 minutes of cerebral hypoxia finally achieved a favourable outcome. This demonstratess that even after frequent episodes of cerebral hypoxia a good recovery is possible. Comparison of these data with other studies performed with $SjvO_2$ show a remarkable similarity.

A study of Gopinath describes a significantly better outcome in patients without any jugular venous desaturation episode. The mortality rate and the percentage of unfavourable outcome among these patients were much higher than in the patients with less than 30 minutes of $PtiO_2$ below 10 mmHg in our study. Again, as a possible cause the technical limitations of monitoring of $SjvO_2$ have to be considered. Monitoring of local brain tissue PO_2 appears to be the more sensitive methodology and is, therefore the method of choice in monitoring of cerebral oxygenation after traumatic brain injury. However, the critical ischemic level for $PtiO_2$ has not been established definitively, though the significant correlation to $SjvO_2$ strongly suggests a $PtiO_2$ below 10 mmHg as ischemic threshold. Hypoxia, hypotension, and intracranial hypertension are known to be the leading causes for cerebral ischemia [1,4]. Sheinberg *et al.* [9] identified the probable cause for desaturation episodes in 20 patients with TBI as intracranial hypertension and hypocarbia. In the 35 patients of the present study, cerebral hypoxia ($PtiO_2$ < 10 mmHg) was associated with hypocarbia with a fourfold frequency than with an elevated ICP or a compromised CPP. It remains unclear whether these data demonstrate the harmful effect of hyperventilation on cerebral oxygenation or simply demonstrate the sufficiency of the ICP/CPP therapy. Meanwhile, it is evident that hyperventilation carries a certain risk to deteriorate cerebral oxygenation even when it is administered moderately [5]. Further prospectively performed studies will be necessary to further elucidate this topic.

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Correspondence: Tillman F. Bardt, M.D., Department of Neurosurgery, Humboldt University, Virchow Medical Center, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Bilateral Monitoring of CBF and Tissue Oxygen Pressure in the Penumbra of a Focal Mass Lesion in Rats

R. Burger, G. H. Vince, J. Meixensberger, and **K. Roosen**

Department of Neurosurgery, University of Würzburg, Würzburg, Germany

Summary

The continuous monitoring of cerebral microcirculation is aimed at preventing secondary ischemic brain damage subsequent to severe head injury. Interrelations between bilateral changes of cortical Laser Doppler Flowmetry (LDF) and intraparenchymal, subcortical $p(ti)O_2$ values were continuously monitored in the forebrain of rodents. A trauma group of 8 animals received an unilateral, focal parietal mass lesion by an expanding epidural balloon. 10 animals served as a sham group. In the sham-operated group the drift of median LDF values was 10.8% in the left and 9.6% in the right hemisphere. The absolute median $p(ti)O_2$ showed values of 31.2 mm Hg (27.9–34.9) in the left and 30.1 mm Hg (27.5–31.7) in the right hemisphere. During maximum brain compression median LDF values decreased ipsilateral to 18.6% (13.3–24.4%) and contralateral to 23.4% (17.1–56.6%) of the baseline values. $P(ti)O_2$ decreased ipsilateral to absolute values of 4.6 mm Hg (3.2–6.7 mm Hg) and contralateral to values of 7.1 mm Hg (6.1–8.5 mm Hg). After balloon deflation cortical LDF was restored much faster but did not reach baseline values [ipsilateral 55.2% (42.6–67.8%); contralateral 67% (53.4–82%) of baseline values]. The $p(ti)O_2$ values reached ipsilateral 77.4% (72.0–93.3%) and contralateral 88.8% (86.0–97.4%) of baseline values. Both parameters showed a significant correlation ($r = 0.57$; $p < 0.02$). $P(ti)O_2$ measurements supplement on-line cortical CBF monitoring and by far outscore discontinuous alternative measurement techniques in detecting hemodynamically relevant events. The small spatial resolution of the $p(ti)O_2$ probes, however, which in the small animal model may be of negligible influence, does raise the question whether the values gained offer a general overview of the microcirculatory situation.

Keywords: Brain compression; CBF monitoring; tissue oxygen; vasoparalysis.

Introduction

Neurovascular multimodal monitoring is aimed at recognizing and preventing secondary brain damage caused by ischemia, edema and hemorrhage in the wake of a head injury [1]. Several techniques have so far been introduced to measure ICP, CBF and oxygen tension in different anatomical regions of the brain with a different spatial resolution. Laser Doppler Flowmetry (LDF) has received particular attention as it can be employed to continuously monitor cortical microcirculation under both experimental [3] and clinical [7] conditions. Recently, a new sensor has been introduced in clinical trials allowing the direct invasive measurement of tissure oxygen partial pressure in the subcortical white matter of trauma patients [2,6,17]. The method has already yielded remarkable results for trauma related disturbance of brain homeostasis, but has raised the question of whether alterations of the locally recorded, subcortical, intraparenchymal oxygen tension are reflected in the CBF of the cortical compartment.

We present a rodent balloon expansion model to correlate bilaterally recorded intraparenchymal $p(ti)O_2$ and LDF. The study focuses on whether invasive $p(ti)O_2$ measurements are reliable enough to replace conventional continuous and discontinuous methods of cortical CBF measurement in clinical routine. To the best of our knowledge, this is the first critical examination of the servicability of this type of polarographic microsensor in small animal experiments.

Material and Methods

The experimental protocol included 18 Sprague – Dawley rats (598 ± 129 g), randomized in a sham – operated (n = 10) and a group with balloon induced mass lesion (n = 8). The animals were artificially ventilated with a gas mixture of 1.0–2.0% Isoflurane, 33% oxygen and 66% nitrous oxide throughout the experiment. The left femoral artery was cannulated for measuring systemic arterial blood pressure (SAP) and gaining samples for blood gas analyses; rectal body temperature was maintained constant. PaO_2

was regulated to a value of 129.5 ± 23.4 mm Hg and $paCO_2$ to 36.7 ± 7.4 mm Hg. After positioning the animal in a stereotactic frame the cranium was exposed. The following burrholes were placed: A left parietal 5 mm burrhole for the balloon trauma device [8] and directly at the coronal suture bilateral 2.3 mm burrholes for the large area integrating laser doppler probes [type P7b (Ø 3 mm), Moor Corp., UK]. We recorded the flux as a percentage of the drift from initial baseline values in a sample volume of 3.14 mm^3. The technique and principles of LDF have already been described [3,7]. The pO_2 microcatheters [Clark-type (Ø 0.47 mm), Licox-System, GMS Corp., Kiel, Germany) were placed in two bilateral 1.5 mm burrholes before the coronal suture directly rostral of the laser doppler probes. The length of the probe had to be slightly shortened to ensure it would not puncture the ventricular system of the rat brain but still remain safely within the slender white matter. The catheter specific calibration values were adjusted on the pO_2 device. Premeasurement zero (left 0.97% ± 0.79, right 0.33% ± 0.27) and sensitivity (left 5.1% ± 2.17/right 5.6% ± 3.5) drift was evaluated. The pO_2 values were corrected according to the rectal temperature. Followingly, a 3 point EEG monitor was connected.

After positioning the balloon expansion device and inserting all of the probes, baseline values of LDF and pO_2 were monitored in the sham – operated group over 58 ± 8 min followed by an observation time of 139 ± 60 min. In the group with balloon expansion, baseline values were measured for 61 ± 9 min followed by balloon inflation with 0.5 ml/h NaCl until the pupils dilated bilaterally as a clinical sign of brain stem compression. Balloon inflation required 61 ± 9 min, and was sustained for 10 min before rapid deflation within 10 s. After decompression all parameters were recorded for a further 178 ± 29 minutes and pupillary reaction was checked. At the end of the observation time, the brains of the animals were removed and immersion fixed in 3.7% paraformaldehyde. Histopathological work up was aimed at evaluating the consistency and degree of damage caused by the balloon induced focal mass lesion and the amount of injury to be expected from the sensors employed. At the end of the experiment the pO_2 microcatheters were checked for postmeasurement zero (left 1.6% ± 0.9, right 1.5% ± 0.6) and sensitivity drift (left 7.7% ± 2.8%/right 10.2% ± 2.1).

Results

The sham – operated animals retained stable mean SAP values between 81.5 ± 9.4 mmHg and 87 ± 11.4 mmHg throughout the whole experiment. PaO_2 varied between 139 ± 22.1 mm Hg and 119.5 ± 24.6 mm Hg and $paCO_2$ between 36.4 ± 13 and 38.8 ± 10 mm Hg. The percentage of drift of LDF during baseline measurement of the sham – operated animals during the first 58 ± 8 min was 5.3% [–4.8% to 17.1%] in the left and 0.4% [–0.5% to 38.6%] in the right hemisphere. During the whole experiment 139 ± 60 min later, left-side LDF drifted 9.2% [–20.9% to 17.6%] and 8.6% on the right-side [–13.6% to 42.7%]. A minor drift of the $p(ti)O_2$ probes was registered in the first hour after insertion. In the right hemisphere absolute $p(ti)O_2$ was 34.6 mm Hg [32–35.7 mm Hg] at the beginning of the baseline measurement versus 32.6 mm Hg [31–33.3% mm Hg] at the end. In the left hemisphere the drift was 32 mm Hg [29–33 mm Hg] versus 32 mm Hg [30–34.2 mm Hg] for the left hemisphere. In time course, left-side $p(ti)O_2$ values after 139 ± 60 min were 31.2 mm Hg [27.9–35.0 mm Hg] and 30.1 mm Hg on the right-side [27.5–31.7 mm Hg] in the frontal subcortical area of the sham – operated animals. $P(ti)O_2$ measurements were surprisingly stable in the control group, LDF values showed a higher drift, but remained below 10% of the median values on average. There was no significant interhemispheric difference for LDF and $p(ti)O_2$ measurements ($p < 0.05$) in the sham – operated animals. In the group with balloon expansion SAP varied between 81.3 ± 11.5 mm Hg and 92.4 ± 11.3 mm Hg, whereby the lowest values were reached during sustained inflation and at the end of reperfusion. PaO_2 varied between 150 ± 36.1 mm Hg and 116.9 ± 26.5 mm Hg and $paCO_2$ between 39.9 ± 6.6 and 32.5 ± 5.3 mm Hg during the experiment, but stayed within physiological range.

Figure 1 illustrates the time course of LDF and $p(ti)O_2$ before and after balloon expansion. LDF baseline values (B1) ipsilateral to the lesion in-

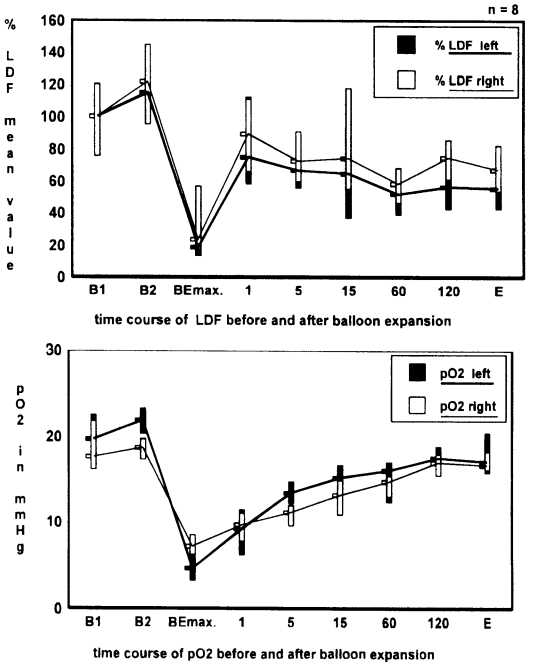

Fig. 1. Bi-fronto – parietal cortical laser doppler flowmetry and subcortical absolute tissue oxygen pressure $p(ti)O_2$ of both hemispheres before, during and after induction of a right parietal, epidural focal mass lesion. *B1* start of baseline; *B2* end of baseline; *BE max* maximum balloon expansion; *1–120* minutes after reperfusion; *E* endpoint of investigation; relative values; *LDF* median and range as percentage of baseline; absolute values: $p(ti)O_2$, median and range in mm Hg

creased to 114% (96–140.6%) and contralateral to 121.6% (95–145%) during baseline measurements (B2). Balloon inflation until pupillary dilation was followed by a marked decrease ipsilateral to 18.6% (13.3–24.4%) and contralateral to 23.5% (17.1–56.7%) of the baseline (BEmax.). After balloon deflation incomplete cortical reperfusion occured. LDF ipsilateral showed median values of 74.8% (58.4–112%) and contralateral 89.1% (66–110.6%) in the first minute after reperfusion. Short reactive hyperemia was only seen in 3 of 8 animals. In time course values again declined ipsilateral until the end of the monitoring period (E) to 55.2% (42.6–67.8%) and contralateral to 67.1% (53.4–82.1%) of the baseline (B1). Absolute $p(ti)O_2$ values after 61 ± 9 min at the end of baseline measurement showed ipsilateral 21.8 mm Hg (23.3–20.2 mm Hg) and contralateral 18.5 mm Hg (19.7–17.2 mm Hg) During the maximum of balloon expansion $p(ti)O_2$ decreased ipsilateral to 4.5 mm Hg (3.2–6.6 mm Hg) and contralateral to 7.1 mm Hg (6.2–8.5% mm Hg). During and after decompression bilateral $p(ti)O_2$ values recovered markedly slower than LD-flowmetry. After one minute of reperfusion ipsilateral $p(ti)O_2$ increased to 42% [9.1 mm Hg (6.1–18.1 mm Hg)] and contralateral to 51% [9.63 mm Hg (7.8–11 mm Hg)] of baseline values. At the end of the monitoring period (E) $p(ti)O_2$ reached 77.5% ipsilateral [16.6 mm Hg (15.7–20.3 mm Hg)] and 88.8% [16.5 mm Hg (16–18.1 mm Hg)] contralateral. Percentage of changes in LD Flowmetry ($p < 0.01$) and absolute $p(ti)O_2$ ($p < 0.02$) values between the hemispheres were significant with higher values of LDF at the contralateral side to the lesion and slightly higher pO_2 values ipsilateral to the lesion. Correlation of LD flowmetry and $p(ti)O_2$ of each hemisphere showed a reduced correlation ($r = 0.57$; $p < 0.02$; Fig. 2) due to the small spatial resolution of of the LDF and $p(ti)O_2$ measurements despite a LDF–pO_2 probe distance of less than 3–4 mm.

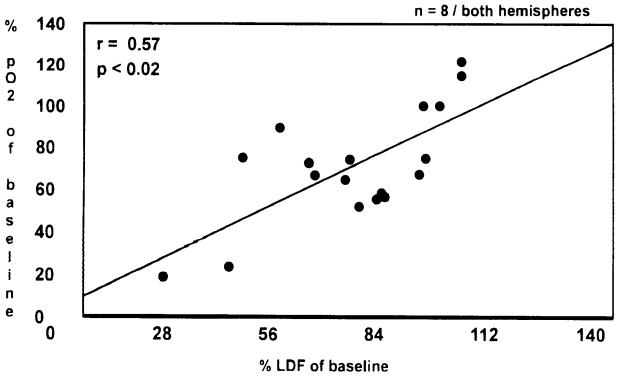

Fig. 2. Regression analysis between LDF and $p(ti)O_2$ of each hemisphere; each point illustrates the cumulated data of all animals at a defined timepoint before, during and after induction of a left parietal focal mass lesion; LDF (B1) and $p(ti)O_2$ (B2); relative values: values as percentage of the baseline

Discussion

Several multimodal neurovascular monitoring techniques are presently available for clinical practice. The purpose of the present study was to compare these methods taking advantage of an experimental setting. We employed an unilateral focal lesion trauma model with an epidural expanding balloon. A typical clinical protocol was followed for measuring both cortical hemodynamics and subcortical $p(ti)O_2$. Cortical microcirculation was recorded bilaterally by laser doppler flowmetry and subcortical $p(ti)O_2$ using routine clinical equipment. The epidural trauma model [8] was chosen and adapted to closely imitate the typical clinical dynamics of the pathological condition. Therefore the presented approach respects the timepoint of pupil dilation as a standardized degree of brain compression and provoked the end of balloon inflation. Nearly always this meant a balloon volume of 0.48 ml. Balloon disruption, microsurgical and technical difficulties during burr-hole trephination were rare occurences. These cases were excluded from the study. The LDF values were expressed as a percentage of the baseline, because calibration to absolute flow values is, as yet, not possible. Due to the heterogeneity of cortical blood flow, scanning procedures of LDF and frequency histograms of cerebral blood flow are necessary to reach a small variability and a high spatial resolution of red cell flux [5]. Since time-resolution is inferior with scanning technique and a crucial point in our model we decided to compromise on a stationary "large area integrating" probe. $P(ti)O_2$ measurements with polarographic microsensors, originally designed for humans, were feasible in the frontopolar region of the rat brain. They in no case punctured the ventricles. Dura opening with a sharp pointed trocar caused only minor injury to the brain surface. $P(ti)O_2$ values of sham-operated animals between baseline and the end of the experiment were stable with a minimal drift of 2% in the left and 4,6% in the right hemisphere. The absolute subcortical brain $p(ti)O_2$ ranged between 18.5–34.5% mm Hg and compares to results both in the white matter of other animal spe-

cies [4,11,13] and in humans measured during tumor surgery [12] or after severe head injury [2,6,17]. The values stated in literature for grey matter range between 20–50 mm Hg in animals, but were on average higher than measurements at greater depth [9,14,16]. The timespan of brain compression required for pupillary dilation and flat EEG remained remarkably stable at 61 ± 9 minutes. Baseline values after one hour observation time showed lower values than in the sham – operated group, but again remained within the normal range found in literature [4,11,13]. At the time-point of maximum ischemia with brain stem compression and widening of pupils $p(ti)O_2$ values decreased below 10 mm Hg, a value which, in clinical and laboratory research, has been proposed s a "critical threshold" of hypoxia [2,6,10,17]. After 10 min sustained inflation decompression was followed by a rapid, but incomplete cortical reperfusion in LDF over time. Histopathological finding in other balloon expansion studies showed that this phenomenon is due to the reduced number of microvessels resulting from compressed and thrombosed pial and cortical vessels [15,18]. Thus, reflow also correlates with the neurological and neurophysiological status at the endpoint of compression. Studies have shown that in the majority of small vessels and capillaries no reflow occurs when EEG was flat and pupils dilated. Reflow was regularly seen in capillaries when this endpoint was not reached [15]. Consequently, the severity of the trauma is responsible for the course of LDF during reperfusion. $P(ti)O_2$ after decompression rises slower. This is explained by a slower reperfusion in subcortical areas with larger diffusion distances from cortical to subcortical areas, but could also be influenced by the pO_2 probe response-time which according to the manufacturer requires 70–90 s [27]. Compared to LD flowmetry pO_2 nearly returned to baseline values, possibly due to the larger distance of the $p(ti)O_2$ probes from the lesion. The correlation of percentage of alteration from baseline values in LD flowmetry between both hemispheres showed significantly lower values ipsilateral to the lesion due to the reduced number of perfused cortical microvessels and intense brain swelling ipsilateral to the lesion [15,18]. In contrast the $p(ti)O_2$ probes showed lower values during maximum compression ipsilateral to the lesion. However, they increased again during the first two hours after reperfusion speculatingly caused by a short, focal, intraparenchymal hyperperfusion following vasoparalysis. This phenomenon remains independent of the low flow state in the ipsilateral cortical penumbra. The percentage of change between the two modalities LDF and $p(ti)O_2$ in each hemisphere was statistically significant, but the correlation remained lower than the correlation between the two modalities in each hemisphere. The impression was gained that each modality measures with a low spatial resolution despite the fact that $p(ti)O_2$ and LDF probes were positioned at a maximum distance of 3–4 mm to each other. Consequently, clincally relevant hypoxic events can be traced with both methods measuring in the cortical or subcortical compartment during major regional or global alterations of CPP, provided that no local pathology interferes with the measurement itself. Hence $p(ti)O_2$ or LDF values should be, as yet, carefully incorporated in clinical therapeutic considerations.

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Correspondence: Ralf Burger, M.D., Department of Neurosurgery, University of Wuerzburg, Josef-Schneider-Str. 11, D-97080 Wuerzburg, Federal Republic of Germany.

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High Cerebral Perfusion Pressure Improves Low Values of Local Brain Tissue O_2 Tension ($PtiO_2$) in Focal Lesions

N. Stocchetti[1], **A. Chieregato**[1], **M. De Marchi**[1], **M. Croci**[1], **R. Benti**[2], and **N. Grimoldi**[3]

[1] Neurosurgical Intensive Care Unit, [2] Department of Nuclear Medicine, [3] Department of Neurosurgery, IRCCS Ospedale Maggiore-Policlinico, Milano, Italy

Summary

Arterial hypertension is widely applied to improve regional cerebral blood flow (rCBF). We measured local brain tissue O_2 pressure ($PtiO_2$) in low density lesions at computerized tomography (CT) of the head before and after manipulation of mean arterial pressure (MAP) in order to increase cerebral perfusion pressure (CPP). Nine patients, 7 subarachnoid hemorrhage (SAH), 1 severe head injury, 1 meningeoma, were included in our study. A flexible polarographic microcatheter for $PtiO_2$ measurement was placed at the border of the low density area found at CT. $PtiO_2$ was continuously measured for 615 hours. Hypoperfusion in low density areas was detected by perfusional single photon emission computed tomography (SPECT). We recorded 22 episodes of induced or spontaneous increase of MAP. Initial $PtiO_2$ regularly improved after the CPP increase (r^2 0.74 in induced episodes). Low $PtiO_2$ showed a greater percent increase for unitary changes of CPP than normal-high $PtiO_2$. Baseline $PtiO_2$ below 20 mm Hg was associated with normal CPPs; 5 readings of $PtiO_2$ below 20 mm Hg normalized when a higher CPP was obtained. Our results show that in ischemic areas $PtiO_2$ is dependent on CPP suggesting both a derangement of pressure autoregulation and high regional cerebrovascular resistences (CVRs). Low $PtiO_2$ was associated with normal CPP, thus indicating that CPP could be an inadequate estimate of rCBF in focal ischemic areas. Arterial hypertension, capable of increasing CPP above normal values, appeared useful in normalizing tissue oxygenation in ischemic areas.

Keywords: Arterial hypertension; brain tissue O_2; cerebral perfusion pressure; tissue oxygenation.

Introduction

Arterial hypertension is widely applied to improve CPP in severe head injury, SAH and stroke. New microsensors measuring $PtiO_2$ in small volumes of the brain have recently been developed. This monitoring appears to be reliable for clinical use and free of complications [8]. Although few experimental studies are available, $PtiO_2$ appears to be mainly a function of rCBF [9]. The objective of our study was the investigation of the changes of regional oxygenation in focal ischemic areas in response to an acute improvement of CPP caused by increased MAP. Focal ischemic areas have been identified by SPECT. We tried to place our sensors at the border of such areas, in order to explore penumbra portions of the lesioned brain. These areas are probably the most appropriate target of a therapy aimed at recruiting collateral flow by means of induced arterial hypertension.

Materials and Methods

Nine patients with acute focal lesions, 7 SAH, 1 severe head injury, 1 menigeoma, were included in the study. Age was 55.8 ± 7 years; 8 of those patients were female. Patients data are described in table 1. $PtiO_2$ was continuously measured for a total of 615 hours (mean duration 68 ± 38 hours) with a flexible polarographic (Clark-type) probe (Microcatheter PO_2 probe, Licox GMS mbH, Kiel, Germany) connected to a computer (Licox PO_2, GMS mbH, Kiel, Germany). The external body temperature was used to correct the PO_2 measurement. Both Licox signals and other data such as arterial pressure, intracranial pressure (ICP), and expiratory CO_2 were sent, through an analog-digital converter, to a computer for storage and analysis. $PtiO_2$ measured during the first 2 hours of monitoring were not used for analysis.

For $PtiO_2$ monitoring, we selected patients with acutely developed low density areas at CT. According to the clinical history, to CT findings and to instrumental (angiographic and trans-cranial doppler) information, the probable cause of the hypodense area was identified (Table 1). We performed a perfusional SPECT in order to demonstrate that hypoperfusion occurs in the low density areas. SPECT was obtained 60–120 minutes after the intravenous administration of Tecnetium-99 m (800 MBq) labelled Ethyl-Cysteinate-Dimer (ECD) (Neurolite-DuPont Pharma, USA). Ra-

Table 1. *Patient Data. mGCS (Motor Glasgow Coma Scale Score) and Hunt & Hess Post Resuscitation, Neurological Level at Discharge from Intensive Care Unit. MCA (Middle Cerebral Artery), ACA (Anterior Cerebral Artery), PICA (Posterior Inferior Cerebellar Artery), ICH (Intracranial Haematoma)*

Pts	Disease	mGCS (score)	Hunt and Hess (grade)	Volume of low density lesion (mm^3)	Etiology of low density lesion	Satisfactory placement of catheter (yes/no)	Neurological level
1	severe head injury-multiple contusion	6		45	contusion	yes	obeying
2	left sphenoidal small wing meningeoma	5		140	surgical arterial stenosis	no	not obeying
3	SAH-clipped left MCA aneurysm	4	4	43	ICH	yes	not obeying
4	SAH-clipped left MCA aneurysm	5	5	81	ICH	yes	not obeying
5	SAH-clipped left MCA aneurysm	5	2	103	vasospasm	yes	not obeying
6	SAH-clipped giant ACA aneurysm	2	4	70	vasospasm	yes	dead
7	SAH-clipped left PICA aneurysm	6	3	24 and 61	angiographic embolism (1st and 2nd) and vasospasm (3rd)	no (1st, 2nd), yes (3rd)	dead
8	SAH-clipped right ACA aneurysm	5	4	21	vasospasm and ICH	yes	not obeying
9	SAH-clipped right ACA aneurysm	5	3	16 and 56	ICH and surgical stenosis (1st) and vasospasm (2nd)	no (1st) and yes (2nd)	dead

dioactive and radiopaque markers were used to fit the information obtained from SPECT and CT in order to guide the placement of the $PtiO_2$ probe into the perifocal areas. The Licox microcatheter was placed through a burr hole made over the selected area of the brain and manually inserted in the brain parenchyma, having previously opened the dura mater. The volume of the low density lesion, in which the microcatheter was placed, was measured according to a method reported by Pasqualin [6] and described in table 1. If the lesion was not completely hypodense, the volume of high-mixed lesion was subtracted from the overall lesion. After inserting the microcatheter, a CT scan was performed to evaluate the final position of the microcatheter in relation to the aimed placement at the border of the low density area (Table 1).

In patients with unstable ICP, spontaneous fluctuactions of $PtiO_2$ have been recorded but, in order to avoid ICP disturbances, MAP was not manipulated. We studied the response of $PtiO_2$ to a 10–20% improvement of MAP obtained with continuous infusion of noradrenaline. We also recorded the changes in $PtiO_2$ following a spontaneous change in MAP, greater than 10% from the baseline, lasting more than 5 minutes but not longer than 30 minutes.

Means were compared with T test, using paired or independent tests when appropriate. A level of $p < 0.05$ was considered significant.

Results

According to the SPECT studies performed, hypoperfusion in the same spatial distribution of hypodense area at CT was detected (Table 1). The location of 8 out of 12 microcatheters was classified as satisfactory because they were placed at the internal border of the hypodense area (Table 1). We recorded 22 episodes of increased MAP, 6 of them induced with noradrenaline (test group) and 16 spontaneous (spontaneous group). Final MAP (111 ± 13 mmHg) and CPP (96 ± 11 mmHg) were higher than the baseline MAP (91 ± 12 mmHg) and CPP (77 ± 9 mmHg) (n 9, $p < 0.001$). Final ICP (15.9 ± 4.5 mmHg) was slightly higher than initial ICP (14.7 ± 4.8 mmHg) (n 9, $p < 0.05$). Final $PtiO_2$ (31 ± 13 mmHg) was higher than initial $PtiO_2$ (24 ± 13 mmHg) (n 9, $p < 0.001$). We found a positive linear correlation (r^2 0.74) between the change of $PtiO_2$ (delta $PtiO_2$) and the change of CPP (delta CPP) in the test group (Fig. 1). In the spontaneous group the r^2 was 0.99 (Fig. 1). The changes of $PtiO_2$ were expressed as percent change over an increase of 1 mmHg of CPP (%/mmHg) and were described by an exponential curve (r^2 0,83) (Fig. 2). Patients with low $PtiO_2$ values had a greater response to CPP improvement. The determinations were divided in two groups according to an initial $PtiO_2$ lower (n 11, 5 patients) or higher (n 11, 6 patients) than 20 mmHg (Table 2). In the group with $PtiO_2$ below 20 mmHg, the low $PtiO_2$ values were associated with average CPPs that were normal (Table 2). In both groups,

only 2 readings out of 11 had CPP below 60 mm Hg. In both groups, $PtiO_2$ improved in response to a "supra-normal" CPP, but in the group with low $PtiO_2$, the values were more responsive to CPP changes, and $PtiO_2$ normalized in 5 readings out of 11.

Discussion

$PtiO_2$ appears to be mainly related to rCBF and CPP [5,9] at stable $PaCO_2$ [2,8] and PaO_2 [8]. Accordingly, our results suggest that $PtiO_2$, measured in low density areas, is highly dependent upon CPP. Acute changes of MAP and CPP were associated with an improvement of $PtiO_2$, even if the baseline CPP was normal. This result is in apparent disagreement with that found by Kiening *et al.* [5] who described stable $PtiO_2$ when CPP was higher than 60 mm Hg and suggested that autoregulation is preserved in nonlesioned areas. In our patients the microcatheter was intentionally placed into the ischemic area, where a defective autoregulation probably occurs, while Kiening [5] recorded $PtiO_2$ from probes placed in nonlesioned areas. The relationship that we found between CPP and $PtiO_2$ is very similar to that which occurs experimentally between CPP and rCBF in the presence of a defective autoregulation [3]. We suggest that this relationship shows a passive dependence of regional perfusion on CPP.

A second result of our study is that low $PtiO_2$ can be detected even when CPP is normal. A normal CPP does not guarantee an adequate rCBF even when mesured with laser doppler flowmetry in patients with SAH [4]. In acute cerebral diseases, ischemia occurs not only as a result of low CPP, but also from a change of CVR which takes place mainly in the large vessels (vasospasm, surgical stenosis, embolism) but is also caused by a damage of the microcirculation [7]. Therefore CPP alone cannot be considered an appropriate monitoring for treatment of focal ischemic areas.

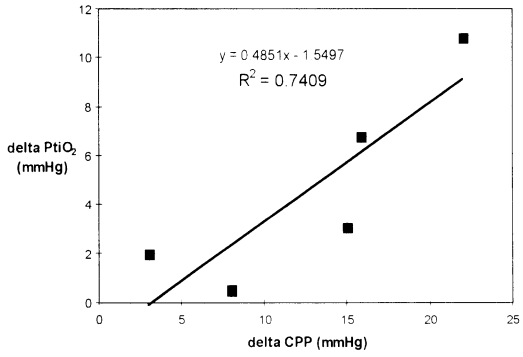

Fig. 1. Change in $PtiO_2$ as a function of CPP variations after induced arterial hypertension. Linear regression is shown

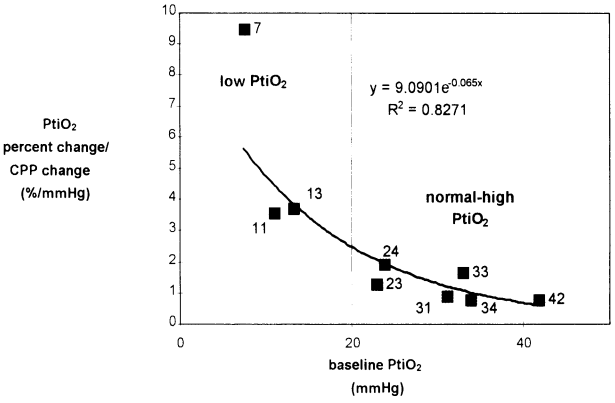

Fig. 2. Percent changes of $PtiO_2$ in response to an increase of CPP of 1 mmHg as a function of the baseline $PtiO_2$. This plot suggests that improvement of $PtiO_2$ after CPP increase is greater when tissue oxygenation is lower. A non linear fit is shown. Since $PtiO_2$ appears in both axes some degrees of mathematical coupling is suspected, but the relationship still appears meaningful

Table 2. *Patients According to PtiO2 Below or higher than 20 mm Hg*

	Baseline $PtiO_2$ < 20 mm Hg	Baseline $PtiO_2$ > 20 mm Hg	Independent samples-T test
Patients (n)	5	6	
% change PtiO2/mm Hg CPP	4.2 (3.1)	0.9 (0.5)	$p < 0.05$
$PtiO_2$ initial (mm Hg)	13 (4)*	36 (8)*	$p < 0.001$
$PtiO_2$ final (mm Hg)	19 (4)*	42 (8)*	$p < 0.001$
CPP initial (mm Hg)	76 (18)^	78 (17)^	NS
CPP final (mm Hg)	94 (16)^	96 (16)^	NS
ICP initial (mm Hg)	16.7 (6.9)	13.6 (4.5)	NS
ICP final (mm Hg)	17.7 (6.5)	14.9 (4.2)	NS

^ ($p < 0.01$) and * ($p < 0.05$) indicates a significant difference at paired samples T test.

Arterial hypertension improved low $PtiO_2$, up to normal values. We considered abnormal a $PtiO_2$ below 20 mm Hg abnormal [5]. The CPP-linked improvement of $PtiO_2$ was more relevant when the baseline $PtiO_2$ was low. The sensitivity of low $PtiO_2$ to CPP improvement is similar to that described in SAH by Darby [1] who found a more significant improvement of rCBF, after the induction of arterial hypertension, when baseline rCBF was low. We suggest that in an ischemic tissue the vessels are maximally vasodilated, and metabolic autoregulation predominates over pressure autoregulation. Following an improvement of CPP, the vessels do not "adequately" constrict. Another explanation is that, in a situation of low $PtiO_2$, abnormally high regional CVRs highly reduce rCBF and make it exquisitely dependent upon CPP [4].

Our preliminary results suggests that: a) $PtiO_2$ in low density-hypoperfused area shows hypoperfusion even if CPP is normal, and b) arterial hypertension and "supra-normal" CPP invariably improve $PtiO_2$, much more when $PtiO_2$ is low. An important limitation of the current treatment with arterial hypertension in neuroscience is the lack of both controlled randomized studies evaluating the final outcome and clinical studies measuring its effectiveness on rCBF. By contrast, arterial hypertension could be contraindicated and could induce collateral side effects. This further suggests that a) therapy of focal brain ischemia may benefit from rCBF measurement because CPP is not an adequate index of regional perfusion probably because of its global nature and because of an unknown CVR b) continuous evaluation of regional oxygenation may be used for validating the efficacy of induced arterial hypertension in focal ischemia.

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Correspondence: Dr. Nino Stocchetti, Terapia Intensiva Neurochirurgica, Servizio di Anestesia e Rianimazione, IRCCS Ospedale Maggiore-Policlinico, Via F. Sforza 35, Milano, Italy.

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Determination of the Ischemic Threshold for Brain Oxygen Tension

E. M. R. Doppenberg, A. Zauner, J. C. Watson, and **R. Bullock**

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, U.S.A.

Summary

Measuring brain tissue oxygenation is now possible due to major advances in the technical development of Clark-electrodes and fiberoptic systems. However, to make this technique clinically useful for both nurses and medical staff, the ischemic threshold for brain tissue oxygen tension (brain pO_2) must be determined. Three end points were used for determination of the critical brain pO_2 value. 1) Infarct determination after permanent middle cerebral artery occlusion in a feline model. 2) Threshold analysis using the schemic threshold for cerebral blood flow (CBF) as a "gold standard" in severely head injury patients. 3) Outcome analysis in severely head injured patients. Brain pO_2 dropped to 19 ± 6 mm Hg and 23 ± 6, 4 to 5 hours after MCA occlusion in the cat (n = 12). In severely head injured patients, a brain $pO_2 \leq 19$ mm Hg was correlated with poor outcome (n = 24). The ischemic threshold for (r)CBF of 18 ml/100 g/min corresponded to a brain pO_2 of 22 mm Hg, in the same patients. By using the above mentioned end points as a reference, we found the critical value for brain pO_2 to be in between 19 and 23 mmHg. Clearly, the difference between our threshold value and the lower critical brain pO_2 level found by other groups using the Licox system, needs to be clarified in a comparison study before a uniform threshold for brain pO_2 can be determined.

Keywords: Brain oxygen tension; Clark-electrodes; middle cerebral artery occlusion; ischemic threshold.

Introduction

Measuring brain tissue oxygenation is now possible due to major advances in the technical development of Clark-electrodes and fiberoptic systems. However, to make this technique clinically useful for both nurses and medical staff, the ischemic threshold for brain tissue oxygen tension (brain pO_2) must be determined.

To determine these values, true end points are needed to refer to as a "gold standard". In animal studies this is the determination of an induced infarct. In humans however, the only end points that are currently available and reliable, both quantitatively and qualitatively, are regional cerebral blood flow (rCBF) measurements and outcome. We therefore, used data obtained in our cat studies and data from our human studies in an attempt to determine "danger levels" for brain pO_2.

Materials and Methods

In all studies a multiparameter sensor was used. It combines a Clark electrode for measuring oxygen tension with fiberoptic sensors for carbon dioxide tension and pH measurements and a thermocouple for temperature (Paratrend 7, Diametrics Medical Inc., Saint Paul, MN, USA). (Carbon dioxide, pH and temperature data will be presented elsewhere.)

To determine the critical value for brain pO_2, 3 objective endpoints were used:

I. Permanent occlusion of the middle cerebral artery in the cat, from two different studies. Verification of sensor placement was done by both macroscopic and microscopic histological examination of the infarcted area of the brain (Fig. 1).
II. RCBF studies in severely head injured humans using the stable Xenon CT technique.
III. Outcome analysis in 25 severely head injured humans using the Glasgow Outcome Score (GOS) after 6 months.

Results

Animals

Two studies were done in which brain pO_2 was measured prior and after occlusion of the MCA in the cat. Zauner *et al.* showed a mean brain pO_2 decrease to 19 ± 6 mm Hg after occlusion (n = 6) [13]. In a subsequent study, Watson *et al.* found a mean

decrease to 23 ± 6 mmHg, 5 hours after occlusion (n = 6) (Table 1) [1,12].

Humans

Previously, we reported the tight correlation between brain pO_2 and cerebral blood flow in 25 severely head injured patients (r = 0.78, P < 0.0001) [3]. Taking the ischemic threshold for cortex of 18 ml/100 g/min for CBF, the regression curve (2nd order) fits 22 mmHg for brain pO_2 (Fig. 2) [4,5,7,10]. Furthermore, Zauner *et al.* showed in 24 severely head injured patients that patients with a brain pO_2 below 19 ± 8 mmHg all had a poor outcome (GOS 4–5) (Table 2) [14].

Discussion

It is clear from our brain pO_2 data obtained during temporary vessel occlusion in humans during aneurysm surgery, that there is a marked variety in both normal brain pO_2 as well as in brain temporarily deprived of substrate, by vessel occlusion (Table 3) [2]. This wide variation is probably the result of several factors such as duration of occlusion, arterial pO_2, the capacity of collateral flow, pre-occlusion state of the cerebral metabolism, vasculature and blood flow, age etc.

However, the need for determination of an ischemic threshold for brain oxygen tension is obvious, in view of the increased interest in the use of brain oxygen pressure monitoring in different fields of neurosurgery (see other papers in this volume). Our data from 4 different studies suggest that this "ischemic danger threshold" lies between 19 and 23 mmHg for this Paratrend system. We arbitrarily use 20 mmHg as the critical value for brain pO_2, as measured by the Paratrend 7. If brain pO_2 falls below this value we propose that measures should be taken to improve brain pO_2 status by such measures as increasing arterial pO_2, and/or increasing cerebral perfusion pressure, depending on the underlying

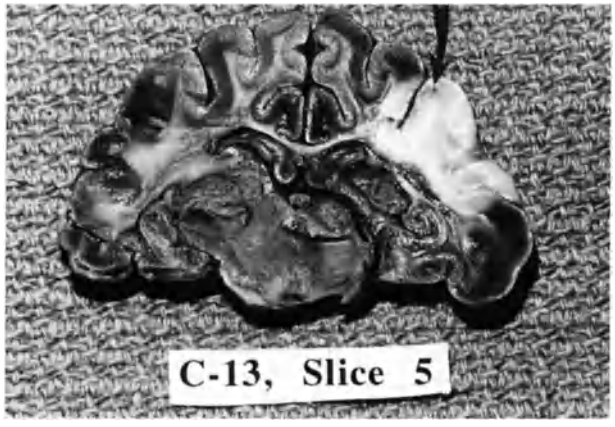

Fig. 1. Cross section of a feline brain showing the sensor tract (arrow) in the infarct. (TTC-stain) (Note: second tract is caused by a microdialysis probe)

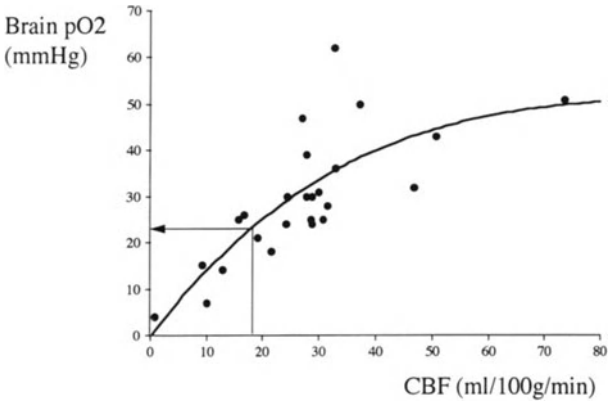

Fig. 2. Regression plot between cerebral blood flow and brain pO_2 (r = 0.78, P < 0.0001). Taking the ischemic threshold for cortex of 18 ml/100 g/min for CBF, the regression curve (2nd order) fits 22 mm Hg for brain pO_2

Table 1. *Changes in Brain pO_2 in 2 Separate Studies after Occlusion of the Middle Cerebral Artery in the Cat (Mean ± SD)*

Zauner et al. [13]	Brain pO_2 (mmHg)	FiO_2 (%)	Arterial pCO_2 (mmHg)
Pre-occlusion	43 ± 11*	30	33 ± 4.0
4 hours post-occl.	19 ± 6*	30	34.2 ± 6.1
Watson et al. [12]	Brain pO_2 (mmHg)	Arterial pO_2 (mmHg)	Arterial pCO_2 (mmHg)
Pre-occlusin	40 ± 15	182 ± 29	27 ± 5
5 hours post-occl.	23 ± 6	167 ± 26	28 ± 3

* P < 0.001.

Table 2. *Correlation Between Glasgow Outcome Score and Brain pO_2 in 24 Severely Head Injured Patients (Mean ± SD).* See Zauner *et al.* [14]

Outcome	Brain pO_2 (mm Hg)	CPP (mm Hg)	CBF (ml/100 g/min)	FiO_2 (%)	Arterial pO_2 (mm Hg)
GOS 1	39 ± 4*	87 ± 7	34.5 ± 14	36 ± 6	150 ± 29
GOS 2–3	31 ± 5*	80 ± 4	22 ± 4	40 ± 10	163 ± 40
GOS 4–5	19 ± 8*	70 ± 18	16 ± 8	48 ± 13	159 ± 32

*$P < 0.01$.

Table 3. *Changes in Brain pO_2 after Temporary Occlusion of a Parent Vessel During Aneurysm Surgery (Mean ± SD).* See Doppenberg *et al.* [2]

		Brain pO_2 (mm Hg)	Arterial pO_2 (mm Hg)	Arterial pCO_2 (mm Hg)
Unruptured	Pre-occ.	60 ± 31*	202 ± 44	31 ± 5
	During Occ.	27 ± 17*	202 ± 44	31 ± 5
Ruptured	Pre-occ.	106 ± 74	262 ± 82	30 ± 6
	During Occ.	87 ± 73	262 ± 82	30 ± 6

*$P < 0.05$.

cause of the reduction in brain pO_2. It is also important to consider arterial blood gas changes during brain pO_2 measurements in order to account for the influence of ventilator settings or pulmonary status of the patient on brain pO_2. In this way a "differential oxygen flux" or "delta pO_2" between arterial and brain values can be created. Our critical brain pO_2 value is higher than data from other groups, using a different system (Licox System, GMS mbH, Kiel, Germany). Van Santbrink *et al.* found that a brain $pO_2 \leq 5$ mm Hg within 24 hours after outcome correlates negatively with outcome [9]. Kiening *et al.* found a critical value of 8.5 mm Hg, using the ischemic threshold of 50% jugular vein hemoglobin saturation as determined by Robertson and Sheinberg *et al.* [6,8,11] The use of different end points cannot fully explain this difference between the 2 systems, especially since both systems use the same principle for measuring pO_2, namely a Clark type electrode. However, both of these studies aim to measure brain pO_2 in the white matter, while all our studies attempted to measure brain pO_2 in cortical tissue, which maybe an explanation for this difference in thresholds.

We have therefore performed an in vitro comparison of these 2 systems. Both systems were remarkably linear, in comparison with conventional blood gas analysis measurements, but the Licox sensor appeared to consistently read 5–10 mm Hg below the Paratrend 7 system (unpublished data). However, oxygen tensions below 25 mm Hg were difficult to achieve due to room air contamination. Robertson *et al.* found a 7–10 mm Hg difference when placing both sensors simultaneously in a "zero oxygen" solution (personal communication). Clearly, this difference needs to be clarified in a comparison study during brain ischemic injury, in which both sensors are placed immediately adjacent to each other. Nevertheless, we are confident that 19–23 mm Hg represents a "danger level" for ischemic/hypoxic brain damage using the Paratrend system.

Acknowledgement

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Correspondence: Ross Bullock, M.D., Division of Neurosurgery, Medical College of Virginia, Virginia Commenwealth University, P.O. Box 980 631, Richmond, VA 23298-0631, U.S.A.

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Brain Ischemia Detected by Tissue-PO_2 Measurement and the Lactate-Oxygen Index in Head Injury

M. Holzschuh, C. Metz[1], C. Woertgen, R. D. Rothörl, and **A. Brawanski**

Department of Neurosurgery and [1]Department of Anesthesiology, University of Regensburg, Regensburg, Federal Republic of Germany

Summary

The aim of the study was to find out whether there is a correlation between the tissue-pO_2 (ti-pO_2) measurement and the lactate-oxygen index (mLOI). Both methods are to be considered as methods to detect brain ischemia. We studied 7 patients after severe head injury (GCS < 8) with a jugular bulb catheter and a tissue pO_2 probe. Possible ischemia was defined with ti-pO_2 below 10 mmHg and mLOI above 0.08. 67 pairs of ti-pO_2 and corresponding mLOI were found. In 5 cases out of the 7 cases with a ti-pO_2 below 10 we found a pathological mLOI above 0.08. In 11 cases with pathological mLOI values, however, we found only 6 cases of decreased ti-pO_2. The absolute values did not correlate. The sensitivity to predict normal values is above 85% with both methods. The specifity to predict ischemia is low (<72%). The reason is the fact, that ti-pO_2 is a local method in contrast to the mLOI values. In cases of diffuse brain injury without major contusions there should be a correlation between ti-pO_2 and the mLOI.

Keywords: Jugular bulb catheters; lactate-oxygen index; secondary brain ischemia; tissue-PO_2.

Introduction

It is generally accepted that the initial clinical status of the patient after trauma, the age and the type of structural brain damage are important factors of outcome prediction after severe head injury [4]. Additionally, to these primary factors there is increasing evidence that secondary brain ischemia after severe head injury is one of the major causes of *poor* outcome after brain trauma [1,5,6]. The modified lactate-oxygen index (mLOI)(2) and the brain tissue pO_2 (ti-pO_2) [3,7] have been proposed as indicators of ischemic brain tissue. The aim of the study was to find out whether there is a correlation between these two methods of brain ischemia detection.

Material and Methods

We studied 7 patients after severe head injury with an initial Glasgow-Coma-Scale below 8. All patients were treated in the intensive care unit. They were treated with sedation, mechanically ventilated and they received routinely two jugular bulb catheters and a clark-type electrode (LICOX, GMS, Germany). The LICOX probe was placed in the frontal white matter. Every six hours blood was drawn from both jugular bulb catheters and the mLOI (mLOI = AVDL/CEO) was calculated. Ti-pO_2 data were stored every 15 seconds on hard disc. We calculated the average of the ti-pO_2 data that were sampled 30 minutes before the time of the blood drawing for the calculation of the mLOI. For comparison of the data we used the mLOI value of the hemisphere where the ti-pO_2 probe was inserted. According to the literature possible ischemia was defined with ti-pO_2 below 10 mmHg and mLOI above 0.08.

Results

We found 67 pairs of ti-pO_2 and corresponding mLOI of the appropriate hemisphere. In 7 cases we found a ti-pO_2 below 10 mmHg. In 5 cases the mLOI was above 0.08 indicating ischemia. In 53 cases out of 60 cases with normal ti-pO_2 values the mLOI values were also in the normal range. In 11 cases with pathological mLOI values we found only 6 cases of decreased ti-pO_2. In 56 cases with normal mLOI the corresponding ti-pO_2 was also normal in 54 cases. Using the ti-pO_2 data, we calculated a sensitivity to predict normal mLOI values of 88.3% and a specificity to predict ischemic mLOI values of 71.4%. Using the mLOI data to predict pathological ti-pO_2 values we calculated a specificity of only 54.5%. The sensitivity to predict normal ti-pO_2 values was 96.4% (Table 1).

Table 1.

n = 67	Normal mLOI	Ischemic mLOI
predicted normal with ti-pO_2	53	7
predicted ischemia with ti-pO_2	2	5
total misclassified	9/67	13.4%
sensitivity	53/60	88.3%
specificity	5/7	71.4%
n = 67	normal ti-pO_2	ischemic ti-pO_2
predicted normal with mLOI	54	2
predicted ischemia with mLOI	5	6
total misclassified	7/67	10.4%
sensitivity	54/56	96.4%
specificity	6/11	54.5%

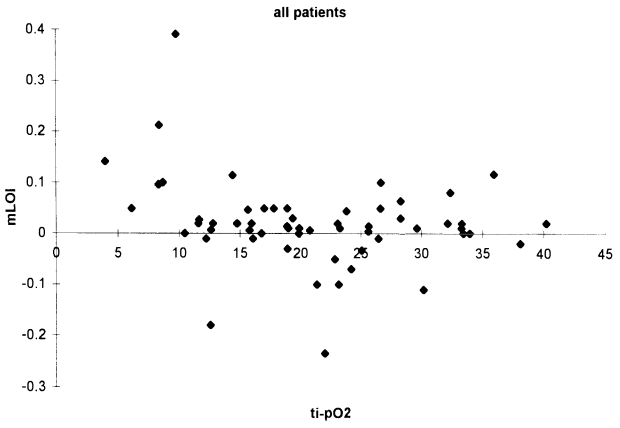

Fig. 1. Correlation between Ti PO_2 and MLOI – Figure 2.0

The absolute values of all patients, however, do not correlate (Fig. 1). In individual patients there might be a better correlation of the absolute values (Fig. 2).

Conclusion

We found a rather high sensitivity to predict normal values with both methods. The specificity to predict ischemic values, however, is markedly lower.

The low specifity to predict pathological values and the rather poor correlation of the absolute values between ti-pO_2 and mLOI may be explained by the fact that ti-pO_2 measurement is a regional method, in contrast to the mLOI values. In cases of brain contusions a lactate production can be detected despite normal ti-pO_2 values because the LICOX probe is

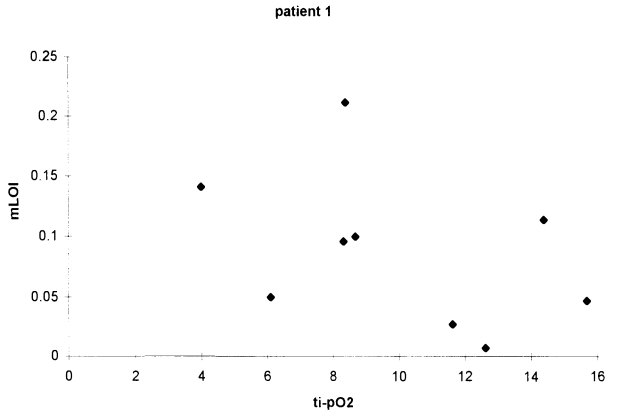

Fig. 2. Correlation between Ti PO_2 and MLOI – Individual patient

placed in an area of the brain with rather undisturbed oxygen supply. Cases of low ti-pO_2 but normal mLOI values may be explained by a very low cerebral blood flow near circulatory arrest where the lactate is not washed out of the tissue. In cases of diffuse brain injury without major contusions, there should be a good correlation between ti-pO_2 and the mLOI. The interpretation of the data obtained by these methods only makes sense with the knowledge of the structural brain damage seen in an actual CT-scan.

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Correspondence: Matthias Holzschuh, M.D., Department of Neurosurgery, University of Regensburg, D-93042 Regensburg, Federal Republic of Germany.

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Bifrontal Measurements of Brain Tissue-PO_2 in Comatose Patients

K. L. Kiening, G. H. Schneider, T. F. Bardt, A. W. Unterberg, and **W. R. Lanksch**

Department of Neurosurgery, Virchow Medical Center, Humboldt University, Berlin, Federal Republic of Germany

Summary

The purpose of this study was to compare brain tissue-PO_2 ($PtiO_2$) in lesioned vs. non-lesioned brain tissue.

$PtiO_2$ was monitored bifrontally with a "Clark"-type micro-catheter in patients following severe head injury (n = 6) and subarachnoid hemorrhage (SAH) (n = 1) from day 2 to day 12 posttrauma/post SAH. Mean arterial blood pressure, intracranial pressure (ICP), cerebral perfusion pressure and end-tidal CO_2 were monitored. Data were stored and analyzed by a multimodal cerebral monitoring system. The CT of five patients was classified as "diffuse injury" and of one patients as "evacuated mass lesion". The patient with SAH (Hunt and Hess °IV) had a concomitant intracerebral hematoma which was removed. In all cases, one catheter was placed close to the lesion, while the other was situated in an area with no visible pathology. For analysis, bifrontal $PtiO_2$ data were taken from both on-line monitoring and O_2 reactivity tests (FiO_2 1.0 for 10 min). Two different patterns were identified: periods of concordance (22% of recordings) and periods in which $PtiO_2$ was lower in lesioned cerebral white matter (78%) but always running parallel. In the latter case, O_2-reactivity response was markedly reduced on the lesioned side.

Our findings demonstrate a decreased $PtiO_2$ and a reduced O_2 reactivity in contused or infarcted brain tissue. Future studies have to clarify which $PtiO_2$ is more important to be used as a guide for therapy.

Keywords: Brain tissue-PO_2; cerebral perfusion; Clark-type micro-catheter.

Introduction

Measurement of brain tissue oxygen tension ($PtiO_2$) has been shown to reliably monitor cerebral oxygenation and to be closely correlated to cerebral perfusion [2,5]. Because this method picks up PO_2 from a small tissue area (~17 mm^2) only, it must be questioned whether this rather local $PtiO_2$ mirrors global cerebral oxygenation. Hence, the objective of this study was to compare $PtiO_2$ in lesioned vs. non-lesioned brain tissue.

Material and Methods

$PtiO_2$ was monitored bifrontally with a Clark-type micro-catheter (LICOX®-system) in patients following severe head injury (n = 6) and aneurysmatic subarachnoid hemorrhage (SAH) (n = 1) from day 2 to day 12 posttrauma/post SAH.

$PtiO_2$, mean arterial blood pressure, ICP, cerebral perfusion pressure and end-tidal CO_2 were monitored. Data were digitized at 0.016 Hz, displayed, stored, and analyzed by a multimodal cerebral monitoring system designed by one of the authors (T.F.B.). Prior to and after $PtiO_2$ catheter insertion, a CT was done. The CT scans were classified as "diffuse injury" (n = 5) and as "evacuated mass lesion" (n = 1) according to Marshall *et al.* [3]. The patient with aneurysmatic SAH (Hunt and Hess grade IV, right middle cerebral artery aneurysm) had a concomitant intracerebral hematoma which was removed immediately post aneurysm clipping.

In all cases, one catheter was placed close to the lesion (e.g. contusion, hematoma), while the other was situated in an area with no visible pathology on CT scan. For analysis, bifrontal $PtiO_2$ data were taken from both on-line monitoring and O_2 reactivity tests (FiO_2 1.0 for 10 min). O_2-reactivity tests were carried out 16 times (1–3 per patient). After termination of monitoring, $PtiO_2$ catheters were removed and side to side differences determined. Results are given as means ±SEM.

Results

Side to side difference of $PtiO_2$ catheters (Δleft vs. right hemispheres) after removal of catheters was 1.1 mm Hg [±0.1]. Two different patterns were identified: an "identical" course – defined as $\Delta PtiO_2$ left vs. right < 4 mm Hg – was observed in 289 hours (34% of recordings) (Fig. 1) and a "parallel" course – defined as $\Delta PtiO_2$ left vs. right ≥ 4 mm Hg – was seen in 561 hours (66% of recordings) (Figs. 1 and 2). Identical and parallel courses could be observed in the same patient (Fig. 1). Lower $PtiO_2$ values in "parallel" courses were always found on the lesioned

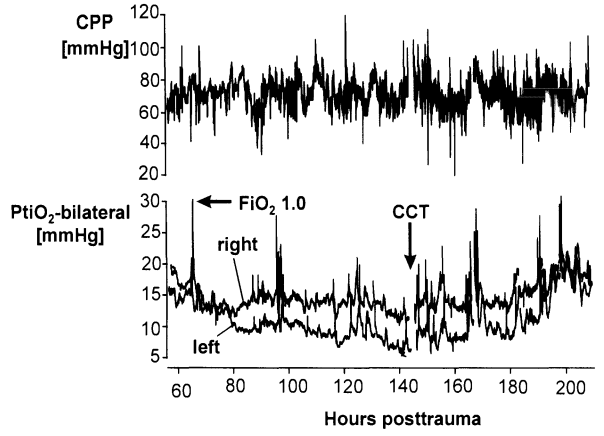

Fig. 1. CPP and bilateral $PtiO_2$ measurements in a 15-year old male patient with contusions on the left hemisphere: 60–80 and 190–210 hrs posttrauma, an "identical" $PtiO_2$ course was observed. In the remaining monitoring time a "parallel" course was seen. The lower $PtiO_2$ values were found in the contused, left hemisphere. O_2-reactivity was reduced on the injured side

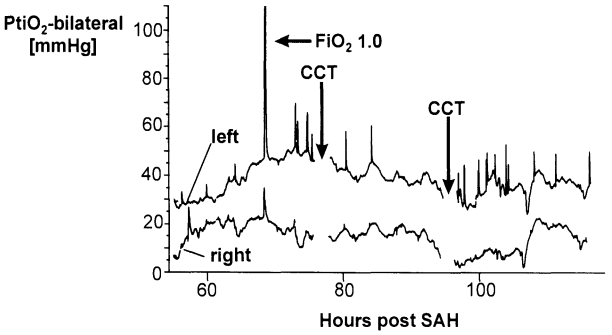

Fig. 2. Bilateral $PtiO_2$ in a 35-year old female patient presenting subarachnoid hemorrhage and concomitant right intracerebral hematoma (Hunt and Hess grade IV; right middle cerebral artery aneursm). A postoperative CT scan revealed right infarction in the area of the removed intracerebral hematoma. The right $PtiO_2$ catheter situated in the "penumbra" of the infarction showed markedly reduced $PtiO_2$ values below the hypoxic threshold of 10 mm Hg. The O_2-reactivity was also considerably diminished

side (Figs. 1 and 2). O_2-reactivity response in "parallel" courses (Figs. 1 and 2) was reduced in the lesioned area.

Discussion

Brain tissue-PO_2 monitoring as a new monitoring method to follow cerebral oxygenation has gained increasing interest in neurosurgical intensive care. This is due primarily to the fact that monitoring of jugular venous oxygen saturation ($SjvO_2$) is limited in its appliance because of a high rate of artifacts and subsequent low "time of good data quality" [1,2]. On the other hand, brain tissue-PO_2 has been shown to be a reliable device, even for long-term monitoring, but does not reflect global cerebral oxygenation as $SjvO_2$ does [2,5]. Hence, there has been discussion as to cohether $PtiO_2$ measurements can lead to misinterpretation of patients" global situation if the catheter is placed in injured regions with potentially high metabolism or low cerebral blood flow (CBF). At this time, there is no information available on $PtiO_2$ values in lesioned vs. non-lesioned areas. Our findings demonstrate – at least for a limited time period – a decreased $PtiO_2$ and a reduced O_2 reactivity in contused or infarcted brain tissue, presumably due to reduced cerebral blood flow. This result is in agreement with Schröder *et al.* [4] who describe in patients with traumatic brain contusions a pronounced reduction of CBF in the pericontusional area, up to 50% accompanied by a zone of edema. In conclusion, one has to keep in mind that the location of the $PtiO_2$ catheter is extremely important for $PtiO_2$ interpretation and subsequent treatment. On the other hand, $PtiO_2$ offers the opportunity to get direct and on-line information of oxygenation in severely injured areas. Future studies will have to clarify which $PtiO_2$ is more important to be used as a guide for therapy.

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Correspondence: Karl L. Kiening, M.D., Department of Neurosurgery, Humboldt University, Virchow Medical Center, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Determining Cerebral Perfusion Pressure Thresholds in Severe Head Trauma

S. Lewis[1], **M. Wong**[1], **J. Myburgh**[2], and **P. Reilly**[1]

[1] Department of Neurosurgery and [2] Department of Intensive Care, Royal Adelaide Hospital, Australia

Summary

Laboratory studies suggest the pulsatile component of the transcranial doppler (TCD) waveform may be useful in determining lower autoregulatory threshold. This study aimed to assess the effect of increasing CPP on jugular bulb oximetry (SjO_2) and middle cerebral artery (MCA) TCD flow velocities in the early management of severe head injury.

16 severely head injured patients (GCS ≤ 8), had intracranial pressure (ICP), mean arterial pressure, SjO_2 and MCA Doppler velocity monitored continuously. CPP was increased by intravenous fluids (right atrial pressure ≅ 10) and supplemented with adrenaline infusion until TCD pulsatility (Gosling pulsatility index [PI]) reached a plateau.

The mean CPP at which SjO_2 surpassed 55% was 62 ± 6.2 mm Hg. TCD PI did not plateau until a significantly higher mean CPP of 74 ± 5.1 mm Hg was achieved ($p < 0.01$). In 8 cases, increased CPP was associated with a fall in ICP, ranging from 1 to 8 mm Hg.

We conclude that a critically low level of SjO_2 is a late indicator of failed autoregulation. CPP values associated with intact autoregulation identified by TCD assessment of MCA flow are significantly higher than those indicated by SjO_2 monitoring. MCA Doppler flow assessment may be useful in determining the level of CPP at which therapy should be aimed in the early resuscitation of head trauma.

Keywords: Cerebral perfusion pressure; Gosling pulsatility index; jugular bulb oximetry; transcranial Doppler.

Introduction

Current head injury management guidelines recommend elevation of cerebral perfusion pressure (CPP) above 70 mm Hg; however, this end point is unclear. Clinical and laboratory studies suggest that the pulsatile component of the TCD waveform may be useful in determining the lower autoregulatory threshold [1,2,6]. Laboratory studies [4,6] investigating MCA Doppler flow velocities have shown a relationship with arterial hypotension, cerebrovascular resistance and cerebral blood flow (CBF). MCA Doppler pulsatility increases as CPP falls and cerebral vessels dilate. This compensatory manoeuvre is associated with maintenance of CBF. When this mechanism is exhausted Doppler flow velocities and CBF fall as the lower limit of autoregulation is surpassed (Fig. 1).

Following severe head injury, the CPP values at which these changes occur may be significantly increased [1].

The aim of this study was to assess the effect of increasing CPP on SjO_2 and MCA Doppler flow velocities in the early intensive care management of patients with severe head injury.

Method

16 patients admitted to the intensive care unit with severe closed head injury (GCS ≤ 8) had intracranial pressure (Codman microsensor), mean arterial pressure, SjO_2 (Abbott, oximetrix 3), MCA transcranial Doppler flow velocity (2 MHz probe, EME 64B) monitored continuously. The side of jugular bulb catheterization was determined according to protocol [5] and the ipsilateral MCA was insonated.

Management aimed to maintain mild hypo or normocarbia (35 to 40 mm Hg), and normothermia. After placement of monitoring lines, CPP was increased by a combination of intravenous fluids (right atrial pressure ≅ 10) and supplemented by adrenaline infusion. CPP was increased until the trend display for transcranial Doppler pulsatility (Gosling pulsatility index) [3] stabilised. All data was recorded continuously by a computer data acquisition system and trend plateaus were determined from visual display at the bedside. The breakpoint thresholds for Doppler flow data were calculated using a ratio of variance technique which calculates significant change in multiple regression coefficients. The CPP value at which SjO_2 surpassed 55% was recorded.

Results

16 patients (13 males:3 females) with a mean age of 29 years (range 15 to 70) and a median GCS 4, were included.

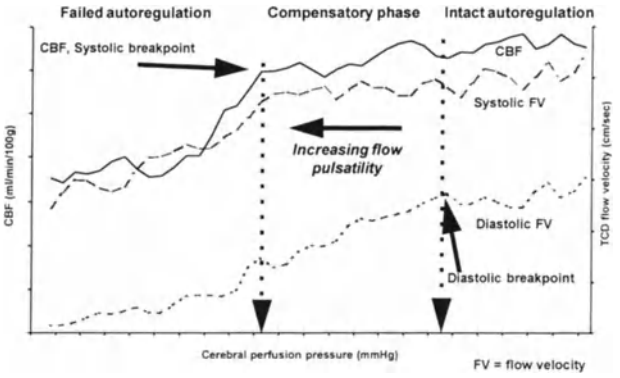

Fig. 1. TCD and CBF breakpoint thresholds

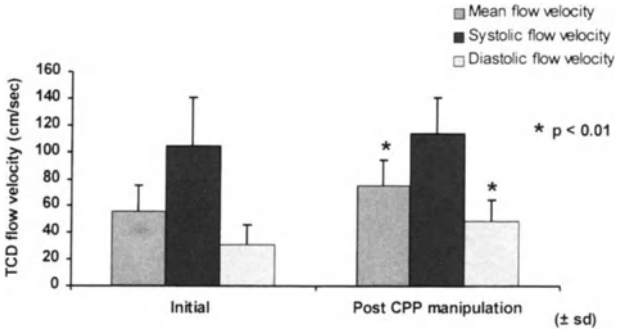

Fig. 2. TCD flow velocities: inital vs post CPP manipulation

As CPP increased the mean CPP threshold at which SjO_2 surpassed the critical value of 55% was 62 ± 6.2 mm Hg. In contrast transcranial Doppler PI did not plateau until a mean CPP of 74 ± 5.1 mm Hg was achieved. For 12 patients, this CPP was greater than 70 mm Hg. 5 of the 16 cases were found to have SjO_2 values <55% on admission to ICU. These cases were associated with an initial CPP of 58 ± 4.4 mm Hg.

A significant fall in transcranial Doppler pulsatility from 1.45 to 0.92 ($p < 0.01$) was observed following CPP augmentation.

Figure 2 illustrates the effect of increased CPP on each component of the transcranial Doppler flow velocity profile.

Systolic flow velocity did not significantly change. Mean and diastolic Doppler flow velocities significantly increased following a rise in CPP. In 8 cases the increased CPP was associated with a fall in ICP. This fall ranged from 1 to 8 mm Hg. Although ICP increased in 4 cases, the final ICP value did not surpass 20 mm Hg.

Discussion

This study examined the effect of increasing CPP on middle cerebral artery Doppler flow velocity and global cerebral oxygen utilization as determined by jugular bulb oximetry during the early phase of head injury management. In all cases, the relationship between systolic and diastolic flow velocity as described by the Gosling pulsatility index reached a plateau at a significantly higher CPP than that associated with an SjO_2 of 55%.

Analysis of the component Doppler flow velocity values indicated that the flow velocity components primarily altered by a change in CPP were the diastolic and mean flow velocities. This finding is consistent with laboratory studies and supports the concept of compensatory pulsatile flow phase described in Fig. 1. It may also indicate that global perfusion as measured by jugular bulb oximetry may be a late indicator of failed autoregulation.

A fall in ICP following augmentation of CPP was observed in 8 cases. An increase in perfusion pressure in these cases may have been associated with reflex cerebral vasoconstriction indicative of intact autoregulation. Other factors which may affect pulsatility indices, particularly elevated ICP and carbon dioxide variation were not significant during this period of observation. It is important to note the effect of these variables when interpreting Doppler flow velocity changes. This emphasizes the importance of multimodality monitoring in managing patients with severe head injury and suggests that transcranial Doppler flow velocity analysis may have a role in the early phase of management.

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Correspondence: Dr. Stephen B. Lewis, Department of Neurosurgery, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia.

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Effects of Injury and Therapy on Brain Parenchyma pO_2, pCO_2, pH and ICP following Severe Closed Head Injury

B. A. McKinley and **C. L. Parmley**

Department of Anesthesiology, University of Texas – Houston Medical School, Houston, TX, U.S.A.

Summary

Simultaneous monitoring of brain parenchyma pO_2, pCO_2, and pH (p_bO_2, p_bCO_2 and pH_b) has been tested in ICU environments using fiber optic sensors incorporated in probes 0.5 mm in diameter. An Institutionally approved protocol was used to test the concept and technology for monitoring p_bO_2, p_bCO_2 and pH_b, and to observe the effects of injury and therapy interventions on each of the variables monitored, including ICP, the clinical standard. ICP and fiber optic pO_2, pCO_2 and pH probes were placed in 10 SCHI patients at bedside in the ICU using sterile technique. The probes remained in place for the duration of ICP monitoring, and were functional in the ICU environment for up to 10 days. Trend patterns recurred in this series of SCHI patients: Extreme p_bCO_2 (high) and pH_b (low) are associated with poor perfusion; increasing p_bCO_2 and decreasing pH_b may be early indicators of ICP crisis, i.e. ICP > 20 mm Hg that tends to be unresponsive to therapy, and; pentobarbital "loading" and maintenance is associated with increased p_bO_2. These preliminary results from monitoring p_bO_2, p_bCO_2 and pH_b in SCHI patients indicate that fiber optic sensor technology functions and is able to be used in this application. Trend patterns from this data may further indicate practical utility as a more direct monitor of the delicate balance between tissue perfusion and cell metabolism than ICP alone.

Keywords: Brain parenchyma; extreme p_bCO_2; pH sensors.

Introduction

Simultaneous monitoring of brain parenchyma pO_2, pCO_2 and pH (p_bO_2, p_bCO_2 and pH_b) has been demonstrated recently by several investigators [2,8,14]. p_bO_2 is monitored clinically in Europe [4]. Probes with fiber optic pO_2, pCO_2 and pH sensors were commercially available briefly for continuous intraarterial blood gas monitoring, and have been used to monitor these variables (i.e., intracranial chemistry, ICC) in the interstitium of the brain parenchyma [6]. (Note: The ICC sensor technology used in these studies was developed by Optex Biomedical, The Woodlands TX, and is now owned by Camino NeuroCare Inc, San Diego CA.) The intent of these studies was to test the concept and the technology for monitoring p_bO_2, p_bCO_2 and pH_b by using technology and methods demonstrated previously in animal studies, and to observe effects of injury and therapy interventions on each of the variables monitored simultaneously, especially ICP, the clinical standard.

Material and Methods

Following an Institutionally approved protocol and written informed consent from next of kin, precalibrated ICC probes with fiber optic pO_2, pCO_2 and pH and thermocouple temperature sensors were inserted through a standard transcranial (ICP) bolt and arterial cannula used as an introducer. The ICC probe was placed ~1 cm into the brain parenchyma of patients with severe closed head (brain) injury (SCHI). Placement of the experimental ICC probe was undertaken after placement of the standard ICP probe. The placement technique for the ICC probe was similar to placement of an intraparenchymal ICP probe in the intensive care unit (ICU). All components were sterile and sterile ICU bedside technique was used. The placement site was guided by neurosurgeons' interpretation of the most recent CT scan. The time of placement ranged from 0–4 days post injury. The ICC probes remained in place for the duration of ICP monitoring. ICC monitoring was discontinued and the probe assembly was removed if an increased risk due to long term monitoring appeared, e.g. bacteremia. Data files from brain parenchymal pO_2, pCO_2, pH and temperature sensors accumulated in the bedside monitor instrument were transferred to a spread sheet program (Excel, Microsoft Corp, Kent WA) for addition of other clinical data and graphical analysis. Management of intracranial hypertension in the institution in which the studies have been conducted (Hermann Hospital, Houston TX) follows an established protocol [1].

Results

10 SCHI patients were monitored (see Table 1). The fiber optic pO_2, pCO_2 and pH sensors functioned to monitor these variables within the ranges found for brain parenchyma with severe metabolic insults (ischemia and hypoxia) in animals [6]. Each sensor was stable and reflecting intraparenchymal pO_2, pCO_2 and pH within 5–10 min following placement.

Case 1

This patient sustained multiple trauma (flail chest, hemopneumothorax) and severely brain injured patient, and arrived in the ICU with very poor prognosis (GCS 3 on hospital admission). ICC probe placement was in the right hemisphere at the time of ICP probe placement in the opposite hemisphere. p_bO_2 declined asymptotically from precalibration to 3 mm Hg during the 1st hour of monitoring and to 2 mm Hg over the next 16 hr. p_bCO_2 increased with similar asymptotic behavior to >600 mm Hg. pH_b decreased to <7.0 during the 1st hour of monitoring, transiently recovered to >7.1, then decreased monotonically to <6.9 at the end of monitoring. ICP was initially >50 mm Hg, transiently decreased with mannitol, but became uncontrollable. CPP decreased to 0 mm Hg within 10 hr of the start of monitoring. A radionucleotide cerebral blood flow study at 15:00 on ICU day 2 indicated no intracerebral blood flow, and the patient was declared brain dead.

Case 2

This patient sustained a moderate severity brain injury due to fall from a moving platform. Injury to the brain involved diffuse shearing and thalamic micro hemorrhages. ICC and ICP probes were placed at the same time with ICC probe in the left hemisphere and ICP probe in the right. Sedation using propofol was the only therapy for ICP management that was used, and ICP generally remained <20 mm Hg with one exception on the 2nd day of monitoring when ICP increased transiently to 22 mm Hg. p_bCO_2 increased steadily from 63 to 83 mm Hg and pH_b decreased from 7.26 to 7.13 in the 8 hr preceding this transient increase in ICP. Paralysis and sedation were administered for nasal to oral ET replacement, after which ICP decreased to 9 mm Hg. p_bO_2 decreased to 4 mm Hg in the 2 hours following probe placement, recovered to 11 mm Hg, transiently decreased to 4 mm Hg, and then increased steadily to >30 mm Hg. ICP monitoring was discontinued after 21 hr. The patient remained comatose in the ICU for ~3 weeks. The patient recovered with resolving left side motor deficits.

Table 1. *Summary Description of Patients and ICC Monitoring*

Case	Clinical presentation	Brain injury	Probe placement	Duration of monitoring	Outcome
1: 45yoLAM	MVA: mult tr; SCHI (GCS 3)	SDH, ICH	R temp; dy1	1 dy	died ICU dy2
2: 18yoWM	Fall: SCHI (GCS 7)	ICH, shear, thalamic hem	L temp; dy1	2 dy	survived; motor def
3: 35yoWF	MVA: mult tr; SCHI (GCS 7)	SAH, shear	[a]L temp; dy2	8 dy	survived; no def
4: 22yoWM	MVA: mult tr; SCHI (GCS 7)	IVH, SAH	[a]R temp; dy1	8 dy	survived ICU; died in hosp
5: 32yoWF	MVA: mult tr; SCHI (GCS 7)	SDH (craniotomy)	R temp; dy4	10 dy	survived; motor, speech def
6: 24yoWM	MVA: mult tr; SCHI (GCS 3)	SDH (craniotomy)	R temp; dy2	5 dy	survived ICU; died ~1 yr
7: 39yoLAM	MVA: SCHI (GCS 7)	SDH (craniotomy)	[a]L temp; dy1	5 dy	died ICU dy 18
8: 32yoBF	MVA: mult tr; SCHI (GCS 7)	SDH (craniot; lobectomy)	[a]L temp; dy2	8 dy	died ICU dy 10
9: 42yoWM	MVA: SCHI (GCS 3)	SDH, ICH	L temp; dy2	1 dy	died ICU dy 2
10: 19yo WM	MVA: SCHI (GCS 6)	ICH	L temp; dy5	3 dy	survived; motor def

[a] Probe placement during mild systemic hypothermia (32–33°C for 48 hr), rewarm over 16–20 hr; rewarm monitored.

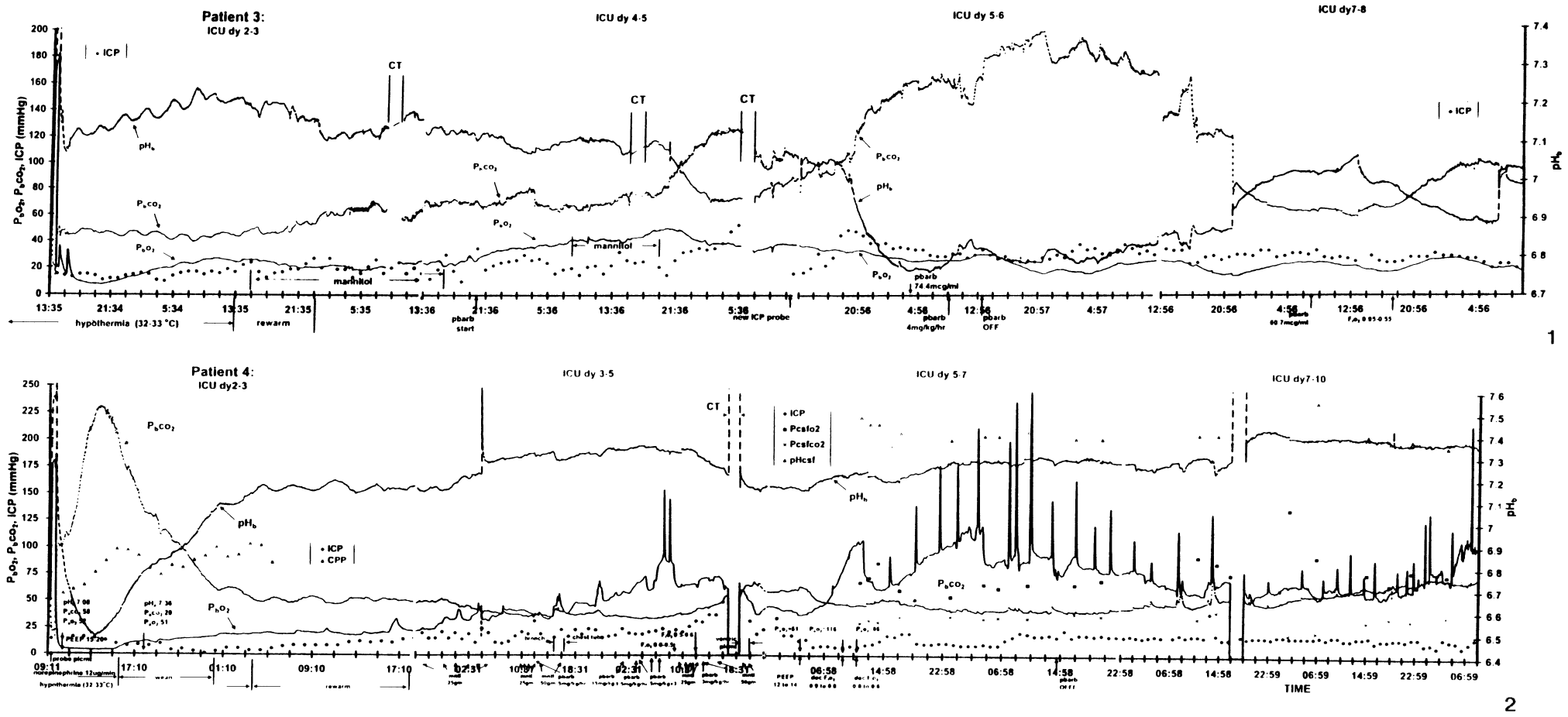

Fig. 1. Extended monitoring (8 days) of brain parenchyma pO_2, pCO_2, pH and ICP following SCHI: Case 3: Cyclic oscillation of pCO_2 and pH coincident with hypothermia temperature controller; pO_2 increases with start of pentobarbital therapy (ICU day 4); pCO_2 increases and pH decreases 9 hr prior to ICP increase to 50 mm Hg (ICU day 4), and 3.5 hr prior to 2nd ICP increase (ICU day 5)

Fig. 2. Extended monitoring (10 days) of brain parenchyma pO_2, pCO_2, pH and ICP following SCHI: Case 4: pO_2 = 4 mm Hg, pCO_2 = 230 mm Hg and pH = 6.48 coincident with arterial pCO_2 = 58 and pH = 7.08, norepinephrine infusion (ICU day 2); pO_2 increases with start of pentobarbital therapy (ICU day 4); pCO_2 increases and pH decreases 10.5 hr prior to ICP increase to 50 mm Hg (ICU day 4)

Case 3

Figure 1 shows data from extended monitoring of an MVA victim who sustained pelvic fractures and SCHI (GCS 7 on hospital admission). Injury to the brain involved subarachnoid hemorrhage and diffuse shearing. This patient was being treated with mild hypothermia in addition to other standard therapies at the time of ICC probe placement. Rewarming from hypothermia was coincident with a steady increase of p_bCO_2 to ~63 mm Hg and decrease of pH_b to ~7.12, and ICP increase that responded to successive doses of mannitol. Following emergency CT scan and maximized serum osmolality due to repeated mannitol doses, pentobarbital coma therapy was started. p_bO_2 increased gradually to 51 mm Hg, p_bCO_2 remained stable at ~70 mm Hg and pH_b at ~7.12. At ~18:30 on ICU day 5, p_bCO_2 began to increase steadily from ~75 to 123 mm Hg and pH_b began to decrease from ~7.11 to 6.96 over ~5 hr. ICP began to increase uncontrollably without immediate therapy options ~2 hr prior to emergency CT scan. This trend repeated ~4 hr later as p_bCO_2 began to increase from 92 to 108 mm Hg and pH_b began to decrease from 7.06 to 7.02 ~3.5 hr prior to ICP increase to 49 mm Hg. With discontinuance of pentobarbital administration, p_bO_2 decreased from 30 to 16 mm Hg over 9 hr, and ranged from 15 to 27 mm Hg over the next 3 days as other ICP management therapies were discontinued. ICP gradually decreased to 20 mm Hg at which time ICP monitoring was discontinued. The patient regained consciousness in the ICU following termination of ICP monitoring, and recovered without deficit.

Case 4

Figure 2 shows similar data from a patient who sustained multiple injuries due to MVA, including SCHI (GCS 6 on hospital admission). Injury to the brain involved mild ventricular and subarachnoid hemorrhages and subdural hygromas. The patient was treated with mild hypothermia in addition to other standard therapies for ICP management. Acute pulmonary edema and hypotension in the 1st 24 hr post injury complicated the clinical course. After probe placement, p_bO_2 decreased to 4 mm Hg, p_bCO_2 increased to 230 mm Hg and pH_b decreased to 6.48 in the 1st 7 hr of monitoring. Over ~12 hr, p_bO_2 increased to 20 mm Hg, p_bCO_2 decreased to 60 mm Hg and pH_b increased to 7.08. These changes coincided with increase of CPP from 58 to 98 mm Hg, increase of pH_a from 7.08 to 7.36 and decrease of p_aCO_2 from 58 to 28 mm Hg, increase of PEEP from 15 to 20 cm H_2O, and infusion and weaning of norepinephrine. Because hemodynamic instability and need for pentobarbital coma therapy were anticipated, pentobarbital infusion was begun ~12:30 on ICU day 4 although mannitol therapy was not maximized. Pentobarbital coma therapy was started early in ICU day 5. p_bO_2 increased from 37 to 75 mm Hg over 28 hr coincident with pentobarbital coma induction. From 10:30 to 17:15 on ICU day 5, p_bCO_2 increased from 37 to 56 mm Hg and pH_b decreased steadily from 7.33 to 7.21. ICP increased steadily from 31 to 50 mm Hg without response to mannitol or pentobarbital therapy from 13:30 to 17:15, when an emergency CT scan was performed. Following CT scan, a ventriculostomy catheter was placed, CSF was drained, and ICP decreased to 20 mm Hg and was able to be controlled with CSF drainage as the primary therapy. This patient survived the ICU stay, but died weeks later from complications related to infection and protracted recovery from laparotomy.

p_bO_2 increase with pentobarbital was monitored in 4 patients during induction and maintenance of pentobarbital coma. p_bO_2 at the time of start of pentobarbital administration and at the time

Table 2. *Change in P_bO_2 with Pentobarbital Coma Induction and Maintenance*

Case	P_bO_2 at start of pentobarbital "loading"	P_bO_2 (mm Hg) at "therapeutic" concentration or confirmation of coma	Difference (mm Hg)
3	28	41	13
4	19	75	56
5	45	91	46
8	22	59	37

Table 3. *Time Interval from P_bCO_2 Increase and pH_b Decrease to Time of Clinical Action for Rapidly Increasing ICP*

Case	ICP crisis	Time interval	Emergency CT
3	50 mm Hg	9 hr 6 min	Yes
	49	3 hr 24 min	No
4	50	10 hr 29 min	Yes
5	60	3 hr 10 min	No
	40	5 hr 12 min	No
7	34	12 hr 2 min	No
8	32	16 hr 15 min	Yes
10	30	5 hr 14 min	Yes

pentobarbital coma was confirmed are indicated in Table 3. The trend pattern of p_bCO_2 increase and pH_b decrease precedent to ICP crisis was apparent in other patients. The time interval from the time p_bCO_2 increase and pH_b decrease began to the time that a clinical decision was made and executed for refractory ICP is indicated in Table 2.

Discussion

Feasibility of p_bO_2, p_bCO_2 and pH_b monitoring using fiber optic sensors in ICU environments is demonstrated with these results. Patterns associated with ICP monitoring and with standard ICP management therapies are apparent and reproducible. Data from Cases 1 and 2 present examples of extremes of SCHI and outcome expectation. p_bO_2, p_bCO_2 and pH_b data from these patients may present meaningful patterns. p_bO_2 data and trends in Case 1 indicated lack of O_2 supply to the tissue in which the sensor was placed. p_bCO_2 data indicates accumulation of CO_2, which is consistent with lack of perfusion (CPP decreased to 0 mm Hg within 10 hr of start of monitoring). Extreme pCO_2 (relative to typical p_aCO_2) in tissues has been reported previously by us and other investigators [2,7,14], and probably reflects accumulation of CO_2 produced through aerobic metabolism in poorly perfused tissues and shift of the bicarbonate buffer system to CO_2 as ATP and ADP hydrolysis and lactate dissociation produce $H^{+(3)}$. Similar progressive increase of p_bCO_2 to >400 mm Hg was monitored in another patient with similar severe injury over the 12 hr period prior to declaration of brain death (Case 9). Data from Case 2 indicates perhaps surprising changes in p_bO_2, p_bCO_2 and pH_b in a patient who required no ICP management therapy. p_bO_2 recovery from ~5 mm Hg in the 1st hour of monitoring to ~30 mm Hg 12 hr later (~30 hr post injury) is consistent with results reported by other investigators [10].

Data from Cases 3, 4 and 5 illustrate capability for prolonged monitoring using this fiber optic sensor technology. The capability for monitoring for periods >10 days is consistent with ICU stay times for SCHI patients. Although post calibration could not be done in these cases, sensitivity of each sensor is retained throughout the monitoring periods, as can be gauged by the similar magnitude of responses to p_bO_2, p_bCO_2 and pH_b perturbations. Data from these cases which involved prolonged ICC monitoring also provide indications of apparently repeated trend patterns:

1. p_bCO_2 increases and pH_b decreases several hours prior to ICP crisis, with the sequence: a) ongoing, controllable intracranial hypertension, b) onset of p_bCO_2 increase and pH_b decrease trend pattern, and c) accelerating ICP increase to >40 mm Hg.
2. p_bO_2 increases coincident with pentobarbital coma induction: In Cases 3, 4, and 5, pentobarbital was administered according to standard protocol for management of ICP as a "2nd tier" therapy. With the start of pentobarbital administration, typically in "loading" doses of 10–15 mg/kg body weight over 15 minutes followed by 3 hourly bolus doses of 5 mg/kg, p_bO_2 began to increase steadily. This trend continued or stabilized with the start of maintenance infusions to maintain therapeutic blood concentration. No coincident effect on p_bCO_2 or pH_b is apparent. This trend pattern is conceptually consistent with the desired effect of pentobarbital, which is to decrease metabolism, and O_2 demand, of the injured brain tissue. Simultaneous EEG and p_bO_2 monitoring with serial serum pentobarbital analyses is needed to determine correlation of EEG burst suppression intervals, p_bO_2 and serum pentobarbital concentrations with time.

p_bO_2, p_bCO_2 and pH_b dynamics and control: That p_bO_2, p_bCO_2 and pH_b vary in apparent response to therapeutic interventions to manage intracranial hypertension suggests that they are also controllable. Whether other useful therapies can be developed using p_bO_2, p_bCO_2 and pH_b as control variables is to be determined [5,9,11–13]. Absolute p_bO_2, p_bCO_2 and pH_b measurements comparable to their physiologic norms may indicate SCHI recovery (See Fig. 2).

Single point assessment of global injury-therapy process: In our studies, we have attempted to assure ICC probe placement in a region of the brain parenchyma that is actively perfused, and that presents low risk to the patient. The similarity of patterns that we have observed among a variety of patients and brain injuries suggests that p_bO_2, p_bCO_2 and pH_b measurements and trends are global within the parenchymal interstitium, with the probable exception of focal lesions.

Conclusion

These preliminary results from monitoring p_bO_2, p_bCO_2 and pH_b in SCHI patients in ICU environments indicate that fiber optic sensor technology

functions and is able to be used in this application. Trend patterns from this data may further indicate practical utility as a more direct monitor of the delicate balance between tissue perfusion and cell metabolism than ICP alone. Early detection of an injury process, i.e. intracranial hypertension, may lead to a preemptory therapy. The potential use of p_bO_2 to monitor onset of pentobarbital coma could improve efficacy of this therapy. Pending further development, test and assessment of this sensor technology, p_bO_2, p_bCO_2 and pH_b may permit more refined control of the injury-therapy process.

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Correspondence: Bruce A. McKinley, Ph.D., Department of Anesthesiology, University of Texas – Houston Medical School, 6431 Fannin, MSB 5.020, Houston, TX 77030, U.S.A.

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Simultaneous Continuous Measurement of pO_2, pCO_2, pH and Temperature in Brain Tissue and Sagittal Sinus in a Porcine Model

M. Menzel[1], **A. Rieger**[2], **S. Roth**[1], **J. Soukup**[1], **C. Peuse**[1], **C. Hennig**[1], **P. Molnar**[3], **I. Furka**[3], and **J. Radke**[1]

Department of Anaesthesiology and [1] Intensive Care Medicine, [2] Department of Neurosurgery, Martin-Luther-University Halle-Wittenberg, Federal Republic of Germany and [3] Department of Experimental Surgery, University of Debrecen, Hungary

Summary

Introduction: The clinical use of brain tissue oxygen measurement in patients with severe head injury is increasing. It is important to compare the findings in brain tissue with cerebrovenous blood oximetry, to obtain normal values and to find out limitations of the method. We evaluated a newly available multisensor probe simultaneously in the brain tissue and in the sagittal sinus in a porcine animal model.

Methods: We placed the Paratrend 7®-probe (BSL, High Wycombe, UK) in the left frontoparietal white matter and measured pO_2 ($p_{ti}O_2$), pCO_2 ($p_{ti}CO_2$), pH and temperature while simultaneously measuring these parameters ($p_{cv}O_2$, $p_{cv}CO_2$) in the sagittal sinus in 7 pigs under general anaesthesia during oxygen enhancement.

Results: The relation between oxygen increase in brain tissue and in the sagittal sinus showed a coefficient of correlation (CC_{mean}) $r_{mean} = 0.96$. The quantitative response in brain tissue was much more sensitive than in the sinus. A close correlation between pCO_2 in brain tissue and sagittal sinus and the increase of the inspired oxygen was seen: CC $p_{ti}CO_2$ to arterial oxygen pressure (p_aO_2) – $r_{mean} = 0.67$, CC $p_{cv}CO_2$ to p_aO_2 – $r_{mean} = 0.88$.

Conclusions: Measuring partial oxygen pressure in brain tissue is more responsive to physiological variations, and the absolute values are more sensitive than oxygen measurement in the cerebrovenous compartment. This is important for interpreting measured values and introducing new coefficients for patient monitoring.

Keywords: Brain tissue oxygen measurement; Clark type electrode; FiO_2 increase; jugular bulb; sagittal sinus.

Introduction

Patients with severe head injury are at high risk for developing neuronal damage caused by secondary ischemia [2]. The continuous monitoring of intracranial pressure (ICP) and calculation of cerebral perfusion pressure (CPP) in patients supposed to develop cerebral ischemic events is not sufficient to detect these events [1]. The continuous pO_2 measurement in brain tissue ($p_{ti}O_2$) with Clark type electrodes or multisensor probes, combining fiberoptical sensors to measure pCO_2 and pH, a thermocouple for measuring temperature and a Clark type electrode for measuring pO_2, is increasingly used in neurosurgical patients to monitor the oxygen supply to the brain and to find out prognostic meanings of the measured values [2,5,6].

The continuous measurement of oxygen haemoglobin saturation with fiberoptics in the jugular bulb in neurosurgical patients (S_jO_2) is another rather recent technical development. It is, however, already established as a clinical routine in patients with severe head injury and elevated ICP [1]. But this continuous spectrophotometric monitoring method has its limitation in clinical use due to technical artefacts caused by low light intensity, motion artefacts or changes in catheter position during the measurement period [4,5].

The aim of this study was to use a new available multiparameter probe, measuring pO_2, pCO_2, pH and temperature, simultaneously in brain tissue and in the cerebrovenous outflow in a porcine model. So the course of oxygen tension in both measurement compartments, related to physiological variations of ventilator settings, was evaluated and compared. Additionally it was the purpose to gain more insight and experience in the values of oxygen tension in normal brain tissue and cerebrovenous blood and of the new available continuous parameter pCO_2.

Methods

Anesthesia and Monitoring of Experimental Animals

Seven 8-week-old domestic pigs weighing 18–22 kg were used in the present study. All experiments were performed in accordance

with the guidelines issued by the Debrecen University Committee on Animal Care based upon: "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985). Anesthesia was introduced by i.v. drug medication, tracheotomy was carried out and the animals were ventilated volume controlled with a mix of oxygen and room air.

A parenchymal multisensor probe (P7) (Paratrend 7, Biomedical Sensors Ltd., Highwycombe, UK) was inserted into the white matter of the left frontoparietal lobe over a length of about 4 cm. In all animals, the superior sagittal sinus was exposed in the bregma region. A second P7 probe was introduced into the superior sagittal sinus via direct puncture of the sinus. ABP and ICP were continuously monitored, and CPP was calculated. All values of brain tissue measurement by the P7 probe ($p_{ti}O_2$, $p_{ti}CO_2$, pH_{ti} and t_{ti}) as well as the values of the cerebrovenous measurement in the sagittal sinus by the P7 probe ($p_{cv}O_2$, $p_{cv}CO_2$, pH_{cv} and t_{cv}) were digitally downloaded onto a terminal program and stored in a 10 second interval on hard disk.

Oxygen Challenge

In all animals a steady state of basic values in tissue measurement and in cerebrovenous measurement was reached approximately 90 min after catheter insertion. During this period, the inspired oxygen ratio (FiO_2) was kept constant at 30%. In a one step maneuver, FiO_2 was increased up to 100% over a period of 5 min and afterwards reduced again to 30%. To make the results of the FiO_2 settings comparable with the results of other working groups we calculated the oxygen reactivity coefficient of Van Santbrink (increase in oxygen tension [%] of the cerebral compartment divided by the absolute increase of arterial oxygen tension [mmHg] [5]. The mean values are expressed as the median ± standard deviation if not indicated in an other way.

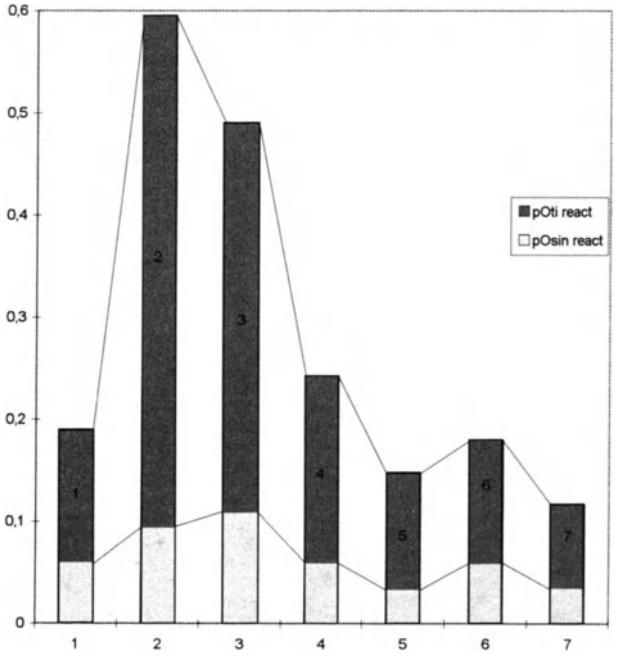

Fig. 1. Coefficient of reactivity (percentage increase of cerebral oxygen measurement results divided by the absolute increase of arterial oxygen increase) related to a period of 5 minutes lasting FiO_2 100% challenge

Results

Physiological Findings Prior to FiO_2 Increase

The mean ICP was 8.24 (5.5) mmHg. CPP was 86.07 (10.75) mmHg. All animals showed a 100% oxygen saturation for the peripheral pulse oximetry. The mean arterial oxygen tension showed to be 136 (22.01) mmHg. The mean p_aCO_2 was 54.02 (5.55) mmHg and the mean pH_a was 7.33 (0.05).

$P_{ti}O_2$ showed to be 25.71 (8.9) and $p_{cv}O_2$ was 39.14 [4]. Two of the animals showed initial $p_{ti}O_2$ values below 20 mmHg. There was no significant correlation between the oxygen levels in both cerebral compartments (r = 0.4). Because of the sensitivity of the PCO_2 measurement in tissue as well as in cerebrovenous blood to changes in arterial PCO_2 it is difficult to compare values between different animals. That's why all values for PCO_2 measurement in cerebral compartments are given as the calculated difference ($_{\delta}$values = P_aCO_2 – compartment CO_2).

The $_{\delta}p_{ti}CO_2$ was 22.9 (7.3) and showed to be distinctly higher than $_{\delta}p_{cv}CO_2$ 11.22 (7.23) with similar standard deviation in both compartments.

Findings During FiO_2 Increase

In both cerebral compartments an increased oxygen tension related to the FiO_2 increase was seen. The mean coefficient of correlation (CC_{mean}) between arterial pO_2 increase and $p_{ti}O_2$ was r_{mean} = 0.67. The relation between $p_{cv}O_2$ and p_aO_2 showed a CC_{mean}: r_{mean} = 0.91. Corresponding to this, the correlation between oxygen increase in brain tissue and in the sagittal sinus showed a coefficient of correlation r_{mean} = 0.96. The mean coefficient of oxygen reactivity (O_2rea) was calculated for the tissue values as 0.21 (0.12) and for the cerebrovenous values as 0.06 (0.02).

A close correlation between pCO_2 in brain tissue and sagittal sinus and the increase of the inspired oxygen was seen: CC_{mean} $p_{ti}CO_2$ to arterial oxygen (p_aO_2) – r_{mean} = 0.67, CC: $p_{cv}CO_2$ to p_aO_2 – r_{mean} = 0.88.

Discussion

Oxygen Measurement

Brain tissue oximetry is a local measurement approach. Although the global cerebral oxygen consumption ($CMRO_2$) under constant metabolic conditions, such as under general anesthesia is an

almost stable value it is well known that oxygen is heterogeneously distributed to brain areas [3].

The $p_{ti}O_2$ results in our experiment prior to FiO_2 manipulations show a mean of 25.71 mm Hg (8.9) mm Hg. Two of the 7 animals had a tissue oxygen tension less than 20 mm Hg and one of these animals started with a $p_{ti}O_2$ of only 9 mm Hg at the beginning of the FiO_2 increase. These normal values are lower compared to other animal and human studies [5,6]. Our experimental data were obtained between 2 and 4 hours after catheter insertion. We suggest, that during the first period of 1 and 12 hours after catheter insertion probably additional heterogeneity of the measurement performance exists. This heterogeneity might be due to the micro compression of the tissue surrounding the catheter site after insertion, and results in patients using this monitoring are to be interpreted cautiously during the early period of measurement.

Cerebrovenous partial oxygen pressure measurement is a global measurement approach. The normal values in our study showed much less heterogeneity, when compared to the simultaneous tissue measurement and are in accordance with the findings in jugular bulb oximetry [1].

Both measurement compartments have proven to be sensitive to global changes in cerebral oxygen supply in our experimental study. All manipulations of FiO_2 were performed when hemoglobin was saturated to 100% with oxygen in the arterial blood. We conclude, that the increase of arterial oxygen pressure to values higher than necessary to saturate arterial hemoglobin to 100% improves the cerebral oxygen supply and might be beneficial in patients who suffer cerebral ischemic events. The oxygen partial pressure in brain tissue responded quantitatively more sensitive to the FiO_2 manipulations and showed a 50% heterogeneity. We conclude, that the $p_{ti}O_2$ measurement is influenced by the different adjacent position to the arterial capillaries of the brain tissue. That indicates that $p_{ti}O_2$ measurement is giving insight in substrate delivery to the brain but is difficult to interpret regarding the metabolic status of the neurons.

Findings in CO_2: In both measurement compartments pCO_2 was highly positive correlated to the FiO_2 increase. We suggest that the increase in pCO_2 during FiO_2 increase reflects compromised cerebral perfusion due to oxygen induced cerebral vasoconstriction. The reduced "wash out" thus leads to an accumulation of metabolic products. PCO_2 should be further explored in relation to other physiological and pathological data to find out the importance of this newly available continuous parameter.

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Correspondence: M. Menzel, M.D., Department of Anaesthesiology and Intensive Care Medicine, Martin Luther-University Halle-Wittenberg, Magdeburger Str. 16, D-06097 Halle (Saale), Federal Republic of Germany.

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Cerebral Oxygenation in Contusioned vs. Nonlesioned Brain Tissue: Moniting of $PtiO_2$ with Licox and Paratrend

A. S. Sarrafzadeh, K. L. Kiening, T. F. Bardt, G.-H. Schneider, A. W. Unterberg, and **W. R. Lanksch**

Department of Neurosurgery, Virchow Medical Center, Humboldt-University, Berlin, Federal Republic of Germany

Summary

Brain tissue PO_2 in severely head injured patients was monitored in parallel with two different PO_2-microsensors (Licox and Paratrend). Three different locations of sensor placement were chosen: (1) both catheters into non lesioned tissue (n = 3), (2) both catheters into contusioned tissue (n = 2), and (3) one catheter (Licox) into pericontusional versus one catheter (Paratrend) into non lesioned brain tissue (n = 2). Mean duration of $PtiO_2$-monitoring with both microsensors in parallel was 68.1 hours. Brain tissue PO_2 varied when measured in lesioned and nonlesioned tissue.

In non lesioned tissue both catheters closely correlated (Δ Licox/Paratrend: mean $PtiO_2$ < 5 mm Hg) after 20 hours post insertion. In pericontusional tissue $PtiO_2$ was reduced relative to non lesioned tissue (Δ lesioned/non lesioned: mean $PtiO_2$: 10.3 mm Hg). In contusioned brain tissue $PtiO_2$ was always below the "hypoxic threshold" of 10 mm Hg, independent of the type of micorsensor used. During a critical reduction in cerebral perfusion pressure (<60 mm Hg), $PtiO_2$ decreased measured with both microsensors. Elevation of inspired oxygen fraction, normally followed by a rapid increase in tissue PO_2, only increased $PtiO_2$ when measured in pericontusional and nonlesioned brain. To recognize critical episodes of hypoxia or ischemia, $PtiO_2$-monitoring of cerebral oxygenation is recommended in nonlesioned brain tissue.

Keywords: Brain tissue PO_2; cerebral oxygenation; O_2-reactivity.

Introduction

Monitoring of cerebral oxygenation in patients with severe head injury is of high clinical value to recognize critical phases of hypoxia [3,8]. Little is known about differences of cerebral oxygenation in contusioned and non contusioned brain tissue. As cerebral blood flow, a major determinant of cerebral oxygenation, varies in lesioned and nonlesioned tissue [7], $PtiO_2$ might differs in these areas. Today two Clark-type microsensors are available to measure $PtiO_2$ in brain parenchyma. The location of the $PtiO_2$-microsensor in respect to the lesion and the catheter used (Licox or Paratrend) might influence the $PtiO_2$-values, important for future interpretation and comparisons of $PtiO_2$-data.

In this study the cerebral oxygenation in contusioned, pericontusional and nonlesioned tissue was investigated in patients with severe head injury. Two different $PtiO_2$-catheters to monitor cerebral oxygenation (Licox and Paratrend) were compared.

Materials and Methods

Patients Characteristics and Multimodal Monitoring

7 severely head injured patients (Glasgow Coma Score < 8) were investigated. Permission was granted by the Local Institutional Ethics committee and informed consent. Median age was 32 years (range 22–54 years). After resuscitation, cranial computerized tomography (CCT) was performed and a diffuse injury III (n = 4) and IV (n = 3) was diagnosed. The following physiological parameters were continuously monitored for as long as ICP monitoring was required: mean arterial blood pressure (MABP), intracranial pressure (ICP, Camino Laboratories, San Diego, CA), cerebral perfusion pressure (CPP), end-tidal CO_2 ($ETCO_2$), arterial oxygen saturation, jugular bulb oxymetry ($SjvO_2$, Abbott Laboratories) and $PtiO_2$ were monitored between day 1 and 11 after trauma.

Monitoring of Brain Tissue PO_2

Two different Clark-type microcatheters to measure continuous brain $PtiO_2$ (Licox System, GMS, Germany and Paratrend, Diametrics Medical, U.K.) and to measure additionally brain tissue CO_2 and pH (Paratrend, Diametrics Medical, U.K.) were used. The $PtiO_2$-micorsensors were inserted both into nonlesioned tissue (n = 3), into nonlesioned (Paratrend) versus pericontusional (Licox) tissue (n = 2) or both directly into contusioned brain tissue (n = 2). Proper location of the catheters in the cerebral white matter and exclusion of catheter-induced hemorrhage was ascer-

tained by CT. Special attention was paid for a deep insertion of the Paratrend sensor. Pericontusional tissue was defined as 1–2 cm rim adjacent to contusioned tissue. Immediately after removal from the brain, the microcatheters were checked for sensitivity drifts.

Mean monitoring time was 3,3 days (range 2,5 to 11,2 days), duration of $PtiO_2$-measurements with the 2 microcatheters in parallel was 2,8 days (range 2,1 to 10,4 days).

Results

There was no complication associated with the insertion of the $PtiO_2$-catheters; in particular no infection or bleeding was observed. The measured values after catheter removal corresponded to the calculated $PtiO_2$-values in room air.

Nonlesioned Tissue

During the first 24 hours after insertion, $PtiO_2$ was reduced compared to the following days, independent of type of microsensor used. Mean $PtiO_2$ measured with the Licox- and Paratrend-sensor closely correlated with a mean difference <5 mm Hg after the first 20 hours of monitoring (Fig. 1). During a marked reduction of MABP and CPP, all oxygenation parameters decreased in parallel (Fig. 2).

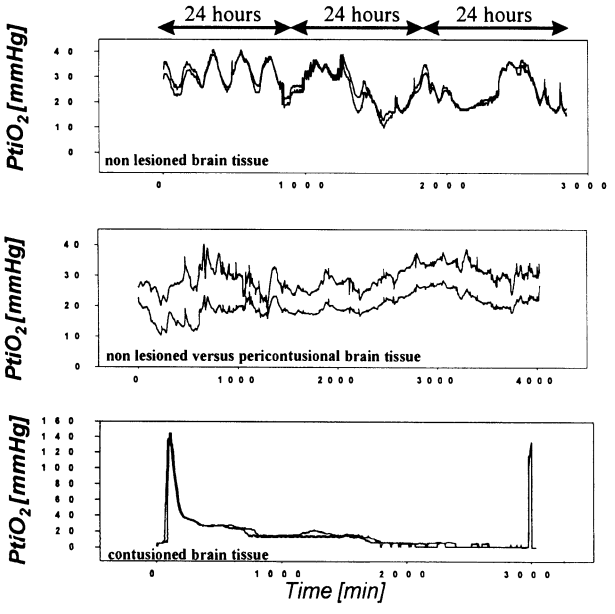

Fig. 1. Three individual examples of $PtiO_2$ monitored in different locations for 3 days. Top: In nonlesioned brain, tissue PO_2 measured with Paratrend and Licox is highly comparable. Middle: In pericontusional tissue, PO_2 (Licox) is always lower than in nonlesioned tissue (Paratrend). Lower: In contusioned brain, $PtiO_2$ is in the hypoxic range. PO_2 on air before and after insertion is shown

Pericontusional Brain Tissue

$PtiO_2$ was reduced in pericontusional brain tissue relative to surrounding nonlesioned tissue (Fig. 2). Mean difference of $PtiO_2$ during 3 days of monitoring was 10.5 mm Hg with the Licox-sensor in the pericontusional and the Paratrend-sensor in nonlesioned tissue. This is similar to previous results obtained from bilateral $PtiO_2$-monitoring in 7 patients with severe head injury [4]. In their study $PtiO_2$ was measured with Licox sensors only and was lower in pericontusional tissue compared to nonlesioned tissue.

Contusioned Brain Tissue

After insertion, $PtiO_2$ decreased below 10 mm Hg, defined as the hypoxic threshold for $PtiO_2$-monitoring measured with Licox [3]. When inspired oxygen fraction was increased to 100%, no change in $PtiO_2$ was observed.

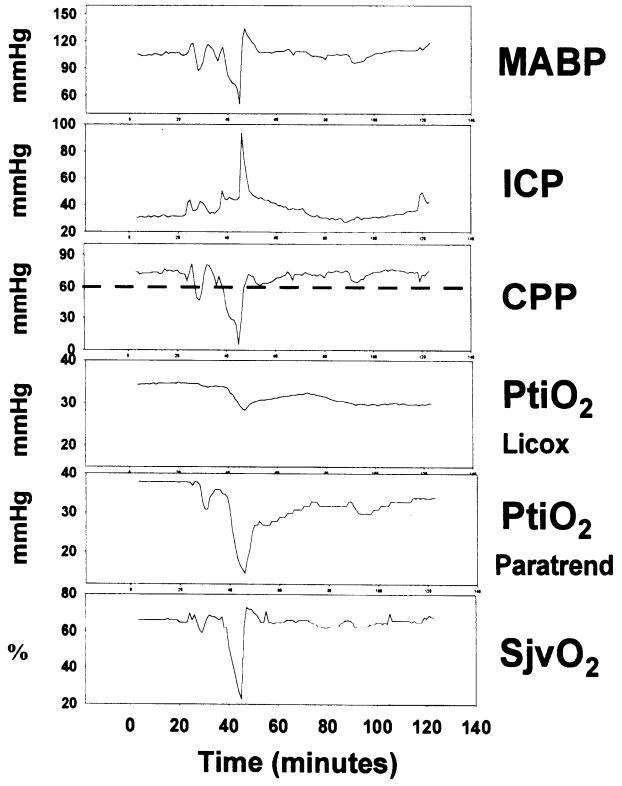

Fig. 2. Cerebral oxygenation during 10 minutes of critically reduced cerebral perfusion pressure. In this patient $PtiO_2$ measured with Licox and Paratrend decreased in parallel. The reduction in cerebral oxygenation is alos reflected by a decrease of $SjvO_2$

Discussion

Monitoring of local brain tissue PO_2 is an appropriate method to detect cerebral hypoxia and ischemia in patients with severe head injury [1,3,8]. For continuous monitoring of cerebral oxygenation, $PtiO_2$-monitoring was shown to be superior concerning artefacts and long-term measurements compared to other available methods like $SjvO_2$- or rSO_2-monitoring [2,5]. So far no on-line comparison between the two microsensors available, Paratrend and Licox, was done. Earlier reports on $PtiO_2$-values obtained with the Paratrend or Licox-sensor describe similar results for both sensors [1]. When monitored with the Paratrend-sensor, mean $PtiO_2$ was 37 ± 12 mm Hg in non-compromized tissue in 6 patients and 9 ± 6 mm Hg in compromized tissue in 8 patients [1]. With Licox, $PtiO_2$ varied in the range of 16.6 ± 9.1 mm Hg to 35.8 ± 14.7 mm Hg, depending on monitoring duration after insertion [8]. The exact location of the sensor in respect to lesions remained unclear though and might explain the wide range of $PtiO_2$ during monitoring. Our results suggest that $PtiO_2$ data obtained with the Paratrend-and Licox-sensor is closely comparable, if both sensors were inserted in nonlesioned white cerebral matter and provided that the PO_2-sensible area of the sensors was inserted sufficiently deep.

There is an increasing discussion as to where to place the $PtiO_2$-probe – in lesioned or nonlesioned brain tissue- for an adequate monitoring of cerebral oxygenation. In brain tissue within and around contusions, a relative hypoperfusion was observed, which may indicate that these tissues are particularly vulnerable to secondary injury [7]. $PtiO_2$ in contusioned tissue was very low (<5 mm Hg) which may be explained by the critically low CBF (<18 ml/100 g/minute) measured in contusioned tissue [6,7]. A low $PtiO_2$ in contusioned tissue had already been observed in one patient by Van Santbrink [8]. A further reduction in cerebral oygenation due to a fall in CPP could not be observed, probably because of the already very low $PtiO_2$. The suppressed O_2-reactivity seen in contusioned tissue may reflect cellular damage unable to metabolize oxygen. Both aspects demonstrate that contusioned tissue is obviously not appropriate to indicate $PtiO_2$-changes.

In pericontusional tissue $PtiO_2$ was reduced compared to nonlesioned tissue. This corresponds to the described hypoperfusion in these areas. Nevertheless, normal CBF and a variable vasoresponsivity have also been measured around contusions [7]. Therefore $PtiO_2$ may vary in tissue around contusions and during time. This has already been observed by Kiening [4], who described considerable $PtiO_2$-variations in pericontusional tissue.

In nonlesioned tissue, $PtiO_2$-values were in a normal range (20–35 mm Hg) but decreased when CPP fell below 60 mm Hg. To follow changes in cerebral oxygenation for detecting cerebral hypoxia and ischemia, nonlesioned tissue seems to be most appropriate. Further studies with an increased number of patients may help to understand oxygenation parameters in brain tissue.

Conclusion

Brain tissue PO_2 varies when measured in lesioned and nonlesioned brain tissue. There are no significant differences in $PtiO_2$ in nonlesioned brain tissue measured with Paratrend and Licox, provided there is a proper location of both sensors in white matter. Following a marked decrease of MABP and CPP, all oxygenation parameters decreased in parallel. In pericontusional tissue, PO_2 is reduced compared to normal. In contusioned brain tissue, $PtiO_2$ was always below the hypoxic threshold. To recognize critical phases of hypoxia and ischemia, $PtiO_2$-monitoring of cerebral oxygenation is recommended in nonlesioned brain tissue.

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Correspondence: Asita S. Sarrafzadeh, M.D., Department of Neurosurgery, Virchow Medical Center, Humboldt-University, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Monitoring Brain Oxygen Tension in Severe Head Injury: The Rotterdam Experience

W. A. van den Brink, H. van Santbrink, C. J. J. Avezaat, C. Hogesteeger, W. Jansen, L. M. H. Kloos, J. Vermeulen, and **A. I. R. Mass**

Department of Neurosurgery, Academic Hospital Rotterdam, The Netherlands

Summary

Cerebral ischemia is considered the central mechanism leading to secondary brain damage in patients with severe head injury. We investigated the technique of continuous monitoring of local brain tissue oxygen tension as parameter for cerebral oxygenation. Eighty-two patients with non penetrating severe head injury were studied. No complications of the monitoring technique were seen. Postmeasurement calibration of the catheters showed a very low zero drift and acceptable sensitivity drift. Low $PbrO_2$ values were seen within the first 12 to 24 hours of injury. Early occurrence of values below 10 mm Hg indicated a poor prognosis. Comparative measurements between two catheters performed in six patients showed differences in absolute values measured, but a good correlation of relative changes was observed.

We conclude that continuous monitoring of $PbrO_2$ is reliable, clinically applicable and provides the clinician with a better insight in cerebral oxygenation and hopefully should help in targeting therapy towards improved cerebral oxygenation.

Keywords: Brain oxygen tension; cerebral hypoxia; cerebral ischemia; cerebral oxygenation.

Introduction

Cerebral ischemia is common after severe head injury. Cerebral ischemia results from intrinsic pathophysiologic pathways and from systemic insults. Such systemic insults are frequent in the early posttraumatic period [18] as well as in the intensive care setting [8]. The adverse influence of systemic insults on outcome has been well documented [3,4].

Our group has previously reported on the feasibility, safety, and experience of continuous monitoring of partial pressure of oxygen in brain tissue ($PbrO_2$) [20]. In 22 patients with severe head injury, we demonstrated the presence of early ischemia at the tissue level. We have now extended our series to 82 patients; in this report we describe the results obtained in these patients.

Materials and Methods

Patients and Treatment Protocols

From September 1992 until February 1997, 82 patients with severe head injury were admitted to the neurosurgical intensive care unit of the Academic Hospital Rotterdam for multimodality monitoring. All patients received standard intensive care treatment and monitoring, conforming to the EBIC-guidelines [10]. Outcome was evaluated at three and six months after trauma, according to the Glasgow Outcome Scale [7]. GOS scores of 1, 2 and 3 were interpreted as unfavourable, GOS scores of 4 and 5 as favourable.

Monitoring, Data Acquisition and Analysis

Intracranial sensors were introduced through a modified three channel subarachnoid screw with an outer diameter of 6 mm, positioned at an undamaged frontal region. ICP was monitored using the Camino® fiberoptic device. $PbrO_2$ was monitored using a Clark type microcatheter and a Licox pO_2 measuring computer (Licox, GMS, Kiel Mielkendorf, Germany). In six patients a second catheter was introduced through the third channel in the bolt. After ending the measurements the catheters were tested for zero and sensitivity drift. Statistical analysis was performed by means of the chi-square statistic when testing for associations of nominal data.

Results

Duration and Reliability of $PbrO_2$ Monitoring

$PbrO_2$ monitoring was started as soon as possible after injury (mean 7.6 +/– 5 hours), intending to last

five days; monitoring was terminated earlier because of early death, or if ICP monitoring was no longer considered indicated. Eighty-eight percent of the patients were monitored more than 24 hours. In three of the 82 monitored patients analysis of measurements was not possible because of computer related errors. The average duration of monitoring was 84 +/– 40 hours (range 3–156 hours).

Adverse events and complications related to catheter introduction and monitoring were not seen. Postmeasurement calibration of the catheters was performed in 67 cases. Average zero drift was 0.54 +/– 0.95 mm Hg and sensitivity drift (at room air): 0.06 +/– 10.46 mm Hg.

Time Course and Pattern of $PbrO_2$

The mean $PbrO_2$ and standard deviation averaged over all patients for a 120 hour period are shown in Fig. 1. Low initial values were observed in 58 patients. Mean $PbrO_2$ increased during the first 12 to 30 hours after injury. In 24 of these patients an overshoot phenomenon was observed after initial low values. Initial low values ($PbrO_2 \leq 10$ mm Hg), not related to low arterial pO_2, were seen to be related to poorer outcome (Table 1).

Eleven out of 20 (55%) patients with initial low episodes, sustaining longer than one hour, die. Sixteen out of 59 (27%) without these initial low values do not survive. The association was statistically significant.

Lower values of $PbrO_2$ were seen on average in patients with low GCS sumscores and in patients with non reactive pupils.

A decrease in $PbrO_2$ was shown to result from increased hyperventilation in 17 out of 23 patients on the first day.

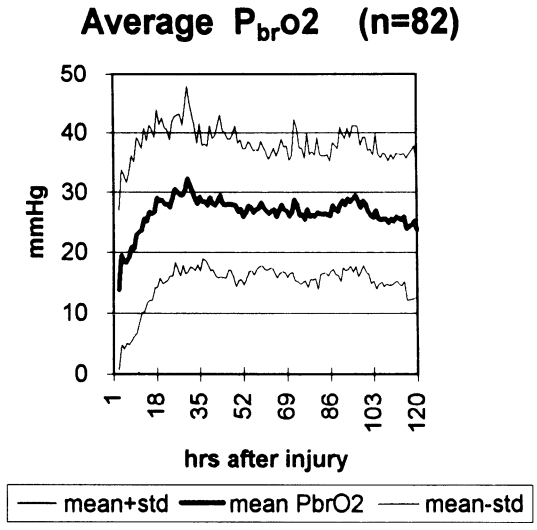

Fig. 1. Average $PbrO_2$ measurements of 82 patients during the first 120 hours. Mean and standard deviations of values measured in hours after injury are displayed. Note the initial low values with a rapid increase during the first hours and a slower increase over the first day. Stabilization occurs at 25 to 30 mm Hg

Comparitive Measurements

In six patients comparitive measurements of $PbrO_2$ were performed with two catheters introduced through the threeway bolt. The second catheter was introduced after a variable period of 4 to 24 hours. Absolute values of $PbrO_2$ between the two catheters differed considerably, but relative changes were well correlated. During a stable $PbrO_2$ recording obtained from the first catheter introduced, initially low values were seen after introduction of the second catheter. Relatively stable values were obtained after a two hour run in period (Fig. 2).

Influence of Routine ICU Nursing Procedures on $PbrO_2$

Routine ICU procedures, such as tracheal suctioning and change of vasopressor pumps have an impact on oxygenation and cerebral perfusion pressure. Tracheal suctioning procedures are routinely performed after preoxygenation. In seven patients, 16 episodes of tracheal suctioning procedures were captured without preoxygenation and 142 episodes with preoxygenation. A decrease of $PbrO_2$ was noted during such procedures without preoxygenation, while in contrast $PbrO_2$ invariably increased on preoxygenation.

In four patients on vasopressor therapy 43 moments of pump exchanges were recorded. Although undesirable, a decrease of cerebral perfusion pressure (65 to 42 mm Hg) was noted during changing of

Table 1.

<10 mm Hg	Alive	Dead	Total
>1 hr	9	11	20
<1 hr	43	16	59
Total	52	27	79

Regional $PbrO_2$ values < 10 mm Hg, sustaining longer than one hour are significantly related with mortality. Fifty-five percent of the patients with an early hypoxic period die.

the infusion pump and a secondary decrease in $PbrO_2$ (26 to 19 mm Hg) resulted (Fig. 3).

Discussion

Reliability of $PbrO_2$ Measurements

Intraparenchymal monitoring of partial oxygen pressure of brain tissue provides the clinician with additional information on the local oxygen status of the injured brain. As no complications of hemorrhage or infection were observed in our series the method is considered safe. The catheters show a low zero drift and acceptable sensitivity drift, demonstrating the method to be reliable in a clinical application. The differences in absolute values of $PbrO_2$ measured in the patients with comparitive measurements reflect the heterogeniety of oxygenation at the tissue level. Recorded values are dependent on the relation between the catheter to the capillary mesh, the diameter of microvascular vessels and to the diffusion distance between the capillary mesh and the oxygen probe. Absolute values may be influenced by the presence of microhemorrhages around the oxygen probe.

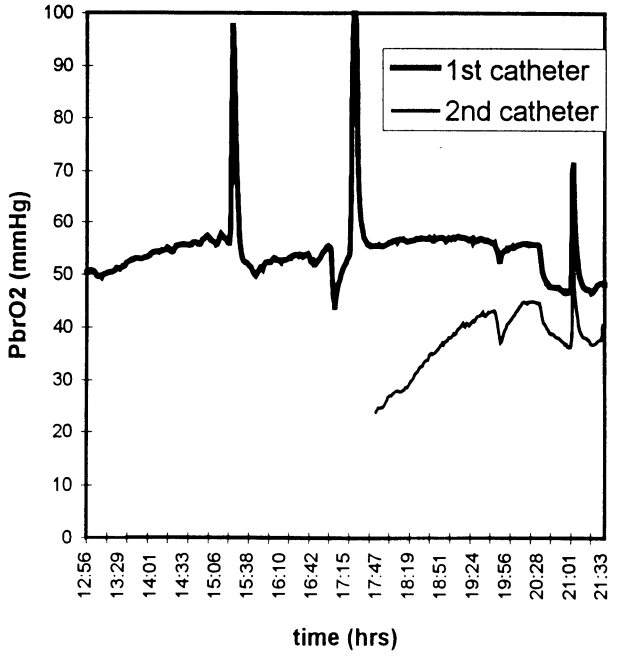

Fig. 2. "Run-in" period $PbrO_2$ catheter. Comparitive measurements. At first during a stable period of the first catheter, a run in rime of two hours of the second catheter can be observed. Hereafter this catheter is also stable, and the $PbrO_2$-fluctuations are equal in both time and relative height

Causes of Tissue Hypoxia and Implications for Monitoring Techniques

Cerebral ischemia is generally considered to result from insufficient oxygen supply in relation to demand. With this concept in mind monitoring of the jugular venous saturation is considered appropriate for detecting cerebral ischemia. Low jugular saturation values indicate a higher extraction of oxygen and thus are indicative of ischemia. Monitoring of venous oxygen saturation will however not detect all causes of tissue hypoxia, f.i. in the presence of anemia or arteriovenous shunting. Low $PbrO_2$ values can occur in the presence of normal or even high oxygen saturation in the cerebral venous blood [19]. Moreover, the technique of jugular oximetry is prone to technical artefacts and may provide unreliable recordings for considerable periods of time. We do agree with Kiening *et al.* [9] that brain tissue pO_2 monitoring is superior to jugular oximetry.

Low Initial $PbrO_2$: Real or Artefact?

Clinical studies have shown critically reduced cerebral bloodflow following head injury [1,2,6,11,13,16]. Microdialysis studies have shown the presence of lactic acidosis indicating ischemia at the tissue level [12]. The observation of low brain tissue pO_2 in the first 24 hours after injury is consistant with these reports. However, preliminary results from the comparative measurements reported indicate an artifactual low value during the first two hours of recordings. Some equilibration time for attaining steady state of the probe tissue interface is required; this duration will probably be dependent on the

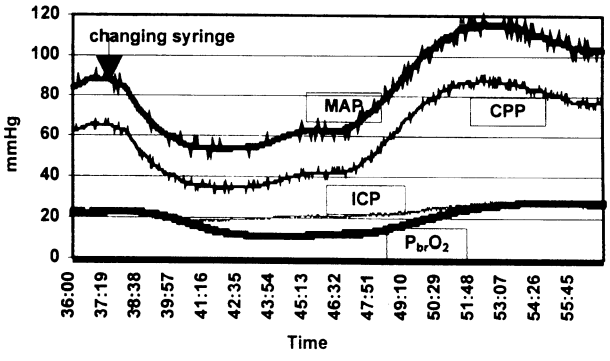

Fig. 3. Typical example of the decrease of mean arterial pressure, cerebral perfusion pressure during the exchange of a vasopressor pump. This patient is extremely dependent on the vasopressors as arterial pressure decreases more than 30%. An immediate decrease of the $PbrO_2$ from normal to ischemic levels is the result

method used for introducing the catheter. The catheters used in our studies have a small diameter (0.5 mm) and are very flexible. For insertion a stiff introducer (outer diameter 1.1 mm) is used, through which the catheter is passed into the brain tissue, after which the sheet is subsequently retracted. The use of this introducer causes a larger degree of local tissue damage than would occur when simply passing the catheter itself into the brain tissue and is conceivable that microvascular flow surrounding the tip of the catheter is disturbed due to this method. This hypothesis would explain the longer run in time, observed in the clinical setting, compared to our experience in the experimental situations, where the microcatheters were introduced directly into the brain without help of an introducer.

The slow gradual increase of $PbrO_2$ observed in early measurements performed on patients, showing a slow gradual increase of $PbrO_2$ over periods upto 12 to 24 hours cannot, therefore, be explained by the shorter run in time of two hours. We conclude that the observed low values of $PbrO_2$ occurring after the run in time of two hours are real, indicating the presence of early local tissue hypoxia. As the aim of our measurements is to monitor relatively undamaged brain tissue, the presence of local ischemia may be considered indicative of global cerebral ischemia.

Low Initial $PbrO_2$: Implications for Therapy

Our studies have demonstrated the frequent occurrence of low $PbrO_2$ values in the first 24 hours after injury, indicating cerebral hypoxia. Moreover the occurrence of low $PbrO_2$ values in this period is related to poor outcome. Continuous monitoring of $PbrO_2$ affords us the possibility of monitoring the hypoxic period of the brain and targeting therapy towards improvement of oxygenation. Such improvement can be obtained either by increasing the oxygen content of the arterial blood, or by improving delivery through increase of flow. The latter concept is the basis for cerebral perfusion pressure therapy. Correcting anemia and ensuring optimal saturation of the arterial blood is the most important method for improving oxygen content of the arterial blood. Increasing FIO_2 in patients already adequately oxygenated will increase arterial pO_2 considerably, but the net effect on arterial oxygen content is small. Despite this, increasing arterial pO_2 leads to a significant increase of brain tissue pO_2. The therapeutic value of increasing arterial pO_2 to supranormal levels however yet has to be determined and theoretically may carry a risk of formation of oxygen radicals potentiating lipid peroxidative damage. Cerebral perfusion pressure therapy would appear the method of choice for improvement of cerebral oxygenation. The critical perfusion pressure required in individual patients conceivably could be determined on the basis of brain oxygen tension monitoring (aiming at a minimal $pPbrO_2$ of 15 mm Hg). More research is required on this issue and will be the focus of our research in the coming years.

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Correspondence: W. A. van den Brink, M.D., Department of Neurosurgery, Academic Hospital Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Expression of Immediate Early Gene c-fos in Rat Brain Following Increased Intracranial Pressure

T. Matsumoto, A. Masago, K. Yamada, A. Iwata, S. Harada, and **M. Mase**

Department of Neurosurgery, Nagoya City University Medical School, Nagoya, Japan

Summary

No attention has been given to an influence of the intracranial pressure (ICP) elevation on the brain at the level of the gene. In the present study, we originally attempted to evaluate the molecular biological changes of the brain, especially the expression of c-fos mRNA as a marker of cellular response, caused by increased ICP. Our results confirm that the neurons and non-neuronal cells are well able to tolerate the stress of increased ICP at the level of the gene, under the condition that cerebral blood flow (CBF) is maintained. A severe increase in ICP, which reduces CBF, enhances the c-fos mRNA expression in a similar fashion as in a forebrain ischemia model, except in the choroid plexus.

Keywords: C-fos; c-fos mRNA; in situ hybridization.

Introduction

Pathological increment in the volume of any of the intracranial components should cause a corresponding elevation of the intracranial pressure (ICP) [3]. It is, furthermore, possible to say that the ICP could be elevated by additional pathologies, such as neoplasm, hematoma and so on. The increased ICP probably participates in the mechanisms of brain damage, together with the insult of the original disease [3,6,11,12]. Various forms of ischemia [7,10,14], as well as neurotrauma [17,19,20], seizures [5] and other neuronal stimulation [2,4] result in an enhancement of gene expression [14]. However, no attention has been given to the influence of ICP elevation itself on the brain at the level of the gene.

In the present study, we attempted to evaluate the expression of immediate early gene (IEG) c-fos, caused by increased ICP using newly developed ICP controllable rats. It might be reasonable that the expression of c-fos mRNA has been used to identify the location of neurons and non-neuronal cells which respond at the genomic level to the phenomenon of increased ICP.

Materials and Methods

General Procedure

Sixteen adult male Wistar rats weighing between 300 and 350 g were used. Rats were anesthetized by inhalation of halothane, and oxygen. The femoral artery and vein were cannulated, respectively, to record systemic arterial pressure (SAP) and fluid infusion. After the tracheostomy, the rats were mounted in a stereotaxic farme in the prone position. Midline scalp and neck incisions were followed by bilateral craniectomy centered 2 mm posterior to the bregma and 3 mm from the mid line. The ICP was monitored using the Camino fiberoptic sensor which was inserted into the cortex at 2 mm depth in the left side. The cerebral blood flow (CBF) was also measured using a Laser Doppler Flowmeter which was placed on the dura in the right side. After exposing the atlanto-occipital membrane, a polyethylene tube (I.D. 0.58 mm, O.D. 0.965 mm) was inserted through the dura into the cisterna magna. This tube was connected to the mock CSF [1] in a bottle. The ICP levels were completely regulated by the height of this bottle [11].

Experimental Protocol

Group 1: Moderate elevation of the ICP in 6 rats.

ICP was adjusted to about 30 mm Hg by elevation of the bottle at around 50 cm in height above the ear of the rats for one hour followed by one hour at normal ICP. Intracranial pressure, CBF and SAP were measured in three of these six rats (group 1a). In the 3 other rats (group 1b), ICP and CBF sensors were not implanted to avoid the brain injury which induces IEG expression [17], while the other procedures were exactly the same as in group 1a. In group 1b, the rats were sacrificed just after the manipulation, and the brains were quickly removed and frozen at –80°C. Serial coronal sections (10 μm thick) were obtained using a cryostat and processed for in situ hybridization (ISH).

Group 2: Severe elevation of the ICP in 7 rats.

The bottle was elevated to around 120 cm in height above the ear of the rats for 30 minutes followed by one hour normalized

ICP. The other procedures were exactly the same as in Group 1a and 1b.

Group 3: Control in 3 rats.

These rats were sacrificed under anesthesia without manipulation. The brains were removed and quickly frozen for ISH. Optical density ratios (ODR) of groups 1 and 2 were estimated in comparison with this control group.

In situ Hybridization

In situ hybridization for c-fos mRNA was performed on the groups with increased ICP (moderate: n = 3, severe: n = 4) and the control group (n = 3). The probe used was complementary to amino acids 60–76 of rat c-fos mRNA. The c-fos oligonucleotide probe was prepared by labelling with [a-^{35}S]dATP using a 3′ labelling system (Takara, Japan) [8] and its specific activity was at least 1×10^9 dpm/μg. Slide-mounted sections were fixed with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2) for 15 min, rinsed 3 times in 4 × SSC (pH 7.0), and incubated in 4 × SSC (pH 7.0) containing 1 × Denhardt's solution for one hour at room temperature (RT). The sections were then dehydrated through a graded ethanol series and air dried. Hybridization was performed by incubating the sections overnight at 42°C with a hybridization buffer containing [a-^{35}S]dATP-labelled probes. After hybridization, the sections were rinsed in 4 × SSC (pH 7.0) for 1 min at RT, followed by four 15-min rinses in 1 × SSC at 55°C. The sections were then dehydrated through a graded ethanol series and dried. The hybridized sections were placed onto X-ray film for 7 days to obtain a macroautoradiogram [8,19,20]. After that, slides were coated with Ilford K-5 emulsion diluted with water (1 : 1). The slides were exposed for 3–4 weeks in a tightly sealed dark box at 4°C, and subsequently developed in Kodak D-19, fixed, counterstained with thionin and coverslipped. The specificity of the oligonucleotide probe was verified by control hybridization experiments using RNase treatment (10 μg/ml) prior to hybridization, or by adding the unlabeled probe in excess (100-fold) to the hybridization buffer. No significant signals above background were detected in the sections processed after RNase treatment, or with a mixture of labeled and excess unlabeled probes.

Quantification of Macroautoradiogram Density

For quantitative assessment of c-fos mRNA expression on the macroautoradiogram, the optical density of the cortex (3.3 mm posterior from the bregma according to the atlas of Paxinos and Watson [15] was measured with a densitometer with an aperture of 0.5 mm (Konica PDA-15, Konishiroku, Tokyo, Japan). The same area was measured five times and the mean values of the counts were used for further analysis. Each ODR was calculated against the backgrounds of the films.

Data Analysis

In all statistical tests, differences were considered significant when $P < 0.05$, and values are mean ± standard error. The student's t-test was used to eliminate blocks compare the data (ICP, CBF, SAP) between pre and post ICP elevation. ODR data were analyzed using the Mann-Whitney U-test with two-tailed probability.

Results

In the group 1a animals, ICP was elevated from 7.3 (±2.9) to 29.3 (±2.3) mm Hg ($P < 0.05$). The differences of CBF and SAP pre and post ICP elevation were not statistically significant in this group. In the group 2a animals, ICP was elevated from 11.3 (±6.6) to 65.7 (±12.2) mm Hg ($P < 0.02$), and CBF was significantly reduced from 16.3 (±3.5) to 4.2 (±1.9) ml/min/100 g ($P < 0.02$). The mean SAP did not show any statistically significant differences.

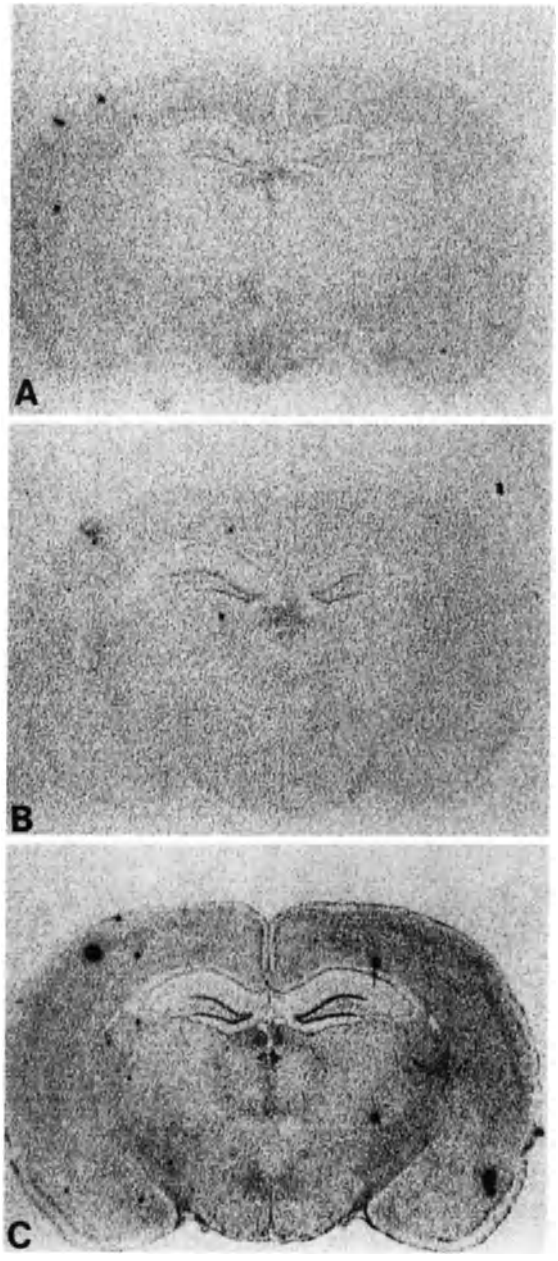

Fig. 1. Regional distribution of c-fos mRNA in representative control (A), mild ICP elevation (B), and severe ICP elevation (C) rat brains. In (A) and (B) brains, c-fos mRNA appeared to be present somewhat in the dentate gyrus and habenulae. In severe elevation of ICP (C), c-fos mRNA expression was strongly enhanced in the cortex, dentate gyrus, habenulae and paraventricle regions of both sides

The distribution of c-fos mRNA in both pre and post ICP elevation rat brains as revealed by ISH is shown in Fig. 1. In control (Fig. 1A) and moderate ICP elevation (Fig. 1B) rat brains, c-fos mRNA appeared to be present some in the dentate gyrus and habenulae, but few labeled cells were detected in other regions. After severely increased ICP (Fig. 1C), the areas with strikingly high levels of c-fos mRNA included the whole cortex, dentate gyrus, habenulae and paraventricular regions of both sides. More moderate c-fos mRNA levels were seen in the internal capsule and hypothalamus. The quantitative assessment of c-fos mRNA expression in the cortex revealed that the ODR of group 1b did not show any significant difference compared to that of the control (from 1.09 ± 0.02 to 1.10 ± 0.03).

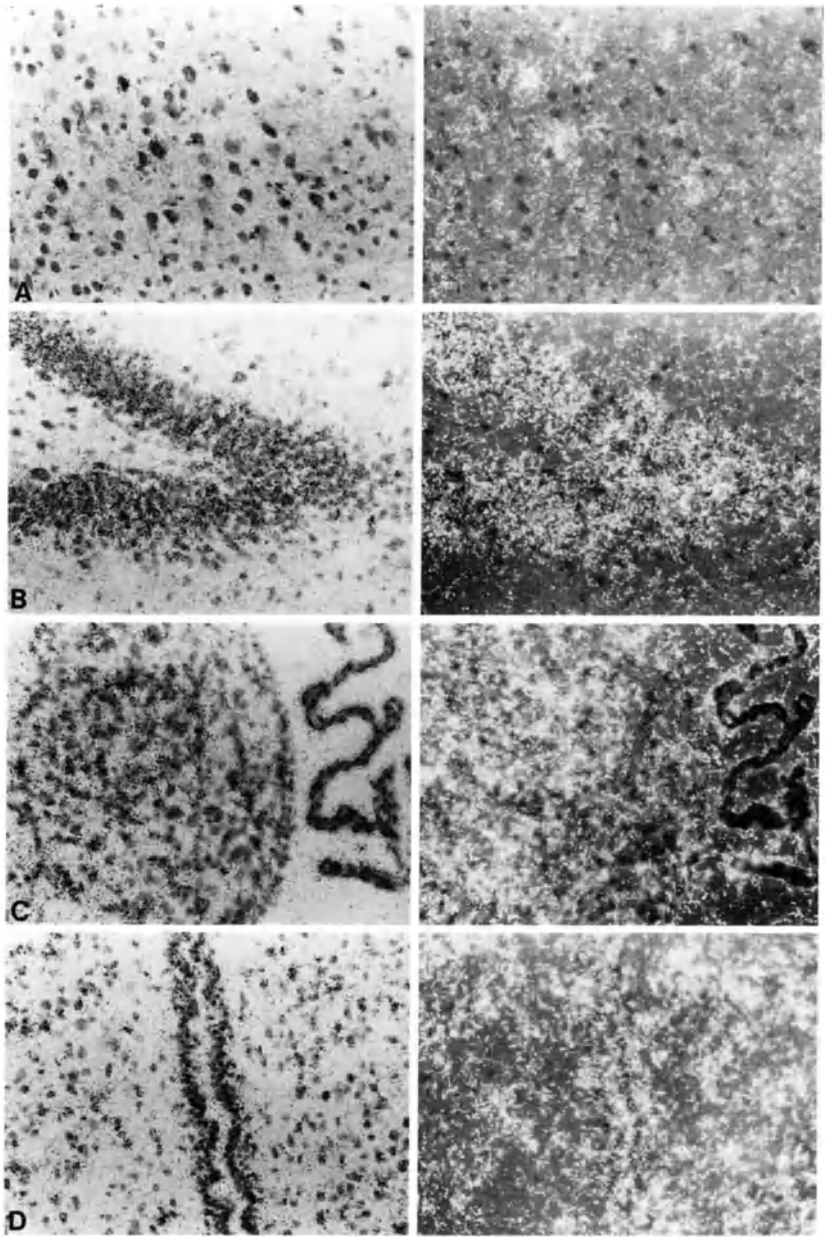

Fig. 2. Photomicroautoradiogram showing c-fos mRNA expression in selected brain regions of group 2b. (×400, Thionin staining, Left: bright field, Right: dark field). In the cerebral cortex, c-fos mRNA signals were detected mainly in the neurons, though they were also observed in the non-neuronal cells (A). The dentate gyrus was strongly labelled by c-fos mRNA (B). Neurons and non-neuronal cells in the habenulae consistently showed intense signals of c-fos mRNA. Inadvertently, evidence has been established that little induction of c-fos mRNA occurred in the choroid plexus (C). A prominant increase in c-fos mRNA was also noted in ependymal layers of third ventricle and its surrounding area (D)

However, in group 2b, c-fos ODR (1.46 ± 0.09) was significantly ($P < 0.03$) higher than that of the control (1.10 ± 0.04).

To reveal details of the signals from the emulsion microautoradiogram, counterstaining of the sections with thionin was carried out in the severely increased ICP rat brains (Fig. 2). In the same planes, bright field and dark field photomicroautoradiograms were taken. In the cerebral cortex, c-fos mRNA signals were detected mainly in the neurons, though they were also observed in the non-neuronal cells (Fig. 2A). The dentate gyrus was strongly labelled by c-fos mRNA (Fig. 2B). Neurons and non-neuronal cells in the habenulae consistently showed intense signals of c-fos mRNA. The choroid plexus has been reported as having a strikingly high level of c-fos mRNA expression area following forebrain ischemia [7]. In this model, inadvertently, evidence has been established that little induction of c-fos mRNA occurred in the choroid plexus (Fig. 2C). In dark fields, no grains were observed on the choroid plexus cells. A prominant increase in c-fos mRNA was also noted in ependymal layers of the third ventricle and its surrounding area (Fig. 2D).

Discussion

Over the past few years it has become increasingly clear that neurons, as well as non-neuronal cells, respond to external stimuli with complex genomic change [2,4,5,7–10,13,14,16,17–20]. Transcription factors encoded by IEG, such as c-fos and c-jun have received particular attention because they are believed to play a crucial role in mediating alterations in gene expression which is followed by synthesis of various proteins [8]. This induction of IEG might be a useful marker with which the effects of pharmacological, electrical and physiological stimuli may be traced in the central nervous system [2,7,18].

However, it should be noted that any brief stimulation could induce an IEG expression [7,9,10]. Therefore, the ability to adequately test the genomic change of the brain which is caused by the elevation of ICP will depend on the availability of a model of increased ICP without any local brain damage. For this purpose, we developed an ICP controllable model in rats by the cisternal mock CSF drip infusion method [11]. In this model, the mean ICP level adjusted completely by the height of the bottle without local brain damage.

It is well known that the changes of CBF and/or vasotonicity exert a marked influence on the expression of IEGs [9,14,18]. In our experiments, the expression of c-fos was not detected in the mild ICP increased group. In general, CBF is maintained until the ICP increased up to 50–60 mm Hg [6], and there is also no remarkable change of the vasotonicity when the ICP is under 30 mm Hg [11]. Therefore, our results could be interpreted as suggesting that the brain is well able to tolerate increased ICP insofar as the CBF and vasotonicity are maintained. On the other hand, the expression of c-fos mRNA increased in the cerebral cortex, dentate gyrus, habenulae and paraventriclular region in the severely elevated ICP rats brains. In this group, CBF decreased dramatically, and cerebral ischemia and disruption of autoregulation probably occurred.

Of great interest is the question of whether or not this gene expression is in our model solely due to the evolving ischemic insult. We could approach this problem by comparing the pattern of genomically enhanced areas in the increased ICP rat brains with that in the forebrain ischemic rat brains. If the comparison reveals a different expression pattern, it might suggest that the original molecular biological changes were caused by the physiological stress of the increased ICP itself. Neumann *et al.* reported that 30 min forebrain ischemia followed by one hour reperfusion caused strikingly high levels of c-fos mRNA in the dentate gyrus of the hippocampus, amygdala, piriform cortex and choroid plexus [14]. Although hardly any difference was detected in the expression pattern between this forebrain ischemic model and our model, one crucial dissimilarity came to light. In the forebrain ischemic model, the choroid plexus was one of the most pronounced c-fos mRNA induction areas. Nonetheless, in our model, c-fos mRNA expression was not enhanced in the choroid plexus. The reason for this difference is not clear at the present time, but it might be due to a difference in the degree of the ischemic insult of the choroid plexus between the forebrain ischemic model and the ICP elevation model. In our model, intraventricular pressure should be above 60 mmHg, which could be a high enough level to stop the circulation of the choroid plexus. Thirty minutes of no blood supply might be long enough for irreversible damage to the choroid plexus, and may even interfere with c-fos mRNA synthesis. Or, direct physical stress of high ICP might play a role in the disruption of choroid plexus function.

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Correspondence: Takashi Matsumoto, M.D., Department of Neurosurgery, Nagoya City University Medical School, Mizuhoku, Nagoya 467, Japan.

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Leukocyte Adhesion Molecule Profiles and Outcome after Traumatic Brain Injury

E. G. McKeating, P. J. D. Andrews, and **L. Mascia**

Department of Anaesthetics, University of Edinburgh, Western General Hospital, Edinburgh, U.K.

Summary

Adhesion molecules have an important role in leukocyte migration into tissue after injury. We hypothesised that changes in ICAM-1 and L-selectin expression after traumatic brain injury would result in altered serum concentrations of these molecules, which would be related to injury severity and outcome. We investigated arterial and jugular venous concentrations of ICAM-1 and L-selectin in 22 patients. The Glasgow Coma Score and Injury Severity Score were recorded. Paired arterial and jugular venous blood samples were taken at designated times after brain injury: on admission, at 24 hours, 48 hours and 96 hours. Glasgow Outcome Scores at 6 months were obtained. Mean serum concentrations of ICAM-1 were normal on admission, but became significantly increased by 96 hours ($p = 0.018$). Mean L-selectin concentrations were markedly below controls at all time points ($p < 0.001$). There were no significant differences between jugular venous and arterial concentrations of either ICAM-1 or L-selectin. Serum ICAM-1 was significantly related to neurological outcome ($p < 0.001$) and to the Glasgow Coma Score ($p < 0.001$). These changes in adhesion molecule expression may be important in the pathophysiology of secondary injury. The highly significant relationship between serum ICAM-1 and neurological outcome suggests that drugs which antagonize adhesion molecule activity may improve outcome after traumatic brain injury.

Keywords: ICAM-1; L-selectin; leukocyte adhesion.

Introduction

Leukocyte adhesion molecules, which are expressed on the surface of leukocytes and endothelial cells, control the migration of leukocytes into tissue. After a primary brain injury, increased expression of these molecules may result in secondary brain damage. There are three families of leukocyte adhesion molecule. The first includes the glycoproteins L-selectin and E-selectin, which are present on the surface of leukocytes and endothelial cells respectively. These mediate the initial tethering of leukocytes to the vessel wall by binding to endothelial receptors [4]. Strong adhesion and migration across the endothelium into tissues are mediated by the other two families – the immunoglobulin superfamily, consisting of ICAM 1,2 and VCAM-1, present on the endothelial surface, and their counter-receptors, the integrins which are present on the leukocyte cell surface. The selectins and immunoglobulins are also found in soluble, active forms in the blood of normal humans (eg sICAM-1, sL-selectin) [3]. We investigated both endothelial (ICAM-1) and leukocyte bound (L-selectin) adhesion molecule concentrations, and hypothesised that an altered expression of both ICAM-1 and L-selectin after traumatic brain injury would result in an increased serum concentration of the soluble form of ICAM-1 (sICAM-1), together with a probable increase in soluble L-selectin (sL-selectin), and that theses changes would be related to type and severity of injury and neurological outcome. We also hypothesised that jugular venous (JV) concentrations would be greater than arterial.

Materials and Methods

We investigated the difference between jugular venous (JV) and arterial concentrations of sICAM-1 and sL-selectin in 22 patients with TBI admitted to the intensive care unit. Data of patient characteristics, consisting of sex, age, Injury Severity Score (ISS) and Glasgow Coma Score (GCS) after non-surgical resuscitation were collected on admission (Table 1). If a patient had an Abbreviated Injury Score >1 for a body region other than the head/neck, he/she was classified as having extracranial injuries. If this was not the case then the patient's injury was classified as an isolated head injury. Injury type was classified as either focal or diffuse from the initial CT scan, read by a single neuroradiologist. Patients whose CT scan appeared normal or showed both diffuse and focal injuries were classified as "neither".

Paired arterial and JV blood samples were taken at designated times after brain injury: on admission (median time 8 h 30 min after injury, range 6 h 30 min – 14 h), at 24 hours, 48 hours and 96 hours. These were allowed to clot and spun down in a refrigerated centrifuge. Serum was then immediately frozen at –25°C. Analysis of serum for sICAM-1 and sL-selectin was performed by ELISA (R&D Systems, USA). 152 samples (76 pairs) were analysed by a single operator. Standards and samples were analysed in duplicate. Standard curves and sICAM-1 and sL-selectin concentrations were calculated by a personal computer interfaced to a microplate reader. Glasgow Outcome Scores (GOS) at 6 months after injury were obtained the patients' family doctors. The GOS refer to the following: 1 – dead, 2 – vegetative, 3 – severely disabled, 4 – moderate recovery, 5 – good recovery. Statistical analysis was by means of SPSS Base 7.0 for Windows with Student's t-test, analysis of variance (ANOVA), linear modelling and linear regression.

Results

Mean arterial concentration of sICAM-1 at each time point is shown in Table 2, together with control values. Concentrations were similar to controls on admission, but rose significantly higher than the controls by 96 hours after injury ($p = 0.018$). Mean concentration of sICAM-1 was significantly higher at 96 hours than on admission and at 24 hours ($p = 0.006$). Figure 1 shows individual patient profiles for arterial sICAM-1.

Table 2 also shows the mean arterial concentrations of L-selectin at each time point, in addition to control data. sL-selectin concentrations were markedly below controls at all time points ($p < 0.001$). There were no significant differences between concentrations of L-selectin at any of the time points. There were no significant differences between JV and arterial concentrations of sICAM-1 or sL-selectin.

Glasgow Outcome Scores were summarized into two categories – the first representing a good outcome (GOS 4–5, n = 12), the second representing a poor outcome (GOS 1–3, n = 9, 1 lost to follow up). There was a significant difference in age between outcome groups (mean/standard error of mean was 28.5/3.8 yrs for "good" and 42.3/5.2 yrs for "poor", $p = 0.039$), however there was no difference in GCS (7.5/0.7 and 5.9/1.2, $p = 0.237$) or ISS (23.4/1.9 and 22.0/2.5, $p = 0.652$) between good and poor outcome groups respectively. There was a highly significant correlation between arterial sICAM-1 and outcome ($p < 0.001$), controlling for time (linear model) (Figs.

Table 1. *Data of Patient Characteristics*

Sex: Male/Female	18/4
Age: Range	17–69
Median	34
Glasgow Coma Score: Range	3–13
Median	7
Injury Severity Score: Range	9–38
Median	25
Glasgow Outcome Score: Range	1–5
Median	4

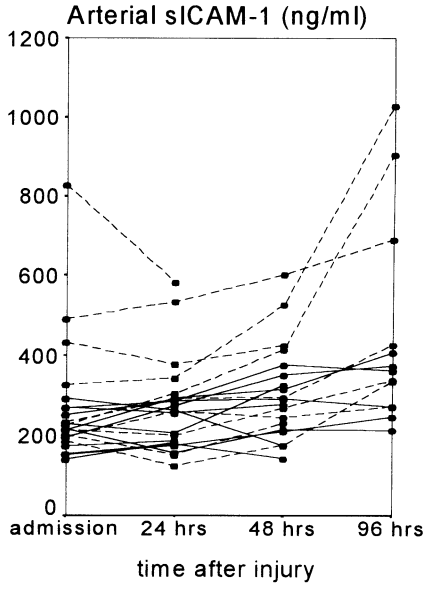

Fig. 1. Patient profiles for sICAM-1. Those patients with poor outcome are shown with broken lines, those with good outcome with solid lines

Table 2. *Mean Concentrations of NSE and S-100 in Arterial Serum in Volunteer Controls and Patients Over a Period up to 96 Hours After Brain Injury. P values are for a two-tailed t-test of patients v controls*

	sICAM-1 (ng/ml)			sL-selectin (ng/ml)		
Time	Mean	95% CI	p value	Mean	95% CI	p value
Controls	254	214–295	–	907	808–1006	–
Admission	267	200–335	0.778	637	565–709	<0.001
24 hours	269	218–320	0.683	590	532–647	<0.001
48 hours	310	252–367	0.154	617	550–683	<0.001
96 hours	453	298–609	0.018	580	488–672	<0.001

1 and 2). When only the concentrations on admission and at 24 hrs were considered, there remained a significant relationship with outcome ($p = 0.003$). There was no significant relationship between arterial sL-selectin concentrations and outcome ($p = 0.062$).

There were significantly higher concentrations of arterial sICAM-1 in those with lower Glasgow Coma Scores ($p < 0.001$, linear model). Surprisingly, there was also a negative relationship between arterial sL-selectin and Glasgow Coma Score ($p = 0.005$, linear model). We looked more closely at the type and severity of injury, and in particular for the presence of extracranial injuries. 11 patients were classified as having isolated head injuries and 11 also had extracranial injuries. There were no significant differences between these two groups with respect to sICAM-1 or sL-selectin ($p = 0.221$ and 0.856 respectively). There was a significant inverse relationship between sL-selectin and ISS ($p = 0.009$, linear model), but there was no correlation between ISS and sICAM-1 ($p = 0.643$, linear model). There was no difference in ISS between good and poor outcome groups (mean/SEM: 23.4/1.9 and 22.0/2.5 respectively, $p = 0.652$).

Finally we looked at type of injury as classified by CT scan. Scans were categorised into normal, diffuse injury, focal injury, or both. Numbers were as follows: 3 normal, 8 diffuse, 10 focal and 1 both. Statistical analysis was carried out excluding "normal" and "both" categories. There was no significant difference between focal and diffuse groups in outcome ($p = 0.657$) and in either sICAM-1 or sL-selectin concentrations ($p = 0.322$ and 0.801 respectively).

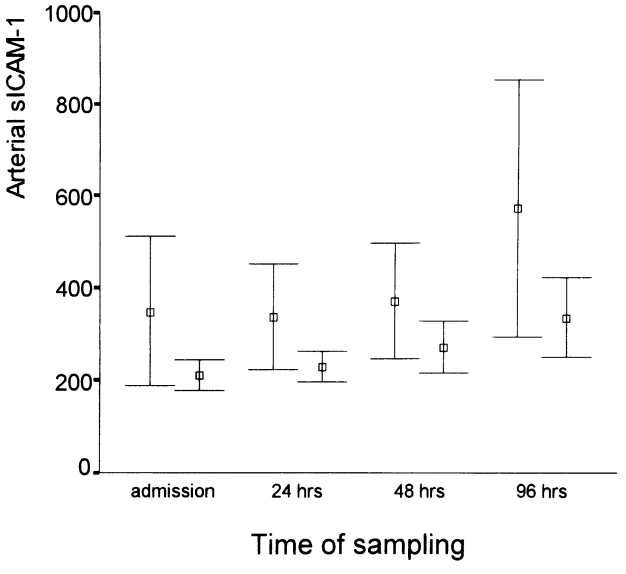

Fig. 2. Graph showing mean (+95% confidence intervals) arterial sICAM-1 concentration in patients with poor outcome (left side) and patients with good outcome (right side) at each time point. P values are: 0.089, 0.064, 0.116 and 0.086 respectively (t-test)

Discussion

The close association between high concentrations of sICAM-1 in serum and poor neurological outcome, together with low Glasgow Coma Scores, suggests that adhesion molecules may play some part in the pathophysiology of inflammatory secondary brain injury, which occurs at variable time intervals after the primary injury. It could be argued that the presence of extracranial injuries would result in both an increase in arterial sICAM-1 and a greater chance of a poor outcome. This was not the case in our sample – there was no correlation between ISS and outcome, and in fact many of those with a high ISS had low arterial concentrations of sICAM-1. Increased concentrations of sICAM-1 could not be explained by the presence or absence of extracranial injuries. This suggests that the significant increase in arterial sICAM-1 is caused by the brain injury itself. Measurement of sICAM-1, for example, on admission and at 24 hours after a traumatic brain injury may assist in prediction of neurological outcome.

More importantly, the effects of the adhesion molecules may be antagonized by antibodies. Investigation of the effects of antibodies to ICAM-1 has been carried out in animal stroke models [1,2]. These studies have shown a reduction in neutrophil infiltration, oedema and infarct size after administration of antibody. It may be that in the future administration of antibodies to the adhesion molecules results in improved outcome after traumatic brain injury.

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Correspondence: E. Grant McKeating, FRCA, Department of Anaesthetics, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, U.K.

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Relevance of Calcium Homeostasis in Glial Cell Swelling from Acidosis

N. Plesnila[1], **F. Ringel**[1], **R. C. C. Chang**[1], **F. Staub**[2], and **A. Baethmann**[1]

[1] Institute for Surgical Research, Klinikum Grosshadern, Ludwig Maximilian University, Munich and [2] Department of Neurosurgery, University of Cologne, Federal Republic of Germany

Summary

Tissue acidosis from trauma or ischemia induces cytotoxic brain edema, mainly affecting astrocytes. In vitro, lactacidosis induces a dose-dependent swelling of glial cells. Activation of membrane transporters and channels, also involved in regulation of intracellular pH (pH_i), has been identified as underlying mechanism, although details are poorly understood. We have currently studied whether Ca^{2+}-ions play a role in acidosis-induced glial swelling and the associated intracellular acidification. The medium pH of a cell suspension (C6 glioma) was lowered from control (7.4) to 6.2 by lactic acid. Cell volume (CV) and pH_i were assessed by flow cytometry. During acidosis in normal medium (2.2 mM Ca^{2+}) CV reached a maximum of 125.1%. In a calcium-free medium swelling from acidosis was inhibited by 74%, while additional buffering of intracellular calcium (Ca^{2+}_i) by BAPTA-AM had no further effect. Buffering of Ca^{2+}_i alone did not affect the CV increase from acidosis at all. pH_i which is decreasing during acidosis was not influenced by the above modifications. The present experiments indicate that lactacidosis-induced glial swelling depends on the presence of extracellular Ca^{2+}-ions, while alterations of Ca^{2+}_i do not seem to be involved.

Keywords: Acidosis; calcium homeostasis; cytotoxic brain; glial cell swelling.

Introduction

Cerebral ischemia and trauma are associated with an intra- and extracellular lactacidosis [4]. Accumulation of lactic acid is involved in the propagation of secondary brain damage following a primary insult. Lactacidosis contributes to the death of neurons and glia and leads to the formation of cytotoxic brain edema [5,6,11]. In vitro administration of lactic acid causes glial swelling in a dose-dependent manner together with intracellular acidification [12]. The present concept of acidosis-induced glial swelling suggests an activation of pH-regulatory membrane channels, such as the Na^+/H^+- and the Cl^-/HCO_3^--antiporter [3,12]. However, details of activation or modulation of these membrane transport processes are currently poorly understood. Ca^{2+}-ions are known to play an important role in many physiological and pathophysiological cellular processes including cell volume regulation [7,10] or cell death from cerebral ischemia or trauma. In vitro studies were currently performed to elucidate the influence of calcium-ions on swelling and intracellular acidification of glial cells from acidosis.

Materials and Methods

The experimental model has been described in detail [3]. Briefly, C6 glioma cells were cultured under standard conditions (37°C, humidified air with 5% CO_2) using Dulbecco's Modified Eagle Medium (DMEM) with 25 mM bicarbonate, 10% fetal calf serum (FCS) and 100 IU/ml penicillin G and 50 µg/ml streptomycin. The cells were harvested upon reaching confluence by addition of 0.05% trypsin/0.02% EDTA in phosphate buffered saline and resuspended in FCS-free medium. The cell suspension was transferred to a custom made Plexiglas incubation chamber with electrodes for continuous monitoring of pH and temperature. pO_2, pCO_2 and bicarbonate were measured sequentially with a standard blood gas analyzer (Radiometer Copenhagen, Copenhagen, Denmark). The suspension was supplemented with a humidified mixture of O_2, N_2 and CO_2 by a membrane oxygenator. Cell sedimentation was prevented by a magnetic stirrer.

Cell volume and pH_i were measured by flow cytometry using an advanced Coulter system with hydrodynamic focusing [1]. For determination of pH_i the pH-sensitive fluorescence dye BCECF was used. The fluorescence emission of BCECF was measured at a pH-sensitive and a pH-insensitive wavelength. The fluorescence data were plotted against each other and the slope of the resulting line was used as a measure of pH_i. The pH_i measurement was calibrated between pH 5.0 and 8.5 using nigericin [13].

Cells were loaded with BCECF for 20 min. Calibration of pH_i was followed by a 60 min control period to assess cell volume, pH_i and the medium osmolarity under baseline conditions. Subsequently, the medium pH was lowered from 7.4 to 6.2 by addition of isotonic lactic acid. Cell volume and pH_i were monitored for 60 min during lactacidosis and for 30 min after neutralization of the medium.

In order to study the role of Ca^{2+}-ions in acidosis-induced cell swelling, experiments were performed in DMEM (in the following named "normal medium") and under different conditions where Ca^{2+}-ions were omitted from the extracellular space and/or buffered in the cytosol. For experiments with no extracellular Ca^{2+}-ions, 0.5 mM of the pH-independent calcium-chelator BAPTA was added to the nominally Ca^{2+}-free medium (Sigma, Deisenhofen, Germany) in order to buffer traces of Ca^{2+} still present in the double distilled water used for medium preparation. The cells were washed three times in this medium to remove residual Ca^{2+}-ions. Ca^{2+}-ions released from intracellular stores were buffered in the cytosol by incubating the cell suspension with 0.1 mM of the membrane permeable acetoxymethylester derivative of BAPTA (BAPTA-AM) for 30 min at 37°C in a glass chamber. In a third group, glial cells suspended in Ca^{2+}-free medium were incubated with BAPTA-AM in addition for cytosolic calcium buffering in the absence of extracellular Ca^{2+}-ions.

Data are presented as mean ± SEM. Statistical analysis was performed using the software SigmaStat 1.0 for Windows. For evaluation of statistical significance between groups the Kruskal-Wallis test followed by the Dunn's test was used.

Results

All parameters remained constant during the control period. Cell volume increased immediately after acidification, reaching a maximum of 125.1 ± 2.5% (% of baseline; n = 9) after 60 min. Upon neutralization of the medium back to pH 7.4, the cell volume recovered to near baseline values (105.4 ± 1.8%; n = 9) within 30 min. The acidosis-induced glial swelling was inhibited by 74% when the experiments were conducted under omission of extracellular Ca^{2+}-ions in the medium. The maximum volume increase was only 106.4 ± 1.9% (n = 5; $p < 0.05$ vs. control). After neutralization of the medium pH the glial cell volume again returned to the control level.

Additional buffering of cytosolic Ca^{2+}-ions by BAPTA-AM in a Ca^{2+}-free suspension medium had no further effect on glial swelling from acidosis. The maximum of cell swelling in the absence of extracellular Ca^{2+}-ions and buffering of cytosolic Ca^{2+}-ions by BAPTA-AM was 108.9 ± 2.1% (n = 5; $p < 0.05$ vs. control) which was not different from the corresponding volume increase in experiments with Ca^{2+}-free medium alone.

Moreover, when the cells were incubated with 0.1 mM BAPTA-AM to buffer release of Ca^{2+}-ions from intracellular stores but suspended in medium with a normal Ca^{2+}-level, the extent of cell swelling upon acidification was not different from that in the control group. A maximum swelling of 120.9 ± 1.8% was attained in this group at 60 min (n = 5; n.s. vs. control).

pH_i of glial cells suspended in standard medium was 7.15 under baseline conditions, but was decreasing immediately to 6.3, once the medium pH was lowered to 6.2. The level of intracellular acidification remained unchanged during the 60 min period of lactacidosis. Following neutralization of the medium, pH_i returned to baseline values. None of the groups with buffering and/or omission of Ca^{2+}-ions from the suspension medium was found to have a different pH_i response, neither under baseline conditions nor in acidosis.

Discussion

The present data show that glial cell swelling from acidosis depends markedly on the presence of extracellular Ca^{2+}-ions. On the other hand, the release of Ca^{2+}-ions from intracellular stores, e.g. mitochondria or the endoplasmatic reticulum, does not seem to play a role in the processes underlying acidosis-induced glial swelling. As demonstrated, buffering of

Table 1. *Volume Response of Glial Cells to Lactacidosis (pH 6.2). The Cells were Suspended in DMEM Medium (Control) or Ca^{2+}-free Medium. Buffering of Cytosolic Ca^{2+}-ions was Achieved by Incubation of the Cells with 0.1 mM of the Cell Permeant Ca^{2+}-chelator BAPTA-AM*

		Cell volume			
Time	pH_e[a]	Control (n = 10)	Ca^{2+}-free medium (n = 5)	Ca^{2+}-free medium +BAPTA-AM (n = 5)	BAPTA-AM (n = 5)
control	7.4	100.73 ± 0.42	99.99 ± 0.38	99.83 ± 0.70	100.21 ± 0.07
1 min	6.2	107.43 ± 0.74	103.57 ± 0.89[b]	102.89 ± 1.17[b]	106.38 ± 0.92
30 min	6.2	120.95 ± 1.46	106.27 ± 1.82[b]	106.74 ± 1.58[b]	117.20 ± 1.15
60 min	6.2	125.12 ± 2.45	105.67 ± 2.19[b]	108.92 ± 2.14[b]	120.93 ± 1.76
recovery	7.4	105.38 ± 1.82	98.18 ± 2.32	104.71 ± 3.37	110.28 ± 1.64

[a] Extracellular pH.
Mean ± SEM.
[b] $p < 0.05$ vs. control (Kruskal-Wallis test with subsequent Dunn's test).

intracellular Ca^{2+}-ions by BAPTA-AM alone did not affect the acidosis-induced cell swelling. Even buffering of intracellular Ca^{2+}-ions in Ca^{2+}-free medium had no additional inhibitory effect as compared to the response in Ca^{2+}-free medium alone. It is as yet unclear, whether the involvement of extracellular Ca^{2+}ions in acidosis-induced cell swelling is attributable (i) to net-influx of Ca^{2+}-ions through the cell membrane or (ii) to the presence of extracellular Ca^{2+} at the external plasma membrane only for the activation of transport proteins.

The response of the intracellular Ca^{2+} level to acidosis is found to vary between different cell types in the CNS. While primary cultured neurons are increasing the intracellular calcium concentration during acidosis [9], primary cultured astrocytes are not [8]. Therefore, an extra-to-intracellular flux of Ca^{2+}-ions might not necessarily be involved in the acidosis-induced swelling process. To our knowledge, however, the dependence of membrane transporter function on the presence of extracellular Ca^{2+}-ions has not been reported so far in the literature. Lohr *et al.* [2] have shown that the regulatory volume decrease after hypotonic swelling of C6 glioma cells requires the presence of extracellular Ca^{2+}-ions. An increase of the intracellular Ca^{2+}-concentration was not detectable. It might thus be possible that extracellular calcium ions are needed for activation of membrane transport proteins. Further investigations are necessary, to elucidate respective details of the involvement of Ca^{2+}-ions.

The present findings suggest in addition, that not all membrane channels and transporters contributing to the acidosis-induced glial cell swelling are also involved in the regulation of pH_i. This conclusion is based on the observation that omission of Ca^{2+}-ions from the medium had no influence on the pH_i of glial cells, neither under baseline conditions nor during acidosis. We assume, therefore, that the response of cell volume and pH_i to lactacidosis are, at least in part, mediated by activation of *different* membrane transporters. This proposal might well be in conflict with the current understanding of cell volume- and pH_i-regulation during acid exposure.

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Correspondence: Alexander Baethmann, M.D., Ph.D., Institute for Surgical Research, Klinikum Großhadern, University of Munich, Marchioninistrasse 15, D-81366 Muenchen, Federal Republic of Germany.

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Cerebral Accumulation of β-Amyloid Following Ischemic Brain Injury with Long-Term Survival

R. Pluta[1,2], **M. Barcikowska**[1], **M. J. Mossakowski**[1], and **I. Zelman**[1]

[1] Department of Neuropathology, Medical Research Centre, Polish Academy of Sciences, Warsaw, and [2] Department of Physiology and Biochemistry, Academy of Physical Education, Biała Podlaska, Poland

Summary

Deposits that are recognized by antibodies specific for the C-terminal and β-amyloid peptide (βA) but not the N-terminal sequences of the amyloid precursor protein (APP) fragments are present in the extra- and intracellular space in ischemic rat brain with 1 year survival. The immunohistochemical profile indicates that the APP in these deposits is truncated between the N-terminal and βA and terminates at the C-terminal. This process probably is reaching into the extracellular space.

Keywords: β-Amyloid; ischemic brain injury.

Introduction

Alzheimer's disease (AD) is characterized by accumulation of β-amyloid peptide (βA). It is a fragment of the much larger molecule, amyloid precursor protein (APP). βA is one of the most extensively investigated proteins of the last decade, it has only recently been recognized that the parenchymal deposits in AD brains consist of several molecular species of βA with variable N- or C-termini [2]. Rats with cardiac arrest (CA) were used as an animal model of some of the neurochemical and neuropathological deficits of AD to investigate the in vivo expression and metabolism of APP [4]. In an earlier investigation, we have found that ischemia of the brain in rats resulted in overexpression of either proteolytically cleaved fragments of the full-length APP or the entire APP molecule during 7 days survival after the incident [4,5]. These findings have prompted us to re-examine ischemic rat brain tissue after long-term survival (1 year) immunohistochemically using a panel of antibodies which recognize different fragments of APP [4].

Materials and Methods

Female Wistar rats (n = 5; 150–200 g; 3 months old) under ether anaesthesia, were subjected to 10 min CA [3]. At 1 year after CA, the rats were perfused with phosphate-buffered saline followed by 2% paraformaldehyde [3,4]. As controls, 5 sham operated rats in due time were sacrificed. For immunocytochemistry, we used antibodies raised against synthetic peptides corresponding to the aa residues of APP; monoclonal antibody (mAb) 22C11 against the N-terminal of APP, mAb 6E10 recognizing 1–17 aa residues of βA, polyclonal antibodies (pAb) SP 28 recognizing 1–28 aa residues of βA, and pAb RAS 57 against the C-terminal of APP (CAPP) [4]. Tioflavine S was used for fibrillar βA labelling.

Results

Increase in the extra- and intracellular CAPP immunoreactivity and the βA, senile plaque protein present in patients with AD, has been shown to occur in a rat model of ischemic neuronal injury (Table 1). The extracellular βA/CAPP deposits ranged from numerous small dots to irregular diffuse plaques (Fig. 1). Following ischemia, blood microvessels of all kinds and sizes showed remarkable extravasation of βA, spreading multifocally outward into the parenchyma. As well as perivascular βA accumulation, neuronal (Fig. 2) and glial cell bodies were observed filled with βA. Changes predominated in the hippocampus, cerebral and entorhinal cortex, corpus callosum and around lateral ventricles.

Discussion

We found a long-term persistent increase of βA/CAPP expression in the extracellular and intra-

Table 1. *Immunohistochemical Profile of Extra- and Intracellular APP Deposits after Global Cerebral Ischemia*

		Reactivity		
			Intracellular	
Antibodies against	Sequence	Extracellular	Neurons	Glia
N-terminal 22C11	60–100	–	–	–
β-amyloid peptide				
6E10	1–17	+	+	+
SP28	1–28	+	+	+
C-terminal RAS 57	672–695	+	+	+

Presence of staining: – no; + yes.

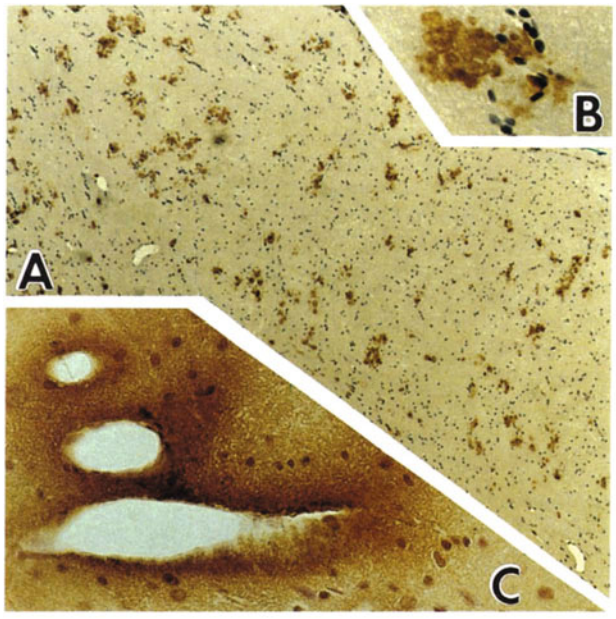

Fig. 1. Extracellular deposits of βA (*A*,*B* entorhinal cortex; mAb 6E10; ×40, ×200) and CAPP (*C* cortex; pAb RAS57; ×400) after ischemia

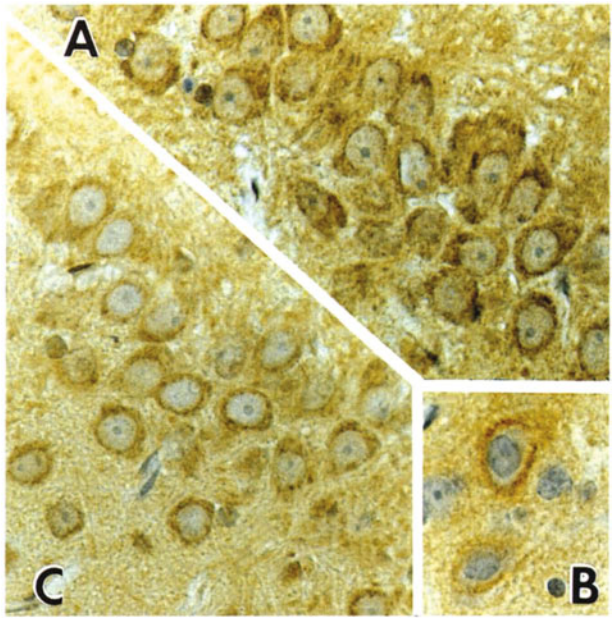

Fig. 2. Intracellular accumulation of βA (*A*,*B* hippocampus, cortex; mAb 6E10, pAb SP28; ×400) and CAPP (*C* hippocampus; pAb RAS57; ×400) after ischemia

cytoplasmic space 1 year after CA. The present findings indicate that late βA/CAPP accumulation after CA may represent a secondary injuring factor that could potentially exacerbate stroke outcome. These data provide a mechanism to explain how an environmental event, such as ischemia of the brain, can generate a similar molecular pathology as found in AD. Importantly, these studies show that βA is induced by lesions that mimic the neurochemical changes in AD. These results, when taken together with those obtained in other models of neuronal damage, clearly suggest that βA expression follows neuronal death [1].

The heavy accumulation of βA and C-terminal epitopes of APP around blood vessels suggests that either the N-terminal fragment of APP is cleaved extravascularly with the C-terminal fragment and the βA being more resistant to degradation or these vessels are permeable only for the βA and C-terminal fragments of APP after intravascular cleavage [6]. However, the absence of βA in normal brain suggests that it is not a product of the normal APP metabolism. At present, it is not possible to determine whether the βA and CAPP are generated extravascular from APP or are derived from the intravascular space [6]. In any event, the accumulation in the extra-

and intracellular space suggests that βA and CAPP fragments of APP are more resistant to further proteolysis than the N-terminal fragments. These data indicate that the deposition of βA and the C-terminal fragments of APP truncated at the position of β-secretase cleavage or close to it in diffuse plaques may be specific for ischemic brain with long-term survival. The identification of extracellular βA suggests that both the β and γ cleavages could occur outside the cell.

Unlike AD, βA/CAPP deposition in ischemic rat brain was not associated with accumulation of fibrillar amyloid. Since tioflavine S labeling was not detected in any region of the ischemic rat brains examined, the compact fibrillar structure of βA was probably not formed. On the other hand, fibrillar βA was probably formed but in an amount too small to be recognized by tioflavine S. Rats may have a higher capacity to metabolize and remove βA from the brain; however, this is not confirmed in our study. Although the rat βA homologue is reported to be as amyloidogenic as is the human, the lack of complete sequence homology between rat and human βA may also be a contributing factor. Moreover, βA deposition may occur in a variety of pathological brain processes, although it is not a simple response to generalized stress [1,4]. Finally, the possibility that 1 year of survival may be insufficient to produce detectable amounts of fibrillar βA cannot be excluded. Deposition of βA in the brain is a slow process that in humans takes decades to develop. In our experimental model time may play a central role in the maturation of βA deposits. Thus, longer study intervals or repeated insults may clarify this issue.

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Correspondence: Ryszard Pluta, M.D., Ph.D., Department of Neuropathology, Medical Research Centre, Polish Academy of Sciences, Pawińskiego 5, 02-106 Warsaw, Poland.

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Diffuse Neuronal Perikaryon Amyloid Precursor Protein Immunoreactivity in a Focal Head Impact Model

C. Van Den Heuvel[1], **S. Lewis**[2], **M. Wong**[2], **J. Manavis**[1], **J. Finnie**[1], **P. Blumbergs**[1], **N. Jones**[2], and **P. Reilly**[2]

[1] Neuropathology Laboratory, Institute of Medical and Veterinary Science, South Australia, and [2] Department of Neurosurgery, Royal Adelaide Hospital, South Australia

Summary

Amyloid precursor protein (APP) has been shown to accumulate in traumatically injured axons as early as 1 hour after injury. This accumulation may be due to interruption of fast axoplasmic transport and/or upregulation of APP synthesis. The aim of this study was to examine the neuronal cell body response to head impact using APP immunostaining in a focal non-missile head impact model.

Ten anaesthetised and ventilated 2 year old Merino ewes were subjected to graded impact in the left temporal region by captive bolt. 2 hours after impact the brain was perfused fixed with formaldehyde. The tissue was mounted in paraffin, sectioned and stained with a monoclonal antibody to APP and standard H&E stain. APP positivity was semi-quantitated using a modification of our previously described sector scoring system [1]. Widespread neuronal APP positivity was found in the cerebral hemispheres and brain stem distant from the site of focal injury in all 10 animals. The most prominent APP positivity was found in the nerve cell bodies of the impacted left cerebral hemisphere. APP positive neurons were also found within regions which were structurally normal when stained with H&E.

These results demonstrate diffuse neuronal perikaryon APP immunoreactivity following a focal head impact injury. The expression of APP within the neuronal cell body may be due to upregulation of APP synthesis or alterations in the availability of epitopes of APP. Further studies are in progress to address these hypotheses.

Keywords: Amyloid presursor protein; head impact model; immunoreactivity.

Introduction

Amyloid precursor protein (APP), a membrane spanning glycoprotein synthesised in the nerve cells and delivered to synapses by fast axoplasmic transport, has been utilized as a sensitive marker for axonal injury in both experimental animal models [4] and human head injury [2]. APP axonal immunoreactivity occurs as early as 60 minutes in a model of early axonal injury in the sheep [3] and has been documented in humans 105 minutes after injury [1]. The accumulation of APP after injury may be due to interruption of fast axoplasmic transport by axoskeletal derangement and/or following upregulation of APP synthesis within the neuronal cell body. The aim of this study was to examine APP immunocytochemical reactivity within neuronal cell bodies following traumatic head injury in the sheep head impact model already established to study axonal injury.

Method

Twelve anaesthetised (isoflurane) and ventilated 2-year-old Merino ewes were used in this study. Arterial blood pressure, intracranial pressure, cerebral blood flow, and core body temperature were monitored continuously. The animals were ventilated with a mixture of oxygen and nitrogen titrated against regular blood gas measurements to maintain a normal blood gas profile.

Sheep were placed in the sphinx position with the head resting on a support to allow free rotational and lateral movement following impact. 10 sheep were impacted in the left temporal region using a captive bolt device with a graded impact force. 2 animals served as controls (no impact). All sheep survived for 2 hours following the insult.

All brains were perfused fixed with 4% paraformaldehyde. The brains were then sectioned at 5 mm coronal intervals, embedded in paraffin, sectioned and stained with standard Haematoxylin and Eosin (H&E). The sections were incubated overnight with a monoclonal antibody to APP and then stained with 3,3-diaminobenzidine tetrahydrochloric (DAB) using avidin-biotin peroxidase method.

Microscopic assessment of the neuronal APP immunoreactivity and axonal injury was undertaken using a semi-quantitative grid system which is a modification of our previously described sector scoring system [1]. The distribution of contusions and haemorrhages were also recorded. Neuronal cell bodies with APP reactive granularity covering at lest 50% of the surface area of

Table 1. *Summary of Pathological Data*

Sheep ID	Skull fracture	Contusions		Subarachnoid haemorrhage		Total APP immunostaining		Distribution of neuronal cell body APP			
								Double hemispheres			
		Right	Left	Right	Left	Axons (% grids)	Neuronal cell body (% grids)	Right	left	Cerebellum (% grids)	Brainstem (% grids)
1	–	–	–	–	+	0	58	53	63	53	47
2	–	+	+	+++	++	0	60	60	69	38	54
3	undisplaced	++	++	++	++	1.03	70	59	75	69	93
4	undisplaced	+	++	++	++	0.02	68	58	66	82	86
5	undisplaced	+	+	++	++	0	53	40	46	60	64
6	undisplaced	+	++	++	++	2.87	70	55	76	83	74
7	depressed	–	+++	–	++	8.22	57	54	63	79	65
8	depressed	–	+++	++	++	6.92	54	38	46	71	86
9	undisplaced	+	+	++	++	0.58	58	42	46	91	95
10	–	–	+	+	+	0.38	85	82	88	93	75
Control	–	–	–	–	–	0	7	8	5	0.5	0
Control	–	–	–	–	–	0	6	8	4	0.5	8

Contusion score: + <20 mm^3.
++ 20 to 100 mm^3.
+++ >100 mm^3.

their cytoplasm were coded as positive. Any grid with >1 APP reactive cell bodies was marked positive. Neuronal cell body APP positivity was then expressed as a percentage of the total brain area examined.

Results

Neuronal APP positivity was found in the cerebral hemispheres, cerebellum and brain stem distant to the site of focal injury in all 10 impact animals. The most prominent APP positivity was found in the neuronal cell bodies of the impacted left cerebral hemisphere compared to the contralateral hemisphere (Table 1).

The neuronal cell body immunoreactivity was more diffuse and widespread than the APP positive axonal injury.

Both control animals showed small numbers of weakly APP positive neuronal cell bodies (Fig. 1).

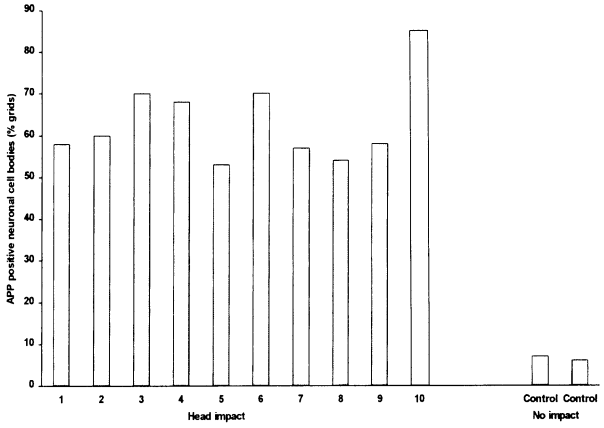

Fig. 1. Comparison of the neuronal APP response between impacted and non-impacted sheep

Disscussion

These results demonstrate diffuse neuronal perikaryon APP immunoreactivity following a focal head impact. Although neuronal APP was identified in the controls, it's presence was measured in significantly smaller quantities compared to the impact group.

The distribution of APP immunoreactivity in the neuronal cell body following trauma was found to be significantly greater than axonal expression. The expression of APP within the neuronal cell body may be due to upregulation of APP synthesis or alterations in the availability of APP epitopes. In situ hybridisation studies are in progress to address these hypotheses.

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Correspondence: Dr Peter Blumbergs, Neuropathology Laboratory, Institute of Medical and Veterinary Science, Adelaide SA 5000, Australia.

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Blood-Brain Barrier Permeability, Neutrophil Accumulation and Vascular Adhesion Molecule Expression after Controlled Cortical Impact in Rats: A Preliminary Study

M. J. Whalen, T. M. Carlos, P. M. Kochanek, and **S. Heineman**

The Safar Center for Resuscitation Research, The Brain Trauma Research Center, and Children's Hospital of Pittsburgh, Departments of Anesthesiology and Critical Care Medicine and Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, U.S.A.

Summary

Previous studies in our laboratory have shown that controlled cortical impact (CCI) produces an acute inflammatory response in rat brain, including neutrophil accumulation and upregulation of cell adhesion molecules. The purpose of this study was to compare the time course of acute inflammation to blood-brain barrier (BBB) breakdown after (CCI) in rats. *Methods:* Male Wistar rats (n = 4–7/group) were subjected to CCI (2.5 mm depth, 4 m/s) and injected with Evans-blue dye (2%, 5 ml/kg) at 30 min, 3.5 h, 7.5 h, or 23.5 h after trauma. 30 min after dye injection rats were saline-perfused. BBB permeability was measured by spectrophotometric quantitation of Evans-blue in injured brain. Alternate cryostat sections from the anterior segment of the injured hemisphere were analyzed immunohistochemically for neutrophils (MoAb RP-3 vs rat neutrophils) or E-selectin (MoAb vs E-selectin). Neutrophils and E-selectin-positive blood vessels were quantitated by light microscopy in 100× cortical and hippocampal fields. *Results and Conclusions:* BBB breakdown was maximal *early* after CCI, whereas maximum E-selectin upregulation (8 h) and neutrophil accumulation (24 h) occurved later. Events other than acute inflammation initiate BBB permeability after CCI. Acute inflammation may contribute to BBB permeability at 4 h to 24 h after CCI.

Keywords: Adhesion molecule; blood-brain barrier; controlled cortical impact; E-selectin; neutrophil accumulation.

Introduction

Numerous studies in animal models of traumatic brain injury (TBI) have demonstrated an acute inflammatory response in the brain after injury, characterized by production of cytokines [1], upregulation of adhesion molecules and accumulation of neutrophils in injured brain [2]. Endothelial (E)-selectin mediates initial leukocyte attachment to activated endothelium. As part of the acute inflammatory response, E-selectin is upregulated on cerebrovascular endothelium by 4 h after CCI in rats [2].

Neutrophils have been implicated in the pathogenesis of BBB damage in CNS infection [3]. The contribution of neutrophils to secondary injury after TBI is, however, less clear [5]. Although neutrophil accumulation was temporally and spatially associated with BBB breakdown after FPI [4], the role of neutrophils in the pathogenesis of BBB damage (or repair) has not been investigated in animal models of TBI. In this study, we compared the time course of BBB permeability with cerebrovascular E-selectin expression and brain neutrophil accumulation after CCI in rats. The results of this study do not support a role for neutrophils in the pathogenesis of *early* BBB injury, during the initial 4 h after CCI.

Methods

Anesthetized, mechanically ventilated male Wistar rats (n = 4–7 per group) were subjected to controlled cortical impact [6], using a 2.5 mm depth of penetration and 4 m/s impact velocity. Rats were then randomized to one of four treatment groups. At 30 min (group 1), 3.5 h (group 2), 7.5 h (group 3), or 23.5 h (group 4) after CCI, rats were anesthetized and Evans-blue (2%, 5 ml/kg) was injected intravenously over 2 min. Thirty min after dye injection, rats were perfused with 250 cc of normal saline. Brains were sectioned coronally through the center of the contusion produced by CCI. The caudal segment was placed in mounting media and used

for immunohistochemistry. Right and left hemispheres from the rostral segment were weighted, and Evans blue was extracted over 5 d in N,N dimethyl formamide for 5 d. Evans-blue was quantitated spectrophotometrically at 620 nm and expressed as absorbance units/g brain.

For immunohistochemistry, cryostat sections 6 μm thick of the caudal segment were stained with either mouse anti-rabbit E-selectin or MoAb RP-3 (anti-rat neutrophil), and detected with biotinylated secondary antibodies and ABC reagent (Vector Labs, Burlingame, Ca.). All immunohistochemical data were analyzed by an observer blinded to treatment group. Neutrophil accumulation in brain, and E-selectin expression on cerebrovascular endothelium was quantitated by counting the number of positively stained neutrophils or blood vessels in all 100× fields within cortex (regions including and adjacent to the lesion) and subcortex (hippocampus/thalamus, i.e., regions remote from the contusion). Corresponding regions ipsilateral and contralateral to the injured side were scored. An index of positively stained cells per 100× field was thus obtained for each rat.

Rectal temperature, brain temperature, and MABP were monitored continuously and recorded 10 min prior to CCI. Arterial pH, $PaCO_2$, PaO_2, glucose, hemoglobin (Hgb), and absolute neutrophil count (ANC) were measured 10 min before CCI. $PaCO_2$ was maintained between 35 and 45 torr, PaO_2 between 100–200 torr.

Physiologic variables, Evans-blue data, and immunohistochemistry data were analyzed by one was ANOVA and the appropriate post hoc tests. Results are mean ± SEM. $P < 0.05$ was required for significance.

Results

All rats survived the trauma protocol. There were no differences among groups in body temperature, brain temperature, MABP, pH, $PaCO_2$, PaO_2, blood glucose, or HCT prior to CCI. Data for BBB permeability, E-selectin expression, and neutrophil accumulation are shown in Table 1. BBB permeability was maximal at 31 min and 4 h after CCI, and was decreased by 50% at 8 h and 24 h after CCI. E-selectin expression and neutrophil accumulation were confined to injured brain hemispheres in all rats. E-selectin was first detected at 4 h, and was maximal at 8 h after CCI in ipsilateral cortex and subcortex. E-selectin expression was decreased in both regions at 24 h. Neutrophils were detected in areas of brain hemorrhage in some of the rats at 30 min. Neutrophils were first detected in brain parenchyma without hemorrhage at 4 h in both cortex and subcortex ipsilateral to injury. Neutrophil accumulation was maximal at 24 h in cortex, and at 8 h and 24 h in subcortex. Thus, peak neutrophil accumulation occurred during *resolution* of BBB damage, at 8 h and 24 h after CCI (Table 1).

Discussion

Our results demonstrate that after controlled cortical impact in the rat, blood-brain barrier disruption is maximal at 1 hour after injury. However, E-selectin is not detected on cerebrovascular endothelium at this early time after trauma, and only a few neutrophils associated with areas of hemorrhage were detected in brain 1 hour after injury. E-selectin upregulation was maximal at 8 hours, and brain neutrophil accumulation was maximal at 8 and 24 hours, at which time BBB permeability was decreased. As maximum BBB permeability preceded the influx of neutrophils into injured brain, it is likely that events other than acute inflammation (i.e., E-selectin expression and neutrophil accumulation) mediate the initial large increase in BBB permeability *early* after CCI in the rat.

Neutrophils have been shown to mediate BBB permeability in animal models of CNS infection [9]. However, in traumatic brain injury produced by weight drop, neutropenia failed to attenuate brain edema early after injury [11]. Our results suggest that vascular injury and tissue damage after impact, which initiates BBB permeability, may serve as an important signal for the subsequent acute inflammatory response. Experiments designed to assess the contribution of neutrophils to BBB permeability up to 24 h after TBI are currently in progress.

Table 1. *Time Course of BBB Permeability, Neutrophil Accumulation, and Cerebrovascular E-Selectin Upregulation after CCI*

Time after CCI	Evans blue	RP-3 (cortex)	RP-3 (subcor)	E-sel (cortex)	E-sel (subcor)
30 min[1]	0.40 ± 0.15[a]	1.75 ± 0.84[b]*	0.23 ± 0.17[b]*	0.00 ± 0.00[c]	0.00 ± 0.00[c]
4 h	0.36 ± 0.12	6.00 ± 1.55*	1.43 ± 0.58*	0.64 ± 0.11	2.65 ± 0.60**
8 h	0.21 ± 0.02	11.25 ± 0.79**	8.00 ± 2.02*‡	13.71 ± 4.06**	4.58 ± 1.92**
24 h	0.20 ± 0.02	17.08 ± 2.79	8.50 ± 2.89	2.89 ± 0.93	1.07 ± 0.37

[1] Evans blue in sham operated (craniotomy only) rats at 30 min = 0.26 ± 0.05 Abs U/g brain.
[a] abs units/g brain; [b] RP-3-positive cells/100× field; [c] E-selectin-positive vessels/100× field.
*$p < 0.05$ vs. 24 h; **$p < 0.05$ vs. 30 min; ‡ $p < 0.05$ vs. 30 min and 4 h.

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Correspondence: Patrick M. Kochanek, M.D., Safar Center for Resuscitation Research, 3434 Fifth Avenue, Pittsburgh, PA 15260, U.S.A.

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Intracranial Pressure, Cerebral Perfusion Pressure, and SPECT in the Management of Patients with SAH Hunt and Hess Grades I–II

G. Gambardella[1], **F. De Blasi**[1], **G. Caruso**[1], **A. Zema**[1], **F. Turiano**[1], and **D. Collufio**[2]

[1] Department of Neurosurgery, "Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria, Italy, and [2] Neurosurgical Clinic, University of Messina, Italy

Summary

The objective of our study was to examine the course of intracranial pressure (ICP) in patients with SAH Hunt and Hess grades I–II and to analyze the relationship between ICP, cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). Twenty-three patients were studied. ICP, arterial blood pressure (ABP) and CPP were continuously recorded. The measurements of CBF with single-photon emission computed tomography (SPECT) were performed in fifteen patients, who showed TCD flow velocities exceeding 120 cnlJsec. In the first two days after SAH four patients (15%) showed a normal ICP, six (25%) patients had a moderate increase of ICP ranged from 15 to 25 mm Hg and thirteen (60%) patients had ICP values higher than 25 mm Hg. Seven of these patients, with ICP values higher than 40 mm Hg, showed clinical signs of delayed ischaemia. After the treatment with osmotic diuretic, ICP decreased and a clinical improvement was observed with the exception of one patient. In this patient, the SPECT study showed middle cerebral hypoperfusion concordant with the clinically ischaemic hemisphere. Our study showed the utility of the monitoring of these parameters in patients with lower grade SAH, because it allows the modulation of the therapeutic approach and defines the onset of neurological deficits secondary to cerebral ischaemia in all grades of SAH.

Keywords: Cerebral ischemia; SPECT; subarachnoid haemorrhage.

Introduction

Delayed ischaemic disfunctions (DID) are one of the main complications following subarachnoid haemorrhage (SAH) [10,18]. The pathogenetic mechanisms leading to delayed cerebral ischemia are complex. It is well-known that intracranial pressure (ICP) plays a determinant role in the development of secondary damage. Increased ICP is often observed after SAH, and the resulting reduction of the cerebral perfusion pressure (CPP) is probably the most important factor to consider in the management of patients with SAH. A number of experimental and clinical studies have correlated the reduction of CPP due to increased ICP and/or decreased arterial blood pressure (ABP) with delayed ischaemia after SAH [2,6,14]. But few studies have compared ICP, CPP, CBF and delayed ischaemia in patients with lower grade SAH. The goal of our study was to examine the course of ICP in patients with SAH Hunt and Hess grades I–II and to analyze the relationship between ICP, CPP, and CBF.

Subjects and Methods

Twenty-three consecutive patients (12 females and 11 males) with SAH grades Hunt-Hess I–II admitted to our department were studied. The mean age of patients was 57 + 8 years (range 33 to 71 years). On admission, the CT scan was used to exclude the presence of intraparenchymal haematomas and CT controls were performed every 48 hours to detect ventricular enlargements. In all patients cerebral panangiography was performed. ABP and ICP were monitored during first nine days, and CPP was calculated. ICP was recorded using an intraparenchymal device (Codman or Camino) inserted in the right frontal lobe. For the purpose of the present analysis of ICP, the patients were divided into three groups based on highest mean ICP values showed during the first two days after SAH. In the first group we included patients with normal ICP, in the second group ICP ranged between 15 and 25 mm/Hg, in the third group we considered the patients with ICP higher than 25 mm Hg.

Transcranial Doppler Monitoring

A TCD study was performed every 24 hours or more frequently if blood flow velocities showed a critical increasing or the clinical status was unstable. For TCD ultrasonography we used a 2-MHz probe over the temporal bone window. The systolic, diastolic, and mean flow velocities in the ICA, MCA and ACA were investigated. TCD monitoring was considered compatible with vasospasm when arterial blood flow velocity reached or exceeded 120 cm/sec [1,3,13,20].

SPECT Measurements

In fifteen patients with significant arterial flow velocities increasing, single-photon emission computed tomography with technetium-99m hexamethylprophylene amine oxime (99mTc HM-PAO SPECT) was performed. This technique provide semiquantitative regional count data displayed on colored tomographic maps, following an intravenous bolus injection of 500 MBq of Tc-99m HM-PAO and acquired with a GE400AC Starcam gamma camera [5]. Changes in regional cerebral uptake were correlated, on colored maps, to that of the cerebellum (cerebral/cerebella ratio). These were compared with a normal average range studied, from a hospital-based population of 10 consecutive patients without a SAH history.

Therapy

In order to maintain mean arterial blood pressure (MABP) between 90–110 mm Hg, we used adequate pharmacological treatment with plasma expanders or furosemide. All patients were treated with an intravenous administration of nimodipine (10 ml/h). Diuretic osmotic therapy was used to maintain ICP within normal range. Standard deviation and Student's t-test were used for statistical evaluation of the findings.

Results

On admission, according to Hunt and Hess's clinical grading we found eight patients grade 1 and fifteen patients grade 2. The severity of SAH on CT scan was rated according to the Fisher's grading system as follows, nine cases grade II and 14 cases grade III. In the first two days after SAH four patients showed a normal ICP and were included in the first group, six patients had a moderate increase of ICP between 15 and 25 mm Hg (second group) and thirteen patients had ICP values higher than 25 mm Hg. Seven of these showed an early severe intracranial hypertension (>40 mm Hg) with an increase of arterial flow velocity, beginning at the third or the fourth day after bleeding. These patients developed clinical signs of delayed ischaemia, with deterioration of consciousness level in five and with lateralizing deficits in three. After the treatment with osmotic diuretic, ICP decreased lower than 25 mm Hg and thereafter also a clinical improvement was observed. In all patients, except one, we obtained normal ICP when TCD studies showed the maximum incidence of vasospasm (Fig. 1). Therefore ICP normalization allowed to maintain CPP in the physiological range and to contrast delayed ischaemic damage (Fig. 2). No patient had evidence of vasospasm in the first forty-eight hours after SAH. However, fifteen patients had elevated TCD velocities more than 200 cm/s four days after bleeding. In patients with increased arterial velocity SPECT study showed normal perfusion with the exception of one. This patient, with delayed ischaemic deficits, had middle cerebral hypoperfusion concordant with the clinically ischaemic hemisphere. In this case the osmotic therapy was not able to reduce ICP, that remained higher than 40 mm Hg when arterial flow velocity was higher than 200 cm/s.

Discussion

Morbidity and mortality after aneurysmal SAH often results from ischaemia secondary to vasospasm. Delayed cerebral ischaemia, nevertheless, is not only determined by the entity and by the distribution of the vasospasm, but also by other factors: ICP, blood viscosity, cardiac output, and the extent of collateral

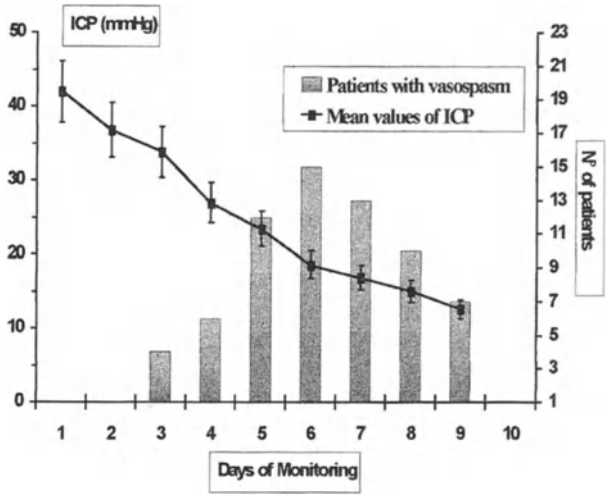

Fig. 1. The graph proves that ICP is near to physiological values when TCD showes an important increasing of CBV more than 120 cm/sec

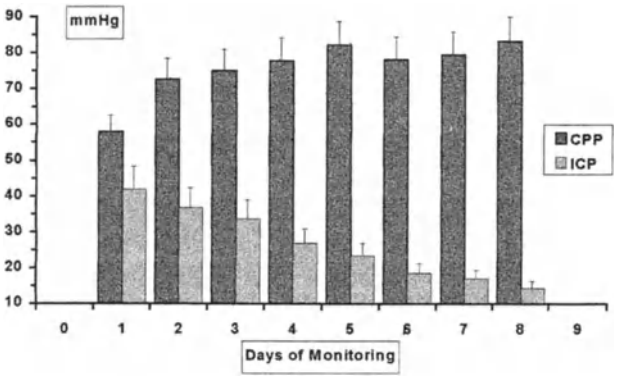

Fig. 2. The course of ICP and CPP during first nine days after SAH

circulation. However, a complete monitoring of the cerebrovascular parameters is considered today of great utility in preventing neurological deficits due to cerebral ischaemia. It's well-known that the intracranial hypertension plays a determinant role in the development of secondary damage and the resulting decrease of CPP is probably the most important factor to consider in the management of patients with SAH. In fact, increasing CPP is the only usable therapeutic method available at the present to prevent and also to reserve neurological deficits due to vasospasm [4,9,12,21]. Augmentation of CPP via induced hypertension or hypervolemia is the method most widely used in patients with SAH [4,9]. This therapeutic approach has been considered safe and effective to improve clinical outcome of these patients. In fact it showed the ability to improve CBF through an increase of the CPP, a reduction of blood viscosity, a sustained cardiac output and a recruitment of the collateral microcirculation [16]. However, this therapeutic method may result in vasogenic brain edema and intracranial hypertension, when autoregulation of CBF is impaired during vasospasm or after SAH [8,17,19]. For this reason CPP must be maintained, not only by increasing MABP, but also by reducing ICP. While the ICP monitoring in patients with high grade Hunt and Hess SAH is an usual procedure, in patients with grade I–II ICP monitoring is rarely used. The goal of our study was to evaluate the course of the ICP in patients affected by low grade SAH and to analyze the relationship between ICP, CPP, CBF and neurological deterioration.

Our data indicate clearly that patients with SAH Hunt and Hess grades I–II showed an early significant increase of ICP before the onset of vasospasm. The continuous monitoring of ICP allowed a rational control of the treatment with osmotic diuretics therapy, that was capable of reducing ICP and maintaining CPP within physiological range. This therapeutic strategy permitted, through an increase of ABP and a reduction of intracranial hypertension, a control of CPP. In our opinion, it prevented delayed ischaemic damage due to cerebral hypoperfusion. Our findings also showed a good relationship between ICP, CPP and CBF. A neurological deterioration with cerebral hypoperfusion has been observed, when the treatment with osmotic diuretics was not sufficient to reduce ICP and to maintain CPP in the physiological range.

In conclusion, our study demonstrated the utility of monitoring of ICP and CPP, particularly in the management of patients affected by SAH Hunt and Hess grades I–II, because it allows the physician to modulate the therapeutic approach and to closely monitor the onset of the neurological deficits secondary to cerebral ischaemia.

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Correspondence: Giuseppe Gambardella, M.D., Divisione di Neurochirurgia, Ospedali Riuniti "Bianchi-Morelli-Melacrino", I-89100 Reggio di Calabria, Italy.

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Hyperglycemia Induces Progressive Changes in the Cerebral Microvasculature and Blood-brain Barrier Transport During Focal Cerebral Ischemia

N. Kawai[1], **R. F. Keep**[2], **A. L. Betz**[2], and **S. Nagao**[1]

[1] Department of Neurological Surgery, Kagawa Medical University, Kagawa, Japan, and [2] Department of Surgery (Neurosurgery), University of Michigan, Ann Arbor, MI, U.S.A.

Summary

Hyperglycemia generally enhances cerebral ischemic injury. Most attention on a mechanism has focused on the adverse effect of increased lactate production (acidosis) leading to neuronal injury. The effects of hyperglycemia on another possible primary target, the cerebral microvasculature, is examined in this study. Focal cerebral ischemia was achieved by thread occlusion of the middle cerebral artery (MCA). Preischemic hyperglycemia was induced by intraperitoneal administration of 50% of D-glucose solution. In contrast to normoglycemic controls, glucose-injected rats showed a well demarcated pale infarct after 2 or 4 hours of ischemia reflecting a reduction in cerebral plasma volume (CPV) to 73 ± 9 and 55 ± 6% of contralateral by 2 and 4 hours respectively. Cerebral blood flow (CBF) measured by laser-Doppler flowmetry indicated that after the initial decline in CBF with MCA occlusion, hyperglycemia led to a further progressive reduction during ischemia. Blood-brain barrier transport measured by permeability surface area (PS) product for glutamine was reduced in both normoglycemic and hyperglycemic rats. However, the decline was greater in the hyperglycemic rats. Hyperglycemia induces progressive cerebrovascular changes and affects blood-brain barrier transport during focal cerebral ischemia. These changes may contribute to the adverse effects of hyperglycemia in stroke.

Keywords: Acidosis; blood-brain barrier; hyperglycemia; ischemia.

Introduction

Hyperglycemia generally enhances cerebral ischemic injury [1]. Most attention on a mechanism has focused on the potentially adverse effects of neuronal acidosis due to increased lactate production [2]. However, the effects of lactate itself to brain damage also has been questioned since brain lactate does not correlate with ischemic damage [3].

In our early studies on rat middle cerebral artery (MCA) occlusion, it was noted that hyperglycemic animals had a very well demarcated pale infarct after 4 hours of ischemia in contrast to normoglycemic rats [4]. In this study, we examined whether this apparent difference was due to cerebrovascular effects of hyperglycemia, including temporal changes in blood volume, cerebral blood flow during ischemia and also examined whether those changes are associated with altered blood-brain barrier transport.

Materials and Methods

Animal Preparations and Experimental Protocols

Adult male Sprague-Dawley rats weighing 250–300 g were used for all experiment. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The MCA was occluded using the suture method of Zea Longa *et al.* [5]. Acute hyperglycemia was induced by intraperitoneal administration of 2 ml of 50% D-glucose 20 minutes prior to MCA occlusion. Normoglycemic rats received a similar osmotic load of mannitol. These rats were used to determine cerebral plasma volume (CPV) using ^{3}H-inulin after 1, 2 and 4 hours of permanent occlusion and cerebral blood flow (CBF) was continuously measured by laser-Doppler flowmetry (LDF) throughout 2 hours of MCA occlusion. Finally, to determine the effects of hyperglycemia on blood-brain barrier transport, permeability surface area (PS) products were measured for ^{14}C-glutamine.

Cerebral Plasma Volume

Twenty μCi of ^{3}H-inulin, a plasma volume marker, was injected into the femoral vein and allowed to circulate for 2 minutes. At the

end of experiment, plasma and both ipsilalteral and contralateral cortex from the center of the MCA distribution were sampled. The samples were weighed and counted in a scintillation counter. The CPV was calculated as (dpm/g brain)/(dpm/ml plasma).

Cerebral Blood Flow Measurement

For continuous CBF measurement, a LDF monitor (model BPM^2 system, Versamedics Inc.) equipped with a probe of 0.7 mm in diameter was used. Flow was measured in an ischemic core area located 6 mm lateral to the midline and 1 mm posterior to the bregma. A stable baseline CBF reading was obtained for at least 20 minutes before MCA occlusion. LDF values were averaged over 10-second intervals and recorded every 20 minutes during the occlusion. The CBF values were expressed as percentage of the baseline value.

Glutamine Influx Rate Constant

For measurement of glutamine uptake, rats received a bolus injection of [^{14}C]-glutamine (15 μCi) and arterial blood was withdrawn at a constant rate using a peristatic pump. Three minutes later, the rats received an intravenous injection of [^{3}H]-inulin (20 μCi) which was allowed to circulate for 2 minutes before a terminal arterial sample was obtained and rats decapitated. Radioisotope count of both blood and tissue samples was determined using a two channel scintilation counter. The influx rate constant (K_1) can be calculated as:

$$K_1 = C_{ev}(T) / \int C_a dt$$

where $C_{ev}(T)$ is the extravascular concentration of isotope at time T and $\int C_a dt$ is the integral of the arterial tracer concentration from time 0 to time T. $C_{ev}(T)$ was calculated from total tracer counts $C_{tot}(T)$ in brain samples, final tracer plasma concentration $C_{pl}(T)$ and the plasma volume PV:

$$C_{ev}(T) = C_{tot}(T) - [PV * C_{pl}(T)]$$

Results

In hyperglycemic rats, there was a demarcated infarct in rats after 2 hours of MCA occlusion and a more evident white infarct after 4 hours of occlusion. This was not evident in normoglycemic rats. The cause of this difference appears to be blood volume. In hyperglycemic rats, the CPV of the ischemic tissue progressively declined with time, being 89 ± 5% of contralateral at 1 hour, but 73 ± 9 and 55 ± 6% at 2 and 4 hours respectively (Fig. 1). In contrast, there was no significant differences between ipsilateral and contralateral tissue at any time points in normoglycemic rats.

Hyperglycemia was also associated with changes in ischemic CBF. After 20 minutes of MCA occlusion, laser-Doppler flow was reduced to 16 to 18% of the baseline in normoglycemic and hyperglycemic rats. However, while flow in the normoglycemic rats remained constant over the next two hours, that in the hyperglycemic rats showed a progressive decline over the first hour following occlusion (to 9%; Fig. 2). The differences in flow between the two groups were significant at the time points between 40 and 120 minutes.

The PS product for glutamine was markedly reduced in hyperglycemic rats, being 39 ± 3% of contralateral at 1 hour, but 19 ± 2 and 15 ± 2% at 2 and 4 hours respectively. In normoglycemic rats, the PS product for glutamine was also reduced with time, but the decline was smaller at each time point.

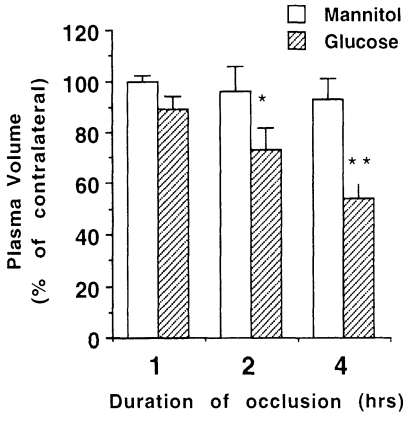

Fig. 1. Cerebral plasma volume in the ischemic core samples from glucose- and mannitol-injected rats. Measurements were made with ^{3}H-inulin after 1, 2 and 4 hours of MCA occlusion and are expressed as a percent of non-ischemic (contralateral) tissue. Values are mean ± S.E.; n = 5–10; * and ** indicate significant difference between the two groups at the $p < 0.01$ and 0.001 levels respectively

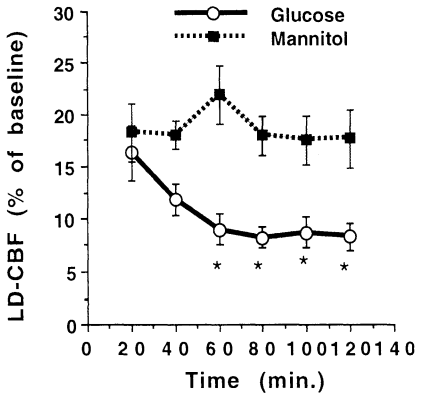

Fig. 2. Cerebral blood flow in the ischemic core area from glucose- and mannitol-injected rats. Measurement were made with laser-Doppler flowmetry throughout 2 hours of MCA occlusion and are expressed as a percent of preischemic value. Values are mean ± S.E.; n = 4; * indicates a significant difference from that value at 20 min at the $p < 0.05$ level

Discussion

A well demarcated pale infarct was observed after 2 or 4 hours of ischemia in hyperglycemic rats. This appears to be due to a decrease in cerebral blood volume in the ischemic tissue as shown in CPV measurement. As well as changes in cerebral blood volume, the laser-Doppler flow measurements indicate that hyperglycemia also affects CBF during ischemia. Although marked reductions in CBF during reperfusion have been reported in hyperglycemic animals [6,7], changes during ischemia have not [7]. This may reflect difficulties due to inter-animal variability, whereas our continuous recording with laser-Doppler flowmetry show a progressive decline in CBF in hyperglycemic rats.

The mechanism by which hyperglycemia modifies cerebral perfusion and ischemic vascular volume has still to be elucidated. The changes in the vascular volume could result from plugging, compression or constriction of the vasculature. Paljärvi *et al.* [8] examined the effect of acute hyperglycemia on endothelial cell morphology after global cerebral ischemia and reperfusion and that brain microvessel outer diameter was unaffected. Also, in our preliminary studies on rat MCA occlusion, the degree of edema was not significantly different between hyper- and normoglycemic rats suggesting that the effect on cerebral blood volume is not due to compression. In a model of global ischemia and reperfusion, Paljärvi *et al.* [8] found that reperfusion caused marked endothelial cell swelling and decreased luminal diameter in hyperglycemic rats while having little effect in normoglycemic rats. They postulated that such changes might hamper postischemic reperfusion and could lead to complete plugging of vessels. The effect of hyperglycemia on endothelial cell swelling during focal ischemia has not been examined.

The decline in ischemic CBF in hyperglycemic rats occurred over the first hour of MCA occlusion and, thus, appears to precede the decline in CPV that was only first observed at two hours. This could mean that the change in CBF leads to the change in CPV since well defined CBF thresholds are of critical importance in the development of irreversible ischemic damage (9). Alternatively, both CBF and cerebral blood volume changes may reflect progressive endothelial damage.

Hyperglycemia induces progressive cerebrovascular changes and affects blood-brain barrier transport during focal cerebral ischemia. These changes may contribute to the adverse effects of hyperglycemia in stroke.

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Correspondence: Nobuyuki Kawai, M.D., Department of Neurological Surgery, Kagawa Medical University, 1750-1 Ikenobe, Miki-Cho, Kita-gun, Kagawa 761-07, Japan.

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Effects of Mild and Moderate Hypothermia on Cerebral Metabolism and Glutamate in an Experimental Head Injury

K. Mori[1], **M. Maeda**[1], **M. Miyazaki**[2], and **H. Iwase**[2]

[1] Department of Neurosurgery and [2] Casualty Center, Juntendo University, Izunagaoka Hospital, Japan

Summary

In this study we sought to determine the optimal brain temperature for treating compression-induced cerebral ischemia. Six cats each were treated with a deep-brain temperature of 37°C (control), 33°C (mild hypothermia), or 29°C (moderate hypothermia). Intracranial pressure (ICP) and cerebral blood flow (CBF) were monitored, as were arteriovenous oxygen difference ($AVDO_2$) and cerebral venous oxygen saturation ($S_{cv}O_2$). The cerebral metabolic rate of oxygen ($CMRO_2$) was calculated. Extracellular glutamate concentration was measured by microdialysis. ICP was increased by inflation of an epidural balloon until CBF became zero. This ischemia was maintained for 5 min, after which the balloon was deflated.

Mild hypothermia showed coupled CBF-metabolic supression, but moderate hypothermia resulted in disproportionately increased $AVDO_2$, decreased $S_{cv}O_2$, and low $CBF/CMRO_2$ (relative ischemia). Reactive hyperemia after balloon deflation was decreased after both mild and moderate hypothermia, as was the tissue volume showing Evans blue dye extravasation. Extracellular glutamate increased in control animals, an effect most effectively supressed in the mild hypothermia group. These data favor 33°C as the optimal temperature for treating compression-related cerebral ischemia.

Keywords: Cerebral metabolism; glutamate; head injury; hypothermia.

Introduction

Increased intracranial pressure (ICP) after head injury is unfavorable for prognosis since it decreases cerebral perfusion pressure. Ischemic brain damage is considered the major cause of poor outcome in severe head injury [3,6]. Since Busto [1] have shown that small differences in brain temperature can determine the extent of ischemic brain injury, many reports have shown a therapeutic effect of hypothermia in treating cerebral ischemia and head injury [2,4]. We sought to determine optimal therapeutic brain temperature in compression-induced cerebral ischemia in relation to cerebral blood flow (CBF), metabolism, extracellular glutamate, and vascular permeability.

Material and Methods

Eighteen cats were anesthetized by continuous infusion of ketamine (10 mg/kg/hr) and pancuronium bromide (1 mg/kg/hr). A tracheostomy was performed for mechanical ventilation to maintain arterial carbon dioxide tension ($PaCO_2$) at 35 to 45 mm Hg. The electroencephalogram (EEG) was recorded over the left sensorimotor cortex. CBF was measured by a hydrogen clearance method using a platinum electrode in the right thalamus. ICP was monitored by a fiberoptic transducer inserted into the right occipital lobe. The superior sagittal sinus was cannulated with a catheter to sample cerebral venous blood for calculation of arteriovenous oxygen difference ($AVDO_2$), cerebral venous oxygen saturation ($S_{cv}O_2$), cerebral metabolic rate of oxygen ($CMRO_2$), and cerebral blood flow equivalent ($CBF/CMRO_2$). A microdialysis probe (4 mm membrane, 0.22 mm outer diameter; Eicom, Kyoto, Japan) was placed stereotactically in the left caudate nucleus. Extracellular glutamate concentrations in the dialysate were determined by high-performance liquid chromatography. Deep brain temperature was monitored by a needle probe in the left occipital lobe. The animals were divided into three equal groups according to deep-brain temperature (controls 37°C; mild hypothermia, 33°C; and moderate hypothermia, 29°C). The target deep brain temperature was maintained by surface cooling with water-circulating blankets. After baseline measurements were completed, a rubber balloon in the right epidural space was inflated to gradually increase ICP until CBF became zero (global ischemia). Complete ischemia was maintained for 5 min, after which the balloon was quickly deflated. All parameters were recorded for 6 hr. The blood-brain barrier was assessed quantitatively by intravenously injecting Evans blue dye 2 hr before the end of experiment. The volume of tissue stained by dye and/or showing erythrocyte extravasation was measured by an imaging system (MCID; Microcomputer Imaging Device Imaging Research Inc., Ontario).

Results

Physiologic Variables

The moderate hypothermia group showed a significant decrease in plasma K^+ concentration and heart rate (Dunnett: $P < 0.01$).

Cerebral Blood Flow and Metabolism

Time courses of CBF and CBF equivalent (CBF/$CMRO_2$) before and after balloon compression are illustrated in Fig. 1. Before balloon inflation, CBF of animals treated with control temperature, mild hypothermia, and moderate hypothermia were 48 ± 4.8, 21 ± 2.6, and 11 ± 1.3 mL/100 g/min. CBF in mild hypothermia represented a reduction of 56%, (Dunnett: $P < 0.01$), and moderate hypothermia, a reduction of 77%, (Dunnett: $P < 0.01$). Moderate hypothermia significantly increased $AVDO_2$ (Dunnett: $P < 0.01$), decreased $S_{cv}O_2$, and produced a low CBF/$CMRO_2$ ratio (relative ischemia; Fig. 1B). After balloon inflation and deflation, all three groups showed reactive hyperemia. This postischemic reactive hyperemia was significantly suppressed in the mild and moderate hypothermia groups (Dunnett: $P < 0.01$). CBF then decreased to 50% of pre-inflation values and $S_{cv}O_2$ decreased, representing a period of postischemic hypoperfusion in which CBF/$CMRO_2$, $S_{cv}O_2$, and $AVDO_2$ did not differ significantly between the three groups.

Extracellular Glutamate Concentration

Time course of change in extracellular glutamate release before epidural balloon inflation and after deflation is illustrated in Fig. 2A. Extracellular glutamate concentration increased in the control animals after the decompression period (to $3.8 \pm 1.72\,\mu M$), an effect most effectively supressed in the mild hypothermia group ($1.0 \pm 0.46\,\mu M$).

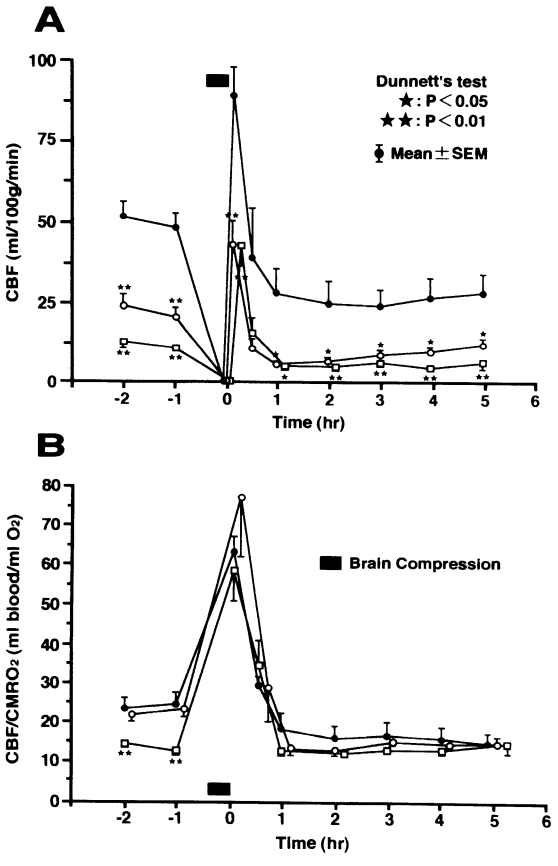

Fig. 1. CBF (A) and cerebral blood flow equivalent (CBF/$CMRO_2$) (B) over time in animals whose deep brain temperature was maintained at 37°C(●), 33°C(○), or 29°C(□)

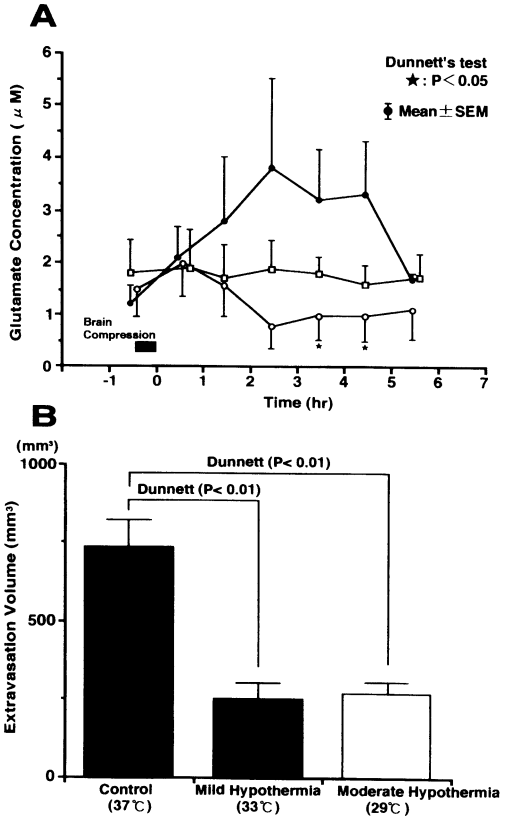

Fig. 2. Two factors in ischemic damage in animals whose deep brain temperature was maintained at 37°C(●), 33°C(○), or 29°C(□). (A) Extracellular glutamine concentration. (B) Vascular permeability (tissue volume showing Evans blue dye and/or erythrocyte extravasation)

Evans Blue Dye and Erythrocyte Extravasation

The observed tissue volumes of Evans blue dye and/or erythrocyte extravasation were 729 ± 89 mm^3 in the control group, 247 ± 56 mm^3 in the mild hypothermia group, and 267 ± 35 mm^3 in the moderate hypothermia group, being significantly; smaller in the mild and moderate hypothermia groups than in controls (Dunnett: $P < 0.01$ Fig. 2B).

Discussion

Cerebral ischemia is a cause of poor outcome in severe head injury and a focus of preventive treatment [3,6]. Our experimental model simulates events in a patient with severe head injury and secondary cerebral ischemia whose intracranial mass lesion is evacuated surgically. Before epidural balloon inflation, the mild hypothermia group (33°C) showed coupled CBF and $CMRO_2$ supression (56%). However, moderate hypothermia (29°C) prior to brain compression increased $AVDO_2$, produced a low CBF equivalent, and decreased $S_{cv}O_2$, indicating an ischemic condition. After balloon inflation and deflation, all three groups showed reactive hyperemia which, however, was suppressed significantly by mild and moderate hypothermia. We believe a hypothermia-related decrease in reactive hyperemia contributes to the reduction in blood-brain barrier damage (dye and erythrocyte extravasation) after compression. These data support the induction of mild hypothermia before decompressive surgery to prevent reactive hyperemia after decompression.

In all groups after reactive hyperemia, CBF decreased to 50% of pre-inflation values, accompanied by decreased $S_{cv}O_2$. This phenomenon, known as delayed postischemic hypoperfusion, continued to the end of the experiment. This postischemic hypoperfusion is believed to cause neuronal damage [3]. Amino acids such as glutamate and aspartate have known neurotoxic effects at glutaminergic receptors resulting in increases of intracellular calcium which produce neuronal injury [5]. In the present study, the increase of extracellular glutamate concentration during postischemic hypoperfusion was most effectively suppressed by mild hypothermia. The difference in glutamate release inhibition between mild and moderate hypothermia appears to reflect the ischemic condition due to moderate hypothermia itself.

The present data suggest mild hypothermia (33°C) as the best condition for treating severe head injury in terms of CBF and metabolism, release of extracellular excitatory amino acids, and cerebral vascular permeability.

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Correspondence: Kentaro Mori, M.D., Ph.D., Department of Neurosurgery, Juntendo University Izunagaoka Hospital, 1129 Nagaoka, Izunagaoka-cho, Tagata-gun, Shizuoka 410-22, Japan.

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Effects of Systemic Hypothermia and Selective Brain Cooling on Ischemic Brain Damage and Swelling

C.-K. Park, S.-S. Jun, M.-C. Kim, and **J.-K. Kang**

Department of Neurosurgery, Kang Nam St. Mary's Hospital, Catholic University Medical College, Seoul, Korea

Summary

The present study investigates the neuroprotective effects of temporary mild systemic hypothermia and selective brain cooling against focal cerebral infarction in the rat and the changes of cortical blood flow, and compares these two treatment modalities. In permanent middle cerebral artery (MCA) model, the treatments were induced 15 min following the artery occlusion. The animals were kept at the desired rectal or brain temperature (about 32°C) for 30 min (each, n = 6) and for 1 hr (each, n = 6), and then allowed to rewarm spontaneously, whereas control animals were kept at normothermia throughout the experiment. The volumes of brain infarction and edema were assessed 24 hr post-occlusion. The blood flow of the dorsolateral cortex was monitored by Laser-Doppler flowmetry (LDF) in the other experiments. Hemispheric infarct volume was attenuated only in the animals treated for 1 hr with systemic hypothermia (49.2%, $P < 0.001$) and selective brain cooling (26.7%, $P < 0.01$). The volume of brain swelling was diminished only in the animals treated with systemic hypothermia for 1 hr (23.6%, $P < 0.05$). LDF examination revealed a sharp drop in blood flow upon MCA occlusion and maintaining in low blood flow throughout the experiment in the control and systemic hypothermia. However, in the selective brain cooling, the reduced blood flow increased from 40% to 70% of baseline value while the brain was rewarmed. The present study indicates that mild systemic hypothermia has much stronger portective effects against focal cerebral infarction and edema than selective brain cooling. The lack of protective effects of selective brain cooling may be caused by post-cooling cerebral hyperemia in the ischemic area.

Keywords: Edema; hypothermia; MCA; swelling.

Introduction

Recently the beneficial effects of mild to moderate hypothermia on ischemic or traumatic brain injury have been demonstrated in various experimental model [1,2,5,6]. In most of these studies, body temperature has been lowered, while some investigators have tried to do selective brain cooling to avoid potential deleterious systemic effects of total body cooling as an alternative mean [6,13]. In the present study, we attempted to draw a comparision between mild systemic hypothermia and selective brain cooling in permanent middle cerebral artery (MCA) occlusion model in the rat in terms of neuroprotective effects and changes of cortical blood flow in the ischemic area, as these two treatment modalities have never been compared to our knowledge.

Materials and Methods

Adult male Sprague-Dawley rats weighing 300–400 g were used in the experiments. The animals were anesthetized with a nitrous oxide-oxygen mixture (70 : 30%) containing 1.0 to 1.3% halothane. The rats were intubated and applied an artificial respirator (Harvard Apparatus, U.K.) during the time required for surgery and hypothermia treatments. The right femoral artery was catheterized for monitoring of blood pressure and blood sampling. Two burr holes (about 2 mm in diameter, each) were made: the one in the center of the left coronary suture for a micro-probe (0.5 mm in diameter) to monitor the brain temperature in the left frontal lobe; the other in the frontal bone, about 3 mm frontal and 3 mm lateral to the center of the left coronary suture for a micro-probe of Laser Doppler flowmer (LDF) to monitor the cortical blood flow. All animals underwent left MCA occlusion under high magnification of surgical microscope via a subtemporal approach. During the surgery, mean arterial blood pressure (MABP) was recorded continuously (Model 7E Polygraph, Grass, USA). Other physiological variables such as blood gases and glucose were also measured. Brain temperature (Therm 2250-1, Ahlborn Me β- und Regelungstechnik, Germany) and rectal temperature were monitored continuously during the surgery and hypothermia treatments.

Experimental Protocol

Thirty rats were randomly assigned to one of five groups: group 1, normothermic control (n = 6); group 2, sytemic hypothermia for 30 min (n = 6); group 3, selective brain cooling for 30 min (n = 6); group 4, systemic hypothermia for 60 min (n = 6); group 5, selective

brain cooling for 60 min (n = 6). In groups 2, 3, 4 and 5, rectal or brain temperature was lowered to about 32°C by active cooling 15 min following MCA occlusion. In groups 3 and 5, the rectal temperature was maintained 36.6–37°C with homeothermic system (Harvard Apparatus, UK). After the hypothermia treatments, the animals were rewarmed gradually in room temperature and the anesthesia was discontinued. Twenty-four hours following MCA occlusion, the rats were sacrificed and infarction size was measured.

An additional 18 rats were randomly assigned to one of three groups to evaluate the changes of regional cerebral blood flow (CBF). Blood flow of the dorsolateral cortex was monitored beginning 5 min before MCA occlusion and continuing for about 1 hour and 30 min until the lowered temperature returned normothermia in the control (n = 6), and the animals treated with systemic hypothermia (n = 6) and selective brain cooling (n = 6) for 30 min.

Infarction Size and Brain Edema Determinations

Immediately after sacrifice, brains were removed from the calvaria and frozen in a cryostat (–25°C). Coronal sections (20 μm thick) were cut with a cryostat and stained with hematoxylin-eosin. Infarcted area and extent of brain swelling were readily delineated. Eight coronal sections which corresponded to planes of the preselected forebrain were selected among the stained slices, and the volume of ischemic brain damage was computed as described previously [13]. To measure the volume of brain edma, the total volume of the nonischemic hemisphere in each brain was subtracted from the total volume of the ischemic one.

Regional CBF Measurement

For CBF measurement, we used a LDF monitor equipped with a small-caliber probe of 2-mm diameter. The LDF probe was held in a micromanipulator and advanced to gently touch the dura mater. A continuous digital display of LDF values was averaged over 5-second intervals and recorded just before occlusion and hypothermia treatments, during hypothermia, and then after returning to normothermia. The CBF values were calculated and expressed as a percentage of the baseline values.

Statistical Analysis

All measurements were expressed as mean ± standard error of the mean. Differences among groups in infarction, brain edema, and CBF were compared by factorial analysis of variance (ANOVA) with the Dunnette test. P values of less than 0.05 were considered significant.

Results

Physiological Variables

Measurements of mean arterial pressure, blood gases, hematocrit, and blood glucose were obtained. They did not differ significantly among the groups.

Infarction Volume

The volume of brain infarction in the cerebral hemisphere and cortex was reduced in the groups treated with mild systemic hypothermia and selective brain cooling when compared with the control group, but not reduced in the caudate nucleus. In the two groups treated for 30 min, animals exhibited small reductions in infarction volume; these effects did not achieve statistical significance. In the two groups treated for 60 min, the infarction volumes of the cerebral hemisphere reduced significantly by 49.2% ($P < 0.05$) in mild systemic hypothermia and 26.7% ($P < 0.05$) in selective brain cooling, repectively (Fig. 1).

Ischemic Edema Volume

The volume of brain edema, obtained by subtracting the nonischemic hemispheric volume from the ischemic hemispheric volume, was reduced only in the groups treated for 60 min: by 23.6% ($P < 0.05$) in mild sytemic hypothermia and by 7.8% ($P < 0.05$) in selective brain cooling, repectively.

Regional CBF

Occlusion of the MCA produced a significant fall to about 40% of baseline value in cortical blood flow of the ipsilateral dorsolateral cortex in the all animals, and the reduced blood flow maintained throughout experiment. However, in the groups treated with selective brain cooling, the lowered CBF increased

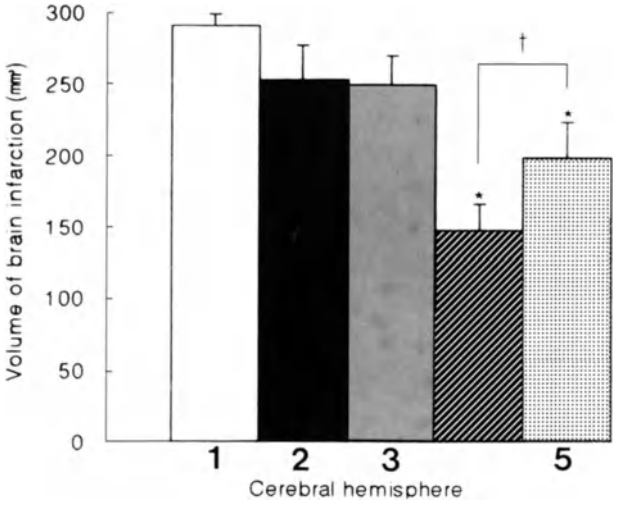

Fig. 1. Effect of mild systemic hypothermia (SH) and systemic brain cooling (SBC) on the volume of infarction in the cerebral hemisphere (Means ± S.E.). Group 1: control; group 2: SH for 30 min; group 3: SBC for 30 min; group 4: SH for 60 min; group 5: SBC for 60 min. *$P < 0.05$, compared to the control (Dunnette test). †$P < 0.05$, compared to SH 30 min and SBC 30 min (2-way ANOVA)

from 40 to about 70% of baseline ($P < 0.05$) while the cooled brain was rewarmed (Table 1).

Discussion

Several theories have been proposed to explain the neuroprotective effects against cerebral ischemia afforded by hypothermia. It is well documented that decrease of the cellular metabolic rate contributes to the protective effects of hypothermia [14]. Hypothermia may also expand the ischemic penumbra by lowering of the critical threshold of cerebral blood flow. Recently, it has been reported that mild systemic hypothermia suppressed the glutamate excitotoxicity within ischemic penumbra of focal cerebral infarction [3,4]. And other mechanisms such as reductions of intracelluar acidosis and edema formation may contribute to its protection [9]. However, hypothermia does not appear to enhance collateral blood flow to ischemic region [8].

Studies of permanent focal ischemia have demonstrated hypothermic cerebroprotection in some instances [10,11]. Our results present that mild systemic hypothermia or selective brain cooling instituted 15 min following MCAO significantly attenuates the infarct volume when hypothermia treatments are actively continued more than 1 hour. SH appears to have much stronger protective effects especially against ischemic cerebral edema than SBC.

In our previous study of SBC [13], we concluded that the reduction of edema formation might not be a major implication for the neuroprotective mechanism of SBC, and the lack of protection against ischemic edema might be caused by the direct effect of hypothermia upon the cerebral micrcirculation. In vitro and vivo studies, hypothermia appeared to have a marked vasodilator effect on intracerebral arterioles [7,12], suggesting that the exacerbation of ischemic brain edema could be caused by hyperemia initiated by SBC. However the present study reversed this assumption.

Our results demonstrated that regional CBF in ischemic area was not influenced by cooling the brain but by rewarming. Rewarming of the brain after SBC increased blood flow in ischemic core from 40% of baseline value to about 70% ($P < 0.05$), whereas rewarming of the body after systemic hypothermia increased only 10% of baseline value in the regional CBF. It was also confirmed that hypothermia did not enhance but rather reduce blood flow in the ischemic region. Consequently, it is conceivable that hyperemia in ischemic core contributes to development of ischemic brain edema more in SBC-treated animals than in SH-treated animals, and counteracts against neuroprotective effects of SBC [14,15].

The mechanisms of hyperemia during rewarming the brain remain undefined, but it can be speculated that perfusion of systemic blood in normothermia into the brain during rewarming exerts harmful hemodynamic effects on ischemic brain in a different way from the animals treated with SH. Further studies of hypothermic cerebroprotection and related hemodynamic changes will clarify the role of hyperemia in ischemic brain edema.

In conclusion, systemic hypothermia appears to have stronger neuroprotective effects against focal cerebral infarction than selective brain cooling. The lack of protective effects of selective brain cooling may be related to cerebral hyperemia in the ischemic core initiated by rewarming of the brain.

Acknowledgement

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Table 1. *Effects of Mild Systemic Hypothermia (SH) or Selective Brain Cooling (SBC) in the Dense Ischemic Region of Rats Subjected to Permanent MCA Occlusion (% of Baseline, mean ± S.E.)*

Group (number)	Time (min)							
	PRE	At MCAO	30	45	60	75	90	105
Control (n = 6)	100	70.4 ± 5.3	39.5 ± 3.6	40.0 ± 2.8	39.5 ± 1.5	39.7 ± 2.6	39.7 ± 1.9	40.0 ± 2.0
SH (n = 6)	100	74.8 ± 6.1	37.7 ± 4.5	29.5 ± 5.3	28.5 ± 7.2	42.4 ± 7.8	40.7 ± 4.3	36.5 ± 3.6
SBC (n = 6)	100	77.6 ± 5.8	34.9 ± 7.8	28.3 ± 8.9	29.0 ± 8.2	43.5 ± 8.1	57.9 ± 9.5	70.0 ± 10.2

PRE preocclusion; *MCAO* middle cerebral artery occlusion.

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Correspondence: Chun-Kun Park, M.D., Department of Neurosurgery, Kang Nam St. Mary's Hospital, Catholic University Medical College, 505, Banpo-Dong Seocho-ku, Seoul 137-040, Korea.

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Increase in Transcranial Doppler Pulsatility Index Does Not Indicate the Lower Limit of Cerebral Autoregulation

H. K. Richards, M. Czosnyka, H. Whitehouse, and **J. D. Pickard**

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Summary

Introduction: Transcranial Doppler pulsatility index was reported clinically to increase when cerebral perfusion pressure decreased, hypothetically marking the lower limit of cerebral autoregulation. We sought to investigate the relationship between pulsatility index, cerenbrovascular resistance, and cerebral perfusion pressure in various states of autoregulation in an animal model of moderate intracranial hypertension.

Method: Eight New-Zealand White Rabbits were studied with basilar artery blood flow velocity (ultrasound Doppler) and cortical blood flow (laser Doppler) monitored continuously during subarachnoid saline infusion to increase intracranial pressure (<55 mm Hg). Four animals demonstrated a stable cortical blood flow, and four demonstrated decreasing blood flow when cerebral perfusion pressure decreased.

Results: Pulsatility index showed the same pattern of increase when cerebral perfusion pressure decreased, independent on whether cortical blood flow was stable or falling. The percentage rate of increase in the pulsatility index was not different in autoregulating and non autoregulating animals. The rate of decrease in cerebrovascular resistance was significantly lower ($p < 0.05$) in non-autoregulating than in autoregulating animals.

Conclusion: The increase in transcranial Doppler pulsatility index when cerebral perfusion pressure falls cannot be interpreted as a phenomenon able to mark the lower limit of cerebral autoregulation.

Keywords: Autoregulation; pulsatility index; transcranial Doppler.

Introduction

An important new method for the assessment of autoregulation has been proposed in recent years by Chan and colleagues [1]. They reported that in head injured patients the lower limit of CPP, below which jugular bulb oxygen saturation started to decrease indicating a decrease in global cerebral blood flow, coincided with an increase in transcranial Doppler (TCD) pulsatility index (PI, defined as blood flow velocity pulse amplitude divided by time averaged flow velocity). They postulated that an increase in pulsatile blood inflow indicated a transition from active to passive behaviour of cerebral resistance vessels when the autoregulation failed. Easy accessibility of PI (which is calculated on-line by almost all TCD ultrasonographs) has resulted in its widespread use. However, the association of rising PI with autoregulation failure in head injured patients has been recently challenged [2].

We therefore sought to investigate the relationship between the limits of autoregulation of CBF, the behaviour of TCD pulsatility index and changes in cerebrovascular resistance. We performed experiments using a well described model of intracranial hypertension in rabbits [4,5] with simultaneous measurement of cortical laser Doppler blood flux and basilar artery blood flow velocity assessed using TCD velocimetry.

Materials and Methods

Preparation and Monitoring

Eight anaesthetised and ventilated New Zealand white rabbits were investigated under the approval of the UK Animals (Scientific Procedures) Act, 1986. The rabbits were prepared using methods described in [5]. Polyethylene cannulae were advanced into both femoral arteries and from one arterial pressure (ABP) was recorded using a direct pressure monitor (Gaeltec Ltd, Dunevegan, UK). An 8 MHz pulsed ultrasound probe connected to a Transcranial Doppler Ultrasonograph (PcDop 842, SciMed, Bristol, UK) was positioned over the exposed dura and adjusted to insonate the basilar artery to measure blood flow velocity (FV). Two burr holes of diameter not exceeding 2 mm were made on the other side of the midline. One was used to position a laser Doppler probe epidurally (CBF monitor, Moor Instruments, Axminster, UK) for the continuous measurement of flux-derived cortical blood flow signal (CBF). The second burr-hole was used for the

control of intracranial pressure (ICP) (Codman & Shurtlef Inc., Randolph, MA).

Intracranial hypertension was induced by subarachnoid infusion of Hartmann's solution at a rate of 0.05 ml/min or 0.1 ml/min. The period from the baseline ICP to end-equilibrium plateau (on average 30 min) was analysed. Monitored signals were converted to digital samples using an analog-to-digital converter (DT 2814, Data Translation, USA) fitted into an IBM compatible personal computer. Data were saved on hard disk using a program designed by W. Zabolotny, Warsaw University of Technology, Poland [8] and analysed off-line with software designed in-house (MC). Mean values designated as CBF (time averaged laser Doppler flux), FV (time averaged FV waveform), CPP (time averaged ABP minus ICP) were calculated as the average over period of 1 min. The Gosling Pulsatility Index, defined as FV amplitude divided by FV time average, was calculated. Laser Doppler flux was corrected by subtracting the biological zero measured post mortem. Cerebrovascular resistance was calculated as CPP divided by the corrected flux (CVR = CPP/(CBF-biological zero)) and expressed as a percentage of the baseline value.

The ratio of the gradient of the real CVR-CPP relationship compared to the gradient of ideal line (i.e. passing through the origin) has been proposed by Aaslid (6) as an index of autoregulation, termed the Static Rate of Autoregulation (SRoR). In our present study, a modified index has been used to describe the manoeuvres involving ICP, substituting ABP by CPP in Aaslid's original formula:

$$\mathrm{SRoR} = 100\%\left(\Delta\mathrm{CVR}/\mathrm{CVR}_b\right)/\left(\Delta\mathrm{CPP}/\mathrm{CPP}_b\right),$$

where Δ denotes static change (i.e. absolute difference between the baseline value and equilibrium value reached during infusion), and index b – baseline value.

A SRoR of 100% denotes an ideal autoregulation and a zero value indicates non-reactive vessels. To study changes in PI, an index of relative percentage changes of PI divided by percentage changes in CPP was calculated:

$$100\%\left(\Delta\mathrm{PI}/\mathrm{PI}_b\right)/\left(\Delta\mathrm{CPP}/\mathrm{CPP}_b\right),$$

Results

Deep vasomotion causing synchronised waves of ABP and cortical blood flow were seen at baseline in three rabbits The mean ABP was 84 mm Hg (17 mm Hg standard deviation), decreasing temporarily to around 60 mm Hg. Mean period of these waves was 3.2 min (1.7 min standard deviation). A relatively stable ABP with no vasogenic oscillation and a mean of 95 mm Hg (15 mm Hg standard deviation), never decreasing below 83 mm Hg was seen in remaining 4 rabbits. One rabbit had stable but significantly lower mean ABP (72 mm Hg).

Rates of increase in ICP and the decrease in CPP during the saline infusion were never greater than 2 mm Hg/min. The mean value of ICP never increased above 55 mm Hg (mean increase: 42 mm Hg, standard deviation 7 mm Hg). Two distinctive patterns of the laser Doppler cortical blood flow were observed:

(i) "Autoregulating animals", when baseline CBF was initially maintained or increased when CPP decreased during infusion until a well-defined lower limit of autoregulation was reached (in 4 animals). In all these animals ABP was stable during the baseline recording (above 83 mm Hg).

(ii) "Non-autoregulating animals" (N = 4), when CBF decreased with CPP from the very beginning of infusion. In 3 of these animals strong vasomotion was observed, lowering ABP temporarily to around 60 mm Hg. In one rabbit baseline pressure was low without vasomotion waves (72 mm Hg).

In all animals PI always increased when CPP decreased without any obvious breakpoints in PI-CPP relationship around the lower limit for autoregulation. CVR decreased when CPP decreased in 7 out of 8 animals. Diagonal lines on CVR-CPP graphs (Fig. 1) show gradients of CVR-CPP curves for

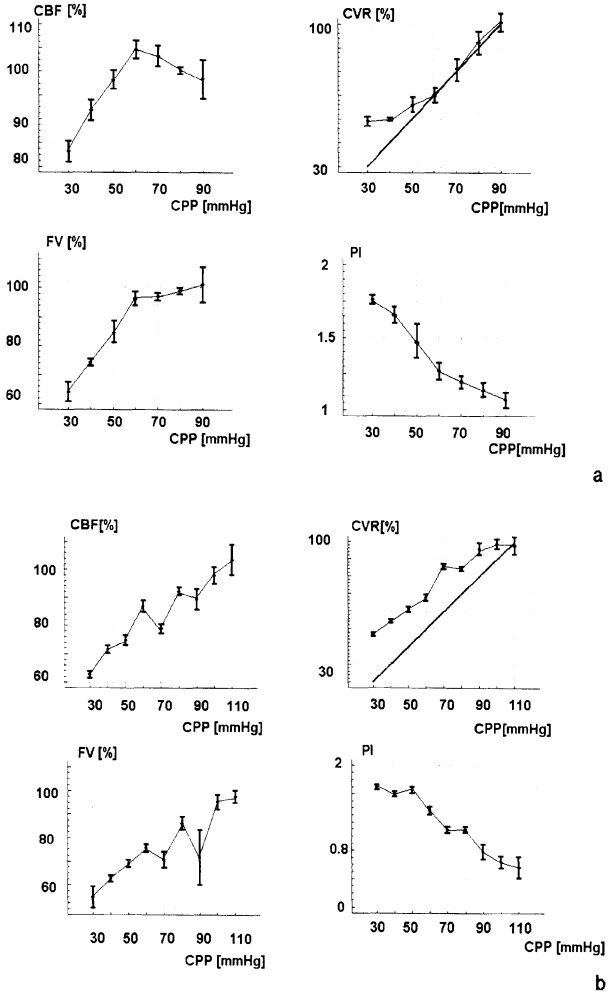

Fig. 1. Plots of averaged percentage change in laser Doppler CBF, basilar artery blood flow velocity (FV), pulsatility index (PI) and cerbrovascular resistance (CVR) versus cerebral perfusion pressure (CPP) in autoregulating (a) and non-autoregulating animals (b)

"ideal autoregulation" (SRoR = 100%). The only difference between the autoregulating and non-autoregulating animals is that CVR-CPP curves for groups (i) animals converged to "ideal autoregulation" lines for CPP above the lower limit of autoregulation. For group (ii) animals CVR-CPP curves were placed always *above* the lines representing an "ideal autoregulation".

The pooled data show that PI-CPP (Fig. 2) relationship did not differ qualitatively in animals from both groups. The percentage rate of increase in PI and the static rate of autoregulation (SRoR) for animals from groups (i) and (ii) are presented in Table 1.

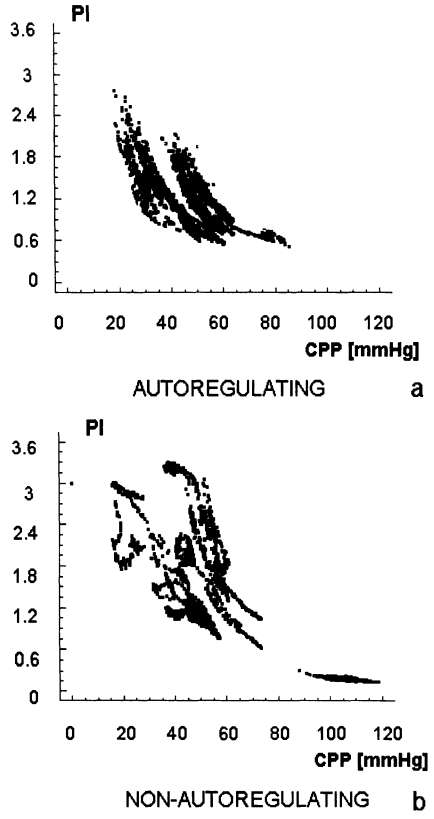

Fig. 2. Pooled scatterplot of PI versus CPP in autoregulating (a) and non-autoregulating animals (b)

Discussion

Both in "autoregulating" and "non-autoregulating" animals PI increased with decreasing CPP. Contrary to earlier observations in head injury [7] and experimental studies [3] no breakpoint manifested by the change in a rate of increase in PI was observed around the lower limit of autoregulation in the autoregulating animals. Pulsatility index started to increase from the very beginning of decrease in CPP and this increase extended far beyond the lower limit of autoregulation. Therefore, the association between the start of increase in PI and the lower limit of autoregulation reported earlier in head injured patients [1] cannot be confirmed in our experimental model. It is likely that the observed phenomena of increase in PI and decrease in SJO_2 were both initiated by decreasing CPP but they both do not necessary indicate the lower limit of autoregulation. Data were presented from the limited group of non-hyperaemic patients (N = 14) and multiple measurements repeated in time were pooled from different patients which increased the reported 'significance level' but undoubtedly decreased the accuracy of the analysis. PI shows a rather smooth inverse association with CPP without visible breakpoints both in autoregulating and non-autoregulating animals, therefore it is of little use for assessment of the autoregulatory reserve.

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Table 1. *SRoR and Percentage Increase in PI Percentage Decrease in CPP. P Value Represents the Significance of Difference between Autoregulating and Non-Autoregulating Animals (Mann-Whitney test)*

	Autoregulating	Non-autoregulating	p value
SRoR	101.7 (9.9)	38 (21.8)	$p < 0.015$
Percentage relative increase in PI	214 (77)	274 (72)	NS

SRoR static reate of autoregulation; *PI* gosling pulsatility index.

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Correspondence: Dr. Hugh K. Richards, Academic Neurosurgical Unit, PO Box 167 Addenbrooke's Hospital, Cambridge CB2 2QQ, U.K.

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Evaluation of Cerebrovascular CO_2-Reactivity and Autoregulation in Patients with Post-Traumatic Diffuse Brain Swelling (Diffuse Injury III)

J. Sahuquillo[1], **F. Munar**[2], **M. Baguena**[2], **M. A. Poca**[1], **S. Pedraza**[3], and **A. Rodríguez-Baeza**[4]

[1] Departments of Neurosurgery, [2] Neurotraumatology Intensive Care Unit, and [3] Neuroradiology, Vall d'Hebron University Hospitals, and [4] Department of Morphological Sciences of the UAB, Barcelona, Spain

Summary

The present study was undertaken to elucidate the status of autoregulation and CO_2-reactivity soon after injury in patients with a post-traumatic diffuse bilateral brain swelling. A prospective study was carried out in 31 consecutively admitted patients with a severe head injury and a Diffuse Brain Injury type III, following the definition stated by the Traumatic Coma Data Bank classification. To evaluate CO_2-reactivity, $AVDO_2$ was measured before and after ventilator manipulations. Assuming a constant $CMRO_2$ during the test, changes in $1/AVDO_2$ reflect changes in CBF. Patients with changes in estimated CBF below or equal to 1% were included in the impaired/abolished CO_2-reactivity group. To test autoregulation, hypertension was induced using phenylephrine. Arterial and jugular blood samples were taken to calculate $AVDO_2$ before and after a steady state of MABP was obtained. Cerebrovascular response to CO_2 was globally preserved in all but two cases (6.5%). In contrast, autoregulation was globally preserved in 10 (32.3%) and impaired/abolished in 21 cases (67.7%). Our data do not support the premise that increasing cerebral perfusion pressure by inducing arterial hypertension is beneficial in those patients with a diffuse brain swelling in whom autoregulation is impaired or abolished. Clinical implications for treatment are discussed.

Keywords: Autoregulation; brain swelling; CO_2-reactivity.

Introduction

Uncontrollable intracranial hypertension is the most frequent cause of death in patients with severe head injury and bilateral brain swelling (Diffuse Injury type III). Many etiological factors have been considered as contributing to bilateral brain swelling: alteration in autoregulatory mechanisms, impaired CO_2-reactivity, increase in intravascular volume, hyperemia and more recently, neurotoxic edema. Until not long ago, the most widely accepted theory on brain swelling was that most of these patients presented an increased CBF and CBV. However, evidence is accumulating to suggest that an increase in intracellular brain water may be the basic mechanism involved in postraumatic brain swelling. The importance of this controversial issue is clear if we consider that to effectively treat high ICP after head injury, the treatment should match the cause [7]. In these patients, treating an increase in cerebral blood volume would follow a completely different approach from treating any form of brain edema. The present study was undertaken to elucidate the status of autoregulatory mechanisms and cerebrovascular CO_2-reactivity soon after injury in patients with a diffuse bilateral brain swelling.

Materials and Methods

A prospective study was carried out in 31 consecutively admitted patients with a severe head injury (post-resuscitation Glasgow coma scale score below or equal to 8) and a Diffuse Brain Injury type III, following the definition stated by the TCDB [5]. The protocol of study presented in this paper was approved by the Institutional Ethical Committee on Human Research of Vall d'Hebron University Hospitals. In all patients, brain hemodynamic studies were performed within 21.7 ± 7.8 hrs of impact. The methodology used to test both autoregulation and CO_2-reactivity has been previously described [10]. Assuming a constant $CMRO_2$ during the test, changes in $AVDO_2$ reflect inverse changes in CBF. CO_2-reactivity (CO_2R %) was calculated as the percent of increase or decrease of estimated CBF ($1/AVDO_2$) per mm Hg change in pCO_2. Patients with $CO_2R_{\%}$ above 1% were considered in the intact CO_2-reactivity group and patients in whom CO_2R% was below or equal to 1% were included in the impaired/abolished CO_2-reactivity group. To test autoregulation, hypertension was induced using phenylephrine. Arterial and jugular blood samples were taken to calculate $AVDO_2$ before (Baseline) and after a steady state of MABP was obtained (15 to 20 minutes after starting the infusion). All $AVDO_2$ values were corrected for spontaneous changes in pCO_2. In those patients in whom ICP did not change after increasing MABP (changes in mean ICP of

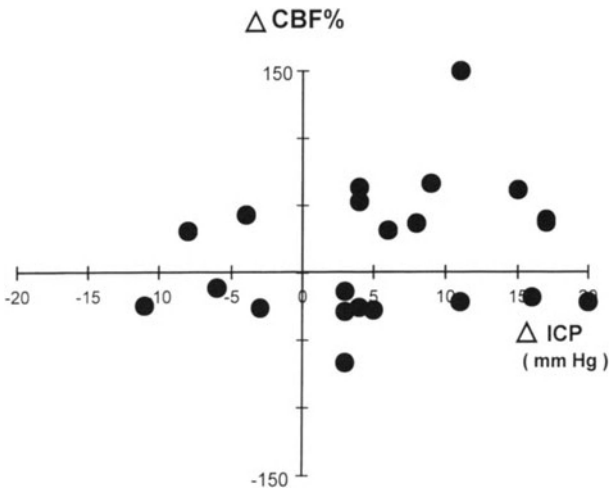

Fig. 1. Changes in ICP and estimated CBF after inducing hypertension with phenylephrine in the group of patients in whom changes in ICP were observed (n = 22). For description see text. Patients included in patterns 1 and 4 were considered to have a preserved autoregulation, while patients in groups 2 and 3 were considered to have an impaired/abolished autoregulation. The zero for CBF axis was set at 20%. Therefore patients with changes in estimated CBF below or equal to 20% and an increase in ICP were included in pattern type II

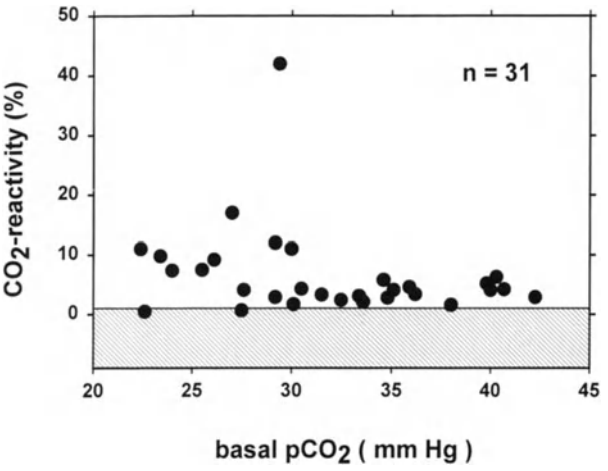

Fig. 2. Basal pCO_2 plotted against CO_2R%. The gray box defines the zone of impaired/abolished CO_2-reactivity. Observe the lack of correlation between the basal pCO_2 before the test and CO_2-reactivity

± 2 mm Hg), we used Enevoldsen and Jensen's criteria to classify autoregulation. Those patients with estimated changes in CBF less than or equal to 20% were included in the intact autoregulation group while patients with estimated CBF changes above 20% were classified as having an impaired autoregulation (impaired/abolished) [3]. In those patients with changed ICP after increasing MABP, different criteria were used. In this second group and according to the calculated degree of change in ICP and estimated CBF, patients were preclassified into four different patterns (Fig. 1): Pattern 1: Decreased ICP and Increased CBF, Pattern 2: Increased ICP and simultaneously increased CBF, Pattern 3: Increased ICP and decreased or unchanged CBF and Pattern 4: Decreased ICP and simultaneously decreased or unchanged CBF. Patients included in patterns 1 and 4 were considered to have a preserved autoregulation, while patients in groups 2 and 3 were considered to have autoregulation impaired/abolished. CBF was considered unchanged when estimated changes after inducing hypertension were below or equal to 20%.

Results

Mean age in our group was 30.4 ± 11.8 years (mean ± STD) and GCS was 6.8 ± 2.6. Twenty-one cases (67.7%) had an ICP above or equal to 15 mm Hg at the moment of testing despite therapy. According to the corrected basal $AVDO_2$ (to a pCO_2 of 35 mm Hg), 23 (74.2%) patients were classified as hyperemic ($AVDO_2$ below 1.74 µmol/ml). Cerebrovascular response to CO_2 was globally preserved in all but two cases (6.5%), where it was impaired or abolished (CO_2R% < 1%) (Fig. 2). In contrast, autoregulation was globally preserved in 10 (32.3%) and impaired/abolished in 21 cases (67.7%). The different patterns found after increasing MABP in those patients in whom changes in ICP were detected are shown in Fig. 1. Pattern 3 was considered characteristic of what has been called "pseudo-autoregulation" [3]. In the two cases where CO_2-reactivity was abolished, autoregulation was also impaired/abolished. At six months, 14 patients had died, two were in a persistent vegetative state and three were severely disabled. A bad outcome was therefore the final result in 61.3% of the patients in this study. Uncontrollable intracranial hypertension was the single most frequent cause of death in this series.

Discussion

The majority of the patients in our study, had $AVDO_2$ reflecting hyperemia very early after injury. The presence of hyperemia in these patients, apparently suggests that an increase in CBV may play an important role in brain swelling. However, low $AVDO_2$ measurements, do not necessarily imply an increase in absolute values of CBF or in cerebral blood volume. Data from other studies, suggest that in many cases hyperemia is actually a relative hyperemia, showing that CBF and metabolism are not functionally coupled in these patients [6,8]. CO_2-reactivity was preserved in most of our patients, although autoregulation, as defined in our study, was impaired in many of them. The status of autoregulatory mechanisms after severe head injury has

been a matter of considerable debate. While for some authors, autoregulation is impaired/abolished in many patients after injury, for others the curve is shifted to the right or to the left [1,4,9]. In diffuse brain swelling, this divergence of opinions is particularly relevant, as increased ICP is still the main cause of death and disability in these patients.

Interpreting the results of autoregulation tests can sometimes be very difficult and is particularly problematic in those patients where increasing MABP simultaneously raises ICP due to an increase in CBV, interstitial brain water or both. In these cases, the effects of increasing MABP on the net brain tissue perfusion and on the microcirculation, are exceedingly variable. In this study we have followed a pragmatic approach to this problem, classifying the patients according to the change that increasing MABP produced in the two variables of interest: ICP and estimated CBF. In 9 of our patients, increasing MABP provoked a simultaneous increase in ICP and in the estimated CBF (changes above 20%). Although this phenomenon could be affected by the fact that some of these patients had a basal CPP below the accepted lower limit of autoregulation, the majority of them had a CPP above 60 mm Hg after iatrogenically raising MABP. In spite of this, vasoconstrictory cascade was not triggered. The hypothesis that in these patients, autoregulatory curve may be shifted to the right, has not yet been proved. Therefore we think that in the absence of more conclusive data, we must consider that in these patients the cerebrovascular response to an increase in MABP/CPP, is severely impaired or abolished. The analysis of the results obtained in patients included in pattern 3, is relevant because the response to MABP challenge is suggestive of what has been called "false autoregulation" [3]. In these cases, the CBF is maintained constant or is even reduced because of an increase in brain tissue pressure and secondary compression of the microcirculation [3].

The benefits of iatrogenically increasing MABP to treat elevations of ICP, looking at CPP as the main variable, has not yet been proven. From a theoretical point of view, this approach has many drawbacks in those patients with impaired autoregulation. What we achieve on one side (increased CPP) is rapidly counterbalanced by either the increase in CBV, increased water content in brain tissue or both. Even in patients in whom autoregulation is globally preserved, the increase in CBF facilitates vasogenic edema in those regions of the brain which are severely injured. In these regions, the permeability of blood-brain-barrier is generally increased making it difficult to predict the individual response of ICP and CBF and the overall benefit of increasing CPP. In those cases with intact autoregulation, stimulating the vasoconstrictory cascade facilitates the management of high ICP. However, in those in whom increasing MABP provokes a simultaneous increase in ICP, induced hypertension should be considered only in those patients in whom CPP is below the lower breakpoint of the autoregulatory curve. When patients are already above this threshold, therapeutic measures should be directed to reduce ICP by other means. In this group, the use of "optimized hyperventilation" [2] or moderate hyperventilation associated to osmotherapy (mannitol or hypertonic saline) seems more rational as a first line of treatment. In those cases in whom those therapies fail to control ICP, barbiturates can be the last resort. The administration of some drugs such as dihydroergotamine, indomethacin and surgical decompression should also be considered as alternatives but still unproven effective options.

Acknowledgments

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Correspondence: Juan Sahuquillo, M.D., Osona 6, 2–4, E-08023 Barcelona, Spain.

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Cortical Extracellular Sodium Transients after Human Head Injury: An Indicator of Secondary Brain Damage?

B. Alessandri, E. Doppenberg, A. Zauner, J. Woodward, H. F. Young, and **R. Bullock**

Virginia Commonwealth University, Medical College of Virginia

Summary

Animal studies indicate that elevated extracellular sodium can increase glutamate-induced excitotoxicity. Therefore, we investigated the relationship between sodium and glutamate and the effect of changes in sodium concentrations on the outcome of head-injured patients. Thirty-four (34) patients were selected for this study and divided into a group of patients having episodes (≥30-min) of high sodium in dialysates (≥200 mM; HIGH, n = 11) and a group of patients having no such episodes (NORMAL, n = 23). Levels for sodium (226 ± 5.7 mM), glutamate (12.53 ± 2.2 μM) and ICP (32.2 ± 4.0 mm Hg,) were relatively high during the high sodium episodes. Overall, mean values for glutamate, ICP and outcome did not differ amono both groups. The mean dialysate sodium concentration, however, was significantly higher in the HIGH (178 ± 6 mM) compared to the NORMAL group (158 ± 3 mM; $p < 0.01$). Spearman rank correlation between sodium and glutamate or ICP were not significant. The HIGH sodium group did not have significantly more patients with poor outcome than the NORMAL group. The results indicated sodium concentrations did not affect the outcome of head-injured patients. However, other sodium monitoring techniques are desirable to elucidate these apparent potentially major sodium transients, which we have observed in the human cortex, after severe head injury.

Keywords: Head injury; microdialysis; sodium transients.

Introduction

The ionic balance of the entire brain is massively disturbed following impact trauma [13] and ischemia [12]. This leads to an accumulation of sodium and chloride ions and a loss of potassium to the ECF space [2]. Disturbance of cellular ion homeostasis may also be secondarily perturbed, by release of glutamate and other neurotransmitters which act on agonist-operated ion channels [9]. Activation of glutamate receptors produces shifts of calcium, sodium and other ions into neurons. The uptake of glutamate by astrocytes is accompanied by sodium uptake, causing astrocyte swelling and increased energy demand to drive ion pumps [5,10]. Recently, two microdialysis reports have shown that elevated extracellular sodium increased glutamate-mediated excitotoxicity in animals [1,6]. The addition of 75 mM sodium to a glutamate containing microdialysis perfusate has been shown to increase the extent of neuronal damage. The mechanism which is responsible for this effect, however, has not been elucidated.

In head-injured patients, massive and long-lasting glutamate release has recently been demonstrated by several authors [3,11]. Glutamate release, in many cases, was accompanied by increased extracellular potassium ($[K^+]_d$). Recently, Goodman and coworkers reported massive potassium, but not calcium or magnesium changes during pathophysiological events [7]. We have reported striking changes in hour-to-hour $[Na^+]_d$ concentrations which were not apparently consistently accompanied by changes in glutamate or potassium concentrations [4].

In the present study we tested the hypothesis that glutamate release is associated with massive extracellular sodium transients, and that this may be an additional potentially dangerous mechanism leading to the development of secondary brain damage after head-injury.

Materials and Methods

Patients: A total of 34 severely head-injured patients were studied. The characteristics of the patient group are shown in Table 1. Microdialysis probes were placed either at the site of ventriculostomy, or during surgery, near a cerebral contusion. Patients were divided into two groups based on the dialysate sodium concentration; namely a first group (HIGH, n = 11) consisting of patients with one (1) or more 30-min episodes of elevated

(>200 mM) sodium in dialysate; and a second group (NORMAL, n = 23) consisting of patients with no sodium elevations over 200 mM in dialysate. Outcome was assessed by Glasgow Outcome Scale (GOS), a GOS score of 0–2 was considered as good outcome and GOS of 3–4 as poor outcome.

Microdialysis: Flexible, custom-made microdialysis probes (outer diameter 0.5 mm) were used with an active membrane length of 10 mm (CMA Microdialysis, Acton, MA). Probes were perfused with 0.9% sterile saline (155 mM) at a flow rate of 2 μL/min. Half-hour samples (60 μL) were collected in sealed glass vials by means of a refrigerated (4°C) autosampler (CMA/170). In vitro probe recovery for glutamate and sodium were 43 ± 3% and 72 ± 5%, respectively.

Glutamate: Glutamate was analyzed in 15 μL dialysate using HPLC with pre-column derivatisation by o-phthalic dicarboxyaldehyde and electrochemical detection (LC-4B detector) [14].

Sodium: Sodium ion concentration in dialysates $[Na^+]_d$ was measured by flame photometry in pre-diluted 15 μL dialysate samples. The system was calibrated against known standards [4].

ICP and CPP management: Ventriculostomy ICP (mm Hg) data, and mean arterial blood pressure (MABP, mm Hg), were continuously acquired by a VAX mainframe computer system. For analysis, time points of microdialysis and physiological parameters were matched [4].

Statistics: The mean glutamate and sodium concentrations in dialysate, age, ICP, CPP, MABP of each group were compared by Mann-Whitney U-test. The frequencies of good or poor outcome were compared by a Chi-square test. Spearman rank correlation was performed between mean glutamate and sodium concentrations and mean ICP and sodium levels. Differences were considered to be significant at p-levels <0.05.

Results

Glutamate, sodium and ICP levels: Overall, the mean values (±s.e.m) for glutamate, sodium and ICP were 11.72 ± 5.0 μM, 178 ± 6 mM and 19.6 ± 3.8 mm Hg for the HIGH sodium group and 24.46 ± 6.9 μM, 158 ± 3 mM and 17.2 ± 2.2 mm Hg for the NORMAL group. The two-sided Mann-Whitney U-test was only significant for sodium ($p < 0.01$).

Relationships – Sodium vs. glutamate, ICP & outcome: Spearman rank correlation and linear regression analysis did not reveal any significant relationship between mean concentrations of sodium and mean levels of glutamate ($r = 0.219$, $p = 0.221$) or ICP ($r = 0.253$, $p = 0.170$). Chi-square analysis of the relationship between sodium and outcome of patients assessed by Glasgow Outcome Scale was not significant. Patients with good outcome, however, had a lower ICP (14.7 ± 0.05 mm Hg) than patients with poor outcome (20.6 ± 3.4 mm Hg). The difference was not significant.

Peak sodium and ICP relationship: Patient in the HIGH sodium group had 5.6 ± 1.1 half-hour episodes of $[Na^+]_d$ ≥200 mM. *During these episodes* of high sodium, the mean (±s.e.m) glutamate, $[Na^+]_d$ concentrations and ICP levels were 12.53 ± 2.2 μM, 226 ± 5.7 mM and 32.2 ± 4.0 mm Hg, respectively. Spearman rank correlation and linear regression analysis did not reveal a clear relationship between the parameters during high sodium periods.

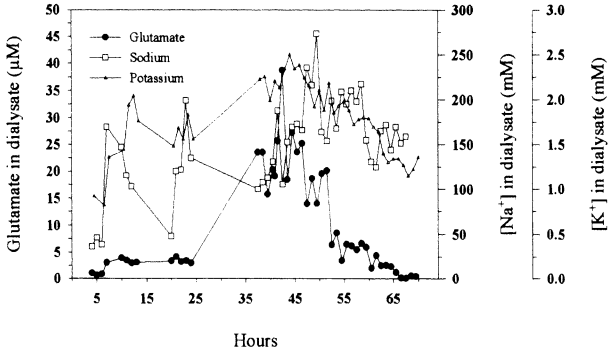

Fig. 1. Microdialysis time-course for glutamate, sodium and potassium in patient S. J. (male; initial GCS = 3; left subdural hematoma/contusion; mean ICP = 15.7 mm Hg; mean CPP = 83.4 mm Hg; 3-month GOS = 2)

Table 1. *Patient Characteristics of 34 Severely Head-Injured Patients. Patients were divided into a group (NORMAL) with no episodes of elevated sodium levels in dialysates and a group (HIGH) with one (1) or more 30-min episodes of elevated sodium in dialysates (>200 mM)*

Parameter		Normal (n = 23)	High (n = 11)
Age (years)		37.9 ± 3.9	48.9 ± 11.5
Sex	female	57.1%	55.5%
	male	42.9%	44.5%
Outcome	good (GOS0–2)	47.8%	45.5%
	poor (GOS3–4)	52.2%	54.5%
ICP (mm Hg)**		17.2 ± 2.2	19.6 ± 3.7
CPP (mm Hg)**		82.4 ± 3.1	75.8 ± 6.8

CPP cerebral perfusion pressure; *GOS* Glasgow Outcome Scale; *ICP* intracranial pressure; **mean value over entire monitoring period.

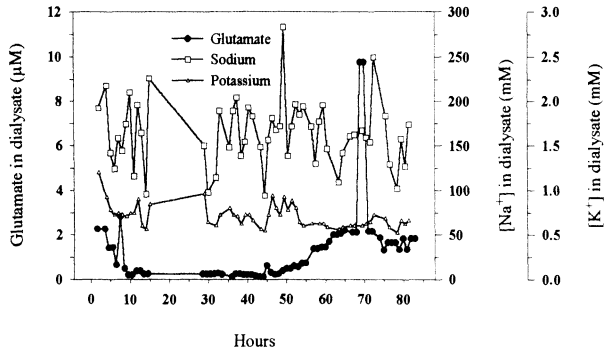

Fig. 2. Microdialysis time-course for glutamate, sodium and potassium in patient Mc.T. (male; initial GCS = 8; left-frontal contusion; mean ICP = 14.8 mm Hg; mean CPP = 109.1 mm Hg; 3-month GOS = 4)

Discussion

There was no apparent correlation between the remarkably large dialysate sodium transients (up to 70 mM) and other clinical and neurochemical parameters tested in this study. Animal experiments clearly indicate that there are dynamic changes in extracellular and intracellular ion concentrations following ischemia or traumatic brain injury [9,12]. Most studies have focused mainly on the glutamate, calcium and potassium inter-relationships. Two animal studies in which glutamate was applied through a microdialysis probe to the cortex of rats, however, showed that increased extracellular sodium levels increase glutamate-induced cortical brain damage [1,6] It has also been shown by Betz and coworkers that ischemia leads to a massive increase in total sodium in the brain [2]. Sodium channel blockers have shown neuroprotective properties in animal models of ischemia, supporting this important role of sodium ions [8].

In these human head-injured patients, however, there seems to be no clear relationship between glutamate and sodium, and patients with high sodium episodes did not have worse outcome than patients without such sodium transients. Although the study could not demonstrate a clear relationship, the analysis of all patients revealed some interesting features. Sodium concentrations fluctuated massively in many patients. The reasons for such dialysate changes is not understood. In addition, increases over 200 mM did not persist longer than 60 to 120 min. In certain patients, there was a *net loss of sodium* from the dialysate perfusate, containing about 155 mM sodium, to the brain. In many such cases, $[Na^+]_d$ levels were decreased during the first few hours after injury. This may accord with findings from animals studiesm which show net *uptake of sodium* into ECF, from the intravscular compartment, during ischemia [2].

We speculate that the lack of correlation seen in this study may have several explanations. First, more prolonged elevations of sodium might be necessary to cause the adverse effects on tissue outcome as seen in animal models. Tissue mechanisms which effectively buffer ECF sodium changes seem to exist. Second, sodium elevations did *not significantly correlate* with glutamate elevations. Thus, the sodium elevations might also have been too short-lasting to cause additional brain damage in patients. Lastly, the methodology we used might not be appropriate for this study. The loss or uptake of sodium, or *of free water* through the microdialysis probe, will clearly influence results, and thus, our findings may simply confirm the highly dynamic changes in sodium, water, and other ions in the ECF space, after trauma. More specific methods for continuous in vivo sodium measurement are needed. The investigation of a larger group of patients will also help to elucidate the potentially important role of sodium in secondary post-traumatic brain damage.

Acknowledgment

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Correspondence: Dr. B. Alessandri, Virginia Commonwealth University, Medical College of Virginia, Dept. of Neurosurgery, P.O. Box 693, Richmond, VA 23298, U.S.A.

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Intraoperative Microdialysis and Tissue-pO_2 Measurement in Human Glioma

S. Baunach[1], **J. Meixensberger**[1], **M. Gerlach**[2], **J. Lan**[2], and **K. Roosen**[2]

[1] Department of Neurosurgery and [2] Department of Psychiatry, University of Würzburg, Federal Republic of Germany

Summary

The amino acid glutamate is one of the major neurotoxins in the pathogenesis of neuronal death after ischemia or trauma. Microdialysis studies in both man and animal have shown elevated extracellular levels after primary lesions. Monitoring of cerebral tissue oxygenation ($p(ti)O_2$) has been used in recent years to detect and prevent episodes of low cerebral oxygenation, e.g. after trauma or subarachnoid hemorrhage.

Intraoperative monitoring of $p(ti)O_2$ combined with microdialysis in the peritumoral edema has been chosen to study the responses of glutamate and oxygen levels during resection. In 7/9 patients $p(ti)O_2$ was below "critical" 10 mm Hg. Elevating inspiratory oxygen concentration to 100% led to an increase of $p(ti)O_2$ by 2,5-4 fold and a decrease of glutamate and aspartate by 50–80%. A close correlation between $p(ti)O_2$ and microdialysis glutamate levels was not clearly shown due to frequent intraoperative manipulations.

Keywords: Human glioma; microdialysis; tissue-pO_2.

Introduction

Excitatory amino acids (EAA) are important mediators of brain injuries after direct trauma, hypoxia or ischemia [2–5]. The intraparenchymal measurement of tissue oxygenation ($p(ti)O_2$) via an oxygen sensitive Clarke-type electrode has been shown to be of high value to detect low cerebral oxygenation [1,6,7]. Long time monitoring studies on cerebral oxygenation today indicate sevalue below 10 mm Hg to be critical for the outcome, e.g., after severe brain injury [1,7]. Microdialysis allows the detection of changes in the composition of the extracellular space. It has been shown that there is a rise in extracellular EAA after brain injury and surgery [2]. Therefore our in vivo study focused on the relationship between $p(ti)O_2$ and amount of EAA in peritumoral edema in glioma surgery.

Materials and Methods

Measurements were performed in 9 patients with high grade glioma (WHO IV) in the frontal [4] or temporal [5] lobe with the consent of the patients and approval from the local ethics commity. Microdialysis probes were constructed according to the method of C.S. Robertson (Baylor college of Medicine, Houston, Tx.). These sterile, loop-type microdialysis probes had a molecular weight cut-off 13,000 u, an outer diameter of 1.5 mm, a 2×0.5 cm loop and a total length of 4.5 m. The probes were perfused at a rate of 2 µl/min with sterile 0.9% NaCl solution. Micodialysis probe and tissue-pO_2 catheter (Licox^R, GMS, Kiel, Germany) were placed in the close vicinity but outside the visible tumor tissue in the peritumoral edema, the tips in a depth of about 2 cm. Samples were collected every 10 min and analyzed by HPLC starting 30 min after probe placement.

Results

In the majority (7/9) of our patients initial (after a stabilization period of at least 30 min) $p(ti)O_2$ was below 10 mm Hg with an inspiratory oxygen concentration ($F(i)O_2$) of 45% (Figs. 1, 2). Elevation of $F(i)O_2$ to 100% lead to an increase in $p(ti)O_2$ by 2,5-4 fold and a decrease of glutamate and aspartate concentrations by 50–80%. The concentrations of glutamate and aspartate showed a close correlation of about 2:1. On the other hand, the concentrations of excitatory glutamate and inhibitory GABA showed a correlation of 10:1. Glutamate levels were correlated with the mean $p(ti)O_2$ value during the sample period but there was no close correlation ($p = -0.143$). Fig. 1 shows an example with an initially (after more than 30 min stabilization) $p(ti)O_2$ of more than 10 mm Hg and a clear reduction of glutamate levels from above 20 µmol/l to below 5 µmol/l during $F(i)O_2 = 1,0$. Fig. 2 shows an example

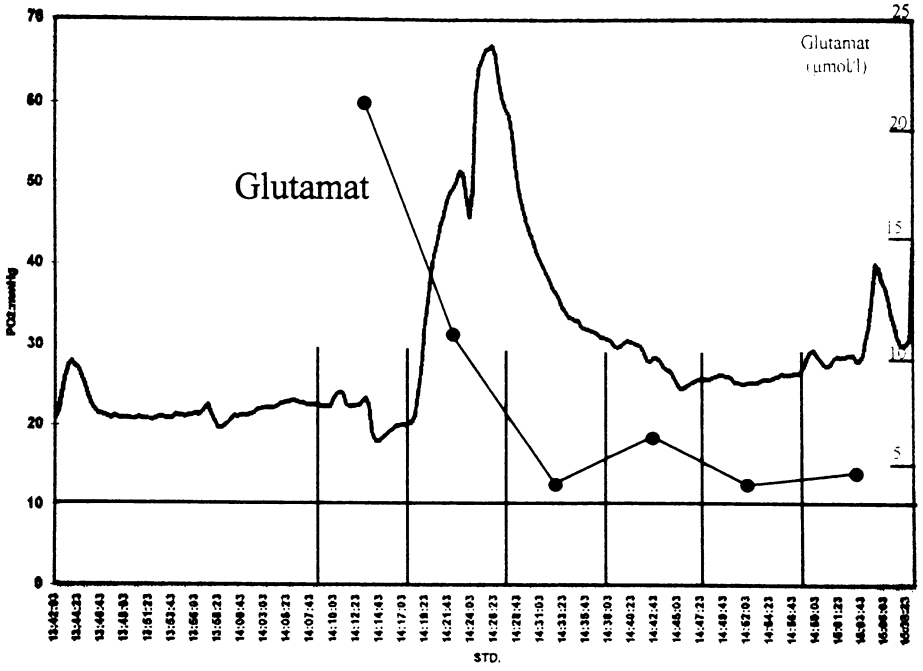

Fig. 1. Tissue p(ti)O_2 and glutamate during glioma surgery with initial p(ti)O_2 > 10 mm Hg. Example with an initially (after more than 30 min stabilization) p(ti)O_2 of more than 10 mm Hg and a clear reduction of glutamate levels from above 20 µmol/l to below 5 µmol/l during F(i)O_2 = 1,0

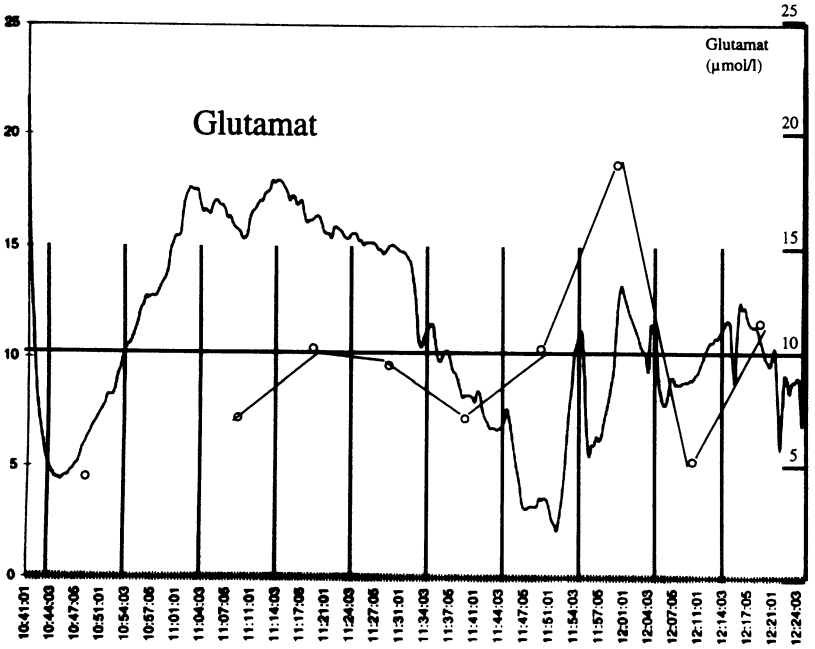

Fig. 2. Tissue p(ti)O_2 and glutamate during glioma surgery with initial p(ti)O_2 < 10 mm Hg. Example with an initially low p(ti)O_2 of less than 10 mm Hg and a clear increase of glutamate levels during surgery together with a significant decrease in p(ti)O_2

with an initially low p(ti)O_2 of less than 10 mm Hg and a clear increase of glutamate levels during surgery together with a significant decrease in p(ti)O_2. Figs. 1 and 2 show the multiple ups and downs of p(ti)O_2 caused by intraoperative manipulations often coming together in one microdialysis collection period.

Discussion

In contrast with p(ti)O_2 or intracranial pressure monitoring, microdialysis is not a means of continuous online monitoring. Samples obtained thus merely reveal the mean concentration of, e.g., glutamate over a 10 min period of time. On the other hand, ups

and downs in local $p(ti)O_2$ may occur in the same period of time and extinguish or mask their effect on extracellular EAA concentrations. This is even worsened by the necessity of various intraoperative manipulations and their effect on local $p(ti)O_2$ (e.g. placement of spatula). In the future, this problem shall be overcome be shorter collection periods. Interestingly sufficient $p(ti)O_2$ in the close vicinity to the tumor is often (7/9) below the "critical" (continuous monitoring e.g. after severe head injury) [6] value of 10 mm Hg and thus be caused by the mass effect compressing the surrounding brain.

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Correspondence: Jürgen Meixensberger, M.D., Department of Neurosurgery, University of Würzburg, Josef-Schneider-Strasse 11, D-97080 Würzburg, Federal Republic of Germany.

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Relationship between Excitatory Amino Acid Release and Outcome after Severe Human Head Injury

S. S. Koura, E. M. R. Doppenberg, A. Marmarou, S. Choi, H. F. Young, and **R. Bullock**

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, U.S.A.

Summary

In previous studies, Katayama and our group have documented a massive increase in excitatory amino acid release following traumatic brain injury, in both rat fluid percussion, and humans [2,5]. To test the hypothesis that the magnitude of this "Excitotoxic Surge" plays a significant role in determining 6-month patient outcome. We have studied 83 consecutive severely head injured patients at the Medical College of Virginia for inclusion into this study. A microdialysis probe was placed within the cortex to continuously measure dialysate excitatory amino acids (Glutamate and Aspartate), along with several other analytes for approximately 5 days after injury. ICP, CPP, and MABP measurements were also time linked with each analyte measurement to create a neurochemical, clinical, and physiological "profile" for each patient. Outcome was determined by follow up using the Glasgow 6-Month outcome scale. A very strong correlation existed between the release of the EAA's glutamate and aspartate after TBI ($p < 0.0001$). Patients with significantly elevated mean glutamate values for the entire monitoring period were most likely to exhibit elevated levels of ICP. The magnitude of glutamate released significantly correlates with 6-month patient outcome ($p = 0.0234$). When patients were subdivided by the CT diagnosis of lesion type, we found that those patients with contusions displayed the highest overall of EAA's.

Keywords: Excitatory amino acid; head injury; outcome.

Introduction

The excitatory amino acids (EAA's) glutamate and aspartate have been found to increase up to 6 fold in rats, and 50 fold in human brain dialysate, after TBI [2,3,5]. However, this may be an epiphenomenon since structural amino acids were similarly elevated, in our human studies. There had been no previous direct evidence that this massive release of EAA's has been associated with significantly worse outcome. Developments in the use of clinical microdialysis have made it possible to continuously measure changes in several brain metabolic analytes in the severely head injured patient [4,7]. We have used these data to test whether increased EAA's correlate with 6-month patient outcome, and whether the lesion type affects the pattern of EAA's release.

Materials and Methods

These studies were approved by the Committee for Conduct of Human Research of the Medical College of Virginia and Virginia Commonwealth University. Eighty-three severely head injured patients (GCS ≤ 8) were studied. Custom-made, commercially produced microdialysis probes were used, with a molecular weight cutoff of 20 KD and a 10 mm active dialysis surface (CMA 20 Custom probes, CMA Microdialysis, Stockholm, Sweden). The probe was placed intraparenchymally in cortex to continuously measure changes in several brain analytes. Samples were collected every 30 minutes for up to 4 days, in 60 µmol aliquots. EAA's were measured by HPLC analysis, and patient outcome was classified by using the 6 month Glasgow outcome scale (0–4). In the ICU, physiological data was collected continuously at three-second intervals, "cleaned", and time linked to the other biochemical endpoints. Patients were classified by lesion type using CT scan. The tissue characteristics, by CT, at the site of the microdialysis probe placement, was used. Spearman's Rank correlation and Linear Regression were used to test the significance of these data, by first testing the intrapatient correlation. For every time point studied, and then tabulating the "r" values, and testing for significance, across the subgroups of patients.

Results

A significant correlation existed between mean dialysate glutamate and aspartate ($p < 0.0001$) and also between EAA's and 6-month patient outcome ($r = 0.332$, $p = 0.02$). (Fig. 1) 85% of patients who displayed favorable outcomes (GOS = 0, 1) had mean glutamate levels for the entire dialysate period that were <20 µMol/L ($n = 29$). Similarly, 72% of patients with mean glutamate concentration >20 µMol/L (n =

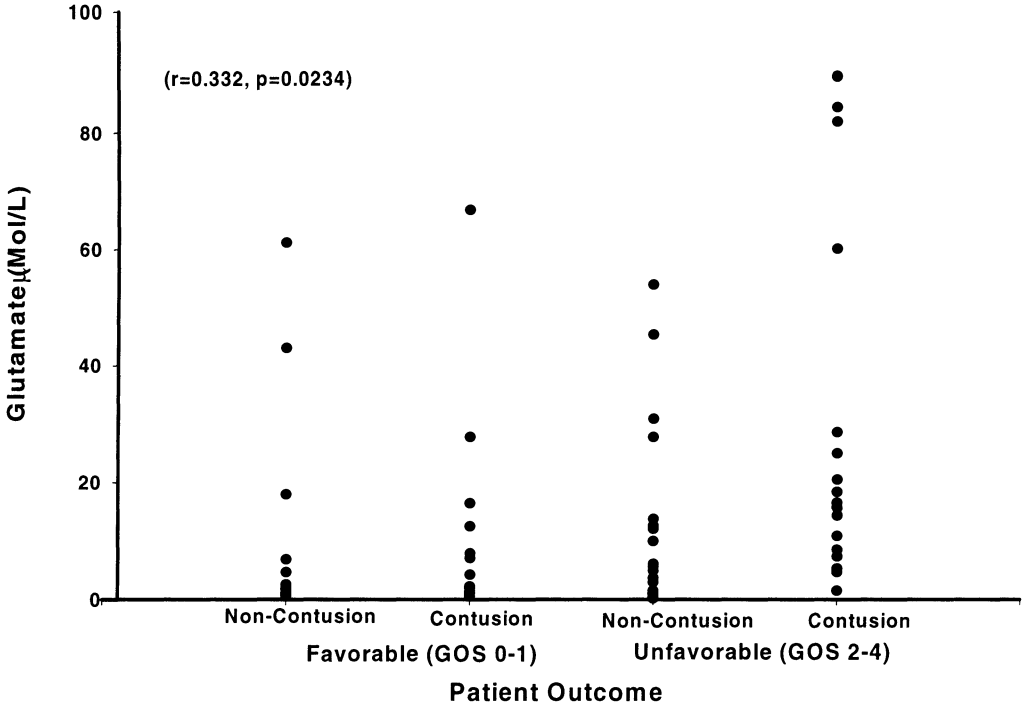

Fig 1. Graph demonstrating the relationship between glutamate levels and outcome in patients with or without contusions

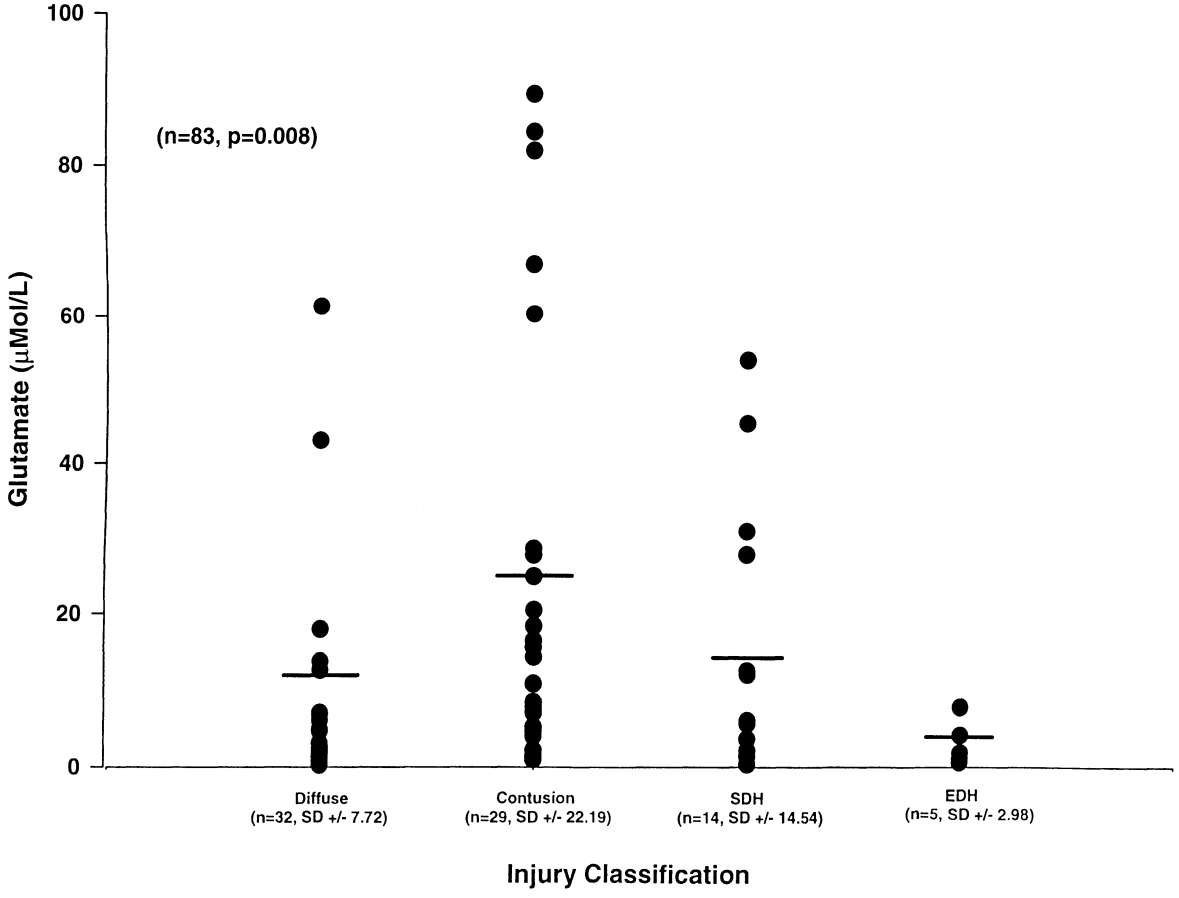

Fig 2. Graph showing glutamate levels with corresponding lesion types

18) displayed unfavorable outcomes (GOS = 2–4). A strong correlation also existed in this 18 patient subgroup between glutamate and elevated ICP ($r = 0.659$, $p = 0.0104$). Within the four lesion groups studied as classified by CT, a significant correlation was found to exist between the lesion type and the glutamate levels ($p = 0.0086$) (Fig. 2). Those patients with contusional lesions had the highest overall EAA levels. With the group as a whole ($n = 83$), those patients whose glutamate levels were the highest (>20 µmol/l), experienced the highest levels of ICP ($r = 0.554$, $p < 0.0001$).

Discussion

Our previous studies have indicated that a strong relationship exists between elevated levels of EAA's and high ICP after a traumatic brain injury [2]. This study confirms this relationship in a much larger patient group, and also shows that increased EAA's were closely linked to patient outcome. These correlations were strongest when subdividing the patient groups into low, medium, and high glutamate categories. Patients whose post-injury mean glutamate values were >20 µMol/L seem to most often demonstrate bouts of elevated ICP, and also much worse outcome.

When the patients were grouped by CT classification, it also became evident that the lesion type had a significant role in determining the neurochemical profile of each patient. Patients with contusional lesions demonstrated the highest EAA levels. The lowest EAA's were see in the small group with uncomplicated epidural hematomas, consistent with their good outcome. Clearly further studies must be performed to further elucidate the relationships between these clinical characteristics, and EAA's and structural amino acids, in ECF, following TBI.

Acknowledgements

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Correspondence: Anthony Marmarou, M.D., Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, P.O. Box 980631, Richmond, VA 23298-0631, U.S.A.

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Selective Hippocampal Damage to Hypoxia after Mild Closed Head Injury in the Rat

H. Katoh, K. Shima, H. Nawashiro, K. Wada, and **H. Chigasaki**

Department of Neurosurgery, National Defense Medical College, Tokorozawa, Japan

Summary

Our previous studies have shown selective neuronal damage in the CA3 region after mild closed head injury (CHI) combined with hypoxia. In the present studies, we examined (1) extracellular concentrations of neuroactive amino acids using in vivo microdialysis technique and (2) neuroactive amino acid binding to their receptors using quantitative autoradiography. Male SD rats were divided into five groups; sham control, mild CHI (sacnficed at 1 h or 24 h after CHI), mild CHI followed by hypoxia (1 h or 24 h). [3H]-Glutamate binding to NMDA receptors, [3H]-muscimol binding to GABAA receptors and [3H]-kainate binding to KA receptors were measured in hippocampus and cortex by quantitative autoradiography. With CHI alone, GLU and TAU levels were transiently increased by 15 min posttrauma. In the CHI with hypoxia, increases in GLU and TAU levels were sustained until 60 min following CHI. GABA level was also increased until 75 min posttrauma Pretreatment of MK-801 significantly diminished the prolonged elevation in GLU and TAU levels. (2) CHI alone did not produce prominent change in the measured receptor binding. When hypoxia was combined with CHI, significant increase in [3H] GLU binding to NMDA receptors and significant decrease in [3H]-muscimol binding to GABAA receptors were observed in CA1 and CA3 at 1 h and 24 h post-insult.

These results demonstrate that selective hippocampal damage to hypoxia after mild CHI may be mediated through an increase in NMDA receptor activation and the further release of GLU and that NMDA antagonist may be beneficial in preventing secondary neuronal damage by hypoxia.

Keywords: Head injury; Hippocampal damage; hypoxia.

Introduction

The hippocampus is selectively vulnerable to many types of insult. Our previous studies have shown selective neuronal damage in the CA3 region after mild closed head injury combined with hypoxia. This selective CA3 lesion may be recognized as an post-traumatic increased vulnerability to hypoxia. Many recent studies demonstrated excessive Ca^{++} influx through NMDA receptor ion-channel is the major cause of neuronal damage. We hypothesized that combined traumatic and hypoxic insults may provoke neuronal damage by altering the extent of excitotoxic and inhibitory amino acid release and receptor binding activity. In this study, we examined (1) extracellular concentrations of neuroactive amino acids using in vivo microdialysis and (2) neuroactive amino acid binding to their receptors using quantitative autoradiography.

Methods

(*1*) Five groups of male SD rats, weighing 400–450 g, were set up: sham control (n = 6), head trauma (n = 6), moderate hypoxia (n = 6), trauma followed by hypoxia (n = 6), and trauma followed by hypoxia with MK-801 pretreatment (n = 6). Microdialysis probe was placed in the midportion of hippocampus. A blunt head trauma was produced by dropping a brass weight (450 g) from a height of 1 m onto the steel disc which was firmly attached on the midportion of the vertex, which was adjusted to represent a mild injury level. Hypoxia was induced by placing the animals for 30 min in a chamber filled with 5% oxygen and 95% nitrogen gas mixture. Microdialysate was collected every 15 min from 2 h before the trauma until 4 h after. The concentrations of glutamate (GLU) and GABA were measured by HPLC and analyzed by ANOVA.

(*2*) Male SD rats, ranging in weight from 350 to 400 g, were used. Ten animals underwent a head trauma followed by hypoxia and were sacrificed at 1 or 24 h after the trauma (each 5 animal). Five animals were comprised of sham control. Trauma and Hypoxia were produced by the abovementioned method. The animals were decapitated and the brains were removed and frozen quickly. Coronal sections (20 μm) of the middorsal hippocampus were thaw-mounted on slides and dried. Regional NMDA, KA and $GABA_A$ receptor bindings were examined following Monaghan *et al.* and Nobrega *et al.*. After preincubation in proper buffers, the slices were incubated in 100 mM [^{3}H]-glutamate (4°C) for 10 min (NMDA), 50 nm [^{3}H]-kainic acid (4°C) for 10 min (KA) or 200 nM [^{3}H]-muscimol (4°C) for 30 min ($GABA_A$), and then rinsed and dried. The slides were placed on imaging plates with autoradiographic [^{3}H]-microscale (Amersham) and exposed for 5 days. Autoradiographic images were obtained using digital imaging system (BAS 2000 system, Fuji Film) and densitometrical analysis was performed in three slices of each animal. Tissue [^{3}H] radioactivity in each four 16-pixel-areas of CA1, CA3 and dentate gyrus (DG) was calculated for each slice

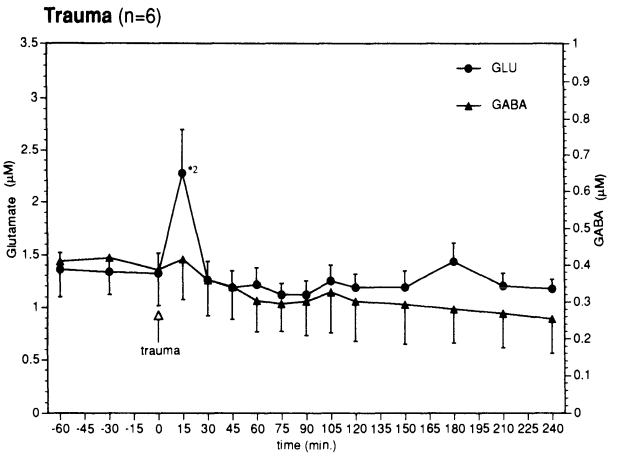

Fig. 1. Trauma (n = 6)

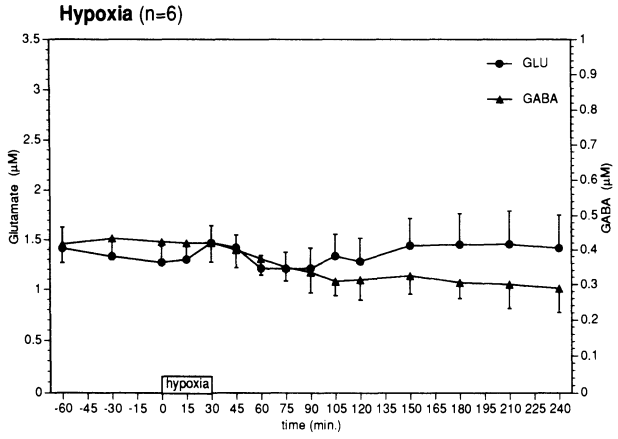

Fig. 2. Hypoxia (n = 6)

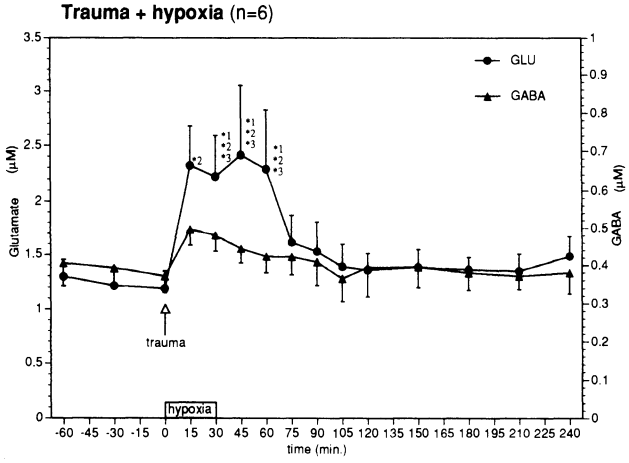

Fig. 3. Trauma + hypoxia (n = 6)

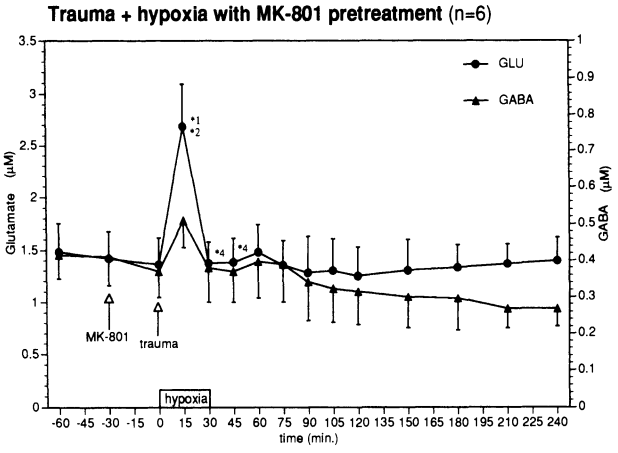

Fig. 4. Trauma + hypoxia with MK-801 pretreatment (n = 6)

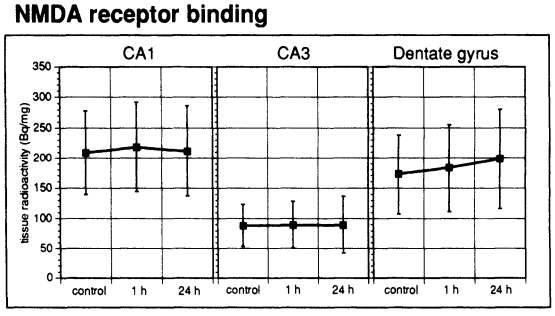

Fig. 5. NMDA receptor binding

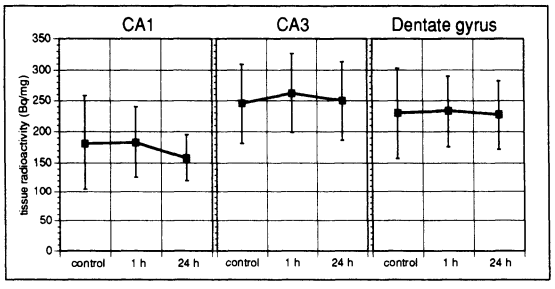

Fig. 6. KA receptor binding

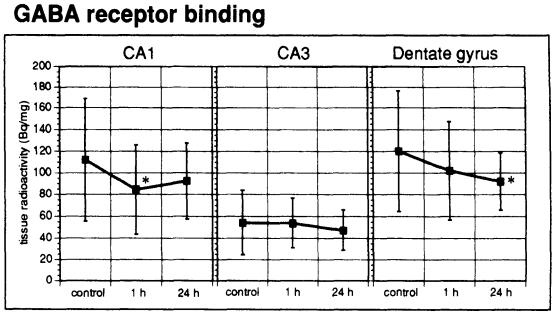

Fig. 7. GABA receptor binding

from optical density values. Statistical analysis was performed by ANOVA.

Results

(*1*) Fig. 1 to 4 shows temporal changes in GLU and GABA concentrations in the hippocampus. Values are means ± SEM. Asterisk shows significant differences ($p < 0.05$, *1 vs. control ; *2 vs. hypoxia; *3 vs. trauma; *4 vc. trauma + hypoxia). Hypoxia alone changed the concentration of neither GLU nor GABA (Fig. 2). With trauma alone, GLU concentrations were transiently increased 72% immediately after the trauma and returned to baseline quickly (Fig. 1). With trauma + hypoxia, GLU increased 95% and sustained until 60 min after the trauma. GABA level was also increased in trauma + hypoxia group, but the change in GABA was less than in GLU (Fig. 3). Pretreatment of MK-801 did not change the immediate increase in GLU concentration, but significantly diminished the prolonged GLU elevation after hypoxia (Fig. 4).

(*2*) Fig. 5 to 7 shows the regional changes in receptor bindings in the hippocampus after head trauma combined with hypoxia. Values are means ± SD. Asterisk (*) shows significant difference from control ($p < 0.05$). NMDA and KA receptor bindings were not altered significantly in any hippocampal region (Figs. 5 and 6). $GABA_A$ receptor binding was decreased 25% in CA1 at 1 h and 23% in dentate gyrus at 24 h posttrauma (Fig. 7).

Discussion

Jenkins *et al.* demonstrated that hippocampal neurons become more vulnerable to ischemia after traumatic brain injury. Nawashiro *et al.* indicated an increased vulnerability to hypoxia of hippocampal CA3 neurons in traumatized rat brains. Recent studies proved that unreasonable release of excitatory amino acids leads to excessive influx of Ca^{++} through NMDA receptor-ion channels resulting in neuronal damage in various types of insult. On the other hand, inhibitory neurotransmitters are considered to have neuroprotective effects against neurotoxicity of excitatory neurotransmitters. In this study, we demonstrated that the combination of head trauma and hypoxia provoked and extended elevation of GLU concentration in the hippocampus. GABA was also increase but the rate of increase was much smaller than that of glutamate. Trauma and hypoxia also had different effects on excitatory and inhibitory receptor binding; they decreased $GABA_A$ receptor binding but did not affect NMDA and KA receptor bindings. Our data suggests that the consecutive traumatic and hypoxic insults may produce an extremely excitotoxic condition in the hipppocampus. Increased vulnerability to hypoxia of hippocampal neurons in traumatized brain may be mediated not only by an imbalance between excitatory and inhibitory neurotransmitter release but also by disordered regulations of excitatory and inhibitory receptor metabolism. Autoradiographic data showed $GABA_A$ receptor binding is less in CA3 than in CA1, and our traumatic and hypoxic insults produced a down-regulation of $GABA_A$ receptor binding in CA1 but not in CA3. These data suggest that GABAergic inhibition may affect CA1 more than CA3 during and after the insults. This might be a cause for selective vulnerability of CA3 neurons in our model. Prolonged elevation of GLU was diminished by MK-801, a noncompetitive NMDA receptor blocker, which might be effective for hypoxic insult after head trauma.

Conclusions

These results demonstrate that selective hippocampal damage to hypoxia after mild head trauma may be mediated through both an imbalanced excitatory and inhibitory neurotransmitter release and uncoordinated receptor regulations. We also demonstrated that NMDA antagonist may be beneficial in preventing secondary neuronal damage by hypoxia.

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Correspondence: Hiroshi Katoh, M.D., Department of Neurosurgery, National Defense Medical College, Tokorozawa, Japan.

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The Use of Near Infrared Spectroscopy (NIRS) in Children after Traumatic Brain Injury: A Preliminary Report

P. D. Adelson, E. Nemoto, A. Colak, and **M. Painter**

Departments of Neurosurgery and Pediatric Neurology, Children's Hospital of Pittsburgh and The Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA, U.S.A.

Summary

Children commonly develop diffuse cerebral swelling after traumatic brain injury (TBI) which is believed due to a secondary response to the injury. Near infrared spectroscopy (NIRS), a continous, direct, and noninvasive monitor of cerebral oxygenation and cerebral blood volume (CBV), could be helpful in understanding these secondary responses. The aims of our study were to determine whether NIRS used in children with severe TBI will provide insight into the pathophysiology of injury.

Ten children (1 mo to 15 years old) with severe TBI (admission GCS ≤ 7) were continously monitored by NIRS by placing optodes over the frontalparietal region. Relative values of oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and total hemoglobin (THb) were obtained and compared to intracranial pressure (ICP), mean arterial pressure (MAP), electroencephalography (EEG), and arterial PCO_2($PaCO_2$).

Episodes of intracranial hypertension (ICP > 20 Torr [T]), changes in ICP > 10 T, changes in $PaCO_2$ ≥ 8 T, and changes in MAP > 20 T frequently resulted in changes in HbO_2, Hb, and THb. Hyperventilation with decreased $PaCO_2$ always resulted in cerebral oxygen desaturation irregardless of ICP. Often, high ICP correlated with increased THb and HbO_2 indicating increased CBV and cerebrovascular dilatation. In two children, posttraumatic seizures were preceded by an unexplained rapid cerebral hyperoxygenation several hours prior to the onset of the clinical seizures.

NIRS reliably detects changes in cerebral hemodynamics in children and may be used to further understand the etiology of the diffuse cerebral swelling seen in children after severe TBI.

Keywords: Near infrared spectroscopy (NIRS); traumatic brain injury.

Introduction

In children, diffuse cerebral swelling more commonly develops as a secondary response after TBI compared to adults and is associated with an approximately 50% mortality and increased disability. Cerebrovascular dilatation due to a loss of autoregulation with hyperemia [3] and cytotoxic edema [6] have been suggested as key events in the evolution of this pathophysiologic response in children. The importance of each of these two pathophysiologic responses in the pediatric population and their effect on morbidity and mortality remains unclear.

The underlying goal in the treatment of patients after TBI is to lessen the effects of secondary injury by creating an environment conducive to cerebral recovery. Success to date in lowering morbidity and mortality has been due to the aggressive management of these patients that focuses on interventions that impact on maintaining adequate cerebral perfusion (eg) early evacuation of mass lesions and the treatment of cerebral swelling through ICP monitoring and manipulation. To further improve outcomes in the child following severe TBI, we must be able to accurately characterize the events that occur in the posttraumatic period that may worsen secondary injury. Though imaging and our present on- line monitoring, including ICP, MAP, CPP, jugular venous bulb sampling and EEG, has aided in a better understanding of the global picture of the cerebral response to injury, they have not provided a clear understanding of the hemodynamic changes that occur during the routine care of these injured patients nor the pathophysiologic responses after injury which may impact on final outcome.

Near infrared spectroscopy (NIRS) is a continuous, direct, and noninvasive monitoring device of cerebral oxygenation and CBV that has been useful for cerebral monitoring during carotid endarterectomy and cardiopulmonary bypass surgery [1,7–9] where extended periods of decreased cerebral perfusion may occur. Due to their relatively thin scalps

and skulls. NIRS has also been shown to be particularly useful in the monitoring of neonates and children [2,4].

Our hypothesis is that the pathophysiologic responses (eg) cerebral ischemia and metabolic aberrations, that occur after severe TBI in children can be detected earlier and better characterized with cerebral oximetry using NIRS than with the monitoring modalities presently employed. For this preliminary report, we sought: 1) to determine the efficacy of NIRS in children after TBI by comparing the findings on the NIRS for cerebral oximetry to standardly measured physiologic parameters that are routinely monitored both continuously and intermittently; and 2) to determine the etiology of the changes in ICP and whether it is predominantly due to increased CBV and hyperemia or edema.

Materials and Methods

Ten children (1 mo to 15 yo) who suffered a severe TBI (admission GCS ≤ 7) were admitted to the intensive care unit after appropriate resuscitation and imaging. A ventriculostomy, an arterial line, and EEG leads were placed in each child, and ICP, MAP, and EEG were continuously monitored throughout their acute care course. Each child received intensive medical management as per our standard severe head injury protocols (IRB approved) including head elevation, mild hyperventilation ($PaCO_2$ 30–35), osmotic diuretics, continuous cerebral spinal fluid drainage, and in some cases, barbiturates. NIRS was performed using both the Hamamatsu (NIRO 500) and Somanetics (INV03100A) by placing optodes over the frontal-parietal region of the more severely affected side based on the initial CT scan. The small 5 mm diameter optodes of the NIRO 500 enabled placement on all the areas of the brain.

The light source at the optodes emits light in the near-infrared range (700 nm to 900 nm) and illuminates the underlying tissue. For the NIRO 500, upon receiving the reflected signal at the optode patch, relative values of oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and total hemoglobin (THb) can be calculated [4]. Of note is that THb reflects the relative CBV. For the Somanetics INV03100A, an estimate of regional cerebral oxygen index (rSO_2) is calculated [5]. Over the first 5 d after TBI, trends up to 24 hours duration were obtained and compared to the standard continuously obtained physiological data including MAP, ICP, CPP, end tidal CO_2 ($ETCO_2$), and EEG as well as intermittent measures including CBF (via stable Xenon CT), and $PaCO_2$ (via arterial blood gases).

Intracranial hypertension (ICP > 20 Torr [T]), changes in ICP and CPP (>10 T), $PaCO_2$, (≥8 T), MAP (≥20 T), seizures, and standard ICU care (eg) suctioning, transport to CT, etc., were recorded and then compared to changes on NIRS specifically, cerebal oxygen saturation, THb, HbO_2, Hb, and rSO_2.

Results

Of the ten children studied, there were 6 males and 4 females, with an age range of 1 months–15 years old. Six were involved in a motor vehicle accident either as a passenger (2), bicyclist (2), or pedestrian (2). Three children were victims of abuse/assault and one child fell from a horse. All had a Glasgow Coma Score (GCS) ≤ 7 on admission. All underwent intensive management of their injuries and were in the intensive care units for 3 days–3.5 weeks. Four of the children died and 4 others are left with severe or moderate disabilities.

Changes in $PaCO_2$ ≥ 8 T always resulted in a change in THb, HbO_2, and Hb (Fig. 1). Hyperventilation or decreasing $PaCO_2$ resulted in a decrease in THb or relative CBV but also decreased HbO_2. NIRS positively predicted cerebral oxygen desaturations with hyperventilation in 100% of cases. Conversely, increases in $PaCO_2$ resulted in increases in THb and HbO_2. These changes along with $PaCO_2$ seemed to indicate that CO_2 vasoreactivity was intact in all of these severely injured children. Arterial oxygen desaturations (PaO_2) could frequently be observed by the cerebral oximeters with a resultant decrease in HbO_2 and an increase in Hb (Fig. 2).

Episodes of intracranial hypertension (ICP > 20 T) and interventions to manage the high ICP often resulted in changes in HbO_2, Hb, and THb (Table 1). High ICP and decreased CPP often correlated with increased THb and HbO_2 indicating increased CBV and cerebrovascular dilatation (hyperemia). Some of the children, though, exhibited cerebral hemoglobin desaturation (decreased HbO_2 and increased Hb), particularly at times of very high ICP, during these episodes of increased THb. This most likely represents local tissue ischemia from decreased perfusion.

In two patients who suffered seizures, a dramatic increase in cerebral oxygenation was observed several hours prior to the onset of seizures. If these observations are specific and reproducible, cerebral oximetry may be useful useful in monitoring for the onset of seizures and appropriate therapeutic intervention.

The findings for MAP were not as associative. Changes in MAP of > 20 T were only correlative with changes in NIRS approximately 50% of the time, and mostly associated with ICP/CPP changes. This finding for MAP seemed to indicate that pressure autoregulation was variably intact in these children. Also, transport of the patient (eg) to CT scan, resulted in cerebral oxygen desaturation in approximately 50% of instances. Interestingly, in two children, we observed that post-traumatic seizures were

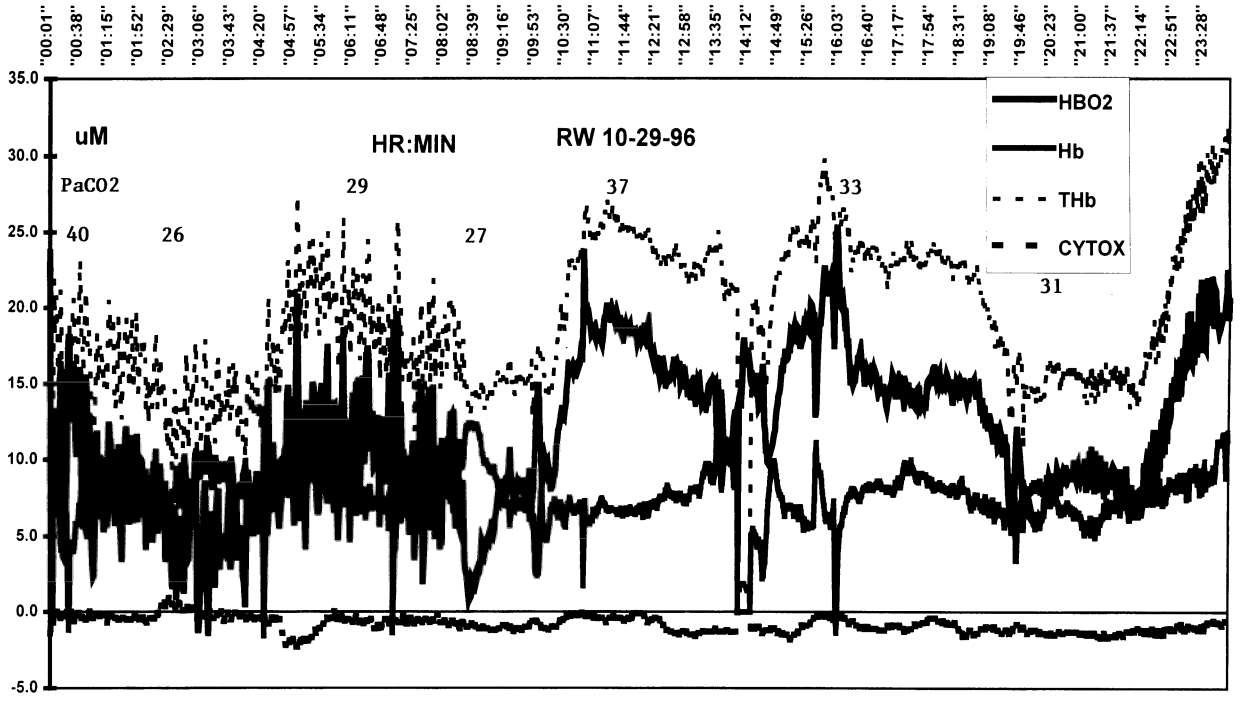

Fig. 1. Cerebral oximetry (NIRO 500) in a 1 mo male two days after severe traumatic brain injury. *HbO_2*-oxyhemoglobin, *Hb*-deoxyhemoglobin, *THb*-total hemoglobin, *Cytox*-cytochrome a,a3, *$PaCO_2$*-arterial PCO_2

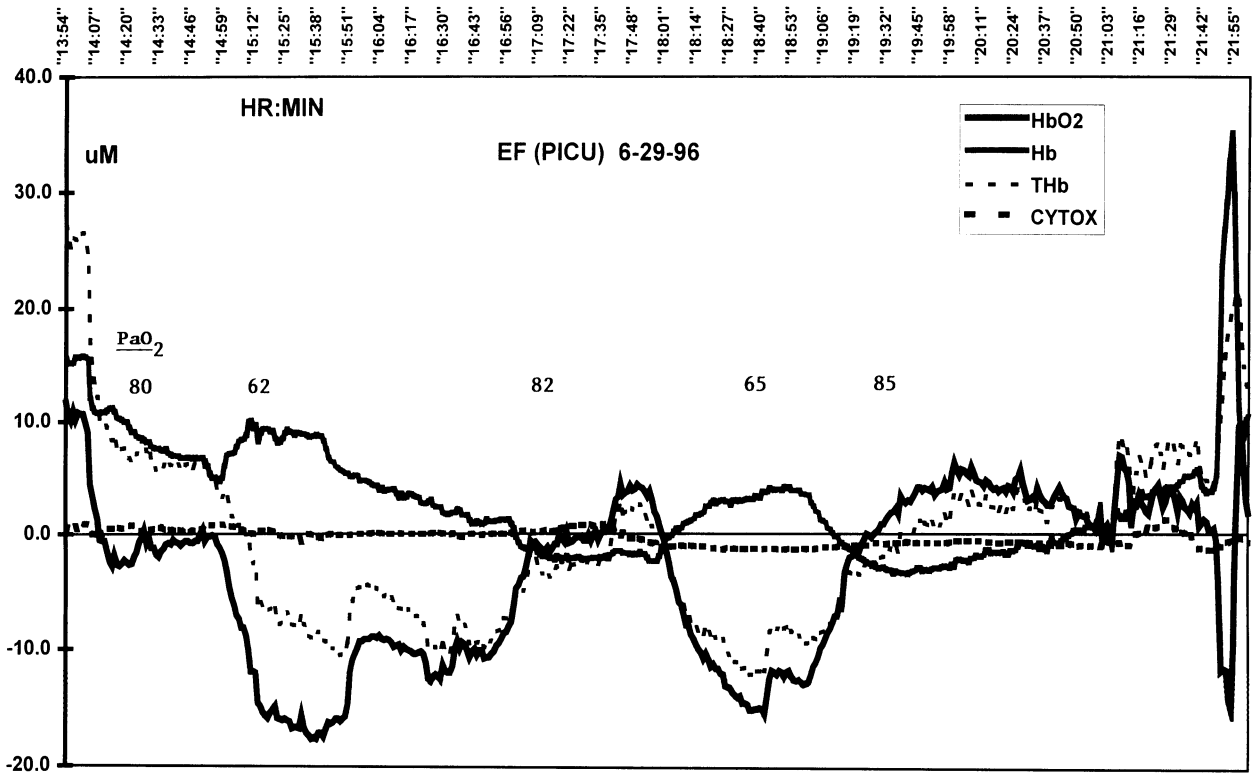

Fig. 2. Cerebral oximetry (NIRO 500) in a 6 yo female who suffered a severe traumatic brain injury 6–7 days after being thrown and trampled by a horse. *ICP*-intracranial pressure

Table 1. *Cerebrovascular Dilatation and ICP Rise with Reduced CPP in a Head Injured Child*

HR:MIN	HbO_2 mmoles/liter	Hb	THb	ICP mm Hg	CPP mm Hg
1:00	4.9	3.5	8.4	9	80
2:00	12.7	2.2	14.9	15	74
3:00	40.5	8.7	49.2	30	52
4:00	10.0	1.7	11.7	7	77

preceded by an unexplained rapid rise in cerebral hyperoxygenation that began within hours before the onset of clinical seizures with no changes in ICP, CPP, nor any other physiologic parameter and then episodic cerebral hyperoxygenation during the ictal event.

Discussion

Cerebral oximetry has previously been shown to be efficacious in the determination of cerebral hemodynamics in adults [1,7,9] and neonates [2,4]. The purpose of this study was to determine if NIRS could provide a continuous, noninvasive monitoring of cerebral oxygenation in the intensive care unit in severely head injured children. We have been able to show for the first time in this preliminary study, that NIRS reliably detects changes in cerebral hemodynamics in children following severe TBI. The aspects of the NIRS that were notable in this study included an ability to, as an early warning, detect periods of cerebral oxygen desaturations and/or changes in CBV during routine care and interventions (eg) hyperventilation (decreased $PaCO_2$), as well as during changes in ICP, CPP, MAP, $PaCO_2$, transport of the patient, and the development of seizures.

NIRS may serve as a better monitor of the adequacy of cerebral oxygenation and perfusion than ICP and CPP, particularly in response to interventions that may cause a pathophysiologic response, changes in $PaCO_2$, PaO_2, or MAP. In all instances, NIRS showed that hyperventilation in these patients caused not only a decrease in THb (CBV), but also decreased HbO_2 which was reversible with an increase in $PaCO_2$ indicating intact CO_2 vasoreactivity. These desaturations, though, also occurred at times when there was no response by ICP measures. As a result, it remains unclear whether this intervention was detrimental in all instances. Instances of increased ICP were often associated with increased THb and HbO_2 indicating increased CBV and hyperemia as the genesis of the raised ICP but there were also instances of increased THb and decreased HbO_2. Though we did not correlate these occurrences with MAP, these may represent periods with hyperemia with local tissue ischemia. We also found that the changes in MAP were correlative in 50% of the instances of cerebral oximetry change. This may be an indication that these were periods of pressure dysautoregulation since with intact pressure autoregulation, there should be no change in THb though maybe an increase in HbO_2 due to improved perfusion. Further analysis is needed.

In conclusion, NIRS may serve as an improved method of earlier detection and monitor of the effects of intervention for cerebral oxygen desaturations and/or changes in CBV in children with severe TBI which may have an impact on final outcome. Also, since NIRS was able to detect increases and decreases in CBV in children with increasing ICP, it may also be a useful device for the further understanding of the etiology of diffuse cerebral swelling and secondary injury in children after TBI.

Acknowledgment

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Correspondence: P. David Adelson, M.D., Department of Pediatric Neurosurgery, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, PA 15213-2583, U.S.A.

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Preliminary Evaluation of a Prototype Spatially Resolved Spectrometer

P. G. Al-Rawi, P. Smielewski, and **P. J. Kirkpatrick**

University Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, U.K.

Summary

Near infrared spectroscopy (NIRS) has become an established research tool and is now being explored in several clinical settings [7]. However, until recently NIRS has not been fully quantified and changes have been difficult to interpret [4]. A new development by Hamamatsu Photonics, called the Spatially Resolved Spectrometer (SRS), proposes to be able to give a quantitative measure of oxygen saturation. We have incorporated the SRS into a multimodality monitoring system in three different clinical situations: 1) patients undergoing routine cardiopulmonary bypass, 2) head injured patients and 3) patients undergoing right-sided carotid endarterectomy. The importance of this investigation is in the development of the SRS machine which shows potential as a useful clinical tool. The results demonstrated good correlation between SRS and jugular venous oximetry (SjO_2) in about 50% of patients. Although these results are encouraging, this study suggests that the SRS, in its present form, is not a reliable clinical monitor of cerebral oxygen saturation.

Keywords: Near infrared spectroscopy (NIRS); oxygenation; spectrometer.

Introduction

The clinical measurement of brain oxygenation is important since episodes of reduced cerebral oxygen saturation are associated with a poor outcome in brain injured patients [9]. Secondary ischaemic damage frequently develops following the primary cerebral insult [1,9]. Current methods of detection tend to be unreliable, time consuming, invasive, expensive and fraught with difficulty [2].

Hamamatsu Photonics, in conjunction with University College London, have developed a new near-infrared spectrometer called the Spatially Resolved Spectrometer (SRS) which proposes to be able to give a quantitative measure of oxygen saturation. Unlike earlier NIRS monitors developed by Hamamatsu, the SRS is capable of measuring the absolute concentrations of haemoglobin (Hb) and oxyhaemoglobin (HbO_2) in cerebral tissue, rather than just the relative changes in concentration of theses chromophores. Our aim was to assess whether the newly developed SRS provides valid measurements of cerebral oxygen saturation in the adult brain by comparing the values generated by the SRS with jugular venous oxygen (SjO_2) measurements. We have incorporated the SRS into out multimodality monitoring in three clinical scenarios. Firstly, in patients undergoing routine cardiopulmonary bypass (n = 24). It has been shown that the period following moderate hypothermic bypass is one of increased neurological risk [8]. We believed that episodes of global desaturation would help to provide direct validation of SRS against jugular venous oximetry. Secondly, in head injured patients (n = 16), since after severe acute head injury, secondary cerebral ischaemic damage is known to occur [1,9]. Our aim was to capture these events and correlate SjO_2 variations with changes in SRS. Lastly we tested the SRS on patients undergoing right-sided carotid endarterectomy (n = 6). Cross-clamping of the internal carotid artery during operation carries the risk of causing temporary cerebral ischaemia [6]. By frequent intermittent blood sampling from the right jugular bulb, we aimed to quantify the degree to which desaturation occurs and to correlate these findings with SRS readings.

Materials and Methods

The SRS differs from conventional NIRS machines by using spatially resolved reflectance spectroscopy to estimate absolute concentrations of Hb and HbO_2 in diffuse intracranial tissue and can in theory provide direct, continuous on-line measurements of measured cerebral haemoglobin oxygen saturation. The SRS de-

livers 4 wavelengths of near infrared light through a flexible fibre optic bundle housing 4 laser diodes. Back scattered light is detected by a new design of detector which consists of 3 closely placed photodiodes arranged in 3 parallel strips. The light detected by each photodiode is used to generate a plot of log of attenuation against distance from source. The rate of increase of attenuation with respect to source/detector spacing, i.e. the slope, can then be calculated. These measurements are converted into estimates of the product of absorption and scattering coefficients of the tissue according to the equation:

$$\mu_a \times \mu_s \approx \left(\frac{\delta A}{\delta d} - \frac{2}{d} \right)^2$$

where μ_a = absorption coefficient, μ_s = scattering coefficient, A = attenuation, d = distance.

In vivo measurements have produced an algorithm which gives the scattering coefficient for the tissue and thereby estimates the total tissue absorption coefficient. These calculations are done at each of the four wavelengths of light. Using a regression model obtained from multiple regression analysis of known Hb and HbO_2 concentrations and absorptions, total absolute concentrations of Hb and HbO_2 for each absorption coefficient can be calculated, and hence mean cerebral haemoglobin oxygen saturation. In each case, the SjO_2 catheter was placed in the right internal jugular bulb [5]. Correct positioning was verified by lateral cervical x-ray [5]. SRS probes were placed high on the ipsilateral forehead, sufficiently lateral from the midline to avoid the superior saggital sinus, and care was taken to ensure no hair was between optodes and skin. Optode spacing was kept at either 5 or 6 cm. Frequent blood samples from the SjO_2 catheter and arterial line were analysed for oxygen saturation and haemoglobin concentration. Events were accurately documented and data signals from all the monitored parameters were digitised and collected on computer using specific multimodality software [3]. For purposes of comparison, linear regression was used to calculate the correlation coefficient between SjO_2 and SRS %sat.

Results

Our results from clinical application 1 (patients undergoing routine cardiopulmonary bypass) demonstrated that correlation between SjO_2 measurements and SRS varied greatly from patient to patient. Dividing the cardiopulmonary bypass (CPB) operations up into four different periods (Fig. 1) demonstrated a significant difference between the jugular bulb saturation values obtained pre-bypass, during early bypass and in the rewarming phase.

Typically the values obtained during bypass were in the region of 75% saturation, and the lowest values obtained were seen during rewarming (Table 1).

The SRS readings follow a very similar pattern, with a significant difference seen between the early bypass period and rewarming. The SRS values are lower than the SjO_2 and the range of changes is smaller.

For individual cases, r values were found to be in the range 0.08–0.97. However, a significant correlation was seen in 50% of patients. When the data for all 24 CPB cases was regressed, the scatter of data points was high (r = 0.41).

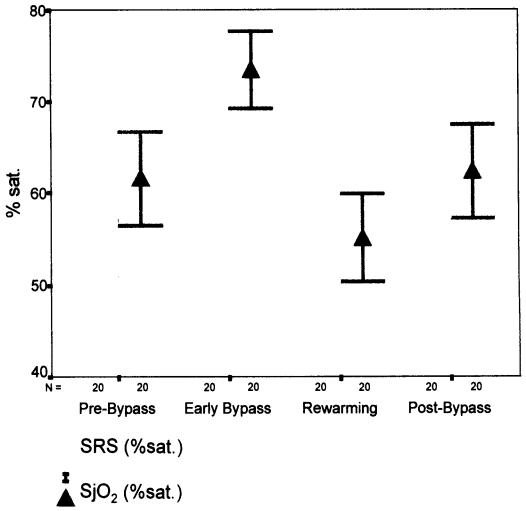

Fig. 1. Graph displaying mean values (±95% confidence limits) of SRS and SjO_2 saturation for all hypothermic bypass cases

Table 1. *Pooled Data (Means ± se) for Different Stages of Hypothermic CABG Operation*

	Pre-bypass	Early bypass	Rewarming	Post-bypass
SRS (%sat.)	54 ± 3.3	57 ± 3.8	49 ± 3.4	54 ± 3.9
SjO_2 (%sat.)	62 ± 5.6	73 ± 4.6	55 ± 5.3	63 ± 5.6
SaO_2 (%)	97 ± 1.0	97 ± 1.1	96 ± 1.0	96 ± 1.0
ABP (mm Hg)	73 ± 5.4	56 ± 6.4	57 ± 5.4	68 ± 3.8

Our results obtained from the head injury group have demonstrated a very similar picture to that obtained in the cardiopulmonary bypass patients. Great variability was seen in correlation between SRS and SjO_2 saturation both between patients (r values ranging between 0.03–0.88) and during the period of monitoring any one patient. Fig. 2, taken from our multimodality software, demonstrates the typical data obtained from a case showing good correlation.

One of the main problems encountered has been the difficulty obtaining adequate intensity readings from the SRS. This has occurred in approximately 50% of the patients monitored. Even with the optode distance as close as 3 cm we often obtained extremely low values for detected light.

Our carotid endarterectomy results have also shown the same variability. Three out of the six patients showed good correlation. In those cases where the SRS did closely follow the SjO_2 readings, the SRS responded to periods of desaturation more rapidly than the jugular bulb catheter.

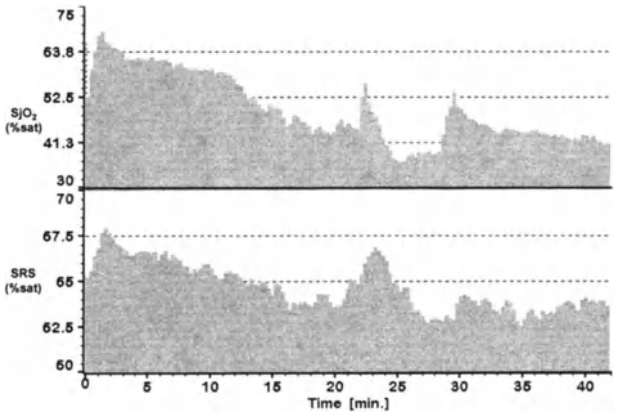

Fig. 2. Graphic display of data obtained from a head injured patient, showing SRS and SjO_2 saturation over a 40 minute period. The SRS and SjO_2 follow a very similar pattern and are closely correlated (r = 0.78)

Discussion

Despite the variation between SRS and SjO_2, the incidences of good correlation are encouraging. There are a number of reasons as to why, on some occasions, the SRS and jugular bulb readings varied so widely. As with all forms of NIRS, extracranial contamination is a problem [4,7]. Modelling calculations based on MRI images and showing PMDF (photon measurement density function) demonstrate that the adult head models show very little sensitivity for near-infrared light in areas of grey and white matter, with most of the light probing skin and skull. This assumes even greater importance in the swollen extracranial tissue of head injured patients. It is also likely that the CSF layer causes a uniform distribution of near-infrared light, which results in a reduction in the calculated slope and ultimately to abnormally low values for saturation.

The small range of SRS values may be expected since the cerebral microcirculation (from which the SRS obtains its values for Hb saturation), although largely of venous composition, has a 25% contribution from the arterial and capillary circulation. Additionally, SjO_2 measurements give an estimation of the global cerebral oxygen saturation whereas the SRS monitors regional saturation. Finally, the conditions of haemodilution, hypothermia and non-pulsatile flow which occur during CPB, could introduce errors into the readings and render the algorithm of the SRS inadequate under these conditions.

Continuous and non-invasive monitoring of oxygenation using SRS shows potential as a method for detecting desaturation. However, the results of our studies suggest that the SRS is not, as yet, a reliable monitor of cerebral oxygen saturation due to a multitude of conflicting variables. In particular, the problems of extracerebral contamination need to be addressed and future developments of this technique will need to be able to extract this signal.

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Correspondence: P. G. Al-Rawi, M.D., University Department of Neurosurgery, Box 167, Level 4, A Block, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, U.K.

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NIRS: Dose Dependency of Local Changes of Cerebral HbO_2 and Hb with pCO_2 in Parietal Cortex

P. B. Benni[1], **C. Quick**[1], **B. Chen**[1], **H. Bada**[2], **C. W. Leffler**[3], and **M. L. Daley**[4]

[1] Department of Anesthesia, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [2] Department of Pediatrics and Obstetrics, University of Tennessee, Memphis, TN, [3] Department of Physiology and Biophysics, University of Tennessee, Memphis, TN, and [4] Department of Electrical Engineering, University of Memphis, TN, U.S.A.

Summary

Regional cerebral oxygenated hemoglobin and total hemoglobin increased systematically with increasing depth of hypercapnia, but the concentration of deoxygenated hemoglobin remained relatively constant. Relative mean changes of oxygenated and total hemoglobin increased nearly linearly, corresponding to the characteristic increase of the cerebral vascular dilation with increasing depth of hypercapnia.

Keywords: NIRS.

Introduction

Carbon dioxide is a cerebral vasodilator. Cerebral blood flow (CBF) increases rapidly over arterial pCO_2 values from 20 to 90 mm Hg, then increases more gradually at values greater than 90 mm Hg, fitting an exponential curve [4]. Cerebral blood volume increases linearly with increasing arterial pCO_2 when computed from measured CBF and cerebral vascular mean transit time by using radiolabeled ^{15}Oxygen as a tracer [3]. A non-invasive technique, near-infrared spectroscopy (NIRS) offers the ability to assess relative changes in regional cerebral blood volume (ΔrCBV) by monitoring the relative changes of oxy-hemoglobin (ΔHbO_2) and deoxy-hemoglobin (ΔHb) [2,5]. The summation of ΔHbO_2 and ΔHb gives relative total hemoglobin changes (ΔTotalHb), which is proportional to ΔrCBV when the hematocrit (Hct) is constant. The purpose of this study was to evaluate the dose-dependency of concentration of the hemoglobin chromophores induced by varying the state of hypercapnia in a laboratory preparation.

Methods and Materials

Eight piglets, weighing 1.5 to 3 kg were used in this study. Each animal was anesthetized with ketamine (33 mg/kg) and acepromazine (3 mg/kg). The animals were intubated and ventilated with a positive pressure respirator set at a rate ranging from 15 to 25 breaths/min and inspiration pressure was about 9–12 cmH_2O. Anesthesia was maintained a-chloralose (50 mg/kg, initially, and 10 mg/kg hourly). Arterial pressure was recorded from a fluid filled catheter placed in the brachial artery. Intracranial pressure (ICP) was recorded using the Camino fiber optic system (Camino Laboratories, San Diego, CA). Arterial pCO_2 was changed by altering the amount of CO_2 gas mixture of the inspired air. Arterial blood gas measurements were made about 15 minutes after each change in gas mixture.

An incision was made in the scalp and the NIRS probe, consisting of two laser diode light sources (wavelengths 750 and 810 nm), with a photodetector located 2 cm away from the laser diodes, was placed on the skull over the right cerebral hemisphere. The ICP probe was inserted in the left cerebral hemisphere via a burr hole in the skull and fixed with dental acrylic. The NIRS system used was of our own design, and similar to the NIRS systems used in other studies [1]. Data were recorded via Dataq DI-220 (Dataq Instruments, Akron, OH) portable data acquisition system and stored on the computer for future analysis.

Results

An example of recorded relative changes of regional cerebral oxygenated and deoxygenated hemoglobin and total hemoglobin as the CO_2 gas mixture was adjusted by steps (pCO_2 set at 30, 45, 65, 100, 65, 45, 30 mm Hg), with each step transition occurring every 15 to 30 minutes is shown (see Fig. 1). Numbers above each arrow represent the measured arterial pCO_2 values at specified time. Both ΔHbO_2 and ΔTotalHb rose with increasing depth of hypercapnia while ΔHb generally decreased slightly. In most cases, ΔHbO_2 and ΔTotalHb decline towards normal levels as arterial pCO_2 decreased. Relative mean changes of regional cerebral hemoglobin with increasing depth of hypercapnia are shown (see Fig. 2).

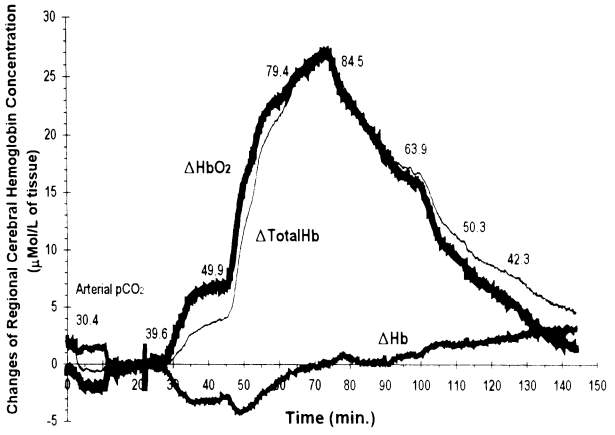

Fig. 1. Example of relative changes of hemoglobin versus arterial pCO_2. Hypercapnia was produced by increasing the inhalation flow of CO_2. Measured arterial pCO_2 values are indicated

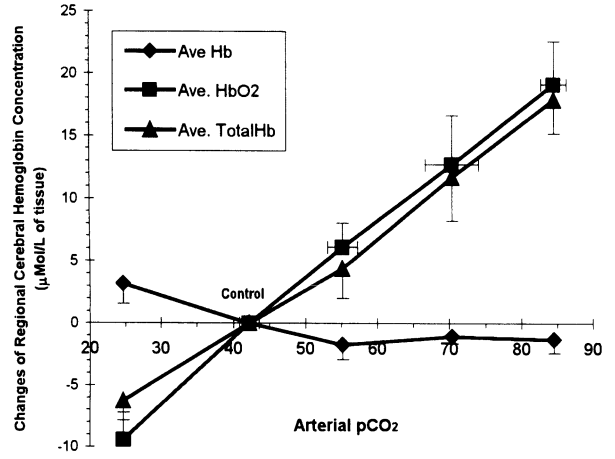

Fig. 2. Relative changes of regional cerebral hemoglobin with increasing depth of hypercapnia. The grand mean values computed from all animals are plotted with standard error bars. Increasing the depth of hypercapnia increases relative blood volume and ΔHbO_2

In constructing this figure, averaged values of ΔHb, ΔHbO_2, and $\Delta TotalHb$ were placed in five categories relative to arterial pCO_2. These values were 25, 42, 55, 70, and 85 mm Hg during the induced increase of pCO_2 to the maximum value. We selected the category of pCO_2 at 42 mm Hg to represent the baseline in which the NIRS parameters were set to zero.

Discussion

Since $\Delta TotalHb$ is proportional to $\Delta rCBV$, our results show a rise of $\Delta TotalHb$ with increasing arterial pCO_2 similar to Grubb *et al.* [3]. The increasing ΔHbO_2 and $\Delta TotalHb$ seems to appear linear with increasing arterial pCO_2. Large, simultaneous changes of ΔHbO_2 and $\Delta TotalHb$ relative to ΔHb could result from greater relative increases of precapillary blood volume as opposed to postcapillary volume. Conversely, and more likely, since NIRS monitors a mixed bed of tissue containing arterioles, venuoles, and capillaries, the results suggest an increasing oxygenated blood volume passing to the venous circulation. Since CO_2 acts as a vasodilator to cerebral vasculature, the lower resulting vascular resistance, mainly from the relaxation of the arterioles, would allow more oxygenated blood to pass to the venous circulation as a result of greater blood flow. Interestingly, the NIRS parameters vary with the respiratory cycle, showing a slight oscillation. With increasing arterial pCO_2, the peak-to-peak respiratory modulated amplitude of ΔHbO_2 and $\Delta TotalHb$ was observed to increase. The changing vascular resistance and compliance during elevated pCO_2 may be responsible for these observations.

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Correspondence: Paul B. Benni, M.D., Department of Anesthesia, UMDNJ-Robert Wood Johnson Medical School, CAB 3100, 125 Paterson Street, New Brunswick, NJ 08901, U.S.A.

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Multimodal Hemodynamic Neuromonitoring – Quality and Consequences for Therapy of Severely Head Injured Patients

J. Meixensberger, A. Jäger, J. Dings, S. Baunach, and **K. Roosen**

Department of Neurosurgery, University of Würzburg, Würzburg, Federal Republic of Germany

Summary

Fifty-five head injured patients (GCS < 8) were studied at an average of 7.5 +/– 3.4 days on the ICU to check quality of hemodynamic monitoring and the consequences for therapy. Multimodal neuromonitoring included intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), endtidal CO_2 ($EtCO_2$) as well as brain tissue – pO_2 ($p(ti)O_2$), regional oxygen (rSO_2) and jugular venous oxygen saturation (SjO_2). Regional $p(ti)O_2$ as well as global SjO_2 were sensitive technologies to detect hemodynamic changes. However analyzing reliability and good data quality regional $p(ti)O_2$ (up to 95%) was superior to jugular bulb oximetry (up to 50%). Longterm – measurements of rSO_2 using near infrared spectroscopy reached, if possible, a restricted reliability (good data quality up to 70%) and sensitivity in comparison to $p(ti)O_2$. Especially $p(ti)O_2$ enabled detection of critical $p(ti)O_2$ (<15 mm Hg) in up to 50% frequency during the first days after trauma and a second peak after day 6 to 8 according to evidence of CPP insults. Knowledge of baseline $p(ti)O_2$ and CO_2 – reactivity allowed minimizing risk of ischemia by induced hyperventilation and improvement on cerebral microcirculation after mannitol administration could be individually recognized.

Keywords: Brain tissue – pO_2; jugular venous oxygen saturation; regional oxygen (rSO_2).

Introduction

Secondary insults, caused by hypoxia or increased intracranial pressure, are major factors worsening outcome of severely head injured patients during longterm intensive care treatment. Therefore, hemodynamic monitoring technologies are necessary to detect and treat early such ischemic events. Nowadays there are different continuous monitoring methods available: The jugular venous oximetry [2] is an invasive global/hemispheric method, which determines cerebral oxygenation only indirectly. Brain tissue – pO_2 ($p(ti)O_2$) measurement [1] is an invasive, regional method. Monitoring of brain $p(ti)O_2$ reflects the balance between the oxygen offer of the blood and the oxygen consumption of the brain tissue. Regional oxygen saturation (rSO_2) using near infrared spectroscopy [3] is a non – invasive technology. The issue of our study was to check the quality of these new hemodynamic monitoring technologies. Additionally time course of ischemic insults was analyzed and consequences for therapy of raised intracranial pressure were evaluated.

Patients and Methods

Totally 55 severely head injured patients (GCS < 9, age 31.3 +/– 9.8) with diffuse or focal brain injury were studied at an average of 7.5 +/– 3.4 days (range 1–16) on the neurosurgical ICU. All patients were treated, using a standard therapeutic protocol. Space – occupying intracranial haematomas were immediately evacuated. All patients were treated to control ICP below 20 mm ICP and CPP above 70 mm Hg using sedation, hyperventilation and mannitol. Permission to perform multimodal neuromonitoring was given by the local ethics committee. Neuromonitoring included ICP (Camino Laboratories, San Diego, U.S.A.), MAP, recorded from a radial arterial catheter calibrated to the Foramen of Monroi, the calculated CPP (= MAP minus ICP), endtidal CO_2 (CO^2et), regional brain $p(ti)O_2$ (LICOX System, GMS mbH, Kiel-Mielkendorf, Germany), rSO2 (INVOS 3100 Oximeter, Somanetics, Detroit, U.S.A.) and SjO_2 (Oximetrix-3 System, Abbott Laboratories, North Chicago, U.S.A.). The brain $p(ti)O_2$ sensor was inserted besides the tissue ICP – probe in CT – visible normal brain (white matter) on the right frontal side, if there was a diffuse brain injury or on the affected side, if there was a hemispheric lesion [1]. Transcranial cerebral oximetry was performed attaching the disposable sensor pad to the patients frontal skin at the same side of ICP –, $p(ti)O_2$ – monitoring [3]. The SjO_2 monitoring was done after placement of a fiberoptic catheter into the jugular bulb corresponding to the technique described by Robertson *et al.* [2]. Data – sampling and – storage (every 10 seconds) in ASCII data files were done using a personal computer (Intel 486/75 Mhz, 16 AD converter, 16 Mbyte RAM, 1 Gbyte

hard disk) working on a MS-DOS / windows program and were statistically evaluated with our own program based on Mathematica running on an UNIX workstation.

Results

Data Quality

Regional $p(ti)O_2$ as well as global SjO_2 were sensitive technologies to detect hemodynamic changes. However, analyzing reliability and good data quality regional $p(ti)O_2$ (up to 95%) was superior to jugular bulb oximetry (up to 50%). Longterm – measurements of rSO_2 using near infrared spectroscopy are sometimes technically impossible. If data reading was possible, reliability (good data quality up to 70%) and sensitivity was restricted in comparison to $p(ti)O_2$.

Based on our data of practicablitiy and reliability, we focused our studies on brain $p(ti)O_2$ and analyzed the time course of brain $p(ti)O_2$ and the effect of therapy.

Time Course of $p(ti)O_2$ after Head Injury

Time course of $p(ti)O_2$ ($n = 40$) is illustrated in Fig. 1. In the first two days after injury $p(ti)O_2$ ranged below 15 mm Hg. On day 3, 4 and 5 a relative increase up to hyperemic $p(ti)O_2$ (>30 mm Hg) could be found, which decrease to normal level of $p(ti)O_2$ after day 6. Analyzing the distribution of three different $p(ti)O_2$ classes (<15 mm Hg, 15–30 mm Hg, >30 mm Hg) critical low $p(ti)O_2$ values <15 mm Hg could be observed in more than 50% on day 1, on day 2 in approximately 25% frequency. A second peak was found after day 6. Ischaemic $p(ti)O_2$ episodes were caused often by raised intracranial pressure, systemic hypotension as well as hypocapnia and rarely systemic hypoxia.

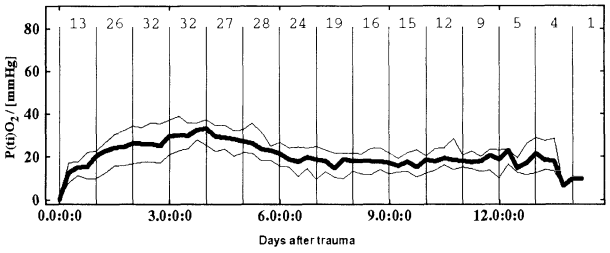

Fig. 1. Time course of brain tissue – pO_2 ($p(ti)O_2$) after severe head injury. Graphs were calculated from ASCII data files of forty patients. Median $p(ti)O_2$ +/– standard deviation every 6 hours, top line: number of included patients per day after trauma

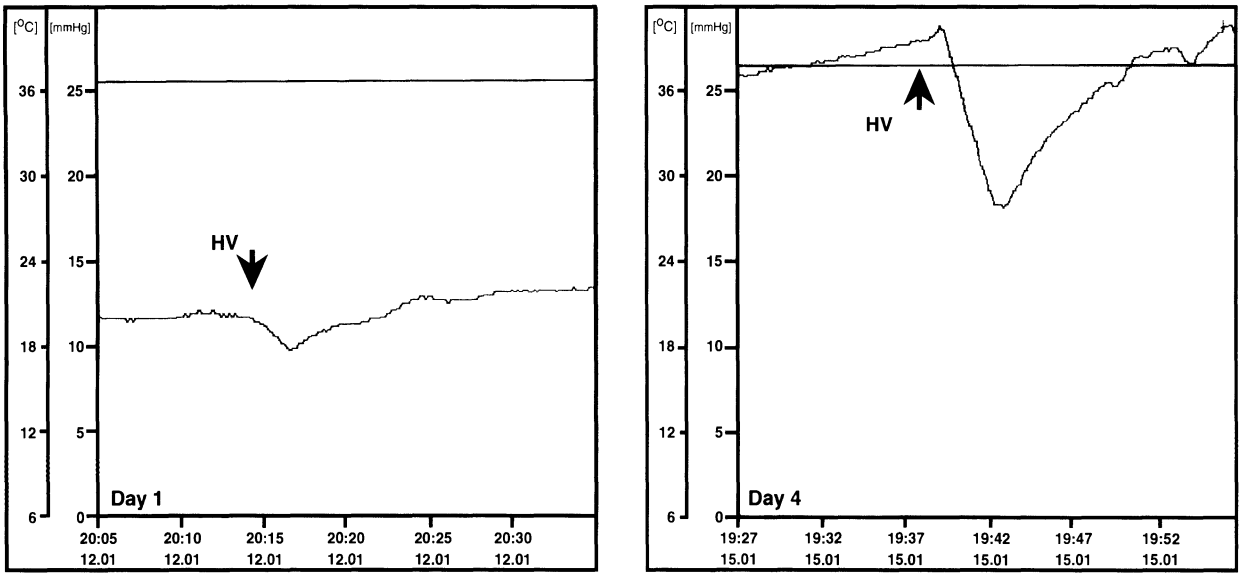

Fig. 2. Hyperventilation therapy (HV) for treatment of raised intracranial pressure – orginal tissue – pO_2 ($p(ti)O_2$) – chart of a severely head-injured patient after change of $paCO_2$: Day 1 after trauma (left): Induced hypocapnia ($paCO_2$ 28 mm Hg) decreased critical low $p(ti)O_2$ ($p(ti)O_2$ < 10–15 mm Hg), which normalized under baseline conditions ($paCO_2$ 34 mm Hg). Day 4 after trauma (right): Induced hypocapnia ($paCO_2$ 27 mm Hg) decreased baseline – $p(ti)O_2$ above 25 mm Hg. However, despite of pronounced CO_2 – reactivity of vessels $p(ti)O_2$ did not decrease to critical level and $p(ti)O_2$ normalized under baseline conditions ($paCO_2$ 33 mm Hg)

Effect of Therapy (Hyperventilation, Mannitol) on p(ti)O_2

Analyzing 80 measurements (performed in 24 patients) after induced hypocapnia (baseline paCO_2 33.4 +/– 1.4 mm Hg decreased to 26.6 +/– 1.3 mm Hg) from day 0–9 after trauma, we could detect in 26% of the cases worsening of cerebral oxygenation below 10 mm Hg, especially in patients with initial critical low p(ti)O_2 < 15 mm Hg and intact CO_2 – reactivity of the vessels. Fig. 2 demonstrates the time – dependent, variable effect of induced hypocapnia and recommended a carefully balanced indication and duration of hyperventilation therapy. Analyzing 34 studies (performed in 11 patients) after administration of mannitol (0.5 g/kg body weight) divided in three groups (p(ti)O_2: < 15 mm Hg, 15–30 mm Hg, >30 mm Hg) a similiar significant decrease of ICP and increase of CPP could be detected in every group. However p(ti)O_2 improved especially in patients with reduced or normal p(ti)O_2 after mannitol administration.

Discussion

Multimodal monitoring of cerebral haemodynamics supplements neuromonitoring (ICP, MAP, CPP) for treatment of severely head injured patients. However actually only regional p(ti)O_2 is a safe, reliable and sensitive method to follow cerebral oxygenation during longterm – period after trauma. Early detection of critical episodes of regional microcirculation (p(ti)O_2 < 10–15 mm Hg) enables a targeted therapy and balance of hyperventilation and mannitol administration. However, further comparative studies of p(ti)O_2 and global CBF measurements are necessary to clarify the value of this regional technique in different patterns of brain trauma (diffuse/local). In addition development of multichannel sensors (pO_2, ph lactate) as well as two – point measurements will help to understand pathophysiology of secondary ischemic brain damage. This may optimize our treatment and improve outcome of severely head injured patients.

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Correspondence: Jürgen Meixensberger, M.D., Neurochirurgische Klinik und Poliklinik, Universität Würzburg, Josef-Schneider-Strasse 11, D-97080 Würzburg, Federal Republic of Germany.

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Assessment of Cerebrovascular Reactivity in Patients with Carotid Artery Disease Using Near-Infrared Spectroscopy

P. Smielewski, M. Czosnyka, J. D. Pickard, and **P. Kirkpatrick**

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, University of Cambridge, U.K.

Summary

The aim of this study was to assess Near-infrared spectroscopy (NIRS) as a tool for testing CO_2 reactivity in patients with carotid occlusive disease. One hundred sixty patients were examined (age range 44 to 85 years). Monitored parameters included transcranial Doppler flow velocity (FV), changes in concentration of oxy- (HbO_2) and deoxy (Hb) haemoglobin, cutaneous Laser Doppler blood flow (LDF), endtidal CO_2, ABP, and SaO_2. Hypercapnia was induced using a 5% CO_2 air mixture for inhalation. To estimate the skin flow contribution to NIRS during reactivity testing, the superficial temporal artery was compressed, and the NIRS changes in response to the fall in LDF recorded. FV and HbO_2 derived reactivity values were related to the severity of the stenosis ($p = 0.0001$ and 0.021 respectively). The correlation between the two modalities was significant ($r = 0.47$, $p < 0.000001$). The average estimated skin contribution to NIRS changes was 16.5%. Reproducibility of HbO_2-reactivity was similar but worse than FV reactivity (19.1% and 13.8% variation respectively). The clinical correlations improved when our method of correction for skin influence was used. NIRS shows potential as an alternative technique for testing CO_2 reactivity in patients with carotid disease provided the conditions are carefully controlled and the contribution from extracranial tissue is taken into account.

Keywords: Cerebrovascular reactivity; near-infrared spectroscopy (NIRS).

Introduction

Near-infrared spectroscopy (NIRS) derives information about the concentrations of oxy-(HbO_2) and deoxyhaemoglobin (Hb) from measurements of light attenuation caused by these chromophores [2]. A recent application for NIRS is the assessment of cerebrovascular reactivity [5,7]. A persisting concern with NIRS, though, is the extent to which light is attenuated by the extracranial tissues. Although initial impressions indicated that the skin contribution is negligible [2], recent investigations indicated that this is not the case [3]. Our earlier experience suggests that extracranial contamination does not appear to be significant during a CO_2 challenge in normal adult volunteers, since the recorded changes in cutaneous blood flow are small [5]. However, in the presence of carotid artery disease, where extra- to intracranial collaterals develop, the cutaneous component to the attenuation of NIRS signals may become important. The aim of this project was therefore to validate near-infrared spectroscopy as an alternative tool for testing CO_2 reactivity in patients with carotid artery disease with a special attention put to the problem of extracranial contamination and reproducibility of the results. In attempt to reduce cutaneous factors, we have chosen to adopt a large interoptode separation (at least 5 cm), and to record other modalities that monitor changes in skin blood flow allowing an estimation of extracranial influences [5].

Materials and Methods

One hundred sixty patients (age 44 to 83 years) with symptomatic carotid artery occlusive disease were examined. The severity of stenosis ranged from 30% to complete occlusion (median 80%) on the ipsilateral side, and 0% to total occlusion (median 30%) on the contralateral side, as demonstrated by carotid angiography. Near-infrared probes (NIRO 500, Hamamatsu Photonics, Japan) were positioned 6 cm apart on the patients' forehead on the side of the transcranial Doppler probe (PC DOP 842, Scimed, UK). A cutaneous laser Doppler probe (LDF, MBF3D, Moor Instruments) was placed in the immediate vicinity of the NIRS probes. Signals of MCA flow velocity (FV), changes in concentration of HbO_2 and Hb, non-invasive arterial blood pressure (ABP) (Finapress, Ohmeda 2300, USA), endtidal CO_2 ($EtCO_2$) and arterial oxygen saturation (SaO_2-Multinex 4200, Datascope) were sampled (50 Hz) and captured using specific software. For calibration of the near-infrared spectrometer readings, a path length factor of 5.93 was adopted [5]. The difference between HbO_2 and Hb (Hb_{diff}) was calculated to improve the signal to noise ratio.

The patients were subjected to 5 minutes of breathing a mixture of 5% CO_2 in air. In 30 patients the CO_2 challenge was repeated after a 5 minute rest period for assessment of the reproducibility of

the test. The same protocol was carried out for both sides. NIRS reactivity indices were defined as absolute increase in concentrations per 1 kPa increase in $EtCO_2$ and TCD reactivity index was defined as relative increase in FV per 1 kPa change in $EtCO_2$. To assess the influence of skin flow changes on NIRS readings, two superficial temporal artery compressions were performed at the end of the reactivity test, and the variation in NIRS parameters during the fall in cutaneous blood flow captured (see Appendix).

Results

All NIRS reactivities were significantly lower on the ipsilateral side than on the contralateral side ($p < 0.008$ for Hb_{diff}), and there was significant association with the severity of stenosis ($p < 0.02$, Fig. 1a). Flow velocity reactivity indices showed a similar relationship with the side ($p < 0.00019$) and severity of stenosis ($p < 0.0001$, Fig. 1b) as NIRS, but the associations were statistically more significant. NIRS derived reactivity indices demonstrated significant correlation with FV reactivity. The highest correlation was obtained with Hb_{diff} ($r = 0.47$, $p < 0.000001$, Fig. 2). There was on average 9.5% (range: –64% to 86%) change in laser Doppler flux during hypercapnia. The estimated skin contribution to HbO_2 reactivity varied from –11% to 105% (median value of 16.5%). Increases in LDF were predominantly associated with increases in ABP; however, the direct correlation between relative ABP and LDF changes was not statistically significant. The correlation coefficient between FV and NIR derived indices improved when corrected values were used ($r = 0.55$ for Hb_{diff}). Mean arterial blood pressure on average rose during the period of hypercapnia (mean increase 14% ± 15.1% S.D). Relative changes in ABP did not show any correlation with FV reactivity; however, they were significantly correlated with NIRS reactivities ($r = 0.26$, $p < 0.022$). Analysis of reproducibility of reactivity parameters showed similar variability in FV and in NIRS parameters (variability of 13.8% versus 19.1% for Hb_{diff} respectively). Analysis of influence of ABP showed significant correlation between variability in ABP and HbO_2 ($r = 0.68$, $p < 0.027$), and between changes in LDF response and changes in ABP ($r = 0.86$, $p < 0.002$).

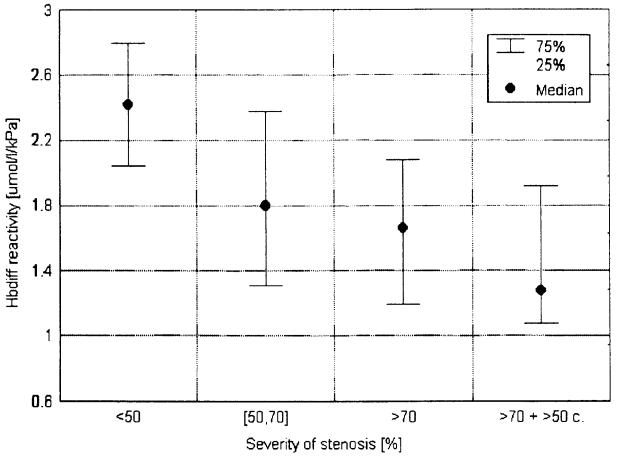

Fig. 1. Bar graph showing relation of the (a) Hb_{diff} and (b) FV reactivity parameters to the severity of ipsilateral stenosis. The bars shows 50 percentile range and the dots denote median values. The last category in the graphs denotes severe stenosis on the ipsilateral side combined with significant (greater than 50%) stenosis on the contralateral side

Discussion

The TCD-derived reactivity indices have been described to decrease with increasing severity of ICA stenosis [1]. Our data showed that both FV and NIRS

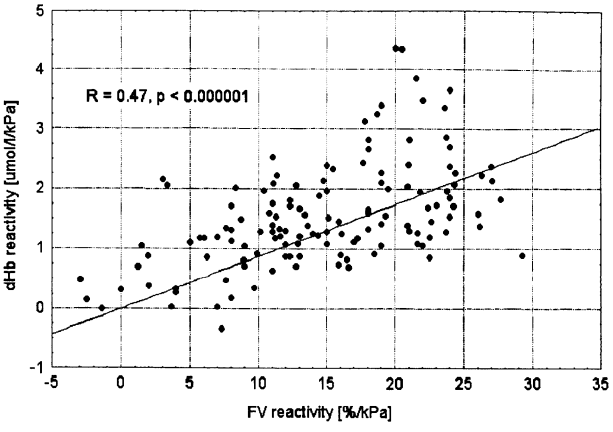

Fig. 2. Scatterplots showing correlation between FV and Hb_{diff} reactivity indices. Correlation coefficient was calculated using non-parametric Spearman formulae. Fitting a linear model without intercept produced regressions with a close fit ($R^2 = 0.8$)

reactivity indices follow this pattern and the relationship is statistically significant for both modalities. This observation supports the notion that there is a major intracranial haemodynamic component to the changes recorded with NIRS. Although there was a strong association between FV reactivity and NIRS parameters, the discrepancy was greater than attributable to measurement errors. In addition to errors associated with the assumptions of the NIRS technique discussed in [5] there are two other important factors that are likely to contribute to discrepancy. The first is the extracranial contamination, here assessed using cutaneous laser flowmetry [4]. The study showed that, despite a relatively large distance between optodes, there is a significant influence of extracranial circulation to NIRS recordings. This was particularly true for cases with marked increases of ABP noted during the CO_2 challenge which is probably mainly due to effect of extracranial circulation responding passively to ABP. With NIRS reactivities corrected for skin influence, a better correlation with the severity of stenosis and with FV reactivity was achieved. The second factor is the anatomical variability of the territories supplied by the six major arteries of the circle of Willis [6]. Thus some measurements could have been taken from the territory supplied by the anterior cerebral artery instead of middle cerebral artery, which becomes important considering haemodynamic disturbances present in carotid disease. Finally, since NIRS measures parenchymal (small vessel) reactivity, these findings may reflect differences in reactivities of the various components of the vascular tree.

The use of NIRS to assess cerebrovascular reactivity in adults with carotid artery disease shows promise, and may be able to supplement those presently used in clinical practice. To achieve this, attention to the examination procedure is essential, with particular attention for identifying and controlling influential variables. In particular, changes in ABP and extracranial blood flow need further consideration. The method of correcting for skin flow changes presented is simple, and offers an improvement.

Appendix – Estimation of Skin Flow Contribution

In order to estimate the skin flow contributions to NIRS parameters linear regressions of Hb and HbO_2 signals versus LDF changes were performed on the data acquired during the superficial temporal artery compressions. The following parameters were defined:

Skin flow contribution:

$$\Delta HbO_{2(SkinFlow)} = rHbO_2LDF \cdot \Delta LDF_{CO2}, \ [umol/l]$$

$$Skin\ \ flow\ \ influence = \frac{\Delta HbO_{2(SkinFlow)}}{\left(\Delta HbO_{2(CO2)}' + \Delta HbO_{2(SkinFlow)}\right)} \cdot 100\%,$$

where $rHbO_2LDF$ is a slope of the HbO_2/LDF regression, ΔLDF_{CO2} denotes change in LDF during CO_2 challenge, $\Delta HbO_{2(SkinFlow)}$ is change in HbO_2 signal due to the skin flow change and $HbO_{2(CO2)}'$ is change in HbO_2 during hypercapnia corrected for the skin flow contribution. Analogous calculations were performed for Hb, tHb and Hb_{diff} parameters.

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Correspondence: Peter Smielewski, Ph.D., Neurosurgery Unit, Level 4, A Block, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, U.K.

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The Relationship of Pulsatile Cerebrospinal Fluid Flow to Cerebral Blood Flow and Intracranial Pressure: A New Theoretical Model

M. Bergsneider[1], **A. A. Alwan**[2], **L. Falkson**[2], and **E. H. Rubinstein**[3]

[1] Division of Neurosurgery, [3] Department of Physiology, [3] Department of Anesthesiology, UCLA School of Medicine, and [2] Department of Electrical Engineering, UCLA School of Applied Science, Los Angeles, CA, U.S.A.

Summary

An electrical-equivalent circuit model of the cerebrovascular system is proposed, components of which directly relate to cerebrospinal fluid (CSF) compartment compliance and the determination of intracranial pressure (ICP). The model is based on three premises: 1) Under normal, physiologic conditions, the conversion of pulsatile arterial to nonpulsatile venous flow occurs primarily as a result of arterial compliance. Nonpulsatile venous flow is advantageous because less energy is required to maintain constant flow through the venous system, which comprises 75–80% of total blood volume. 2) Dynamic CSF movement across the foramen magnum is the primary facilitator by which intracranial arterial expansion occurs. Interference of the displacement of CSF during systole results in pulsatile venous flow and increased venous flow impedance. 3) Tissue hydrostatic pressure (here defined as ICP) is a dependent variable which is a function of capillary hydrostatic pressure and the osmotic/oncotic pressure gradient created by the blood-brain-barrier (BBB).

An interference of transcranial CSF movement results in a decrease in cerebral blood flow (CBF) due to inertial effects impeding pulsatile venous flow. Feedback regulation in response to this decreased CBF leads to arteriolar vasodilatation (decreased resistance), thereby lowering the pressure difference between internal carotid and capillary pressures. Assuming no changes in the BBB potential, ICP increases linearly as capillary pressure increases.

Keywords: Cerebrospinal fluid flow; theoretical model.

Introduction

The pathophysiology of intracranial hypertension remains incompletely understood. The hemodynamic theory of ICP physiology proposed here differs significantly from previously proposed models [2,4,5,7]. First, the theory is not founded on the tenet that an increase in intracranial volume is the mechanism by which ICP increases. Rather than considering volume changes as the primary disturbance, the hemodynamic theory defines ICP as a function of hydrostatic forces acting at the capillary level. It is hypothesized that changes in capillary pressure dynamics arise secondary to altered cerebral arterial-venous hemodynamics. In addition, instead of modeling obstruction of bulk CSF flow, primary emphasis is placed on dynamic, pulsatile CSF flow, specifically in regard to intracranial compliance.

Methods

The theoretical foundation of the proposed theory is based on physical principles, hemodynamics, and Starling's capillary law.

Premise 1: Cerebrovascular impedance is a function of the intracranial Windkessel phenomenon. As a generalization, arterial blood flow is pulsatile, whereas venous flow is steady. Flow oscillations have been shown to be absent in veins as small as 1 mm in diameter [6], therefore suggesting that the transformation of pulsatile to nonpulsatile flow occurs in the arterial system. The elasticity of arterial walls is responsible for transforming the pulsatile cardiac outflow into a relatively steady motion of blood in peripheral vessels (the phenomenon termed the Windkessel effect).

The importance of nonpulsatile venous flow lies in the fact that cerebral venous blood pool constitutes 70–80% of the total brain blood volume [1]. Under normal physiologic conditions, the overall efficiency of the cardiovascular system is high because less energy is required to maintain the venous blood pool at a steady flow than would be required to constantly accelerate and decelerate this mass of blood.

In the peripheral (non-cranial) circulation, the arterial expansion is facilitated by the pliable nature of the skin. The adult cranial compartment, on the other hand, is practically indistensible. Cerebral arterial expansion instead is a function of the dynamic intracranial volume buffering system: the CSF.

Premise 2: The cerebrospinal fluid system is the primary facilitator of the intracranial Windkessel effect. The functioning of the intracranial Windkessel effect mandates that the cerebral arteries be allowed to expand within the intracranial compartment. Since this compartment is of fixed volume, this imposes strict relationships regarding intracranial volume and pressure. According to the Monro-Kellie doctrine, a net addition of volume to the intrac-

ranial space is not possible within the realm of physiologic pressures. In the normal physiological state, the difference between pulsatile internal carotid artery flow and near-steady internal jugular flow signifies that a net volume of blood entering the intracranial compartment varies within the cardiac cycle. This net change in cerebral blood volume during the cardiac cycle is accommodated by the intracranial cavity by the dynamic translocation of CSF across the foramen magnum to the compliant spinal compartment [3].

One of the fundamental assertions of the hemodynamic theory is that an interference of the CSF translocation system will directly affect the efficiency of the intracranial arterial Windkessel effect. The resulting decrease in arterial compliance (capacitance) will increase venous pulsatility, and therefore increase venous flow reactance. Given the disparity of the blood pool distribution, an increase in venous flow impedance will have a disproportionately large effect on total cerebrovascular impedance. In summary, the integrity of the CSF translocation system is directly related to cerebrovascular impedance, and therefore cerebral blood flow (CBF).

Premise 3: Local intracranial pressure is determined primarily by hydrostatic forces acting at the capillary level. For conceptual purposes, ICP will be considered here as equivalent to brain tissue hydrostatic pressure. It is proposed that ICP is predominantly determined by Starling's forces occurring at the capillary level. The hydrostatic pressure gradient (capillary pressure BP_{Cap} minus ICP) will equal the oncotic-osmotic pressure gradient generated by the blood-brain-barrier (P_{BBB}). Under steady state:

$$ICP = BP_{Cap} - P_{BBB} \qquad \text{(Eq. 1)}$$

An electrical-equivalent model is proposed to diagrammatically present the respective components of the cardio-cerebrovascular system (Fig. 1). The circuit is a first-order approximation, consisting of lumped elements representing general components of the circulation. The brain is considered to be uniform in terms of vascular motor tone and blood-brain-barrier function, thereby limiting this analysis to global changes in ICP. A convention is adopted equating voltage to pressure and current to flow.

The intracranial arterial system is divided into two segments. The proximal segment (large and medium arteries) is presumed to primarily subserve the Windkessel capacitor. The capacitive reactance is a function of the intracranial compliance and the transmural pressure difference between internal carotid artery blood pressure BP_{ICA} and ICP. The distal segment of the arterial tree is modeled as a variable resistor which is responsive to mean CBF (metabolic autoregulation).

At the capillary, or tissue level, the pressure gradient due to oncotic-osmotic forces is depicted as a constant voltage (pressure) source P_{BBB}, the value of which varies with integrity of the BBB. BP_{Cap} is the difference between BP_{ICA} and the pressure drop, which occurs across arterioles due to resistive losses (R_{art}):

$$BP_{Cap} = BP_{ICA} - (CBF)(R_{art}) \qquad \text{(Eq. 2)}$$

It should be emphasized that R_{art} does not represent what is commonly referred to as "cerebrovascular resistance."

The intracranial venous system is modeled by an inductor, the electrical equivalent to inertia, in series with a resistor representing the venous resistive component. The value of the inertance, L, is related to the mass of blood contained within the venous system.

Combining Eqs. 1 and 2, ICP can be defined as:

$$ICP = BP_{ICA} - (CBF)(R_{art}) - P_{BBB} \qquad \text{(Eq. 3)}$$

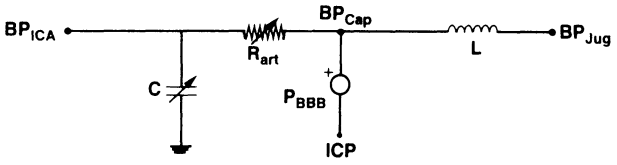

Fig. 1. Electrical equivalent circuit of the cerebrovascular circulation, the blood-brain-barrier, and intracranial pressure (ICP). BP_{ICA} internal carotid blood pressure (here depicted as a voltage), C variable arterial capacitance (analog to compliance), R_{art} arteriolar resistance, BP_{Cap} capillary blood pressure, P_{BBB} pressure (voltage) gradient generated by the osmotic potential difference of the blood-brain-barrier, L venous inductance (analog to mass), BP_{Jug} internal jugular vein blood pressure

Results

The pathogenesis of intracranial hypertension: Perturbation of the normal intracranial homeostasis can occur by a variety of mechanisms. ICP-related perturbations can be grouped into four categories: 1) interference of the dynamic CSF translocation system, 2) disruption of the blood brain barrier, 3) obstruction of venous outflow, and 4) changes in the input pressure and waveform. This analysis will focus on the CSF system primarily.

As proposed in Premise 2, the efficiency of the Windkessel mechanism is intimately related to the functioning of the CSF translocation system. When the dynamic egress of CSF from the intracranial compartment is hindered, an increase in venous flow pulsatility occurs. Due to inertial forces impeding acceleration and deceleration of the blood mass, total CBF will decrease. The normal physiologic response to a decrease in CBF is arteriolar vasodilatation, mediated by metabolic autoregulation (decrease in R_{art}). If there is no change in BP_{ICA} or P_{BBB}, the result of this physiologic compensation is an increase in ICP:

$$BP_{ICA} - (\downarrow R_{art})(CBF) - P_{BBB} \Rightarrow \uparrow ICP$$

In this hypothetical situation of intracranial hypertension, in which there is only a minor impairment of CSF-translocation, CBF can be maintained at the normal (baseline) level.

A further impairment of the CSF-translocation mechanism can result in a more severe reduction in arterial compliance. If the resulting increase in venous impedance (due to greater venous pulsatility) reduces CBF beyond the limits of metabolic autoregulation (maximal arteriolar vasodilatation), CBF will remain inadequate. In this case, the increase in ICP will be further augmented:

$$BP_{ICA} - (\downarrow\downarrow R_{art})(\downarrow CBF) - P_{BBB} \Rightarrow \uparrow\uparrow ICP$$

In this uncompensated state, an elevated ICP will be found in conjunction with a reduced CBF.

Discussion

The proposed hemodynamic theory and model predicts an association between ICP and CBF which is opposite of that of the "standard" model. Rather than ICP causing a reduction in blood flow, the hemodynamic model predicts that early phase determinants of intracranial hypertension result from compensatory mechanisms responding to reduced CBF. The finding of intracranial hypertension likely signifies arteriolar vasodilatation in response to the increased venous flow impedance. Therefore, if autoregulatory mechanisms are intact, therapeutic maneuvers such as hyperventilation may be deleterious due to depriving the brain of demanded CBF. Both the hemodynamic and the "standard" models predict that hyperventilation will reduce ICP, although with opposing consequences.

The general equation of ICP (Eq. 3) also applies to many common clinical scenarios not primarily associated with interference of CSF movement. Opening of the blood-brain-barrier is known to elevated ICP, here modeled as a decrease in P_{BBB}. It should be noted that the variables in Eq. 3 are not independent. For example, an increase in BP_{ICA} would not necessarily cause an increase in ICP due to pressure autoregulation effects on R_{art}.

In summary, the hemodynamic theory establishes a correlation between the cardio-cerebrovascular system, the CSF system, and ICP. Analysis of the model predicts a cascade of *compensatory* phenomena leading to increased ICP which occurs following interference of the CSF translocation system. Experimental and clinical studies will be necessary for the validation of this theory and model.

Acknowledgement

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Correspondence: Marvin Bergsneider, M.D., UCLA Division of Neurosurgery, Box 957039, 18-218 NPI, Los Angeles, CA 90095-7039, U.S.A.

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Indices for Decreased Cerebral Blood Flow Control – A Modelling Study

S. Piechnik[1,2], **M. Czosnyka**[1,2], **P. Smielewski**[1,2], and **J. D. Pickard**[1]

[1] MRC Cambridge Centre for Brain Repair and Academic Neurosurgery Unit, U.K., and [2] Warsaw University of Technology, Poland

Summary

Time-dependent interactions between pressure, flow and volume of cerebral blood and cerebrospinal fluid were mathematically modelled. The model was designed to simulate blood inflow and storage, arteriolar and capillary blood circulation controlled by cerebral autoregulation, venous blood outflow and storage modulated by intracranial pressure, and cerebrospinal fluid production, storage and reabsorption. The software implementation of the model was used to calculate the response to a gradual decrease in cerebral perfusion pressure corresponding to either systemic hypotension or intracranial hypertension. We computed flow pulsatility index (PI) and short range correlation coefficients between systolic, diastolic and mean flow velocity (FVs,d,m) and mean cerebral perfusion pressure (CPP). In simulation, the changes in cerebral flow produced by intracranial hypertension and systemic hypotension were practically indistinguishable. The relationship between PI and CPP was reciprocal, independent of the state of autoregulation. The short range running correlation coefficients between FVs, FVm and CPP indicated both combined safe CPP range and preserved autoregulation, promising a clear clinical detection of "non-worsening" blood supply conditions. A similar procedure was applied to selected clinical data to illustrate the theoretical considerations.

Keywords: Cerebral blood flow control; modelling; TCD.

Introduction

Transcranial Doppler ultrasonography (TCD) has proved to be useful for both intermittent and continuous assessment of blood flow in major cranial arteries. TCD provides non-invasive direct measurement of flow velocity in insonated artery. However, the true cerebral perfusion may only be estimated because of confounding factors such as unknown vessel cross-section area and insonation angle. These considerations have stimulated studies on other TCD-derived parameters that may provide more information about the adequacy of brain perfusion [1,2,4,5].

Method

The study was conducted using computer simulation and followed by an illustrative analysis of clinical data. To provide fully controlled environment for our investigations we used the mathematical model of cerebral blood flow and circulation of cerebrospinal fluid (CSF) [6]. The model input variables are arterial blood pressure (ABP) and venous pressure in saggital sinus. The model simulates pressure and flow conditions in two major pathways of fluids transported in intracranial space: blood and CSF. The arterial part was represented by just five lumped components: the resistance of basal intracranial vessels; arterial compliance responsible for intermittent storing of the inflowing arterial blood volume; the cerebral resistance vessels (CVR) able to accommodate to dynamic changes in cerebral perfusion pressure (CPP); compliance of capillary and small veins and a Starling resistor portraying the venous outflow to dural sinuses through the collapsible brain surface veins. The pathway of CSF has been reduced to constant rate formation of CSF from arterial blood, storing of CSF inside non-linear cerebrospinal compliance and reabsorption to dural sinuses through one-way resistance. The model was represented by an equivalent electrical circuit and described by non-linear differential equations, which are the subject of computer evaluation in purpose-written simulating software running on IBM-PC. The differential equations are solved using Runge-Kutta IV method with manual step size correction.

To obtain gradual cerebral hypoperfusion we used two methods: ICP increase by means of simulated stepwise infusion tests or progressing systemic hypotension. In all simulations the rate of CPP was maintained at 1 mm Hg/min until diastolic flow values reached zero. FV was calculated from volume flow using an arbitrary chosen scaling factor. The simulations were repeated several times at different levels of autoregulatory capacity. The strength of autoregulation (SA) was defined as a proportion of the ideal gradient of CVR(CPP) relationship in its middle semi-linear part, where stable flow is maintained independently of CPP variations. SA was changed from 0% to 125%. Other parameters of the model were left constant, except for arterial compliance which initial value was adjusted every time to obtain standard starting flow pulsatility index PI = 0.65 for CPP = 90 mm Hg. Each simulation was used to calculate systolic, diastolic and mean FV and PI as function of CPP. In addition, to assess FV reactivity to CPP changes, we computed local correlation coefficients between flow parameters and CPP over every 5 mm Hg of CPP. These indices

may be estimated on-line at the patient's bed-side using short-time running correlation coefficients [2].

The theoretic study was followed by analysis of typical clinical data. Results of monitoring of one patient were used. Case description: 17 year old male cyclist hit by car: GCS 5/15 on admission; CT: bilateral frontal and parietal contusions, no other major injuries, cardiovascular system stable; pupils equal and reacting. 6-month's outcome was unfavourable. After admission patient was sedated, intubated and ventilated. ABP, ICP and MCA FV were sampled (50 Hz) and stored in computer memory (WREC, W. Zabolotny, Warsaw University of Technology, Poland). The whole monitoring lasted 4 hours. For further analysis we selected two periods with substantial plateau waves lasting one hour in total. 8-second epochs were used to calculate mean CPP, PI, systolic diastolic and mean flow (CVR-Test, P. Smielewski, University of Cambridge, UK). Moving correlation coefficients were then calculated from every 40 epochs (5 minutes) to simulate static correlations obtained previously from modelling study. The recording gave evidence that the patient's autoregulatory response was preserved and similar to simulated 100% SA characteristics.

Results and Discussion

The mean flow velocity changes closely followed the same pattern in response to either systemic hypotension or intracranial hypertension. However, the amplitude of FV pulsation (FVa) tended to increase more rapidly due to a decrease in ABP than increase in ICP. This effect was less marked when autoregulation was weak. In consequence, in both autoregulating and non-autoregulating systems the PI was marginally less sensitive to an increase in intracranial pressure than to a corresponding decrease of arterial pressure. This was explained by reduction of compliance of intracranial CSF space following intracranial hypertension. The resulting decrease in total arterial input compliance was absent in simulations involving systemic hypotension. Simulations clearly indicated that PI can increase due either to increase in flow velocity amplitude or a decrease in its mean value. In regulating systems the initial increase in PI was due mainly to the FVa change, whereas in a non-autoregulating the increase in pulsation was moderate and PI rise related mostly to decreasing mean FV. In this way by changing SA the proportion between the two effects was changed. Nevertheless, the shape of relationship between PI and CPP was always reciprocal, in both autoregulating and non-autoregulating systems. PI changes observed in clinical data were close to the simulated reciprocal line. Although, each hypoperfusion episode followed a slightly different curve. Further analysis revealed that this discrepancy was due to baseline change in ABP pulsation. When normalised, SPI (PI divided by ABP amplitude) fitted closely the reciprocal model SPI = 0.358/CPP (R = 0.95).

The short range correlation coefficients between flow velocity and CPP have the same advantage as the pulsatility index of being independent of the angle of insonation and vessel diameter. Also, they are not prone to errors due to unavoidable occasional adjustments of the TCD probe. Despite the fact that long term TCD and CPP monitoring would be necessary to calculate them, the short range correlation coefficients between flow parameters appeared to be more selective in terms of combined safe CPP range and unaffected autoregulation (Fig. 1). Negative correlation between FVm and CPPm corresponded to the situation, when the level of CPP was high enough to provide "non-worsening" value of mean flow for the particular percentage of the strength of autoregulation. In this way the index provided composite information on both autoregulatory strength and appropriateness of CPP level. Matching coefficients were calculated for systolic and diastolic flow. The CPP relation of both of them was generally similar to the R(FVm,CPP) presented on Fig. 1, except for different distribution between positive and negative values. For R(FVs,FVm) the transition toward positive values took place for much lower CPP and SA, indicating much longer-standing regulation of systolic flow. The R(FVd,CPP) was nearly always positive – thus possibly lacking any informative value. The correlation indices based only on FV signal,

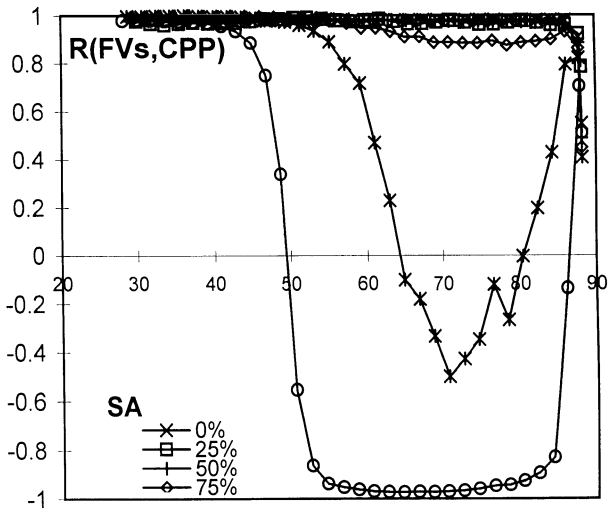

Fig. 1. Simulated short range correlation between mean flow velocity (FV) and cerebral perfusion pressure (*CPP*) in relation to CPP. Negative values correspond to satisfactory strength of autoregulation (*SA*) and appropriate CPP – capable to provide non-decreasing mean FV with CPP drop

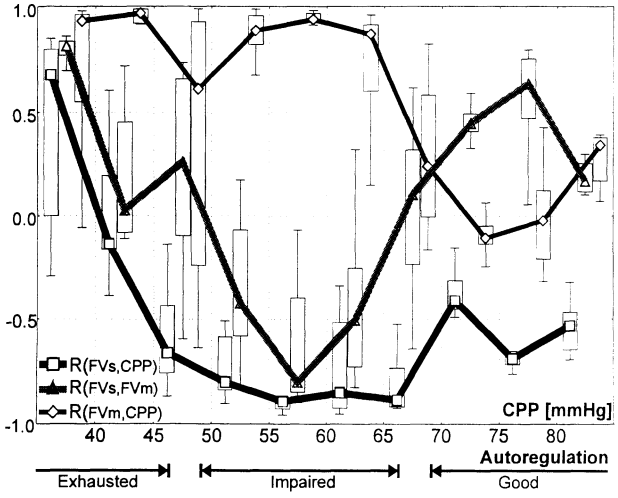

Fig. 2. Clinical recording in presence of deep plateau waves fully matched the simulation in wide range of CPP. The course of changes in running correlation coefficients between systolic, diastolic and mean FV and CPP, allowed to clearly define good and exhausted regulation regions, with a transient zone in between. On the plot: token – median, box – 25/75 percentile, whisker – non-outlier min/max

R(FVs,FVm) and R(FVs,FVd) lacked the ability to detect autoregulatory reserve as such, but they did mark its borderline. Since their calculation does not require any invasive methods, they may also find application as indicator of critical perfusion – provided that very good autoregulation is excluded using other methods, for example transient hyperaemic response test [8]. In clinical data, running correlation coefficients have proved to have the same, CPP-dependent properties, as their static parallels obtained in simulation (Fig. 2). The expected response to good, challenged and abolished autoregulatory capacity could be easily seen for each parameter: R(FVm,CPP) – close to zero for CPP above 65 mm Hg, but consistently positive below; R(FVs,CPP) – normally negative, but immediately switches towards +1 when perfusion becomes critical; R(FVs,FVm) – marks the transitional area between very good and very poor autoregulation. The close corerspondence between clinical observation and simulation supports our final conclusion, that the short-range correlation coefficients between CPP and FV parameters are promising sensitive indices for cerebral blood flow autoregulation.

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Correspondence: Stefan Piechnik, M.D., Academic Neurosurgery Unit, P.O. Box 167, Level 4, A Block, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 2QQ, U.K.

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Pathogenesis of Traumatic Brain Swelling: Role of Cerebral Blood Volume

G. J. Bouma, J. P. Muizelaar, and **P. Fatouros**

Medical College of Virgina, Richmond VA, U.S.A., and Academic Medical Center, University of Amsterdam, The Netherlands

Summary

The pathogenesis of traumatic brain swelling is unclear. Brain edema (increased water content) is considered an important cause of swelling, but there is also evidence that vasodilatation with increased cerebral blood volume (CBV) plays a role. We have evaluated early posttraumatic changes in CBV in 37 head-injured patients, using dynamic contrast-enhanced computerized tomography (CT) in combination with stable Xenon-enhanced CT for measurement of cerebral blood flow (CBF). This technique enables rapid determination of CBV without interfering with patient care.

CBV values ranged from 2.0 to 10.1 ml/100 g. There was no relationship the time after injury at which the measurements were taken. CBV did not correlate with CBF in the early posttraumatic period. Patients with raised ICP (>20 mm Hg) had significantly higher CBV that patients with normal ICP (5.4 ± 2.1 vs 3.7 ± 0.9 ml/100 g). Yet, the presence of signs of brain swelling on CT had no relation to the level of CBV.

These data suggest that increased CBV may contribute to raised ICP, but that brain swelling is not caused by increased CBV alone, and is more likely accounted for by brain edema. We speculate that cerebral energy failure is the unifying cause of both intracellular edema and cerebral vasodilation leading to swelling of brain tissue.

Keywords: Blood volume; brain swelling.

Introduction

Brain swelling, defined as enlargement of the brain tissue volume at the expense of intracranial CSF spaces, is a common complication following severe head injury, that contributes importantly to intracranial hypertension, and is a major factor determining clinical course and outcome [9]. Its pathogenesis and treatment remain unresolved. Probably, a complex series of events leads to the development of traumatic brain swelling, the relative contribution of each depending on the type of injury and the time after it was sustained. Theoretically, cerebral swelling may be caused either by an increase in brain tissue water content (edema), or by an increase in cerebral blood volume (CBV), due to vasodilation and engorgement of the cerebrovascular bed. Vascular contributions to raised ICP (which have been estimated at 68% based on parameters of CSF dynamics in intracranial hypertension [10]) may not be well reflected by CBF measurements because CBF is not linearly related to the level of CBV [11].

Published data of CBV measurements in patients with severe head injury are scarcely available, partly because of the lack of a suitable method for quantitative measurement of CBV in head-injured patients. Although CBV values can be obtained by positron emission tomography (PET) or single-photon emission tomography (SPECT), these techniques are considered impractical for use in critically ill and unstable patients. Yet, as effective therapy of brain swelling and raised ICP will depend on appropriate diagnosis of its cause, CBV measurements in the acute stage of head injury may be of value.

We have developed a method for rapid measurement of CBV based on dynamic CT scanning. In the present study, we have used this technique to assess CBV in severely head-injured patients, and its correlation with ICP and brain swelling.

Patients and Methods

Forty-six simultaneous determinations of CBF and CBV were performed in 37 severely head-injured patients within the first week after injury. The patients' age ranged from 14 to 64 (mean ± standard deviation: 27.9 ± 11.1) years, and 25 of them were male. Written informed consent was obtained from the family in all cases. The protocol was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia.

All patients were comatose (Glasgow Coma Scale score of 8 or less) at the time of study. They were intubated, artificially ventilated, well oxygenated (pO_2 > 80 mm Hg), and hemodynamically stable (systolic blood pressure >100 mm Hg) during the measurements. Vital signs, oxygen saturation, and expiratory CO_2 were continuously monitored. Arterial blood gases were checked twice

during the studies. ICP was monitored from an intraventricular catheter.

CBF was measured using the stable xenon-enhanced CT technique (Xe-CT) [6] on a General Electric 9800 CT scanner equipped with standard hardware and software. A gas mixture containing 32% stable xenon was administered through a volume-cycled respirator for 4.5 minutes. No significant rise in ICP was observed during xenon inhalation. Analysis of the obtained flow images was performed using two large ROIs each outlining the cerebral hemispheres to obtain an average flow value that included both white and gray matter.

CBV was determined by rapid sequential ("dynamic") CT scanning [1], which was also performed on the GE 9800 system. Immediately following an i.v. bolus injection of 50 cc iodine contrast (Omnipaque 300™) through a large-bore catheter, ten CT scans with a scan time of 2.0 sec and minimum interscan delay of 2.3 sec were performed at the same level for which CBF was previously determined. The cerebral hemispheres, as well as the anterior cerebral artery and the superior sagittal sinus were chosen as ROIs. The raw scan data were segmented and a time versus density curve was constructed for each ROI. The curves were fitted to a gamma variate function using a minimum chi-square procedure in a repetitive approach. CBV was computed by dividing the area under the time-density curve of the hemispheric brain tissue by the area under the curve of the sagittal sinus, the latter representing the cumulative vascular concentration of the contrast agent. To calculate CBV, this ratio was corrected for the difference between central and capillary hematocrit using an arbitrary correction factor of 0.85, based on previous data [12].

Results

CBF and CBV in Relation to the Time After Injury

Forty-six measurements of CBF and CBV were obtained at various intervals after head injury. Global CBF values ranged from 6 to 67 ml/100 g/min (mean ± s.d.: 42.0 ± 12.5 ml/100 g/min), and CBV ranged from 2.0 to 10.1 ml/100 g (mean ± s.d.: 4.3 ± 1.8 ml/100 g). Table 1 shows the data with respect to the time after injury at which the measurements were performed. Within 12 hours after injury, significantly lower CBF values were found, but one-way analysis of variance revealed no statistically significant differences between the various time interval groups for CBV or pCO_2. The relationship between CBF and CBV is plotted in Fig. 1. Overall, there was no significant correlation between the two parameters. When CBF approached ischemic levels, there was a trend of higher CBV values, but this could not be statistically verified due to the small number of observations.

Relationship of CBV to Intracranial Pressure and Brain Swelling

In Table 2, the results of the measurements are summarized grouped according to the level of CBV. The CBV criteria were chosen based on data previously reported in the literature. When CBV was elevated (above 5.2 ml/100 g), significantly higher ICP values were found, but no correlation with CBV was demonstrated. In sixteen cases, signs of brain swelling were present on CT, consisting of effacement of the ventricles or basal subarachnoid cisterns. The various parameters obtained in this group were compared to 28 cases without swelling (Table 3). Two cases for which the CT scans were not available for review

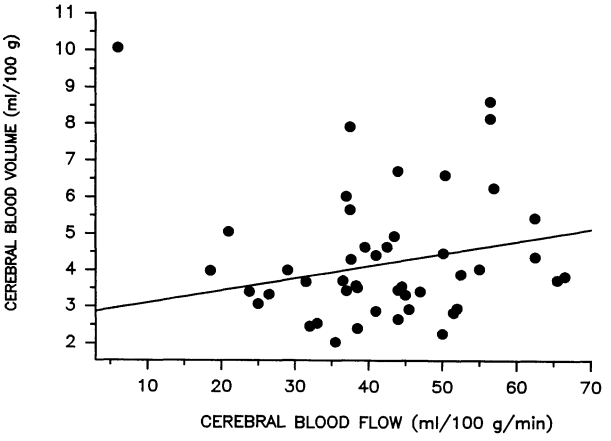

Fig. 1. Relationship between CBF and CBV in head-injured patients. Linear regression equation: CBV = 0.034 · CBF + 2.762 (r = 0.25, not significant)

Table 1. *Cerebral Blood Flow, Cerebral Blood Volume, and Arterial pCO_2 in Relation to the Time after Injury*[a]

Hours after injury	No. of studies	CBF (ml/100 g/min)	CBV (ml/100 g)	pCO_2 (mm Hg)
<12	15	33.1 ± 10.2[b]	3.9 ± 1.8	32.7 ± 5.7
12–24	5	51.4 ± 10.7	3.8 ± 0.9	37.8 ± 6.8
>24	26	45.3 ± 11.1	4.7 ± 1.8	37.4 ± 7.2

[a] Values are mean ± standard deviation.
[b] Significantly lower than values at later time intervals (Student-Newman-Keuls' test, $p < 0.01$). The differences of the other parameters between the groups were not statistically significant (one-way ANOVA).

Table 2. *Cerebral Blood Flow and Intracranial Pressure at Different Levels of Cerebral Blood Volume*[a]

	Cerebral blood volume		
	<3.6	3.6–5.2	>5.2
No. of cases	20	16	10
CBF (ml/100 g/min)	39.6 ± 8.2	43.3 ± 14.2	44.5 ± 15.6
ICP (mm Hg)	19.2 ± 7.6	20.4 ± 10.2	28.7 ± 10.0[b]

[a] Values are mean ± standard deviation.
[b] $p < 0.05$, Student-Newman-Keuls' test.

Table 3. *Cerebral Blood Flow, Cerebral Blood Volume, and Intracranial Pressure in Relation to the Presence of Brain Swelling*[a]

	Brain swelling on CT	
	yes	no
No. of cases	16	28
CBF (ml/100 g/min)	37.9 ± 13.8	43.9 ± 10.5
CBV (ml/100 g)	4.6 ± 1.7	4.2 ± 1.8
ICP (mm Hg)	26.3 ± 12.5 (13)[b]	20.4 ± 7.1 (20)

[a] Brain swelling was considered to be present if CT showed compression of ventricles or cisterns. Values are mean ± standard deviation.
[b] Significantly higher value than in patients without swelling ($p < 0.05$, determined by Student's t-tests). Other differences were not statistically significant.

were excluded from this analysis. Patients with brain swelling had significantly higher ICP, but the differences found between the CBF and CBV values were not statistically significant.

Discussion

Methodology

Determination of CBV by dynamic CT scanning has considerable practical advantages for the use in head-injured patients. The theoretical background of the analysis of mean transit time and CBV with dynamic CT has been described previously [1,5]. The reliability of the determination of mean transit time is limited due to the relatively poor resolution in time with interscan delays of 2.3 seconds, but the determination of CBV based on the ratio of integrals of the tissue and vascular enhancement curves is more stable and to a large degree independent of bolus dispersion. Preliminary validation studies have provided support for this approach [2]. A correction for the difference between intravascular and tissue (capillary) hematocrit must be taken into account. A factor of 0.85 has been used by several authors, which yielded satisfying results [7,12]. In addition, disruption of the blood-brain barrier does not adversely affect the calculations, as the measurements are based on first-pass kinetics [5]. Thus, the data acquired in the present study appropriately reflected CBV.

Role of CBV in Pathogenesis of Raised ICP and Brain Swelling After Head Injury

The normal range of CBV as reported in the literature, varies depending on the technology that was used and the population considered. Based on such data, we have defined CBV as normal when found to be between 3.6 and 5.2 ml/100 g. Despite these relatively permissive limits, we found elevated CBV in 22% of cases in the present study, and increases larger than 100% of normal did occur. Yet, the majority of patients (43%) had reduced CBV, while the overall average was in the normal range. Decreased or increased CBV was not related to a specific period after injury. Previous data on CBV changes in acute head injury, against which the present results can be assessed, are very limited. Kuhl *et al.* [7] studied a series of 30 head-injured patients and found CBV values in the normal range with deviations no larger than 13%. However, these studies were performed at varying times after injury in a heterogeneous population with regard to injury severity, and may not be comparable to our series.

A vascular origin of traumatic brain swelling was postulated based on experimental and clinical observations of rapidly progressing swelling, apparently not compatible with edema formation, and cortical vasodilation with bright red coloring of veins, suggesting hyperperfusion [8]. Measurement of cerebral blood flow (CBF) indicated a possible relationship between increased CBF and intracranial hypertension, but reports have not been unequivocal [4,11]. In the present study, we found an association of intracranial hypertension with elevated CBV. Notably, the presence of intracranial hypertension bore no relationship with the level of CBF, which supports the idea that measurement of CBF alone does not provide enough information about the vascular contribution to ICP.

No relationship was found between the level of CBV and the presence of brain swelling on CT. Although this picture was associated with higher ICP, it could be accompanied by normal, increased or decreased CBV, which concurs with CT density measures reported by others. This finding indicates that the relative contribution of CBV to brain swelling may vary between patients. Brain swelling associated with decreased CBV may indicate compression of the cerebrovascular bed by edema.

Possibly, in cases of severe acute brain swelling, edema and raised CBV have a common mechanism: cerebral ischemia. Ultra-early CBF measurements have revealed high incidences of global and focal ischemia in patient with diffuse brain swelling [3]. In these cases, a primary disruption of cerebral perfusion, through some yet unknown mechanism, would

induce autoregulatory dilation of cerebral arterioles, leading to elevated CBV. If this response fails to restore CBF, cellular energy failure will occur, leading to membrane dysfunction, sodium influx and osmotic swelling of the cell (ischemic or cytotoxic edema). Eventually the dilated vessels will be compressed by the edematous brain tissue, leading to secondary decrease in CBV with persistent high ICP. The clue to possible treatment in these cases may lie in the very early reversal of biochemical derangements caused by ischemia, rather than in vigorous attempts to reduce blood volume or tissue water per se.

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Correspondence: Gerrit J. Bouma, M.D., Ph.D, Department of Neurosurgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

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Subdural Monitoring of ICP during Craniotomy: Thresholds of Cerebral Swelling/Herniation

H. Bundgaard, U. Landsfeldt, and **G. E. Cold**

Department of Neuroanaesthesia, Aarhus University Hospital, Aarhus, Denmark

Summary

It is possible to define thresholds for cerebral swelling or herniation during craniotomy. In 178 patients subjected to craniotomy for space occupying processes subdural ICP was measured before opening of dura. The subdural ICP was correlated to the degree of cerebral swelling or herniation after opening of dura. At subdural ICP <7 mm Hg cerebral swelling/herniation after opening of dura rarely occurs, while at ICP ≥ 10 mm Hg cerebral swelling/herniation occurs with high probability. These ICP thresholds are independent of the patophysiology (SAH, cerebral tumor), the anaesthetic agent (isoflurane, propofol) and the $PaCO_2$ level (≤4.0 kPa, >4.0 kPa).

Generally, a good correlation between the tactile estimation of dural tension and the tendency to cerebral swelling or herniation after opening of dura was found. However, in 8.5% the surgeons were unable to predict swelling/herniation.

Keywords: Cerebral swelling; dural tension; subdural ICP.

Introduction

During craniotomy it is unquestionable that the level of ICP is of utmost importance. Opening of dura is especially critical. At high ICP, dura is tight and opening of dura will inevitably result in cerebral swelling or herniation. Normally the neurosurgeons tactile estimation of dural tension is the ultimate guide.

The aims of this study were to correlate ICP immediately before opening of dura with the tendency to cerebral swelling/herniation after opening of dura, and to define thresholds for cerebral swelling/herniation.

Furthermore, we correlated the neurosurgeons tactile estimation of dural tension to the degree of cerebral swelling/herniation after opening of dura.

Material and Methods

178 patients subjected to elective craniotomy for either subarachnoid haemorrhage (SAH) (n = 52) or supratentorial cerebral tumor (n = 126) were included.

Anaesthesia

106 patients underwent propofol/fentanyl anesthesia and 72 patients were subjected to isoflurane/N_2O/fentanyl anesthesia.

Measurement of ICP, Evaluation of Dural Tension and Estimation of Brain Herniation

After removal of the bone flap and exposure of dura, the neurosurgeon estimated the tension of the dura as follows: 1) dura slack, 2) normal tension of dura, 3) tension of dura, and 4) pronounced tension of dura.

Immediately before opening of dura, ICP was measured by the subdural approach [1]. A thin needle (Venflon 22 G/0.8 mm) connected via a water-filled polyethylene catheter to a pressure transducer was introduced tangentially through dura. Simultaneously with the measurement of subdural ICP, mean arterial blood pressure (MABP) was recorded, and arterial blood was analysed for $PaCO_2$, pH and PaO_2.

After opening of dura, the degree of cerebral swelling/herniation was evaluated as follows: 1) The brain below the level of dura, 2) no swelling or herniation of the brain, 3) swelling or herniation of the brain, 4) pronounced herniation of the brain.

Statistical Analysis

Median, 5% and 95% confidence intervals are indicated. Mann-Whitney test was used to analyse data between groups. Kruskal-Wallis One Way Analysis of Variance on Ranks was used to compare groups. Statistical significance was considered to be $p < 0.05$.

Results

A statistically significant difference in the ICP values among the swelling/herniation groups was disclosed. Pairwise multiple comparison showed a significant difference between all groups except group 1 versus 2 and group 3 versus 4 (Fig. 1). At ICP < 7 mm Hg cerebral swelling/herniation rarely occurred after opening of dura. At ICP ≥ 10 mm Hg, cerebral

Table 1. *The Total of 178 Subdural ICP Measurements Divided into Subgroups Concerning Pathophysiology (SAH, Cerebral Tumor), the Anaesthetic Agent (Isoflurane, Propofol) and the $PaCO_2$ Level (≤4.0 kPa, >4.0 kPa). Medians, 5% and 95% Confidence Intervals are Indicated*

A:	Tumor Cerebri (N = 126) $PaCO_2$ = 4.5 kPa		MABP = 77 mm Hg		SAH (N = 52) $PaCO_2$ = 4.3 kPa		MABP = 77 mm Hg	
Degree of herniation	1	2	3	4	1	2	3	4
ICP (mm Hg)	1	5	11	18	1	5	10	21
	(1–4)	(1–10)	(6–21)	(11–31)	(1–4)	(1–13)	(6–19)	(13–30)
Number of patients	5	78	30	13	5	29	13	5
B:	Isoflurane (N = 72) $PaCO_2$ = 4.3 kPa		MABP = 73 mm Hg		Propofol (N = 106) $PaCO_2$ = 4.5 kPa		MABP = 80 mm Hg[a]	
Degree of herniation	1	2	3	4	1	2	3	4
ICP (mm Hg)	2	5	20	17	1	5	11	23
	(1–4)	(1–12)	(6–19)	(11–31)	(1–4)	(1–10)	(6–20)	(13–30)
Number of patients	4	36	19	13	6	71	24	5
C:	$PaCO_2$ ≤ 4.0 kPa (N = 50)		MABP = 79 mm Hg		$PaCO_2$ > 4.0 kPa (N = 128)		MABP = 77 mm Hg	
Degree of herniation	1	2	3	4	1	2	3	4
ICP (mm Hg)	1	5	9	20	1	5	10	17
	(1–4)	(1–10)	(5–15)	(17–30)	(1–4)	(1–11)	(6–21)	(10–32)
Number of patients	5	28	10	7	6	79	33	10

[a] $p = 0.03$.

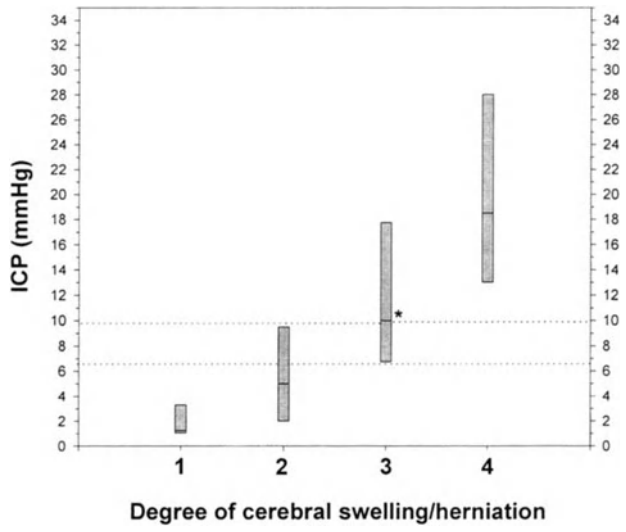

Fig. 1. Degree of cerebral swelling/herniation correlated to subdural ICP (N = 178) *1* The brain below the level of dura (n = 10). *2* no swelling or herniation of the brain (n = 107). *3* Swelling or herniation of the brain (n = 43). *4* Pronounced herniation of the brain (n = 18). The dotted lines indicate the thresholds for cerebral swelling/herniation. At ICP below the bottom line cerebral swelling or herniation rarely occur. At ICP above the top line cerebral swelling or herniation occur with high probability. Median and 5% to 95% confidence intervals are indicated. *Indicate $p < 0.05\%$ (comparison between 2 and 3)

swelling/herniation did occur with high probability after opening of dura.

At the same degree of cerebral swelling/herniation no significant intergroup differences in ICP were disclosed, when the 178 patients were divided into subgroups concerning patophysiology (SAH, cerebral tumor), anaesthetic agents (isoflurane, propofol) and the $PaCO_2$ level (≤4.0 kPa, >4.0 kPa). The ICP thresholds were found to be independent of the these factors (Table 1).

Generally, a good correlation between the tactile estimation of dural tension and the tendency to swelling/herniation after opening of dura was found. However in 15 studies (8.5%) where swelling/herniation were disclosed the surgeon predicted normal tension of dura, and in 13 studies (7.5%) the surgeons estimated tension of dura, but no swelling or herniation occurred after opening of dura.

Discussion

This study indicates that cerebral swelling/herniation after opening of dura rarely occurred at ICP < 7 mm Hg. On the other hand, at ICP ≥ 10 mm Hg, cerebral swelling/herniation did occur with high probability (Fig. 1). At ICP between 7 mm Hg and 10 mm Hg a grey zone was disclosed. In this zone it

was not possible to predict whether or not swelling or herniation would occur. However, at ICP < 10 mm Hg, pronounced cerebral herniation was never disclosed. The ICP thresholds were found to be independent of the pathophysiology, the anaesthetic agent and the $PaCO_2$ level (Table 1). The ICP level found in each subgroup, indicating the degree of swelling/herniation, was lower than the ICP level found by Todd *et al.* [2]. The discrepancy might be methodological (epidural contra subdural technique, zero-point adjustment, time from the ICP measurement to the cerebral herniation score). More reasonable, the difference in pressure is caused by the intact bone flap in the study by Todd *et al.* Removal of the bone flap in the present study exerts some degree of cerebral decompression.

In conclusion, we recommend measurement of ICP immediately before opening of dura. The subdural method is cheap and can easily be obtained within 1 min. Together with the tactile estimation of dural tension subdural ICP measurement gives important information. If the subdural ICP is increased, therapeutical measures to reduce ICP can be taken, ensuring that opening of dura is performed under optimal conditions.

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Correspondence: Georg Emil Cold, M.D., Department of Neuroanaesthesia, Aarhus University Hospital, DK-8000 Aarhus C, Denmark.

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ICP during Anaesthesia with Sevoflurane: A Dose-Response Study. Effect of Hypocapnia

G. E. Cold[1], H. Bundgaard[1], G. von Oettingen[2], K. A. Jensen[1], U. Landsfeldt[1], and K. M. Larsen

Department of [1] Neuroanaesthesia and [2] Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

Summary

In patients with a supratentorial cerebral tumor, an increase in sevoflurane concentration from 1.5% (0.7 MAC) to 2.5% (1.3 MAC) did not change the intracranial pressure (ICP) significantly (12 to 14 mm Hg (medians)). However, a significant increase in cerebral blood flow (CBF) from 29 to 39 ml/100 g/min (medians) was disclosed. During administration of sevoflurane 1.5% and 2.5%, a significant decrease in ICP (3.5 and 3.0 mm Hg (median) respectively) was found when $PaCO_2$ was decreased by 0.8 kPa.

Keywords: Hypocapnia; sevoflurane; subdural pressure.

Introduction

Sevoflurane is a cerebral and systemic vasodilator with the potential to decrease cerebral perfusion pressure (CPP) by lowering arterial blood pressure and increasing ICP. In experimental studies sevoflurane like halothane and isoflurane increases ICP dose-dependently [6,8]. CBF was either unchanged or increased when the sevoflurane concentration was increased [5–7].

The aim of this investigation was to study ICP and CBF during 1.5% and 2.5% sevoflurane anaesthesia in patients with a supratentorial cerebral tumor subjected to craniotomy.

Materials and Methods

Anaesthesia

Twenty patients, subjected to craniotomy for surgery of a supratentorial cerebral tumor, were included. For induction of anesthesia, propofol 1–2 mg/kg and fentanyl 0.2 µg/kg were used. A normocapnic $PaCO_2$ level was achieved. The patients were randomised into two groups according to the anaesthetic procedure. Group 1 (n = 10) received continuous 1.5% sevoflurane and fentanyl 2 µg/kg/h. Group 2 (n = 10) received continuous 1.5% sevoflurane and fentanyl 2 µg/kg/h, followed by an increase in sevoflurane to 2.5% with unchanged fentanyl. Finally the minute-ventilation was increased by 50% in a five min. period in both groups.

Measurement of Subdural Pressure and Cerebral Blood Flow

After removal of the bone flap, the ICP was measured by the subdural approach. This technique has recently been described [4]. With a thin needle (Venflon 22 G/0.8 mm), connected via a saline-filled polyethylene catheter to a pressure transducer, the dura was tangentially perforated. ICP was measured continuously. CBF was measured with a Cerebrograph 10a by intravenous administration of a radioactive tracer 133-Xe (3–4 mCi). Two angular detectors were placed on each side of the head. CBF was calculated as initial slope index (ISI) using 10-min clearance curve. CBF was first measured after exposure of the dura, when both groups received 1.5% sevoflurane. The second measurement of CBF was performed 30 min later, at 1.5% sevoflurane (group 1) and 2.5% sevoflurane (group 2). Simultaneously, mean arterial blood pressure (MABP) was recorded, and arterial blood was analysed for $PaCO_2$, pH and PaO_2.

Statistical Analysis

Median and range were calculated. The Wilcoxon test was used to analyse data within the groups, and the Mann-Whitney test was used to analyse data between the groups. Statistical significance was considered to be $p < 0.05$.

Results

No significant differences between the two groups were disclosed with regard to the age of the patients, body weight, gender, awake MABP, and the volume of the tumors.

During administration of 1.5% sevoflurane, no significant differences between the two groups were found concerning ICP, CBF, $PaCO_2$ and CPP, while a significant difference in MABP between the two

Table 1. *Rectal Temperature, $PaCO_2$, Mean Arterial Blood Pressure (MABP), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP) and Cerebral Blood Flow (CBF)*

	Temperature (°C)	$PaCO_2$ (mm Hg)	MABP (mm Hg)	ICP (mm Hg)	CPP (mm Hg)	CBF (ml/100 g/min)
Group 1						
Sevoflurane 1.5% (0.7 MAC)	36.0 (35.5–36.9)	4.9 (4.3–5.1)	67 (64–80)	12 (0–22)	55 (47–80)	33 (16–43)
Sevoflurane 1.5% (0.7 MAC)	36.0 (35.4–36.9)	4.9 (4.3–5.4)	67 (64–104)	13 (0–23)	54 (47–77)	31 (15–40)
Group 2						
Sevoflurane 1.5% (0.7 MAC)	35.9 (35.0–36.9)	4.9 (4.5–5.7)	77[b] (64–104)	12 (0–19)	65 (55–96)	29 (15–46)
Sevoflurane 2.5% (1.3 MAC)	35.9 (35.0–36.9)	5.0 (4.4–5.7)	77[b] (59–89)	14 (0–22)	63 (49–89)	39[a] (17–53)

Median and range are indicated. [a] Indicate $p < 0.05$ within the groups and [b] indicate $p < 0.05$ between the groups.

Table 2. *Hyperventilation Test. Minute-ventilation was Increased by 50% during a Five Min. Period*

	$\Delta PaCO_2$ (kPa)	ΔICP (mm Hg)
Group 1		
Sevoflurane 1.5% (0.7 MAC)	0.81 (0.45–1.1)	3.5 (0–6)
Group 2		
Sevoflurane 2.5% (1.3 MAC)	0.80 (0.67–0.98)	3.0 (0–9)

$\Delta PaCO_2$ Difference in $PaCO_2$ before and five min. after a 50% increase in minute-ventilation.
ΔICP Difference in ICP before and five min. after a 50% increase in minute-ventilation. No statistical difference was found between the two groups.

groups was disclosed (Table 1). In group 1 $PaCO_2$, MABP, ICP and CBF did not change significantly. In group 2, a non-significant increase in ICP from 12 mm Hg during administration of 1.5% sevoflurane to 14 mm Hg during administration of 2.5% sevoflurane was found. Simultaneously a significant increase in CBF from 29 ml/100 g/min to 39 ml/100 g/min was disclosed.

When the minute-ventilation was increased by 50% a 0.8 kPa decrease in $PaCO_2$ was found in both groups. A significant decrease in ICP (3.0 mm Hg and 3.5 mm Hg respectively) was disclosed.

Discussion

During 1.5% sevoflurane a significant difference in MABP was found between the two groups. The imbalance in the gender-distribution, the inter-patient variance, and the fact that the awake MABP in group 1 was lowest, are supposed to influence the level of the MABP during anaesthesia in the two groups. However, within the groups, the MABP was unchanged throughout the study, and no changes were observed when the sevoflurane concentration or minute-ventilation was increased.

At 1.5% sevoflurane ICP was 12 (0–22) mm Hg in both groups. When the sevoflurane concentration was increased to 2.5% a non significant increase in ICP to 14 (0–22) mm Hg was found. This result was surprising, because studies of other volatile anaesthetics (halothane, isoflurane) have demonstrated a dose-related increase in ICP [1,2]. When the sevoflurane concentration was increased from 1.5% to 2.5%, a significant increase in CBF from 29 ml/100 g/min (15–46) to 39 ml/100 g/min (17–53) was disclosed. This significant increase in CBF was not associated with changes in $PaCO_2$ and MABP. The CBF level during sevoflurane anesthesia was comparable to the CBF level during isoflurane/nitrous oxide anesthesia [3]. However, at identical levels of $PaCO_2$ and MABP, the ICP level during sevoflurane was significantly higher than the ICP (8 mm Hg) found during isoflurane/nitrous oxide anesthesia.

In all patients a significant decrease in ICP averaging 3 mm Hg was disclosed when the $PaCO_2$ was decreased by 0.8 kPa, indicating that the response to hyperventilation, with regard to the change in ICP, was present in all patients independent of the sevoflurane concentration.

The effects of sevoflurane upon ICP and CBF are similar to those of isoflurane, a drug that has already found acceptance in neuroanesthetic practice. The present study indicates that sevoflurane might be an alternative to isoflurane in patients subjected to craniotomy for space-occupying lesions. However, the relatively high ICP level during sevoflurane anaesthesia suggests that a comparative study of ICP during isoflurane and sevoflurane anesthesia is necessary.

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Correspondence: Georg Emil Cold, M.D., Department of Neuroanaesthesia, Aarhus University Hospital, DK-8000 Aarhus C, Denmark.

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Radiation-Induced Blood-Brain Barrier Changes: Pathophysiological Mechanisms and Clinical Implications

D. d'Avella[1], **R. Cicciarello**[2], **F. F. Angileri**[1], **S. Lucerna**[1], **D. La Torre**[1], and **F. Tomasello**

Neurosurgical Clinic and Institute of Oncology of the University of Messina Medical School, Messina, Italy

Summary

The pathophysiology of whole-brain radiation (WBR) toxicity remains incompletely understood. The possibility of a primary change in blood-brain barrier (BBB) associated with microvascular damage was investigated. Rats were exposed to conventional fractionation in radiation (200 ± cGy/d, 5 d/wk; total dose, 4,000 cGy). BBB changes were assessed by means of the quantitative ^{14}C-α-aminoisobutyric acid (AIB) technique coupled with standard electron microscopy (EM) and morphometric techniques as well as studies of the transcapillary passage of horseradish peroxidase (HRP). At 15 days after WBR, AIB transport across BBB increased significantly in cerebral cortex. EM disclosed vesicular transport of HRP across the intact endothelium without opening of the tight junctions. Ninety days after WBR, well-defined alterations of the microvasculature were observed. The main feature of cortical microvessels was their collapsed aspect, associated with perivascular edema containing cell debris. Data suggest a possible association between damage of the microvascular/glial unit of tissue injury and development of radiation-induced brain cerebral dysfunction. We hypothesize the following sequence of pathophysiological events: WBR causes an early increase in BBB permeability, which produces perivascular edema and microvascular collapse. The interference with microcirculation affects blood flow and energy supply to the tissue, resulting in structural damage on an ischemic/dysmetabolic basis.

Keywords: Blood-brain barrier; radiation.

Introduction

Radiotherapy plays an important role in supplementing surgical and medical therapy for malignant cerebral tumors. WBR can produce acute and chronic effects in the central nervous system (CNS) which range from transient functional changes to overt encephalopathy with widespread morphological changes and, occasionally, late parenchymal necrosis [6]. All these effects have well-known clinical importance, particularly in young patients in whom long-term intellectual and neuropsychological impairment have been reported after therapeutic irradiation [8]. Though widely investigated, the pathogenesis of WBR adverse reactions remains a subject of continuing controversy. Brain dysfunction has been ascribed either to alterations in the cerebral microvasculature leading to BBB dysfunction and brain edema and/or ischemia, to demyelinization phenomena, or to metabolic alterations [3,7,9]. Previous work from our laboratory has documented the feasibility of using a rodent model employing fractionated WBR to study radiation-induced structural and functional changes in the CNS and their temporal progression [2–5]. The present study further examined potentially adverse effects of WBR in this model and was designed to investigate the possibility of a change in BBB function as a causative factor for WBR-induced cerebral dysfunction.

Materials and Methods

Details of the experimental procedures have been described elsewhere [2–5]. Briefly, 24 male Sprague-Dawley albino rats (280–320 g body weight) were exposed to conventional fractionation radiation (200 ± 4 cGy/day, 5 days/week; total dose 4,000 cGy), using a linear accelerator delivering 6 MeV photons. AIB permeability studies were performed in 6 control and in 6 irradiated rats 15 days after the completion of the exposure. Capillary permeability was determined using the method of Blasberg *et al.* [1] and with standard techniques that originated in our laboratory [4]. Ultrastructural studies were performed 15 (n = 6) and 90 (n = 6) days post-irradiation, employing standard EM [4] and morphometric [2] techniques. Studies of the transendothelial passage of HRP provided information about the BBB functional status.

Results

In irradiated rats, the transport of AIB across the BBB increased significantly in cerebral cortex and cerebellar gray matter. This increase ranged from 1.3

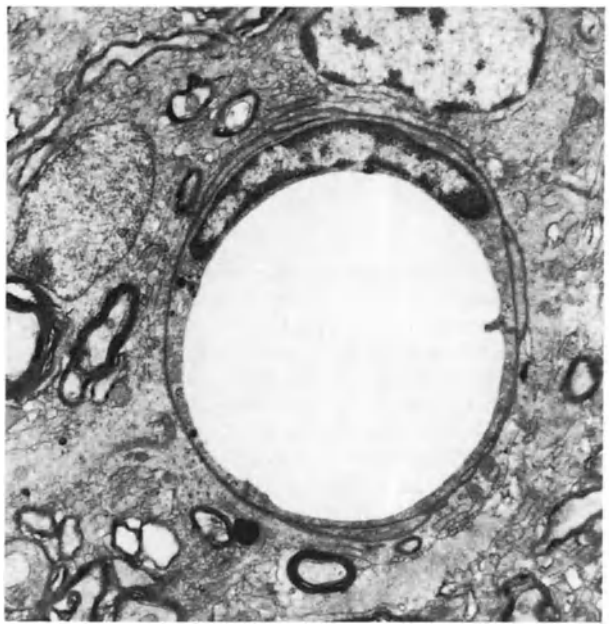

Fig. 1. Electron micrograph of a specimen at 15 days after irradiation. This microvascular profile displays abundant vesicular activity. Several vesicles filled by HRP and abluminal pits are evident. The reaction product also is localized within the perivascular basal lamina (×12,000)

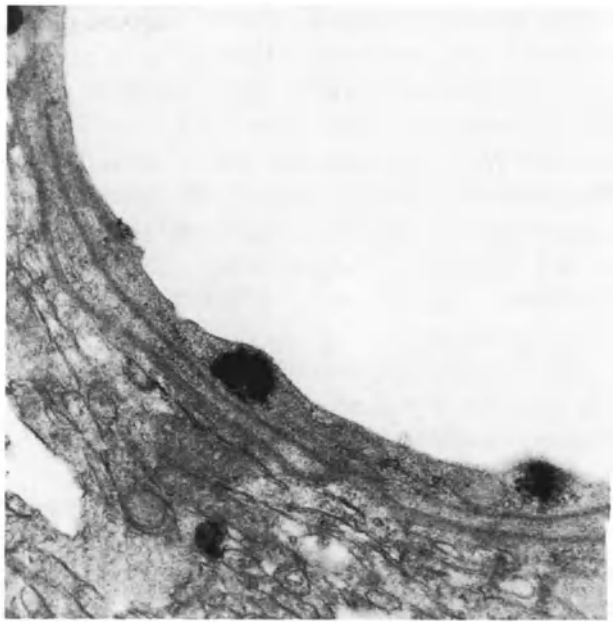

Fig. 2. High-magnification electron micrograph of a microvascular endothelium specimen at 15 days after irradiation. The reaction product fills numerous abluminal pits and vesicles. Larger forms of the indicated vesicles also are filled by HRP (×36,000)

times the normal value for the cerebellar hemisphere to 1.5 times the normal value for the cerebral cortices. EM observations were limited to loci in the frontal, parietotemporal, and occipital cortices. In animals sacrificed 15 days after irradiation the endothelial cells lining the microvasculature showed HRP-positive material present either in luminal pits or in vesicles dispersed throughout the cytoplasm and abluminal front of the cells (Figs. 1 and 2). The tracer-containing vesicles appeared to have a typical pinocytotic form. The number of vesicles averaged 7.2 ± 0.9 per microvascular profile. Such vesicular activity apparently moved the tracer from the luminal surface and extruded it into the basal lamina. HRP-positive material was also identified in the subendothelial space at the level of the basal membrane. HRP was never visualized in the interendothelial gaps that were continuously sealed by tight junctions. No ultrastructurally visible tearing of endothelial membranes or frank endothelial destruction was observed, and the vascular tight junctions appeared intact. In rats sacrificed 90 days after irradiation, EM observations revealed the presence of diffuse ultrastructural alterations involving the microvasculature. The main ultrastructural feature of cortical microvessels was their collapsed aspect, associated with prominent perivascular edema. The clear perivascular spaces contained cell debris probably due to rupturing of swollen neuropil elements and/or astrocyte processes. Examination of the capillary endothelium revealed HRP-filled pinocytotic vesicles at the luminal surface, within the endothelial cytoplasm, and at the level of the basal lamina. The number of vesicles averaged 3.5 ± 0.4 per microvascular profile. The interendothelial junctions appeared to be intact and devoid of reaction product.

Discussion

The purpose of this investigation was to quantitate the acute and sub-acute effects of x-irradiation on normal rat brain capillary permeability. Studies of AIB blood-to-tissue transport were coupled with standard electron microscopy (EM) and morphometric techniques as well as studies of the transcapillary passage of HRP. The combination of these two methods with powerful and complementary capabilities provided quantitative and qualitative regional analyses of BBB alterations after WBR. The major observations derived from this study are as follows. 1) Cranial irradiation given in conventional fractionation caused regional alterations in the permeability of the rat's BBB to AIB. 2) EM observations consis-

tently disclosed an intense vesicular response of the microvascular endothelium, which occurred without opening of the tight junctions and resulted in an intense transport of HRP across the intact endothelium. 3) WBR caused morphological alterations in the rat's brain involving primarily the microvasculature; the severity of these ultrastructural alterations is time-dependent, being detectable 15 days post-irradiation, and increasing in magnitude 90 days post-irradiation.

These findings are consistent with the theory that the vascular compartment is the primary target of the radiation insult and other structural changes are secondary to microcirculatory perturbations. In this respect, it has been reported [9] that changes in blood vessels and perivascular astrocytes after local irradiation of the rat brain are highly correlated and when combined, appear to represent a "unit of tissue injury". In the present investigation, the incidence and severity of this "unit of tissue injury" appeared to increase with time after irradiation. The concept that radiation-induced damage to cerebral endothelial cells might result in progressive microcirculatory and hemodynamic perturbations and compromised cerebral vascular supply, is also supported by previous work from our laboratory employing the same rat model [2,3,5]. Taken together, these data suggest a possible association, not necessarily causal, between damage of the "microvascular/glial unit of tissue injury" and development of radiation-induced brain toxicity.

In conclusion, we hypothesize that the following sequence of pathophysiological events occurs. Radiation causes an early increase in BBB permeability [4], which produces perivascular edema and vascular collapse [2]. The interference with microcirculation affects blood flow and energy supply to the tissue [3,5], resulting in structural damage on an ischemic/dysmetabolic basis. Further studies will be required to investigate this potentially clinically important area of research.

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Correspondence: Domenico d'Avella, M.D., Neurosurgical Clinic, Policlinico Universitario, University of Messina Medical School, I-98100 Messina, Italy.

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Correlation Coefficient between Intracranial and Arterial Pressures: A Gauge of Cerebral Vascular Dilation

M. L. Daley[1] and **C. W. Leffler**[2]

[1] Department of Electrical Engineering, University of Memphis, Memphis, TN and [2] Department of Physiology and Biophysics, University of Tennessee, Memphis Memphis, TN, U.S.A.

Summary

With the use of a laboratory model, arterial and intracranial pressure signals were obtained under conditions of varying depths of hypercapnia ranging from normocapnia to deep hypercapnia. Also, with the use of a closed cranial window, measures of cerebral arteriolar diameter and estimates of cerebral venous flow were obtained. The correlation of the intracranial and arterial pressure signals, arteriolar diameter, and estimates of venous flow exhibit a dose-dependent characteristic by increasing monotonically with increasing progressive states of increasing hypercapnia. These results indicate that the correlation between intracranial and arterial pressure signals provides an estimate of the gauge of the cerebral vasculature.

Keywords: Coherence; vascular dilation.

Introduction

Following a system analysis approach, Portnoy and his colleagues proposed a method of detecting impaired autoregulation based on the coherence of spectral components of the intracranial and arterial pressure signals [1]. Generally, their observations have suggested that the more similar the spectral components of the intracranial pressure signal are to those of the arterial pressure signal, the more likely cerebral autoregulation is impaired [1]. Recently, we have reported that loss of vascular tone can be detected by correlation of the intracranial and arterial pressure signals in the time domain [2]. Since correlation analysis of two signals in the time domain is analytically similar to coherence analysis in the frequency domain, our finding was not unexpected. In particular, the more similar the intracranial and arterial pressure signals are, the higher the value of the correlation coefficient [2].

The purpose of this present study was twofold. First, by evaluating changes of flow in cortical veins during increasing PCO_2 in arterial blood, we tested the hypothesis that venous drainage during positive pressure inhalation is restricted when vascular tone is intact and flow is unrestricted during loss of vascular tone. And secondly, we evaluated the dose-dependency of the value of the correlation coefficient, diameter of cortical arterioles and veins, and venous blood flow increase with increasing hypercapnia.

Materials and Methods

Six α-chloralose anesthetized piglets ranging in weight from 2 to 4 kg were used in this study. The procedures used were similar to those described for other animal studies employing this model [3]. In each piglet a cranial window was placed and video micrometer recordings were made as described previously [4]. A fluid-filled catheter inserted in either the brachial artery or femoral artery was used to record arterial pressure. Inspiration pressure was recorded with a pressure transducer connected to the endotracheal tube. Intracranial pressure was recorded using the Camino fiber optics system, Camino Laboratories, San Diego, CA 921214. The skull was trephined approximately 1 cm lateral to midline and 2 cm below the coronal suture, a hole was made in the dura, and the fiber optic transducer was placed in the parenchyma and secured to the skull.

The three physiologic signals, inspiration pressure, arterial pressure, and intracranial pressure, were simultaneously acquired at a rate of 250 samples/sec/channel by procedures similar to those previously described [2]. Each physiologic channel was calibrated prior to the start of each experiment. Data obtained from the laboratory experiments were imported into DADiSP (DSP Development Corp., Cambridge, MA 02139), a signal processing software package used for correlation analysis. The accuracy of the correlation analysis of this commercial software was verified with a known analytical signal. The normalized correlation function of the two signals was computed as:

$$r(t) = E[ICP(t), \text{Art. Pres}(t)] \Big/ \text{sqrt}\Big(E[ICP(t), ICP(t)] * E[\text{Art. Pres}(t), \text{Art. Pres}(t)]\Big) \quad (1)$$

where the expectation operation is denoted as E [F(t)], and ICP(t) and Art. Pres(t) represent intracranial and arterial pressure signals with their mean value removed respectively. The value of this function at the origin is the correlation coefficient for the two functions; it is an analytical measure of the similarity between the two signals which varies between −1 and 1. If the two signals are proportional, then the signals are strongly correlated, and the correlation value is close to either 1 or −1. However, if the correlation coefficient is less than 0.70, then the signals are not similar.

The hypercapnia was produced by elevation of P_{ICO2}. Each time this manipulation occurred, intracranial pressure increased and arterial pressure decreased over a time course of approximately 5 to 8 minutes to a new steady-state condition. Five levels of arterial partial pressure of carbon dioxide (PCO_2) were used from approximately 35 mm Hg (normocapnia) to about 85 mm Hg. For each of five levels of PCO_2, the correlation coefficient of the intracranial and arterial pressure signals, the diameter of an arteriole, and the diameter of a parasagittal vein in the field of the cranial window were measured twice. Specifically, the level of PCO_2 was manipulated from normocapnia to deep hypercapnia and at each level the measures were completed. After obtaining the deepest state of hypercapnia, the animal was returned to normocapnia and the entire process was repeated. Freeze frame analysis of the velocity of clusters of venous blood cells was used to estimate the flow. Specifically, the distance traveled of a cluster of blood cells was determined over a specific number of frames both during the phases of inhalation and expiration. Velocity of the cluster of cells was computed. Knowing the diameter and assuming a cylindrical geometry, an estimate of flow was determined twice for each state of PCO_2. To compute group averages and standard deviations for each measure, the 12 measures, two for each animal, were grouped according to the level of arterial PCO_2.

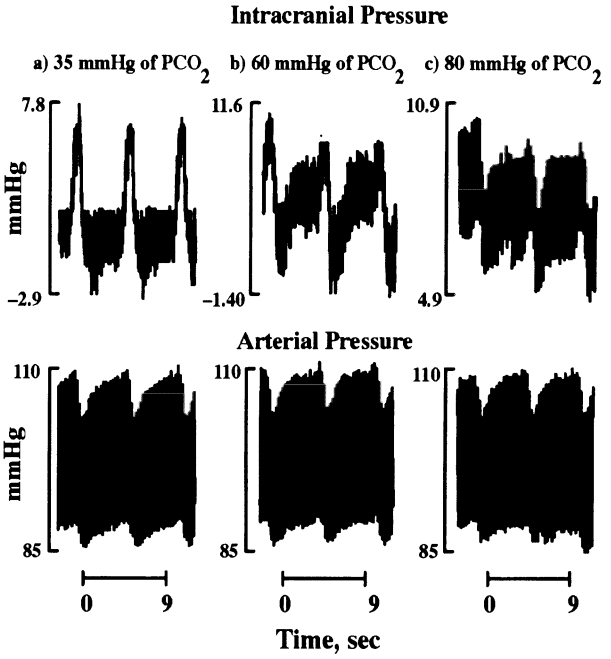

Fig. 1. Examples of Intracranial and Arterial Signals Recorded During Different Levels of Arterial PCO_2. (a) Recordings of intracranial and arterial pressure obtained at 35 mm of Hg of PCO_2 are shown. The abrupt increase in the baseline of intracranial pressure corresponds to the onset of positive pressure inhalation. At the onset of expiration the intracranial pressure signal rapidly decreases and returns to a stationary baseline value. The computed correlation coefficient for these two signals was 0.41. (b) Recordings of intracranial and arterial pressure obtained at 60 mm of Hg of PCO_2 are shown. An increase of intracranial pressure during inhalation is still evident, but the baseline of the ICP signal is no longer stationary during the later phase of expiration. The computed correlation coefficient for these two signals was 0.58. (c) Recordings of intracranial and arterial pressure obtained at 80 mm of Hg of PCO_2 are shown. The abrupt increase and decrease of intracranial pressure coincident with the onset and offset of positive pressure inhalation is no longer evident. Changes in the contour of the ICP signal follow changes in the arterial pressure signal. The computed correlation coefficient for these two signals was 0.84

Results

Examples of the intracranial and arterial pressure signals for the conditions of normocapnia, and moderate, and deep hypercapnia are shown (see Fig. 1). Low frequency changes in the baseline of intracranial pressure correspond to ventilation. During normocapnia positive pressure inhalation, ICP increases abruptly over the course of inhalation and decreases rapidly at the onset of expiration, suggesting corresponding increases and decreases of cerebral blood volume (see Fig. 1a). The onset of expiration is denoted by the synchronized decrease of both the intracranial and arterial pressure signals. The baseline of the ICP signal during the later phase of expiration reaches a stationary steady condition. Thus, during normocapnia with PCO_2 at 35 mm Hg, the primary characteristics of the ICP signal which are not similar to that of the arterial pressure signal are: 1) the salient increase of intracranial pressure during positive pressure inhalation; and 2) the stationary baseline during the later phase of expiration. For this example, the correlation between the two signals is 0.41. During moderate hypercapnia with PCO_2 at 60 mm Hg, the abrupt increase of intracranial pressure during positive pressure inhalation is still evident, but the baseline of the ICP is no longer stationary during the later phases of expiration and begins to follow changes of the arterial pressure signal (see Fig. 1b). The correlation coefficient for these two signals is 0.58. Finally during deep hypercapnia with PCO_2 at 80 mm Hg and maximal vasodilation, abrupt increases and decreases of intracranial pressure coincident with the onset and offset of positive pressure inhalation are no longer evident. Changes in the baseline of the intracranial pressure follow the corresponding changes in the arterial pressure (see Fig. 1c), and the computed correlation coefficient for these two signals is 0.84.

For the 6 preparations with increasing level of arterial PCO_2, the mean correlation coefficient, mean diameter of arterioles and veins, and venous flow increased (see Fig. 2). Standard error bars for both the correlation coefficients and diameters of the arterioles and veins are within the solid squares for all points. The mean for each level of PCO_2 is significantly different than the mean of the previous level ($p < 0.005$). With each successive level of PCO_2 the correlation coefficient increased. The lowest mean value of the correlation coefficient is significantly different than the highest value with a level of confidence of at least $p < 0.05$ (see Fig. 2a). Similarly, the two smallest mean values of the diameter of the vein are significantly different than the greatest mean diameter ($p < 0.01$). Each mean value of arterial diameter was significantly different than the other mean values at a confidence level of at least $p < 0.05$ (see Fig. 2b). All the mean values of venous flow during inhalation were significantly different at least at $p < 0.05$. However, every other successive value of mean venous flow during expiration was significantly different ($p < 0.005$). The difference in flow between the two phases of respiration remained relatively uniform at 6.6 (±1.52) pL/sec ranging from 89 to 102 pL/sec during inhalation and 95 to 112 pL/sec during expiration (see Fig. 2c).

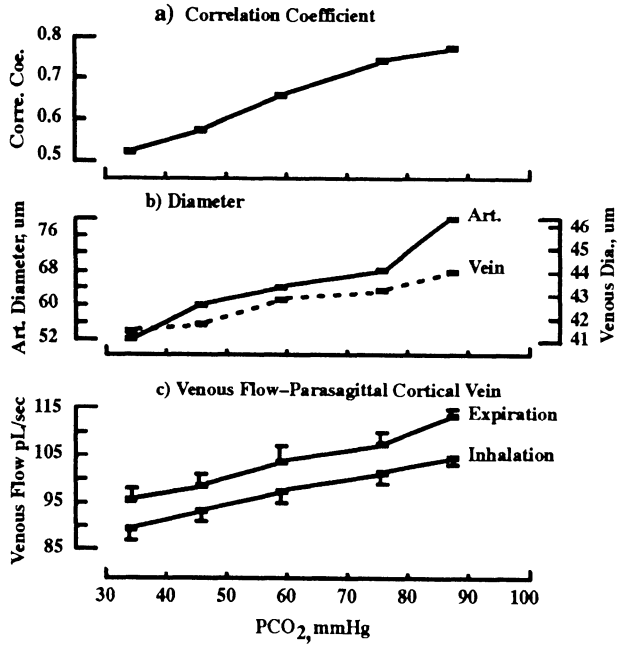

Fig. 2. Indices of Cerebral Vascular Dilation. (a) Mean computed values of correlation increase progressively with increasing depth of hypercapnia. Standard error bars are within solid square. (b) Mean diameter of arterioles and parasagittal cortical veins with increasing depth of hypercapnia. (c) Average flow in parasagittal cortical veins during expiration and inhalation

Discussion

With the use of a coherence function which is similar to a cross-correlation function in the frequency domain, Portnoy and his colleagues showed that during normocapnia coherence is low but is high during deep hypercapnia [1]. Moreover, they suggested that during deep hypercapnia the cerebral vasculature acts as a distended tube. As a result, there is a linear transmission of the arterial pulse wave through the vasculature, and the arterial and intracranial pressure pulsations have nearly identical contours [1]. Unlike previous approaches, we have noted that the salient increase of the baseline of the intracranial pressure during positive pressure inhalation during normocapnia is not present during deep hypercapnia (see Fig. 1) [2]. Moreover, to quantify the comparison between the intracranial and arterial pressure signals, we have used an application of correlation analysis in the time domain. The illustrated recordings were obtained at 35, 60, and 80 mm Hg of arterial PCO_2. The computed correlation coefficient for each set of recordings was 0.41, 0.58, and 0.84 respectively. Because these recordings were obtained during a steady-state period in which the mean level of intracranial pressure was relatively constant, it is not surprising that the mean value of the intracranial pressure for recordings obtained at PCO_2 60 and 80 mm Hg are about equal (see Fig. 1b and 1c). For these conditions of equilibrium, it is likely that the absorption of cerebral spinal fluid compensated for the increase in blood volume due to vascular dilation. Estimates of cerebral perfusion pressure based on the difference between arterial and intracranial pressure for these three conditions are not significantly different. However, for the deepest hypercapnic condition, it was likely that the vasculature was maximally dilated and autoregulation was severely reduced or absent [5]. Thus, impaired autoregulation can occur with a relatively low value of intracranial pressure. We have obtained similar recordings from pediatric patients with traumatic brain injury. In particular, the intracranial and arterial pressure signals were highly correlated, yet mean intracranial pressure was well below 20 mm Hg, and the cerebral perfusion pressure was above 60 mm Hg [6].

The relationship between correlation coefficient and level of PCO_2 is shown in Fig. 2a. Each point

represents the mean average for all animals with each measured twice (n = 12). It should be noted that once a steady-state condition is reached the value of the correlation coefficient remains relatively constant. For example, for the steady state conditions used to obtain the recordings illustrated in Fig. 1, the correlation coefficient was computed on eight different 15 second epochs. The mean value and standard deviation of the computed correlation coefficients for each condition were 0.434 ± 0.014, 0.60 ± 0.010, and 0.844 ± 0.005. The differences between these mean values of the computed correlation are highly significant at a level of conference of $p < 0.005$. Also, shown in Fig. 2 are the average diameters of selected pial arterioles and parasagittal pial veins in each preparation for each level of arterial PCO_2. These results demonstrate that increasing the depth of hypercapnia increases both the strength of correlation between the intracranial and arterial pressure signals and the degree of dilation of the vasculature. There is a dose dependency between both strength of correlation and degree of dilation of the cerebral vasculature and level of arterial PCO_2. For these preparations, a value of correlation above 0.75 is an indicator of impaired autoregulation independent of the level of mean intracranial pressure.

In summary, this study demonstrates that the correlation between the arterial and intracranial pressure signals becomes significantly stronger, arterioles and superficial parasagittal veins progressively dilate, and flow through these veins increases significantly with increasing arterial PCO_2. Flow was greater during expiration, and the difference in flow through these veins between inhalation and expiration remained relatively constant for all states of dilation.

Acknowledgments

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Correspondence: Michael L. Daley, Ph.D., The University of Memphis, Electrical Engineering, Campus Box 526574, Memphis, TN 38152, U.S.A.

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Pathogenesis of the Mass Effect of Cerebral Contusions: Rapid Increase in Osmolality within the Contusion Necrosis

Y. Katayama, T. Mori, T. Maeda, and **T. Kawamata**

Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, Japan

Summary

The non-hemorrhagic mass effect of cerebral contusions is commonly attributed to vasogenic edema and/or cytotoxic edema (cellular swelling). We propose that a marked increase in osmolality within the *contusion necrosis proper*, in which the cellular elements uniformly undergo shrinkage, disintegration and homogenation, represents an important and unique mechanism underlying the contusion edema. The present study demonstrates in a rat model of cerebral contusion, that 1) the osmolality of the contused brain tissue increases rapidly, 2) the increase in osmolality is not caused by changes in inorganic ion contents, suggesting a metabolic production of osmoles or release of idiogenic osmoles, and 3) the contused brain tissue strongly attracts water, provided that blood supply is maintained. We suggest that the primary driving force of water accumulation into contused brain tissue is the elevated colloid osmotic potential of contusion necrosis.

Keywords: Cerebral contusions; contusion necrosis; osmolality.

Introduction

In patients with cerebral contusions, conservative therapies have generally been advocated unless there are hemorrhages contributing significantly to an elevation of the intracranial pressure (ICP). Despite intensive conservative therapies, however, some patients exhibit a progressive neurological deterioration and parallel elevation of their ICP within the period of the initial 24 to 48 h post-trauma [4]. Such a non-hemorrhagic mass effect is sometimes so severe that surgical excision of contused brain tissue is the only therapy which can provide satisfactory control of the ICP and avoid death. The precise mechanism underlying the non-hemorrhagic mass effect of cerebral contusions is not yet clearly understood.

Computerized tomography (CT) scans and magnetic resonance imaging (MRI) have revealed that two distinct types of edema occur in patients with cerebral contusions: one is an early massive edema which develops within the initial 24 h post-trauma, and the other is a delayed peri-contusion edema which becomes cleared, at more than 24 h post-trauma (e.g., [1]). The delayed peri-contusion edema exhibits characteristics that are consistent with vasogenic edema [11]. T2-weighted MRI has demonstrated that such edema spreads widely within the white matter. Evaluation of the vascular permeability based on 99mTc pertechnetate single photon emission CT [2] and gadolinium (Gd)-DTPA enhanced MRI [6,7] has revealed a peri-contusion "halo" of 99mTc pertechnetate activity and Gd-DTPA enhancement. The delayed peri-contusion edema is often observed, however, in the absence of an elevation of ICP and signs of neurological deterioration.

In contrast, the early massive edema, which is temporally correlated with ICP elevation and signs of neurological deterioration, does not display the characteristics of vasogenic edema. Evaluation of the vascular permeability by 99mTc pertechnetate single photon emission CT [2] and Gd-DTPA enhanced MRI [7] failed to reveal any evidence of an increased vascular permeability within the area of contusion during the initial few days post-trauma. An immunohistochemical study of the post-mortem brain of such patients failed to disclose any protein extravasation into the area of contusion during this early period [10]. Many studies have demonstrated the development of microthrombosis and a profound decrease in blood flow within the peri-contusion area in experimental animals (e.g., [9,10]), as well as in patients [1,2]. The area affected by microthrombosis spreads progressively into the surrounding area until 12–24 h post-trauma, and numerous swollen cells are ob-

served in this area. These findings suggest that the early massive edema is, at least partially, cytotoxic in nature.

In the present paper, we discuss another mechanism for the non-hemorrhagic mass effects of cerebral contusions. An area affected by contusion necrosis, as a direct consequence of mechanical impact (*contusion necrosis proper* [8]), is already evident as early as at 3 h post-trauma [3]. The cellular elements in this well-demarcated area, both neuronal as well as glial cells, uniformly undergo shrinkage, and then disintegration, homogenation and cyst formation. Unlike the cells in the area surrounding the *contusion necrosis proper*, they never exhibit swelling [8]. We test the hypothesis that elevated osmolality within this area plays an important role in the non-hemorrhagic mass effects of cerebral contusion.

Methods

Experimental data were obtained from cerebral contusions produced with a controlled cortical impact injury model in the rat. Impact was applied to the lateral aspect of the frontal lobe perpendicularly to the contour of the cortical surface (penetration depth, 3 mm) with a rod of 5 mm in diameter at 6 m/s. Massive intracerebral hemorrhages were rarely produced and, data from animals with such hemorrhages were excluded. In some animals, isolation of the frontal lobe with transection was performed immediately post-trauma to examine the effects of interruption of the blood supply to the contused brain tissue. Animals were divided into 3 groups: Group 1 (contusion only), Group 2 (isolation of the frontal lobe only), and Group 3 (contusion and isolation of the frontal lobe). The isolation alone is equivalent to complete focal ischemia. These procedures were performed under nitrous oxide and halothane anesthesia and infiltration of xylocaine into the wound edge. The craniotomy site was sealed tightly with a silicone plate glued to the skull and the wound was closed after the experimental insult. The animals were then allowed to recover from the anesthesia.

The animals were sacrificed by decapitation under barbiturate anesthesia at varying intervals post-trauma. The osmolality (mmol/kg · wet tissue) and water content of the contused brain tissue obtained from the center of the cerebral contusion were determined by vapor pressure osmometry and specific gravimetry, respectively (n = 45). In separate subgroups of animals, the contents of water (%), Na^+, K^+ and Cl^- (mmol/kg · wet tissue) within the contused brain tissue were determined by dry/wet weight measurement and high performance liquid chromatography, respectively (n = 10). In other subgroups of animals, the ICP was monitored from the cisterna magna for 12–24 h (n = 15) while nitrous oxide and halothane anesthesia was continued.

Results

The osmolality of the brain tissue underwent a marked elevation in all groups ($p < 0.01$ at 6 and 12 h post-trauma; Table 1). The increase in osmolality was significantly lower in the Group 1 animals, as compared to that in the Group 2 and 3 animals ($p < 0.05$ at 12 h post-trauma; Table 1). In contrast, the specific gravity of the brain tissue decreased clearly only in the Group 1 animals ($p < 0.01$ at 6 and 12 h post-trauma; Table 1). The decrease in specific gravity in the Group 1 animals was highly significant as compared to the Group 2 and 3 animals ($p < 0.01$ and 0.05, respectively, at 12 h post-trauma; Table 1). The less marked increase in osmolality observed in the Group 1 animals can be accounted for by this concomitant decrease in specific gravity (increase in water content), indicating that osmotically active substances are produced similarly in all the groups but water is accumulated only in the contused brain tissue in which blood supply is maintained. Consistent with these findings, the most pronounced increase in ICP was observed in the Group 1 animals, reaching a maximum level (>20 mm Hg) at 12 h post-trauma.

In the Group 1 animals, a large increase in Na^+ ($p < 0.05$ at 6 h post-trauma) was observed concomitantly with the increase in % water content ($p < 0.03$ at 6 h post-trauma; Table 2). It was noted, however,

Table 1. *Changes in Osmolality and Specific Gravity of Brain Tissue after Trauma and /or Isolation Ischemia*

Group	Pre-insult	6 h post-insult	12 h post-insult	Comparison with contusion
Osmolality (mmol/kg · wet tissue)				
Contusion	311.4 ± 11.3	406.6 ± 18.9[a]	402.8 ± 15.1[a]	–
Isolation	319.5 ± 9.3	415.2 ± 16.6[a]	438.4 ± 20.3[a]	$p < 0.05$
Contusion + isolation	310.0 ± 9.0	424.0 ± 21.0[a]	445.0 ± 29.0[a]	$p < 0.05$
Specific gravity				
Contusion	1.043 ± 0.003	1.035 ± 0.005[a]	1.031 ± 0.005[a]	–
Isolation	1.042 ± 0.004	1.042 ± 0.003	1.041 ± 0.002	$p < 0.01$
Contusion + isolation	1.042 ± 0.001	1.039 ± 0.003	1.037 ± 0.003	$p < 0.05$

Mean ± SD. n = 5 for each group at each time point.
[a] $p < 0.01$ as compared to pre-insult (unpaired t test).

Table 2. *Changes in Water Content and Inorganic Ion Concentrations of Brain Tissue after Trauma (Contusion Only)*

	Pre-trauma	6h post-trauma	Difference	Significance
Ion contents (mmol/kg·wet tissue)				
$Na^+ + K^+ + Cl^-$	181.9 ± 29.8	193.1 ± 53.1		NS
$Na^+ + K^+$	139.1 ± 18.3	144.7 ± 35.7		NS
Na^+	46.5 ± 6.5	66.4 ± 13.7	+42.8%	$p < 0.05$
K^+	92.7 ± 11.9	78.3 ± 22.0		NS
Cl^-	42.8 ± 11.5	48.4 ± 17.4		NS
Water content (%)	79.7 ± 1.3	83.6 ± 2.6	+4.9%	$p < 0.03$

Mean ± SD. n = 5 for each time point. *NS* not significant.

that K^+ decreased in parallel to the increase in Na^+ (Table 2). In addition, Cl^- did not increase as much as Na^+. As a result, the net change in inorganic ions was in total very modest. The combined Na^+ and K^+ content of the brain tissue was maintained at a level (144.7 mmol/l) which was approximately the same as that of the plasma (144.0 mmol/l), although a non-significant small increase was observed in the contused brain tissue. Such an increase (4.0%) was in a range comparable to the increase in water content (4.9%).

Discussion

When the cell membrane is disrupted and intracellular colloid substances are allowed to pass through, these substances become osmotically inert and the cells may shrink. The cellular shrinkage observed in the area of *contusion necrosis proper* [8] may be attributable to such a mechanism. The process of cellular disintegration and homogenation within the area of *contusion necrosis proper*, can be detected in patients as the formation of a fluid-blood interface on CT scans or MRI, which represents the sedimentation of red blood cells within the well-demarcated softened necrotic tissue. This type of fluid-blood interface is not uncommonly detected in contusion hemorrhages, if we examine the CT scans or MRI carefully [5]. The interface began to become visible at as early as at 12h and was clear at 48h post-trauma, suggesting that the process of cellular disintegration and homogenation progresses very rapidly.

Under such circumstances, the contused brain tissue can be regarded as though it consists of a single huge extracellular space having a high colloid osmotic pressure. Thus, water in the plasma compartment is directly faced by a high colloid osmotic pressure. In addition, the concentrations of various inorganic ions within the extracellular space undergo drastic alterations because of mixing of extracellular and intracellular ions. This implies that the ion pumps of the capillary endothelial cells have to substitute for the function of the ion pumps of the cell membrane of the brain tissue for controlling the brain volume.

Furthermore, the present study has revealed that 1) the osmolality of the contused brain tissue increases rapidly, 2) the increase in osmolality is not caused by changes in inorganic ion contents, suggesting an increase in colloid osmotic pressure through the metabolic production of osmoles and/or a release of idiogenic osmoles, and 3) the contused brain tissue strongly attracts water, provided that the blood supply is at least partially maintained. These events should stimulate further the ion pumps of the capillary endothelial cells for controlling the brain volume. We have examined the vascular permeability at 12h post-trauma by slow infusion of Gd-DTPA and delayed MRI [6]. We have observed only a slight, if any, enhancement in the white matter surrounding the contusion in some cases. A more striking finding was the enhancement of the necrosis area, which was noted to a greater or lesser extent in all of the cases. Enhancement of the necrosis area with delayed MRI implies that there is a large pressure gradient between the necrotic brain tissue and damaged capillary wall, and bulk flow of water towards the *contusion necrosis proper* rather than the surrounding white matter.

The water accumulation in the contused brain tissue may be due either to the elevated extracellular colloid osmolality or to failure to equilibrate the increased osmolality with ion pumps. We propose that the primary driving force of water accumulation into contused brain tissue is the elevated colloid osmotic potential of the contusion necrosis, and this repre-

sents an important and unique mechanism underlying the contusion edema. The beneficial influence of surgical excision of contused brain tissue on the outcome is commonly explained by an increase in space compensation. We believe also that excision of the contusion necrosis does facilitate or secure an elimination of the mechanisms of water accumulation.

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Correspondence: Yoichi Katayama, M.D., Department of Neurological Surgery, Nihon University School of Medicine, Tokyo 173, Japan.

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Control of ICP and the Cerebrovascular Bed by the Cholinergic Basal Forebrain

M. Maeda[1] and **M. Miyazaki**[2]

Department of [1]Neurosurgery and [2]Casualty Center, Juntendo University Izunagaoka Hospital, Japan

Summary

The involvement of the cholinergic basal forebrain in the control of ICP and the cerebrovascular bed was investigated by simultaneous measurement of CBF, BP, ICP and $ETCO_2$ in rats and cats. Single unit spikes were also continuously recorded during ICP changes in the dorsomedial hypothalamic nucleus (DMH) of cats.

Glutamate or acetylcholine (Ach) microinjection into the magnocellular basal nucleus (nucleus basalis Meynert: NBM, substantia innominata: SI) of rats or the DMH of cats caused persistent increases in ICP associated with slightly decreased BP. Microinjection of Ach into the NBM or the DMH also induced consistent increases in CBF in the cerebral cortex. Spike activities in DMH neurons increased before and during spontaneous ICP elevation. The firing rate of the DMH neurons increased in phase with the plateau wave-like ICP variations elicited by microinjection of Ach into the cholinoceptive pontine area or the contralateral DMH.

Glutamate-or Ach-induced increases in ICP resulted from an increased CBV in response to a reduced cerebral vasoconstrictor tone. Activity within the cholinergic basal forebrain, as well as the central noradrenergic system, contribute to ICP changes and may be the intrinsic neuronal origin of the plateau waves occurring in some pathological conditions.

Keywords: Cholinergic basal forebrain; control of ICP; locus coeruleus complex.

Introduction

Episodic elevation of intracranial pressure (ICP), the so-called "plateau waves" [5], may be caused by persistent intracranial hypertension or cerebral vasomotor reaction [2]. Plateau waves are associated with an increased cerebral blood volume (CBV) [10] due to dilatation of the cerebral blood vessels, and result from an intact autoregulation responding to changes in cerebral perfusion pressure [11]. Previously we have investigated the function of noradrenergic cell groups (locus coeruleus complex: LC, medullary reticular formation: MRF) and the cholinoceptive pontine area (CPA) in the generation of plateau waves [6–8]. This study investigated the involvement of the cholinergic basal forebrain in the control of ICP and the cerebrovascular bed.

Materials and Methods

Twelve cats with kaolin-induced hydrocephalus under chloralose anesthesia and eight normal rats were used for the experiments. The animals were immobilized with pancuronium bromide and artificially ventilated. The ICP was continuously monitored using a Camino fiber optic transducer inserted into the white matter of the right occipital lobe. The systemic blood pressure (BP) and end-tidal CO_2 concentration ($ETCO_2$) were measured continuously. The cerebral blood flow (CBF) was measured by the hydrogen clearance method. In the first series of experiments glutamate or acetylcholine (Ach) was injected through microinjection needles into the magnocellular basal nucleus (nucleus basalis of Meynert: NBM, substantia innominata: SI) of the rats or the dorsomedial hypothalamic nucleus (DMH) of the cats. In the second series of experiments single unit spikes using tungsten microelectrodes were continuously recorded during spontaneous or induced ICP variations in the DMH of the cats. The frequency of consecutive discharges was measured during 1, 3 or 5 sec periods. The neurons were identified using a reference point at the end of the experiment.

Results

Insertion of the injection needle into the DMH of the cats evoked an increase in ICP associated with a transiently slightly increase in BP. Microinjection of Ach into the DMH of the cats produced a persistent increase in ICP with a marked decrease in BP, and induced a remarkable increase in CBF (from 35 ml/100 g/min to 49.3 ml/100 g/min). However, there were no measurable changes in $ETCO_2$ concentration during the induced ICP variations (Fig. 1C). Microinjection of glutamate or Ach into the NBM and SI of the rats caused consistent increases in ICP associated with slightly increased or decreased BP, respectively

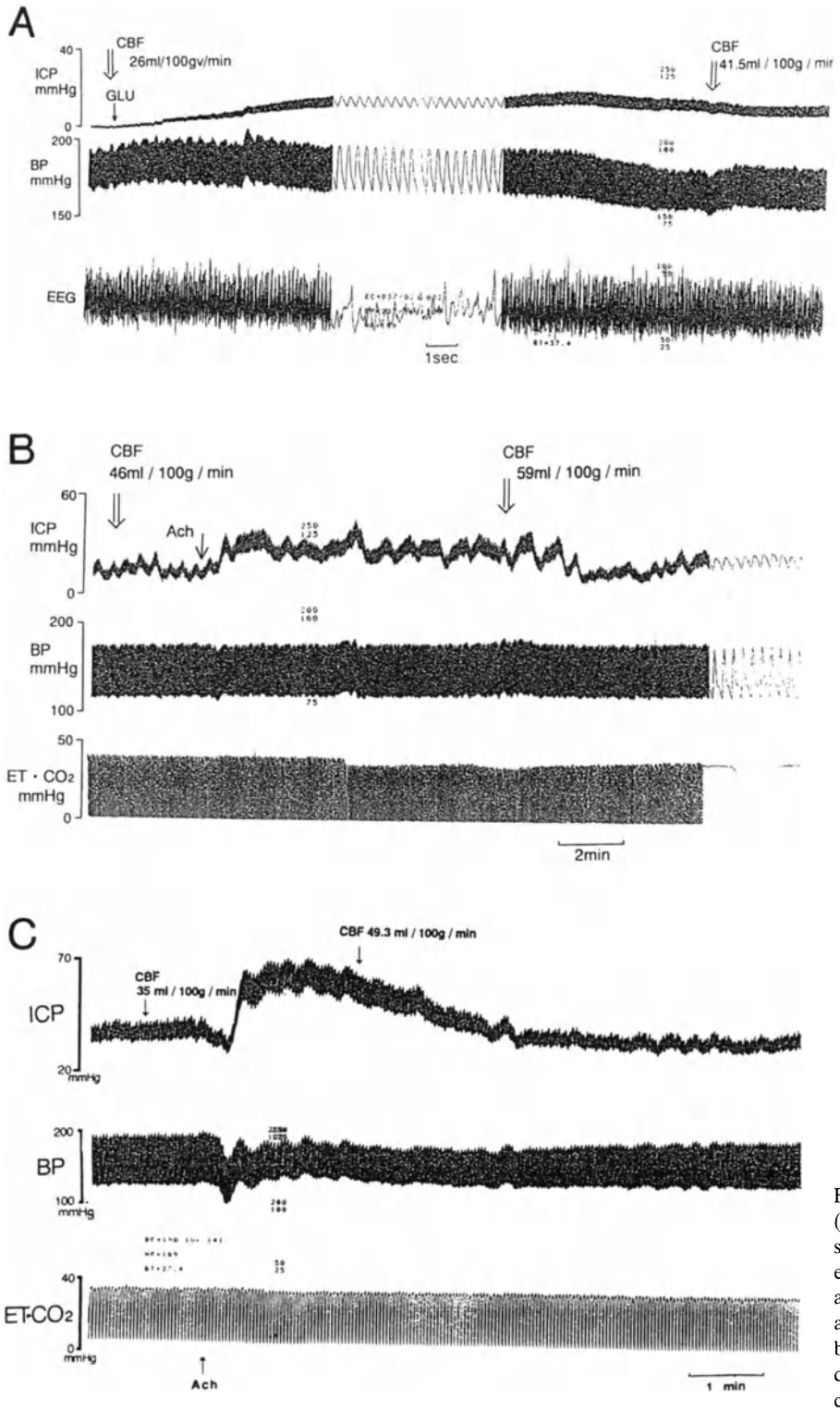

Fig. 1. Changes in cerebral blood flow (*CBF*), intracranial pressure (*ICP*), systemic blood pressure (*BP*), and end-tidal CO_2 concentration ($ETCO_2$) after microinjection of glutamate or acetylcholine (Ach) into the cholinergic basal forebrain of rats (A, B) or the dorsomedial hypothalamic nucleus of cats (C)

(Fig. 1A and B). Microinjection of glutamate or Ach into the NBM of the rats also induced consistent increases in CBF in the cerebral cortex (from 26 ml/100 g/min to 41.5 ml/100 g/min and 46 ml/100 g/min to 59 ml/100 g/min, respectively).

The spike activities in the DMH neurons related to the spontaneous ICP variations are shown in Fig. 2A. The firing rate increased in phase with the plateau wave-like ICP elevation. The spike frequency increased about 30 sec before the rising phase and de-

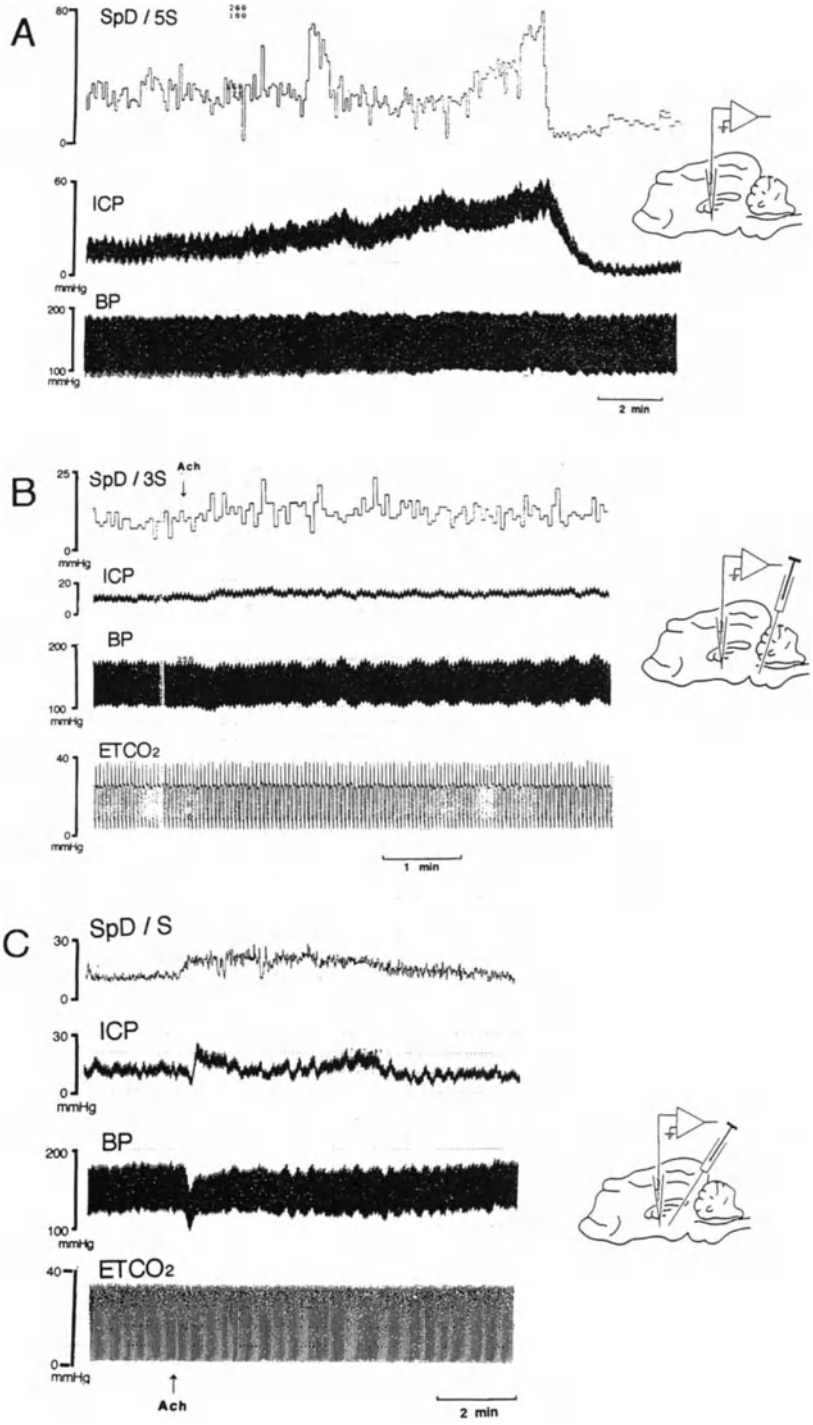

Fig. 2. Discharge patterns of dorsomedial hypothalamic nucleus (DMH) neurons of cats during ICP changes. (A) Spontaneous ICP changes, (B) and (C): ICP elevations induced by microinjection of Ach into the cholinoceptive pontine area (B) or the contralateral DMH (C). Simultaneous recording of spikes (SpD) of DMH neurons, ICP, BP, and $ETCO_2$. The frequency of consecutive discharges was measured for 5 sec (A), 3 sec (B), or 1 sec (C)

creased sharply about 15 sec before the falling phase. There were no remarkable changes in BP during the plateau wave. Ach microinjection into the CPA caused consistent increases in ICP associated with slightly decreased BP. The spike activities in the DMH neurons associated with the ICP increase are shown in Fig. 2B and C. Tonic DMH-neuron discharges gradually increased about 10 sec before the ICP began to increase. There were almost no changes in the $ETCO_2$ concentrations during these ICP changes (Fig. 2A). Some DMH neurons demonstrated no suppression or promotion of spike activities during increased ICP caused by Ach microinjection into the CPA. Activation of the NBM or the SI of the rats or the DMH of the cats by microinjection of glutamate or Ach produced a consistent

increase in ICP associated with an increase in CBF (Fig. 1). The firing rate of the DMH neuron on the left was increased in phase with the plateau wave-like ICP elevation caused by Ach microinjection into the DMH on the right (contralateral) (Fig. 2C). The spike frequency increased about 15 sec before the rising phase and decreased about 10 sec before the falling phase.

Discussion

Cerebral blood vessels receive adrenergic innervation from at least two sources: the cervical sympathetic system, and the medulla oblongata (MRF), pons, and midbrain (LC) which directly affect the intramedullary arteriole walls. Previously, we found that spontaneous LC neuron activity was clearly suppressed during plateau waves, the spontaneous activities of MRF neurons were suppressed during increased ICP, and the spikes in CPA neurons were synchronized with plateau waves [7,8]. Our previous studies have also demonstrated that CPA neurons suppress activities in both LC and MRF neurons, which form the central noradrenergic system [8]. Therefore, activation of CPA neurons would result in reduced activity in the central noradrenergic system, and so an increase in CBV would occur in response to dilatation of the cerebral vessels. The plateau waves would thus result from the increase in CBV [2,3,5–10]. The present study showed that activation of the cholinergic basal forebrain (NBM, SI, DMH) caused increases in both ICP and CBF. Ach-induced ICP and CBF changes may result from increased CBV in responses to reduced cerebral vasoconstrictor tone. Activation of the intracranial cholinergic fibers originating in the NBM releases Ach in the cortex, which results in vasodilation and increased rCBF in the cortex [12]. Local metabolites are considered to be important in regulating rCBF. However, the regulation of rCBF by the central cholinergic nerves seems to be independent of regional metabolism [1,4,12]. In our study, the DMH neurons fired in phase with the plateau wave or ICP increase. Therefore, DMH neurons show a discharge pattern very similar to CPA neurons. The previous and present results suggest that activity within the cholinergic basal forebrain, as well as the CPA, LC, and MRF, contributes to ICP changes and provides an endogenous neuronal basis for the plateau waves observed in some pathological conditions such as disturbed cerebrospinal fluid absorption (kaolin-induced hydrocephalus).

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Correspondence: M. Maeda, M.D., Department of Neurosurgery, Juntendo University, Izunagaoka Hospital, 410-22 Japan.

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The Relationship of Vasogenic Waves to ICP and Cerebral Perfusion Pressure in Head Injured Patients

D. J. Price, A. Saxena, and **M. Czosnyka**

Department of Neurosurgery, Pinderfields Hospital, Wakefield, West Yorkshire, U.K.

Summary

Slow vasogenic waves are characterised by sudden rises and falls in both the mean ICP and its cardiac pulsatile amplitude for periods of up to an hour. On reviewing the on-line computer records of a series of 200 consecutive head injured patients, some 650 waves with increases in mean ICP of at least 15 mm Hg were recognized. The mean ICP, pulsatile amplitude, perfusion pressure, arterial pressure and pulse rates which had been generated every minute were reviewed in each of a 100 randomly selected waves in the hopes of allocating them into defined groups according to precipitating factors. We had expected to find that the majority of waves were precipitated by a preceding fall in cerebral perfusion pressure as a result of a transient arterial hypotension. Only in 19 of the 100 waves did this sequence become apparent and in the remainder, no recognizable precipitating factors were found. In 21 of the records, there was a fall in ICP of at least 5 mm Hg before the onset of the pressure wave.

Keywords: Cerebral perfusion pressure; vasogenic waves.

Introduction

During the last 20 years, two computerised monitoring systems have been in use in the Intensive Care Unit at Pinderfields Hospital. We have endeavoured over the years to take advantage of the additional information obtained by continuous analysis of changes in the waveform. Cardiac pulsatile amplitude is affected by both the pulsatile component of cerebral blood volume and on changes in the cerebrospinal elasticity. We have taken a particular interest in following the changing relationship between this amplitude and the ICP mean and this has provided valuable information about the current states of compensatory and auto-regulatory reserves [1,2].

Computerised signal processing has many advantages over conventional chart recorders. Not only does it provide averaging and compression for trend recognition (3) but it also allows easy access for retrospective surveys. For this study, it has been convenient to transfer all the ICP records onto the hard disc of a lap-top computer, which has provided an excellent opportunity to review all the vasogenic waves recorded in patients with head injury during the last 8 years.

Both Lundberg in Sweden and Janny in France independently published their observations about these spontaneous and acute elevations in ICP in 1960. This phenomenon is associated with transient falls in cerebral perfusion pressure (CPP) and it has been suggested that it might occur as a result of an intact or almost intact auto-regulatory response to a preceding small fall in CPP [5]. There was evidence at that time that a gradual decline in systemic arterial pressure would cause vasodilatation by auto-regulation and the subsequent rise in ICP reduced the CPP which in turn initiated this vasogenic wave proper.

The purpose of this study is to review the changes just before and during these waves in the hopes of confirming Rosner and Becker's observations during the early eighties [5].

Method

In a consecutive series of 200 patients with severe head injury, ICP monitoring was set up within 4 hours of injury in 92% of the patients. An external transducer with fluid filled ventricular or subdural catheters have replaced the Camino system which in earlier years had intolerable zero drifts. ICP and arterial waveforms were sampled at a frequency of 18 Hz. The amplitude of the cardiac pulsewave was calculated every 8 seconds using a 128 Fast Fourier Transform. The mean ICP, CPP, amplitude, arterial pressure and heart rate were stored in a circular buffer to allow the generation of one minute averages to provide a continuously updated graphical display and an archive.

The archive of data from the last 200 patients consists of one minute mean values of these physiological variables and were reviewed on the lap-top computer. The vasogenic waves with elevations of 15 mm Hg or more were identified and counted. 100 waves were then randomly selected for statistical evaluation. Five time points on each wave were visually identified. The first point is 5 minutes prior to the steep rise in mean ICP and amplitude. The second point is at the onset of the wave. The third and fourth time points are at the peak of the ICP and the trough of the CPP, respectively and the fifth point is at the end of the wave when the ICP has fallen to near to its original pressure. The 5 time points along with the values of each of the 5 parameters for each time point were then transferred to a data base for subsequent distribution histogram analysis.

In addition, all the 200 patient records were transferred to a statistical package to audit the overall distribution of ICP and CPP values. The conditional averages of the amplitude as a dependent variable were plotted against the independent variable CPP in data bins 10 mm Hg wide and also against ICP in data bins 5 mm Hg wide.

Results

For 11% of the time CPP was less than 60 mm Hg. For 27% of the time in this group of 200 patients, it was less than 70 mm Hg. The mean ICP was above 25 mm Hg for 19% of the time.

There were 650 vasogenic waves with rapid elevation of ICP of at least 15 mm Hg and with concurrent rise in amplitude. The rise in mean ICP varied from 10 to 70 mm Hg. 41% had a rise of between 10 and 20 mm Hg and 37% of between 20 and 30 mm Hg. In the remainder, the rise was above 30 mm Hg. The pulsatile amplitude increased by 0–3 mm Hg in 17%, by 3–6 mm Hg in 41% and by more than 6 mm Hg in 42%.

60% of the records showed that the peak in ICP and the trough in CPP occurred at the same time (Fig. 1). There were 19 records out of a 100 who had the maximum reduction in CPP 4 minutes or more before the ICP peak, and it is reasonable to presume that on these occasions, the fall in CPP precipitated the rise in ICP. In 7 records, the CPP trough occurred 4 minutes or more after the ICP peak. 77% had reached the peak before the midpoint in time between the beginning and the end of the wave and 58% had reached the peak within 20 minutes. The ICP wave was shorter than 30 minutes in 81% of the records but 2 did extend just beyond an hour. 43% of the falls in CPP were for up to 20 mm Hg and in 45%, there were falls of 20–40 mm Hg with the remainder showing reductions in excess of 40 mm Hg.

During the ICP rise, the arterial pressure rose at least 15 mm Hg in 22 patients but it fell by at least that amount in 2 patients. The heart rate rose by more

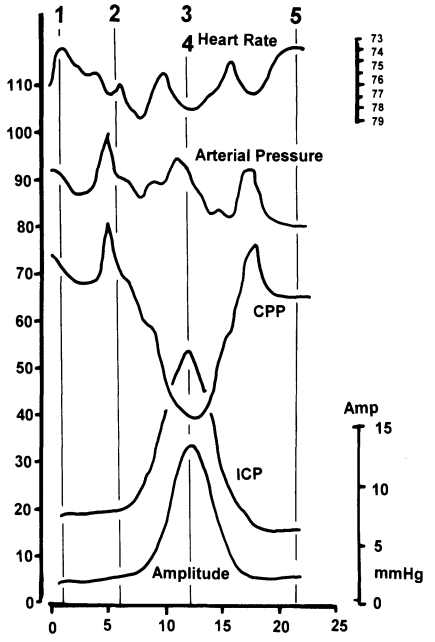

Fig. 1. An example of a typical vasogenic wave showing the parameter values at each of the time points (1, 2, 3, 4, & 5) used in this study. The ICP peak and CPP trough of this wave occur at the same time

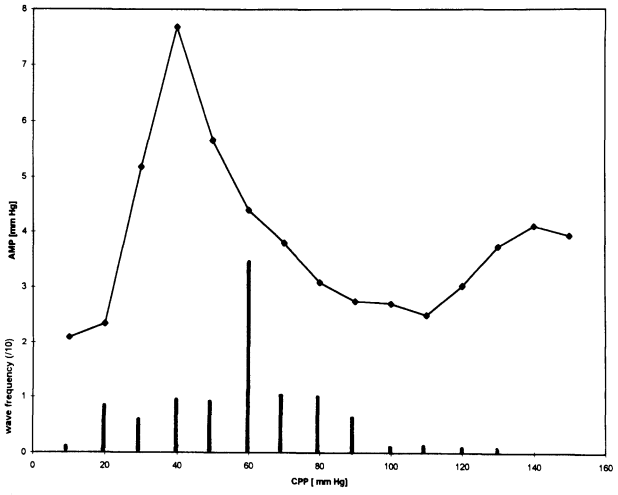

Fig. 2. Frequency histogram of pressure waves and empiric regression of amplitude plotted against CPP

than 15 beats per minute in 9 records and fell below 15 beats per minute in 4. On reviewing the changes during the 5 minutes prior to the onset of each pressure wave, we were rather surprised that there was an equal chance of a fall in perfusion pressure occurring prior to the wave as a rise and in 56% of the records, there was no significant change. Conversely, preceding falls in ICP did occur in 21% of the waves and

there was never a preceding rise. There was a greater chance of a fall in blood pressure (18%) than a rise (4%).

Despite our earlier add hoc observations that pressure waves became less frequent if the CPP is maintained [4] we were only able to confirm this in this study in the minority. Fig. 2 shows the frequency histogram of pressure waves along with the empiric regression of the conditional averages of the amplitude as a dependent variable plotted against the independent variable of CPP. As the CPP falls from 110 mm Hg to 80 mm Hg, the amplitude rises slightly, when it falls further from 80 mm Hg to 40 mm Hg it rises rapidly and there is a break point at 40 mm Hg below which the amplitude falls with progressive loss of auto-regulation. The wave frequency histogram failed to show the expected critical threshold CPP level of 80 mm Hg above which waves would be abolished.

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Correspondence: D. J. Price, M.D., Department of Neurosurgery, Pinderfields Hospital, Wakefield, West Yorkshire, WF1 4DG, U.K.

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CSF Dynamics in a Rodent Model of Closed Head Injury

M. U. Schuhmann[1], **S. Thomas**[2], **V. H. J. Hans**[2], **H. Beck**[2], **T. Brinker**[2], and **M. Samii**[1,2]

Departments of Neurosurgery, [1] Medizinische Hochschule Hannover and [2] Krankenhaus Nordstadt, Hannover, Federal Republic of Germany

Summary

Using ICP measurements and the bolus injection technique dynamic parameters of the cerebrospinal fluid system as there are pressure-volume-index (PVI) and resistance to CSF outflow (Rout) were investigated in a new model of diffuse closed head injury (CHI) in the rat. It was found that in the absence of brain oedema and ICP alterations an increase in PVI and Rout was present in the early (4 h) period following head injury. This may be indicative for a reduction in cerebral blood flow and cerebral blood volume, both shown previously to occur after CHI. Furthermore an early impairment of CSF absorption mechanisms is evident.

To answer the question, whether bolus injection techniques are advisable for clinical routine and whether results might have a predictive value, further investigations covering longer observation intervals and in the presence of secondary insults to the brain are necessary.

Keywords: Closed head injury; CSF dynamics; pressure-volume-index (PVI).

Introduction

With the introduction of the impact acceleration model by Marmarou *et al.* [1,4] a type of closed head injury (CHI) with diffuse and global tissue damage can be studied in the rat. Earlier investigations have shown that during the first hours following CHI there is no marked development of brain oedema or rise in ICP, if secondary insults like hypoxia and hypotension are avoided [3,10]. However, the influence of CHI on dynamic CSF parameters in the early posttraumatic period remains to be further elucidated. We, therefore, analysed in a controlled setting the behaviour of ICP, pressure volume index (PVI), resistance to CSF outflow (R_{out}) and ICP pulse wave amplitude (A) in the four hours following experimental CHI.

Materials and Methods

30 Lewis rats (367 ± 35 g) were investigated. 15 animals respectively were either subjected to CHI according to the previously described set-up [4] by dropping a weight of 500 g from a height of 1.5 m or served as controls undergoing sham treatment without trauma (ST). Animals were anaesthetised using ketamin/xylazin i.p. initially, followed by a continuous ketamin i.v.-infusion (40 mg/kg/h) breathing spontaneously throughout the study. A catheter was placed in the subfrontal subdural space to measure ICP and to apply bolus injections of 0.05 ml saline 10 min before CHI and 15 min, 1 h, 2 h, 3 h and 4 h after CHI. ICP data were stored with a sampling rate of 20 Hz on a PC. Animals were sacrificed and brains subjected to either determination of brain water content (wet-dry weight method) or to spectrophotometric evaluation of Evans Blue extravasation (2 mg/kg i.v. prior to CHI). ICP readings were used to calculate PVI and R_{out} as explained by Marmarou *et al.* [5] and for determination of pulse wave amplitude (A) immediately before bolus injections. Arterial blood pressure (ABP) was recorded discontinuously from the femoral artery.

For comparison of results at different times (t) relative changes after trauma $\Delta x = ((x_t - x_{pre})/x_{pre}) * 100$ [%] were used in order to correct for different pre-trauma-baselines (pre). Statistical analysis was performed using commercially available software. Friedman's two way ANOVA followed by Wilcoxon signed rank test was applied on paired, Mann-Whitney U test on unpaired data. Differences were regarded as significant if $p < 0.01$. Data are represented as mean ± SD.

Results

There was no immediate mortality following CHI. Two animals died after 1 h and 3 h, respectively and data were excluded from further analysis. Skull fractures were not detected. In 6 control animals the quality of ICP readings was insufficient. Hence values for ΔICP, ΔPVI, ΔR_{out} and ΔA were derived from 13 CHI and from 9 ST animals. Animals responded to CHI with transient apnoea (up to 20 s), convulsions and transient loss of corneal reflexes. CHI was prompted by a short rise of ABP (maximum 180–200 mm Hg) followed by a period of mild hypotension (50–70 mm Hg) returning to baseline (80–100 mm Hg) within 5 min remaining stable fur-

ther on. Animals breathing rates were in the upper normal range (90–110/min).

Regarding the investigated parameters ST and CHI animals did not show any differences in the measured and calculated pretrauma baseline values. Furthermore, no significant changes or consistent trends were observed during investigation in any of the parameters in ST rats. However, following CHI all parameters except ICP showed obvious alterations during the 4 hours observation period, with ΔPVI and ΔR_{out} changing significantly ($p = 0.003$ and $p = 0.0004$, respectively). As Fig. 1 displays ΔPVI increased immediately after CHI to a maximum of 30 ± 17% at 15 min and remained elevated thereafter (15–18%). ΔR_{out} started to rise at 1 h and increased continuously up to 4 h (maximum 217 ± 234%) after CHI (see Fig. 2). ΔA was enlarged as a trend at 3 h and 4 h (57 ± 93% and 68 ± 97%, respectively), however, without reaching statistical significance due to great interindividual variations. ICP showed a tendency to decrease after CHI for 2–3 h; however, there were again great variations. Brain water content was slightly but not significantly lower ($p < 0.05$) following CHI than in ST animals (78.06 ± 0.53% vs. 78.80 ± 0.24%, respectively). No significant Evans Blue extravasation could be detected in either group.

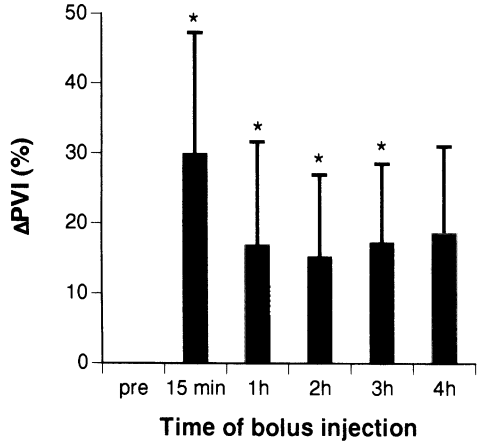

Fig. 1. Changes of PVI after CHI in trauma animals (ΔPVI). There is an immediate increase of PVI after CHI by 30% probably as a result of reduced cerebral blood volume and hypoperfusion. *Indicates significant changes at $p < 0.01$

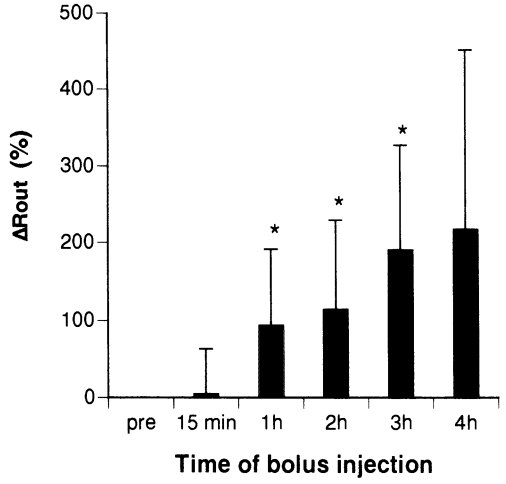

Fig. 2. Changes of R_{out} after CHI in trauma animals (ΔR_{out}). Beginning at 1 h there is a progressive increase of R_{out} probably as a result of trauma induced intracranial bleeding. * Indicates significant changes at $p < 0.01$

Discussion

The impact acceleration model of acute closed head injury has been studied intensively with respect to its morphological changes, effects on blood-brain barrier integrity and changes of perfusion indices as well as of static CSF parameters (ICP) [1,3,4,6,7,9–11]. However no acute changes of CSF dynamics have been investigated yet. We, therefore, measured for the first time changes of PVI and R_{out}, which can be obtained by bolus injections without elaborate technical equipment, making the method available also to clinical routine in patients with ventricular catheters.

The most prominent finding was the immediate increase of PVI by 30% after trauma. PVI remained elevated for 4 hours. At the same time ICP did not change significantly from pre-trauma baseline levels. Since our animals did not experience secondary brain insults like hypotension or hypoxia we did not expect significant ICP increases as a sign of brain swelling in the first hours. Earlier studies in the same model focusing on haemodynamic changes have shown a general hypoperfusion as early as 15 min after CHI [9] and a decreased cerebral blood volume (CBV) 2 hours after CHI [3]. Similar results of a local and general decrease in cerebral blood flow (CBF) were seen in other models of head injury as well [2,8,12]. Thus, we interpret the increase of PVI as a result of a posttraumatic decrease of CBF and/or CBV. Furthermore, we regard the observed tendency to lower ICP values after CHI as another indicator of reduced CBV.

The resistance to CSF absorption (R_{out}) seems to be unaffected initially with no change at 15 min but a progressive increase at 1 h. Most likely this is a result of traumatic subarachnoid haemorrhage and of intra-

ventricular bleeding that was observed macroscopically at autopsy of the animals. A persisting increase of R_{out} could contribute as one factor to the development of intracranial hypertension following CHI. Brain water content was rather slightly decreased and no extravasation of Evans Blue could be detected. This is in agreement with the findings of others [3,10] and together with the unchanged ICP, supports the conclusion that there is no significant development of brain oedema in the early phase after trauma in this model.

In conclusion, this study suggests that the relatively simple bolus test can reveal disturbances of dynamic CSF parameters in the early posttraumatic period and might thus serve as a simple indicator of posttraumatic hypoperfusion. Furthermore, an early dysfunction of CSF absorption may be detected. It remains to be investigated to which extent these dynamic parameters change, if the initial trauma is augmented by secondary insults (hypotension and hypoxia) and how far these changes might be predictive for the development of intracranial hypertension later on.

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Correspondence: Madjid Samii, M.D., Department of Neurosurgery, Neurochirurgische Klinik, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Federal Republic of Germany.

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Magnetic Resonance Imaging Studies with Cluster Algorithm for Characterization of Brain Edema after Controlled Cortical Impact Injury (CCII)

R. Stroop[1], **U. W. Thomale**[1], **S. Päuser**[2], **J. Bernarding**[2], **W. Vollmann**[2], **K.-J. Wolf**[2], **W. R. Lanksch**[1], and **A. W. Unterberg**[1]

[1] Department of Neurosurgery, Virchow Medical Center, Humboldt University of Berlin, and [2] Department of Radiology, Benjamin Franklin Medical Center, Free University Berlin, Federal Republic of Germany

Summary

Objective of this study was the characterization of traumatic brain injury induced by a "Controlled Cortical Impact" with magnetic resonance imaging techniques. The impact was applied to the intact dura of the left hemisphere in Sprague-Dawley rats. The pneumatic impactor was accelerated to a velocity of 7 m/s contusing the left temporo-parietal hemisphere to a depth of 2 mm. Posttraumatic hemispheric swelling and water content were determined gravimetrically, Evans Blue extravasation photometrically, and volume of ischemia by TTC-staining and planimetry. Magnetic resonance imaging was performed by a Bruker biospec 24/40, 90 min, 24 and 72 h post trauma using a T2w RARE sequence, a T1w sequence, before and after application of contrast agent, and a set of diffusion weighted images for calculation of ADC-maps. Data analysis was performed using a cluster algorithm enabling to interpret corresponding image pairs simultaneously. T2w imaging indicates the maximum edema about 24 h post trauma. Blood-brain barrier damage, detected by T1w imaging, is more predominant in the early posttraumatic phase. The cluster algorithm detects different edema components: from the necrotic core to the perifocal vasogenic rim. MRI in combination with the cluster algorithm will hopefully be a valuable tool in testing neuroprotective agents.

Keywords: Brain edema; cortical impact; magnetic resonance imaging.

Introduction

Significance, origin, and nature of posttraumatic brain edema are still under debate [1,2]. The role of a cornucopia of mediators involved in aggravation and maintenance of secondary brain damage is extensively discussed. Accused are, among others, excitatory amino acids, free radicals, Ca^{2+} [3]. Neuroprotective drugs, designed to inhibit their deteriorating effects, have to be proven with regard to their efficacy. The Controlled Cortical Impact Injury (CCII) models human contusions best and is therefore invaluable to test potential neuroprotective agents for traumatic brain injury. Magnetic resonance imaging (MRI) is a noninvasive diagnostic tool enabling one to characterize the time course of brain edema and to detect blood-brain barrier disruption by extravasation of an i.v. administered contrast agent. Beside this morphological information MRI is capable of elucidating pathophysiological aspects using diffusion weighted imaging (DWI). A relative signal enhancement in diffusion weighted images, together with a decrease of the so-called apparent diffusion coefficient (ADC), which is calculated from a set of DWI with increasing diffusion weighting, is supposed to be characteristic of cytotoxic edema [4]. Simultaneous data analysis of these various image qualities with a cluster algorithm facilitates data interpretation substantially.

The CCII-model, analysed with MRI and interpreted with the cluster algorithm was presently used, together with histopathological investigations, to characterize brain edema, providing a basis for testing neuroprotective drugs.

Materials and Methods

Animal Model

For the study, 28 Sprague Dawley rats (250–330 g b.w.) were used. The animals were anesthetized by inhalation of a mixture of

$N_2O:O_2$, 2:1 and 2% isoflurane. Body temperature was maintained at 37°C. A medial skin incision was performed over the skull and the temporal muscle was partially resected for temporoparietal trephination in this region, leaving the dura intact. Using a computer-controlled pneumatic impactor [5] of 7 mm in diameter with a convex tip surface, a standardized cortical impact injury was applied to the cortex. Reaching a depth of 2 mm, the impactor was accelerated to a velocity of approximately 7 ms^{-1}. The trephination defect was subsequently filled with dental cement, the skin incision was sutured.

Histological Examinations

Animals used for histological analysis were sacrificed 24 h post injury to remove the brain. Posttraumatic hemispheric swelling and water content were determined gravimetrically (n = 8). Ischemic tissue was visualized by 2,3,5 triphenyltetrazolium chloride (TTC) staining of serial brain cuts of 2 mm (n = 4). The areas were planimetrically measured and the volume of ischemia and tissue infarction was calculated. Blood-brain barrier damage was assessed by extravasation of i.v. Evans Blue (1 ml/kg b.w. of a 2% solution, given 1 hour before sacrifice) using fluorescence microscopy and photometry (n = 8).

NMR experiments were performed by a 100 Mhz BIOSPEC system (Bruker, Karlsruhe, F.R.G.) with a 40 cm horizontal magnet (n = 8). The system was equipped with an actively shielded gradient coil system (maximum gradient: 50 mT/m). A crossover surface coil, 50 mm in diameter was used. Animals were anesthetized by rompun®/tilest®, breathing spontaneously. Body temperature was monitored and kept at 36.5–37.5°C. To prevent movement artifacts the animals were placed in a stereotactic frame. A set of T2-weighted images (RARE: TR = 3,300 ms, TE = 30 ms, Rarefactor = 8, FOV = 80 mm, slice thickness (SD) = 2.0 mm, number of accumulation (NA) = 8) was acquired to quantify the extension of posttraumatic edema. T1-weighted imaging (SE: TR = 500 ms, TE = 12.2 ms, NA = 6) was performed before and after injection (2, 10, 20, 30, 45, 60 min p.i.) of 300 µmol Gd-DTPA/kg b.w. in a lateral tail vein for detection of blood-brain barrier damage 90 min and 24 h after CCII. For diffusion-weighted imaging a STEAM sequence was used (STED: TR = 1,000 ms, δ = 7.5 ms, Δ = 240 ms, SD = 2 mm, b = 0, 500, 1,000, 1,500, 2,000 s/mm^2, max. grad. strength: 40 mT/m, NA = 4). The apparent diffusion coefficients (ADCs) were calculated to generate ADC-maps.

Image analysis was performed by a Silicon Graphics Indy R4000 with a histogram-based segmentation algorithm allowing volumetry of the lesion and the simultaneous interpretation of corresponding image pairs [6].

Results

Histological Studies

The impactor induced a unilateral hemorrhagic contusion leading to a posttraumatic swelling 24 hours after CCII of 14.3 ± 3.1%. Brain water content increased to 82.5 ± 0.5% in the lesioned hemisphere compared to 79.9 ± 0.2% in the control hemisphere. Following TTC staining, the average ischemic tissue volume was 56.7 ± 19.2 mm^3. There was a moderate uptake of Evans Blue into the lesioned hemisphere 24 h p.t.

MRI-Studies

In T2-weighted images the total edema volume was determined within the lesioned hemisphere. The edema volume increased from 35 ± 9 mm^3 90 min p.t. to 57 ± 3 mm^3 24 h p.t. and decreased to 30 ± 5 mm^3 at 72 h p.t. T1w postcontrast images revealed Gd-DTPA uptake indicating blood-brain barrier damage that was more pronounced 90 min p.t. than after 24 h p.t. Maximal signal enhancement was observed 30 min after injection of the contrast agent. In the DWI the relative contrast of the lesion to unaffected regions became more prominent with increasing diffusion weightening. The following mean ADC-values, 90 min p.t., were calculated:

non-traumatized cortex:

$$0.63 \pm 0.07 * 10^{-3}\,mm^2 s^{-1}$$

traumatized cortex:

$$0.32 \pm 0.03 * 10^{-3}\,mm^2 s^{-1}$$

Data Analysis

A histogram-based image analysis was used to differentiate the lesion into various regions by clustering image pairs in different regions within the clustered image pairs of T2w images and ADC maps, T2w- and

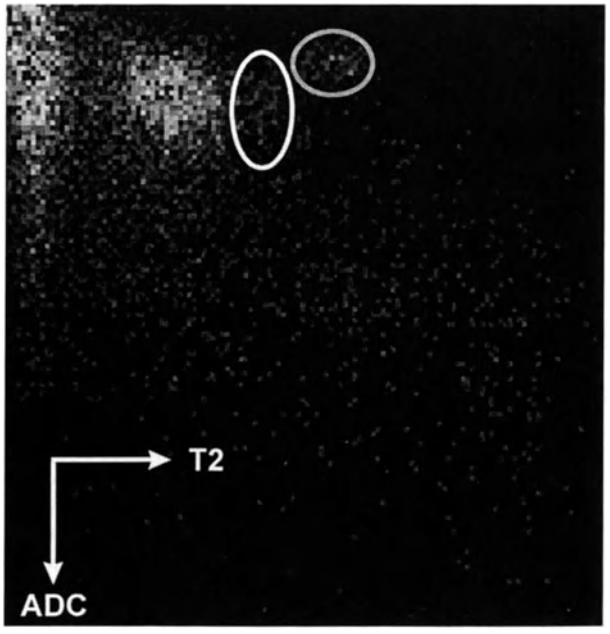

Fig. 1. Histogram of the intensities of a T2-weighted image and a corresponding ADC-map: the edema core (grey) and rim (white) are segmented. The frequencies of intensity pairs are represented in a grey level coded manner (white = high frequencies, dark grey = low frequencies)

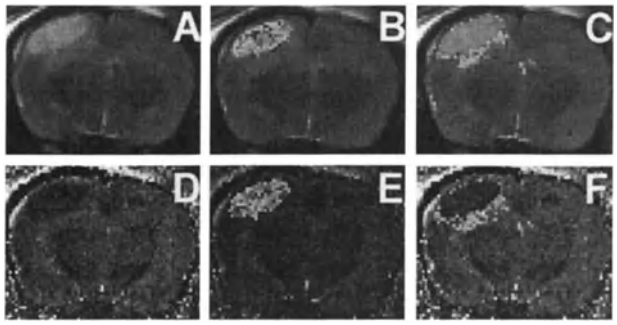

Fig. 2. T2-weighted image (A) and ADC-map (D), 90 min after trauma, used for generating the histogram in Fig. 1 Image (D) shows a region of decreased signal intensity indicating the predominant cytotoxic edema component. Core-region (B, E) and edema-rim (C, F) segmented out of the histogram, are high lighted in both images

T1w and T1w images and ADC-maps. Thereby, a perilesional rim, a core region embedding a cylindrical subregion in the direction of the impact was identified.

Discussion

Edema generation and resolution in this model are reflected by T2w imaging showing a maximum about 24 h p.t., corresponding to the gravimetrically determined posttraumatic swelling of 14.3 ± 3.1%. The time course of the blood-brain barrier defect is traced by T1w postcontrast imaging. There is a remarkable blood-brain barrier disruption 90 min p.t., which at 24 h p.t. is less pronounced, as additionally verified by Evans Blue extravasation.

The ADC value is assumed to distinguish between cytotoxic edema, indicated by a lower diffusional rate of water in ischemia leading to a decreased ADC, and vasogenic edema, reflected by increased ADC-values. The ADC-map (Fig. 2D) 90 min p.t. delineates a region of markedly decreased ADC-values, corresponding to the ischemic lesion, detected by TTC-staining. In a cluster analysis of a T2w image and an ADC-map this region can be distinguished as core (Fig. 2B, 2E) and a perilesional zone (Fig. 2C,F). In relation to the core region, this perilesional zone is specified by lower T2 intensities and less decreased ADC-values. This might be explained by relative ischemia. A cylindrical cone within the core region, aligned to the direction of the impact, is marked by further decreased ADC-values and increased T2 intensities, probably indicating necrosis, as seen in hematoxylin eosin stainings.

In the infralesional region a small area of increased ADC-values is indicative of vasogenic edema. Nevertheless, the cytotoxic edema component is prevailing in this experimental model.

Conclusion

CCII produces significant posttraumatic brain swelling and edema which is both of cytotoxic and vasogenic nature. Cluster analysis of MRI data is, in context with histological examinations, a valuable tool for characterization of edema components and their distribution as well as the time course of edema development. Thus, it opens new avenues for therapeutical studies focusing on novel neuroprotective substances.

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Correspondence: Ralf Stroop, M. Sc., Department of Neurosurgery, Humboldt University of Berlin, Virchow Medical Center, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.

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Estimation of the Main Factors Affecting ICP Dynamics by Mathematical Analysis of PVI Tests

M. Ursino[1], **C. A. Lodi**[1], **S. Rossi**[2], and **N. Stocchetti**[2]

[1] Department of Electronics, Computer Science and Systems, University of Bologna, Bologna, Italy and [2] Neurosurgical Intensive Care, Ospedale Policlinico IRCCS, Milano, Italy

Summary

A simplified model of intracranial dynamics is used to reproduce the intracranial pressure (ICP) time pattern in 20 patients with severe brain damage during PVI tests. A comparison of model responses and clinical tracings was achieved by minimizing a least square criterion function and adjusting just 5 parameters. These are: the CSF outflow resistance, the intracranial elastance coefficient, the autoregulation gain and time constant, and the basal values of arteriolar compliance. Based on the value of the autoregulation gain, the patients were classified into two groups: those with damaged autoregulation (8 out of 12) and those with preserved autoregulation (12 out of 20). Finally, analysis of the correlation between parameter estimates provided suggestions on the combination of parameter changes which may have the greater impact on ICP in the individual cases. Once these parameters have been identified, they may become possible targets for therapeutic interventions.

Keywords: Pressure-volume-index (PVI).

Introduction

Pressure-Volume Index (PVI) tests were first introduced by Marmarou *et al.* in the mid-seventies [1], as a method to derive quantitative information on intracranial dynamics in patients with severe brain damage. These tests consist of injecting or withdrawing small amounts of saline into or from the cranial cavity, and in monitoring the consequent intracranial pressure (ICP) time pattern. PVI tests are frequently used in neurosurgical intensive care units to estimate two important parameters: the cerebrospinal fluid (CSF) outflow resistance, which summarizes the status of CSF circulation pathways, and the PVI, which is an index of the intracranial storage capacity.

Recently, however, using a multi-compartment mathematical model of intracranial hemodynamics and CSF dynamics, we suggested that the ICP time pattern following volume perturbations may also contain important information on the action of cerebrovascular regulatory mechanisms [3]. Results of this study emphasize that the strength and time constant of cerebral autoregulation may be estimated with sufficient accuracy using PVI tests.

The model adopted in the previous study, however, was too complex and computationally onerous to be of practical usefulness in routine clinical conditions. Hence, we recently developed a drastically simplified mathematical model, in which the main relationships between ICP, cerebral blood volume (CBV), CSF and autoregulation are incorporated with a minimum of mathematical details [4].

In this work, the simplified model is applied to the analysis of PVI tests in patients with severe brain damage. We have two main purposes: i) to show that the main parameters characterizing intracranial dynamics can be estimated in each patient, through a comparison of model response and clinical data; ii) to evaluate the correlation between parameter estimates in order to derive information on the combination of parameters which have the greater impact on ICP in the individual cases. Once these parameters are known, they may become possible targets of therapeutic interventions.

Method

ICP monitoring was instituted in comatose trauma patients admitted to an intensive care unit. The measurement was done through a system composed of a ventricular catheter, a monitoring line commercially available (Cordis Intraventricular Pressure Monitoring Catheter with Stopcock 910-127) and a disposable

transducer (Monitoring Kit Abbott, MK 5-04DTNVF) connected to a Siemens monitor (SIRECUST 1281 mod. 8791137). Arterial pressure was simultaneously measured through a catheter inserted into the radial artery. Arterial CO_2 pressure and arterial oxygen content were carefully controlled in each patient. ICP and arterial pressure data were sent to a Macintosh IIcx computer through an AD converter (MacLab, World Precision Instruments), sampled at a rate of 20 Hz and stored in the *hard disk*. The silicon catheter was positioned in the Surgical Room: it was inserted into the frontal horn of a lateral ventricle and tunneled for about 5 cm under the scalp. All the pressure lines were filled with sterile saline; the transducer was zeroed, having the external acoustic meatus as a reference point. The pressure-volume maneuver consisted in the injection or withdrawal of 1 to 4 ml of saline, according to the bolus technique described by Marmarou *et al.* [1]. In all the maneuvers, the injection rate was approximately ±0.66 ml/s.

Data obtained in 20 patients from the PVI tests were low-pass filtered and then analyzed by means of the mathematical model described in Ursino and Lodi [4]. The main biomechanical and physiological factors considered in the model are: i) the hemodynamics of the arterial-arteriolar cerebrovascular bed, described by means of a hydraulic resistance and compliance, both actively regulated; ii) the CSF production and reabsorption processes, both mimicked as passive phenomena; iii) the non-linear pressure-volume relationship of the craniospinal compartment, simulated through a mono-exponential characteristic; iv) the cerebral venous vascular bed, which behaves as a Starling resistor. Finally, autoregulation of arterioles is simulated by means of a first order differential equation arranged in series with a sigmoidal static characteristic. The latter accounts for the existence of upper and lower autoregulation limits.

A comparison of model simulation curves and ICP clinical tracings was achieved in each patient by using an automatic least square minimization algorithm, and adjusting just five parameters. These are: the CSF outflow resistance, the intracranial elastance coefficient (inversely related to the PVI), the gain and time constant of CBF autoregulation, and the basal arteriolar compliance (related to arteriolar blood volume). In order to elucidate the mechanisms responsible for ICP changes in each patient, the correlation between parameters was also evaluated by computing the covariance matrix of the estimates.

Results

A good reproduction of the ICP time pattern during several consecutive bolus injection and withdrawal maneuvers was achieved in all the 20 patients examined. Moreover, in most cases the accuracy of parameter estimates was satisfactory, with a coefficient of variation of the estimates generally smaller than 20%.

Based on the numerical value of the autoregulation gain, the patients were then approximately classified into two distinct groups: those with impaired autoregulation (first group, 8 patients out of 20) and those with preserved autoregulation (second group, 12 patients out of 20). The characteristics of the two groups are briefly commented below.

First group – Patients in this group were characterized by a strongly reduced autoregulation [lower than 0.2 of the basal value. The basal value of autoregulation was established "a priori" as the value which warrants approximately a constant cerebral blood flow (CBF) in the range 50–150 mm Hg]. As a consequence of the low autoregulation gain, active changes in CBV are negligible in these patients, and cerebral vessels behave passively. Hence, the time pattern of ICP usually exhibits a monotonic trend; it progressively decreases toward the initial level following bolus injection, and increases following bolus withdrawal. An example of best fitting between model response and clinical tracing in a patient of this group is shown in Fig. 1.

Second group – Patients were classified in this group when the estimated autoregulation gain was higher than 20% of the basal value. This value warrants a partial maintenance of CBF, and the occurrence of active changes in CBV prevailing over passive volume recoil. As a consequence of active vasodilation and vasoconstriction, these patients usually exhibit a paradoxical response to PVI tests: i.e., a secondary delayed ICP increase following injection, and a secondary delayed ICP lessening following withdrawal. Moreover, while the amplitude of the paradoxical response is mainly related with the autoregulation gain, its time pattern reflects a balance between the autoregulation time constant and

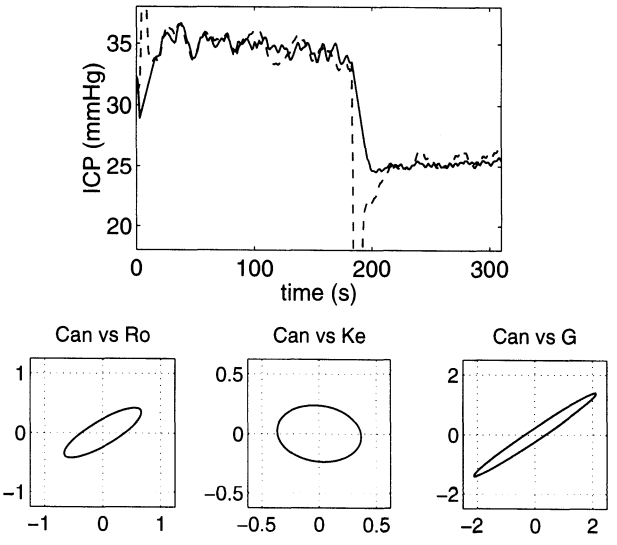

Fig. 1. Upper panel: comparison between a clinical ICP tracing (dashed line) and model simulation curve (continuous line) in a patient of the first class during a bolus injection and a bolus withdrawal maneuver. Lower panel: 5% indifference regions showing the correlation between arteriolar compliance (Can), CSF outflow resistance (Ro), intracranial elastance coefficient (Ke) and autoregulation gain (G). The axes report the parameter percentage changes

the rate of CSF outflow. An example of ICP time pattern in a patient of the second group is shown in Fig. 2.

Finally, analysis of the correlation between the parameter estimates permits us to detect the combination of parameter changes which have the greater impact on ICP in the individual cases. This is attained by computing the so-called ε-indifference regions. These are regions in the parameter space where parameters can change simultaneously without causing excessive changes in ICP (below a given tolerance ε). If a small tolerance is considered (for instance ε = 5%) the regions are elliptic in shape. The greater axis of the ellipse represents the direction of minimum ICP sensitivity to parameter changes, whereas the smaller axis is the direction of maximum sensitivity. Some examples of indifference regions, obtained by changing two parameters together, and leaving the remaining parameters at the estimated value, are shown in the lower panels of Figs. 1 and 2. It is evident that the directions of maximum and minimum ICP sensitivity are different in the two groups of patients, indicating that the mechanisms causing ICP changes are different.

Discussion

The results of this work show that a simple theoretical model, including some aspects of cerebral hemodynamics, autoregulation and active CBV changes, is able to reproduce both traditional monotonic ICP time patterns (Fig. 1) and paradoxical responses (Fig. 2) quite well. Moreover, in all cases the estimated parameters lie in the range reported in the clinical literature. This observation contributes to validate the model, and supports the hypothesis that information on cerebral autoregulation can be extracted from PVI tests through appropriate computer simulation techniques.

An important new aspect of this work, which might be of great value in clinical studies, consists in the evaluation of indifference regions. These show the directions of maximum and minimum ICP sensitivity to parameter changes, hence can contribute to discover the particular mechanisms responsible for ICP alterations in the individual subjects.

The ellipses of Fig. 2 suggest that, in patients with preserved autoregulation, the active CBV changes have a detrimental effect on ICP, through a mechanism analogous to Rosner's vasodilatory cascade (2). In fact, the shorter axis of the ellipse shows that an increase in cerebrovascular compliance (which means to have greater CBV changes) may induce significant ICP alterations if associated with a small increase in CSF outflow resistance, a small increase in autoregulation gain or a small increase in intracranial elastance (which means a smaller PVI). By contrast, in patients with impaired autoregulation, CBV plays only a minor role in developing intracranial hypertension, or may even contribute to buffer ICP changes through its passive decrease. In fact, following the direction of the greater axis (Fig. 1), one can observe that increasing vascular compliance compensates for an increase in CSF outflow resistance and for an increase in autoregulation gain, and it is poorly correlated with changes in the intracranial elastance coefficient.

In perspective, discovering the directions of parameter changes which have the greater impact on ICP may be exploited in the clinical practice, to avoid improper maneuvers for the patient, and to design more appropriate therapies against acute intracranial hypertension.

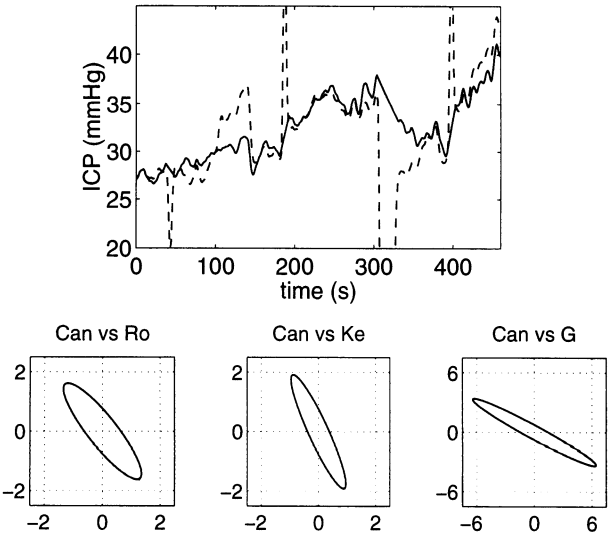

Fig. 2. Upper panel: comparison between a clinical ICP tracing (dashed line) and model simulation curve (continuous line) in a patient of the second class during two bolus withdrawal and two bolus injection maneuvers. Lower panel: 5% indifference regions showing the correlation between parameter estimates. The meaning of symbols is the same as in Fig. 1

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Correspondence: Mauro Ursino, M.D., Department of Electronics, Computer Science and Systems, University of Bologna, viale Risorgimento 2, I-40136 Bologna, Italy.

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Brain Tissue Pressure Gradients are Dependent upon a Normal Spinal Subarachnoid Space

C. E. Wolfla and **T. G. Luerssen**[1,2]

[1] Division of Neurosurgery, Indiana University Medical Center, and [2] Pediatric Neurosurgery Service, James Whitcomb Riley Hospital for Children, Indianapolis, IN, U.S.A.

Summary

Reports from our laboratory have shown that regional brain tissue pressure (RBTP) gradients develop in response to supratentorial but not posterior fossa extradural masses. We undertook this experiment to discover the mechanism of this differing response. RBTP was measured in the right and left frontal lobes (RF, LF), temporal lobes (RT, LT), midbrain (MB), and cerebellum (CB) of ten pigs. Balloons were expanded in the epidural space at C2 to occlude the subarachnoid space. A temporal extradural mass was expanded incrementally. The C2 balloon was deflated after temporal mass expansion. Expansion of the cervical balloon resulted in a homogeneous rise in RBTP. Expansion of the temporal mass resulted in the development of small RBTP gradients with the following relationship: RT > LT = LF > RF = CB > MB. In comparison with a previous series of animals without cervical balloons, animals in this series demonstrated higher global ICP in response to equal size masses and smaller RBTP gradients. Cervical balloon deflation resulted in decreased global ICP and increased RBTP gradients. The development of RBTP gradients in response to expanding supratentorial masses therefore appears to be at least partially dependent upon the presence of a normal communication between the supratentorial space and the spinal subarachnoid space.

Keywords: Spinal subarachnoid space; tissue pressure gradients.

Introduction

To characterize the regional brain tissue pressure (RBTP) response to intracranial masses in various locations, we performed a series of experiments systematically examining RBTP in the presence of frontal, temporal, and posterior fossa extradural masses. In the presence of a frontal or temporal mass, RBTP gradients develop in which the RBTP is highest adjacent the lesion [3,4]. In response to a posterior fossa mass, however, no such gradients occur [5]. The present study was undertaken in order to discover the mechanism of this differing response.

Materials and Methods

The experimental procedure described below was approved by the Indiana University-Purdue University at Indianapolis Animal Resource Committee. This procedure with minor modifications has been previously described [3]. Ten common domestic pigs weighing 9–14 kg were anesthetized, intubated, and paralyzed. Intraparenchymal ICP monitors were placed in the right (RF) and left (LF) frontal lobes, right (RT) and left (LT) temporal lobes, and midbrain (MB) [3]. Monitors were placed directly into the cerebellum 1 cm inferior and to the left of the inion.

Right temporal extradural masses were created using the previously described protocol [4]. A high cervical intraspinal mass was also created by making a small midline laminotomy between C1 and C2. After opening the ligamentum flavum, a 5 Fr Foley catheter was advanced into the epidural space to the level of the C2 body.

After a stable baseline had been achieved, the cervical balloon was inflated to totally occlude the spinal canal. The temporal mass was then expanded by 1 cc over one second. Expansions were repeated at five minute intervals until a volume of 2 cc had been attained in five animals, and until a volume of 6 cc had been attained in the remaining five. The cervical balloon was deflated and pressures recorded for an additional five minutes. The experiment was then terminated and the animals were sacrificed and autopsied in order to confirm monitor and mass placement.

All pressure measurements were collected, using a computer, at 50 msec intervals as described previously [3,4]. From the data, the maximum pressure in each brain region at each mass volume, as well as at subsequent time intervals, was extracted from the data. Comparisons were made between brain regions using the two-tailed t-test for paired samples. Comparisons between data from this series of animals and a prior series [4] were made using the two tailed t-test for unpaired samples. The level of statistical significance was set at $p < 0.05$.

Results

RBTP data for the entire series of animals is shown in Table 1. Prior to expansion of the cervical balloon, RBTP was slightly, but significantly, higher in the LT

than in the RF, LF, MB or CB. Cervical balloon expansion resulted in a nearly homogeneous rise in RBTP. After cervical balloon expansion, RBTP was slightly, but significantly, higher in the temporal lobes and slightly, but significantly lower in the MB and CB.

Subsequent temporal mass expansions in the development of small but definite RBTP gradients. After temporal mass expansion to a volume of 2 cc, the RBTP values had the following relationship: RT > LT = LF > RF = CB > MB. Significant differences were seen between all regions except between the RF and MB and between the LF and LT. In five animals the experiment was continued to higher mass volumes. After mass expansion to 5 cc in these animals, the RBTP relationship was the same as that seen at lower mass volumes. Significantly higher pressures were seen in the RT compared to the MB or CB, and in the LT compared to the RF, MB, or CB.

After temporal mass expansion, the cervical balloon was deflated (Fig. 1). The resultant drop in RBTP was significant in all brain regions at both mass volumes. The gradient between RT and CB rose from 1.74 to 4.34 mm Hg after deflation at 2 cc, and from 7.26 to 27.08 mm Hg after deflation at 6 cc. The rise in RT-CB gradient was significant after deflation at 6 cc.

The results of the present study were compared with the results of a previous study which was identical except that a cervical balloon was not utilized [4]. Prior to temporal mass expansion but after expansion of the cervical balloon, RBTP in all regions was significantly higher in the present study. At a mass volume of 2 cc, RBTP was significantly higher in the present study in all regions, except for the RT. At a mass volume of 6 cc, RBTP was significantly higher in the CB in the present study. Significantly lower gradients (3.13 vs. 8.74 mm Hg) between the RT and CB were seen in the present experiment at a mass volume of 2 cc. Lower RT – CB gradients were also seen in the present experiment at a mass volume of 6 cc,

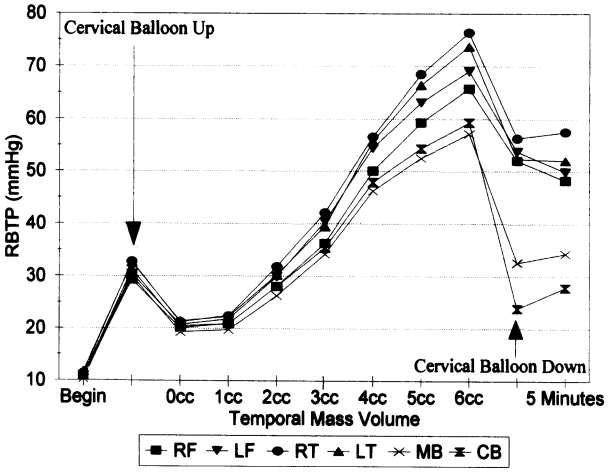

Fig. 1. Chart displaying mean maximum RBTP for each brain region for the group of animals that underwent mass expansion to a volume of 6 cc. This illustrates the effect of cervical balloon expansion, equilibration to a new higher baseline, temporal mass expansion, and release of the cervical balloon. Note the lower overall RBTP values and larger RBTP gradients after deflation of the cervical balloon

Table 1. *RBTP Data (mm Hg)*

All animals	RF	LF	RT	LT	MB	CB
Begin	10.94	10.87	11.37	11.79	10.26	10.94
Cervical balloon up	29.34	30.45	32.81	32.63	30.01	31.22
Temporal mass 0 cc	20.04	20.68	21.20	21.37	19.23	20.31
Temporal mass 1 cc	20.83	21.78	22.36	22.24	19.67	20.84
Temporal mass 2 cc	28.07	29.96	31.83	30.25	26.25	28.07
Animals in which temporal mass expansion was stopped after 2 cc						
Cervical balloon Down	14.36	14.41	19.00	14.69	9.37	11.45
Animals in which temporal mass expansion was stopped after 6 cc						
Temporal mass 3 cc	36.24	40.37	42.06	39.50	34.21	35.37
Temporal mass 4 cc	50.05	54.51	56.67	55.82	46.24	47.89
Temporal mass 5 cc	59.35	63.16	68.50	66.44	52.58	54.40
Temporal mass 6 cc	65.81	69.07	76.39	73.78	57.19	59.39
Cervical balloon Down	52.03	53.83	56.39	52.35	32.63	23.87

though this difference did not reach statistical significance (14.10 vs. 36.79 mm Hg, p = 0.053).

Discussion

Through a systematic study in a pig model, we have attempted the characterize the RBTP response to experimental epidural masses in different locations. The first and second series of experiments, utilizing frontal and temporal epidural masses, revealed that, in the presence of masses in these locations, RBTP gradients develop with a fairly consistent relationship: RBTP is highest in the brain regions closest to the mass and lowest in the most remote regions [3,4].

Other experiments, involving an epidural posterior fossa mass, did not result in the formation of RBTP gradients, even with ventricular or cisternal CSF diversion. The only clue as to the mechanism of this differing response was the observation that a large gradient developed between the lumbar CSF pressure and intracranial pressure early in mass expansion [5]. We hypothesized that the lack of RBTP gradient formation might be at least partially due to occlusion of the CSF pathways at the level of the foramen magnum by the mass and resultant exclusion of the pressure-buffering capacity of the spinal subarachnoid space from the craniospinal axis.

To test this hypothesis, the present series of experiments was undertaken. Starting with an experimental model, the temporal extradural mass, that was known to produce large and reproducible RBTP gradients, we added a second balloon, at the level of C2, to isolate the spinal subarachnoid space from the intracranial space. The experimental protocols were otherwise identical.

With expansion of the temporal balloon, RBTP gradients developed with the following relationship: RT > LT = LF > RF = CB > MB. This relationship was the same relationship as that seen in animals without the cervical balloon except that the relationship between the MB and CB RBTP was reversed. The reason for this is unknown. When the cervical balloon was deflated, there was a significant drop in RBTP in all brain regions and a significant increase in the gradient between supratentorial and infratentorial RBTP. When the RBTP values for the animals with and without cervical balloon were compared, the animals with cervical balloons had higher overall RBTP and lower RBTP gradients.

The results suggest that the presence of a normally patent spinal subarachnoid space is at least partially necessary for the development of RBTP gradients in the presence of a temporal extradural mass. Other authors have reported that the spinal CSF space accounts for 30–32% of the compliance of the craniospinal axis [1,2]. Apparently this pressure buffering capacity, when present, is not equally effective on all brain regions. Brain regions more remote from the mass appear to be more effectively buffered than those adjacent the mass. Because this effect is not uniform, we propose that there may be at least functional compartmentalization of intracranial CSF. We also suggest that the lack of gradient formation with a posterior fossa mass is due to obstruction of CSF flow and pressure transmission at the foramen magnum by the mass. Because the pressure gradients in the present series of experiments were attenuated but not obliterated, there must exist one or more, as yet to be elucidated, factors which contribute to the formation of RBTP gradients.

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Correspondence: Thomas G. Luerssen, M.D., Pediatric Neurosurgery Service, James Whitcomb Riley Hospital for Children, One Children's Square, Room 2510, Indianapolis, IN 46202-5200, U.S.A.

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Resolution of Experimental Vasogenic Brain Edema at Different Intracranial Pressures

E. Wrba[1], **V. Nehring**[1], **A. Baethmann**[2], **H.-J. Reulen**[1], and **E. Uhl**[1]

Department of [1] Neurosurgery and [2] Institute for Surgical Research, Grosshadern University Hospital, University of Munich, Federal Republic of Germany

Summary

Resolution of vasogenic brain edema was examined using the infusion edema model in rabbits. Texas Red-albumin (MW 66,000 D) and sodium fluorescein (MW 376 D) dissolved in artificial cerebrospinal fluid (aCSF) were infused into the white matter of the left frontal lobe of the brain. To quantify the edema fluid cleared by the ventricular system, ventriculo-cisternal perfusion was performed with aCSF. A closed cranial window, implanted above the left parietal brain, served for studying resolution of the artificial edema fluid via the subarachnoid space. CSF-samples were collected in 30 minutes-intervals and analysed with a spectrophotometer. Clearance of edema fluid was examined under low (2–5 mm Hg), medium (9–12 mm Hg), or high (14–17 mm Hg) intracranial pressures (ICP). In the low pressure-group, both edema fluid markers were found in the ventriculo-cisternal and subarachnoid perfusate at 60 and 90 min, in the group with moderately increased ICP at 90 and 120 min, respectively. In the high ICP-group both fluorescence dyes appeared not less than 90 min in the ventricular system, while no increase at all could be found in the subarachnoid space. Our results imply that resolution of edema fluid via both the ventricular system and the subarachnoid space depends on the actual ICP level.

Keywords: Resolution; vasogenic brain edema.

Introduction

Resolution of vasogenic brain edema occurs mainly via bulk flow along a hydrostatic pressure gradient from the site of fluid entry to compartments with lower pressure [5]. Previous studies have shown that part of the edema fluid is reabsorbed into the cerebral ventricles or taken up by the vascular system [3,6–8]. Little is known, however, whether and to what extent clearance of edema fluid into the subarachnoid space is involved, and how the actual ICP level influences reabsorption of the edema fluid into the CSF compartments. The aim of the present study was to quantitatively analyze the clearance of experimental vasogenic edema fluid into the ventricles and the subarachnoid space under three different ICP-levels, utilising fluorescence indicators of different molecular size and excitation and emission wavelengths for labelling of the edema fluid.

Materials and Methods

New Zealand white rabbits (n = 29) were used as experimental animals as described previously [9]. Briefly, anesthesia was induced with thiopental, and continued with alpha-chloralose (50 mg/kg). After tracheostomy the animals were mechanically ventilated. The body temperature was regulated by a heating pad and kept at 38.0°C during the whole experiment. The arterial blood pressure was continuously recorded, while blood gases were studied every hour. For surgical preparation the animals were placed in a stereotactic device. The skin overlying the skull was surgically opened in the midline. For administration of mock edema fluid an infusion cannula was stereotactically inserted into the white matter of the left frontal lobe, a second cannula into the right lateral ventricle serving as inflow line for the ventriculo-cisternal perfusion at a rate of 3 ml/h. An outflow cannula was implanted into the cisterna magna after preparation of the atlanto-occipital membrane. By adjustment of the height of the cisternal outflow tube the ICP could be modified. For superfusion of the subarachnoid space a closed cranial window was implanted over the left parietal cortex as previously described in detail [2], and the brain cortex was permanently superfused with mock CSF (3 ml/h). After termination of the surgical preparation, ventriculo-cisternal perfusion and superfusion of the subarachnoid space commenced at the same time, 30 min before the onset of edema infusion. The cisternal outflow tube was adjusted to a given height depending on the ICP level which was desired (group 1: 2–5 mm Hg, n = 11; group 2: 9–12 mm Hg, n = 11; group 3: 14–17 mm Hg, n = 7). Vasogenic edema was induced by infusion of 1 mM sodium fluorescein (MW 376 D) and 0.9 mM Texas Red-albumin (MW 66,000) dissolved in artificial CSF at a rate of 100 µl/h over 5 hrs into the white matter. CSF-samples were collected from the beginning of edema infusion in 30 minutes-intervals for 8 hours. Clearance of edema fluid into both perfusates was calculated by analysing the CSF-samples with a fluorescence spectrophotometer

Table 1. *Clearance of Fluorescence Markers of Edema Fluid at Different ICP-Levels*

ICP-level	Resolution via . . .	\time\ marker\	30 min	120 min	210 min	300 min	390 min	480 min
Group 1	ventr.	NaFl	0.2 ± 0.2	6.4 ± 2.0	8.3 ± 2.4	8.6 ± 2.3	10.3 ± 2.6	10.7 ± 2.7
(low	system	TeRe	0.5 ± 0.4	11.3 ± 3.2	15.5 ± 4.0	16.6 ± 3.7	21.6 ± 4.4	23.0 ± 4.7
ICP,	subar.	NaFl	0.5 ± 0.4	1.9 ± 0.9	3.1 ± 1.4	3.0 ± 1.2	3.5 ± 1.3	3.7 ± 1.4
n = 11)	space	TeRe	0.7 ± 0.6	2.1 ± 0.8	3.7 ± 1.6	3.8 ± 1.4	4.3 ± 1.4	4.7 ± 1.5
Group 2	ventr.	NaFl	0 ± 0	2.4 ± 1.4	4.6 ± 2.3	6.4 ± 2.8	8.2 ± 3.5	8.6 ± 3.8
(medium	system	TeRe	0.1 ± 0.1	4.0 ± 2.0	8.1 ± 3.2	11.2 ± 3.8	14.4 ± 4.8	15.7 ± 5.3
ICP,	subar.	NaFl	0 ± 0	1.1 ± 0.9	1.9 ± 1.1	2.3 ± 1.4	2.4 ± 1.4	2.4 ± 1.4
n = 11)	space	TeRe	0 ± 0	1.4 ± 1.3	2.6 ± 1.5	30 ± 1.7	3.2 ± 1.7	3.2 ± 1.7
Group 3	ventr.	NaFl	0 ± 0	1.0 ± 0.7	1.0 ± 0.5	1.2 ± 0.5	1.7 ± 0.8	2.2 ± 1.2
(high	system	TeRe	0 ± 0	2.1 ± 1.3	2.2 ± 1.2	2.5 ± 1.3	3.5 ± 1.8	4.7 ± 2.7
ICP,	subar.	NaFl	0 ± 0	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
n = 7)	space	TeRe	0 ± 0	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.2

The proportion of both fluorescent dyes reabsorbed via the ventricular system or the subarachnoid space, respectively, is given as cumulative amount in % of the total amount of label infused up to the time of sampling (mean ± SEM).
ventr. system ventricular system; *subar. space* subarachnoid space; *NaFl* sodium fluorescein; *TeRe* Texas Red-albumin.

using different filter sets for the two fluorescence dyes (sodium fluorescein: exc.: 485 nm, em.: 515 nm; Texas Red-albumin: exc.: 590 nm, em.: 650 nm).

Results

The mean ICP in group 1 was 1.9 ± 1.0 mm Hg, while 10.5 ± 1.0 mm Hg in group 2, and 14.9 ± 0.5 mm Hg in group 3, respectively. Both fluorescence labels started to appear in the cerebral ventricles at 60 min following onset of edema infusion in group 1 (low ICP), whereas at 90 min in group 2 (medium ICP), and group 3 (high ICP), respectively. The three groups differed as to the edema clearance kinetics of both fluorescent dyes with regard to the actual ICP-level, demonstrating the most rapid ventricular clearance in group 1. A similar dependence of the clearance efficiency on the ICP was found in the subarachnoid space, although the differences were not as striking as in the ventricular system. Virtually no fluorescence markers at all could be found in the subarachnoid perfusate in group 3. The total amount of marker clearance and the time of their appearance in the subarachnoid space and the ventricular system was found to depend on the actual ICP-level. The results are given in Table 1.

Discussion

The present findings demonstrate and confirm that vasogenic edema fluid is cleared via both the ventricular system and the subarachnoid space. The proportion of clearance of edema fluid into the subarachnoid space was smaller as compared to the ventricular reabsorption. The total amount of edema fluid reabsorbed into the ventricles as well as the subarachnoid space was found to be dependent on the ICP. The reabsorption of the edema is mainly attributable to bulk flow of the fluid along a hydrostatic pressure gradient from the site of the edema towards the ventricular system [5], which was also found in this study. There was no differential clearance behavior of the low- and the high-molecular weight edema marker, as concluded from the similar clearance kinetics of both labels. Obviously, the clearance does not depend on diffusion mechanisms, which is at variance with respective conclusions of Ohata *et al.* [4] using FITC-dextran of different molecular size as edema label.

In conclusion, the present findings show that edema fluid is reabsorbed via the ventricular system and the subarachnoid space, although the latter route appears to be less significant, especially at higher ICP-levels. Thus, reduction of the ICP acquires a great priority for the therapy of traumatic brain edema to enhance reabsorption of the edema fluid.

Acknowledgements

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Correspondence: Eberhard Uhl, M.D., Department of Neurosurgery, Grosshadern University Hospital, University of Munich, Marchioninistr. 15, D-81366 Munich, Federal Republic of Germany.

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Jugular Saturation ($SjvO_2$) Monitoring in Subarachnoid Hemorrhage (SAH)

G. Citerio, M. Cormio, G. Portella, E. Vascotto, D. Galli, and **S. M. Gaini**[1]

ICU, [1] Neurosurgery, Hospitale San Gerardo, Monza (Mi), Italy

Summary

Jugular saturation ($SjvO_2$) monitoring was performed in 26 SAH patients to evaluate the incidence of normal (0.56–0.74) and pathological $SjvO_2$ values in this population and to describe its time course in the first 12 days. We also attempt to quantify the influence of systemic and cerebral hemodynamics on $SjvO_2$ and to assess the relationship between cerebral injury volume measured on CT scan and $SjvO_2$. Mean $SjvO_2$ was 0.66 ± 0.07 (354 samples, median 0.67, range 0.43–0.89). 73% of the observations (259/354) were in the normal range. On serial measurements, we identified only 37/354 (10%) desaturation episodes (D.E.). ICP was significantly higher during low $SjvO_2$ observation ($p = 0.008$). No statistical differences were noted regarding the influence of MAP, CPP, $PaCO_2$, PaO_2 on $SjvO_2$ but during D.E., lower $PaCO_2$ and CPP were more frequently observed. CT scan lesions >25 ml were associated initially with lower $SjvO_2$ values and with higher values at second CT.

Keywords: Jugular saturation; subarachnoid hemorrhage.

Introduction

In subarachnoid haemorrhage (SAH) patients mortality and morbidity are at first mainly related to the bleeding and, later, to the development of cerebral ischemia. Ischemic damage is caused not only by vasospasm but also by alterations in cerebral hemodynamics after SAH, such as poor collateral circulation due to low perfusion pressure with high ICP, impairment of autoregulation in whole brain and ischemia at the onset of the hemorrhage. SAH, with and without vasospasm, produces significant decreases in cerebral blood flow (CBF) and cerebral metabolic rate ($CMRO_2$). Clinical, CT scan, and pathological features suggest that delayed cerebral ischemia after SAH is a multivascular or diffuse process in most patients [3]. Remarkably, literature reports [6–9,11,12] of CBF studies showed a global CBF and $CMRO_2$ reduction, inversely proportional to the clinical grade (lowest flow and metabolism in the higher grades HH IV–V). Nevertheless, these alterations are also described in patients without neurological deficits. Apparently, therefore, SAH from a ruptured aneurysm affects the perfusion of the brain as a whole and it is not a focal problem.

A primary goal in neurosurgical intensive care is to minimize, or even prevent, secondary brain damage, generally ischemic, after an acute cerebral insult. To prevent and to treat such a phenomenon we need to detect it. $SjvO_2$ is usually monitored in the intensive care setting as an estimate of global cerebral oxygenation since it is a practical bedside technique for evaluating $CBF/CMRO_2$ ratio (Fick's principle). An $SjvO_2$[2] 55% is considered critical for adequate cerebral perfusion, and it reliably indicates cerebral hypoperfusion that may eventually proceed to ischemia. Therefore, $SjvO_2$ may be effective in the SAH patient, to understand if any impairment in global cerebral supply or consumption occurs and also to target our therapeutical manoeuvres.

In this study, investigation of $SjvO_2$ in SAH patients was performed to evaluate the incidence of normal $SjvO_2$ (0.56–0.74), desaturation events (<0.56) and elevated $SjvO_2$ (>0.74), and to describe $SjvO_2$ time course. We also attempt to quantify the influence of systemic and cerebral hemodynamics on $SjvO_2$, and to assess the relationship between cerebral injury volume measured on CT scan and $SjvO_2$.

Materials and Methods

Data gathered on 26 patients (16 female, 10 males; mean age 52 ± 15 y., range 20–80 y.), in which cerebral oxygenation with $SjvO_2$

Table 1. *Mean of Principal Physiological Parameters of Our Population*

	$SjvO_2$ %	MAP mm Hg	ICP mm Hg	CPP mm Hg	CVP mm Hg	$PaCO_2$ mm Hg	PaO_2 mm Hg	Hb mg/dl	Na mEq/L	Temp C°
Mean	0.66	101.4	20.9	79.4	7.08	35.8	133.4	10.3	143.6	37
SD	0.07	8.3	13	14	2.9	3.4	24	1.3	5.2	0.9

was monitored, were retrospectively analyzed (Table 1). All were admitted to our ICU from December 1994 to March 1997 following cerebral aneurysm bleeding. Hunt&Hess grading at ICU admission was: I–II 7 patients (27%), III 6 (23%), IV–V 13 (50%). Mean GCS was 9 (median 9, range 3–15). Treatment was ultraearly endovascular (during the first angiography) in 9 patients (35%), early clipping (<48 hrs) in 14 patients (54%); 3 patients (HH IV–V) received only medical treatment. All patients were managed with a standardized protocol that included euvolemia, normo/hypertension, normal reology, normonatremia, normocapnia, adequate blood oxygen content and normotermia. Intracranial pressure (ICP) was monitored in 17 patients (65%) by a ventriculostomy or by a Codman intraparenchimal microtransducer. Cerebral perfusion pressure (CPP) was derived (CPP = mABP – ICP). $SjvO_2$ was monitored by fiberoptic or conventional P.E. catheters. In 82% of our cases the jugular ipsilateral was cannulated to the lesion side; in patients with bilateral or midline lesions (18%) we selected the angiographically identified predominant jugular (Table 2). The correct catheter tip positioning was checked with a 2 projection X-ray. $SjvO_2$ was monitored up to 12 days. $SjvO_2$ blood samples (totally 354 samples) were drawn at 6-hour intervals and immediately analyzed by a Co-oximetry (Radiometer Osm 3 Co-oximeter). In addition, at the same time of $SjvO_2$ determination, the following parameters were recorded: arterial and jugular blood gas analysis, mean arterial pressure (MAP), ICP, central venous pressure (CVP), Hb concentration, natremia and temperature.

CT scan at entry and a scan performed in a subacute period (on day 7 ± 2) were evaluated for the presence of any parenchymal lesion. Quantification of the total volume of injured parenchyma is liable to be semi-quantitative and subjective. Keeping this in mind, we decided to utilize the Cavalieri's direct estimator described by Clatterbuck. All summary data are expressed as mean ± standard deviation (SD). Mean values of the physiological measurements were compared by analysis of variance followed by Fisher's LSD post hoc test when multiple comparisons were made. Differences in proportions were analysed with the Chi-square test.

Outcome was evaluated at ICU discharge expressed as "obeying simple commands", "not obeying (still in coma)", "died".

Table 2. *Mean Values for ICP, MAP, CPP, $PaCO_2$, PaO_2 According to the $SjvO_2$ Level (Low, Normal, High)*

$SjvO_2$	ICP* mm Hg	MAP mm Hg	CPP mm Hg	$PaCO_2$ mm Hg	PaO_2 mm Hg
Low	21 ± 10	105 ± 12	83 ± 18	35.3 ± 4.4	113 ± 27
Normal	15 ± 8	102 ± 13	83 ± 13	36.2 ± 4.4	130 ± 42
High	17 ± 13	100 ± 12	83 ± 14	36.5 ± 4.8	133 ± 54

Results

Principal physiological parameters of our population are described in Table 1.

Incidence of Normal and Pathological $SjvO_2$ Values

Mean $SjvO_2$ was 0.66 ± 0.07 (354 samples, median 0.67, range 0.43–0.89). 73% of the observations (259/354) were in the normal range.

On serial measurements, we identified only 37/354 (10%) desaturation episodes (D.E.). Nine patients (34%) presented at least one desaturation episode at some time during the monitoring course; however, 5/9 presented only 1 D.E.; in 2/9 were identified 2–5 episodes, 2/9 more than 5 desaturations. In 58/354 samples $SjvO_2$ was high (17%). Mean ICP was 20.9 ± 13 mm Hg. Higher ICP values were recorded in the first day (mean 29.6 ± 14 mm Hg) followed by mean values in a range between 13 and 18 mm Hg (day 2–12). Higher values were recorded in HH IV-V grades. An ICP[3] 20 mm Hg accounted for 14% of ICP observation in HH I–II, 30% observation in HH III and 35% in HH IV–V. CPP mirrored the ICP trend. Mean CPP, remaining MAP constantly high during the observation period, was lower in day 1 with a mean value of 67.2 ± 23 mm Hg), rose on day 2 at 79 ± 15 mm Hg and remained in a high range, i.e. 80–93 mm Hg, from day 3 to day 12. All the patient were adequately oxygenated and normocapnic. Both normal CVP and Hb indicated adequate circulating blood volume. Natremia was in the upper normality range (mean 143 mEq/l).

Time Course in the First 12 Days

In Fig. 1 are summarised the time course of $SjvO_2$ and CPP. As described in Fig. 1, mean $SjvO_2$ values were within 0.62 and 0.69. The time course of more severe patients is interesting. HH V patients presented mean value on day 1 in the low saturation range (0.54 ± 0.7), followed by a steep rise toward high $SjvO_2$ (>0.75), reaching a plateau on day 3 (mean 0.78 ± 0.2).

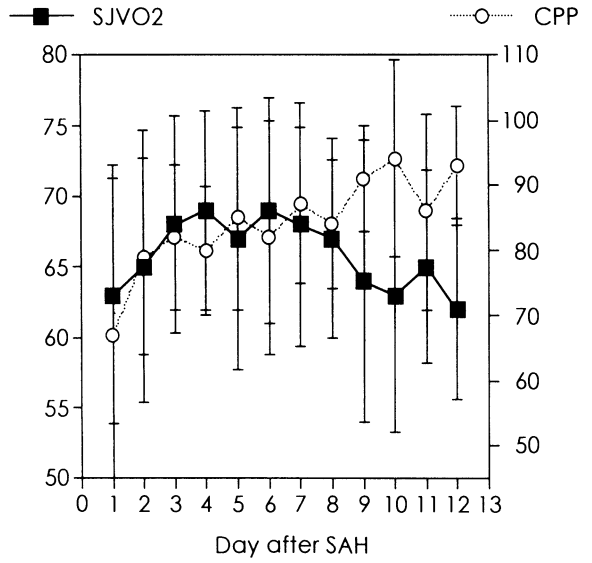

Fig. 1. $SjvO_2$ and CPP time course in the first 12 days

Influence of Systemic and Cerebral Hemodynamics on $SjvO_2$

We investigated the influence of systemic and cerebral hemodynamics on $SjvO_2$ values. In Table 2 we reported mean values for ICP, MAP, CPP, $PaCO_2$, PaO_2 according to the $SjvO_2$ level (low, normal, high). ICP was significantly higher during low $SjvO_2$ observation ($p = 0.008$). No statistical differences were noted regarding the influence of MAP, CPP, $PaCO_2$ PaO_2 on $SjvO_2$ but during desaturation episodes, lower, but not significantly different, $PaCO_2$ and CPP values were more frequently observed (Table 3).

Cerebral Injury Volume Measured on CT Scan and $SjvO_2$

We measured all lesions (hypo/hyperintense) on first CT scan and on a second done in a subacute phase (7 ± 2 days) utilizing the Cavalieri's direct estimator [1] method. Mean lesion volume on first CT was 24 ± 27 ml. Mean $SjvO_2$ closer to the first CT scan was 0.64 ± 0.9. We classified patients in three groups: without lesions, lesion <25 ml, greater than 25 ml. In patient without any lesion on first CT, ICP was 9 ± 4 mm Hg and $SjvO_2$ was 0.63 ± 0.1; in presence of lesion <25 ml, ICP rose to 20 ± 12 mm Hg and $SjvO_2$ was 0.67 ± 0.6. If volumes were >25 ml, ICP was higher (29 ± 15 mm Hg) and $SjvO_2$ was statistically lower (0.59 ± 0.6) ($p < 0.05$).

Table 3. *$PaCO_2$ and CPP Values During D.E and $SjvO_2 > 0.55$*

	$PaCO_2$[2] 30 > 30 mm Hg		CPP[2] 60 > 60 mm Hg	
$SjvO_2 > 0.55$	28 (8.9%)	288 (91%)	6 (3%)	189 (97%)
$SjvO_2 < 0.55$	6 (16%)	31 (84%)	3 (13%)	21 (87%)

On second CT mean volume was higher, increased to 43 ± 57 ml. Associated $SjvO_2$ (0.71 ± 0.8) is statistically higher compared to the first CT ($p < 0.05$). no lesions were detected, on second CT, only in one patient (ICP 4.2 mm Hg; $SjvO_2$ 0.69); in presence of lesion <25 ml $SjvO_2$ was 0.67 ± 0.9 and if lesion volume was >25 ml mean $SjvO_2$ and ICP were respectively 0.74 ± 0.5 and 22 ± 24 mm Hg.

Eight patients died (31%) and 18 patients did obey commands (69%) at ICU discharge.

Discussion

$SjvO_2$ is an expression of the relative balance between cerebral oxygen delivery and $CMRO_2$. It might be useful in SAH patient to understand if CBF and $CMRO_2$ are unbalanced. We analysed $SjvO_2$ in a 26 patients population. Mean $SjvO_2$ in our SAH population was 66.6 ± 0.73%. This value is very close to mean $SjvO_2$ in healthy volunteers suggesting that, in the majority of our observations, CBF and metabolism were coupled. This does not necessarily imply that levels of both, CBF and metabolism, are in a normal range. Subarachnoid hemorrhage produces significant global decreases in CBF and $CMRO_2$ more marked in patients with more severe neurological deficits. The causes remain partly obscure. The reduction in $CMRO_2$ may be due either to depression of the mental activity (damage to the brain stem and the reticular formation) or cellular damage. Moreover aneurysm rupture provokes a short-lasting severe increase in ICP, securing hemostasis; the adverse effect is a marked reduction in the cerebral circulation which may produce ischemic damage and $CMRO_2$ decrease.

In the present study, abnormal reduction of $SjvO_2$ was only observed in 10% of total serial measurements. These data resemble previous reports. Voldby [13] found no cases with abnormally low $SjvO_2$ in 31 patients and, in a more recent study, low $SjvO_2$ was observed in only 5 of 42 patients [7]. The real incidence of D.E. could be underestimated. Our population was intensively treated in order to maintain low ICP, normal $PaCO_2$, adequate cerebral per-

fusion pressure and oxygen transport. Moreover our analysis comes from retrospective data, collected at six-hour periods and shortlasting desaturations may probably have passed unnoticed without continuous $SjvO_2$ monitoring. We didn't utilize for the analysis data coming from continuous monitoring due to poor quality data obtained with fiberoptic jugular catheters. At least one desaturation episode was recorded in nine (34%) patients in our study population. However, the majority (5/9) presented only 1 desaturation episode; in 2/9 were identified 2–5 episodes and 2/9 more than 5 desaturations. Unexpectedly, 3/4 of patients with multiple episodes did obey commands at ICU discharge. These 4 patients with multiple D.E., like the remaining patients except HH V, didn't present any characteristic $SjvO_2$ time course. HH V patients presented lower saturation in the first observations, followed by a steep rise of $SjvO_2$ to supernormal values. Early desaturation could be the expression of a still maintained metabolic requirement not adequately met by CBF. Remarkably, if the $SjvO_2$ pattern moves to fixed high saturation, it probably might express the development of cerebral infarction with no O_2 extraction. All HH V died.

Single observations of low $SjvO_2$ were statistically associated with higher ICP. During D.E., although non statistically significant, $PaCO_2 < 30$ mm Hg (16% observations vs 8.9% in non desaturated) and CPP < 60 mm Hg (13% observations vs 3% in non desaturated) were more frequently observed. $SjvO_2$ is the alarm that these condition could be dangerously reducing cerebral blood supply and they have to be treated if possible. During cerebral aneurysm surgery also, Moss [10] described desaturation due to mean arterial pressure below 80 mm Hg; MAP increases were associated with $SjvO_2$ normalisation.

First and second CT scan were statistically different for associated $SjvO_2$ values. Larger lesion volumes (>25 ml) were associated in the first CT scan with low $SjvO_2$ values and higher ICP. Conversely, in the second CT larger lesions were coupled with high $SjvO_2$ but lower ICP. Again, low $SjvO_2$ in the early phase may reflect a temporary perfusion problem. Literature reports lower $SjvO_2$ values only in patients with large intracerebral hematoma or intraventricular haemorrhage and high ICP. When a critical point in O_2 extraction is reached, ischemia develops and higher $SjvO_2$ are observed.

$SjvO_2$ monitoring is a valuable tool in identifying a situation in which a global imbalance between CBF and $CMRO_2$ is present. In our SAH patients population desaturations episodes were not very frequent. However, the association with high ICP, lower CPP and $PaCO_2$, indicates that conditions that could reduce cerebral blood flow, may produce global imbalance between CBF and $CMRO_2$. Low $SjvO_2$ value are an alarm signal and they have to be treated, if possible, in order to avoid the development of cerebral infarction.

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Correspondence: G. Citerio, Rianimazione, Hospitale San Gerardo, via Donizetti, 106, 1-20052 Monza (Mi), Italy.

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Complications of Internal Jugular Vein Retrograde Catheterization

M. Gemma[1], **L. Beretta**[1], **A. De Vitis**[1], **C. Mattioli**[1], **M. R. Calvi**[1], **A. Antonino**[1], **B. Rizzi**[2], **L. Crippa**[2], and **A. D'Angelo**[2]

[1] Neurosurgical Intensive Care Unit and [2] Coagulation Service, Scientific Inst. Hosp. S. Raffaele, Milano, Italy

Summary

We report on the incidence of complications of 172 internal jugular vein retrograde catheterizations (IJVRCs) performed on 126 patients. Standard cannulation and X-ray control of the catheter tip placement were performed. Difficulties encountered during the manouvre were registered. Patients with a jugular catheter in place for more than one day had neck echography on catheter removal and one week later. Carotid artery puncture occured in 20 (12%) cases and lymphatic vessel puncture in one. In 13 (8%) cases IJVRC failed due to difficulties in advancing the guide. X-ray films documented catheter misplacement in 39 (23%) cases: loop into the internal jugular vein in 11 (6%); paravertebral venous plexus cannulated in one; other extracranial jugular afferent cannulated in 4 (2%); catheter tip into the jugular lumen in 10 (6%); catheter tip beyond the jugular bulb in 13 (8%). First neck echography documented: one perivascular hematoma (absent one week later); 3 (4%) jugular vein thrombosis (2 asymptomatic and absent one week later; one symptomatic and still evident one week later). Positive neck echography was not associated with difficulties, length of catheterization, diameter of the catheter.

IJVRC is a simple and safe procedure with a low incidence of serious complications.

Keywords: Complications; jugular vein.

Introduction

From its proposal in 1927 [1], internal jugular vein retrograde catheterization (IJVRC) for jugular bulb blood sampling has been increasingly used in neurosurgical intensive care unit (nICU) patients to evaluate cerebral venous oxygen saturation [2]. The incidence of possible early and late complications of this technique has not yet been clearly established.

In this prospective study we report on the incidence of complications related to 172 IJVRC performed in 126 patients.

Methods

IJVRCs performed in patients admitted to the nICU of S. Raffaele Hospital between August 1994 and March 1997 were prospectively studied.

IJVRCs were performed in comatose patients in whom intracranial pressure was monitored by experienced nICU physicians and following a standard technique [9]. During the manouvre, patients were kept supine on the horizontal plane and no rotation of the neck was performed.

For the purpose of the present study we assumed that an IJVRC was performed if the guide wire was inserted through the searching needle, whether or not the procedure could be succesfully fulfilled.

When possible, an attempt was made to identify the internal jugular vein in which the cerebral blood drainage was prevalent ("dominant" jugular vein). This was accomplished during routine cerebral angiograhy or CT scan imaging. In the absence of any evidence of "dominance" we decided to attempt cannulation on the right side first.

After IJVRC the placement of the catheter tip was documented by means of antero-posterior and lateral skull X-ray films. In the anteroposterior projection, the tip should be placed just medial to the mastoid bone, at the level of its base, and curved slightly medially [3]. In the lateral projection the tip should be placed above the level of C2 [2].

At the end of the procedure the physician involved in it was asked to fill in a form documenting every possible difficulty encountered during the manouvre.

Catheter patency was maintained by a heparinized saline (2 U/ml) flush at 2 ml/hour.

Patients with a jugular catheter in place for more than one day had neck echography on catheter removal and one week later. Catheters that have been in place for more than one day were cultured after removal.

Continuous variables are expressed as mean (SD).

Analysis of variance and chi-square tests have been used where appropriate.

Results

IJVRC was indicated on clinical grounds [2] on 130 patients admitted to our nICU during the time span of this study. In 4 (3%) of them IJVRC was not even attempted because of anterior neck traumatic injuries.

IJVRCs have been performed on 126 patients (caucasian; 103 (60%) males; age 42 (18%) years), who were admitted to our nICU because of serious central nervous sistem injury: there were 62 (49%) head injuries, 29 (23%) subarachnoid hemorrhages, 26 (21%) operated on arterovenous malformations or brain neoplasms, 6 (5%) other spontaneous intracranial hemorrhages, 3 (2%) cerebral abscesses. In 47 (37%) patients the "dominant" internal jugular vein was radiologically identified and was invariably the right one.

We studied 172 IJVRCs.

IJVRCs were on the right side in all but 15 (9%) cases, in which failure to advance the guide wire (1 case) or the occurrence of previous prolonged right side cannulation (14 cases) prompted us to perform IJVRC on the left side.

An Opticath fiberoptic catheter was positioned through a 14-G introducer in 18 (10%) IJVRCs. By the end of May 1995 we abandoned the use of fiberoptic catheters in favour of 16-G (124 (72%) IJVRCs) or 18-G (30 (18%) IJVRCs) one-lumen catheters.

Inadvertent ipsilateral carotid artery puncture with the searching needle occured during internal jugular vein search in 20 (12%) cases: succesful IJVRC could always be eventually accomplished after adequate external compression of the neck over the damaged artery. No arterovenous fistula nor prominent hematoma occured in these cases.

In one case the diagnosis of inadvertent lymphatic vessel puncture was made, because milky white-yellowish fluid could be aspirated from the searching needle. Also in this case the neck was compressed and correct IJVRC was eventually performed.

In 13 (8%) cases IJVRC failed due to difficulties in advancing the guide wire through the searching needle. Correct right IJVRC could be accomplished at a further attempt in all but one case, in which the contralateral (left) jugular vein was cannulated without problems.

After the insertion of the catheter X-ray films documented catheter misplacement in 39 (23%) cases. In 11 (6%) cases the catheter tip turned caudally after making a loop into the internal jugular vein (IJVRC was succesful at a further attempt in all of these cases); in 1 case a paravertebral venous plexus was inadvertently cannulated (IJVRC was not attempted again; however no complication ensued in this patient); in 4 (2%) the catheter was erroneously advanced into another extracranial jugular afferent (IJVRC was not attempted again in 1 of these, while it was succesul at a further attempt in 3). In 23 (13%) cases misplacement could be corrected without further cannulation: in 10 (6%) the caheter had to be slightly advanced, since its tip was into the jugular lumen, and in 13 (8%) it had to be slightly retracted, since its tip was beyond the jugular bulb.

No pneumothorax occured due to IJVRC manouvres.

In our series retrograde internal jugular vein catheters were in place for several days (min. 1, max, 13 days).

Neck echography was performed at the moment of catheter removal and one week later in the 80 (63%) patients. The second scheduled neck echography, one week later, could be accomplished in 74 (59%) patients.

In one patient the first neck echography documented a perivascular hematoma, which was no more apparent one week later.

Neck echography documented internal jugular vein thrombosis in 3 (4%) patients at the moment of catheter removal. Two of these patients were completely asymptomatic and no sign of jugular thrombosis could be evidenced by the second echography one week later. On the other hand the third patient presented a warm and red oedema of the soft tissues surrounding her right jugular vein, which could be felt as a stiff rope behind. Neck echography was still positive one week later in this patient. Unfortunately no further follow-up was possible for this patient.

In no patient with subsequent positive neck echography any of the aforementioned difficulties in cannulation occured. These patients did not differ significantly from echography-negative patients

either as to length of catheterization or as to diameter of the catheter employed ($p > 0.05$).

Catheter tip cultures were positive due to contamination [15] with Staphylococcus Aureus or Epidermidis in 13 patients out of 80 (17%). None of these met the criteria for the diagnosis of catheter related septicaemia [15], since none had positive concomitant blood cultures obtained from separate venipuncture.

Discussion

When dealing with invasive monitoring, a high level of suspicion must be maintained in order to frequently assess to what extent patients can benefit from doctors' intervention.

Jugular bulb blood sampling permit cerebral venous monitoring and can be easly accomplished by IJVRC [2]. This has become common practice in very many nICUs worldwide and the interest in it is still increasing. The present study does not address the topic of the benefits of IJVRC, but wishes to contribute to the assessment of the potential risks of this invasive practice.

Trendelemburg position and rotating the patient's head can virtually make the search for the jugular vein easier. On the other hand the adverse effect of these practices on intracranial pressure is well known [6] and we performed IVRC with the patient's head midline and flat on the horizontal plane.

Moreover head rotation >40° has been demonstrated to increase the risk of inadvertent carotid artery puncture during internal jugular vein cannulation, due to increased overlap of carotid artery and internal jugular vein [7]. Notwithstanding the neutral head position, in our series the incidence of inadvertent carotid artery puncture is relatively high (12%), when compared with internal jugular vein anterograde cannulation series. In the majority of these the incidence of carotid puncture ranges from 3% to 15% [10,12,13] although a pediatric series [11] reports a 23% incidence.

Since misplacement of the catheter tip was disclosed by X-ray films in 23% of our cases, we argue that radiographic confirmation of catheter tip location is essential. Most authors do agree with this statement [3–5,9], while others do not [8].

A previous pediatric series of IJVRC in 123 patients [4] reported a 3% incidence of carotid puncture and a 3% incidence of misplacement of the catheter at X-ray control. In another series [8] of IJVRC in 100 neurosurgical patients carotid artery puncture occured in 2% but catheter misplacement was not routinely assessed. We are not aware of other published IJVRC series.

Our series reports on the practice of IJVRC as it is routinely performed in most European nICUs. The experienced physician performing the manouvre was always the doctor in charge for the patient at the time when the IJVRC was required. Although "a priori" identification of different degrees of skill and experience among the attending physicians was impossible in our series, our data clearly indicated that specific complications, such as carotid puncture, occured exceedingly often to specific doctors. The latter should be considered a valuable result in the perspective of training members of the nICU team.

Although seldom symptomatic, thrombosis is known to occur frequently where central venous catheters have been in place. A phlebography study [14] demonstrated that on catheter removal some of the catheter related thrombi can become detached in blood or removed with the catheter itself. For this reason we performed neck echography on catheter removal in 80 patients. Seventifour of these patients had a second echographic examination of the neck one week later. We arbitrary decided not to perform neck echography in patients whose jugular catheter was in place for less than 24 hours, since the risk of thrombosis should be exceedingly low in this group of patients. Dead patients had no postmortem jugular vein examination: this represents a limitation of the present study.

It is noteworthy that 2 out of 3 jugular thrombosis were diagnosed only by the first echography and were otherwise completely asymptomatic. Unfortunately the third patient, in whom prominent symptoms and repeated echographic diagnosis ensued, was lost at follow up. It should be stressed that neither the occurrence of complications during IJVRC nor the duration of catheterization were associated with a positive neck echography.

Although contamination of the catheter could be demonstrated in 13 patients out of 80 (17%), no catheter related septicaemia occured in our series [15]. In our opinion, full aseptic precautions in inserting the catheters and in subsequent nursing play a key role in this setting. However, no infusion of parenteral nutrition or drugs is ever performed through jugular retrograde catheters: this helps in reducing the incidence of serious catheter related infections [15]. On the other hand frequent handling of the catheter and

blood sampling through it should increase the risk [15].

In summary, our data provide evidence that IJVRC is a simple and safe procedure with a low incidence of serious complications. We strongly recommend the routine X-ray control of correct catheter tip placement.

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Correspondence: Dr. Luigi Beretta, Neurosurgical Intensive Care Unit, Scientific Inst. Hosp. S. Raffaele, Via Olgettina 60, I-20132 Milano, Italy.

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Jugular Bulb Monitoring of Cerebral Oxygen Metabolism in Severe Head Injury: Accuracy of Unilateral Measurements

C. Metz[1], **M. Holzschuh**[2], **T. Bein**[1], **B. Kallenbach**[1], and **K. Taeger**[1]

Departments of [1] Anesthesiology and [2] Neurosurgery, University Hospital of Regensburg, Federal Republic of Germany

Summary

To investigate the accuracy of unilateral jugularvenous monitoring, we performed bilateral jugularvenous monitoring in 22 comatose head injured patients. Fiberoptic catheters were placed upstream in both internal jugular veins and advanced into the jugular bulbs. Arterial and bilateral jugularvenous blood samples were obtained simultaneously for in vitro determination of jugularvenous oxygen saturation (SJO_2), arterial minus jugularvenous lactate content difference (AJDL) and modified lactate-oxygen-index (mLOI). Ischemia was assumed, if one of the following pathologies occured at least unilaterally: SJO_2 < 55%, AJDL < –0.37 mmol/L, mLOI > 0.08. The mean and maximum bilateral SJO_2 differences varied between 1.4% to 21.0%, and 8.1% to 44.3% respectively. The bias and limits of agreement (mean differences ±2SD) between paired samples were –0.4% ± 12.8%. Regarding AJDL bias and limits of agreement were – 0.01 mmol/L ± 0.18 mmol/L. At best 87% of defined ischemic events could be evaluated by monitoring at the side of predominant lesion or, in diffuse injuries, at the side of the larger jugular foramen in CT scan (CT approach). We conclude, due to the wide limits of agreement in bilateral SJO_2 and AJDL the reliability of unilateral jugularvenous monitoring in patients with intracranial pathology is questionable. For diagnosing ischemia the CT approach has the highest sensitivity and is therefore recommended.

Keywords: Jugular bulb; oxygen metabolism.

Introduction

Monitoring of global cerebral hemodynamics and metabolism based on the Fick principle provided a lot of information concerning the pathophysiology of severe head injuries and has become an important tool for clinical management. Cerebral venous blood samples for oxygen saturation monitoring as well as for all derived calculations are usually obtained from unilateral jugular bulb catheterization. However, as recently demonstrated, marked differences can occur in patients suffering from severe head injuries [14]. To investigate the accuracy of unilateral jugularvenous monitoring and to determine the appropriate side, we performed bilateral jugularvenous monitoring in 22 comatose head injured patients.

Materials and Methods

After approval by our local ethics committee, 22 patients with Glasgow Coma Scale (GCS) scores <8 upon admission were enrolled in the study. All patients were managed according to our standard intensive care protocol which is aimed at preventing cerebral ischemia [11]. Fiberoptic catheters were placed upstream in both internal jugular veins and advanced into the jugular bulbs. Catheter positions were verified by x-ray in anteroposterior and lateral projections or by CT scan. Whenever the SJO_2 monitors appeared to show significant changes, and additionally in 6 hours intervals, arterial and bilateral jugularvenous blood samples were drawn simultaneously for in vitro determination of jugularvenous oxygen saturation (SJO_2), arterial minus jugularvenous lactate content difference (AJDL) and modified lactate-oxygen-index (mLOI). To avoid contamination of the samples with extracerebral blood, jugularvenous blood was slowly withdrawn (ca. 2 ml/min). All blood samples were analysed in vitro for SJO_2, cerebral extraction of oxygen ($CEO = SaO_2\text{-}SJO_2$) and AJDL. The blood gases were measured on a Radiometer 520 blood gas analyzer. (Fa. Radiometer, Copenhagen) To improve the accuracy of the lactate determinations, duplicate whole blood lactate concentrations in arterial and venous blood were determined in each case by an enzymatic method and average values were calculated. (Beckman CX 7, Beckman Intruments Inc., Fullerton, California, U.S.A.). Data were excluded from analysis if the results from the same sample differed more than 5%. The mLOI [$mLOI = -AJDL\ (mmol/L)/SaO_2\text{-}SJO_2(\%) \times 10$] represents the ratio of the amount of glucose metabolized anaerobically to the amount metabolised aerobically [3]. Global as well as regional cerebral ischemia can be diagnosed by the AJDL, or by calculating the mLOI [3,13]. Ischemia was assumed if AJDL was <–0.37 mmol/L, and/or mLOI was >0.08. In the case of SJO_2 <55% without pathological AJDL or mLOI values, compensated cerebral hypoperfusion was assumed. To determine the appropriate side for jugularvenous monitoring

according to various recommendations in the literature, the incidence of ischemia and or hypoperfusion appearing on the actual suggested side was compared with the maximum possible incidence detectable using bilateral monitoring [3,4,13]. The following recommendations were studied: Monitoring at the side where there was the most severe injury, or the right side in case of diffuse lesions [13]. Monitoring at the side of predominant venous outflow which was identified by the larger jugular foramen on a computerized tomography of the head [4] and monitoring exclusively at the right side [3]. For statistical analysis bilateral SJO_2 and AJDL data were compared by the method, described by Bland and Altman [2]. To determine if the bilateral measurements are in agreement and therefore interchangeable a plot of the difference between the paired results from both sides against the average of the paired results was done. The agreement between bilateral measurements can be summarized by calculating the bias, estimated by the mean difference, and the standard deviation of the differences as a measure of precision. The limits of agreement (95% confidence interval) are defined by the bias ±2SD of the differences.

Results

In 22 patients the catheters were used for 5.4 ± 2.9 days (range 2–16 days). During the study period 396 paired samples of right and left SJO_2 were obtained. Out of 317 cases the corresponding AJDL and mLOI values were determined simultaneously. With respect to lactate measurements the cumulative variation coefficient was 3.1% ± 0.1 mmol/L. In individual patients the mean bilateral SJO_2 differences varied between 1.4% and 21.0%, and the maximum SJO_2 differences were between 8.1% and 44.3%, respectively. 18 of 22 patients had an SJO_2 difference above 10% at least once, and discrepancies greater than 20% were found in every third patient.

As shown in Fig. 1 the bias between the mean right and left SJO_2 was –0.4%, and the corresponding wide limits of agreement were 0.04 ± 12.8%. The mean AJDL was –0.16 ± 0.19 mmol/L. The mean overall AJDL difference (accomplished by subtracting the smaller number from the larger one) between both jugular bulbs was 0.05 ± 0.06 mmol/L; the maximum differences in individual patients varied greatly between 0.04 and 1.52 mmol/L. Using the Bland and Altman plot for AJDL data, we found a bias of –0.01 mmol/L and corresponding limits of agreement of –0.19 mmol/L and 0.17 mmol/L, respectively (Fig. 2). Next we investigated the reliability of unilateral measurements in identifying patholgical values indicative of cerebral hypoperfusion and ischemia (Table 1). Using bilateral jugularvenous monitoring we found a total of 134 pathologies, representing a sensitivity of 100%. In our patient population a maximum of 117 events or 87% could be evaluated if the side of monitoring was chosen according to the so called CT approach. Based on CT-scan the side of predominant lesion, or in case of diffuse lesions the side of the largest jugular foramen was selected for jugularvenous monitoring.

Discussion

In this study, conducted on severely head injured patients, we investigated the accuracy of unilateral jugularvenous monitoring on parameters indicating cerebral hypoperfusion and ischemia (SJO_2, AJDL, mLOI) as compared to bilateral measurements, which yield the maximum information available. Regarding SJO_2 in head injured patients, differences of 5% in bilateral SJO_2 seem acceptable; a difference of 10% is highly suspicious and differences above 15%

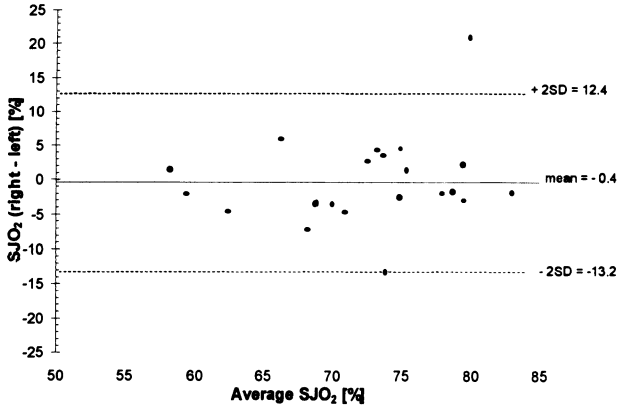

Fig. 1. Distribution of individual differences between mean bilateral SJO_2 against their average values. The solid line represents the bias, dashed lines correspond to mean ± 2SD of the differences (i.e. 95% confidence interval)

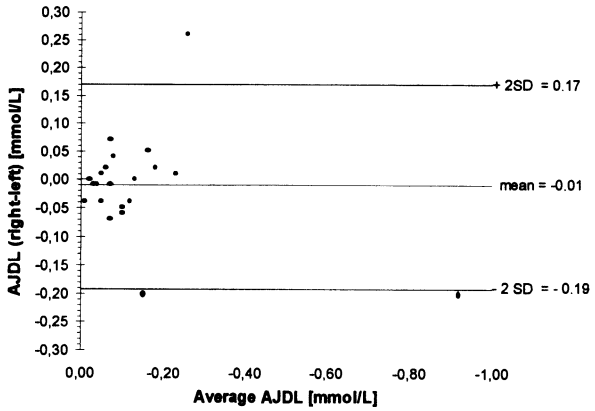

Fig. 2. Distribution of individual differences between mean bilateral AJDL against their average values. The solid line represents the bias dashed lines correspond to mean ± 2SD of the differences (i.e. 95% confidence interval)

Table 1. *Sensitivity of Various Recommendations for Unilateral Jugularvenous Monitoring in Detecting Compensated Cerebral Hypoperfusion and/or Cerebral Ischemia in Unilateral and Diffuse Brain Injuries*

		Robertson's approach [13]		Deardens's approach [4]		Exclusively right side [3]		CT approach	
Pathology	Total	n	Sensitivity	n	Sensitivity	n	Sensitivity	n	Sensitivity
$SJO_2 < 55\%$	30	25	83%	24	77%	22	73%	26	87%
AJDL < -0.37 mmol/L	17	14	82%	14	82%	11	65%	16	94%
mLOI > 0.08	87	69	79%	72	83%	67	77%	75	86%

n = number of pathologies detected.

are unacceptable [14]. We found a mean bilateral SJO_2 difference of 4.6 ± 4.5% which corresponds to those reported previously in the literature [14]. Although mean bilateral differences suggest minor discrepancies, Fig. 1 shows that the limits of agreement between both sides were poor. For example, if right SJO_2 was 65%, which was well within the normal range, left SJO_2 values might have been between 52% and 78%. The lowest SJO_2 would suggest hypoperfusion, while the highest value indicates relative hyperemia. This lack of agreement would significantly influence patient management. Global cerebral hypoperfusion can be diagnosed by a jugularvenous desaturation below 55% [4]. However SJO_2 alone is unable to detect regional cerebral hypoperfusion or ischemia. In this case hypoperfused or ischemic areas with low SJO_2 overlap with areas of normal or even elevated CBF and corresponding normal or high SJO_2 [1]. The resulting SJO_2 in the jugular bulb represents mixing of blood drained from these heterogenous areas and, therefore, could be in the normal range [11]. If CBF fails to meet metabolic demand, anaerobic metabolism occurs causing accumulation of lactate in ischemic tissue [5,7]. Lactate in brain tissue and blood increases in proportion to the severity of injury, and the point of most negative AJDL coincides with the point of maximum brain tissue lactate content [7]. In healthy men there is a mean AJDL of 0.17 ± 0.1 mmol/L [6]. The mean AJDL found in our patients was nearly equal to that value. The mean AJDL differences between both jugular bulbs we obtained in individual patients were usually low. However their maximum values were marked and increased with increasing pathology (i.e. more negative) AJDL. From the anatomical point of view, blood entering the brain via each internal cartotid artery is distributed almost completely to the ipsilateral hemispere. On the venous side the large dural sinuses in the midline drain both hemispheres, dividing their contents at the torcular with the blood being conveyed to the torcular via the lateral sinuses. Thus, almost complete mixing of the venous drainage from the two hemispheres should be expected. However, the venous drainage of the brain is characterized by high interindividual variability, because the cross section of any given vessel in the torcular is extremely variable and superficial cerebral veins surpass the torcular and join directly to the lateral and petrosal sinuses [15]. Nethertheless, in individuals without intracranial pathology the blood in either jugular bulb was found as representative of the drainage of all histological regions of the brain [8,9]. Using Fick's equation, according to the regional coupling between cerebral blood flow (CBF) and metabolism ($CMRO_2$) the arterial to venous oxygen content difference ($AJDO_2$) remains constant ($CBF/CMRO_2 = AJDO_2$). Consequently, the oxygen saturation in venous blood drained from different areas of the brain should not be significantly different. Under these conditions, despite incomplete mixing of cerebral venous blood, the corresponding SJO_2 values in both jugular bulbs are expected to agree within narrow bounds. However, in most severely head injured patients, coupling of CBF and $CMRO_2$ is disturbed, resulting in regionally increased or decreased CBF independent of regional metabolic demand (10). Thus $AJDO_2$, and consequently SJO_2, will vary markedly between different areas of the brain. Now incomplete mixing of cerebralvenous blood causes marked bilateral discrepancies. The final remaining question was whether or not we could at least prospectively identify the more appropriate side for diagnosing cerebral hypoperfusion and/or cerebral ischemia. For each different pathology investigated, the CT approach for selecting the appropriate side showed the highest sensitivity (Table 1). One might assume that these data support sufficient accuracy of unilateral monitoring, provided that the objective is

detection of cerebral ischemia. However, it must be kept in mind that even a single ischemic episode may cause cerebral infarction associated with poor neurological outcome [12]. Some of the possible limitations such as inappropriate positioning of the catheter tip and additional extracerebral contamination should also be addressed. In our study, the correct positioning of both catheter tips high in the jugular bulbs just below the skull base was always confirmed by radiography and venous sampling via the catheters was performed slowly (i.e. about 2 ml/min). We did not measure cerebral blood flow and, therefore, evidence about absolute interhemispheric differences in $CMRO_2$ and cerebral lactate production, as well as the true mixed cerebral venous oxygen saturation cannot be given. Nethertheless, even unilateral occurence of pathological values in SJO_2, AJDL and mLOI indicates at least regional disproportion of cerebral oxygen delivery and consumption and therefore requires therapeutic intervention. However, the significance of the differences in SJO_2 falling in the nomal range between 55% and 75% cannot be judged by unilateral monitoring. We conclude that in an individual patient presenting intracranial pathology, as it is true in severe head injury, even calculated unilateral jugularvenous monitoring has an unpredictable risk for misleading or missing data. Therefore, whenever data obtained from unilateral jugularvenous monitoring are inconsistent with data from other monitoring techniques such as CPP, ICP, or CCT, an additional catheter should be placed for intermittent blood sampling to evaluate the possibility of significant side to side differences which would thus influence treatment.

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Correspondence: Dr. Christoph Metz, Department of Anesthesiology, University Hospital of Regensburg, D-93042 Regensburg, Federal Republic of Germany.

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Comparison of P_{csf} Monitoring and Controlled CSF Drainage Diagnose Normal Pressure Hydrocephalus

M. A. Williams, A. Y. Razumovsky, and **D. F. Hanley**

Neurosciences Critical Care Division, Johns Hopkins Medical Institutions, Baltimore, MD, U.S.A.

Summary

We evaluated 86 patients for possible normal pressure hydrocephalus (NPH) by: 1) CSF pressure (Pcsf) monitoring and analysis for percent of time with A or B-waves, and 2) controlled CSF drainage for 3 days via a lumbar subarachnoid catheter. Clinical outcome after CSF drainage and shunt surgery was assessed as change of clinical exam, with grades of none, minor, moderate, or marked change. For outcome analysis in 47 patients after shunt surgery, NPH was defined as moderate or marked clinical improvement.

We assessed the diagnostic discrimination of percent-of-time thresholds of A and B-waves for 38 patients. At 10%, sensitivity for NPH is 91%, specificity is 13%, positive predictive value (PPV) is 62%, and the false positive rate is 38%. At the 25% threshold, sensitivity is 78%, specificity is 40%, PPV is 67%, false positive rate is 33%, and the false negative rate is 22%. For CSF drainage (threshold of minor improvement or better), the sensitivity is 97%, specificity is 60%, PPV is 84%, negative predictive value (NPV) is 90%, and the false negative rate is 3%.

We conclude: 1) clinical response to controlled CSF drainage accurately predicts the outcome after shunt surgery in patients suspected of having NPH, and 2) A or B-waves poorly predict which patients will respond to shunt surgery. Three days of CSF drainage seems to encompass critical thresholds of CSF volume removal or duration of P_{csf} reduction necessary for neuronal function to begin returning and symptoms to begin resolving in patients with NPH.

Keywords: CSF Drainage; normal pressure hydrocephalus.

Introduction

Normal pressure hydrocephalus (NPH) is an important, treatable syndrome of dementia, gait apraxia, and urinary incontinence that may represent as much as 5% of demented patients [14]. NPH is treated by surgical cerebrospinal fluid (CSF) shunting, often with significant neurologic recovery [1,12,13]. The presence of unstable CSF pressure (P_{csf}), predominantly B-waves, in NPH is well documented [2,3,9,11], and the correlation of unstable P_{csf} with NPH shunt responsiveness varies from 50% to 90% [2,8,11]. Clinical response to CSF drainage via a lumbar catheter has been reported to correlate with response to shunting in NPH [5,7].

Since 1988 we have evaluated patients suspected of having NPH with a strategy of: 1) initial clinical evaluation and testing for treatable diseases with clinical overlap, and 2) P_{csf} monitoring via a lumbar subarachnoid catheter followed by a 3-days of controlled CSF drainage. The purpose of this report is to compare the diagnostic accuracy of Pcsf monitoring and controlled CSF drainage in predicting the clinical response to treatment with CSF shunt insertion.

Methods

Of 103 patients referred, 86 were evaluated for NPH. Significant coexisting diseases were either treated first, or patients were excluded from further evaluation. After patients or their surrogates provided informed consent, P_{csf} monitoring and controlled CSF drainage were accomplished via a lumbar subarachnoid catheter inserted percutaneously. The P_{csf} and other variables (O_2 saturation, pulse rate, respiratory excursion) were recorded continuously for 2 to 3 days on an 8-channel strip chart recorder or a Macintosh computer with an analog-to-digital signal converter and software (MacLab, ADInstruments, Inc., Milford, MA). P_{csf} was analyzed for resting mean pressure, abnormal wave forms, peak pressure, and pulse pressure. Abnormal P_{csf} wave forms were identified according to criteria adapted from Lundberg's original description (10). We defined B-waves as P_{csf} oscillations with a B-wave frequency and an amplitude (peak systolic P_{csf} minus baseline systolic P_{csf}) of ≥3 mm Hg (40 mm H_2O). Although P_{csf} was recorded continuously, significant amounts of recording were unsuitable for P_{csf} analysis because of movement artifacts. Therefore P_{csf} was analyzed only during artifact-free epochs when the

record indicated the transducer was properly levelled and the patient was quiet. In most circumstances this resulted in P_{csf} analysis only during sleep or quiet rest.

A 3-day trial of controlled CSF drainage followed P_{csf} monitoring. Drainage rate was controlled to approximately 10 cc/hour (240 cc/day), which is 1/4 to 1/2 of daily CSF production. Patients were clinically examined for response to drainage once or twice daily. Individualized definitions of clinical improvement were chosen for each patient, based on the clinical exam prior to CSF drainage. A single, broad definition of clinical improvement was not feasible given the extreme variation in symptom severity. Outcome after CSF drainage and shunt surgery was assessed as *change* in clinical exam, rather than absolute level of clinical exam, with grades of better or worse (none, minor, moderate, marked change) scored as 0, ±1, ±2, and ±3. For the purposes of determining sensitivity and specificity of the diagnostic tests, the definition of NPH was moderate or marked improvement (>1) after shunt surgery. Minor improvement, no change, or deterioration (≤1) were not considered NPH. This definition is based on a value assumption that minor improvement after shunt surgery is insufficient benefit compared to the risk.

Results

We assessed the diagnostic discrimination of three thresholds of B-wave activity (10%, 25%, 50%) for moderate or better improvement after shunt surgery (Table 1A–C). At the 10% threshold, sensitivity is high (91%) but specificity is low (13%), and approximately 1/3 of patients with >10% B-waves did not improve after shunt surgery. At the 25% threshold, the sensitivity is 78%. Using this threshold, 20% of patients who benefitted from a shunt would not have received it, and 33% of patients who received a shunt would not have benefitted. At the 50% threshold the sensitivity falls to 43%, and over half the patients who benefitted from a shunt would not have received it and one third who received a shunt would not have improved.

Table 1. *(A–C) Comparison of Three Thresholds of % Sleep Time with B-Waves to Outcome after Shunt Surgery in NPH. (D–E) Comparison of Two Thresholds of Clinical Response to Controlled CSF Drainage to Outcome after Shunt Surgery in NPH*

Table 1A

		Clinical Outcome After Shunt: >1, NPH	≤1, Not NPH		
Sleep ICP B-wave Threshold	>10%	21	13	34	PPV = 61.76%
	≤10%	2	2	4	NPV = 50.00%
		23	15	38	
		Sensitivity 91.30%	Specificity 13.33%		

Table 1D

		Clinical Outcome After Shunt: >1, NPH	≤1, Not NPH		
Clinical Outcome After CSF Drainage Trial	>1	21	2	23	PPV = 91.30%
	≤1	11	13	24	NPV = 54.17%
		32	15	47	
		Sensitivity 65.63%	Specificity 86.67%		

Table 1B

		Clinical Outcome After Shunt: >1, NPH	≤1, Not NPH		
Sleep ICP B-wave Threshold	>25%	18	9	27	PPV = 66.67%
	≤25%	5	6	11	NPV = 54.55%
		23	15	38	
		Sensitivity 78.26%	Specificity 40.00%		

Table 1E

		Clinical Outcome After Shunt: >1, NPH	≤1, Not NPH		
Clinical Outcome After CSF Drainage Trial	>0	31	6	37	PPV = 83.78%
	≤0	1	9	10	NPV = 90.00%
		32	15	47	
		Sensitivity 96.88%	Specificity 60.00%		

Table 1C

		Clinical Outcome After Shunt: >1, NPH	≤1, Not NPH		
Sleep ICP B-wave Threshold	>50%	10	5	15	PPV = 66.67%
	≤50%	13	10	23	NPV = 43.48%
		23	15	38	
		Sensitivity 43.48%	Specificity 66.67%		

PPV Positive Predictive Value; *NPV* Negative Predictive Value.

The diagnostic discrimination of two thresholds of clinical improvement (>1 and >0) after controlled CSF drainage is shown in Table 1D–E. The lower threshold of minor improvement or better (>0) after controlled CSF drainage more accurately discriminates the diagnosis of NPH than does the higher threshold of moderate improvement or better (>1) after controlled CSF drainage. In this selected population, 84% of patients who had minor improvement or better after CSF drainage had NPH, whereas only 1 patient out of 10 who had no improvement after CSF drainage had NPH. More significant is that the false negative diagnostic rate is less with the lower threshold (1/32 or 3%) than with the higher threshold of improvement after CSF drainage (11/32 or 34%).

Discussion

Our results indicate that the outcome after shunt surgery in patients suspected of having NPH is more accurately predicted by the clinical response to three days of controlled CSF drainage than by evidence of unstable P_{csf} (A- or B-waves). The presence of unstable P_{csf} wave forms (predominantly B-waves) in NPH is well documented [2–4,6,8,9,11], but the correlation of unstable P_{csf} with clinical outcome after shunt surgery varies from 50% to 90% (2,8,11). Our results support previous studies showing that there does not appear to be a direct correlation between unstable P_{csf} and clinical recovery. Thus evidence of unstable P_{csf} (A- or B-waves) may be a sensitive test for identifying patients with impaired intracranial compliance, but it is not specific for NPH. This can be explained by two potential mechanisms: 1) unstable P_{csf} may persist after the neuronal injury in NPH is irreversible, or 2) other causes of subcortical deficits and ventriculomegaly can make P_{csf} unstable.

The physiologic basis for the better accuracy of outcome prediction with controlled CSF drainage may be that it corrects disordered CSF circulation just as a shunt does, and therefore provides an indication of the *potential* for neurological recovery. Thus the accuracy of this test also depends on detailed observation and documentation of changes in neurological function. Our results suggest that 3 days of CSF drainage at 10 cc/hour encompasses critical thresholds of time and volume of CSF removal necessary for reversible neuronal injury to begin to recover and symptomatic improvement to become apparent in NPH.

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Correspondence: Michael A. Williams, M.D., Neurosciences Critical Care Division, Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Meyer 8-140, Baltimore, MD 21287-7840, U.S.A.

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Does CSF Outflow Resistance Predict the Response to Shunting in Patients with Normal Pressure Hydrocephalus?

A. J. W. Boon[1,8], **J. Th. J. Tans**[1], **E. J. Delwel**[3], **S. M. Egeler-Peerdeman**[4], **P. W. Hanlo**[5], **J. A. L. Wurzer**[2], **C. J. J. Avezaat**[3], **D. A. de Jong**[3], **R. H. J. M. Gooskens**[6], and **J. Hermans**[7]

Departments of [1] Neurology and [2] Neurosurgery, Westeinde Hospital, The Hague, Department of Neurology, University Hospital, Rotterdam, Departments of Neurosurgery, University Hospitals, [3] Rotterdam and [5] Utrecht, [4] Free University Hospital, Amsterdam, [6] Department of Childeurology, University Hospital Utrecht, and [7] Department of Medical Statistics, University Hospital, Leiden, The Netherlands

Summary

The value of the measurements of CSF outflow resistance (Rcsf) relative to predicting outcome after shunting was studied. In a group of 101 patients with mainly idiopathic normal pressure hydrocephalus (NPH) Rcsf was obtained by lumbar constant flow infusion. Gait disturbance and dementia were quantified using an NPH scale (NPHS) and disability by the Modified Rankin scale (MRS). Patients were assessed before and at 1, 3, 6, 9 and 12 months after surgery. Outcome measures were differences between the preoperative and last NPHS and MRS scores. Improvement was defined as a change of ≥15% in NPHS and ≥1 grade in MRS. Intention-to-treat analysis of all patients at one year yielded improvement of 57% in NPHS and 59% in MRS. Efficacy analysis, excluding comorbidity unrelated to NPH, revealed positive predictive values of around 80% at Rcsf <18, and between 90% and 100% at Rcsf ≥18 mm Hg/ml/min. For Rcsf ≥18, the likelihood ratios were also higher.

We conclude that the best predictor of the response to shunting is an Rcsf ≥18 mm Hg/ml/min. Since two-thirds of the patients with Rcsf <18 showed improvement as well, these patients should not be denied shunting.

Keywords: CSF outflow resistance; normal pressure hydrocephalus.

Introduction

Previous studies on the prediction of outcome in NPH patients using Rcsf measurement have shown conflicting results with both good [2,9,10] and poor [3,5,7,8] predictive values. Because most of these studies were carried out in single institutions by experienced investigators, broader applicability of the infusion test has not yet been demonstrated. Another limitation was that patients with "normal" Rcsf values were usually not shunted. The purpose of this multicentre, prospective study was to determine the positive and negative predictive values of Rcsf for the results of ventriculo-peritoneal shunting in NPH patients.

Patients and Methods

Gait disturbance was quantified using a gait scale (GS), which evaluates the presence of 10 features of gait and measures the number of steps and seconds required for a 10-metre walk[1]. Dementia was assessed by a dementia scale (DS) comprising the 10-word test, digit span forwards and backwards, trail making and finger tapping. Together, gait (range 2–40) and dementia scale (range 4–40) yielded the NPH scale (NPHS; range 6–80). The modified Rankin scale (MRS) was used as a disability score (range 0–6).

In 5 years 101 NPH patients were enrolled, fulfilling strict inclusion criteria: 1) gradually developed gait disturbance of both legs, (unexplained by other conditions) and gait scale score ≥12; 2) subcortical dementia and dementia scale score ≥12; 3) MRS score ≥2; 4) CT scan showing a communicating hydrocephalus without clinically relevant parenchymal lesions and marked cortical atrophy. Exclusion criteria were (sub)acute symptomatic NPH, age ≥85 years, and severe comorbidity with restricted life-expectancy or contraindications for surgery.

All patients underwent a lumbar constant flow infusion test [6] and were randomized to a low or a medium-high pressure Medos Hakim shunt, irrespective of the Rcsf value. Patients were assessed prior to and at 1, 3, 6, 9 and 12 months after surgery.

Outcome measures were calculated as the differences between the preoperative and last NPHS and MRS scores. "Any improvement" was defined as a change between entry and last score of at least 15% in NPHS and one grade in MRS. Intention-to-treat analysis was performed using all the available outcome information at 12 months or at last follow-up. Patients who died were categorized as unimproved. For efficacy analysis 17 serious events and 15 deaths unrelated to NPH but interfering with neurological

function were excluded. The last follow-up examination before such an event was taken for the assessment of outcome.

Results

Five patients died of diseases unrelated to the shunt procedure before the first follow-up and in one patient Rcsf could not be determined, leaving 95 evaluable patients. Much comorbidity was present at entry leading, together with the NPH signs, to a Rankin scare of 5 or 6 in 28% of the patients.

The distribution of Rcsf values are shown in Fig. 1. Taking 12 mm Hg/ml/min as the upper limit of a normal Rcsf, 83% of patients showed increased Rcsf. These data demonstrated the presence of a disturbance of CSF resorption in the majority of the study population.

According to intention-to-treat analysis, of all 101 patients, 57% showed improvement in NPHS and 59% in MRS after one year. Efficacy analysis of 95 patients showed improvement rising to 76% in NPHS and 69% in MRS.

Using improvement in NPHS after shunting as a criterion for the diagnosis of NPH, diagnostic indices were calculated at 6 Rcsf cut-off points. Positive predictive values were appoximately 80% at Rcsf 10, 12 and 15 mm Hg/ml/min and between 90 and 100% at Rcsf 18, 21 and 24 mm Hg/ml/min (Fig. 2). Because of the considerable number of patients who improved despite a negative test, the negative predictive values were low. Sensitivity gradually decreased with rising Rcsf values. The increase of specificity was less gradual with a relatively high value for Rcsf 18. The likelihood ratios (sensitivity/1-specificity) were less than 1.5 for Rcsf limits <18, compared to a ratio of 3.5 for Rcsf of 18 mm Hg/ml/min (Fig. 2).

Discussion

This large multicentre study is the first presented in which all patients with idiopathic NPH were shunted, irrespective of Rcsf values. Because we wanted to quantify the NPH syndrome, we developed a gait and a dementia scale. To create one outcome measure, both scales were added to the NPH scale. Disability was evaluated by the Rankin scale. The improvement rate of nearly 60% one year after shunting compares well with previous findings [2].

Determination of Rcsf can be accomplished by constant flow, constant pressure and bolus infusion techniques. We recomend the lumbar constant flow infusion as the best compromise between simplicity and accuracy. The participants in the 4 centres easily adopted this method.

Presently, there is no consensus on the level of Rcsf above which patients should be shunted. Thresholds varied from 8 to 15 mm Hg/ml/min [2–5,9,10]. This study offers the opportunity to better define that limit. Calculation of positive predictive values, sensitivity, specificity and likelihood ratios at different Rcsf cut-off points clearly showed that good prediction of outcome is obtained only from an Rcsf value of 18 mm Hg/ml/min onwards. The negative predictive values were quite low at all levels of Rcsf.

We propose to raise the Rcsf limit for shunting from around 12 to 18 mm Hg/ml/min. If we had used that criterion, 92% of patients would have shown

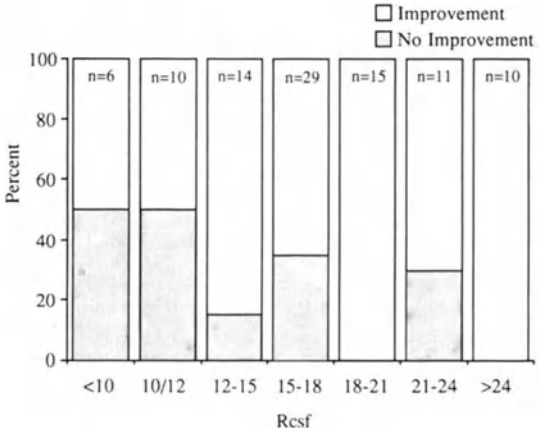

Fig. 1. Rcsf versus outcome in NPH scale

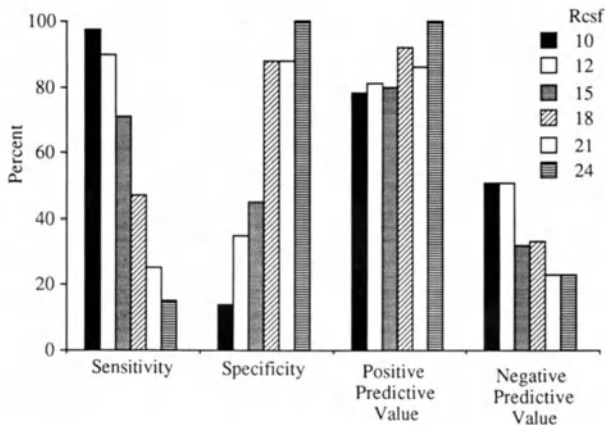

Fig. 2. Diagnostic indicer at 6 Rcsf cut-offs

improvement at the expense of 8% who did not. Patients with an Rcsf below 18 mm Hg/ml/min and the combination of clinical as well as CT findings typical for NPH also should have a shunt.

Patients not improving despite an increased Rcsf significantly more often developed comorbidity during follow-up. Extra- and intracranial vascular diseases in particular occurred rather frequently and appeared to have a deleterious effect on outcome.

In conclusion, one year after shunting almost 60% of this group of mostly idiopathic NPH patients showed a clinically relevant improvement using quantitative evaluation. Lumbar constant flow infusion proved to be manageable and reliable. An accurate prediction of good outcome is obtained when the Rcsf threshold for shunting is raised to 18 mm Hg/ml/min. Comorbidity was an important prognostic factor.

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Correspondence: J. Th. J. Tans, Department of Neurology, Westeinde Hospital, Post Box 432, 2501 CK, The Hague, The Netherlands.

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Hydrodynamic Properties of Hydrocephalus Shunts

Z. Czosnyka, M. Czosnyka, H. Richards, and **J. D. Pickard**

U.K. Shunt Evaluation Laboratory and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Summary

Hydrodynamic properties of hydrocephalus shunts are not always properly characterized by the manufacturer. Therefore, the choice of the shunt should be made, by matching performance of the shunt to the disturbed profile of CSF circulation of a given patient. The aim of the present shunt evaluation study is to evaluates all types of shunts presently in use in the U.K. and make this information available to neurosurgeons. Ten most common models of valves have been tested to date: Medtronik PS Medical: Delta Valve, Flow Control Valves and Lumbo-Peritoneal Shunt, Heyer-Schulte: In-line, Low Profile and Pudenz Flushing Valve, Codman: Medos-Programmable, Hakim-Precision, Sophy Programmable Valve, Cordis Orbis-Sigma. Our results show the majority of valves have low hydrodynamic resistance (exception: PS Lumboperitoneal, Orbis-Sigma), which increase by 100–200% after connection of a long distal catheter. A few shunts with siphon-preventing mechanism (Delta, Hayer-Schulte Low Profile, Pudenz-Flushing) offer reasonable resistance to negative outlet pressures, however, these valves may be blocked by raised subcutaneous pressure. All programmable valves are susceptible to siphoning. Programmed settings may be changed by external magnetic field.

Keywords: Hydrocephalus.

Introduction

Complications related to shunt functioning may be very heterogeneous in nature [4]. It is estimated that 50% of complications are directly or indirectly caused by shunts' inadequate hydrodynamic performance. Further, technical data provided by the manufacturer are frequently fragmentary and misleading. Moreover, various shunt evaluation programs [1–4] revealed that some of the shunts may fail to work according to the manufacturer's specification.

The aim of the UK Shunt Evaluation Laboratory (funded by the Medical Devices Agency, an Executive Agency of the Department of Health) is to assess the shunt's hydrodynamic properties independently of the manufacturer, to evaluate whether the shunt works according to the manufacturer's technical data and whether to determine the shunt complies with the new international standard (ISO/DIS 7197). Finally, our data are intended to help neurosurgeons to correlate the type of shunt to the specific presentation of the patient (clinical, pressure-volume compensation, CT, MRI, psychometric, etc.). Ten types of shunts (at least 3 samples from each type) have been studied to date, using a fixed protocol which including 2–3 months of rigorous, computer controlled tests. The results, are of immediate relevance to the neurosurgeon.

Material and Methods

Ten models of shunts were tested (see Table 1) according to a protocol based on ISO/DIS 7197 standard. Three identical, computer controlled rigs (described in details in [3]) working independently of each other. As are tested simultaneously time. The protocol for shunt testing includes long-term evaluation of three shunts of the same performance level for a minimum of 28 days. During this period the shunt's pressure-flow performance and hydrodynamic resistance are evaluated. The effects of siphoning, external pressure, differential pressure, pulsation, presence of residual resistance to CSF outflow, temperature and presence of graded particles in reagent are tested. Further optional tests may be performed (4–5 weeks) to compare how different performance levels of shunt affect the measured hydrodynamic parameters.

Results

The summary of the performance parameters including hydrodynamic resistance, mean intracranial pres-

Table 1. *Summary of Most Important Parameters of the Tested Shunts*

	PS Medical CSF-Flow Control	Heyer-Schulte In-line	PS Medical Lumboperitoneal	Codman-Hakim Precision	PS Medical Delta Valve	Heyer-Schulte Low Profile	Heyer-Schulte Pudenz Flushing	Codman Medos Programmable	Sophysa Programmable	Cordis Orbis-Sigma
Programming	no	no	no	no	no	no	no	yes	yes	no
Number of performance levels	4 (low-low only in Button Valve	3	1	5	2 (3: valve of performance 1.5 is now available)	3	3	18	3 (8 intermedia te steps in valve SU8)	1
Resistance without distal catheter (in mm Hg/(ml/min))	1.5 (0.5)	7.5 (1.3)	25 (6.2)	1.4 (0.5)	1.9 (0.2)	2.9 (1.2)	1.7 (0.3)	1.4 (0.34)	2.8 (0.9)	Very high
Resistance with distal catheter	3.1 (1.1)	9.3 (1.7)	NA	5.1 (1.1)	3.8 (0.5)	5.6 (2.1)	5.2 (2.1)	5.1 (0.83)	5.6 (2.1)	Very high
Expected average ICP in horizontal body position (for different performance levels[1]; in mm Hg)	1.2 (l-l) 3.5 (l) 7.2 (m) 10.5 (h)	4 (l) 10.4 (m) 19 (h)	28	0.5 (v-l) 3.1 (l) 5.2 (m-l) 7.1 (m-h) 10 (h)	2 (level 1) 6 (level 2)	3.5 (m) 9.1 (l) 12.4 (h)	3.9 (m) 8.7 (l) 12 (h)	from 3 to 22 (programmable)	from 6 to 15 (programmable)	from 7 to 25 (variable)
Expected average ICP in vertical body position (30 cm siphoning; for different performance levels[1]; in mm Hg)	NA (l-l) −20 (l) −15 (m) −13 (h)	−19 (l) −13 (m) −5 (h)	around 0	−22 (v-l) −19 (l) −17 (m-l) −15 (m-h) −13 (h)	around 0	around 0 (for shunt with ASD) Without ASD: −19.5 (l) −13.9 (m) −10.6 (h)	around 0 (for shunt with ASD) Without ASD: −19.1 (l) −14.3 (m) −11 (h)	form −20 to −1 (programmable)	from −17 to −8 (programmable)	from −15 to 2 (variable)

Performance levels. *m* medium, *l* low, *h* high, *v-l* very low, *m-l* medium low, *m-h* medium high, *l-l* low-low.

sure simulated in the horizontal and vertical positions are presented in Table 1. Pressure-flow performance curves are presented in Fig. 1. Short characterization of performance of all tested valves is listed below:

Medtronic PS Medical CSF-Flow Control Valve

The CSF-Flow Control Shunts are classicly differential valves, which intend to stabilize intraventricular pressure after implantation. The valve allows the drainage rate to increase when the body position is upright, thus, drainage rate may become very high as this shunt has low hydrodynamic resistance. In patients likely to develop clinical complications related to overdrainage, implantation of Delta Valve instead of CSF-Flow Control Valve should be considered. The closing pressure is defined as a range (4–5 mm Hg wide) rather than the strict value and my fluctuate in time.

Heyer-Schulte In-line Valve

The operating pressure is specified as a range rather than a definite value, which may range between 5.3–8.5 mm Hg for Medium Pressure Values. The valves, particularly Medium and High Pressure have high hydrodynamic resistance. This may be contradictory for application in patients presenting with high vasomotor-induced fluctuations of intracranial pressure. The high hydrodynamic resistance may limit an overdrainage in upright position. This shunt is potentially safer from this point of view than other differential-pressure valves. However, overdrainage is still possible, particularly in patients presenting with gross ventricular dilatation.

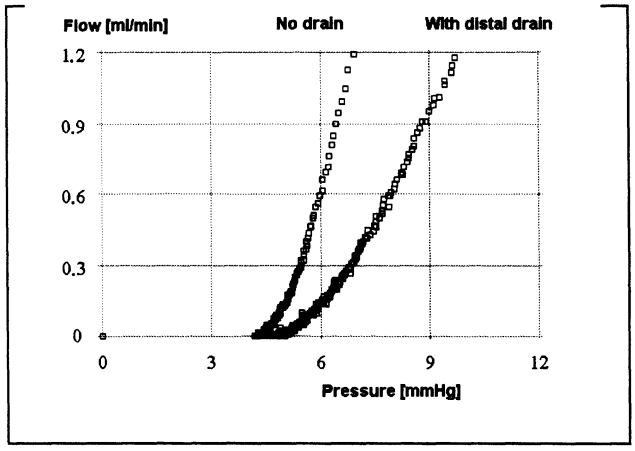
Medtronic PS Medical Lumboperitoneal Shunt

The shunt has a high resistance and a high opening pressure. This helps to maintain a physiological level of CSF drainage in the vertical position, but may lead to underdrainage in the horizontal position. Therefore, the shunt will drain insufficient CSF when patients are bed bound for long periods. The shunt increases both its opening pressure and its resistance with time (leading to possible underdrainage). Resistance to drainage of CSF may increase when the shunt is blocked by particles of a diameter greater than 25 microns. Once the shunt is blocked, there is little facility for external flushing to clean the shunt of debris. Therefore the shunt can be regarded as a temporary measure, able to drain CSF, over a limited period.

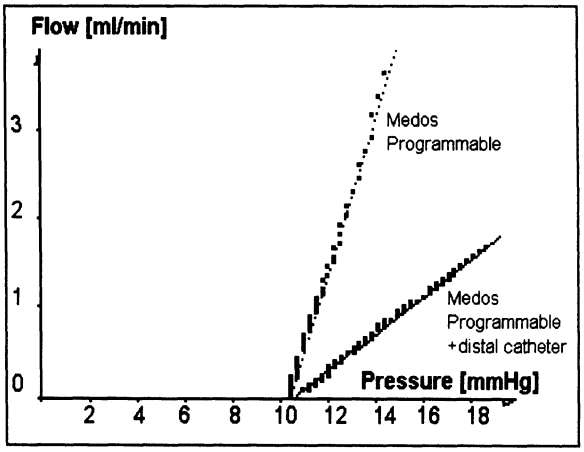
Codman Hakim-Precision Valve

This device is a classic differential valve, intended to stabilize intraventricular pressure after implantation. Five fixed performance levels offer flexibility in the treatment of hydrocephalus of various types. The valve shares some design features developed for the Codman-Medos Programmable Valve. The valve, having low hydrodynamic resistance, allows the drainage rate to increase when the body position is upright. In patients likely to develop clinical

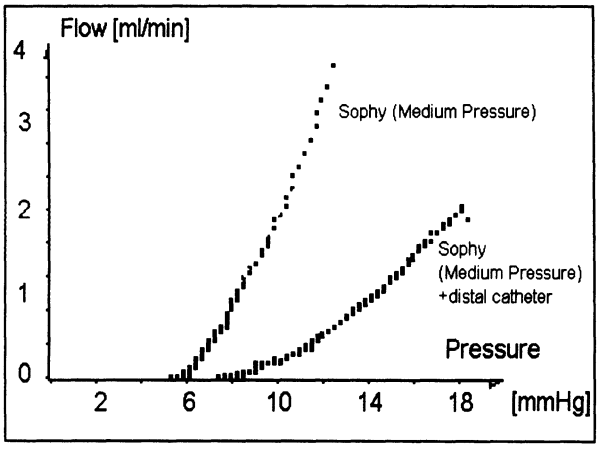
Heyer-Schulte Pudenz Flushing Valve



Codman-Medos Programmable Valve



Sophy Programmable Pressure Valve



Orbis-Sigma Valve

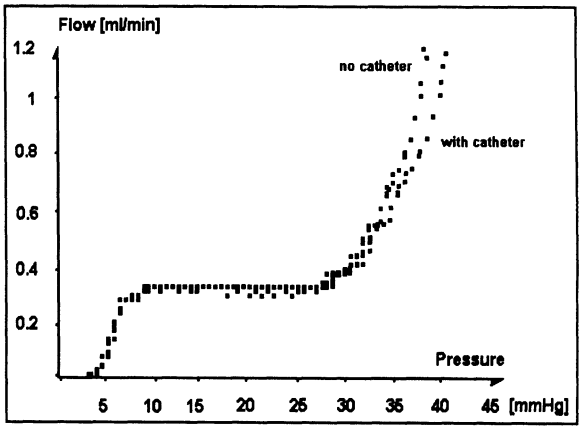
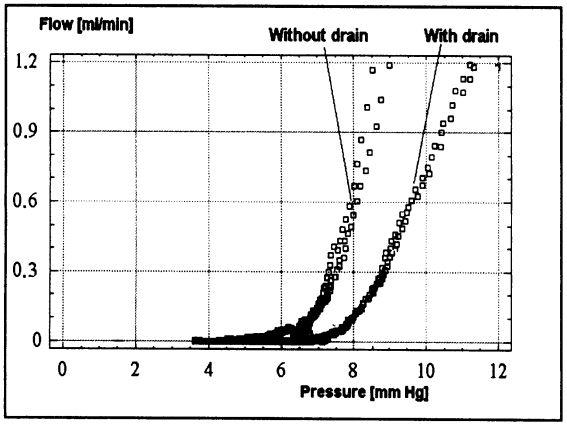
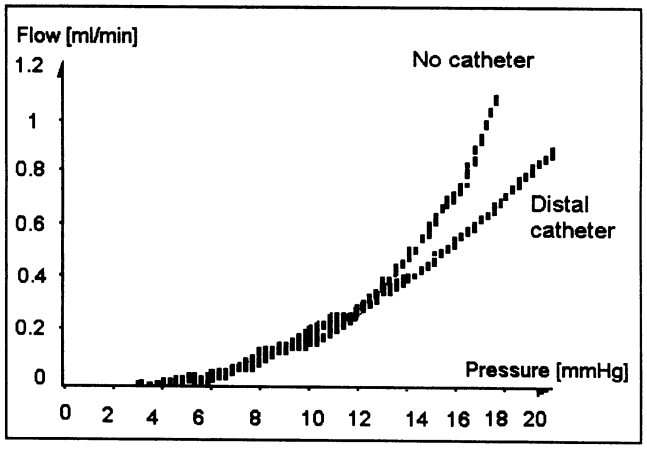


Fig. 1. Pressure-flow performance curves for shunts with and without distal drain. X-axis- pressure in mm Hg. Y-axis: flow in ml/min

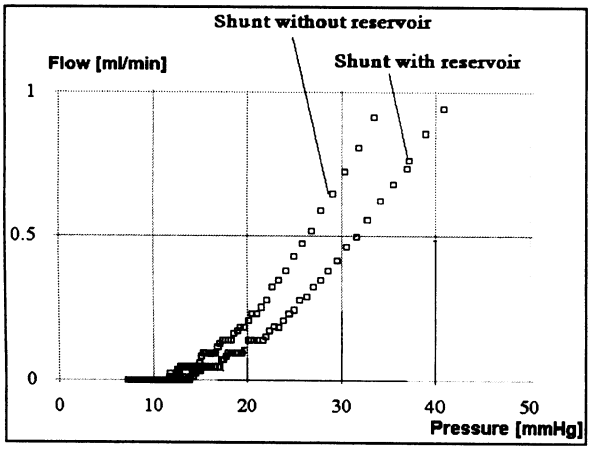
Medtronic PS Medical CSF Flow Control



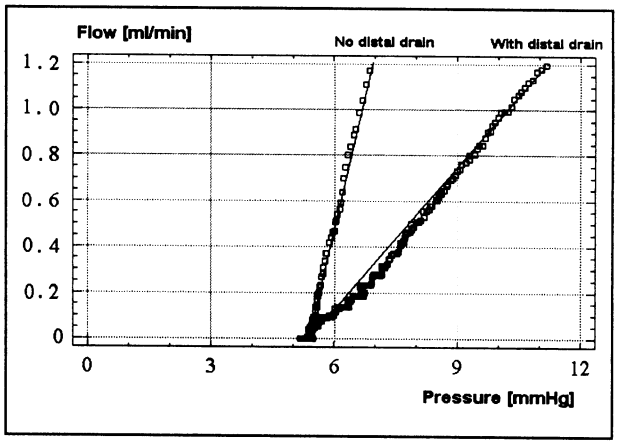
Hayer-Schulte In-Line Valve



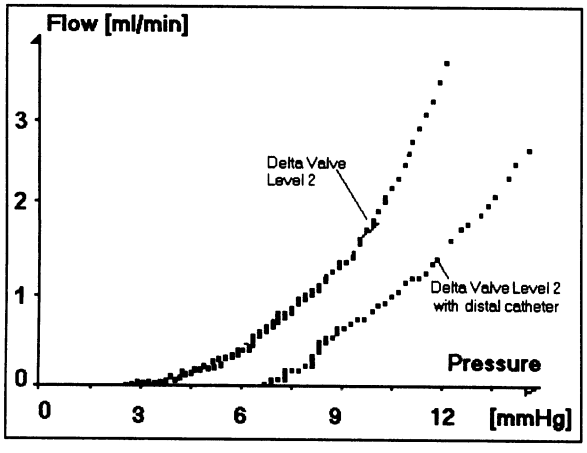
Medtronic PS Medical Lumboperitoneal Shunt



Codman Hakim-Precision Valve



Medtronic PS Medical Delta Valve



Heyer-Schulte Low Profile Valve with ASD

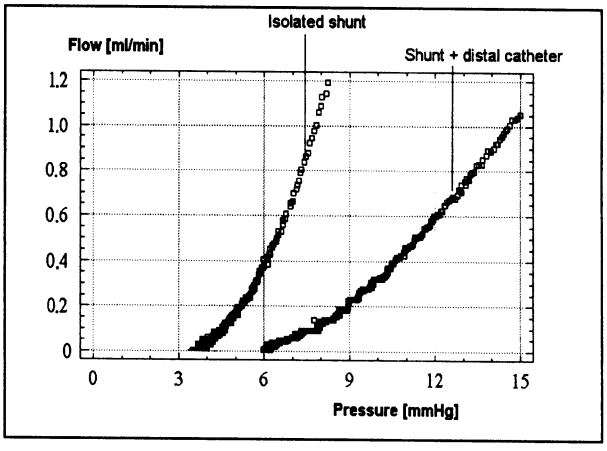


Fig. 1 (continued)

complications related to overdrainage, implantation of an anti-siphon device should be considered.

Medtronik PS Medical Delta Valve

This shunt incorporates a Siphon Control Device (SCD) preventing CSF overdrainage in vertical body position. The SCD has been designed to minimize the effect of tissue fibrosis while remaining sensitive to changes in atmospheric pressure. External pressure may affect the performance of the SCD component. The SCD may stop all CSF drainage unless the patient is supine. Similar to the CSF Flow Control Valve the closing pressure may fluctuate to values lower than specified, particularly when the valve is tested without distal drain.

Heyer-Schulte Low Profile Valve (with Anti-Siphon Device)

The Heyer-Schulte Low Profile Valve with Anti-Siphon Device is a classic differential valve incorporating a mechanism preventing overdrainage related to posture. Three fixed performance levels offer flexibility in the treatment of hydrocephalus of various types. Differences between hydrodynamic properties of Heyer-Schulte Low Profile Valve with the Anti-Siphon Device and PS Medical Delta Valve are practically negligible. The shunt may be blocked by raised subcutaneous pressure. It probably works predominantly in horizontal body position, as the physiological value of intracranial pressure in vertical body position is negative.

Heyer-Schulte Pudenz-Flushing Valve with ASD

The Heyer-Schulte Pudenz Flushing Valve is a classic differential burr-hole valve optionally incorporating a mechanism preventing posture-related overdrainage, the same as used in the Low Profile Valve. The shunt is available in three fixed performance levels. Hydrodynamic properties are the same as in Heyer-Schulte Low Profile Valve.

Codman-Medos Programmable Valve

This shunt can be programmed in 18 precise steps from 3 to 20 cmH_2O. The flow through the valve is sensitive to negative hydrostatic outlet pressures. This may cause overdrainage, particularly in the ventriculo-peritoneal arrangement. The valve setting should be adjusted in small steps (max. 4 cmH_2O). An isolated valve exhibits extremely low resistance to fluid flow. Therefore, its function should be considered not in isolation but in combination with the distal catheter, peritoneal or atrial, with careful thought given to any shortening of the catheter. When necessary, implantation of a siphon-preventing device in-line with the valve may be considered. The shunt may be accidentally re-programmed by strong dynamic magnetic field.

Sophy Programmable Pressure Valve

The shunt can be programmed in 3 precise steps. Precision of 5 intermediate steps is lower (available only in model SU8). Air bubbles, as in almost all contemporary valves, may disturb fluid drainage. They can be removed by gentle pumping of proximal reservoir. The Sophy valve, unlike valves with an elastic chamber, is a little more difficult to free of air bubbles. The flow through the valve is sensitive to a posture-related negative hydrostatic outlet pressure. This may cause acceleration of CSF drainage, particularly in the ventriculo-peritoneal mode. Similarly to the Codman-Medos valve an isolated valve offers an extremely low resistance to fluid flow. The shunt may be accidentally re-programmed by magnetic field.

Cordis Orbis-Sigma Valve

Pressure-flow curve indicates the shunt's ability to stabilize the drainage rate. The intracranial pressure (ICP) after shunt implantation may be as high as 24 mmHg or may fluctuate. High ICP does not indicate shunt malfunction, as the shunt stabilizes drainage not pressure. The valves have very high hydrodynamic resistance. This may contradict its application in patients presenting with high vasomotor-induced fluctuations of ICP. The high hydrodynamic resistance decreases the rate of drainage in upright body position. Therefore, the shunt is potentially safer from the point of view of complications related to overdrainage than other classic-differential constructions.

Discussion

The majority of tested valves had a non-physiologically low hydrodynamic resistance (with the exception of Orbis-Sigma, PS Lumbo-Peritoneal and

Heyer-Schulte In-Line). This may result in overdrainage both related to posture and during nocturnal cerebral vasogenic waves. A long distal catheter increases the resistance of these valves by 100–200%. A few shunts (Delta, LowProfile and Pudenz-Flushing with Anti-Siphon Devices) offer a reasonable resistance to a negative outlet pressure, hence may potentially prevent complications related to overdrainage. Drainage through valves without siphon-preventing mechanism is sensitive to body posture. This may produce grossly negative intracranial pressure after implantation. In most of silicone-diaphragm valves closing pressure varied and reached values lower than specified by the manufacturer (exception: Heyer-Schulte Pudenz Flushing Valve). Valves with an siphon-preventing device may be blocked by raised subcutaneous pressure. All programmable valves are susceptible to overdrainage in the upright body position. Programmed settings may be changed by external magnetic fields. Most shunts are very sensitive to the presence of small particles in drained fluid. In conclusion, this study show the behaviour of a valve, is of immediate relevance to the surgeon and may not be adequately described in the manufacturer's product information.

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Correspondence: Zofia Czosnyka, M.D., Academic Neurosurgical Unit, P.O. Box 167, Addenbrooke's Hospital, Cambridge CB2 2QQ, U.K.

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Cine Phase-Contrast MR Imaging in Normal Pressure Hydrocephalus Patients: Relation to Surgical Outcome

S. M. Egeler-Peerdeman[1], **F. Barkhof**[2], **R. Walchenbach**[1,3], and **J. Valk**[2]

Departments of [1] Neurosurgery and [2] Radiology, University Hospital Vrije Universiteit, Amsterdam, and [3] Department of Neurosurgery, University Hospital, Leiden, The Netherlands

Summary

Phase-contrast cine MR flow imaging through the aqueduct was used to establish the diagnosis of normal pressure hydrocephalus (NPH), and to predict outcome after shunting. From 1990–1994 16 patients, who were participants in the Dutch Normal Pressure Hydrocephalus Study [3], were studied. The patients included in this study met clinical and CT-scan criteria as described in this study, underwent cine phase-contrast MR imaging prior to placement of a CSF shunt, and had a follow-up 12 months after the operation. Claustrophobic patients, patients with a pacemaker or extremely agitated patients were excluded. Normal Flux was calculated in each patient, as the average difference in caudal and rostral flux (F_{diff}) + 2 times standard deviation (0.97 cc/sec) [2]. The clinical outcome was measured with a modified scale of activities of daily living (ADL) as described by Rankin. Of the 16 patients, 8 could not be evaluated due to restlessness during MR measurements, disabling cerebral vascular accidents or death before the end of the follow-up period. Of the remaining 8 patients, 5 had a normal flux, of which only one improved. Two patients had a F_{diff} twice the normal range, which improved in both patients. One patient had no measurable flux, consistent with an aqueduct stenosis; he too improved. Overall, there was a concordance of MR findings with final outcome after shunting in 7 out of 8 patients. This pilot study, therefore, supports the need to futher evaluate flow with MR imaging techniques to select patients with shunt responsive NPH.

Keywords: Cine phase-contrast; normal pressure hydrocephalus; shunt responsive NPH; surgical outcome.

Introduction

Normal pressure hydrocephalus (NPH) is a disorder characterized by a triad of clinical symptoms which include gait disturbance, mental deterioration and urinary incontinence [1], in combination with communicating hydrocephalus as seen with computed tomography (CT)-scan. Prediction of the possible improvement of the symptoms by a shunting procedure is difficult. Patients with a known cause of the disease (e.g. previous subarachnoid hemorrhage or infection) respond better than the idiopatic cases. Since the incidence of shunt responsive NPH is low, and the benefit-harm ratio is low [6], there is a need for a paraclinical predictor. Magnetic resonance (MR) imaging of NPH patients shows ventricular enlargement without cortical atrophy. It has been suggested that patients with an increased flow-void in the aqueduct respond more favorably to shunting than those who do not (4). The presence of a flow-void phenomenon in the aqueduct is a qualitative measure, which is influenced by many acquisition parameters, and often may be difficult to quantify. Phase-contrast cine MR flow imaging provides a simple way to better characterize CSF flow. Quantative measurements can be obtained non-invasively with high spatial and temporal resolution. Normal values of CSF flow in the aqueduct have been described with this method [2]. Previously increased values have been associated with NPH [5].

The aim of this study was to determine the plausability of using phase-contrast cine MR flow imaging through the aqueduct as a method to establish the diagnosis of NPH and to predict outcome after shunting.

Materials and Methods

Between 1990 and 1994 a total of 16 patients from our hospital participated in the Dutch Normal Pressure Hydrocephalus Study. All patients were included based on clinical and CT-scan criteria according to this study protocol [3]. They were assesed by a gait scale, a dementia scale and the modified mini mental state examination. The modified Rankin scale (MRS) was used as a handicap score to determine general outcome. It was extended to a seven point scale by inserting a grade 4, defined as moderate disability and needing assistance for less than 50% of the day. A communicating hydrocephalus as seen with a CT-scan was also one of the

inclusion criteria. All 16 patients underwent cine phase-contrast MR imaging before placement of a CSF shunt. Claustrophobic patients, patients with a pacemaker or extremely agitated patients were excluded from this study.

The follow-up period was 12 months. The primary clinical outcome was the modified Rankin scale as a score to determine general outcome. An improvement of one point on the scale was considered to be a favourable outcome.

Phase contrast MR imaging was performed at 0.6T in an oblique plane perpendicular to the aqueduct at the level of the inferior colliculus. A cardiac-gated gradient-echo technique was used [TR 52/TE 32/NEX 2/FA 45] with an inplane resolution of 1 mm and a slice thickness of 5 mm. Maximum velocity encoding was set at 20 cm/sec. According to the heart rate, 9–16 images were obtained throughout the heartcycle. The volume displacement per slice, called flux, was measured by multiplying the average velocity within the aqueduct with its area (cc/sec). The difference between the maximal rostral and caudal flux (F_{diff}) was used as the outcome variable. Normal flux, measured in a previous study [2] was determined to be within the mean F_{diff} and 2 standard deviations (=0,45 + {2 × 0,27}) or 0,97 cc/sec. Any flux higher than this value was considered abnormally elevated; absence of flow was also considered abnormal.

Results

Of the 16 patients, 2 could not be assesed due to restlessness during the flow measurements. Four patients died of non-shunt related problems before the end of the follow up period. Two further patients had a severely disabling cerebral vascular accident during the follow-up period. Of the remaining 8 evaluable patients, 5 had a normal F_{diff}. Of these 5, only 1 improved. One patient had no measurable flux through the aqueduct, consistent with aqueductal stenosis; this patient too markedly improved. Two patients had a F_{diff} of more than twice the normal range; both of them improved (Fig. 1).

Overall, MR imaging was in concordance with the general outcome in 88% of cases (Table 1).

Table 1. *MR Imaging Findings Related to Outcome*

	MR flux normal	MR flux abnormal
Modified Rankin scale not improved	4	0
Modified Rankin scale improved	1	3

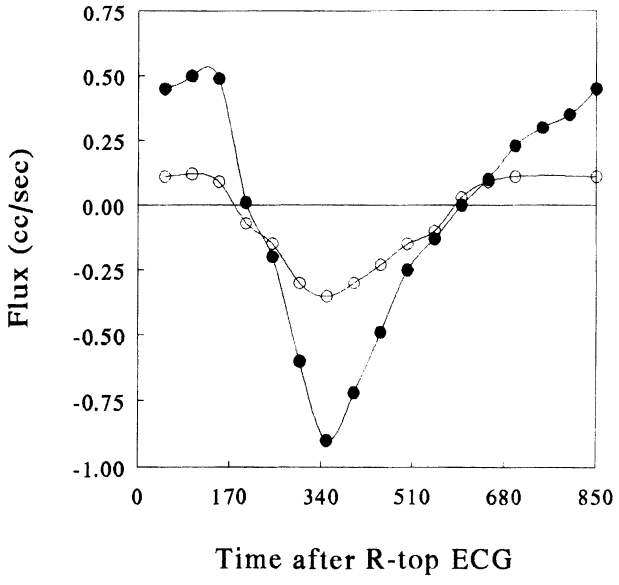

Fig. 1. Aqueductal flow patterns. ○ Control, • NPH

Discussion

This study again demonstrates the fact that improvement of outcome after shunting is not very frequent [6], and that better diagnostic criteria are imperative.

These patients all were included on well defined clinical and CT-scan criteria. Although previously described differently [5], in these NPH patients a group with a normal flow pattern and a group with an abnormal flow pattern could be distuingished. In 4 clinical responders, MR showed abnormally increased flow in 2, while in 1 an abnormal low flow was detected. In the latter patient the clinical symptoms were caused by aqueductal stenosis [6]. In the 4 non-responders, MR showed normal flow in all, confirming earlier MR observations that the absence of increased aqueductal flow markedly reduces the chances of a favourable outcome [4]. Although the group is small (only eight patients finally could be evaluated), the results indicate that the MR flow imaging and final outcome are concordant in 7 out of 8 cases.

This pilot study suggests that patients with an abnormal flux through the aqueduct on cine phase-contrast MR imaging are more likely to benefit from a shunting procedure than those with a normal MR flow pattern.

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Correspondence: S. M. Egeler-Peerdeman, M.D., Department of Neurosurgery, University Hospital Vrije Universiteit, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.

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Cine MR CSF Flow Study in Hydrocephalus: What are the Valuable Parameters?

M.-H. Kim, K.-M. Shin, and **J.-H. Song**

Department of Neurosurgery, Ewha Womans University College of Medicine, Seoul, South Korea

Summary

To evaluate the changes of intracranial cerebrospinal fluid (CSF) dynamics in hydrocephalus, we studied the various parameters of cine phase contrast (PC) magnetic resonance (MR) CSF flow images in cases of acutely progressive hydrocephalus, comparing them with those in normal CSF circulation.

The MR images were obtained with 1.5 T unit using the 2 dimensional cine PC sequence with cardiac gating in 10 non-obstructive hydrocephalus (NOH), 3 obstructive hydrocephalus (OH), and 10 controls. The temporal velocity information from the anterior and posterior cervical pericord spaces, third and fourth ventricles, and aqueduct were plotted as wave form. The wave forms were analyzed for configurations, amplitude parameters (Smax, Smin, Sdif), and temporal parameters (R-S, R-SMV, R-D, R-DMV). The statistical significance of each parameter was examined with paired t-test. All patients with OH underwent endoscopic thrid ventriculostomy, whereas all NOH underwent shunting procedures.

In 5 ROIs, distinct reproducible configuration features were obtained at aqueductal and cervical pericord spaces. Statistically significant differences between control and hydrocephalus only in temporal parameters were determined. In NOH, the graph showed R-DMV shortening ($p < 0.01$) at anterior cervical pericord space. In OH, there were R-DMV shortening ($p < 0.05$) at anterior cervical pericord space, R-SMV shortening ($p < 0.02$) at posterior cervical pericord space. Also the level of obstructions could be determined in all OHs.

The analysis of MR CSF flow images may give us valuable information on the site of obstruction, explaining the cause of hydrocephalus, thus deciding the necessity of shunting procedures using in vivo images.

Keywords: Cine MR CSF flow; hydrocephalus; phase contrast.

Introduction

Evaluation of CSF flow was accomplished by the use of cardiac gated gradient echo MR technique [3,7,8,12,13]. The qualitative cine MR allows a rapid and dramatic evaluation of both normal and abnormal patients in a visual form. Quantitative evaluation via phase reconstruction permits a more precise mapping of the flow patterns and is more sensitive in detecting fluid motion and allows calculation of CSF velocity [12]. Our investigation was undertaken to characterize and quantify CSF flow at key locations in the neuraxis of normal and abnormal situations by means of PC cine MR.

Methods

We studied 10 patients (mean 47.6 years) with NOH, and 3 patients (mean 35.3 years) with OH. All NOHs underwent shunting procedures, and all OHs underwent endoscopic third ventriculostomy. All patients fulfilled the following criteria: a history of progressive dementia, gait disturbance, and/or urinary incontinence; hydrocephalus on CT and MRI (Table 1). Mean Evans index was about 0.32 in NOH and 0.40 in OH. We also examined 10 healthy volunteers (mean 30.4 years): 6 men and 4 women, none of whom had any history of neurological disease; none was taking medication, and all had a normal brain MRI.

Using a 1.5 (GE Signa, GE Medical Systems, Milwaukee, USA) super-conducting magnet, head and spine cine images were obtained in the mid-sagittal and axial plane. All the CSF flow studies were cardiac gated and a reduced flip angle (15 degrees) gradient echo technique, with a TR determined by the patient's R-to-R interval, and a TE of 15 ms, and a section thickness of 5 mm were used. Multiple images in the same plane were obtained during each R-to-R interval. Intracranially, we examined primarily the aqueduct of Sylvius, the third ventricle, fourth ventricle, dorsal and ventral pericord spaces. The analysis of PC images alone was not sufficient to assess the subtle physiologic details of the CSF flow. Further precision was obtained by plotting the temporal velocity information from the images as a waveform. The following velocity and temporal parameters were also evaluated [13]: maximum systolic signal intensity (Smax), maximum diastolic signal intensity (Smin), difference between Smax and Smin (Sdif), R-wave to onset of CSF systole (R-S), R-wave to Smax (R-MSV), R-wave to onset of CSF diastole (R-D), and R-wave to Smin (R-MDV) (Fig. 1). The results of volunteers and patients were compared by the paired *t* test or Mann Whitney rank-sum test.

Table 1. *Clinical Summary of Obstructive and Non-Obstructive Hydrocephalus*

Case	Sex	Age	Diagnosis	Etiology	Evans index	Operation	GOS
1	M	10	NOH	meningitis	0.32	VP shunting	V
2	M	20	NOH	meningitis	0.34	VP shunting	III
3	M	32	NOH	meningitis	0.39	VP shunting	V
4	M	35	NOH	hemorrhage	0.3	VP shunting	V
5	M	60	NOH	hemorrhage	0.29	VP shunting	V
6	M	67	NOH	unknown	0.29	VP shunting	V
7	M	70	NOH	hemorrhage	0.3	VP shunting	V
8	F	50	NOH	hemorrhage	0.29	VP shunting	V
9	F	61	NOH	hemorrhage	0.31	VP shunting	V
10	F	71	NOH	unknown	0.32	VP shunting	V
11	M	1	OH	congenital	0.52	3rd ventriculostomy	V
12	M	45	OH	cbll tumor	0.34	3rd ventriculostomy	V
13	M	60	OH	cbll tumor	0.35	3rd ventriculostomy	V

GOS Glasgow outcome scale (*I* dead, *II* vegetative, *III* severely disabled, *IV* moderately disabled, *V* normal); *M* male; *F* female; *NOH* non-obstructive hydrocephalus; *OH* obstructive hydrocephalus; *cbll* cerebellum; *VP shunting* ventriculo-peritoneal shunting 3.

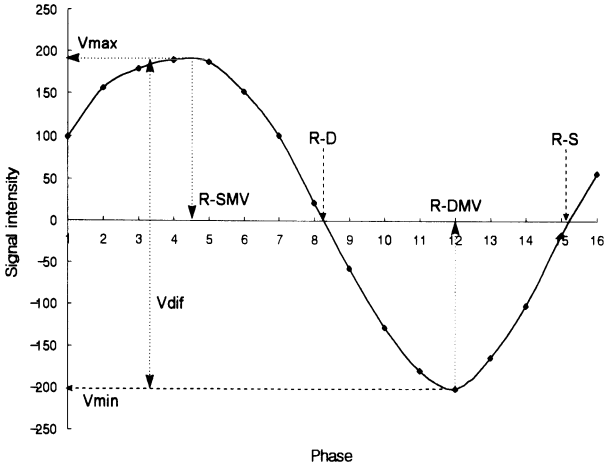

Fig. 1. The graph showing CSF flow wave and the meaning of various parameters. *Smax* maximum systolic signal intensity (velocity); *Smin* minimum diasolic signal intensity; *Sdif* difference of Smax-Smin; *R-S* R wave to onset of CSF systole; *R-MSV* R wave to maximum systolic signal intensity; *R-D* R wave to onset of CSF diastole; *R-MDV* R wave to minimum diastolic signal intensity

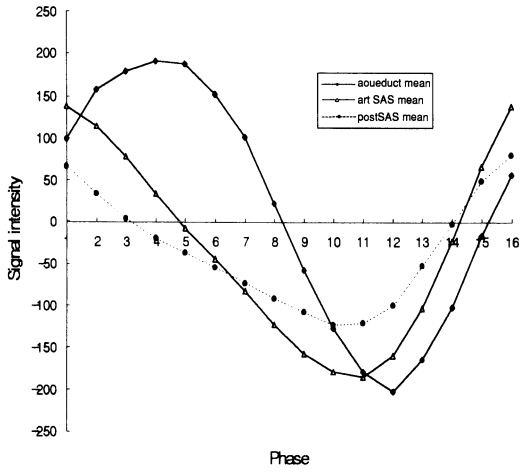

Fig. 2. The mean CSF flow wave showing different phase shift at various ROI in normal persons. The CSF flow wave of pericord spaces procede that of aqueduct. (ant SAS or post SAS, anterior or poterior cervical subarachnoid space)

Results

Normal CSF Flow

R-SMV occurred at 25.2% through the cardiac cycle, whereas R-DMV occurred at 74.4% through the cardiac cycle (Fig. 2) at aqueduct. Flow was reversed simultaneously in the aqueduct at 56% through the cycle. Mean Smax and Smin were nearly equivalent: 204 (SD = 124) and 212 (SD = 131), respectively. The third and fourth ventricle represented mixing chambers. The CSF pulsation dynamics in cervical location showed well-defined systolic and diastolic components. R-SMV occurred at 3% (SD = 3.1%) through the cardiac cycle, and R-DMV occurred at 66.5% (SD = 5.2%) through the cardiac cycle. Mean Smax in the anterolateral recess was 145.1 (SD = 53.3), while Smin was 187.7 (SD = 60.8). Considerable variation of the amplitude parameters (Smax, Smin) were seen with a wide range between maximal and minimal values. R-S in the postcord space was either simultaneous with or earlier than in the precord CSF space (1.4%). R-D in the postcord space was earlier than in the precord space ($p < 0.005$). R-S and R-D in pericord spaces was always earlier than in the aqueduct ($p < 0.05$, $p < 0.0001$,

respectively) (Fig. 2). The temporal parameters were valuable at the level of aqueduct and pericord spaces which showed relatively constant flow, as and compared to normal vs patients.

Alterations of Intracranial CSF Flow

Non-Obstructive Hydrocephalus (NOH)

No remarkable differences were seen between normals and NOH with either qualitative analysis or wave configuration analysis. Considerable variation of the amplitude parameter was seen with a wide range in both normals and patients. As for the analysis of temporal parameters, only R-DMV was significantly different between normals and patients in the ventral pericord space ($p < 0.01$).

Obstructive Hydrocephalus (OH)

The level of obstruction was visible with qualitative measures. In one case, wave configuration was typically reversed like a mirror image. There was no significant difference in amplitude parameters. The temporal parameters, R-DMV in ventral pericord space and R-SMV in dorsal pericord space ($p < 0.02$), were significantly different ($p < 0.05$, $p < 0.02$ respectively) (Tabe 2).

Discussion

The CSF flow waveforms, representing flow within a small region of interest, have distinct configuration and temporal patterns. Flow waveform analysis appears to be reliable, reproducible, and sensitive [13]. It is important for studies of CSF production and flow to take into account the circadian variation in CSF production, which is minimal around noon and reaches a maximum just after midnight [9]. The measurements in the present study were all performed during the afternoon. Large variations in normal velocities should be expected in all CSF spaces. The probable reasons for these normal variations are multiple but relate most likely to the size of nearby vasculature, the compliance of surrounding brain/spinal cord tissue, the anatomy of the CSF containing spaces, the volume and vascularity of the choroid plexus, and the systemic hemodynamics [12]. The distensibility of the venous structures also play a role in the pulse wave effects as Du Boulay has pointed out [5,6]. Velocity measurements in the basal cisterns and upper cervical subarachnoid space are more reliable than the velocity measurements obtained from smaller space such as aqueduct of Sylvius [12].

Many authors showed the peak caudal and rostral flow in the aqueduct to be significantly increased in NOH, compared to healthy volunteers. This has been

Table 2. *Summary of Variable Parameters and Statistical Significance*

	Amplitude parameter			Temporal parameter			
	Smax	Smin	Sdif	R-SMV	R-D	R-DMV	R-S
Aqueduct							
normal	53.2	−70.7	124.9	0.25	0.51	0.74	0.95
NOH	43.9	−56.5	100.4	0.26	0.54	0.77	0.96
OH	60.2	−66.3	126.5	0.08	0.34	0.66	0.86
ant. pericord							
normal	50.4	−46.6	97	0.03	0.31	0.67	0.9
NOH	45.7	−57.8	103.5	0.01	0.24	0.49[a]	0.76
OH	54.6	−42.1	96.7	0.04	0.2	0.6[a]	0.88
post. pericord							
normal	47.7	−49.8	97.5	0.04	0.21	0.62	0.88
NOH	35.5	−44	95.8	0.07	0.29	0.81	0.87
OH	52	−46.2	96.4	0.04	0.19	0.56[a]	0.91

NOH non-obstructive hydrocephalus; *OH* obstructive hydrocephalus; *ant.* or *post. pericord* anterior or posterior cervical pericord space; *Smax* maximal systolic signal intensity (velocity); *Smin* minimal diastolic signal intensity; *Sdif* difference of Smax − Smin; *R-SMV* R-wave to maximum systolic signal intensity; *R-D* R-wave to the onset of caudocranial flow; *R-S* R-wave to the onset of craniocaudal flow; *R-DMV* R-wave to minimum diastolic signal intensity.
[a] Statistically significant values ($p < 0.05$) by paired t-test.

suggested in previous studies using the flow void [2,4] and velocity-sensitive phase methods [1,10,12]. Nitz *et al.* [10] found a tendency towards higher flow velocities and volumetric flow rates in NPH. Bradley *et al.* [4] suggested that the finding of normal aqueduct CSF dynamics in patients suspected of having NPH probably indicates that they have central atrophy rather than NPH, and should not be shunted. Unfortunately, our results showed substantial variation of amplitude parameters in normals and patients, and could not give us valuable information relative to hydrocephalus. Similar observations have been previously documented [7,12]. We believe that temporal parameters of the flow waveforms may have clinical applications due to prior experiments which show changes in temporal parameters of CSF pressure waveforms with altered craniospinal dynamics [11,13]. In both NOH and OH, R-DMVs were significantly shortened ($p < 0.05$) in the anterior pericord space. Additionally, R-SMV was significantly shortened only in OH ($p < 0.01$). This means that there are considerable changes in configuration of flow-waves, especially in phase shifting. These may be explained by early diastolic recoil due to increased extraventricular CSF volume in NOH, by shortening of arterial input and reduced capacitance due to increased intracranial pressure.

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Correspondence: Myung-Hyun Kim, M.D., Ph.D., Department of Neurosurgery, Ewha Womans University College of Medicine, Mok-6-dong 911-1, Yangcheon-Ku, Seoul 158-710, South Korea.

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Cerebral Blood Flow in Chronic Hydrocephalus – A Parameter Indicating Shunt Failure – New Aspects

P. Klinge-Xhemajli, H. E. Heissler, J. Fischer[1], K. König, M. Zumkeller, and **E. Rickels**

Neurochirurgische Klinik, [1] Abteilung Nuklearmedizin, Medizinische Hochschule Hannover, Federal Republic of Germany

Summary

Prediction of outcome after shunt-therapy in chronic hydrocephalus syndrome is uncertain. Pathology reveals an impairment of cerebral blood flow (CBF). Based on this, we evaluated CBF and its significance for the assessment of prognosis.

In 21 patients (mean age 69 years) selected for surgery, CBF was measured by PET ($^{15}0$-H_20) before, about one week and 7 months (n = 14) after shunting. CBF was computed by a 1-compartmental model in the territories of the ACA, MCA and PCA. One PET slice in the height of the maximum projection of both cellae mediae was chosen. CBF data were standardized by cluster analysis.

Three CBFClusters with significantly different CBF levels prior to shunting in the ACA, MCA and PCA territory, respectively, referred to the sample average (38.2 ml/100 ml/min) were found. These CBFClusters differed in clinical outcome: almost 50% and 90% of patients improved clinically in CBFCluster I, with a perfusion level lower than average, after one week and 7 months, respectively. In contrast, patients of CBFCluster II with an average perfusion did not improve.

CBF changes 7 months after shunting related to global CBF before surgery showed a relationship with the clinical course. Clinical outcome corresponded with preoperative global CBF values. Cerebral blood flow lower than average forecasts clinical improvement. Our results suggest that measurement of CBF adds to the indication for surgery.

Keywords: Cerebal blood flow; chronic hydrocephalus; PET-methodology.

Introduction

Despite well-known symptomatology in the chronic hydrocephalus syndrome, outcome after surgery is unsatisfactory, especially in the idiopathic form. This complicates therapy in the individual in respect of the considerable risks of shunt surgery.

There are some clues for an impaired cerebral blood flow from pathologists [2,4] and also from clinicians [7], that the chronic hydrocephalus syndrome is frequently associated with cerebrovascular disease (CVD). As a consequence, it is questioned whether CBF measurement prior to and post surgery helps in selecting patients who are most likely to improve after surgery. Recent investigations by SPECT [1,10] and Xenon-CT [3] in chronic hydrocephalus syndrome showed a typical regional perturbation of CBF. In the present study CBF was computed by PET-methodology, a tool to get absolute CBF values [9].

Methods

21 patients (11 female and 10 male) with indication for shunt surgery were investigated based on symptomatology and imaging. In the equivocal cases, epidural ICP long-term measurement and CSF volume-pressure testing was carried out in 18 and ten patients, respectively. The ages ranged from 49 to 81 years (mean 69.8 years). History revealed no cause of hydrocephalus in 18 patients. In three cases, the chronic hydrocephalus syndrome was suspected to be secondary to a moderate head injury and surgery and radiation of a high-grade astrocytoma and exstirpation of a plexus-papilloma. Surgery was performed by ventriculoperitoneal shunting. Based on the results of the CSF-pressure testing, medium pressure valves (PUDENZ-SCHULTE®) or programmable valves (HAKIM-MEDOS®) were implanted in 15 and six patients, respectively. Symptomatology prior to surgery was graded according to the intensity of symptoms and the degree of the patient's functional impairment according to a modification of the classification of Stein and Langfitt [8]. The criterion of clinical outcome was classified in ordinal fashion by a four-point score. Clinical improvement and no clinical improvement or deterioration were considered if the horizontal sum of symptom scores resulted in ≥3 and <3, respectively. Cerebral blood flow was measured by PET (SIEMENS ECAT 951/31®) before and one week after surgery. PET studies were repeated seven months after shunting in 14 patients, 7 patients got lost from follow-up. PET offers quantitative CBF computation based on a 1-compartmental model approach using tracer activities (3.7 GBq $^{15}0$-H_20) in arterial blood and brain tissue. Tissue activity was measured dynamically over five minutes by parametric flow maps [9]. One representative PET-slice was selected that runs parallel with the orbitomeatal plane in the height of the maximum diameter of both cellae mediae. Cortical cerebral blood flow was assessed in regions of interest marking the territories of the ACA, MCA and PCA. Global

blood flow was calculated by averaging regional CBF of both hemispheres. Regional CBF prior to and short after surgery showed great deviations and gave the impression of a stratification. To objectify this, CBF data were analysed by WARD's minimum variance cluster analysis to find different groups of similar blood flow pattern, denoted as CBFClusters. For statistical analysis $p < 0.05$ was regarded as significant. The data are expressed as the means ± the standard deviation of the mean. If not otherwise noted units of CBF are ml/100 ml/min.

Results

Gait or motor disturbances were predominantly found in 15 patients. In only two patients a mental disorder was presenting. 13 patients had urinary incontinence. Concomitant CVD of a different degree could be verified in 13 patients by history (TIA, PRIND, stroke) and imaging (CCT, MRT). Ventricular dilation was moderate or marked in 10 and 11 patients, respectively. Areas of periventricular lucency were found in 13 CCT. In long-term measurements (at least 48 hours) ICP ranged from 4 to 27 mm Hg (mean 15 mm Hg). Volume pressure testing results revealed, showed median CSF resorption of 12 mm Hg/ml/min and a median pressure response to 8 ml NaCl of 22 mm Hg. Early after surgery eight of 21 patients improved clinically (38%). After a period of seven months nine of 14 patients (64%) had definitely improved.

Preoperative global blood flow ranged from 20.2 to 69.2 (mean 38.2). Cluster analysis revealed the presumed stratification. Its existence became evident when a three-cluster solution was chosen resulting in significantly different perfusion levels in the ACA, MCA and PCA territory. In the PCA territory highest perfusion levels could be observed; however, regional CBF differences within CBFClusters were negligible. Considering the global CBF, CBFCluster I, II and III revealed a perfusion level lower than (29.8 ± 6.2), close (42.3 ± 3.5) to and higher (63.3 ± 5.3) than sample average, respectively. These levels reached statistical significance. Changes in global CBF early after surgery could be regarded as negligible for CBFCluster I (+2.8 ± 6.8) and II (+3.9 ± 8.9), although both groups had a considerable increase and also decrease in overall perfusion in the individual case. CBFCluster III had a drop in CBF (−18.5 ± 12.8). In late CBF measurement overall perfusion tended to increase in patients of CBFCluster I (+4.4 ± 11.1), whereas CBF decreased in CBFCluster II (−4.6 ± 7.1) (Fig. 1). No statistical differences in age and intracranial pressure levels between CBFClusters were obvious prior to surgery. Ventricular dilatation was moderate in most patients of CBFCluster I, whereas in CBFCluster II marked ventricular enlargement was presented (Table 1). Grading of symptoms according to Stein and Langfitt

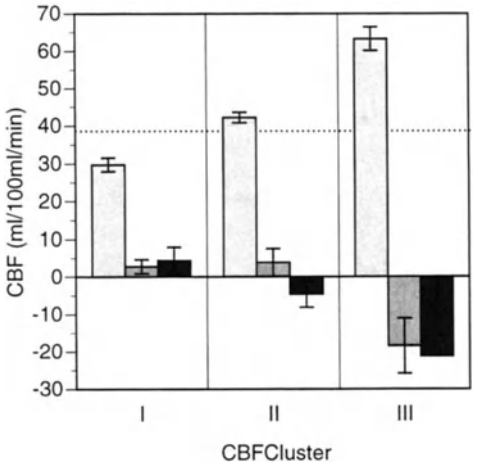

Fig. 1. *Cerebral blood flow (cluster-related)*. CBF is given as mean ± 1 standard error of the mean. Dashed line indicates the global CBF sample mean. *Light grey*: global CBF prior to surgery; *dark grey*: CBF change 7 days after shunt surgery (n = 21 patients); *black*: CBF change 7 months after shunt surgery (n = 14 patients). All CBF changes are related to CBF before surgery

Table 1. *CSF Parameters*

CBFCluster	Age	ICP	Ventricle size (VS)	VS change
I	69 ± 10	14.4 ± 6.9	58/42/12	88/12/8
II	69 ± 7	13.6 ± 4.3	33/67/6	50/50/4
III	75 ± 2	14.5 ± 7.8	33/67/3	*/*/1
	years	mm Hg		

Age and ICP data are given as mean ± 1 standard deviation. Ventricular size (VS) data separated by slashes are percentage of moderate dilation, percentage of marked dilation, and number of patients rated before surgery. VS change data 7 months after surgery separated by slashes are percentage of marked reduction in VS, slight reduction in VS, and number of patients rated. Asterisks indicate one patient not rated.

Table 2. *Early and Late Outcome (Cluster-Related)*

CBFCluster	7 days, n = 21	7 months, n = 14
I	50/50/12	89/11/9
II	17/83/6	0/100/4
III	33/67/3	*/*/1

Data separated by slashes are percentage of clinical improvement (bold), percentage of patients with no clinical improvement, and number of patients rated. Asterisks indicate one patient not rated.

[8] showed that the median severity score was at the same rank in every CBFCluster. The distributions, however, seemed to differ in shape. In CBFCluster I about 50% of clinical improvement (6/12 and 4/9 patients) could be verified one week after surgery. Seven months later, the majority of CBFCluster I patients had definitely (8/9 patients) improved in contrast to CBFCluster II patients who showed only a transient recovery from symptoms. CBFCluster III has not been considered because of a low sample size (Table 2).

Discussion

The present study suggests that global cerebral blood flow is decisive for prognosis and might add to surgery indication. Clincial outcome corresponds to perfusion levels prior to surgery: a relatively low perfusion before surgery indicates a positive outcome (CBFCluster I), and the beneficial effect from shunting in those patients became evident after seven months. Poor outcome is to be expected when perfusion is on average (CBFCluster II). Furthermore, CBF data later after surgery revealed a relationship with the clinical progress: global cerebral blood flow tended to increase in patients who showed further clinical improvement (CBFCluster I) seven months post surgery contrary to those patients who did not recover from symptoms (CBFCluster II). As we are faced with elderly patients with a concomitant cerebro-vascular disease, CBF should draw ones attention. It is commonly accepted that both aging [5] and CVD [6] affect global and regional cerebral blood flow. In our data, however, blood flow was not related to age. We assume that the cluster solution here describes the influence of CSF circulatory disorders and cerebrovascular disease on CBF in either cluster. We further assume that a CBF lower than average is likely on indication of pronounced CSF circulatory disorder which could benefit from artificial CSF drainage resulting in a restoration of CBF and subsequent clinical improvement. Measurement of CBF offers a reasonable tool to complete diagnostics in chronic hydrocephalus syndrome.

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Correspondence: Dr. Petra Klinge-Xhemajli, Neurochirurgische Klinik, Medizinische Hochschule Hannover, D-30623 Hannover, Federal Republic of Germany.

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Quantitative Analysis of CSF Flow Dynamics using MRI in Normal Pressure Hydrocephalus

M. Mase[1], K. Yamada[1], T. Banno[2], T. Miyachi[2], S. Ohara[3], and T. Matsumoto[1]

Departments of [1] Neurosurgery and [2] Radiology, Nagoya City University Medical School, [3] Department of Neurosurgery, Meitetsu Hospital, Nagoya, Japan

Summary

In order to clarify the flow dynamics of cerebrospinal fluid (CSF) in normal pressure hydrocephalus (NPH), a phase-contrast cine magnetic resonance (MR) imaging technique with retrospective cardiac gating was used to measure the quantitative flow velocity of CSF in the aqueduct in patients with NPH after subarachnoid hemorrhage (SAH-NPH group, n = 17), idiopathic NPH (1-NPH group, n = 2), asymptomatic ventricular dilatation or brain atrophy (VD group, n = 7) and healthy volunteers (control group, n = 19). Intracanial pressure (ICP) and pressure volume response (PVR) were also measured during the shunt operation in six of the SAH-NPH group. The maximum CSF flow velocity (Vmax) in the aqueduct was significantly larger in the SAH-NPH group (9.21 ± 4.12 cm/sec, mean ± SD) than in the control group (5.27 ± 1.77, $p < 0.001$) and the VD group (4.06 ± 1.81, $p < 0.005$). Vmax was not different between the control and VD groups. There was a positive correlation between the PVR and the peak CSF flow velocity in the SAH-NPH group. These findings suggest that the changes of CSF flow velocity in the SAH-NPH group might be caused by a moderate decrease of intracranial compliance. The CSF flow study using MRI is useful to differentiate NPH from brain atrophy or asymptomatic ventricular dilatation and also to estimate the intracranial compliance.

Keywords: CSF flow; normal pressure hydrocephalus; phase-contrast cine.

Introduction

The driving force of both intracranial pressure (ICP) pulse wave and pulsatile movement of cerebrospinal fluid (CSF) is cerebrovascular and brain pulsation is synchronized with the heart beat [11,13]. Since ICP pulse wave changes in various intracranial pathologies [1,7,15], CSF flow movement may also be affected by changes of intracranial conditions. Therefore, there is a possibility that non-invasive observation of CSF flow movement using magnetic resonance imaging (MRI) could be used to estimate the pathophysiology of hydrocephalus.

The recent development of MR systems and imaging techniques makes it possible to perform quantitative analysis of CSF flow velocity [3,4,16]. The increase of CSF flow velocity in the aqueduct has been demonstrated in patients with normal pressure hydrocephalus (NPH) [5,9,12,17]. We have already shown the possibility that the CSF flow pattern might be affected by changes of the compliance of the craniospinal cavity [8,14].

In order to clarify the CSF flow dynamics in NPH, we performed quantitative analysis of CSF flow velocity and flow pattern in the aqueduct using a phase-contrast cine MR imaging technique and estimated whether the MRI study was useful for the diagnosis of NPH.

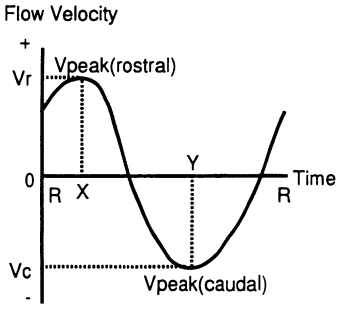
Materials and Methods

Patients and Healthy Volunteers

We studied 45 cases including patients with NPH after SAH (age range: 43–81 years, mean age: 63.3 years, SAH-NPH group, n = 17), idiopathic NPH (36–76, 56.0, I-NPH group, n = 2), asymptomatic ventricular dilatation or brain atrophy (49–79, 70.0, VD group, n = 7) and healthy volunteers (25–81, 45.8, control group, n = 19).

MRI Study

On a 1.5 T MR system (Philips Gyroscan ACS II, Netherlands), the quantitative flow data were obtained from two-dimensional phase contrast images using a gradient echo (T1-FFE) pulse sequence with retrospective cardiac triggering techniques which enabled continuous measurement through the cardiac cycle [12,18]. This sequence was used with parameters of 20–23 / 12–15 msec (TR/TE), acquisition matrix of 256 × 256 or 128 × 128, flip angle of 20 degrees, slice thickness of 3 mm, number of heart phases of 20 and



$$\text{Maximum Flow Velocity : (Vmax)} = \frac{|Vr| + |Vc|}{2}$$

$$\text{Vr-Vc interval (with R-R correction)} = \frac{Y - X}{\text{R-R interval}}$$

Fig. 1. Maximum flow velocity (Vmax), and interval between the rostral and caudal peaks (Vr-Vc interval) of the time-velocity curve of CSF in the aqueduct

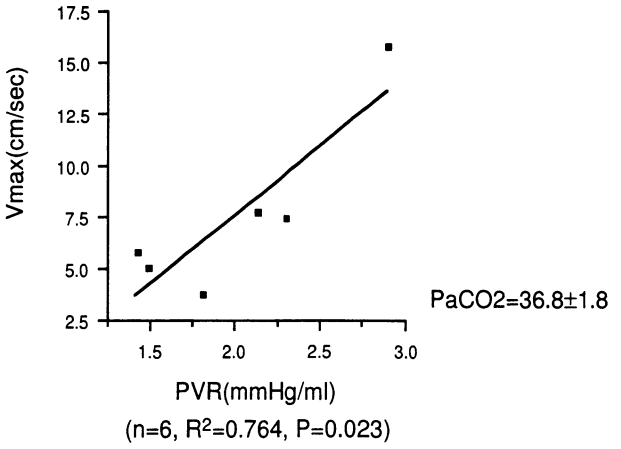


Fig. 2. Relationship between pressure volume response (PVR) and the peak CSF flow velocity (Vmax) in the SAH-NPH group. There was a positive correlation between the PVR and the Vmax in the SAH-NPH group

FOV (field of view) of 150. Velocity encoding gradient was set to 5–20 cm/sec in parallel with the aqueduct, and the region of interest (ROI) for the velocity measurement was placed on the axial plane which crossed the aqueduct at right angles.

Maximum CSF flow velocity (Vmax) in the aqueduct was calculated as an average of the absolute values of rostral peak (Vr) and caudal peak (Vc) flow velocity. The interval (Y-X) between rostral peak (X) and caudal peak (Y) time, which were corrected by R-R interval of electrocardiogram (ECG), were used for estimation of CSF flow pattern (Vr-Vc interval) (Fig. 1). These parameters were compared between the groups.

ICP and PVR Measurement

During the shunt operations, intracranial pressure (ICP) and pulse pressure (PP) of ICP pulse wave in the lateral ventricle were recorded in six patients of SAH-NPH group. Pressure-volume response [PVR; ICP changes after a bolus injection of saline (5 ml/5 sec) to the lateral ventricle] was also obtained as an index of the intracranial compliance. $PaCO_2$ was kept within normal range during the measurement (36.8 ± 1.8 mm Hg).

Statistics

Shapiro-Wink W test and unpaired t-test were used for the statistical analysis, and data were considered significant at the level of $p < 0.05$. Data are shown in mean ± SD.

Results

CSF Flow Velocity and Pattern

The maximum flow velocity (Vmax) was significantly larger in the NPH group (9.21 ± 4.12 cm/sec) than in the VD group (4.06 ± 1.81, $p < 0.005$) and the control group (5.27 ± 1.77, $p < 0.001$). Vr-Vc interval with R-R correction in the NPH group (0.44 ± 0.08) was significantly longer than in the VD group (0.37 ± 0.05, $p < 0.05$) and the control group (0.34 ± 0.06, $p < 0.0005$). These parameters were not different between the control and VD groups. Patients with I-NPH (Vmax: 7.00 ± 2.12, Vr-Vc interval: 0.46 ± 0.04) were excluded from the statistics because they were only two cases.

CSF Flow Velocity, ICP and Compliance

There was a linear correlation between the PVR and the Vmax in the SAH-NPH group (Fig. 2). However, there was no relationship between Vmax and mean ICP or PP.

Discussion

The present study clearly revealed changes of maximum flow velocity and the pattern of CSF flow in the aqueduct in patients with NPH after SAH. Bradley suggested that the CSF flow velocity in the aqueduct increased in patients with NPH because aqueductal flow void phenomenon was most pronounced in them [2]. Recent quantitative analysis also shows that CSF flow increases significantly in patients with NPH [5,12], corresponding to our results. However, there has been no report showing changes of the CSF flow pattern, e.g. an increase of the interval of the rostral and caudal peaks in patients with NPH. Gideon showed that there were no significant differences in the shapes of the time-velocity curves between idiopathic NPH and normal cases [5]. Nitz reported two NPH cases whose caudal peaks of CSF flow velocity were delayed at 40–50% of cardiac

cycle compared with health subjects with the caudal peak at 30–40%. Nitz did not conclude that the difference was significant because of the small number of the cases [12].

In our study, most of the subjects with NPH were not idiopathic NPH but NPH after SAH. There might be a possibility of some pathophysiological differences among them, and they cannot be compared simply. Though the reason for changes of CSF flow pattern in our patients with NPH after SAH is not clear, we consider the possibility that SAH causes changes in the nature of intracranial components, including brain tissue, resulting in changes of pulsatile movement of the brain and its transmission. However, the I-NPH group, which included only two cases, had the same tendency of changes in the Vmax and Vr-Vc interval as the SAH-NPH group.

Ohara suggested that the occurrence of signal void phenomenon in the aqueduct was related to the different elastance in the intracranial and intraspinal cavities [14]. Kudo supported his hypothesis based on the fact that neonates and infants with small intracranial elastance had a decrease of CSF pulsatile movement at cervical subarachnoid spaces [6]. It has been shown that the pulse pressure of ICP was larger in NPH than that in normal controls, which suggested NPH had relatively small intracranial compliance compared with the controls [10]. On the other hand, there is a report that patients with brain atrophy, whose intracranial compliance is relatively large, have hardly any flow void in the aqueduct [2]. In the present study, Vmax of the VD group was significantly smaller than Vmax in the NPH group. Wachi also showed a decrease of CSF pulsatile movement after removal of CSF by lumbar puncture [19]. Therefore, there is a possibility that the small intracranial compliance is a factor which increases CSF flow velocity and changes the flow pattern in patients with NPH. This hypothesis is now supported by a linear correlation between the PVR and the Vmax in the SAH-NPH group in the present study.

From these findings, we believe that there is a negative correlation between the intracranial compliance and maximum flow velocity of CSF in the aqueduct when the compliance is large or moderately small. However, this hypothesis may not be applied in cases where there are some obstructions in the CSF flow pathway. Aqueductal flow void was not observed in an obstructive hydrocephalic case [13]. On the contrary, if compliance is very small, with a lack of compensatory capacity of ICP, CSF would no longer move freely and flow velocity might be reduced.

We clarified the characteristic changes of CSF flow dynamics in the aqueduct in patients with NPH. Estimation of CSF flow study could differentiate NPH from brain atrophy. We suggest that CSF flow study using MRI is useful for the preoperative diagnosis of NPH. Although further investigation is needed, CSF flow study may become an essential preoperative examination.

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Correspondence: Mitsuhito Mase, M.D., Department of Neurosurgery, Nagoya City University, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, 467, Japan.

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Magnetic Resonance Imaging, Unstable Intracranial Pressure and Clinical Outcome in Patients with Normal Pressure Hydrocephalus

A. I. Qureshi, M. A. Williams, A. Y. Razumovsky, and **D. F. Hanley**

Divisions of Neurosciences Critical Care, Johns Hopkins Hospital, Baltimore, U.S.A.

Summary

To identify features on magnetic resonance imaging (MRI) scans that are associated with unstable intracranial pressure (ICP) and outcome after CSF shunting in patients with NPH, we reviewed MRI scans of 17 patients who had continuous ICP monitoring performed prior to ventriculo-peritoneal shunt insertion. We evaluated the association between periventricular/deep white matter lesion burden, focal impingement of the corpus callosum, aqueductal CSF flow void, and B-waves with outcome after shunting. The change in neurological function between pre- and post CSF shunting evaluation was scored according to a standard scale (range −3 or +3). Patients were divided into those with clinical improvement (score > 0) or without improvement (score ≤ 0) after shunt surgery. Focal impingement of the corpus callosum was more frequent in patients who improved after CSF shunting compared to those without improvement (8 of 13 vs 0 of 4, $p = 0.05$). Patients with focal impingement of corpus callosum had more B-wave time than those without impingement (60.5% vs 24.7%, $p = 0.02$). Focal impingement of corpus callosum on MRI may be associated with unstable intracranial pressure in patients with NPH and may be useful in identifying patients who will benefit from CSF shunting.

Keywords: Clinical outcome; corpus callosum; magnetic resonance imaging; normal pressure hydrocephalus.

Introduction

Normal pressure hydrocephalus (NPH) is a progressive form of dementia accompanied by gait disturbance and urinary dysfunction [1]. Recent studies have demonstrated periods of unstable intracranial pressure waves in patients with NPH using continuous intracranial pressure (ICP) monitoring [2,3]. Preliminary data suggests that CSF shunting is most beneficial in patients who have unstable intracranial pressure waves during continuous ICP monitoring [4]. We reviewed our experience with NPH patients who underwent ICP monitoring and magnetic resonance imaging (MRI) to determine features that may identify patients with NPH who have unstable intracranial pressure and may benefit from CSF shunting. We evaluated the relationship between white matter lesion burden, aqueductal CSF flow void and corpus callosum impingment on MRI (all reported to be increased in patients with NPH [5]), with the prevalence of unstable pressure waves during ICP monitoring.

Methods

We reviewed the ICP recordings and MRI scans of patients who underwent ICP monitoring for the diagnosis of NPH at the Neurosciences Critical Care Unit at the Johns Hopkins Hospital. Only MRI scans performed within 12 months of the ICP monitoring were included in the analysis. All MRI images were evaluated by one of the investigators (AQ), who was unaware of the clinical and ICP monitoring findings. Analysis of hyperintensities was performed on the T_2-weighted images using the system used by Ylikoski *et al.* [6] and Fazekas *et al.* [7]. Periventricular hyperintensities were rated in eight areas: adjacent to frontal horns, ventricular body, trigone, occipital horns in both hemispheres. In each, periventricular hyperintensities were rated from 0 to 3 : 0, no hyperintensity; 1, mild (punctate, small foci); 2, moderate (cap, pencil lining); and 3, severe (nodular band, extending hyperintensities). The hyperintensities in the centrum ovale including watershed areas were rated similarly in the eight areas from 0 to 3 : 0, no hyperintensity; 1, mild (punctate, small foci); 2, moderate (beginning confluent); 3 severe (large confluent areas). The total score reflecting the white matter lesion burden was calculated by adding the scores from the eight areas of periventricular and deep white matter. The CSF flow void sign in the aqueduct of Sylvius, defined as loss of signal in flowing CSF relative to more stationary CSF in the ventricles, was graded as present or absent. Focal impingement of corpus callosum was recorded as present or absent [5]. Fig. 1 demonstrates focal impingement of corpus callosum in a patient with NPH. ICP monitoring was performed in all patients with a lumbar catheter for 48 hours. B-waves were defined as rhythmic or semi-rhythmic oscillations of 1 to 2 cycles per minute with an amplitude (peak systolic minus baseline systolic) ≥3 mm Hg (40 cm H_2O). The prevalence of unstable ICP (B waves) was expressed as percentage of time with B waves over total time of artifact free ICP recording. Patients were clinically evaluated before and after shunting procedure by a neurologist

(MAW). The change in neurological function which included gait and cognition was scored according to a standard scale (range –3 or +3). Patients were divided into those with clinical improvement (score > 0) or without improvement (score ≥ 0). The association between periventricular/deep white matter lesion burden, focal impingement of corpus callosum, aqueductal CSF flow void, and B-waves with outcome after shunting were analyzed with EPI Info 5.0. Means and frequencies were compared with analysis of variance (ANOVA) and chi-square method respectively.

Results

There were 17 patients (11 men and 6 women) who underwent ventriculoperitoneal shunt insertion after ICP monitoring for the diagnosis of NPH from 1990 through 1996 and who had a recent MRI scan prior to ICP monitoring. The mean age was 75.8 ± 5.9 years. The MRI features are shown in Table 1. Focal impingement of the corpus callosum was more frequent in patients who improved after CSF shunting (8/13 vs 0/4, p = 0.05). There was no difference in the prevalence of B waves, periventricular and deep white matter burden, or the presence of aqueductal CSF flow void between groups. Patients with focal impingement of corpus callosum had more B-wave time than those without (60.5% vs 24.7%, p = 0.02) shown in the Fig. 2.

Discussion

Our results demonstrate that focal impingement of the corpus callosum was frequently associated with B-waves and favorable response to CSF shunting in patients suspected of having NPH. Our study suggests that MRI appearance in patients with NPH may help identify patients who may respond to CSF shunting.

Dorsal flattening and thinning of the posterior corpus callosum is recognized in other forms of hydrocephalus [10] and is attributed to static and intermittent pulsatile expansion of the ventricles.

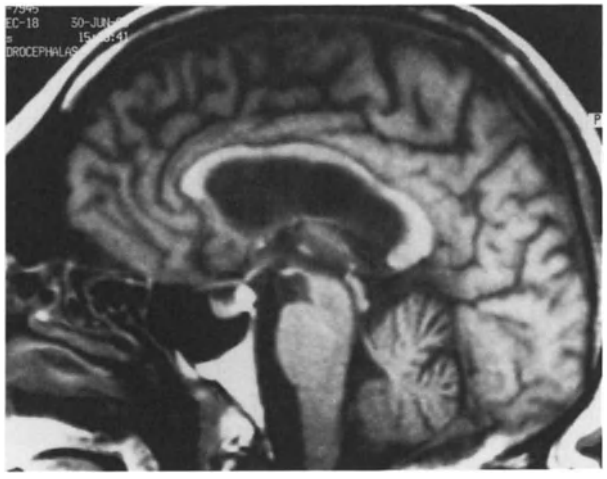

Fig. 1. Focal impingement of corpus callosum in sagittal T-1 weighted image in a patient with NPH

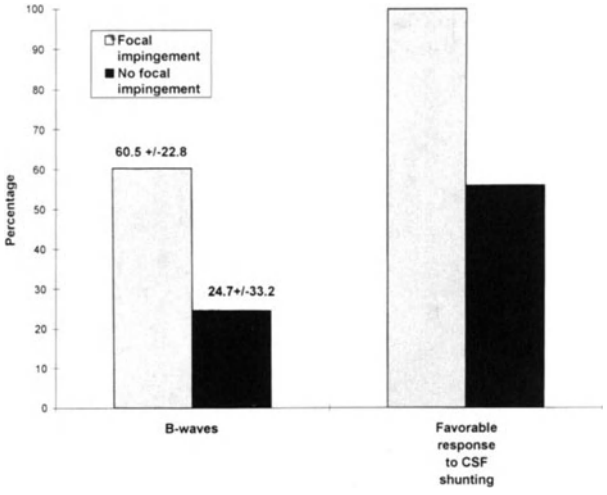

Fig. 2. Focal impingement of corpus callosum, B-waves, and favorable outcome after CSF shunting procedure

Table 1. *MRI Features of Patients with CSF Shunting for NPH and Clinical Outcome*

Variables	Patients with clinical improvement (n = 13)	Patients without improvement (n = 4)	p-value
Mean age (years)	75.4 ± 6.6	77.3 ± 2.9	0.5
Focal impingement of corpus callosum	8	0	0.05
CSF flow void	8	3	1.0
Periventricular WM score	10.8 ± 6.9	12.5 ± 9.3	0.7
Deep WM score	6.1 ± 4.4	6.8 ± 6.5	0.8
B-waves	45.1 ± 30.0	30.0 ± 46.0	0.4

The pressure effects are thought to cause local biochemical and ischemic changes or microtrauma of the corpus callosum [10]. However it is not clear whether corpus callosum lesions are sufficient to cause symptoms of NPH because patients undergoing corpus callosum resection (commissurotomy) do not have impairment of cognition, gait abnormalities, or incontinence [10]. It is possible that thinning of the corpus callosum is an anatomical indicator which differentiates true hydrocephalus from ventricular enlargement due to cerebral atrophy associated with normal aging or dementia. Ventricular distension from impaired CSF circulation would expand the corpus callosum against the falx cerebri. This finding may not be sensitive because patients without focal impingement of the corpus callosum also improved after CSF shunt surgery.

We did not find an association between B-waves or clinical outcome and white matter lesions on MRI. Previous studies have reported a higher frequency of white matter changes in patients with NPH [5,8]. However, Krauss *et al.* [9] found that presence of white matter lesions does not influence the response to CSF shunting procedures. We also found a poor correlation between presence of white matter lesions and response to CSF shunting. Our data do not support using the presence or absence of white matter lesions as a criterion for selecting patients for CSF shunting.

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Correspondence: Michael A. Williams, M.D., Division of Neurosciences Critical Care, 600 North Wolfe Street, Meyer 8-140, Baltimore, MD 21287-7840, U.S.A.

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Clinical Significance of Ventricular Size in Shunted-Hydrocephalic Children

H. Sakamoto, S. Kitano, M. Nishikawa, and **K. Fujitani**[1]

Departments of Pediatric Neurosurgery and Neurosurgery, Osaka City General Hospital, and [1] Osaka Municipal Rehabilitation Center for the Disabled, Osaka, Japan

Summary

For maintaining the intracranial buffering capacity against shunt obstruction, we tried to seek the most suitable size of the lateral ventricles in hydrocephalic children. Thirty-seven shunted-hydrocephalic children who required emergent revision of the shunt were analyzed. At the time of shunt obstruction, the lateral ventricle remained small (0.35 or less than 0.35 on the Evans' index) in 13 patients (Slit-like group), but it enlarged (more than 0.35 on the Evans' index) in 24 patients (Dilated group). The mean age in the Slit-like group was significantly older than in the Dilated group and there was no patient younger than 3 years in the Slit-like group. Compared with the Dilated group, the Slit-like group showed significantly rapid deterioration into lethargy after shunt obstruction. Also, at the time of obstruction CT scans showed a significantly higher rate of narrowing of the ambient cistern. While the shunt was working well before shunt obstruction, the Evans' index was less than 0.33 in all patients of the Slit-like group. In conclusion, because small ventricles after shunt strongly suggest the presence of ventricular tautness, the lateral ventricular size should be maintained at more than 0.33 on the Evans' index in shunted children at an age of 3 or more than 3 years.

Keywords: Evans' index; hydrocephalic children; ventricular size.

Introduction

Chronic overdrainage of the ventricular cerebrospinal fluid (CSF) through a shunt often induces taut ventricles or decreased intracranial compliance, in which the ventricle hardly dilates even under the influence of intraventricular CSF accumulation due to shunt obstruction. We know that taut ventricles develop into serious conditions in association with rapid deterioration after shunt obstruction, slit ventricle syndrome or massive CSF edema along the ventricular catheter [1,4]. However, there has been little information available comparing the ventricular size and tautness in shunted hydrocephalic children.

In the present report, we tried to find out some predictable indicators of taut ventricles after CSF shunt. Also, for maintaining the intracranial buffering capacity in response to the shunt obstruction, we tried to seek the most suitable size of the lateral ventricles in hydrocephalic children.

Materials

Out of hydrocephalic children who required emergent revision of the shunt in our hospital from 1990 to 1996, 37 (18 males and 19 females) were retrospectively selected for analyzing the relationship between the ventricular size and its tautness. Their ages ranged from 6 months to 17 years with a mean of 7 years. To eliminate differences associated with the type of shunt system installed, the same kind of shunt system with a medium pressure valve was used in each case. The shunt obstruction was verified by imaging in all patients. All 37 patients (congenital hydrocephalus 15, myelomeningocele 12, intraventricular hemorrhage 7, postmeningitis 2, tumor 1) were recognized to be shunt dependent. We divided the patients into two groups, "Dilated group" and "Slit-like group," by the size of the lateral ventricle at the time of shunt obstruction. The Slit-like group comprised patients in whom the size of the lateral ventricles was equal or less than 0.35 on the Evan's index and the Dilated group comprised patients in whom the size of the lateral ventricles was more than 0.35. As one of the indicators for transtentorial herniation, narrowing of the ambient cistern was observed on CT scans at the time of shunt obstruction.

Results

Table 1 shows the clinical features at the time of shunt obstruction in the two groups. The age at the time of shunt obstruction in the Dilated group ranged from 3 months to 9 years with a mean of 3.0 years and that in the Slit-like group ranged from 4 to 17 years with a mean of 7.0 years. The mean age at the time of shunt obstruction in the Slit-like group was significantly greater than that in the Dilated group. The Dilated group had 14 patients younger than 3 years, whereas the Slit-like group contained no patient younger than 3 years. At the time of shunt

Table 1. *Clinical Data at the Time of Shunt Obstruction*

	Dilated group	Slit-like group
Number of patients	24	13
Evans' index (mean)	0.37–0.80 (0.44)	0.24–0.33 (0.28)[b]
Age (mean)	3 mos–9 yrs (3 yrs)	3 yrs–17 yrs (7 yrs)[a]
Hospitalization after onset (mean)	1–18 days (5.0 days)	0–5 days (2.8 days)[a]
Lethargy after onset	4/24 (17%)	10/13 (77%)[a]
Ventricular pressure (mean)	15–30 cm H_2O (18 cm H_2O)	20–30 cm H_2O (26 cm H_2O)

[a] $p < 0.01$, [b] $p < 0.05$.

obstruction, all patients in the Slit-like group and 13 out of 24 patients (55%) in the Dilated group complained of vomiting and/or headache. At the time of hospitalization, 77% of the patients in the Slit-like group and 13% in the Dilated group were lethargic. Thus, there were significant differences between these two groups in the rates at which symptoms were presented. The mean duration after onset to hospitalization was 5.0 day in the Dilated group and 2.8 days in the Slit-like group, respectively. The mean duration in the Slit-like group was significantly shorter than that in Dilated group. Out of 10 lethargic patients in the Slit-like group, 9 became lethargic within 2 days after onset. These results indicate that the patients in the Slit-like group deteriorated rapidly into lethargy after onset.

The mean ventricular pressure in the Dilated group was 18 cmH_2O and that in the Slit-like group was 26 cmH_2O. The difference was not statistically significant. However, the intraventricular pressure could not be measured in 54% of the patients in the Slit-like group because of obstruction of the ventricular catheter. On CT scans at the time of shunt obstruction, narrowing of the ambient cistern was seen in only 29% of the patients in the Dilated group, although 69% in the Slit-like group had such a finding. The Slit-like group had a significantly higher rate of cisternal narrowing than the Dilated group. This finding corresponded well to the fact that the patients in the Slit-like group showed a significantly higher rate of lethargic patients than that found in the Dilated group.

The Evans' index before the initial shunt ranged from 0.32 to 0.74 (mean 0.41) in the Dilated group and 0.34 to 0.73 (mean 0.45) in the Slit-like group, respectively. There was no difference between the Dilated and Slit-like groups in the mean value on the Evans' index before the initial shunt. However, on the latest CT before shunt obstruction when the shunt was performing well, the Evans' index in all patients of the Slit-like group was less than 0.33, and all patients except 3 in the Dilated group had more than 0.33 Evans' index. The ages of these 3 patients were 6 months old, 1 year old and 7 years old, respectively. The results indicated that in 3 or over 3-year-old, shunted hydrocephalic children, with less than 0.33 on the Evans' index, the ventricles hardly dilate at all at the time of shunt obstruction.

Discussion

A clinical study on CSF dynamics has clearly demonstrated markedly reduced buffering capacity of the intracranial volume in shunted hydrocephalic children with rapid deterioration after shunt obstruction [5]. However, the relationship between the ventricular size and its tautness was not described. In the present study, we investigated the relationship between the size of the lateral ventricle and its tautness, in shunt-dependent hydrocephalic children who required emergent revision of the shunt. Most of the patients in the Slit-like group deteriorated rapidly into lethargy, while their lateral ventricles remained small (0.35 or less than 0.35 on the Evans' index) at the time of shunt obstruction. In addition, we considered the age of the patient, as taut ventricle after shunt is usually observed only in older patients, slit ventricle syndrome, characterized by taut ventricles, rarely developed in infants [2]. The results of the present study demonstrated that, in children more than 3 years old, small ventricles after shunt indicate ventricular tautness resulting in rapid deterioration without significant enlargement of the ventricles after shunt obstruction. We can draw the conclusion that small ventricular size of older children after

shunting corresponded well to clinical characteristics observed in patients with ventricular tautness.

From the present analysis of changes in the lateral ventricular size, the ventricular size is quite a good indicator of taut ventricles. Small lateral ventricles (Evens' index smaller than 0.33) when the shunt is patent rarely dilate because of shunt obstruction in patients older than 3 years. This suitable size of the lateral ventricles is slightly larger than the normal size, because normal size of the lateral ventricle is up to 0.31 in normal subjects over 3 years old [3]. Therefore, since none of the patients complained of symptoms or signs due to underdrainage through a shunt, it is safe to suggest that the size of the lateral ventricles after shunt should be maintained at more than 0.33 on the Evan's index.

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Correspondence: Hiroaki Sakamoto, M.D., Department of Pediatric Neurosurgery, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima-ku, Osaka, 534 Japan.

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Dual-Switch Valve: Clinical Performance of a New Hydrocephalus Valve

H. A. Trost[1], **Ch. Sprung**[2], **W. Lanksch**[2], **D. Stolke**[3], and **C. Miethke**[4]

[1] Neurosurgical Department, Krankenhaus Bogenhausen, Munich, [2] Neurosurgical Department, Virchow Klinikum, Berlin, [3] Neurosurgical Department, University of Essen, and [4] Christoph Miethke KG, Berlin, Federal Republic of Germany

Summary

The Dual-Switch valve (DSV) is the first construction on the market which changes between two different valve-chambers in parallel depending on the posture of the patient. In the lying position the valve acts like a conventional differential pressure valve, in the vertical position the high-pressure chamber only opens, when the pressure exceeds the hydrostatic pressure difference between the formanen of Monro and the peritoneal cavity.

The new device has been implanted in 32 adult patients with hydrocephalus of different etiology. The clinical results are excellent to good accompanied by a remarkable slight reduction of the ventricular size. Apart from one case with a nonsymptomatic transient hygroma, we saw no valve related complications like overdrainage, underdrainage or dysfunction. Contrary to conventional differential-pressure valves, adjustable devices and other hydrostatic constructions like the Anti-Siphon-device (ASD) or Deltavalve, the DSV reliably controls the IVP independently of the posture of the patient, the CSF viscosity or the subcutaneous pressure. In contrast to the Orbis-Sigma-valve (OSV) or the Diamond-valve, the DSV does not control the flow but the physiological IVP avoiding the increased risk of mechanical failure. The results of this study give strong evidence that the shunt-therapy of adult hydrocephalic patients can be significantly improved by the DSV.

Keywords: Dual-switch valve; hydrocephalus; overdrainage.

Introduction

Although the introduction of valve regulated shunts during the fifties has been a breakthrough in the treatment of hydrocephalus, we are still confronted with severe biomechanical problems. In the last years an increasing number of new devices has been presented aiming to avoid overdrainage related problems. But none of these devices can physiologically regulate the IVP of hydrocephalic patients independently of the posture, the CSF production rate or viscosity. Especially, sophisticated devices have a tendency to get blocked leading to underdrainage as well as to overdrainage [1,6].

With reference to the long list of overdrainage related complications like slit ventricles, obstruction of the ventricular catheter or hygromas/hematomas (Table 1), it seems very important to develop a valve which does reliably work in physiological limits in the lying position of the patient as well as in the standing position.

Materials and Methods

The dual-switch valve presents for the first time a construction which consequently takes into account that the hydrocephalic patient is in the horizontal position for only 8–12 hours, but for the rest of the day is in the upright position. Depending on the posture of the patient, the valve switches over between two autonomous valve chambers with a completely different opening pressure [4,9]. The valve, which has to be implanted in the subcutaneous tissue of the thoracic region, has opening pressures of 10, 13 or 16 cm of water for the lying and 30, 40 or 50 cm of water for the vertical position.

To investigate the clinical performance of the DSV a controlled prospective clinical trial was carried out. The study started in January 1995. The design of the study is shown in Table 2. In this study we used a DSV with an opening pressure of 13 cm of water (medium pressure) for the recumbent posture and 40 cm of water for the upright position. The clinical status before and after shunting was assessed according to the scale of Stein and Langfitt [10] and changes in the ventricular size were documented on follow-up CT with measurement of the Evans-Index. The DSV was implanted in 32 adult patients with different etiologies of the hydrocephalus (Table 3). The mean follow up was 17,3 months (12,5–25,4).

Results

The clinical outcome was excellent to good except in 3 cases with previous severe posttraumatic or post-hemorrhagic brain damage. In the majority of cases we saw only minimal to slight reduction of the ventricular size (Fig. 1) accompanied by very satisfying

clinical improvement (Fig. 2). There has been only one transient asymptomatic hygroma. One patient had a persisting hygroma due to a too inclined implantation in the upper part of the barrel-shaped thorax so that the high-pressure chamber was not activated in the upright position. After correction of the position of the valve, the hygroma resolved and the patient went back to work. At the beginning of the trial 3 revisions in 2 patients were necessary because of disconnections of the peritoneal catheter, probably due to sharp edges at the distal connectors of the DSV and thin peritoneal catheters. Changes in the design of the connectors and thicker catheters solved this problem.

Discussion

Worldwide there are more than 50 different valve constructions on the market. These valves can be

Table 1. *Sequelae of Overdrainage Reported in the Literature*

- Low intracranial pressure – syndrome (Foltz 1988)
- Slit-ventricle-syndrome (Epstein 1978)
- Subdural hygroma/hematoma (Anderson 1952)
- Craniosynostosis, hyperpneumatisation and thickening of the calvarium (Griscolm 1970)
- Aquaeductal stenosis, isolated IV. and lateral ventricle (Foltz 1966, Salmon 1970)
- Deteriotation of shunt-dependency (Epstein 1978)
- Precocious obstruction of ventricular catheter (Sainte-Rose 1993)
- Upper hind brain herniation (Emery 1965)

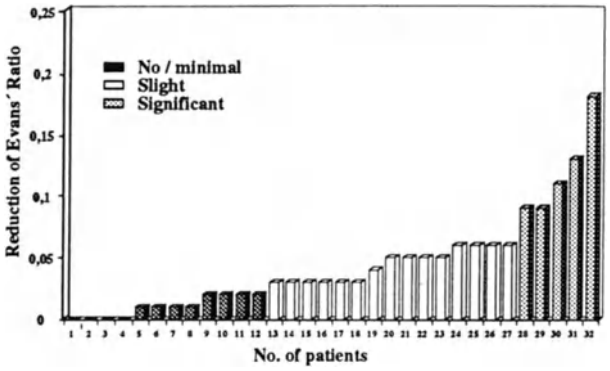

Fig. 1. Changes of Evans-Index after shunting with the DSV

Table 2. *Design of the Clinical Study*

Protocol
- Etiology of hydrocephalus
- Clinical status and CT before shunting
- Intraoperative measurement of ICP
- Clinical status and CT: 14 days, 3 and/or 6 months after surgery
- Registration of complications

Criteria of Inclusion
- Prospective study
- All kinds of hydrocephalus
- Patients older than 17 years
- Exspectation of life more than 1 year
- First implantation of revision
- VP-shunts, frontal burr-hole

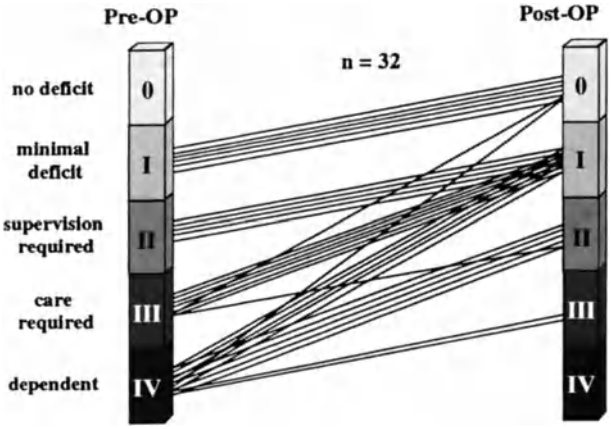

Fig. 2. Clinical improvemant according to Stein and Langfitt [10]

Table 3. *Patients with DSV*

n	Sex m	f	Age at operation (Years)	Etiology of Hc		Follow up (Months)
32	11	21	22–82	idiopath. NPH	9	14,5–27,4
			Mean	post-SAH	10	Mean
			56,3	posttraumat.	5	18,3
				Hc with MMC	2	
				Occl.-Hydroc. Tu./Hem.	2	
				Aqueduct. Stenosis	3	
				Pseudotumor c.	1	

divided into three groups: simple differential-pressure valves with only one opening pressure for the lying position, adjustable valves, again with an opening pressure for the lying position but with the possibility to adjust the pressure level after surgery and hydrostatic valves.

Valves belonging to the first group act similarly to the valves introduced in the fifties. Their opening performance depends on the lying position of the patient. The technical differences between valves of this type refer to the material, the kind of valve seat, the geometry or the flow characteristic. They are available with different pressure ranges beginning with 4 cm of water (very low) reaching up to 16 cm of water (very high). But independently of the chosen pressure range, these valves systematically lead to unphysiologic IVP as soon as the patient moves into the upright posture. These valves cannot keep the IVP within physiological limits due to the changes of hydrostatic pressure in the drainage-system. As many patients tolerate such negative values without clinical symptoms, it is quite understandable that such valves are still implanted. Most important for the clinical performance of the various valves of this group are the reliability of the valve-seat and the flow characteristics. A valve should definitely close if the differential pressure acting on the valve is lower than the opening pressure. Especially for the ventriculo-atrial drainage the safety against reflux has high priority. But besides these aspects there are no important differences in the physical performance of the various differential pressure valves on the market [2].

In principle, the same physics apply to the second group of valves, the so-called adjustable valves. The decisive difference with this group of conventional differential pressure valves lies in the possibility to change the valve performance between the different pressure ranges without surgery. Hereby, it is possible to reduce the negative IVP in the standing position of the patient by increasing the opening pressure of the device. On the other hand, this leads to an increased IVP in the lying position. The highest possible opening pressure of available adjustable valves implies a pressure of 20 cm of water. This pressure is much too high for the lying position and still too low for the standing position because the hydrostatic pressure of the adult patient is in the range of 235 to 250 cm of water. Neither in the horizontal position nor in the upright position the IVP is in physiological limits.

Therefore, adjustable valves can only be a compromise between a reduced negative IVP in the standing position and an increased IVP in the lying position.

The third group of valves represents the most sophisticated valves. There are very important technical differences between the different types of hydrostatic valves. All hydrostatic devices aim to reduce the flow through a shunt-system when the patient moves into the upright position.

The Orbis-Sigma valve [8] and the new Diamond valve [5] do not act depending on the posture of the patient but depending on the differential pressure acting on the system. These constructions aim to regulate a constant flow of about 20 ml/h, nearly independent of the differential pressure, by decreasing the opening while the pressure is increasing. In the standing position these devices can lead to over-drainage as soon as partial physiological absorption occurs or the production rate is lower than 20 ml/h. Both valves assume that the reason for an increased differential pressure on the valve must be a change in the position of the patient. The increased differential pressure is counteracted by a decrease of the opening area in the valve seat. This fact has two drawbacks: first, the reason for the increased differential pressure can be an increased production rate instead of changes of posture. In this case the opening area at the valve seat should not be smaller but larger and the flow should increase. Second, the delicate mechanism for the pressure induced flow regulation is very susceptible to mechanical complications. Very small changes in the opened area of the valve seat lead to dramatical changes of the flow. Therefore, debris or remnants of blood cells significantly influence the function of the valve.

The ASD and the Delta valve as well as the new Beverly valve directly depend on the subcutaneous tissue pressure which leads to unpredictable physical situations. Many authors [1,3,6] clearly demonstrated that the mechanism is extremely influenced by height of the positioning of the device and changes in the subcutaneous pressure by the development of a cellular capsule around the device or by the weight of the patients head lying on the device.

In contrast to other hydrostatic valves, the DSV always acts like two reliable differential pressure valves in parallel with different opening pressures depending on the position of the patient.

The results of the patients with the DSV in our series confirm that there is a remarkable difference between the physics of a lying and standing

hydrocephalic patient. The fact that we saw – except one transient hygroma – no overdrainage related problems like symptomatic hygromas or hematomas in comparison to reports about other valves in the literature [7] together with the remarkable slight reduction of the ventricles produces strong evidence that the DSV presents a new possibility to improve the outcome of shunt-regulated patients with hydrocephalus avoiding underdrainage as well as overdrainage. In our opinion, the IVP and not the ventricular size defines the clinical outcome. If the IVP is kept within physiological limits, the individual clinical outcome and the ventricular size will show the optimal result for each individual patient.

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Correspondence: H. A. Trost, M.D., Neurosurgical Department, Krankenhaus Bogenhausen, Englschalkinger Str. 77, D-81925 München, Federal Republic of Germany.

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CSF Dynamics in a Patient with a Programmable Shunt

O. Tsuji[1] and **K. Sato**[2]

[1] Department of Neurosurgery, HITACHI General Hospital, Ibaraki, and [2] Department of Neurosurgery, Juntendo University, Tokyo, Japan

Summary

The Codman®-Medos® programmable shunt system was designed by Drs. Hakim to relieve under and over drainage problems. The system allows for non-invasive post-implantation adjustment of the opening pressure of the valve through a range of 30 to 200 mmH_2O in 10 mm differentials. However, its wide adjustability does not simplify determination of the optimal pressure setting.

The bolus injection method was used to study the intracranial pressure environment of nine adult hydrocephalic patients treated with the Codman®-Medos® programmable shunt. Changes in CSF hydrodynamics with manipulation of the pressure valve setting, and the effectiveness of the bolus injection method to determine the optimum valve pressure setting were investigated.

Initial valve pressure setting at shunt implantation was determined on the basis of preoperative CSF dynamics test. Another CSF dynamics test was carried out after surgery, and the pressure setting was revised if necessary. The new setting was the maximum obtained within normal CSF hydrodynamics. If shunt overflow was suspected, pressure was set at a higher level. After resetting of the shunt, no patient encountered serious shunt-related problems in the follow-up period.

This method was considerably useful for understanding of the intracranial pressure environment of patients with a programmable shunt, and determination of a better shunt setting.

Keywords: CSF dynamics; hydrodynamics; programmable shunt.

Introduction

The essential and sole role of a ventriculo-peritoneal shunt (V-P shunt) in a hydrocephalic patient is to obtain appropriate diversion of cerebrospinal fluid. However, under and over drainage problems remain still unsolved. In particular, over-drainage leads patients into such difficult situation as subdural hygroma/hematoma and slit ventricle syndrome.

Various types of shunt systems have been designed to counter this. A large number of such reports pointed out the effectiveness of programmable shunt system in preventing and treating under/over drainage syndrome [2,7]. Codman®-Medos® programmable shunt system is in wide use now, and its reliability and accuracy have been well demonstrated in both laboratory and clinical settings [1]. However, its wide and fine adjustability does not simplify determination of the optimal pressure setting.

The purpose of this study was to clarify changes in intracranial pressure (ICP) environments by pressure setting manipulations, and to determine the optimal setting with a CSF dynamics test utilizing the bolus injection method (CSF dynamics test) described by Marmarou *et al.* [6].

Materials and Methods

There were a total of nine (4 women, 5 men; mean age 58.2, range 34–76) adult patients with hydrocephalus. Eight of the 9 were secondary hydrocephalus patients (seven with subarachnoid hemorrhage, one intracerebral hemorrhage), and one patient was idiopathic (Table 1). The CSF hydrodynamics of all patients were examined by means of the bolus injection method (CSF dynamics test) via lumbar puncture, lumbar drainage, or external ventricular drainage. ICP was measured by fluid-coupled strain gauge (Uniflow™, Baxter) connected to an amplifier (AP-601G, Nihon-Koden), and recorded into a personal computer (Macintosh IIci, Apple) through an A/D converter (MacLab 8/e, ADInstrument).

Initial pressure (IP), absorption pressure (AP), pressure volume index (PVI) and CSF outflow resistance (Ro) were utilized as indicators of CSF hydrodynamics. Following this test, all patients underwent a V-P shunt. Ventriculostomy was performed through an occipital burr hole, a shunt device (Codman-Medos programmable shunt) was placed on the mastoid process, and a peritoneal catheter was inserted 10 in. into the subphrenic space. At the time of the operation, the shunt valve pressure setting was 20~40% below AP obtained during the first CSF hydrodynamics test (Table 2).

Ten to 14 days after the shunt operation, another CSF dynamics test was carried out by lumber puncture. After IP was recorded, shunt pressure was set at maximum (200 mmH_2O), and then the

Table 1. *Case Description and Results of Preoperative CSF Dynamics Test*

Number of case	Age (yr)	Sex	Etiology	Modality	IP (mm Hg)	PVI (ml)	Ro (mm Hg/ml/min)	PA (mm Hg)
1	73	M	SAH	LP	11.9	13.4	24.3	21.4
2	53	M	SAH	LP	3.8	19.3	5.9	11.8
3	49	F	SAH	EVD	15.5	21.9	4.3	21.8
4	51	M	SAH	LP	20.3	27.6	13.1	28.6
5	65	M	Idiopathic	LD	19.5	15.3	2.1	22.9
6	76	F	SAH	LP	9.2	15.2	8.4	16.4
7	59	F	SAH	EVD	10.5	17.6	4.5	12.8
8	34	M	ICH	LD	12.5	16.5	8.7	18.4
9	64	F	SAH	LD	11.7	16.8	4.7	20.0

SAH subarachnoid hemorrhage, *ICH* intracerebral hemorrhage, *LP* lumber puncture, *LD* lumber drainage, *EVD* external ventricular drainage, *IP* initial pressure, *PVI* pressure volume index, *Ro* CSF outflow resistance, *PA* absorption pressure.

Table 2. *Pressure Setting and Initial Pressure at Postoperative Study*

Number of case	1	2	3	4	5	6	7	8	9
Initial setting (mm H_2O)	180	80	140	180	180	130	80	140	160
AP at setting level (mm Hg)	14.1	7.2	9.1	14.4	14.7	10.7	12.3	12.1	15.4
IP (mm Hg)	13.0	1.5	3.9	11.5	14.3	4.9	9.4	9.8	10.5
Final setting (mm H_2O)	140	150	160	140	120	130	80	120	100
Setting change	↓	↑	↑	↓	↓	→	→	↓	↓

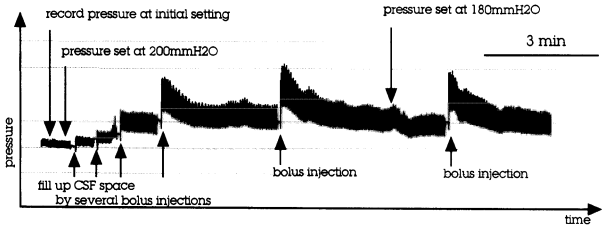

Fig. 1. Time course of post-shunt study: After initial pressure recording, shunt pressure setting was adjusted to maximum level (200 mmH_2O). CSF space was filld up by several bolus injection of saline. Repeated CSF dynamics tests were performed at each pressure setting level every 20 mmH_2O to 40 mmH_2O

CSF space was filled with several bolus injections of saline. Once a steady state was obtained, a bolus injection was carried out. The pressure setting was changed to 180 mmH_2O after three minutes of observation. This procedure was repeated every 20 mmH_2O to 40 mmH_2O (Fig. 1).

Results

Preoperative CSF Dynamics and Shunt Initial Pressure Setting

Results of the preoperative CSF dynamics test are shown in Table 1. One patient (case 2) only displayed low IP, while three patients case 3, 4, 5) had moderately elevated IP. Relatively high IP was observed in the rest of the patients, whereas AP was elevated beyond normal limits in all patients while there was reduced PVI in seven patients and Ro increase in eight patients. There was no correlation among these parameters, however. At the time of surgery, shunt pressure settings were decided on the basis of this study (20~40% below AP) (Table 2).

Postoperative CSF Dynamics, Revised Shunt Setting and Patient Outcome

IP was much lower than AP at the set level in three patients (case 3, 4, 5). Since cases 3 and 5 indicated high IP in the preoperative study, overflow was suspected. AP, PVI and Ro results with setting manipulations are shown in Fig. 2. AP showed a gradual decrease in accordance with settings, but within a range of 5 mm Hg in each case. PVI increased gradually and reached a normal range in eight of nine cases. Rapid decrease was observed in one case (case 1), and a paradoxical increase was observed at one step in case 4.

After completion of the study, the pressure level was reset to maximum within the normal range of AP, PVI and Ro. In cases in which marked discrepancy between IP and AP was observed, a higher

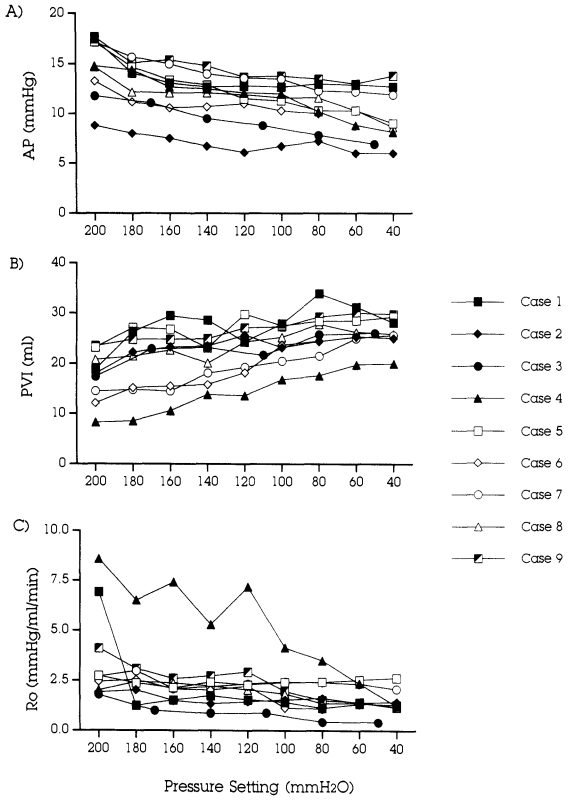

Fig. 2. Alterations of absorption pressure AP (A), pressure volume index *PVI* (B) and CSF outflow resistance *Ro* (C) in individuals with manipulation of pressure setting

setting was selected with consideration of the "siphon effect" of the shunt (Table 2).

In this series, only one patient complained of a dull headache, possibly due to low ICP, and resetting of the shunt was required. No patient encountered serious shunt problems in the follow-up period (5~25 months). All patients were free from hydrocephalic symptoms.

Complications

No major complications were experienced in this study. Due to the long duration of study (approx. 60 min), some patients were not able to remain motionless for the entire period. Sedation was required in such cases to exclude the artifact of movement. A few patients complained of a temporary "burning sensation" in the sacral area. Since the total volume of saline injected was considerably large (60~70 ml), alterations in temperature and CSF composition may have possibly influenced the nervous condition.

Discussion

The driving force of CSF flow through a differential pressure valve is generated by the difference in pressure between the inlet and the outlet of the valve. The inlet pressure mainly consists of intracranial pressure, and the outlet pressure is determined by the abdominal pressure, flow resistance of the catheter, and the hydrostatic pressure. These parameters are constantly changing with posture [3], alteration of brain condition caused by the concurrent disease, and such physiological phenomena as cough and REM sleep [4]. The CSF flow rate through the shunt at a certain pressure difference depends on the characteristics of the valve, in which there are considerable errors. As ordinary differential pressure shunts find it difficult to cope with these conditions, the programmable pressure shunt was developed and now is in wide use. There are no established criterion for determination of the optimal pressure setting. In general, pressure is set on the high side initially and then lowered in accordance with clinical symptoms and neuroradiological findings. This method requires frequent CT scannings and takes a long time to attain the optimal setting. Some investigations revealed that in adults, the opening shunt pressure does not greatly influence the clinical effect [5]. Therefore, the main benefit in using a programmable shunt is prevention of excess functioning.

CSF dynamics test using the bolus injection method by lumber puncture is an easier way of obtaining information about the intracranial pressure environment including the shunt system. Although laboratory investigations confirmed the small manufacturing error and accuracy of the Codman-Medos programmable shunt system, non-linear alterations in CSF hydrodynamics were recognized. Information pertaining to characteristics obtained by this study is helpful in avoiding unexpected alterations at certain steps in pressure setting changes. This method can, as a matter of course, only be performed in the recumbent position, and information about the dynamic changes in pressure associated with postural change cannot be obtained. In this series, the pressure difference between IP and AP at the setting level can be adopted as an indicator of the "siphoning effect" playing an important role in over-drainage.

In conclusion, a programmable shunt cannot be exampt from unexpected overflow due to the siphoning effect, but the possibility of this can be reduced by setting manipulation based upon the information

obtained by CSF dynamics test utilizing the bolus injection method.

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Correspondence: Osamu Tsuji, M.D., 2-1-1 Jonan-cho, Hitachi-shi, Ibaraki-ken, 317 Japan.

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Evaluation of Shunt Function in Patients Who are Never Better, or Better than Worse after Shunt Surgery for NPH

M. A. Williams, A. Y. Razumovsky, and **D. F. Hanley**

Neurosciences Critical Care Division, Johns Hopkins Medical Institutions, Baltimore, MD, U.S.A.

Summary

We investigated the cause of poor outcome in patients with normal pressure hydrocephalus (NPH) who did not respond as expected after shunt surgery. Two methods were used to evaluate shunts: radionuclide shunt patency study, or continuous ICP monitoring.

33/52 shunted patients (64%) from 1989 to 1995 had poor outcome, and 28/52 (54%) were investigated. Of those investigated, 9/28 (32%) were never better, and 19/28 (68%) were initially better then worse. Of 9 patients who were never better, ineffective shunt function was seen in 7; 5 had shunt revision (2 declined), and 1 improved. Of 19 patients who were initially better then worse, 15 had ineffective shunts; 15 underwent shunt revision, and 13 improved.

Poor clinical outcome occurred in two-thirds of all patients after shunt surgery for NPH, but a potentially treatable cause (i.e. obstruction of the shunt or a shunt system that was patent but did not adequately correct the CSF circulatory disorder) was found in nearly 80% (22/28) of those investigated. The predominant cause of ineffective shunt function was obstruction of the peritoneal catheter. Clinical recovery occurred in 70% (14/20) of patients who had shunt revision surgery.

We conclude that ineffective shunt function is a frequent cause of poor outcome after shunt surgery to treat NPH that should be sought and treated. These results have implications for longitudinal studies of the diagnosis and treatment of NPH. The effect of unrecognized shunt ineffectiveness on prior studies is unknown. Future studies should be designed to confirm that shunts are functioning before the diagnosis of NPH is considered incorrect.

Keywords: NPH; outcome; shunt function; shunt surgery.

Introduction

Normal pressure hydrocephalus (NPH) is an important, treatable syndrome of dementia, gait apraxia, and urinary incontinence that may represent as much as 5% of demented patients [16]. NPH is treated by surgical cerebrospinal fluid (CSF) shunting, often with significant neurologic recovery [3,12,13]. On average, only 50% of patients with suspected NPH have a good response to shunt surgery [2,7,9,13–15]. Clinical improvement after CSF shunt insertion in NPH is predicated on the effectiveness and continued functioning of the shunt. Few, if any, outcome studies of NPH have included investigation of shunt function [3,5]. We systematically evaluated shunt function in patients who were never better, or were better then worse after shunt surgery for NPH.

Methods

This report comprises patients whose first shunt for NPH was inserted between July 1, 1989 and October 1, 1995 so that a minimum of one year post shunt outcome evaluation was possible. Radionuclide shunt patency studies were performed by injection of approximately 0.5 mCi of Indium-111 DTPA into the shunt reservoir. To prevent radionuclide from being forced through the outflow tubing by the pressure of the injection (causing a false positive study), the occluder valve was compressed in those shunts that had them. Shunt obstruction was determined when elimination half-life of radioactive counts in the shunt reservoir was more than 10 minutes. If the shunt was patent, 24–48 hours continuous ICP monitoring was performed by inserting a 25-gauge needle into the reservoir and recording on an 8-channel strip chart recorder or a Macintosh computer with an analog-to-digital signal converter and software (MacLab, ADInstruments, Inc., Milford, MA). ICP was analyzed for resting mean pressure, abnormal wave forms, peak pressure, and pulse pressure. Abnormal ICP wave forms were identified according to criteria adapted from Lundberg's original description [10]. We defined B-waves as ICP oscillations with a B-wave frequency and an amplitude (peak systolic ICP minus baseline systolic ICP) of ≥3 mm Hg (40 mm H_2O). Shunts were considered ineffective if A or B-waves were identified, or if the mean ICP exceeded the expected operating characteristics of the shunt.

Results

33/52 shunted patients (64%) had poor outcome, and 28/52 (54%) were investigated. Fig. 1 shows the evaluation algorithm including the number of pa-

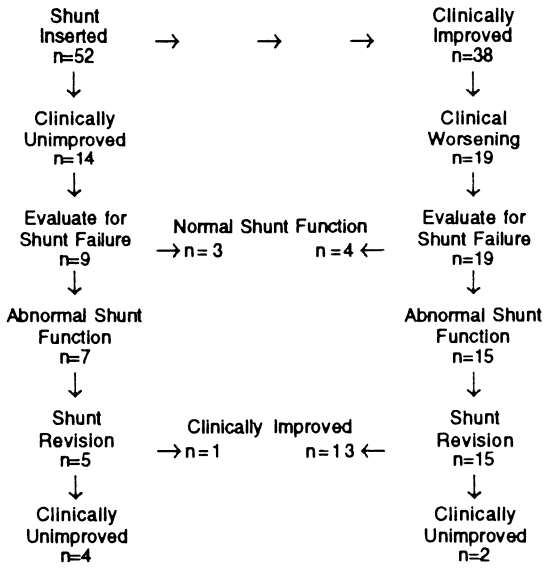

Fig. 1. Evaluation and outcome algorithm

Table 1. *Inserted and Ineffective Shunts*

Type of shunt	Number inserted	Number ineffective
PS medical delta valve, level 1.0	15	5 (33%)
PS medical delta valve, level 1.5	5	3 (60%)
PS medical delta valve, level 2.0	9	3 (33%)
Orbis-sigma valve	11	3 (27%)
Mishler low pressure	2	1 (50%)
Heyer-Schulte medium pressure	1	1 (100%)
VP shunt, brand unidentifiable	3	1 (33%)
LP shunt, brand unidentifiable	6	5 (83%)
Total	52	22 (42%)

No statistical difference between shunt types.

tients seen at each point in the algorithm. Of the 28 patients investigated, 9 (32%) were never better, and 19 (68%) were initially better then worse. Of 9 patients who were never better, ineffective shunt function was seen in 7 (78%); 5 had shunt revision (2 declined), and 1 improved. Of 19 patients who were initially better then worse, 15 (79%) had ineffective shunts; 15 underwent shunt revision, and 13 improved. Shunt ineffectiveness was seen in all types of shunts inserted (Table 1).

Radionuclide shunt patency study was performed for 25 patients, revealing delayed outflow or obstruction in 17. The site of shunt obstruction or malfunction was the peritoneal catheter in all 15 of the 17 who had shunt revision. ICP monitoring was performed in 9 patients, revealing A or B-waves, or ICP higher than expected for the shunt type in 3. One patient was evaluted by CT scan and plain abdominal x-rays, revealing edema along the shunt tract in the brain and pre-peritoneal position of the distal catheter. One patient was evaluated by exploratory laparotomy and discovered to have intestinal volvulus involving the peritoneal catheter.

Discussion

These data shows that poor clinical outcome occurred in two-thirds of all patients after shunt surgery for NPH. A potentially treatable cause (i.e. obstruction of the shunt or a shunt system that was patent but did not adequately correct the CSF circulatory disorder) was found in nearly 80% (22/28) of those investigated, and clinical recovery occurred in 70% (14/20) of patients who had shunt revision surgery. The predominant cause of ineffective shunt function was obstruction of the peritoneal catheter.

The concept of shunt ineffectiveness has received little attention in the literature regarding outcome in shunted NPH patients. Crockard *et al.* demonstrated the presence of B-waves in five previously shunted patients who were being evaluated for shunt malfunction [5]. Shunt insertion or revision abolished B-waves in these patients. No other reports of ICP monitoring and NPH have commented on shunt ineffectiveness in non-responders [2,4,6–9,11,13], yet as many as two-thirds of shunts vary from manufacturer's specifications by more than 30% [1].

The predominance of peritoneal catheter obstruction suggests either that alternate types of shunts should be inserted, such as ventriculo-atrial or ventriculo-pleural, or that efforts to design peritoneal catheters to make them resistant to envelopment by the peritoneum and omentum are necessary. Our study did not include patients with ventriculo-atrial or ventriculo-pleural shunts; thus we cannot determine whether these sites are less prone to obstruction.

We conclude that ineffective shunt function is a frequent cause of poor outcome after shunt surgery to treat NPH that should be sought and treated. These results have implications for longitudinal studies of the diagnosis and treatment of NPH. The effect of unidentified or unrecognized shunt ineffectiveness on prior studies is unknown. If the true predictive value of preoperative tests or clinical findings is to be known, then the true response rate of surgical shunting must be known, and it must be demonstrated that patients who fail to respond to surgical

shunting have properly functioning shunts. Future outcome studies of NPH should be designed to confirm that shunts are functioning before the diagnosis of NPH is considered incorrect.

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Correspondence: Michael A. Williams M.D., Neurosciences Critical Care Division, Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Meyer 8-140, Baltimore, MD 21287-7840, U.S.A.

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Differential Diagnosis of NPH and Brain Atrophy Assessed by Measurement of Intracranial and Ventricular CSF Volume with 3D FASE MRI

M. Yoshihara[1], **A. Tsunoda**[2], **K. Sato**[3], **S. Kanayama,** and **A. Calderon**[4]

Department of Neurosurgery, [1] Ohta General Hospital, [2] Koshigaya Municipal Hospital, [3] Juntendo Hospital, and Toshiba R&D Center, Japan

Summary

Differential diagnosis of NPH and brain atrophy is sometimes difficult. Recently, a new method using MRI was introduced as a noninvasive, direct technique for the measurement of intracranial CSF volume. Using this new technique, we measured the intracranial and ventricle CSF volume in patients with enlarged ventricles in order to differentiate between NPH and brain atrophy. Ten healthy volunteers (control group) and 21 patients with enlarged ventricles were enrolled in this study. Eleven out of 21 patients were clinically diagnosed as having NPH (shunted group) and the remaining 10 patients were considered to have cerebral atrophy (non-shunted group). Intracranial and ventricular CSF volume in each case were measured by 3D FASE (Fast Asymmetric Spine-Echo) MR imaging sequence with region growing method. Ventricular/intracranial CSF volume ratio was also calculated. Ten out of 11 patients showed improvement in clinical symptoms and/or dementia scale after shunting. Our results clearly indicate that the ventricular volume in the shunted group was enlarged and that the ventricular/intracranial CSF ratio was significantly high. Thus we concluded that enlarged ventricle with high ventricular/intracranial CSF volume ratio strongly suggests NPH.

Keywords: Brain atrophy; CSF volume; 3D FASE MRI; NPH.

Introduction

Since the introduction of CT scanning, ventricular dilatation has frequently been observed and the diagnosis of hydrocephalus has become relatively easy. However, differential diagnosis of Normal Pressure Hydrocephalus (NPH) and brain atrophy is sometimes difficult. From the morphological point of view, the presence or absence of dilated cortical sulci and cisterns associated with ventricular dilatation are the key findings in differentiating NPH from brain atrophy [2–4]. Recently, a new method using magnetic resonance (MR) imaging was introduced as a noninvasive, direct technique for the measurement of intracranial cerebrospinal fluid (CSF) volume. In the present study, the three-dimensional Fast Asymmetric Spin Echo (3D-FASE) method [1], in combination with the Region Growing Method (RGM)(8), was used to perform quantitative analysis of the intracranial and ventricular CSF volume. Using this new technique, we measured the intracranial and ventricular CSF volume in patients with enlarged ventricles in order to differentiate between NPH and brain atrophy.

Materials and Methods

Subjects

A total of 31 subjects were enrolled in this study. Twenty-one patients with enlarged ventricles were divided into two groups: 11 patients (age, 63.3 ± 13.35 years; range, 34–80 years) were clinically diagnosed as having NPH and underwent shunting (shunted group), and the remaining 10 patients (age, 74.3 ± 10.56 years; range, 52–86 years) were considered to have cerebral atrophy and did not undergo shunting (non-shunted group). Ten healthy volunteers with no history of neurological diseases (age, 38.7 ± 9.80 years; range, 27–55 years) were selected as a control group.

Intracranial Pressure Monitoring

Before shunting, the intracranial pressure was monitored by lumbar puncture to confirm the diagnosis of NPH. The mean CSF outflow resistance was 11.3 ± 5.67 mm Hg/ml/min. All monitored patients but one had high CSF outflow resistance (greater than 5.0 mm Hg/ml/min).

MR Data Acquisition

MR images were obtained using a 1.5-T MR system (VISART, Toshiba Corporation, Tokyo). The imaging parameters employed were the 3D-FASE method with a repetition time of 6,000 ms, an echo time of 250 ms, a matrix of 256 × 256 × 100, and a slice thickness of 1.5 mm. In FASE scanning, the imaging time is further reduced by the FSE fast-scan method and also by the combined use of the Half-Fourier method [1]. The images obtained by the FASE method are heavily T2-weighted images in which only free water is visualized at high signal intensity. The imaging area was set to include all of the subarachnoid space above the superior margin of the atlas. The time required for imaging was approximately 10 minutes.

Data Analysis

Images were processed using an SGI workstation (Indigo 2) and universal image processing software (AVS version 5.02). In Region Growing Method (RGM), the region expands from a point in the specified area of sampling objects to include adjoining areas which are considered to belong to the same region [8].

With regard to the measurement of ventricular volume (VV), the region for measurement was first specified manually for 10 slices as a unit. Then, the CSF space showing a high signal intensity in the specified region was extracted using RGM (Fig. 1). With regard to the measurement of intracranial CSF volume (ICV), the specified region was set to exclude the paranasal sinuses and the orbits, and processed again using RGM (Fig. 1). All data processing was completed within about 20 minutes. VV and ICV were measured in all subjects, and the ratio between VV and ICV (VV/ICV ratio) was calculated. Each parameter was compared among three groups using the unpaired t test.

Assessment of Outcome

Outcome was evaluated at 3 months after shunting. The Hasegawa dementia scale or Glasgow coma scale was used to evaluate of outcome. Improvements in gait disturbance and urinary incontinence were also evaluated clinically.

Results

Intracranial CSF Volume, Ventricular CSF Volume and Ventricular/Intracranial CSF Volume Ratio in Each Group

Typical 3D displayed images in each group for volume calculation are illustrated in Fig. 2. The mean intracranial CSF volume(ICV), ventricular CSF volume(VV) and ventricular/intracranial CSF volume ratio(VV/ICV ratio) in each group are shown in Table 1.

The mean ICV and VV were increased in both the shunted and non-shunted groups compared with the control group ($P < 0.01$). A statistically significant

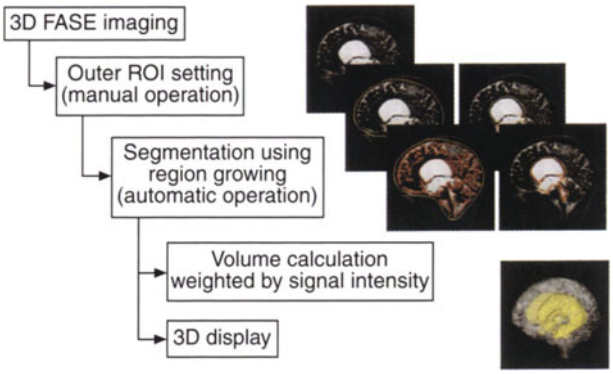

Fig. 1. A process of CSF volume measurement with 3D-fast asymmetric spin echo imaging and region growing method

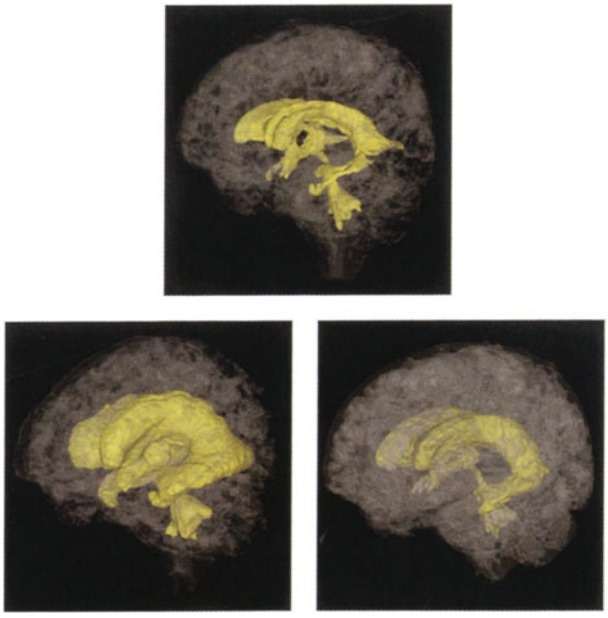

Fig. 2. 3D-display of the segmented regions. Representative case in control group (upper), shunted group (lower left), and non-shunted group (lower right)

Table 1. *Average Values of Intracranial CSF Volume, Ventricular CSF Volume and Ventricular/Intracranial CSF Volume Ratio*

	Intracranial CSF volume (ml)	Ventricular CSF volume (ml)	Ventricular/intracranial CSF volume ratio (%)
Control group (N = 10)	142.4 ± 48.88	14.9 ± 5.84	10.4 ± 1.52
Shunted group (N = 11)	193.0 ± 66.46	67.2 ± 15.81	38.2 ± 14.23
Non shunted group (N = 10)	247.9 ± 87.85	46.3 ± 26.73	17.9 ± 5.16

difference was also noted in VV/ICV ratio between the shunted and control groups ($P < 0.01$), but not between the non-shunted and control groups ($p = 0.56$).

Outcome

Ten out of 11 shunted patients showed improvement in clinical symptoms and/or dementia scale after shunting. Only one patient was unchanged, and no patients showed deterioration.

Discussion

Accuracy of CSF Volume Measurement

The first measurements of the intracranial CSF space were obtained in studies involving cadavers, and reports concerning clinical applications were performed using CT and MR imaging [5–7,9]. MR imaging seems to have a number of advantages over CT in terms of spatial resolution and ability to characterize the composition of the fluid. Furthermore, compared with conventional MR imaging methods, the 3D-FASE method employed in this study has the following advantages in measuring CSF volume.

(1) The most difficult problem in analyzing volume data is related to partial volume effects, with accuracy dependent on slice thickness. The conventional 2D imaging method employed in a number of studies is limited in terms of reducing the slice thickness because of deterioration of the signal-to-noise (S/N) ratio. The 3D imaging method permits continuous thin slices to be obtained without deterioration of the S/N ratio, resulting in more accurate volume measurement than 2D imaging. Moreover, 3D-FASE employs the Fase Spin Echo method for fast image acquisition in combination with the Half-Fourier method for image reconstruction (1), making it possible to visualize the entire intracranial area within a practical period of time.

(2) 3D-FASE provides heavily T2-weighted images, and demonstrates the CSF at high signal intensity with a longer relaxation time, resulting in improved visualization of the CSF space.

(3) The use of the spin-echo method permits images to be obtained with less distortion caused by magnetic inhomogeneities and chemical shift. 3D-FASE is less affected by these factors, which are often a problem in fast imaging field echo methods such as the Echo Planar Imaging method and the FE method. Therefore, it is suitable for depicting morphological structures and measuring volumes.

In the control group, the mean intracranial CSF volume was 142.4 ± 44.88 ml and the mean ventricle CSF volume was 14.9 ± 5.84 ml. These values are comparable to those reported in previous studies.

Diagnosis of NPH

Even when the diagnosis of NPH is based on clinical features and characteristic findings on CT scans [2–4], it is difficult to predict the effectiveness of shunting. This is probably because patients with brain atrophy may sometimes be misdiagnosed as having NPH. Black reported improvement in 85% when ventricular enlargement was associated with little or no sulcal enlargement, and only in 33% when there was sulcal enlargement [3]. Therefore, the chances of improvement after treatment are increased when patients with atrophic changes were excluded. Our results clearly showed that the ventricular volume in the shunted group was markedly enlarged and that the ventricular/intracranial CSF volume ratio was significantly elevated. These results indicate that the increase in CSF volume is mainly in the ventricles. This distribution of CSF strongly supports the diagnosis of NPH. Moreover, 91% of patients (10 out of 11) in the shunted group showed improvement after shunting. Based on these results, the patients in the shunted group in the present study could be diagnosed as having NPH with a high degree of confidence.

On the other hand, in the non-shunted group, the intracranial volume was markedly enlarged, but with only a moderate increase in ventricular volume. Consequently, the ventricular/intracranial CSF volume ratio was slightly increased compared with the control group, indicating that the increase in CSF volume was mainly in the cortical sulci and cisterns. This distribution of CSF strongly supports the diagnosis of brain atrophy.

Thus, we conclude that quantitative assessment of the intracranial CSF distribution makes it possible to accurately differentiate between NPH and brain atrophy, with ventricular enlargement (greater than 50 ml) and a high ventricular/intracranial CSF volume ratio (greater than 30%) strongly suggestive of NPH.

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Correspondence: Masaaki Yoshihara, M.D., Ohta General Hospital, Division of Neurosurgery, 1-50 Nisshin-cho, Kawasaki-ku, Kawasaki City, Kanagawa Pref., Japan.

Abstracts

Tenth International Symposium on Intracranial Pressure

O - 1 - 01

MULTIMODAL MONITORING OF REFRACTORY INTRACRANIAL HYPERTENSION

John D. Pickard, Marek Czosnyka, Peter Kirkpatrick

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, UK

Introduction : Measures to manage refractory intracranial hypertension are limited. Consensus classification of refractory hypertension is lack of response to classical attempts (CSF drainage, anaesthesia, hyperventilation, osmotherapy) to reduce ICP increasing above 40 mmHg over a period longer than 3 hours. High dosage barbiturate is nonproven . Decompressive surgery may induce local herniation, when ICP is already grossly elevated but has a role. Methods of monitoring of cerebral dynamics to anticipate terminal ICP rises would be helpful.

Methods: Our own experience is based on continuous multi-modal monitoring of 200 consecutive patients suffering from head injury. 18 deaths were associated with severe intracranial hypertension.

Results: Computer supported data analysis demonstrated examples of deranged cerebrovascular pressure responses seen when cerebral perfusion pressure was declining below 50 mmHg. A positive association of slow waves in arterial pressure and ICP and also pressure-passive behaviour of transcranial Doppler waveform have been selected as particularly useful for anticipating death from severe intracranial hypertension by several hours. Also derangement of relationship between pulse amplitude of ICP and mean ICP level was found to be a good predictor of fatal termination. Impending intracranial hypertension should normally be accompanied by a rise in pulse amplitude of ICP. Where the increase in ICP (>30 mmHg) is associated with a distorted amplitude-pressure relationship the critical threshold of intracranial hypertension has been reached with limited time for large decompressive craniotomy to reduce ICP.

Conclusion: Multimodal monitoring supported by computer on-line data analysis may be useful for anticipating terminal rises in ICP.

O - 1 - 02

NIR Reflexion-Spectroscopic Assessment of Cerebral Oxidative Metabolism during Intracranial Hypertension using a novel Spectroscopic System: Multiscan OS 30

Kai-Michael Scheufler and Josef Zentner

Department of Neurosurgery, University of Bonn, Germany

Introduction: Increases of ICP beyond autoregulatory capacity following head trauma significantly increase mortality by producing deleterious effects on cerebral microcirculation with impairment of cerebral oxygenation. This study investigates the influence of cerebral perfusion pressure (CPP) on local intracapillary hemoglobin oxygenation (SO_2), cytochrome aa3 ($Cytaa_3$) redox state and local tissue hemoglobin concentrations (HbO_2/ total Hb) recorded in real time by a new reflexion-spectroscopic system. These parameters were referenced to simultaneous recordings of spontaneous cortical electrical activity.

Methods: Multiscan OS 30 is a new multiwavelength reflexion spectroscopic system designed for in vivo studies of oxidative metabolism. Newly developed algorithms based on the entropy pattern of photons allow for quantitative assessment of SO_2 (100-0%), $Cytaa_3$ redox state ($Cyaa_3ox/red$ [%]) and absolute tissue concentrations of $Cytaa_3$ (µg/ml), HbO_2 and total Hb (mg/ml) within a tissue sector of defined geometry. 10 male rabbits were subjected to artificially raised ICP by cisternal infusion of artificial CSF. Local SO_2, $Cytaa_3$ redox state and tissue concentrations of HbO_2, total Hb and $Cytaa_3$ were recorded through a transdural window exposing the cerebral hemispheres during stepwise reduction of cerebral perfusion pressure (CPP). Electrocortical activity was monitored by 8-channel EEG.

Results: Cerebral SO_2, $Cyaa_3ox$ and and HbO_2 concentrations were tightly correlated to CPP (r^2: 0.98;P< 0.001), whereas total Hb conc. were not (r^2< 0.6; P< 0.1). CPP values varied by up to 100% between individual animals for any given SO_2 (HbO_2/ oxidised $Cytaa_3$)-level and thus were not predictive of tissue oxygenation (see table 1). Contrarily, distinct SO_2-levels were associated with either autoregulatory responses to ischemia (decreasing EEG-frequency/ischemic arterial pressor response at cerebral SO_2-levels around 30%) or signs of cellular hypoxia (EEG-flatline, bradycardia at SO_2-levels approaching 0%).

Conclusions: SO_2 and $Cytaa_3$ redox state appear to reflect cellular energy metabolism and cerebral autoregulation as well as disturbed local hemodynamics in a quantitative and reproducible fashion with a sensitivity similar to the EEG. Definition of both functional and structural ischemic thresholds may be feasible using this model of global cerebral ischemia.

O - 2 - 10

Disturbances of Cerebral Haemodynamics in the Patients with Benign Intracranial Hypertension Syndrome *(radionuclide aspect).*

Kulakova Svetlana, V, Scherbakova E. Ya., Gasparian Sergey S. Burdenko Neurosurgical Institute, Moscow, Russia.

Introduction:

It is well-known, that one of the reasons of intracranial hypertension is CBF abnormalities, including venous outflow disorders. The aim of this study was to investigate disturbances of blood flow in extracranial vessels (carotid and vertebral arteries) and cerebral (anterior, middle and posterior)arteries in patients with benign intracranial hypertension (BIH) syndrome, with special attention to impairment of venous outflow (dural sinuse and jugular veins).

Patients and Methods:

We studied 51 patients with BIH syndrome (39 females and 12 male, aged 14-67), who were underwent to radionuclide cerebral angiography (RCA), including carotid angioscintigraphy (CAS), vertebral angioscintigraphy (VAS) and sinusoscintigraphy (SS). In order to verify thrombosis of dural sinuses 7 patients had MR angiography and 3 patients had digital subtraction angiography. All the patients wre investigated by both standard neurological/opthalmological examinations and CT.

Results:

Findings of CAS showed participation of internal carotid artery in the pathological process of three patients. VAS revealed vertebral artery blood flow disturbances in 17 patients. More frequently middle and posterior cerebral arteries dysfunction was observed. Sinoscintigraphy showed normal patterns in none of the patients. The following three pathological sinoscintigraphic patterns have been found:

- transversal sinus, signoid sinus and jugular vein were visualized only unilaterally;
- uneven distribution of tracer in one of these formations;
- pathological sigmoid sinus or jugular bulb enlargement.

Conclusion:

RCA always revealed venus outflow disorders in patients with RIH syndrome. We continue to recommend its routine use as a screening test.

O - 2 - 11

METABOLIC CHANGES IN THE BRAIN DURING TRANSIENT ISCHEMIA MEASURED WITH MICRODIALYSIS

S.P. Gopinath, M. Uzura, A.B. Valadka, J.C. Goodman, C.S. Robertson. Departments of Neurosurgery and Pathology, Baylor College of Medicine

Introduction

Transient jugular venous desaturation has been observed in 40% of patients with severe head injury, and has been associated with a poor neurological outcome. The purpose of this study was to examine the changes in cerebral metabolism that occur during transient jugular desaturation.

Methods

A loop design microdialyisis probe constructed of .2mm diameter dialysis tubing (MW cut-off 6000 daltons) was placed in frontal cortex of 77 patients with severe head injury. The dialysis probe was perfused with sterile saline at 2 µl/min, and sample were collected at 30 minute intervals. Glucose, lactate, glutamate, and potassium were measured in the samples. Samples collected before, during, and after an episode of jugular venous desaturation were analyzed, and compared to changes in physiological parameters.

Results

Twenty-five episodes of jugular venous desaturation occurred during the period of microdialysis monitoring. The biochemical changes are summarized in the table below. Brain tissue pO_2 decreased with the $SjvO_2$. The dialysate concentrations of lactate and glutamate were significantly increased as $SjvO_2$ decreased. The concentrations of dialysate glucose tended to be decreased but the changes were not significant. The concentrations of dialysate potassium were not changed.

	Before Episode	During Episode	After Episode
$SjvO_2$	69±2	43±2*	66±2
$PbtO_2$	33±2	13±7*	42±30
Lactate	.56±.09	1.25±.17*	.50±.07
Glutamate	10±3	25±8*	9±3

An additional 5 episodes of jugular venous desaturation were observed terminally in patients with refractory intracranial hypertension. With this severe irreversible ischemia, dialysate concentrations of lactate, glutamate, and potassium were increased, and dialysate glucose concentrations fell to zero.

Conclusions

$SjvO_2$ monitoring identifies episodes of cerebral hypoxia/ischemia which are associated with alterations in cerebral metabolism that can be measured with the microdialysis technique.

O-2-12

Shunt Systems and Quality Control - a Fully Automated Test Stand for Medical Microvalves.

M. Walter[1], S. Leonhardt[1], P. Wabel[1], A. Aschoff[2]

[1]Department of control Engineering, University of Technology Darmstadt
[2]Department of Neurosurgery, University of Heidelberg

Introduction
In this paper, a fully automated test stand for medical microvalves used in Hydrocephalus therapy is presented. Although these microvalves ("Shunts") have been used rather successfully for more than 30 years, some major problems have not yet been solved. The valves may be obstructed by blood or proteins or remain open due to ageing and mechanical malfunction. Other problems are production faults and constructive insufficiencies. Since the "disaster" with Holter-Hausner Valves in the 80's, the need for reliable test methods and equipment is inevitable. The presented test stand allows the measurement of pressure flow characteristics of shunt systems. It may be used for pre- or post implantation quality control or as a design platform for new systems.

Setup of the test-stand
The differential pressure applied to the test specimen is measured with a high precision pressure sensor and the flow is measured with a newly designed flowmeter. Both values may be used as the desired value in a closed loop control and are adjusted via a proportional valve. The test-stand features facilities to test the shunt sensitivity to bending, variation of orientation and vertical acceleration. Furthermore the shut properties at dynamic excitation can be evaluated. A user friendly application software has been developed in order to support the user in the fully atomized execution of several testing protocols and in handling the measurement data.

Experimental results
More than 30 different Shunt constructions were tested with the new designed test rig and were compare with measurements mad by Aschott. The results matched, except of only a few cases, where the characteristic of the test specimen changed due to handling and ageing. Some exemplary testing results will be presented.

Conclusions
The presented test stand allows to determine the characteristics of medical microvalves. In addition to the hydraulic properties the influence of everyday stress may be simulated. The test rig may be of interest to medical device manufacturers or technical test laboratorys as well as to surgeons for testing shunt systems pre-or post operatively.

O-3-13

PREVENTION OF SECONDARY INSULTS AFTER HEAD INJURY

C.S. Robertson, A.B. Valadka, S.P. Gopinath, M. Cormio, M. Uzura, C.F. Contant, R.G. Grossman

Department of Neurosurgery, Baylor College of Medicine

Introduction
Secondary ischemic insults severe enough to result in jugular venous desaturation have been observed in 40% of patients with severe head injury and have been associated with a poor neurological outcome. The most common preventable causes of these ischemic insults were hypotension and hypocarbia. The purpose of this study was to determine if a management protocol emphasizing maintenance of cerebral perfusion and therefore prevention of secondary ischemic insults improves neurological outcome after head injury.

Methods
The following three hypotheses were tested: patients managed with the experimental protocol will have (1) a reduced incidence of transient cerebral ischemia, (2) a reduced incidence of refractory intracranial hypertension, and (3) a better long-term neurological recovery than patients managed with the standard protocol. Adult patients admitted to Ben Taub General Hospital between July 1994 and March 1997 were eligible for the study if they had a motor GCS ≤ 5 due to head injury. Patients with GCS 3 or a contraindication to placement of a jugular bulb catheter were excluded from the study. Patients admitted to the study were randomly assigned to one of two treatment protocols, the standard protocol emphasizing control of ICP and the experimental protocol emphasizing optimizing cerebral perfusion and prevention of ischemic insults. The major differences in the 2 treatment protocols are outlined in the table.

	Goals for Standard Protocol	Hypothesized Critical Values	Goals for Experimental Protocol
ICP	< 20 mm Hg	25 mm Hg	< 20 mm Hg
MAP	> 70 mm Hg	80 mm Hg	> 90 mm Hg
CPP	> 50 mm Hg	60 mm Hg	> 70 mm Hg
pCO_2	25-30 mm Hg	25 mm Hg	35-40 mm Hg

The primary outcome measure for the study was the incidence of jugular venous desaturation, defined as a decrease in $SjvO_2$ to less than 50% for more than 10 minutes. Secondary outcome measures were the incidence of refractory intracranial hypertension and 6 month neurological outcome (GOS and DRS). The sample size calculation of 91 in each treatment arm was based on an expected reduction in the incidence of jugular venous desaturation from 40% to 20% (80% power at the alpha level of 0.05). The effects of the 2 management protocols on the incidence of jugular venous desaturation and the incidence of refractory intracranial hypertension will be presented.

O-3-14

NEUROINTENSIVE CARE WITH SPECIAL ATTENTION TO ICP AND EARLY ANEURYSM SURGERY IMPROVED SURVIVAL AFTER SAH. A 12 YEAR STUDY.

Kristina G Cesarini, Hans-Göran Hårdemark and Lennart Persson

Departments of Neurosurgery and Neurology, Uppsala University Hospital, Uppsala, Sweden

Introduction
In the mid-eighties we decided to change our management of patients with aneurysmal SAH based on the concept that unfavourable outcome was a consequence of all ischemic impacts sustained by the brain during the acute phase of the disease. Management was focused on detection and treatment of such ischemic impacts e.g. increased ICP, hypotension, hypoxemia, pyrexia, seizures, hyperglycemia and arterial vasospasm.
Special attention was payed to the control of ICP. Intracranial hematomas were evacuated promptly. CSF drainage at a level of 15 mm Hg was regularly used. Most patients were operated on within 3 days. The care included 3-H-therapy, nimodipine and artificial ventilation in patients not obeying commands.

Methods
We studied all patients with aneurysmal SAB admitted between 1981-92 [(n=874). (1981-1985 retrospect., 1986-92 prospect.)]. A large number of parameters reflecting the state on admission and the clinical course were registered. Clinical outcome was assessed as mortality at 30 days and 6 months and GOS at 2-9 years.

Results
During the last years of the studied period more patients with severe SAH were admitted and the number of patients from our defined referral region increased from around 60 to 80 per year. The 30-day mortality dropped from 29% to 9% and the 6 months mortality from 33% to 15%. At 2-9 years, the favourable outcome (GOS: good recovery and moderate disability) increased from 58.6 to 66% and the proportion of patients with severe disability increased from 6% to 17%.

O-3-17

Simultaneous Measurement of Brain pO_2, pCO_2, pH und Temperature in the Right and Left Frontal White Matter in a Porcine Model

A. Rieger, M. Menzel, S. Roth, J. Soukup, C. Peuse, I. Miko, I. Furka, W. Burkert
Department of Neurosurgery, Anaesthesiology, Martin-Luther-Universität Halle-Wittenberg, Germany
Department of Experimental Surgery, University Debrecen, Hungary

The clinical use of brain tissue oximetry to monitor patients with severe head injury is increasing (1,2). We evaluated a newly available multiparameter probe in both hemispheres in brain tissue in an intracranial pressure porcine model. Pathological and physiological conditions were studied with this methodology to obtain normal values and to find out limitations of the method.

Methods
Paratrend 7® probes (BSL, Highwycombe, UK) were placed in the left and the right frontal white matter to measure pO_2 ($PtiO_2$), pCO_2 ($PtiCO_2$), pH and temperature during increased intracranial pressure by inflating an infratentorial Fogarty balloon catheter in 9 pigs under general anaesthesia. The intracranial pressure was measured by interparenchymal probes in both hemispheres simultaneously as well. After the end of the non survival experiment 5 mm thick coronar slices were made and the histology was studied.

Results
The ICP was increased to an ICP_{mean}=60mmHg (SD±10). The course of ICP in both hemispheres correlated well: r_{mean}=0.987 ($p<0.001$). All 4 parameters of the multisensorprobe showed in both hemispheres a similar change in relation to the induced decline to the cerebral perfusion pressure (CPP). Excellent correlation regarding all 4 parameters was seen between the simultaneous measurements in both hemispheres: r=0.66-0.99 ($p<0.001$).
However, the absolute values of the 4 parameters were different. The ranges between the bihemispherical measurements were PtiO2: 0.65-18.33 mmHg, PtiCO2:1.30-18.71, pH:0.023-0.168. This findings would not be explained by histology.

Summary and Conclusions
Brain tissue oximetry showed a close correlation to CPP changes in this model. The additionally three parameters of the multiparameter probe did as well. The differences of absolute values in bilateral measurements indicate a limitation of the method. This is important especially interpreting measured values and introducing threshold values for patient monitoring.

Literature: [1] J Neurosurg (1996) 85: 751-756
[2] J Neurosurg (1996) 38: 21-31

O - 3 - 18

PET ASSESSMENT OF VASODILATORY EFFECT OF CO_2 AND ACETAZOLAMIDE ON CEREBRAL VASCULATURE

Inao S, Kuchiwaki H, Bundo M, Terada K, Mizutani N, Yoshida J, Tadokoro M*, Nishino M*, Gambhir S*

Department of Neurosurgery, and Department of Radiology*, Nagoya University School of Medicine

We quantitatively compared the vasodilating effect of 5% CO_2 inhalation and 1g of intravenous acetazolamide by positron emission tomography (PET). Cerebral blood flow was assessed in 6 patients with chronic cerebrovascular disease (unilateral ICA or MCA occlusion) using oxygen-15 labeled water in the following conditions; 1) at rest, 2) during 5% CO_2 inhalation for 4 minutes (post-CO_2), 3) at 10 minutes after intravenous injection of 1g acetazolamide (post-ACZ10), 4) at 25 minutes after injection (post-ACZ25). Cerebrovascular reserve capacity (dCBF) was obtained and expressed as a change in cerebral blood flow from baseline under a vasodilatory stimulation. Arterial blood gas and systemic blood pressure were obtained in each measurement.

Mean increase of $PaCO_2$ after CO_2 inhalation was 3.7 mmHg. Systemic blood pressure didn't change throughout the experiment. Cerebrovascular reserve capacity (dCBF) showed a significant linear correlation between post-CO_2 and post-ACZ10 in both non-lesion side ($r=0.701$, $p<0.001$) and in lesion side ($r=0.626$, $p<0.005$). However, in non-lesion side cerebrovascular reserve capacity showed inverse proportion between post-CO_2 and post-ACZ25 ($r=0.784$, $p<0.001$). In the lesion side, cerebrovascular reserve capacity showed non significant relation between post-CO_2 and post-ACZ25. The mean value of reserve capacity was different between CO_2 (5%) and acetazolamide (35-50%).

Although a similar vasodilatory response is elicited by both vasodilators, acetazolamide seems to be more potent and therefore should be preferred to detect patients with serious limitations of cerbrovascular reserve capacity. However, the results should be carefully evaluated because the vasodilatory effect of acetazolamide was dependent upon both the resting flow state and tissue lesion.

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Evaluation of cerebral autoregulation by jugular bulb oximetry

Bauhuf C, Hofmann R, Steinmeier R, Fahlbusch R
Neurochirurgische Klinik, Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction: Knowledge about the individual autoregulatory capacity provides useful information for the management of the severely head injured patient as well as in high-grade subarachnoid hemorrhage. With transcranial Doppler sonography and jugular bulb oximetry, two real time monitoring tools are now available for continuous bedside assessment of intracranial hemodynamics. In order to evaluate cerebral autoregulation, we postulated the following hypotheses: (1) In case of preserved autoregulation, decrease of cerebral perfusion pressure (CPP) leads to cerebral vasodilatation and therefore results in an elevation of intracranial pressure (ICP) by increase of intracranial blood volume. (2) Under the condition of intact autoregulation cerebral oxygen extraction remains constant when CPP changes.

Material and Methods: In 11 individuals (7 suffering from subarachnoid hemorrhage (SAH), 4 with traumatic brain injury (TBI) overall 26 autoregulation tests were performed with nitroprusside-induced reduction of arterial blood pressure (aBP). We used a digital multimodal data acquisition system for continuous measurement of aBP, ICP, flow velocity within the middle cerebral artery (FV_{MCA}), and jugular bulb oxygen saturation (SjO_2). Pre-test mean values and maximum Δ-values were calculated for each signal and normalized. Since the degree of autoregulatory action should express itself in a change of intracranial pressure, an autoregulation index (ARI) was calculated as follows: $ARI = \Delta ICP/\Delta aBP$.

Results: Mean ΔCPP was -21.2mmHg. In case of ARI<0.2 (n=14) there was a strong positive correlation between ΔCPP and ΔFV ($r=0.78$) as well as between ARI und ΔSjO_2 ($r=0.71$). ΔFV was -15.4 ±3.5cm/s and ΔSjO_2 was -5.1 ±2.3% in this group. In the group of high autoregulation index (ARI≥0.2, n=12), corresponding regression analyses showed no significant correlation. Both, ΔFV(-11.3 ±2.3cm/s) and ΔSjO_2 (-2.9 ±2.8%) was lower in this group.

Conclusions: Strong positive correlation between ΔCPP and ΔFV as well as between ARI and ΔSjO_2 indicates impaired autoregulatorey capacity. In these cases, reduction of aBP is not followed by a significant elevation of ICP. Missing correlation between ΔCPP and ΔFV as well as between ARI and ΔSjO_2 supports the suggestion of adequate autoregulatory response. Therefore, cerebral autoregulatory action can be assessed by means of jugular bulb oximetry.

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Comparison of Vasopressor and Mannitol Therapy in a Model of Steadily Rising ICP

Koji Hayasaki,M.D,Ph.D, A. Beaumont Bsc(Hons), Anthony Marmarou,Ph.D.

Division of Neurosurgery, Medical College of Virginia, Richmond, Virginia, U.S.A.

Introduction
Previous studies have shown that elevating blood pressure in damaged brain exacerbates edema. The objective of this study was to compare cerebral perfusion and edema development with CPP managed by elevating blood pressure vs CPP managed by reducing ICP.

Methods
An impact acceleration model was used to induce closed head injury. 26 animals were separated into 5 groups. Two groups were sham operated and dosed with either dopamine(n=4) or mannitol (n=4). Two groups were injured and treated with either dopamine(n=6) or mannitol(n=6) and one group was injured and not treated.(n=6) Following TBI, a 30-minute insult of hypoxia (PaO2 40 mmHg) and hypotension (mean arterial blood pressure (MABP) 35 mmHg) was imposed and the animals were resuscitated. 2 hours post trauma, systemic vasopressor (dopamine) was used to maintain cerebral perfusion pressure (CPP) at or above 70 mmHg or mannitol was administered intravenously in a dose of 1 mg/kg. MABP, ICP, CPP, and cerebral blood flow (CBF) were monitored. 5 hours post trauma, the animals were sacrificed and brain water content was measured.

Results
In the untreated THH group, CPP and CBF after second insult remained at low levels despite resuscitation, with a monotonic increase to 46 mmHg in ICP. In the mannitol treated THH group, ICP was reduced significantly ($p<0.01$) and both CPP and CBF were increased. ($P<0.05$) In dopamine treated THH group, both CPP and CBF also increased ($p<0.05$). ICP was reduced transiently in the dopamine group but continued to rise and reached the same level as the untreated group at the end of the 5 hour experiment. Water contents in injured animals were significantly higher than that of sham ($p<0.01$), but there was no difference in water content between these three injured groups.

Conclusions
There was no difference in CBF profiles with CPP management with either dopamine or mannitol, and pressor therapy did not result in increased edema.

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Fronto-occipital CBF ratio in severe head injury: correlation with severity and prognosis.

Della Corte F., Caricato A., Clemente A., Sabia G., Anastasi F., Giordano A.* - Institutes of Anesthesiology and Intensive Care - *Nuclear Medicine - Catholic University of the Sacred Heart School of Medicine - Rome - Italy

Cerebral blood flow (CBF) in acute head injury (HI) is characterized by a great variability both in global mean values and in regional pattern of flow depending on time of determination, type of primary lesions, age, kinetics of trauma. A common feature of CBF distribution in posttraumatic coma is frontal hypoperfusion (1). Our study was aimed to evaluate CBF fronto-occipital ratio (F/O) in the acute phase of severe HI in comparison with distribution in normal subjects and its correlation with prognosis.

Methods
CBF was determined in 23 comatose pts (GCS $\leq$ 8) in the first 48 hrs after trauma by a brain dedicated tomograph capable of performing both static and dynamic ^{133}Xenon SPECT (CERTO 96). 12 pts (56.5%) showed on CT scan a diffuse brain lesion, 11 pts (43.5%) isolated focal lesions. The ratio of averaged CBF values of the anterior, superior and middle frontal regions and of occipital CBF of both sides referred to as F/O ratio. Outcome was evaluated according to the GOS. Data are expressed as mean or median values $\pm$ SD.

Results
The mean F/O ratio was 0.78 $\pm$ 0.28 and it was significantly lower than in age-matched controls (1.12 $\pm$ 0.11; $c^2 = 11.889$, $p < 0.01$). F/O ratio did not correlate with GCS.There were no significant differences in F/O ratio between pts with GOS I-II and pts with GOS III-V.

Discussion
Our dynamic SPECT study documented a significant reduction of frontal perfusion and an inverse F/O ratio in the very acute phase after a HI that are not related to the type of lesions, GCS and GOS. It appears to be due not to a structural damage but to a general effect of any state or condition involving lowered directed mental activity.

Reference
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RELATIONSHIP OF BRAIN OXYGEN TO GCS, ICP, CPP, AND OUTCOME IN SEVERELY HEAD INJURED PATIENTS

Alois Zauner, Egon Doppenberg, Matthias Menzel, Harold Young, Ross Bullock

Neurosurgery, Medical College of Virginia, Virginia, USA

Introduction
Ischemia is the major cause for secondary damage after head injury, and leads to brain swelling, edema and poor outcome. Monitoring of ICP and CPP is often not sufficient to guide therapy for these critically ill patients. With the development of fiberoptic technology, continuous brain tissue oxygen ($PtiO_2$) monitoring is now available. We therefore conducted a study to test whether $PtiO_2$ can differentiate patients at risk for brain ischemia, and predict outcome.

Methods
We compared continuous $PtiO_2$ to clinical parameters such as GCS, ICP, CPP and outcome. A fiberoptic sensor (Paratrend 7) was inserted into frontal cortex, via a transcranial bolt, along with a standard ventriculostomy catheter in 43 severely head injured patients.

Results
In patients with good outcome, $PtiO_2$ was initially low, and progressively increased, over the monitoring period, to a "steady state level", around 35-50 mmHg. In patients with moderate disability brain oxygen was between 20-35 mmHg. In those who died or remained vegetative, $PtiO_2$ fell, to anaerobic levels (< 20 mmHg). Multiple logistic regression analysis showed brain oxygen to be the strongest predictor for outcome. The diagnostic sensitivity was 92%, and specificity was 84%. Mean brain oxygen was significantly correlated with the initial GCS and CPP, whereas ICP was inversely related to brain oxygen (all $p \leq 0.001$).

Summary and Conclusions

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Safety Profile of Enadoline, A Potential Neuroprotective Agent

A.C. Pande and the Enadoline Clinical Study Group

Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105, USA

Introduction
Enadoline is a selective kappa receptor agonist which reduces the volume of infarcted tissue in experimental cerebral ischemia in several species.

Methods
The safety and pharmacokinetic profile of enadoline are being studied in patients with severe head injury (Glasgow Coma Scale Scores of 4-8). Blocks of eight patients (4 on drug, 4 on placebo) receive escalating doses of enadoline as a continuous intravenous infusion for 12 hours.

Results
Four blocks have been completed with enadoline doses of 0.06, 0.2 , 0.6, and 2 μg/Kg/hr. Three more dose levels are planned (6, 18, and 35 μg/Kg/hr), but the study may terminate earlier either if dose-limiting safety problems arise or if the plasma enadoline concentrations reach 100-150 ng.eq/mL, the range of concentrations associated with neuroprotective effects in the animal studies. The adverse events reported to date in this study are as expected for this patient population. Of 34 patients, 3 have died due to brain herniation, all deaths being considered unrelated to study drug by the investigators. Potentially significant adverse events observed in more than one patient which are being closely monitored include marked diuresis (a known kappa-opioid effect), electrolyte changes and liver enzyme elevations.

Summary and Conclusions
So far the administration of enadoline for 12 hours to head injured patients has been well tolerated. Complete safety data will be reported and the potential for enadoline to enter efficacy testing in head injury will be discussed.

Enadoline Clinical Study Group: M.R. Bullock (Richmond, VA), C. Greeley (Parke-Davis, Ann Arbor, MI), T. Harrington (Phoenix, AZ), J. Hinton (Parke-Davis, Ann Arbor, MI), D. Marion (Pittsburgh, PA), J. Pickard (Cambridge, UK), G. Teasdale (Glasgow, UK), J. Wilberger (Pittsburgh, PA)

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REACTIVE ASTROCYTOSIS IN A NEW MODEL OF OBSTRUCTIVE HYDROCEPHALUS. Martha J. Johnson, Mark G. Luciano, Igor Ayzman, Arcangela S. Wood, James P. McAllister, II. Department of Neurosurgery, The Cleveland Clinic Foundation, Cleveland, Ohio, USA.

In order to characterize histopathologic changes during the progression of ventriculomegaly and to allow subsequent correlation with functional imaging and analysis of the efficacy of surgical treatments, we have developed a canine model of obstructive hydrocephalus. Acute procedures on 13 animals allowed determination of location and size of the obstruction immediately after surgery. In 17 chronic animals, hydrocephalus was induced by injecting cyanoacrylic glue into the fourth ventricle and the progression of ventriculomegaly was monitored using MRI. Animals were also monitored post-operatively for neurological changes. At 5-10 weeks post-induction, animals were perfused with fixative, and tissue from sensorimotor cortex was processed for Nissl staining or immunohistochemical analysis of glial fibrillary acidic protein (GFAP). Hydrocephalus was successfully induced in 13 of 17 (76%) chronic animals. The severity of ventricular enlargement was determined by comparison of Evans' ratios. Nissl staining failed to reveal any apparent changes in the white matter of hydrocephalic animals relative to acute surgical controls. Gray matter regions stained for Nissl substance revealed mild disorientation of neurons. However, GFAP immunoreactivity in both gray and white matter was altered in hydrocephalic tissue depending on the degree of ventricular enlargement. Animals with moderate to severe hydrocephalus exhibited qualitative increases in the number of GFAP positive astrocytes. Morphological changes were manifested by increased astrocyte somal size, process thickness, number, and length. Apparent increases in the number of vascular endfeet were also observed in hydrocephalic brains. Increases in GFAP content in hydrocephalic tissues relative to controls strongly suggest a process of traumatic brain injury as a function of ventricular size. The detected change may either reflect a secondary effect of impaired neuronal function, or it may be a cellular response to direct injury of astrocytes. In contrast to routine Nissl staining, immunohistochemical labeling of GFAP appears to be a more sensitive indicator of histopathology following chronic hydrocephalus. In order to further understand the consequences of histopathological change, the occurrence of reactive astrocytosis must be correlated with neurophysiological deficits, intracranial pressure, and brain compliance. The large animal model of obstructive hydrocephalus developed during this study will enable subsequent examinations of the temporal progression of pathophysiology during ventricular enlargement, and the efficacy of clinical intervention in reversing this process.

Support: Johnson & Johnson Professional, Inc., The Leede Hydrocephalus Fund, and the Cleveland Clinic Foundation

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FAILURE OF THE COMPETITIVE NMDA ANTAGONIST SELFOTEL (CGS19755) TO IMPROVE OUTCOME AFTER SEVERE HEAD INJURY: RESULTS OF PHASE III TRIALS

Authors: Bullock R, Marshall L, Marmarou A, Marshall S, Faleck H, Kotake A, Selfotel Investigators

Introduction

Glutamate antagonists are the most powerful of neuroprotectants in laboratory studies in both trauma and ischemia models. Selfotel, a competitive glutamate antagonist at N-methyl-D aspartate (NMDA) receptors is the first of these agents to be tested in Phase III clinical trials. Following Phase II studies in severe neurotrauma which demonstrated an ICP lowering effect with this agent, efficacy studies were constructed to test the ability of the compound to improve outcome (dichotomised GOS) at 6 months after severe head injury (GCS 4-8) in two large trials (n=800). The Protocol 08 trial was conducted in the U.S. and Israel, and the Protocol 11 trial was conducted in Europe, Argentina, and Australia. Similar trials were commenced for ischemic stroke.

Results

All four trials were halted prematurely because of: 1) Significant excess mortality in the Selfotel group for both stroke trials. 2) Low probability of demonstrating efficacy using either 3 or 6 month GOS, in neurotrauma. Demographic and clinical variables were well distributed between both groups. Subgroup analysis did not demonstrate benefit in any subcategory. No specific adverse events were thought to be drug related.

Conclusion

Selfotel at 5mg per kilogram, (4 doses each 24 hrs apart,) did not demonstrate a satisfactory risk/benefit ratio in severe head trauma. Because this compound is competitive with glutamate at the receptor, and glutamate levels are elevated, up to 50 fold or more, in certain patients after severe head injury, the compound may be unable to influence events at the receptor.

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Simultaneous measurement of cerebral intraventricular and subarachnoidal space pressure in patients with normal pressure hydrocephalus (NPH).

H. Stephensen*, M. Tisell*, M. Tullberg** and C. Wikkelsö**.
Institute of Clinical Neuroscience, Department of Neurosurgery* and Neurology**, Sahlgrenska University Hospital, Göteborg, Sweden.

Introduction: A transmantle pressure gradient (P_{grad}), with higher pressure in the ventricles than in the subarachnoidal space has been suggested as the cause for dilatation of the cerebral ventricles in hydrocephalus(1-2). The purpose of this project was to develop a method to measure the cerebral transmantle pressure in humans.
Material and methods: The intracranial pressure was measured simultaneously in the lateral ventricle (ICP_{iv}) and in the subarachnoidal space over the cerebral convexity (ICP_{sub}), using microsensor ICP transducers (MicroSensor™ Codman) in five patients with NPH in connection with shunt implantation. The study was appproved by the local ethical committee and informed consent was obtained from the patients and their relatives. In general anaesthesia the sensors were inserted, through a right sided frontal burr hole, near the coronal suture. One sensor (inside a ventricle catheter) was placed in the lateral ventricle and the other in the subarachnoidal space about 15mm in front of the burr hole. The ventricle catheter passed trough a silicon cap that closed the burr hole. The distance between the two sensors was 4.5cm. To document the angle of the ventricle catheter and calculate the hydrostatic pressure difference (ΔP_{hydro}) between the two sensors, skull radiographs were obtained. The microsensors were connected to a monitor and data was collected on a personal computer using a data acquisition system (BIOPAC Systems, Inc). The signals were sampled with 50Hz for 18-24 hours and the patients behaviour and body positions were documented by a nurse. The transmantle pressure gradient was calculated with the patients in different positisions awake and during sleep. The pressure gradient was calculated as $P_{iv} - P_{sub}$ (corrected for Δp_{hydro}).
Results: The ICP_{iv} and ICP_{sub} curves were coherent and almost identical with respect to form and amplitude. Four patients had transmantle pressure 0±2 mmHg, the variation within each patient was less than 2 mmHg (most values below zero) and in one patient values varied between -2 and -5 mmHg.
Conclusion: To measure the subarachnoidal and intraventricular pressure simultaneously seems to be a safe and reliable method. Our preliminary results do not indicate that the pressure in the ventricles is higher than in the subarachnoidal space in patients with NPH.

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Prognosis and CSF shunt dynamics in patients with idiopathic adult hydrocephalus syndrom. A long-term study.

Jan Malm[1], Bo Kristensen[1], Lars-Ove Koskinen[2], Markku Fagerlund[3], Tomas Karlsson[4].

Departments of Neurology[1], Neurosurgery[2], Radiology[3] and Psychiatry[4], University Hospital, S-901 85 Umeå, Sweden.

Introduction: the outcome of surgery in patients with adult hydrocephalus syndrome (AHS; normal pressure hydrocephalus) have fascinated many authors in recent years. Many of these studies have been retrospective, containing mixed cases of both idiopathic and secondary forms of AHS, without assessment of shunt function and have only provided information with respect to the short-term prognosis. In two previous studies[1,2], we described the short-term prognosis and the CSF shunt dynamics in idiopathic AHS patients (IAHS). In the present study 42 IAHS patients were investigated preoperatively and 3, 9, 18 and 36 months after the operation in order to evaluate the long-term prognosis.

Methods: the decision to operate was not influenced by ancillary investigations i.e., CSF tap-test or CSF hydrodynamics but based on neuroradiological and conservative clinical diagnostic criteria[3]. CT scan and a constant pressure infusion method in order to evaluate shunt function were performed at follow-up visits. Outcome measures were: gait function (blinded semiquantification of serial videotaping of gait), cognitive performance (assessed by a comprehensive neuropsychological battery) and activities of daily life (Barthel index).

Results and conclusion: Fortytwo patients with IAHS were included (32 men and 10 women; 71.9±4.7 years (mean age ± S.D.)). The study was concluded September 1996. Twentythree patients completed the study protocol, 11 died (26%)(postoperative complications, 1; intracerebral hemorrhage unrelated to the shunt procedure, 4; myocardial infarction, 4; cancer, 1; ruptured abdominal aortic aneurysm, 1) and another 4 patients could not be evaluated at the last follow-up visits (major stroke, 1; severe dementia, 1; patient refused, 1; administrative reasons, 1). During the study period 2 patients were operated on due to subdural hematoma. The shunt valve was replaced in four patients due to dysfunction.

Detailed long term results will be presented concerning shunt function dynamics, complications, neuroradiology and outcome measures.

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TREATMENT OF TRAUMATIC BRAIN INJURY WITH MODERATE HYPOTHERMIA

Donald W. Marion, M.D.; Louis E. Penrod, M.D.; sheryl F. Kelsey, ph.D.; Walter D. Obrist, Ph.D.; Patrick M. Kochnanek, M.D.; Alan M. Palmer, Ph.D; Stephen R. Wisniewski, Ph.D.; Steven T. DeKosky, M.D.
The Brain Trauma Research Center, University of Pittsburg Medical Center

Background: Traumatic brain injury initiates several metabolic cascades which produce molecules that can secondarily increase the injury. There is evidence that some of these deleterious metabolic responses may be limited by hypothermia.

Methods: In a randomized, controlled trial, we compared the efficacy of moderate hypothermia and normothermia in 82 patients with severe closed head injuries (Glasgow Coma Scale (GCS) score 3 to 7). The patients assigned to hypothermia were cooled to 32° to 33°C a mean of 10 hours after injury, kept at that temperature for 24 hours, then rewarmed. A physiatrist unaware of treatment group assignment evaluated the patients 3-, 6-, and 12-months later using the Glasgow Outcome Scale.

Results: The demorgraphic characteristics, mechanisms of injury, and injury severity were similar in the hypothermia a normothermia groups. At 12 months, 62 percent of the hypothermia patients and 38 percent of the normothermia patients had good outcomes (moderate, mild, or not disabilities)(Ristk Ratio: 0.4; 95% confidence interval: 0.2, 0.9). Hypothermia did not improve outcomes if the admission GCS score was 3 or 4 but was associated with significantly better outcomes at 3 and 6 months among patients with admission GCS scores of 5 to 7. Hypothermia also was associated with significantly lower cerebrospinal fluid concentrations of interleukin-1B and glutamate in patients with initial GCS scores of 5 to 7.

Conclusions: Moderate hypothermia for 24 hours after severe traumatic brain injury hastened neurologic recovery for patients with admission GCS score of 5 to 7, and may have improved their outcome.

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A Comparative Study of the Spiegelberg Compliance Device with a Manual Volume-Injection Method: A Clinical Evaluation

I. Piper, A. Spiegelberg, A. Bernardo, L. Mascia, D. Signorini, I. Whittle & J.D. Miller
Clinical Neurosciences, Western General Hospital, Edinburgh,UK.

Introduction: Measurement of craniospinal compliance in brain injured patients offers the potential for early detection of raised intracranial pressure (ICP) before it rises to levels damaging to brain function. Despite the benefits of compliance measurement, the usual manual injection/withdrawal method is time-consuming and can increase the risk of infection to the patient. A new automated method of compliance measurement has been developed which may overcome some of the problems of the manual method. We report on the results testing this new method against a manual volume pressure response method in patients with hydrocephalus and subarachnoid hemorrhage.
Methods: Patients had a double lumen ICP catheter placed intraventricularly. The outer lumen allowed CSF access and measurement of ICP through a fluid-filled link to an external strain-gauge pressure transducer. The other lumen of the catheter was connected to the "Spiegelberg Device" which could, under computer control, add or remove known volumes of air (0.07 - 0.1 ml) into a small balloon situated at the tip of the catheter which was also within the ventricle of the patient. Compliance is calculated, over several minutes, from a time-average of up to 200 injection/withdrawal pulses. Each patient had compliance measured in sequence first by the new automated method which was then followed by a second set of compliance measurements using the traditional manual volume injection/withdrawal method. Finally, a third set of compliance measurements was obtained, again using the new compliance measurement method. Unless an obvious change in compliance occurred, the new method compliance was calculated as the average of the measurements taken before and after the traditional manual technique.
Results and Conclusions: Fourteen pairs of compliance measurements have been obtained from 7 patients. The compliance values obtained ranged from 0.152 to 1.105 ml/mmHg (average of both methods). There was a strong correlation between the two methods ($r^2 = 0.732$, $p < 0.001$). The average bias in compliance between the two methods was 0.105 ml/mmHg with the old manual method underestimating compliance compared with the new method. These results indicate the new automatic method of compliance measurement does correlate well with an independent measure of compliance and defines the bias and limits of agreement by which the new method measures craniospinal compliance.

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A NEW, PRACTICAL CLASSIFICATION OF TRAUMATIC SUBARACHNOID HEMORRHAGE

GF Morris, LF Marshall; University of California at San Diego, USA

Introduction: Traumatic subarachnoid hemorrhage (tSAH), an increasingly recognized concurrent intracranial diagnosis, demonstrates a distribution of blood that is markedly different from nontraumatic SAH. This study serves to identify patterns of tSAH and their relationships to outcomes, allowing definition of a predictive classification specific to tSAH. **Methods:** Fifty-one centers from 11 countries collaborated in prospective data collection of 404 adults with severe head injury (GCS 4-8), who were then followed for six months. The initial CT scans were re-examined, characterizing tSAH by site and quantity. Outcomes were evaluated using the Glasgow Outcome Score (GOS). Favorable outcome includes GOS of good or moderate. **Results:** Patients with tSAH (n=317) had 26% mortality, those without tSAH had 13%; likewise, those with tSAH had 51% favorable outcome, those without tSAH 78% ($p<0.001$). When tSAH occurred at an isolated site (n=158), mortality was 18% and favorable outcome 59%. The location of the site did not result in variation. If the site of tSAH had such a large quantity of blood as to fill that structure or if there were two nonfilled sites of tSAH (n=85), mortality was 25% and favorable outcome 51%. The presence of tSAH at three or more sites (n=59) resulted in a 44% mortality, and 28% favorable outcome. The combination of two sites of tSAH including the tentorium filled with hemorrhage (n=169) produced mortality of 31% and favorable outcome of 44% (74). **Discussion and conclusions:** The presence of tSAH results in a significant difference in both mortality and favorable outcome. The patterns of distribution and quantity of tSAH vary. The number of sites displaying tSAH has a direct relationship with outcome. When filled with blood, and in combination with another site of tSAH, the tentorium has a worse prognosis. We propose a new, simple, graded classification of tSAH, allowing rapid classification using initial CT scan, and providing information to aid in accurate outcome prediction. Table 1.

Table 1: Classification of Traumatic Subarachnoid Hemorrhage

	CT Scan Findings
Grade 0	No CT evidence of traumatic subarachnoid hemorrhage (tSAH)
Grade 1	tSAH present only in one location
Grade 2	tSAH present at only one location, but quantity of blood fills that structure OR tSAH is at any two sites, filling neither of them
Grade 3	tSAH present at two sites, including the tentorium filled with blood
Grade 4	tSAH present at 3 or more sites, any quantity

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DETECTION OF SECONDARY ISCHEMIA IN PATIENTS WITH SUBARACHNOID HEMORRHAGE (SAH) USING INTRACEREBRAL MICRODIALYS (MD) MONITORING.

P Enblad[1], J Valtysson[1,2], J Andersson[4], A Lilja[4], B Långström[4], L Hillered[1,3], L Persson[1]

Depts of Neurosurgery[1], Anaesthesiology[2], Clinical Chemistry[3], University Hospital, and Uppsala University PET Centre[4], Uppsala, Sweden

Introduction
The aim of the study was to evaluate intracerebral microdialys as an monitoring instrument for identification of secondary brain ischemia in patients with severe SAH.

Patients and Methods
Ten patients with severe SAH were monitored by intracerebral MD during operation and neurosurgical intensive care (NIC). The levels of the energy-related metabolites (lactate, lactate/pyruvate ratio, glucose, hypoxanthine) and excitatory amino acids (EAAs; glutamate, aspartate) were analysed in the MD dialysates. The MD data was compared with other indirect signs of secondary ischemia, i.e. clinical course including secondarycomplications, CT findings and clinical outcome. In six of the patients, positron emission tomography (PET) measurements of rCBF, rOER and $rCMRO_2$ was performed and compared with MD.

Results
The extracellular fluid levels of lactate, lactate/pyruvate ratio, glucose, hypoxanthine, and glutamate appeared to be useful markers of secondary ischemia. When the sensitivity and specificity of the chemical substances in MD dialysates with regard to ischemia disclosed by PET was calculated, the lactate/pyruvate ratio showed both the highest specificity and sensitivity.

Conclusions
Intracerebral MD may serve as an instrument for identifying secondary ischemia during aneurysm surgery and NIC of SAH patients. The lactate/pyruvate ratio is one possible marker of secondary ischemia which can be used in the clinical setting.

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Identification of the Compartment Responsible for Traumatic Brain Swelling using Simultaneous Measures of Blood Volume, Brain Tissue Water and Diffusion Weighted Imaging in Head Injured Patients

Marmarou A., Fatouros P., Bullock R., Barzo P., Yamamoto T., Bandoh K., Yoshihara M., Doppenberg E., and Young H.

Division of Neurosurgery, Medical College of Virginia, (U.S.A.)

Introduction: The compartment primarily responsible for traumatic brain swelling and subsequent rise of ICP remains unclear. Both vascular engorgement (CBV) and increased brain water (BW) have been implicated but heretofore simultaneous measurement of CBV and BW in Head Injured patients has not been possible. The objective of this study was to compare changes in blood volume and brain water in head injured patients to determine their relative contribution to the swelling process. A second objective was to determine if the developing edema was primarily extracellular or cellular using diffusion weighted MRI.

Methods: Severely brain injured patients (GCS<8, n=60) were transported to imaging facilites for non-invasive measure of brain water and cerebral blood volume and flow within 72 hours of injury. Brain water was measured by obtaining "water maps" of the brain and calculating the global water content expressed in gm/h20 per gm tissue. Diffusion weighted images were also obtained for calculation of the apparent diffusion coefficient. Cerebral blood volume was measured by indicator dilution techniques utilizing CT which involved measure of both transit time and cerebral blood flow.

Results: Studies, approved by an internal review board, were conducted with no complication to the patient . MR determined water values showed an increase in brain water in head injured patients which averaged +1.0+/- 1.71sd gmH20/gm tissue and ranged from (-1.37 to +5.62). The corresponding measures of blood volume were reduced and averaged (- 0.98 +/- 1.46 ml/100gm) , ranging from (+2.94 to-3.03). The percentage brain swelling based on the developed edema averaged 5.2 +/- 9.2 and shrinkage due to blood volume decrease 1.0 +/- 1.5 %. Diffusion weighted images indicated that a signficant edema component was of cellular orgin. As stable patients with low ICP were selected for study, correlation of swelling to percent time > 20 mmHg in this cohort was poor.

Conclusion: Brain edema is the predominant cause of traumatic brain swelling. The magnitude of swelling by water volume requires compensation by reduction of blood volume as observed in these studies. The observation that a significant edema component was cellular implicates neurotoxic mechanisms.

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NON - INVASIVE ASSESSMENT OF CEREBRAL PERFUSION PRESSURE

Basil Matta*., Marek Czosnyka, Piotr Smielewski ,Peter Kirkpatrick , John D. Pickard

University Department of Anaesthesiology and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Background: The non-invasive assessment of cerebral perfusion would be helpful for clinical practice. However, formulae introduced by Aaslid [1], based on a the waveform of transcranial Doppler blood flow velocity, have a prediction error of +/- 25 mmHg [2].

Method : We developed a new simple estimator of CPP (eCPP) calculated using mean arterial pressure and TCD mean and diastolic flow velocity. The estimator was verified using continuous monitoring over controlled periods (20 minutes to 2 hours) of ICP, arterial pressure and MCA blood flow velocity in a group of 96 severely head injured patients (nearly 400 examinations).

Results: eCPP correlated better with real CPP than the estimator proposed previously [1] (r=0.62 and r=0.39 respectively). In 68% of examinations an estimation error was less than 10 mm Hg and in 79% less than 15 mmHg . Low estimate of CPP (eCPP<60 mmHg) had a high sensitivity for reduced CPP (CPP<60 mmHg; 96%), but specificity was low (52%). The most important feature of eCPP was that it was reactive to real changes in CPP (r=0.92; $p<0.0001$) in situations such as plateau and B waves of ICP, refractory intracranial hypertension, arterial hypotension and hypertension.

Conclusion: The estimation of the absolute value of CPP is possible, however accuracy is still limited. The estimated CPP can be used in all situations where continuous monitoring of relative changes in CPP is required without invasive measurement of ICP.

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An exploratory analysis of the impact of pretreatment values of intracranial pressure, arterial blood pressure and cerebral perfusion pressure on outcome in patients with traumatic subarachnoid hemorrhage: a comparison between nimodipine and placebo.

Torreman, M., Heininger K., Armah, B., Kuebler J. Bayer Research Center, Wuppertal, Germany.

The calcium antagonist nimodipine has been investigated in patients with traumatic subarachnold hemorrhage (tSAH). Xx beneficial effect on outcome at 6 months in this patient group compared to placebo has been described in the past (1).
The aim of this anlaysis was to investigate the impact of pretreatment values of age, intracranial pressure (ICP), arterial blood pressure (BP) and cerebral perfusion pressure (CPP) on outcome at 6 months in SAH patients receiving either nimodipine or placebo. From the HIT 1-iii studies all patients with tSAH as confirmed by a review committee evaluation were selected. The resultant combined study population of 449 patients (213 nimodipine, 236 placebo) was used for this analysis. The dichotomized GOS ("favorable outcome": GOS 1-2; "unfavorable outcome". GOS 3-5) at 6 months after onset of treatment was used as outcome measure. The statistical methods used were descriptive and exploratory, not allowing hard statistical statements. Yet, it allowed some insight in the effects values of these parameters in certain ranges had on outcome both in the placebo and nimodipine group. Ranges for the different parameters not described below were difficult to interpret due to the small number of patients (indirectly shown by larger log odds ratios).
Results: Age: From 20 - 80 years the percentage of patients with favorable outcome slowly decreased in the placebo group. Although, nimodipine shows a beneficial effect compared to placebo in the whole range, this therapeutic effect is most evident below 45 years. It seems to peak in the range 30 - 40 years.
BP: For pretreatment systolic BP values outcome in the placebo group seems rather stable in the range 100 - 150 mmHg (30-40% having favorable outcome at 6 months). In the nimodipine group the largest beneficial effect seems to occur around 100 mmHg with a decrease towards 150 mmHg. A similar effect is seen for diastolic BP. In the placebo group outcome in the range 50 - 110 mmHg (about 40% having favorable outcome at 6 months) seems rather stable. In the nimodipine group the largest beneficial effect seems to occur around 50 mmHg with a decrease towards 110 mmHg.
ICP: In the placebo group the percentage of patients with favorable outcome steadily decreases (from about 55% to 20%) for pretreatment ICP values in the range of 0-30 mmHg. After peaking around 30 mmHg the difference between nimodipine and placebo decreases slowly.
CPP: In the placebo group the percentage of patients with favorable outcome increases more or less steadily for pretreatment CPP values in the range 50-90 mmHg. The beneficial effect of nimodipine seems to manifest across the whole range of 50 - 90 mmHg.
Conclusion: Although no hard conclusions can be drawn from this analysis due to the statistical technique used (descriptive and exploratory), this technique may allows to get some insight in the effects certain pretreatment parameters have on outcome by showing trends. It permits to delineate a pattern of predictors of favorable outcome in patients with tSAH treated with nimodipine.
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CEREBRAL HEMODYNAMICS CHANGES DURING AND AFTER RETROGRADE CEREBRAL PERFUSION

Alexander Y. Razumovsky, Elaine E.Tseng, William A. Baumgartner, Daniel F. Hanley

The Johns Hopkins University, Baltimore, MD, USA

Introduction
Early clinical and experimental data show better brain protection during hypothermic circulatory arrest (HCA) with retrograde cerebral perfusion (RCP) than HCA alone. However, the changes in cerebral blood flow leading to reperfusion injury are not well understood. In this study our aim was to describe cerebral hemodynamics changes during and after HCA with RCP in dogs.
Methods
An established canine model of HCA was used. Eight colony bred hound dogs, seven to nine months old, 25-30 kg, were placed on closed chest nonpulsatile cardiopulmonary bypass (CPB), cooled down to 18^{0}C, and underwent two hours of HCA with RCP through bilateral internal maxillary veins. The animals were then rewarmed on CPB until normothermic and weaned off. The animals were sacrificed at two hours after CPB. The right middle cerebral artery (MCA) cerebral blood flow velocity (CBFV) and Gosling Pulsatility Index (PI) was studied using a transcranial Doppler (TCD) technique. All data are expressed as mean ± standard deviation. Means were compared using the student t-test.
Results
At baseline and during pre- and post-arrest CPB there was anterograde direction of blood flow in the MCA. During HCA with RCP there was retrograde direction of blood flow in the MCA. There was no difference in CBFV between CPB (18.1± 8.9 cm/sec) and HCA with RCP (CBFV = 12.6 ± 3.8 cm/sec), p=0.098. There was a difference in CBFV between baseline (29.7 ± 11 cm/sec) and at all timepoints during HCA with RCP. After post-arrest CPB there were TCD wave form changes that were consistent with increased ICP (decreased diastolic compartment, and sharp systolic peak), as well a significantly increased PI (2.4±0.9) compared to the baseline (0.8±0.3), p=0.0042.
Summary and Conclusions
The retrograde cerebral perfusion provides MCA CBFV that is comparable with the MCA CBFV during cardiopulmonary bypass. Differences in patterns of brain perfusion can not be assessed with CBFV. Our results suggest that after retrograde cerebral perfusion, a rising pulsatility index and TCD waveforms changes may correlate with increasing ICP that could lead to a severe reduction in cerebral perfusion.

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Reduction of Hyperglycolysis Following Fluid Percussion Brain Injury Increases Cell Death. Hovda,DA, von Stück,S., Hufford,A., Glenn,T., Patel,A., Martin,N., and Becker, D.P. Div. Neurosurg. and the Depts. Surgery and Mol. and Med. Pharm., UCLA Sch. of Med., Los Angeles, CA 90095-6901, USA
Introduction: Following traumatic brain injury cells that are not biomechanically and thereby irreversibly damaged, are exposed to an increase in extracellular K^{+1}. In the cells' effort to reestablish normal ionic-membrane homeostasis Na+/K+ pumps are activated. These pumps require ATP derived from glucose metabolism and the increase in this fuel consumption has been described in both animal[2] and human [3]traumatic brain injury. To determine the significance of this injury-induced hyperglycolysis in terms of cellular survival, this metabolic process was restricted in situ and the effect on histological outcome was assessed.
Methods: Under ethrane anesthesia (2ml/min) male Sprague-Dawley rats were implanted with cerebral microdialysis probes positioned -3 AP and +6 ML to bregma at a depth of 3mm below the cortical surface. Ringers lactate or 2-deoxy-D-glucose (2DG) was infused through the probe (2 µl/min for 30 min). Following this period of dialysis, animals sustained either a lateral fluid percussion or sham injury. For fluid percussion the injury cap was positioned directly over the site of dialysis and a mild (1.35-1.45 ATM) level of percussion was induced. After the injury, animals were allowed to survive for 17 days at which time they were euthanized with Nembutal, the brain perfused and processed for cresyl violet histology (20 µm coronal sections). The extent of contusion formation was drawn under a projection microscope and the volume of injury around the probe was calculated.
Results: The volume of tissue around the dialysis probe which exhibited cell loss ranged from .024-.637 mm^3 in sham injured animals who were dialyzed with 2DG. Animals who received an lateral fluid percussion injury and received ringers lactate through the probe exhibited a volume of cell loss ranged from .389-.489mm^3. In contrast animals who received a lateral fluid percussion injury and received 2DG through the dialysis probed exhibited a volume of cell loss ranging from .806-1.166 mm^3.
Discussion: These data suggest that the hyperglycolysis following experimental traumatic brain injury is a fundamental component of the cellular response for survival.
Supported by NS30308 and the Lind Lawrence Foundation
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PO - 1 - 001

ICP MONITORING DURING PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY (PEJ) EARLY AFTER SEVERE HEAD INJURY

Michael W. deBoisblanc and Anthony P Borzotta

Trauma Service, Legacy Emanuel Hospital; and Department of Surgery, Oregon Health Sciences University, Portland, Oregon

Introduction
The benefits of early enteral feeding after major trauma are well established. The use of PEJ tubes following acute head injury has been described, but the effect on intracranial pressure (ICP), especially if done early in the course of care, is unclear. We hypothesized that PEJ could be safely done early after severe brain injury.
Methods
Prospective observations on ICP, cerebral perfusion pressure (CPP), mean arterial pressure (MAP), sedation and duration of procedure were gathered on 25 patients with GCS≤8 and ICP monitors. PEJ was done in the intensive care unit using parenteral sedation and occasionally neuromuscular blocking drugs. There were 19 men and 6 women of average age 29.5±12.4 years. Baseline values were averaged over 3 hours prior to PEJ, and observations were made at each phase of the procedure and every five minutes following entubation.
Results
PEJ was done on post-injury day 2.8±1.2 (range 1 to 6). Procedure time from entubation to pull-out was 35.6±14.1 minutes. One case was aborted due to inability to transilluminate the abdomen (96% success rate). Baseline ICP was 14.4±6.6 mmHg; ;baseline CPP was 80.2±7.9 mmHg. Peak ICP usually occurred during entubation (22.5±9.5 mmHg) and averaged 16.6±7.5 mmHg overall, but CPP was essentially unchanged at 78.6±8.4 mmHg.
Summary and Conclusions
PEJ tube placement can be performed early after severe closed head injury with a small, transitory rise in ICP. More importantly, CPP was maintained at nadir levels above 67 mmHg. Performance of PEJ in the ICU is 96% successful in a short period of time, with safety, cost and efficiency advantages.

PO - 1 - 002

TREATMENT OF SEVERE BRAIN INJURY BASED UPON CEREBRAL BLOOD FLOW

James Brennan, Paul Tompkins, FA Stevens, and L. Philip Carter

Department of Neurosurgery, University of Oklahoma, HSC, Oklahoma City, OK

INTRODUCTION

The severely head injured patient is currently treated by monitoring intracranial pressure (ICP) and attempting to keep cerebral perfusion pressure (CPP) over 70mmHg. This presumes that cerebral blood flow (CBF) will be best maintained by controlling CPP. There is, however, a wide variation in CBF in head injured patients. We have therefore attempted to base our therapy on CBF, at the same time monitoring ICP and maintaining adequate CPP. We currently employ a commercially available thermal diffusion CBF monitor (Flowtronics, Phoenix, AZ).

METHODS

After reviewing the CT scan of head injured patients, intracranial pathologies (if present) are treated surgically. The thermal diffusion sensor is then placed over a normal appearing cortex. If no surgical lesion is present, the sensor is placed over a relatively normal frontal lobe. ICP, mean arterial blood pressure (MABP) and oxygenation are also monitored. Normal CBF is in the order of 40-70 ml/100gm/min. When CBF is below 40, we attempt to maximize flow by improving CPP through either reducing ICP or giving mannitol to improve the microcirculation. To augment this effect, blood volume and MABP are carefully controlled. If CBF is over 70, then hyperventilation and early barbiturate coma may be used to reduce blood flow and prevent development of malignant cerebral edema.

RESULTS

Preliminary measurement of CBF was made in 6 head injured patients with Glasgow Coma Scores of 4-6. Average CBF values were obtained pre- and post treatment. Of the three patients treated for low CBF, two showed good response to volume expansion (16 pre, 42 post and 18 pre, 36 post; ml/100gm/min). One patient treated with mannitol showed no change in CBF (remained 29 ml/100gm/min). Of three patients treated for high CBF, one showed no response to sedation (76 ml/100gm/min throughout), one showed moderate response to barbiturate therapy (96 pre, 86 post; ml/100gm/min), and the third showed good response to barbiturate therapy (95 pre, 49 post; ml/100gm/min). There were no infectionsand no episodes of malignant cerebral edema.

SUMMARY and CONCLUSIONS

Treatment based on CBF is safe and may aid in preventing the development of malignant cerebral edema. It is obvious that larger groups are necessary, and data collection is continuing.

PO - 1 - 003

ICP AND CPP DURING TRANSLARINGEAL TRACHEOSTOMY (TLT) IN NEUROSURGICAL PATIENTS.

Parma A, Songa V, Lamperti M and Stocchetti N.
NeuroICU Ospedale Maggiore Policlinico IRCCS Milano Italy

Introduction

Tracheostomy is frequently necessary in the management of comatose patients with severe brain damage. TLT has been introduced as an alternative to standard surgical tracheostomy because it is safe and easy to be perform (1).We investigated the effect of this procedure on ICP and CPP in order to assess its safety for neurosurgical patients.

Methods

We prospectively studied 10 patients with acute brain damage (median GCS 5) who underwent TLT. ICP, MAP, CPP, Jugular pressure (Pj), internal jugular saturation (SjO2), respiratory and hemodynamic parameters were monitored at 7 different points; arterial blood gases were continuously monitored with Paratrend (2). All patients were sedated, paralyzed and ventilated. Moderate hypocapnia (mean PCO2 33.19±4.47) was induced.

Results

4 TBI, 3 SAH, 3 brain tumors were studied.Main parameters are reported in the following table:

	ICP	MAP	CPP	pCO2	pJ
1) Baseline	10 ±5	90 ±13	79 ±13	37 ±4	8 ±4
2) Induction anesth	12 ±7	82 ±15	74 ±14	31 ±4	12 ±6
3) Reintubation	13 ±7	103 ±38	96 ±38	32 ±6	11 ±4
4) Tracheal puncture	14 ±5	92 ±29	86 ±34	33 ±4	10 ±5
5) Cannula placement	18 ±9	100 ±19	87 ±33	35 ±5	10 ±5
6) Stop anesthesia	15 ±8	93 ±34	90 ±34	33 ±5	8 ±6
7) Control	16 ±9	87 ±11	73 ±12	31 ±6	9 ±4

SJO2 was constantly greater than 60% in every patient.

Summary and conclusions

a) Since with this technique artificial ventilation can be maintained during the whole procedure, a resonable control of pCO2 is achieved.

b) TLT, even without lowering CPP, causes an ICP rise. Therefore the indication to perform a tracheostomy, including TLT, should be carefully weighted in any patient with unstable ICP.

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PO - 1 - 007

EFFECT OF TROMETHAMINE (THAM) ON BRAIN TISSUE-PO_2, -PCO_2, AND -pH IN SEVERELY HEAD-INJURED PATIENTS.

Karl L. Kiening, Asita S. Sarrafzadeh , Tillman F. Bardt, Roger Härtl, Andreas W. Unterberg, and Wolfgang R. Lanksch.

Department of Neurosurgery, Virchow Medical Center, Berlin, Germany.

Introduction

The buffering agent tromethamine (THAM) has been shown to ameliorate intracellular brain acidosis and to reduce cytotoxic edema (1). Moreover, THAM reduces intracranial pressure (ICP) (2). Purpose of this study was to assess effects on invasively measured brain tissue-PO_2 ($PtiO_2$), -PCO_2 ($PtiCO_2$) and pH (*ti*pH) during application of THAM in severe head injury (SHI).

Material and Methods

12 patients with SHI (Glasgow coma score ≤ 8) were prospectively studied. Multimodal computerized monitoring was carried out measuring mean arterial blood pressure (MABP), ICP, cerebral perfusion pressure (CCP), end tidal CO_2 ($ETCO_2$), $PtiO_2$, $PtiCO_2$ and *ti*pH (Paratrend 7 system). THAM was given in a dosage of 1 mmol/kg b.w. over 20 minutes. Arterial blood gas analyses were taken at baseline, 15, 30 and 45 minutes after start of infusion. 31 THAM dosages (2-4/patient) were followed from day 1 to day 10 posttrauma.

Results

Compared to baseline, THAM application led to a significant reduction in ICP (Δ8±1,8mmHg), $ETCO_2$,(Δ3±0,6mmHg), *ti*PCO_2 (Δ2±1,7mmHg), and arterial PCO_2 (Δ3±0,8mmHg) and significant increase in *ti*pH (Δ0,03±0,03) and apH (Δ0.07±0,01). $PtiO_2$ always decreased (Δ5±3mmHg) despite of the increased CPP. Maximal effects were observed at 15 min post baseline.

Conclusions

Application of THAM improves ICP, CPP and parenchymal acidosis but even impairs cerebral oxygenation. The reduction in $PtiO_2$ may be due to cerebral vasoconstriction induced by alkalosis and consecutively reduced cerebral blood flow.

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PO - 1 - 009

Effect of antihypertensive substances on regional cerebral blood flow (CBF) and intracranial pressure (ICP)

A.Hartmann, C.Dettmers, T.Rommel, Z.Cernizki
Neurologische Univ.-Klinik Bonn, 53105 Bonn, FRG

Introduction Reduction of art.blood pressure (aBP) reduces CBF if autoregulation is impaired.If the drugs to reduce aBP results in vasodilatation of the intracerebral vessels, ICP might increase and neutralize the decrease of peripheral resistance. This may further impair tissue perfusion.

Material and Methods Animals: Effects of the antihypertensives Sodiumnitroprusside (SNP), Nitroglycerine (NG) and Trimethaphan (TM) on CBF and ICP have been studied in baboons. ICP was increased by a subdural balloon.

Patients: Effects of Nifedipine and Urapidil on CBF have been evaluated in patients with acute stroke.

Results Animals: During normal ICP all substance decrease aBP with no effect on CBF,if mean aBP was kept above 70mmHg. Only SNP and NG increase ICP slightly without a significant effect on CBF. If ICP is increased by inflating the subdural balloon above 20 mmHg, both SNP and NG increase ICP further with subsequent reduction of CBF by a maximum of 35%. TM did not increase ICP and did not affect CBF within the limit of normal autoregulation. CO_2-reactivity was affected again only by SNP and NG.

Patients: In patients with acute infarcts to the brain and increased aBP at the time of the measurement the effect of Nifedipine and Urapidil on CBF have been evaluated. CBF was measured with the iv Xenon^{133}-technique. Both Nifedipine and Urapidil led to a repeatable decrease of aBP. In the area of infarct with low CBF both substances provoke a further decrease of CBF. This was also observed in perinfarct tissue by adminstration of Nifedipine but not by Urapidil. The contralateral hemisphere was not affected by both substances.

Conclusion: Antihypertensive drugs with direct vasodilating effects may increase ICP and thus decrease tissue perfusion. Urapidil and Nifedipine may decrease CBF in the focal ischemic area, but the CBF reducing effect in the periinfarct tissue has been observed only by Nifedipine. From this point of view substances like Trimetaphan and Urapidil seem to be safer drugs than others to reduce hypertension in the acute state of cerebral ischemia.

PO - 1 - 010

Evaluation of Cerebral Oxygenation at High Arterial PO2.

Bruzzone P.. , Bellinzona G., Imberti R., Pugliese R.($), Ilardi M., Ticozzelli G., Raimondi M., Dionigi R.V.

2nd Anaesthesiology Service, IRCCS Policlinico San Matteo, Pavia;
$ Neurosurgical Clinic, University of Pavia..

INTRODUCTION Preservation of cerebral oxygenation can be regarded as the main purpose treating Severe Head Injured (SHI) patients. We studied the effects of large changes in arterial PO2 on oxygen partial pressure of brain tissue (PbrO2) and on parameters commonly derived from jugular bulb blood gas analysis.
METHODS In 10 patients with SHI (GCS<=8), PbrO2 (Licox GMS), arterial and jugular bulb gas analysis (ABL3 and OSM3 Radiometer) were recorded during changes of FiO2 in a wide range (30-100%). Data (N=235) were classified in 4 classes on the basis of PaO2 (80-150,150-250,250-350,>350). Analysis of variance was applied to study the effects of PaO2 on mean value of PbrO2, SjO2, CEO2, artero jugular difference of CO2 and of oxygen content.
RESULTS Data are displayed in the table. A displacement of the symbol X denotes a significant difference between classes ($p<0.001$).

classes	PaO2	se		PbrO2	se	*	SjO2	se	*
1	105.71	2.01		27.74	1.07	X	71.15	1.09	X
2	184.19	4.66		31.53	2.03	X	70.95	2.05	X
3	302.97	6.52		43.88	4.60	_X	77.13	1.17	_X
4	427.84	9.90		52.60	5.32	_X	78.93	2.54	_X
classes	CEO2	se	*	DajO2	se	*	DajCO2	se	*
1	27.19	1.06	X	4.64	0.18	X	6.89	0.89	X
2	28.51	2.02	X	5.14	0.33	X	6.94	0.46	X
3	22.33	1.42	_X	4.57	0.24	X	7.07	0.49	X
4	20.89	2.51	_X	4.71	0.41	X	8.08	0.56	X

* multiple range analysis for group homogeneity.

CONCLUSION PbrO2 shows a clear dependence on PaO2 especially when it is over 200 mmHg, the same behaviour is observed with jugular bulb oxygen saturation and with the derived parameter CEO2. However if artero-jugular differences for O2 and CO2 are considered no relevant changes are observed indicating that the overall cerebral oxygen extraction and cerebral blood flow remain quite constant. At PaO2, over 200 mmHg adequacy of global cerebral perfusion and oxygen availability should be evaluated by means of artero jugular differences.

P - 1 - 011

MANNITOL FOR RESUSCITATION IN ACUTE HEAD INJURY: EFFECTS ON CEREBRAL PERFUSION AND OSMOLALITY

John A Myburgh, Stephen B Lewis

Intensive Care Unit and Department of Neurosurgery Royal Adelaide Hospital, South Australia

Introduction
The theoretical beneficial effects of mannitol in head injury relate to changes in cerebral blood flow rather than osmotic dehydration provided cerebral perfusion is maintained. Resultant hyperosmolal states and hyperviscosity due to mannitol overdose will negate these effects, particularly if cerebral hypoperfusion due to hypovolaemia ensues.

Methods
This study retrospectively reviewed the indications for and dosage of mannitol during the period from resuscitation to admission to ICU and commencement of neuromonitoring in patients with severe closed head injury (GCS<8) over a 24 month period. Effects on osmolality, initial cerebral perfusion pressure (CPP) and jugular venous saturation (SjO_2) were compared to patients who did not receive mannitol for the first 24 hour period in ICU.

Results
Forty patients were reviewed: 19 who received mannitol were subdivided into two 12 month periods. Two of these patients had lateralizing neurological signs or witnessed deterioration; 17 received empirical mannitol. There was no difference in initial GCS or demographics.

	n	Mean dose g	Osmolality mosmol/l	CPP mmHg	ICP mmHg	SjO_2 %
Total Mannitol	19	47.4	293	66	16	64
Mannitol 1994	10	28	284	72	14	63
Mannitol 1995	9	68.8	304	59	18	65
No mannitol	21	0	279	71	17	67

No difference in 6 month Glasgow Outcome Scores between groups was demonstrated.

Conclusions
The empirical overuse of mannitol is common. Mannitol did not exert any beneficial effect on CPP, ICP or SjO_2 in the initial phases of management. Larger doses (>20g) are associated with increased osmolality which may reduce CPP.

P - 1 - 012

ANTIOXIDATIVE PROPERTIES OF NIMODIPINE IN THE INTENSIVE CARE OF NEUROSURGICAL PATIENTS.

Valery Amcheslavski [1], Grigory Toma [1], Maria Demchuk [2], Ivan Savin [1]
[1] Department of Intensive Care and [2] Laboratory of Biochemistry Burdenko Neurosurgical Institute, Moscow, Russia

Introduction
Brain edema (BE), belongs to one of the most severe complications of postoperative period in neurosurgery. It is well known, that activation of lipid peroxidation (LP) plays an important role in the pathogenesis of BE [1]. That's why antioxidants are traditionally used in BE therapy [2].The aim of our work was to investigate the antioxidant properties(AP) of Nimodipine (Nimotop-S) (N) and the possibility of its usage in the treatment of neurosurgical patients with BE.

Methods
The indications to N administration were the following: 1) the severe condition of the patient (8-9 GCS); 2) CT- examination, showing BE without haemorrage into the operative wound or subarachnoid space; 3) laboratory investigations revealing activation of LP. We estimated the level of one of the most stable LP products MDA and total AOA in blood: a)before the N injection; b) an hour after the start; c) 24 hours after the start of treatment. 124 examinations were made 1-5 days after surgery in patients with gliomas of large hemispheres,for determination of AOA of drugs and blood serum we worked out a new modification of the model system where alcohol-water emulsion of linolenic acid was the substrat of oxidation [3].

Results
In the experimental conditions it was found out, that N possessed high AOA (20 mg N revealed 87% AOA). In clinical investigations improvement of neurological functions was observed in 90% of patients. Biochemically- revealed stable decrease in MDA content in dynamics (2.7 ±0. 7 nmol/ml; 1,7 ± 0,3 nmol/ml; 1,3 ± 0,22 nmol/ml);($p<0,01$). Increase of total AOA was observed in all blood samples (70±0,6%; 88±4,9%; 94±7,2%; $p<0,01$). So the main result of our investigations is the discovery of the AP of N, previously unknown.

Summary and Conclusion
Influence of N on LP in vitro and in vivo examinations was investigated. High AP of N were found in experiments on the model system. These AP were also confirmed by patients with BE and allowed us to recommend it for the treatment of BE in neurosurgical patients. The advantage of N, is the possibility of its controlling intravenous administration.

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P - 1 - 013

CHANGES IN CEREBRAL BLOOD FLOW SECONDARY TO HEAD ELEVATION

MJ Souter*, L Mascia **, M Alvarez†, PJD Andrews*.
(*University of Edinburgh, Scotland; **University of Bari, Italy; †Hospital Mutua de Terrassa, Barcelona, Spain)

Introduction
Optimal positioning of the head injured patient is unresolved. Previous studies have examined changes in intracranial pressure(ICP) and cerebral perfusion pressure(CPP) to assess the optimum position(1). Only 1 study to date has examined cerebral blood flow with changes in posture in neurotrauma(2).
Methods
We measured cerebral blood flow on 20 occasions in 15 patients with acute brain injury(GCS<8). At each occasion, CBF was measured twice - with the patient nursed at 30 degrees and then at zero degrees of head elevation. * measurements were performed with the use of Xenon [133], and 12 by the use of a modification of the Kety-Schmidt technique. Mean arterial pressure (MAP) was zeroed at the pinna prior to the measurements.
Results
The change in posture from 30 degrees to zero degrees was accompanied by an average increase in cerebral blood flow of 4.61 mls/100g/min (SEM 2.7) which comprised an average increase of 17.7% (SEM 8.4%). There was an average increase in MAP of 21 mmHg (SEM 1.4). ICP increased by an average of 5 mm Hg (SEM = 0.9) and the overall change in CPP = 14 mm Hg (SEM = 2). Lactate and oxygen were measured from arterial and jugular cannulae with each CBF measurement. The overall change in arteriovenous lactate difference (AVDL) was a minimal increase at 0.04 mmols/liter. The change in arteriovenous oxygen content ($AJDO_2$) was also minimal at 0.01 micromoles/liter of a decrease and the lactate/oxygen ratio was slightly increased by 0.01. Examination of individual changes revealed a large degree of variability with some patients experiencing increases in CBF and 7 experiencing decreases in CBF. Three of those decreases were detected with the Xe [133] method and the other four were detected via the Kety-Schmidt technique. Both increases and decreases in CBF were seen in one patient over consecutive days.
Summary
Most patients can tolerate a descent to zero degrees of head elevation, with an accompanying increase in MAP, ICP,CPP and CBF. There are some patients who will experience an increase in ICP and while not visibly reducing CPP will experience a reduction in CBF. For this reason, it may be safer overall to nurse patients at 15 -30 degrees of head elevation.
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PO - 1 - 014

USE OF STRAIN GAUGE MICROSENSORS IN MANAGEMENT OF PEDIATRIC PATIENTS

F.C. Barnett, M.D., A.M. Flannery, M.D.

Section of Neurosurgery, Medical College of Georgia Augusta, Georgia

Introduction
In order to evaluate the benefits, versatility and drawbacks to the utilization of strain gauge transducer microsensors in the evaluation and management of patients with potential increased intracranial pressure, we have reviewed on data over the past 12 months. Special emphasis was given to review of pediatric patients.

Methods
Over the last year, we have evaluated and treated a total of 57 patients requiring intracranial monitoring with a strain gauge transducer microsensor apparatus. Of these patients, 14 were between the ages of 4 years and 21 years. These patients presented with a variety of problems including cranio-synostosis, ventriculo-peritoneal shunt malfunction with slit ventricle syndrome, cranial trauma, as well as postoperative intracranial monitoring.

Results
Benefits of this system including ease of installation, versatility of monitoring mode (parenchymal, subdural or ventricular), accuracy of data derived and cost effectiveness. There is potential for inaccuracy in the preloaded catheter tip design, however, due to blockage of CSF flow by debris.

Summary and Conclusions
Based upon our clinical experience, we feel that this strain gauge transducer monitoring system is an effective and efficient way of monitoring intracranial pressure in the pediatric population. We are continuing to accrue data in this particular aspect of intracranial monitoring.

PO - 1 - 015

BEHAVIOR OF THREE MODERN EXTRADURAL PRESSURE SENSORS DURING SIMULTANEOUS INTRAPARENCHYMAL OR INTRAVENTRICULAR PRESSURE MEASUREMENT

Andreas Raabe, Ralf Totzauer und Ole Meyer

Neurosurgical Clinic and Technical University Chemnitz, Germany

Introduction
Despite the attractive concept of extradural sensor placement, this method is not accepted uniformly as a reliable intracranial pressure measurement technique. In the last years, new devices were developed and the manufacturer emphasise an improvement in measurement accuracy. We report about our observations with three different modern extradural sensors during simultaneous measurement of intraventricular (IVP) or intraparenchymal pressure (IPP).

Methods
Twenty-five patients with severe head injury and simultaneous recording of extradural (EDP) and IVP or IPP were included in this study. IVP was measured in 10 patients and IPP in 15 patients. The EDP sensor was inserted in a 2 cm extradural pocket. In 23 of the 25 patients, EDP was measured via the same burr hole and in 2 patients an additional burr hole was placed on the same side with a maximum distance of 3 cm to the first burr hole. After explantation of sensors, zero drift was measured and bench testing of transducer function was performed to exclude technical errors.

Results
Periods of erroneous EDP recording occurred in 6 of 20 measurements (30 %). In these cases, erroneous EDP recording ranged from 5 % to 85 % (mean 60 %) of measurement time. In 2 of 6 cases (33 %) with faulty EDP recording, the difference between the EDP and the IVP or IPP remained nearly stable, whereas in 4 of 6 cases (67 %) a significant drifting of mean EDP was observed. Analysis of transfer funcion between the EDP and the IVP or IPP showed in all cases of extradural recording a stable time course, even in cases with progressive drift of mean pressure.

Summary and Conclusions
Even with the last generation of EDP sensors unaccaptable large differences to the IVP or IPP occur. Analysis of transfer function shows that this difference is mainly caused by a constant or more often variable extradural offset pressure, which seems not to be of technical but of biological origin.

PO - 1 - 016

Is third ventriculostomia always sufficient treatment of hydrocephalus of hydrocephalus caused by primary aqueductal stenosis in adults?

Odd Almström, Hannes Stephensen and Carsten Wikkelsö

Institution of Clinical Neuroscience, Department of Neurology and Neurosurgery, Göteborg University, Sahlgrenska University Hospital, Sweden.

A third ventriculostomia (IIIv) is generally considered to be the safest and most effective treatment for non-communicating hydrocephalus in adults. However it has been reported that IIIv was insufficient treatment for some patients and that an additional shunt operation had to be performed. We have had reason to question the sufficiency of IIIv in several of our patients why we decided to perform a reinvestigation of our patients operated upon by a IIIv.
Material: In Göteborg a total of 65 patients were operated with a IIIv between June -91 and July -95. At follow-up children, patients with secondary aqueductal stenosis (tumors, cyst etc.), patients already having a working shunt (at the time for the operation) and deceased were excluded. Twenty patients, 13 men and 7 women, with age range 17-81 years (mean 46y) were included for follow up.
Methods: These 20 patients were reexamined clinically and by a CT scan. Further investigations as MRI, radioisotope cisternography and regional CBF were performed if necessary for evaluation of the effect of the IIIv.
Results: Nine patients were well-being and showed no signs of hydrocephalus. One patient deteriorated shortly after surgery due to meningitis and received a ventriculo-peritoneal (vp) shunt. Another patient deteriorated for unknown reasons a few days after the operation and was operated with a vp shunt. Of the remaining 9 patients one experienced no changes, two a slight persisting improvement and six only improved temporarily. The deterioration in these six patients appeared within 1 year. The patency of the IIIv was confirmed by an MRI in these 9 patients. Seven of these 9 patients were operated by a vp shunt device while two declined surgery. All 7 operated improved and in some cases rather dramatically.
Conclusions: IIIv was only sufficient treatment in about 50% of adult patients with a primary aqueductal stenosis. Even if patients improve after a the IIIv it is important to be aware of the possibility of a later deterioration or a non optimal effect. Improvement was achieved in all patients after shunt surgery despite of a patent IIIv.

PO - 1 - 017

Systematic errors in clinical measurement of Cerebral Perfusion Pressure

Dieter Woischneck, Michael Schütze, Raimund Firsching

Neurochirurgische Klinik, Otto-von-Guericke-Universität, Magdeburg Germany

Introduction
Cerebral Perfusion Pressure (CPP) in patients should not drop below 50 to 60 mmHg. This limit has been proposed by several authors for adults. In clinical use, problems in correct measurement of Mean Arterial Pressure (MAP) and mean Intracranial Pressure (ICP) lead to serious doubts on the reliability of this range. This study evaluates systematical errors in CPP-measurement and quantifies deviations.

Methods
The study includes measurements in 60 patients from intensive care unit, suffering from a severe head and brain injury: In 30 patients, a parallel invasive monitoring of MAP in arteries of a different distance to the heart was performed. Additionally, MAP was zeroed on different levels parallel to the skull base. In 20 patients, we prooved the existence of transhemispherical ICP-gradients by bifrontal epidural measurement. In 10 patients, we tried different models for arithmetical and planimetrical calculation of MAP and meanICP.

Results
Using different conditions of MAP-registration let to deviations in the resulting CPP of 20%. Interhemispheric ICP- gardients last for 4 days maximally and reached 40 mmHg. They resulted in CPP -differences up to 10%. Another 10% error in CPP-evaluation based on the comparison of the different formulas forcalculation of MAP and mean ICP.This error increased in cases of head elevation due to its influence on the shape of the arterial and intracranial pulse wave form.

Summary and Conclusions
In summary, our study leads to serious doubts on the CPP-ranges, recommended in literature because of the inconsistant parameters of registration. The study encourages investigastions on internationally standardized CPP-measurement as a basis for further discussion on ranges and normal values.

PO - 1 - 018

AN IN - VIVO ASSESSMENT OF THE NON - INVASIVE ICP MONITORING SYSTEM

Gediminas Daubaris, Vytenis Deltuva*, Egidijus Jarzemskas*, Algimantas Matukevicius* and Arminas Ragauskas

*Kaunas Medical Academy Neurosurgical Clinics and
Telematics Sc. Lab., Kaunas University of Technology

Introduction
The Vittamed non - invasive ICP monitoring system (1) provides diagnostic information on hemodynamics of the smallest intracranial vessels. It is impossible to obtain such an information applying TCD or other known technologies. This study was designed to assess the practical performance of the system in a typical group of head injury and subarachnoid haemorrhage ICU patients.

Methods
7 head injured and 3 subarachnoid haemorrhage ICU patients (mean age 49) were fitted with Vittamed non - invasive device and Camino invasive transducer. During periods of patients stability paired ICP dynamic values were recorded during body tilting tests (tilting angle - 15°). This process was carried out periodically, where possible, on 3 consecutive days.

Results
The ICU patients gave more than 300 paired dynamic ICP reactions on body tilting tests recorded by both ICP monitors. Differences between non - invasive and invasive readings were plotted and showed individual limits of agreement of measuring results from [-0.1, +0.1] mmHg until [-3.0, +3.0] mmHg within the interval of measured ICP mean values [5.0, 19.0] mmHg.

Conclusion
Comparison plots of the individual non - invasive and invasive ICP traces show very good agreement in terms of the timing and absolute value of any changes within the limited interval of measured ICP. Further examination is required in more wide interval of absolute ICP values near 25 mmHg threshold.

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PO - 1 - 019

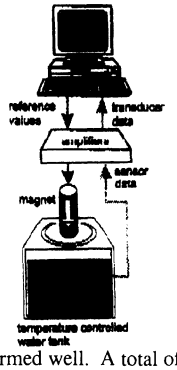
A COMPUTERIZED TEST STAND TO EVALUATE THE STATIC AND DYNAMIC PROPERTIES OF 4I ICP TRANSDUCERS

Steffen Leonhardt*, Oliver Kuklok*, Marian Walter* and Alfred Aschoff+

*Institute of Control Engineering, +Department of Neurosurgery
Technical University of Darmstadt University of Heidelberg

Introduction
Accurate measurements of ICP in the rough environment of a ICU require the pressure transducers to have certain properties regarding long term stability and temperature drift. In addition, if a waveform analysis of the ICP signal is desired, the transducers should also have specific dynamic properties. So far, only few reports on the technical properties of ICP transducers have been published, see e.g. (1). This work aims at presenting a tool and a standarized method for these test, with the final goal of arriving at an accurate, practical and oeconomically feasible solution.

Methods
A computerized test stand was developed and built. The following test were performed :
- l ong term stability (2 weeks)
- temperature drift (31 °C - 41 °C)
- frequency response (1 .. 20Hz)
- electromagnetic sensitivity
- sensitivity to dislocation and spatial load differences
- possible calibration and handling problems



Results
The test stand works fully automatic and performed well. A total of 41 transducers (28 intraventricular/parenchymal and 13 subarachnoid) was tested. The results will be discussed in the presentation.

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P - 1 - 020

MANAGEMENT OF SEVERE BRAIN INJURY BASED CPP AND P(TI)O2

Th.J. Kuhn, H. Mewes, A. Schneider, D. Hellwig, B.L. Bauer

Department of Neurosurgery, Philipps-University of Marburg, Germany

INTRODUCTION In cases of severe brain injury, we propose the early application of the neuromonitoring moduls ICP, P(ti)O2, CPP and MABP as a basement for therapeutical decisions within 5 hours after admission to the ICU by a special trained stuff. The multimodal neuromonitoring is an assistant equipment to evaluate critical situations for the injured brain in order to protect secondary brain damage.

METHODS Head injured patients with a GCS <8 and Marshall-criteria III by CT scan, admitted at our ICU where monitored by CAMINO-ICP probe and LICOX P(ti)O2-Catheter (Clark-Type). The multimodal registration and treatment of CPP, MABP, temperature and PCO2 where monitored by the ZEPPELIN-Neurotec-System.

RESULTS From 79 patients with severe brain injury from 03/95 to 12/96 we monitored 25 severe brain injured patients. From these patients where 8 female and 17 male, the mean age was 31 years. We report about modulation of P(ti)O2-levels and treatment in following situations: changing MABP-level and decreasing ICP-levels, preoxygenation before bronchial suction, therapy of bronchospasm, and barbiturate therapy. Treatment has to be based on CPP-management, in fact of a positive correlation from CPP and P(ti)O2 in 20/25 Patients. We detected a significant positive correlation between the parameters CPP/MAP, CPP/P(ti)O2, and a significant negative correlation between ICP/P(ti)O2 and ICP/CPP with alpha=0,05. The measurement showed valid effects in situations of brain ischemia and brain death in 5 Patients. We also present data about pitfall measurements and complications in 3 Cases.

CONCLUSION Multimodal hemodynamic neuromonitoring including P(ti)O2 is a new and helpful method to give information about brain oxygenation in situations of increased ICP and brain edema. Parameters such as MABP(>90mmHg) and CPP(>60 mmHg) and additionally the therapy of elevated ICP should be forced by hemodynamic methods.

P - 1 - 022

VALIDITY OF EPIDURAL ICP-MONITORING IN SEVERE HEAD INJURIES - EXPERIENCES IN A LEVEL 1 TRAUMA CENTER

Jörn Deneke, Günter Fröschle, Pattrick Schmitt, Jürgen Volker Wening*, Karl-Heinz Jungbluth

Department of Trauma and Reconstructive Surgery, University Hospital of Hamburg, General Hospital of Altona*, Germany

Introduction
The discussion about different methods of intracranial pressure (ICP) monitoring still remains controversial (1, 2). The aim of this study was to prove the validity of epidural measurement in comparison to other methods, and to analyze cost factor, complication rate and clinical practicability.
Methods
During a 5 year period, the ICP was monitored in 53 patients (33 male, 20 female) with severe head injury by 2 types of epidural transducers, and the cerebral perfusion pressure (CPP) was calculated. 29 had multiple injuries, 24 isolated head traumas. The average age was 36 years (1 - 83). The Glasgow Coma Scale at admission was 5.2 (3 - 15). The ICP and CPP values were compared with physical examination, radiological or intraoperative findings and clinical outcome, defined by the Glasgow Outcome Scale (GOS).
Results
The average time of measuring was 8.5 days (1 - 22). The overall survival rate was 79 %. The evaluation with the GOS showed 5 points in 19 %, 4 in 17 %, 3 in 13 %, 2 in 11 %. The average ICP values of the survivors revealed 19.8 mmHg, the CPP 71.9 mmHg, in the non survivors 27.6 mmHg and 62.2 mmHg, respectively. In 60 % of our patients the measurements were considered as reliable to clinical course and outcome. We saw 11 failures of the transducers, in 13 cases (25 %) we observed a displacement of the ICP-device. 7 transducers had to be replaced. There was no infection.
Summary and Conclusions
These findings indicate that the assessment of the ICP by epidural measurement remains a useful method of monitoring the ICP with a low rate of complications. It may help to detect complications in an early phase and to estimate the outcome.

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PO - 1 - 025

COMPUTER SOFTWARE FOR FREQUENTIAL MONITORING OF SLOW INTRACRANIAL PRESSURE WAVES AND RELATED SIGNALS.

J.J. Lemaire[1,2], J.F. Burlat[1,3], T. Khalil[1,2], A. Chabane[1,2], B. Irthum[2], J. Chazal[2].
(1) Neurosurgery Research Unit, University Medical Center; (2) Service of Neurosurgery, University Hospital; (3) Superior Institute for Computer Science, Modeling, and their Applications, Blaise Pascal University.
Clermont-Ferrand, France.

Because ICP slow waves are in the core of pressure-volume relationships, in particular the vascular component, we developed computer software to explore the time evolution of the frequential characteristics of these waves.

Technical environment: Software development used a programming software, LabWindows© ver.3.1/CVI (National Instruments®), and was carried out in C language. The hardware consisted of two PC computers: a Pentium© 100 MHz (16Mo RAM, 850Mo hard disk) for the experimental research, and a portable 486 100 MHz (12Mo RAM, 525Mo hard disk) for bedside recording. Signals are digitized using two A/D cards (National Instruments®): a Lab-PC+© for the Pentium©PC and a DAQ-Card 1200© (PCMCIA II slot) for the portable PC.

Software description: Four signals can be recorded (with possible messages) and analyzed simultaneously. The sampling rate is 100 Hz then the pulse wave is withdrawn (elliptic band cut filter) and the signal is re-sampled. The analysis bases were adapted from a previously implemented method (1). Frequential analysis is performed every 2 sec over the last period acquired (from 32 sec to 68 min. for experimental research, and 2 min. 13 for human studies) which allows a quasi real time monitoring of specific frequencies. The time evolution of these frequencies is watched in frequency bands (BW from 0.008 Hz to 0.050 Hz, UB for 0.050 Hz to 0.200 Hz, IR from 0.200 Hz to 1.200 Hz and breath 1.200 Hz to 3.300 Hz) by detection of the harmonic (F) with the highest amplitude (P) in each of the bands. Frequential data (F and P values, frequency and amplitude spectra) for each bands are continuously displayed with the mean value of the signal and its standard deviation.

Applications: The software are in evaluation in two research protocols: an experimental work on the physiological regulation of slow ICP waves; a clinical research on the detection of predictive parameters of the ICH decompensation.

Research is supported by a grant from Codman®- Johnson and Johnson Medical®.

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PO - 1 - 026

A MULTI-DISCIPLINARY APPROACH TO THE IMPLEMENTATION OF A NEUROINTENSIVE CARE MONITORING SYSTEM FOR PATIENT CARE, ADMINISTRATION AND RESEARCH

Dunn L.T., O'Brien G., Piper I.A., Wagstaff, A., Teasdale G.M. Wyper D.

Departments of Neurosurgery and Medical Physics, University of Glasgow, Southern General Hospital, GLASGOW, UK.

Introduction.
The recent installation of Hewlett Packard's Merlin based "Doc Vu" patient care system in our ITU provided an opportunity to design a system configured to meet the requirements of several different disciplines and to provide information useful for patient care, administration and research.

Methods.
Representatives of the different disciplines involved in patient care, research and administration on the neurointensive care unit were approached and asked to prioritise their requirements for a computerised neurointensive care monitoring system. This information was then integrated and a configuration for the system settled upon.

Results.
The ability to input clinical (particularly neurological) and nursing information directly from the bedside via pre-configured menu driven commands and the facility to produce customised trend plots of the information for ward rounds and patient reviews were identified as important properties of the system by both clinical and nursing staff. The direct transmission of blood gas and lab data to the bedside monitor and the tracking of therapy intensity levels was of particular value to the neuroanaesthetic staff. The ready availability of demographic, blood gas, laboratory data, locally entered textual data and minute by minute trends in physiological data makes the system well suited to obtaining and maintaining research data. The data is stored in an ODBC compliant database and can be interrogated locally or remotely using structured query language thus providing additional flexibility for data analysis.

Conclusions.
The implementation of a flexible, user-configurable neurointensive monitoring system has allowed the diverse requirements of the multiple disciplines involved in neurointensive care to be catered for in a single dedicated system. Potential advantages in the ready availability and improved presentation of data for the clinical management of patients as well as the sophisticated data collection and analysis available for research purposes are being monitored and quantified.

PO - 1 - 027

CORRELATION BETWEEN CEREBRAL OXYGEN SATURATION BY NEAR-INFRARED SPECTROSCOPY AND SVJO2 IN SEVERELY HEAD INJURED PATIENTS.

A. Ter Minassian, C. Leguerinel, S. Adnot, M. Ursino, F. Bonnet, L. Beydon.
Surgical Intensive Care Unit H. Mondor Hospital. Créteil, and INSERM U256. Paris, France. Dept of biomathematics, University of Bologna, Italy.

Introduction
Near-infrared spectroscopy is a new method which theoretically allow non invasive continuous measurement of cerebral saturation in oxygen (ScO_2). It includes an algorithm which correct for the participation of extracerebral structures. By analogy to other tissues, it is admitted that cerebral venous compartment amounts to 70% of total cerebral blood volume. Accordingly, ScO_2 is expected to correlate to $SvjO_2$. However, ScO_2 has not been convincingly validated in pathology. This study reports clinical values of ScO_2 obtained during CO_2 rebreathing and during the assessment of autoregulation.

Material and Methods
Twelve injured patients, sedated and paralyzed (GCS<8) were studied after informed consent. ScO_2 (Somanetics,® Invos) was continuously recorded. Jugular venous saturation ($SvjO_2$) was measured by blood samples. We analyzed these parameters obtained 1) during normoventilation, hyper- and then hypoventilation at constant mean arterial pressure (MAP) 2) and also at two different levels of arterial pressure, using Norepinephrine under constant moderate hyperventilation.

Results
During CO_2 test, absolute ScO_2 and $SvjO_2$ were positively correlated ($r=0.66$, $p<0.001$). A Bland & Altman test showed that mean difference was 1.6 ± 11.9%. Relative values of ScO_2 and $SvjO_2$ also positively correlated ($r=0.85$, $p<0.001$) but the slope was significantly different from unity ($p<0.001$). During autoregulation test, absolute ScO_2 and $SvjO_2$ positively correlated ($p=0.01$) whereas variations in ScO_2 negatively correlated to variations of $SvjO_2$ ($p<0.05$).

Summary and conclusions
We conclude that the ability of ScO2 to reflect SvjO2 can be questioned for two reasons : moderate accuracy possibly due to a contamination by the signal from extracranial structures and also possible changes in the partition between the arteriolar and venous cerebral blood volume, depending on the clinical context (CO_2 vs. norepinephrine).

PO - 1 - 028

CORRELATION BETWEEN LASER DOPPLER FLOWMETRY AND ABSOLUTE UNITS OF LOCAL CEREBRAL BLOOD FLOW USING QUANTITATIVE AUTORADIOGRAPHY

John I. Miller, Mike W. Chou, Diana Dow-Edwards, Jeff Pan, and Paolo Bolognese

Departments of Neurosurgery and Pharmacology
SUNY Health Science Center At Brooklyn
Brooklyn, New York

Introduction
Laser Doppler Flowmetry (LDF) provides continuous assessment of local cerebral blood flow (CBF) in arbitrary units (a.u.). Its clinical utility has been limited by the lack of data expressed in absolute flow units (ml/100g/min) over a broad range of local CBF levels.

Methods
In male adult Sprague-Dawley rats (n=16), LDF measurements of local CBF, using both surface and depth locations, were compared with Quantitative Autoradiographic (QAR) measurements expressed in ml/100g/min. Under general anesthesia, a clinically compatible and calibrated LDF probe (Camino, San Diego) was rigidly, stereotactically secured to either the cortical gray surface or within subcortical gray matter. Temperature and invasive blood pressure were monitored, as well as arterial blood gas sampling. LDF data were recorded by computer digital acquisition. Following a ramp infusion of C^{14}-iodoantipyrine, the animals were sacrificed and their frozen brains were sequentially sectioned for both histologic and autoradiographic study according to standard QAR technique (1).

Results
QAR values ranged between 27 and 109 ml/100g/min in proximity to probe placement. LDF values ranged between 41 and 762 a.u. Statistical based software was used to correlate corresponding QAR (dependent variable) and LDF (independent variable) values for each animal. A statistically significant cubic correlation ($r = 0.8993$, $p<0.001$) was obtained.

Summary and Conclusions
The foregoing data acquired, thus far, indicates a statistically significant relationship between absolute flow units and LDF. A uniform application of LDF probe design, placement, and signal processing is implicit to this observation (2).

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PO - 1 - 029

Improving Our Models: The Case for Monitoring Craniospinal Compliance Simultaneously to ICP and TCD Waveform Analysis. Considerations for the Design of a Multi-Centre Study

I. Piper, C. Contant, M. Czosnyka
Clinical Neurosciences, Western General Hospital, Edinburgh, UK
Department of Neurosurgery, Baylor College of Medicine, Houston, USA
Academic Neurosurgical Unit, Addenbrookes Hospital, Cambridge, UK.

Introduction: Over the last twenty years there has been interest in studying the ICP waveform and, more recently, the MCA flow velocity waveform in order to provide information to help either predict raised ICP or the limits of cerebral blood flow autoregulation[1,2,3]. Despite much effort and a considerable number of publications, a good predictive model, based on waveform indices, has failed to materialise. Those working in this field agree that the models could be improved if data on compliance were obtained along side the data on the ICP and MCA flow velocity waveform. This is pertinent as it is known that pressure and flow transmission through the cerebrovascular bed are dependent both on the resistance of the vascular bed and also on processes which affect the craniospinal compliance, some of which may be non-vascular in origin.

Methods: An automated method for measurement of craniospinal compliance has been developed[4] which is now in the final stages of a clinical validation study. In light of this recent development, the authors are organising a multi-centre study, co-ordinated by three centres with an active interest in this field, to obtain data, prospectively, on compliance and the ICP and MCA flow velocity waveform. Data will be collected continuously during normal monitoring but also during reactivity testing of the patient to CO2 and mild pressor challenge. Data will be stored in a shared database with Internet access to encourage a multi-centre approach to analysis and modelling of the data.

Results: A protocol has been designed and an analysis methodology is being developed. We propose to present the protocol to both encourage international discussion on its design and to mobilise interest in participating in the study.

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PO - 1 - 030

BRAIN TEMPERATURE IN HEAD INJURED PATIENTS

C. S. Rumana, S. P. Gopinath, M. Uzura, A. B. Valadka, C. S. Robertson.
Department of Neurosurgery Baylor College of Medicine

Introduction

The injured brain is sensitive to variations in temperature. In experimental studies, brain temperature is directly monitored and controlled independent of systemic temperature. Clinical practice, however, has been to use rectal temperature as an estimate of brain temperature. The purpose of this study was to measure rectal temperature, jugular bulb temperature, and brain temperature in patients with severe brain injury, and evaluate the factors that might be related to the gradient between brain and rectal temperature.

Methods

Eighteen patients with severe head injuries had measurement of brain and rectal temperatures. Nine patients also had measurements of jugular venous blood at the level of the jugular bulb. No complications occurred as a result of the measurements. Temperatures were compared in the different locations. Temperature differences were compared to demographic characteristics and to global CBF and $CMRO_2$ measurements and changes in temperatures were observed during clinical events.

Results

Brain temperature was elevated an average of 0.9°C over rectal temperature. In individual patients the average brain temperature elevation above the rectal temperature ranged from -0.70°C to 1.70°C. Jugular venous and rectal temperatures were similar.

The only demographic characteristic which was significantly related to temperature was age. The age of the patient was inversely related to both the average brain temperature (r^2=.48, p=.002) and the difference between brain and rectal temperature (r^2=.35, p=.010). Temperature was not significantly related to injury severity, sex, type of injury, or outcome.

Brain temperature was not significantly related to global CBF or $CMRO_2$ in the stable patient. However, with extreme changes in CBF or metabolism, changes in brain temperature were observed. Brain temperature increased initially by an average of 1.7°C when cerebral perfusion pressure decreased from 50 to 20 mm Hg, and then brain temperature fell at a rate of .5°C/hr with brain death. The difference in the brain and rectal temperatures decreased in those patients treated with barbiturate coma by an average of 0.4°C.

Conclusion

Direct measurement of temperature in head injured patients is a safe procedure, and temperatures in the brain are typically elevated above core body temperature. Jugular venous temperature measurement is not an accurate substitute for brain temperature, even though it is less invasive.

PO - 1 - 031

PERFORMANCE OF THE BAYESIAN DYNAMIC LINEAR MODEL DURING CLINICAL EVENTS MONITORED IN THE NEUROSURGICAL INTENSIVE CARE UNIT

Charles F. Contant, Jr., Shankar P. Gopinath, Alex B. Valadka, Claudia S. Robertson

Department of Neurosurgery, Baylor College of Medicine

Introduction

The Bayesian dynamic linear model (B-DLM) has been proposed as a method for analyzing neurosurgical intensive care unit (NICU) monitoring data. This method can perform real-time estimation of the relationship among monitored parameters. There have been several technical problems in the application of the model. To address these, a program has been written in S-Plus which will allow easy application of this method to large time-series and multiple patients. In addition, the parameters which define the model can be easily modified, and the sensitivity of the model performance to these parameters can be assessed. Performance of the B-DLM when applied to a large number of patients has not been assessed.

Methods

Patients in the NICU at Ben Taub General Hospital who are admitted not following commands are routinely monitored for intracranial pressure(ICP), mean arterial pressure(MAP), end-tidal CO_2($ETCO_2$), jugular venous oxygen saturation($SjvO_2$), pulse oximetric arterial oxygen saturation(SaO_2) and heart rate(HR). Cerebral perfusion pressure is calculated from ICP and MAP. Two applications of the B-DLM will be examined. One relates $SjvO_2$ to ICP, MAP, $ETCO_2$ and SAO_2, and the second relates CPP to HR and $ETCO_2$. Each of the individual parameters of each application has a single parameter B-DLM fit to detect outliers. At the time of each documented clinical event, the values of the model parameters will be collected and compared to the values seen during "non-event" times.

Results

In its original form, the B-DLM is unable to react to the appearance of instability in the patient's condition. A modification which varies one of the parameters of the model as a function of the complexity of the data has been performed. The results of applying the B-DLM to a large number of selected patients will be presented.

P - 1 - 032

COMPUTER SUPPORTED MULTIMODAL BEDSIDE MONITORING FOR NEURO-INTENSIVE CARE; OBSERVATIONAL STUDY

Pippa Al-Rawi, Marek Czosnyka, Peter Kirkpatrick, Piotr Smielewski, Stefan Piechnik, Spencer Harland, John D. Pickard

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Introduction: Various techniques are employed for neuro-intensive care monitoring and testing of cerebral autoregulation of patients following severe head injury.

Method: We use multiple modalities for monitoring cerebral haemodynamic reserve, including intracranial pressure, cerebral perfusion pressure, blood flow velocity in the middle cerebral artery, jugular bulb oxygen saturation, laser Doppler cortical flowmetry, near infrared spectroscopy of cerebral cortex, tissue gas analysis. Such a large volume of information demands specialised computer support for proper interpretation and artefact filtration. Also some secondary indices, resulting from on-line waveform analysis of signals like ICP, transcranial Doppler blood flow velocity have proved to be clinically helpful.

Results: Long-term computer monitoring of multiple modalities in over 200 head injured patients is summarised in this report, containing observations of specific patterns such as:

- progressing haemodynamic failure in deep intracranial hypertension,
- dynamic responses to temporary variations in arterial blood pressure,
- vasogenic waves in intracranial pressure and their relationship to haemodynamic data,
- coupling between jugular bulb oxygen saturation and near infrared spectroscopy

Conclusion: Although clinical validation of this multimodal information has yet to be established, this observational study gives a good insight into the complex nature of secondary brain insults.

P - 1 - 036

The significance of jugular oxygen saturation in pressure autoregulation in head injured patients

L Mascia [1], G E McKeating[2], M Souter[2], I Piper[2], P Andrews[2].

[1] University of Bari, Italy, University of Edinburgh, UK[2]

INTRODUCTION Pressure autoregulation can be impaired after head injury (1). If it is preserved, the percentage change of cerebral blood flow (CBF) should be narrow and similar to the percentage change in jugular oxygen saturation (Sj02) provided Hb and Sa02 remain constant (2).
We have tested pressure autoregulation in 8 head injured patients measuring simultaneously the percentage change in Sj02.
METHODS: 8 head injured patients (mean GCS = 7) sedated and ventilated admitted to the iCU were studied and autoregulation was considered preserved if %CPP/%CVR < 2 (1). Mean arterial pressure (MAP), intracranial pressure (ICP) and Sj02 were measured continuously. Cerebral perfusion pressure (CPP) was calculated and regional CBF measured using the inhalation Xe133 clearance technique. The increase in CPP of 33% from baseline was obtained by norepinephrine infusion (0.06 -0.1 γ/Kg/min).
RESULTS: all the patients had a preserved autoregulation. However half of them had a positive change in CBF = 47%±39 with a positive change in Sj02 = 23%±3; the others had a negative change in CBF = -33%±9 with a positive change in Sj02 = 5%±1. The difference between the two groups was significant for % CBF change (ANOVA p=0.04) and for % change in Sj02 (ANOVA p< 0.01).
The result was not affected when CBF was normalised for PaC02 = 34 mmHg
DISCUSSION: these data show that in this patient population pressure autoregulation was preserved but there was a significant difference in terms of Sj02 % change related to the change in CPP.

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PO - 2 - 038

COMPUTER CONTROLLED CISTERNAL INFUSION OF BLOOD, A NEW SMALL ANIMAL MODEL OF SUBARACHNOID HEMORRHAGE

Heike Beck, Thomas Brinker, Madjid Samii
Department of Neurosurgery, Nordstadt Hospital, Hannover, Germany

Introduction: The initial increase in intracranial pressure after the rupture of a cerebral aneurysm is responsible for acute ischemic neurological deterioration which determines decisively the outcome of the patients. Until now it has been difficult to reproduce the typical ICP pattern of SAH in small animal models (Matz et al. 1996). As a disadvantage of contemporary models the extent of the hemorrhage in the individual animal cannot be predicted and is varying widely. We present a model in which the typical pattern of ICP increase like recorded in man is produced by a computer controlled infusion of blood into the cisterna magna.

Methods and Results: The infusion rate used in the experiments decreased exponentially within 7 minutes from 1,00-0.01 ml/min and was computed by a mathematical model of the CSF system during SAH. The cisternal infusion of fresh autologous blood was performed in 20 anesthetized and ventilated rats via a 1.0 mm Nylon catheter implanted through the occipital bone.
During the infusion the ICP rised abruptly from baseline ICP 8,5 ± 1,5 (mean ± SD values) to 115 ± 18 mmHg. Within the following minutes of infusion it increased further to 197 ± 35 mm Hg in spite of the exponentially decreasing infusion rate. The infused volume was 0,75 ml. After the end of the infusion, the ICP returned to baseline levels within 15 minutes. All animals survived the hemorrhage, but remained lethargic within the next three days.
After 7 days the rats were killed and brain slices were stained with celestine blue and acid fuchsin for histological evaluation. Severe cell necrosis was found in the hippocampus in the animals. The CA1 hippocampal subfield is more sensitive than the CA3 sector or the dentate gyrus and shows severe neuronal loss in 80-90% by 7 days' recovery.

Conclusion: The presented model allows pharmacological studies on the effects of drugs for the treatment of acute ischemic brain damage following SAH.

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PO - 2 - 042

THERMAL DIFFUSION CEREBRAL BLOOD FLOW IN A PIG FLUID-PERCUSSION HEAD INJURY MODEL

Paul Tompkins, F.A. Stevens, Jeff Nees, and L. Philip Carter

Department of Neurosurgery, University of Oklahoma, HSC, Oklahoma City, OK

INTRODUCTION
A variety of models have been used to investigate severe head injury. One measurement lacking in all models is continuous cerebral blood flow (CBF). Thermal diffusion flowmetry (TDF) has been approved for human use and can provide real time quantitative CBF values. We have used TDF in a pig fluid-percussion head injury model to map temporal changes in CBF.

METHODS
After sedation with Ketamine (10mg/kg IM), pigs (5-10kg) were anesthetized with isoflurane. Following insertion of femoral arterial and venous catheters, animals were placed in a head frame and craniotomies were made for the fluid-percussion device and thermal blood flow sensors. Following surgery and a 30 min stabilization period, a 30 min baseline data set was collected. Data includes bilateral CBF, mean arterial blood pressure (MABP), intracranial pressure (ICP), and calculated cerebral perfusion pressure (CPP). At time 0 the fluid-percussion trauma was initiated and data collected for an additional 120 minutes post trauma.

RESULTS
Immediately following cerebral trauma, there was a bilateral decrease in CBF (49% ipsilateral, 23% contralateral). This was accompanied by an increase in ICP (4.6mmHg pre-trauma, 10.8mmHg post-trauma). There were no significant changes in MABP or CPP during the 150 minutes of data collection. At 60 min post-trauma, CBF remained reduced (-27% ipsilateral, -30% contralateral) and ICP elevated (11.1mmHg). At 120 min post-trauma CBF was still reduced from pre-trauma levels (-17% ipsilateral, -19% contralateral), while ICP had returned to a normal level (7.3 mmHg).

SUMMARY and CONCLUSIONS
We found a significant immediate bilateral reduction in CBF in this fluid-percussion head injury model. This reduction in CBF was accompanied by an increase in ICP, both of which persisted through the first hour post-trauma. CBF remained reduced bilaterally by 18% at 2 hours post-trauma. This early compromise in cerebral blood flow could contribute to long term consequences. We believe that TDF offers significant information relating to the temporal changes in CBF following traumatic brain injury.

PO - 2 - 043

THE PRESENCE OF EDEMA SURROUNDING TRAUMATIC INTRAPARENCHYMAL HEMATOMAS ON INITIAL POST-INJURY CT SCANS: A POOR PROGNOSTIC INDICATOR

H Ehsan, GF Morris, LF Marshall
Division of Neurosurgery, University of California at San Diego, USA

Introduction: Traumatic intraparenchymal hematomas (tIPH) are diagnosed by the post-injury CT scan demonstrating the presence of a high or mixed density mass lesions. Often, these are accompanied by a variably sized zone of surrounding low density representing edema. **Methods:** Data was prospectively collected from 404 patients who sustained severe head injury (GCS 4-8) and were entered into an international multicenter clinical trial. At the central trial coordinating center all CT scans were examined to quantify the number, the volume and the amount of surrounding edema of tIPHs. Clinical outcome was evaluated using the Glasgow Outcome Score (GOS) six months after injury. **Results:** The presence of edema in patients harboring only a single tIPH (n=28), was associated with a 32% mortality compared to a 10% mortality in cases without edema (n=31) [p<.001]. In patients who had multiple tIPHs, the mortality was 40% when edema was present surrounding any tIPH (n=65), and the mortality was 37% when edema was present surrounding all tIPHs (n=38) [not significant]. In striking contrast, the mortality seen when there was no edema surrounding any tIPH (n=38) was 11% [p<.001]. **Discussion:** A higher mortality is seen with the presence of any edema surrounding tIPH, regardless of whether there are single or multiple tIPH's, and regardless of the quantity of surrounding edema. Neither the initial GCS, the presence of traumatic subarachnoid hemorrhage, nor the presence of extra-axial mass lesions in any group altered these findings. Interestingly, in survivors surrounding edema had no effect on the rate of favorable outcome, defined as GOS good or moderate. **Conclusion:** Increased mortality, but not increased morbidity is seen in patients who demonstrate any edema surrounding any tIPH on initial post-injury CT scan. By elucidating the causative mechanisms, targeted therapy may be developed.

PO - 2 - 044

POST INJURY HYPERGLYCEMIA INCREASES BEHAVIORAL DEFICITS FROM SECONDARY ISCHEMIA

H. Julia Hannay, Greg Vagner, Leela Cherian, J. Clay Goodman, Charles S. Contant, Claudia S. Robertson. Department of Psychology, University of Houston and Departments of Neurosurgery and Pathology, Baylor College of Medicine

Introduction

The purpose of the present study was to determine if post injury glucose administration would result in increased behavioral deficits when cortical impact injury was followed by a secondary ischemic insult.

Methods

Long Evans rats were fasted overnight anesthetized with isoflurane and given a 4 m/sec, 2.5 mm deformation impact injury, followed in 1 hour by 40 min of bilateral carotid occlusion. Forty min before the carotid occlusion, either 2 gm/kg glucose in 4 ml saline(GL group) or saline was infused over 20 min. To control for temperature effects of glucose infusion previously observed, half of the animals infused with saline had their brain temperature kept at 37°C throughout the experiment by external heating (BT group) and half did not (SA group). Recovery of reflexes, beam balancing, beam walking, and Morris water maze performance were examined in surviving animals.

Results

Some of the significant results are summarized here. Post injury infusion of glucose resulted in a significant relationship between group and the number of trials in which the animal could not complete the beam walking task and could not find the hidden platform on the Morris water maze. There was also a significant group effect for time to find the platform. Poorer performance as measured by these variables was significantly related the presence of fewer viable CA1 and CA3 cells and inversely related to contusion volume as might be expected.

Percent of Trials Animals Unable to Complete Task Post Injury and Ischemia

Beam Walking	Day 1	Day 2	Day 2	Day 4	Day 5
GL (n=9)	92.6%	88.9%	88.9%	70.4%	59.3%
BT (n=14)	73.8%	69.0%	61.9%	57.1%	52.4%
SA (n=16)	64.6%	29.2%	31.3%	27.1%	22.3%

Water Maze	Day 11	Day12	Day13	Day 14	Day 15
GL (n=9)	61.1%	38.9%	30.6%	13.9%	5.6%
BT (n=13)	55.8%	53.8%	5.8%	7.7%	11.5%
SA (n=14)	25.0%	0.0%	0.0%	0.0%	0.0%

Conclusions

Post impact injury infusion of glucose resulted in greater behavioral deficits from a secondary ischemic insult and has implications for clinical administration of glucose containing fluids in the early post injury period.

P - 2 - 045

THE CLOSED HEAD INJURY MODEL, STANDARDISATION OF ACCELERATION MECHANISMS

W.A. van den Brink, D.A. de Jong, I.K. Haitsma, C.J.J. Avezaat
Dept. of Neurosurgery, Dijkzigt University Hospital
Rotterdam, The Netherlands

A variety of animal models to study an even larger variety of pathological sequelae following head injury have been developed. The Closed Head Injury Model in the rat is most recently developed to study head injury due to high levels of acceleration. The apparatus excels in its simplicity with which the head is subjected to high levels of impact and acceleration without causing skull fractures. A 450 gram weight is dropped from either 1 or 2 meter height on the helmet-protected rodent skull. Mortality levels of 50% can be reached and the histopathological substrate is comparable to human head injury. Intracranial pressure following closed head injury increases when secondary insults are added to the primary concussion. The parameters with which the severity of injury can be altered are ideally only two: the weight of the impactor and the height from which it is dropped. However, resistance of the thread connected to the impactor, resistance of the weight in the guiding tube, and partial obstruction of outflow of air can all, theoretically, impair the final velocity of the impactor. The foam stiffness is of major concern in determining the initial energy transfer to the skull. Physical calculations emphasise the importance of a constant foam stiffness and viscosity in this matter. The early acceleration is extremely dependent on only minor changes in foam elasticity. Any foam will eventually age, thereby loosing its mechanical properties. Especially if soiled with spill of blood. Careful determination and preservation of foam characteristics are paramount. We added to the apparatus a magnetic weight release and an LED-optical velocity measuring device to control weight drop velocity. The foam is calibrated in both a static and dynamic way. By means of a simple pressure transducer, that is compressed into the foam, the compression force deflection under static load conditions is measured. The dynamic testing device consists of a pendulum impactor (1 mtr, 180°). The angular velocity and deceleration is measured and inferences to the dynamic properties of the foam are made. The Closed Head Injury Model has thus been made less simple. It is, however, constant in its baseline important parameters of energy transfer, improving reproducability.

P - 2 - 046

EFFECTS OF TRIS(HYDROXYLMETHYL)AMINOMETHANE DURING REPERFUSION AFTER FOCAL TEMPORARY ISCHEMIA IN THE RAT BRAIN

Stefan Krömer, Kathrin König*, Eckhard Rickels*, Hans E. Heissler*, Dietrich Henzler, Siegfried Piepenbrock

Zentrum Anästhesiologie, Abt. I, *Neurochirurgische Klinik, Medizinische Hochschule Hannover, Germany

Introduction To assess the influence of a Tris(hydroxylmethyl)aminome (THAM) on cerebral infarction changes in extracellular ion activities and cortical DC potentials were measured during 1 hour of focal cerebral ischemia and reperfusion.

Methods 27 male WK rats were anaesthetized, intubated and controlled ventilated. Infarction was induced by reversible clipping of the left MCA for 1 hour. The blood pressure, heart rate, extracellular pH and potassium activity, and cortical DC potential were measured. Animals were randomly assigned to receive isovolumetric infusions of THAM (n=16, 0.73 ml/h/kg KG 3 M THAM buffer solution) or saline (n=11, controls). Infusion started 10 min prior to ischemia and was maintained for 1 hour. For histological examination the brains were cut into serial slices and infarction was calculated morphometrically.

Results During ischemia no statistical significant differences between the groups were found in both the circulatory and extracellular parameters. Reperfusion is characterized by a accellerated and complete restoration of extracellular pH in THAM animals whereas the controls remained acidulous. No differences in infarction were calculated for the histological findings.

Conclusion The administration of THAM does not ameliorate ischemic injury in the rat brain after 1 h of ischemia in comparison to a group of untreated animals. .

P - 2 - 047

Pentobarbital Coma: Outcome Analysis in 9 Patients with Severe Closed Head Injury.

S.H. Khan, H.C. Onyiuke, M. Palter

Department of Neurosurgery, Hartford Hospital/University of Connecticut

Introduction

Pentobarbital induced coma is possibly the last resort (1) in the management of refractory intracranial pressure (ICP). The outcome of pentobarbital coma in severe closed head injury (CHI) was reviewed.

Materials and Methods:

Among 60 consecutive patients with severe CHI, between March 1992 and September 1995, we identified 9 who were placed in petobarbital coma for refractory inracranial hypertension (ICP>30). All 9 patients had Glasgow coma score (GCS) of <8 at admission and were treated with hyperventilation, mannitol, lasix, sedation, paralysis and cerebrospinal fluid drainage. Their demographics, GCS, ICP profile, computed tomography (CT) findings, duration of monitoring, complications and Glasgow Outcome Scale (GOS) were recorded. A retrospective, comparative analysis between the survivors and non-survivors was conducted, using Kruskal-Wallis one way analysis of variance with chi square approximation and Mann-Whitney U tests.

Results

The median age was 25.8 years (range 13-45). In this treatment group, there were 4 responders (ICP<20) and 5 nonresponders, who eventually expired (p=0.005). All who expired had loss of basal cisterns, while the survivors did not (p=0.02). The mean duration of stay in the neurosurgical intensive care unit (NICU) amongst survivors was 19.0 (median 17.5, range 15-26) days, in non-survivors, it was 5.4 (median 4.0, range 3-11) days (p=0.01). The mean duration of hospitalization among survivors was 35.5 (median 36, range 23-47) days and 9.4 (median 5.0, range 3-24) in non-survivors (p=0.02). At transfer from NICU, 1 patient improved to a GCS between 9-12. At discharge from hospital, 3 survivors were in GOS 3, and 1 in GOS 2. No complications associated with pentobarbital induced coma were documented.

Conclusion

Our data suggests an improved functional outcome in survivors, whereas non-responders expired early.

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P - 2 - 048

Epidural hematoma: characteristics and evolution according to age.

Petitjean ME, *Liguoro D, Dixmerias F, Lassié P, Thicoïpé M, Dabadie Ph.
Emergency Departement and Neurosurgical Unit, C.H.U. Bordeaux, France.

Introduction

Epidural hematoma is a true neuroemergency and outcome is greatly influenced by time elapsed between diagnosis and surgical evacuation. This prospective study had two objectives: to evaluate the initial characteristics and the final outcome according to time elapsed before surgical treatment in child and adult populations.

Method

Between May 92 and April 94, any patient admitted in the Emergency Departement (ED) with an epidural hematoma was included in this prospective study. Population characteristics, initial neurologic evaluation, final outcome, timing of complementary investigation and surgery were collected. Results are expressed as mean ± standard deviation.

Results

Seventy nine consecutive patient, mean age 30±19 years (range, 7 months-75 years), were included. Children under 15 years represented 28% of inclusion. Traffic accident was the leading cause (51%), followed by falls (35%). The initial Glasgow Coma Scale Score (GCS) was 11±3.6 in adults and 14±1.7 in children. Neurologic deficit and/or pupillary signs were present in 27% of children and 56% of adults. An initial coma was noted in 21% of adult and 4% of children. Five children were discharged without any complementary investigation though headache and nausea were present. Mean time elapsed between injury and diagnosis was 7h40min. (Children: 10±13h, adults: 3.30±5h. Midline deplacement over 0.5mm was present in 11 children; none except two had abnormal examination (18%). On the contrary, 80% of adults had pupillary signs and/ormotor deficit when midline deplacement was present. All patients underwent surgical evacuation and mean time between diagnosis and surgery was 3±2hours. Six patients had burr-holes before transfer, and 8 were operated with fixed bilateral pupils: outcome was good for 3 patients, a moderate disability was noted in 3 and death occured in two patients. ICP was monitored in 13 patients: 4 had ICP>20mmHg. Functional recovery was good in all children and concern 53%in adults. No severe disability was observed in this study.

Discussion

Children can tolerate brain mass lesion without initial neurologic abnormality. But headache, nausea or vomiting should be taken into account for complementary investigation before discharge. When CT is not available, pediatric patients should be transfered without delay.

Reference

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P - 2 - 049

THE CEREBRAL THERMAL DYSREGULATION AND HYPOTHERMIA TREATMENT IN SEVERE BRAIN INJURY PATIENTS

Nariyuki Hayashi, Tadashi Shibuya, Kousaku Kinoshita, Shigeo JO, Takeo Azuhata, Kouichi Mera and Katuhisa Tanjo.

Nihon University, Department of Critical Care & Emergency Medicine, Japan

Introduction

The cerebral hypothermia is very successful to the neuroprotection, however, very stresses to the cardiopulmonary functions and immunoprotective system. We have recently illustrated this mechanism precisely. The pharmacological activation of A10 nervous system and pituitary function with cerebral hypothermia produced much advanced clinical results in severe head injury patients.

Method

Sixty-eight critical head injury patients who have pupil abnormality (GCS≤6) underwent multiple physiological monitoring involving ICP, SjO2, SvO2, cardiac output, brain tissue temperature (BTT), tympanic membrane temperature (TMT). Brain tissue temperature was controlled by systemic hypothermia for 1-3 weeks in 48 patients. The analysis of jugular venous blood catecholamine, pituitary hormones, NO-radicals induced NO2, NO3 and systemic immunological activities were studied during cerebral hypothermia treatment.

Results

Within the initial 15-17 hours, the main pathophysiological changes were related to cerebral thermo-dysregulation (BTT in range of 38-44°C) rather than severe ICP elevation. The combined findings on SjO2 and BTT/TMT ratio demonstrated cerebral hypoperfusion, which was associated with systemic dysoxia as well. The adequate control of BTT in the range of 32-33°C was very successful to reduction of dopamine and NO2 in jugular venous blood and suppression of cortical synaptic responses in sensory evoked potentials. The major issue of hypothermia treatment was growth hormone (GH) and Zn deficiency induced immunological depletion. The combination of cerebral hypothermia and replacement therapy of GH, ZnCl, L-arginine, estrogen, amantadine and GABA agonist anesthesia recorded good recover in 26(52%), MD in 7(14%), SD in 2(4%), VS in 3(6%) and death in 10(21%) of 48 cases of acute subdural hematoma with diffuse brain injury patients. It was easy to recovery from vagitative state.

Conclusion

The pharmacological activation of immunological function produced cerebral hypothermia treatment for long times without severe systemic infections. Adequate control of brain tissue temperature and replacement of pituitary hormone and activation of dopamine nervous system may be regarded as a promising therapeutic tool in the clinical setting.

PO - 2 - 051

Monitoring of cerebral O_2 metabolism - comparison of local tissue pO_2 and jugular-bulb oxygen saturation

Bauhuf C, Hofmann R, Steinmeier R, Fahlbusch R
Neurochirurgische Klinik, Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction: Maintenance of cerebral oxygen supply is an important therapeutic aim in neurosurgical intensiv care. For the continuous monitoring of the cerebral O_2-metabolism, tissue polarography ($p_{ti}O_2$) and jugular bulb oximetry (SjO_2) as two different modalities are available. Aim of this study was to investigate the correlation of both methods during changes of cerebral perfusion pressure (CPP).

Methods: In 11 individuals (7 SAH, 4 traumatic brain injury) arterial blood pressure (aBP), intracranial pressure (ICP), $p_{ti}O_2$, SjO_2 and endtidal pCO_2 was monitored simultaneously with a digital data acquisition system. Arterial hypotension was induced by administration of nitroprusside sodium in over-all 26 monitoring sessions. All patients were sedated and ventilated. Arterial pCO_2 was maintained at 32 ±1mmHg. Mean values for aBP, ICP, CPP, $p_{ti}O_2$ and SjO_2 were calculated from intervals of 15s previous to test beginning and at the time of maximal hypotension. Autoregulation tests were terminated if cardiac arrhythmia, excessive raise of ICP or CPP below 60mmHg arose.

Results: Mean ΔCPP was -20.2 ±9.3mmHg. Regression analysis showed no correlation between $\Delta p_{ti}O_2$ and ΔCPP (r=0.2) respectivly between ΔSjO_2 and ΔCPP (r=-0.02). A positiv, statistically significant correlation was found between ΔSjO_2 and $\Delta p_{ti}O_2$ (r=0.48**).

Conclusion: Tissue polarography and jugular bulb oximetry register cerebral oxygen metabolism at different levels, since the polarographic probe has a cylindric sample volume of a few mm^3 and jugular venous oxygen saturation represents whole brain venous oxygen outflow. Nevertheless, reduction of local cerebral pO_2 correlates with desaturation in jugular venous blood when cerebral perfusion pressure decreases.

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PO - 2 - 052

CEREBRAL OXIMETRY AFTER HEAD INJURY IN ADULTS.

Edwin M. Nemoto and Donald W. Marion

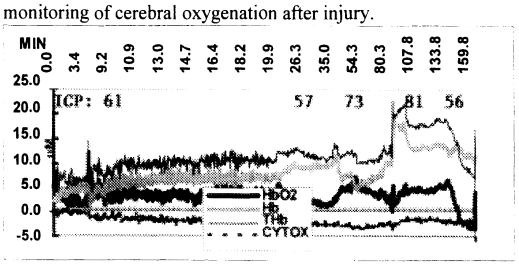
Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15213.

Introduction: Cerebral oximetry may be used to follow the time course of cerebral hypoperfusion and hyperemia after traumatic brain injury (TBI). It may also determine whether intracranial hypertension after TBI is attributable to cerebrovascular dilation or brain edema. This study correlates changes in cerebral oxygenation and blood volume with changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP) after head injury in adults.

Methods: Cerebral oximetry was used to study the time course of changes in oxygenation and cerebral blood volume relative to changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in head injured patients (admission GCS ≤ 8).

Results: Cerebral oximetry successfully tracked the initial early postinsult hypoperfusion followed by, a progressive hyperemia and hyperoxygenation which in some cases, led to infarction verified by CT. After severe TBI, a relentless course of refractory intracranial hypertension could be attributed to cerebrovascular dilation (see Fig. below).

Summary and Conclusions: Although cerebral oximetry monitors cerebral oxygenation in a small area of the cortex roughly 4 cm in diam, it is a useful method for direct, continuous, and nonvasive bedside monitoring of cerebral oxygenation after injury.



PO - 2 - 054

BRAIN TISSUE $P0_2$ MONITORING: TECHNIQUE, COMPLICATIONS AND QUALITY

J. Dings, J. Meixensberger, K. Roosen

Department of Neurosurgery, University of Würzburg, Germany

Introduction
Avoiding secondary insults is a major goal in the treatment of patients with severe head injury (SHI) and subarachnoid hemorhage (SAH). Brain tissue pO_2 ($p(ti)O_2$) monitoring offers the possibility to monitor on-line cerebral microcirculation / oxygenation. The authors present their experience with 90 $p(ti)O_2$-microcatheters on 60 patients with SHI and 25 with SAH.

Methods
The polarographic $p(ti)O_2$-microcatheter has a diameter of 0.5 mm and a pO_2-sensitive surface of 8 mm^2, lying 2.5 cm in the frontal white matter. Insertion in the ICU takes about 10 minutes. Correction for temperaturechanges is done automatically (catheter-dependant, usually 4.5 % per °C). After removal the catheter is checked for sensitivity (= drift at room air with H_2O-pressure-correction (temperature-dependant)) and zero-drift.

Results
Complications: Mean monitoring time was 7.6 +/- 3.4 days. So far (using 90 catheters) no infection caused by the catheter was observed. Two times (= 2.2 %, n=90) a small contusion was seen; an evacuation was not necessary. Four times the catheter showed a malfunction: 2 times due to kinking during CT-scan transport, 2 times caused by an "unprofessional" dysconnection. Once the screw broke: both parts could be taken out without effort. Three times the $p(ti)O_2$-catheter could not be inserted via the introducer, making it necessary to use a new introducer.
Sensitivity: Mean sensitivity was -9.5 +/- 8.7 % (7.6 +/- 3.4 days, n = 80). Catheters removed after less than 5 days showed a greater drift (-11.8 +/- 5.4 %, n = 22) compared to those removed after 5 days (-6.5 +/- 4.3 %, n = 58); so, during the first 5 days of monitoring, a slight underestimation of the $p(ti)O_2$ can occur. Comparing initial catheter charges to the latest, a clear quality-improvement can be shown (-12.5 +/- 6.5 %, n = 26 to -7.8 +/- 3.3 %, n = 54). Mean zero-drift was 1.4 +/- 1.5 mm Hg (n = 78); highest drift is seen after 5 days (2.0 +/- 1.8 mm Hg, n = 57).

Conclusions
Brain tissue pO_2 monitoring is a practicable, safe and reliable monitoring method, reflecting changes of cerebral microcirculation/oxygenation.

PO - 2 - 055

BILATERAL MONITORING OF CBF AND TISSUE OXYGEN PRESSURE IN THE PENUMBRA OF A FOCAL MASS LESION IN RATS

R. Burger, G.H.Vince, J. Meixensberger, K. Roosen
Dept. of Neurosurgery, University of Würzburg, Germany

Introduction
Continuous monitoring of cortical CBF and subcortical brain tissue pO_2 was measured using an epidural balloon expansion model in rats. With particular regard to the microcirculation in different compartments of the brain, time-related effects of both parameters were measured simultaneously ipsi - and contralateral to the focal mass lesion before, during and after ischemia.

Methods
CBF was measured bifrontoparietal by Laser Doppler Flowmetry (LDF), pO_2 bifrontal to the lesion with polarographic microsensors in 18 Spraque-Dawley rats (598±129g). After balloon placement and evaluation of the baseline values (58±8min), pO_2, CBF, SAP and EEG were measured during unilateral parietal induced balloon expansion (BE) until pupillary dilation and flat EEG. After 10 min prolonged inflation, rapid deflation was followed by the monitoring of all parameters for 178±29 min. Animals were then sacrificed. Histopathological examinations were carried out. The study protocol included a sham group (n=10) and a group with balloon expansion (n=8).

Results
Median and range of baseline values for LDF was stable with a drift of 10,2% (4-16%), PO_2mean was 31,2 mmHg (27,9-34,9mmHg) in the left and 30,1 mmHg (27,5-31,7mmHg) in the right hemisphere. After total inflation ipsilat. CBF decreased to 18,6% (13,3-24,4%) of baseline value and pO_2 from 31,2 mmHg (27,9-34,9mmHg) to 4,6 mmHg (3,2-6,7 mmHg). Contralateral. CBF decreased to 23,4% (17,1-56,6%) and PO_2 from 30,1 mmHg (27,5-31,7mmHg) to 7,1 mmHg (6,1-8,5 mmHg). After deflation ipsilat. CBF increased to 55,2% and contralat. to 67%, pO_2 increased ipsilat. to 77,4% and contralat. to 88,8% of baseline values. After decompression cortical LDF was restored much faster but incomplete in comparison to tissue pO2 (r = 0,71).

Summary and Conclusions
LDF and pO_2 measurements usually showed simultaneous changes. Cortical CBF seemed to be restored earlier than subcortical pO_2 values. Uncoupling between CBF and pO_2 depended on the individual position of the probes.

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PO - 2 - 057

MONITORING CEREBRAL TISSUE PO2, PCO2, PH AND CORTICAL BLOOD FLOW DURING TEMPORARY ISCHEMIA

Fady T. Charbel, William E. Hoffman, Mukesh Misra, James I. Ausman
Department of Neurosurgery, University of Illinois at Chicago, Chicago, Illinois, USA

Introduction: In an effort to improve the safety of temporary arterial occlusion during surgery, as well as to extend the tolerance of temporary clipping, we prospectively evaluated the impact of the following multimodal, intraoperative monitoring devices in aneurysm and EC-IC bypass surgery.

Methods: Our goal was to simultaneously measure circulatory changes after temporary clipping, in addition to detecting the onset of ischemia in cerebral tissue. For these purposes, residual/collateral blood flow was measured using (1) perivascular microprobes placed around the involved vessels, and (2) cortical laser doppler flow in the areas at risk. In addition, the effect of temporary clipping on tissues was monitored using a probe which measures tissue O_2 CO_2 temperature, and pH, which was inserted into cerebral tissue at risk for ischemia during brain artery occlusion. Furthermore, the effect of cerebral protective agents on the above parameters was recorded.

Results: Data has been collected in 87 patients (67 aneurysms, 20 EC-IC bypass). Prior to temporary artery occlusion, burst suppression EEG was induced, using 3–7 mg/kg etomidate or 9% desflurane. During EEG burst suppression with etomidate, tissue PO_2 decreased from 24±30 mmHg to 18±15 mmHg (p=0.002); with desflurane, PO_2 increased from 15±10 mmHg to 30±21 mmHg (p=0.001).

Conclusions: We found that neurological outcome was more closely related to hypoxic time as determined by the above multimodal monitoring than to actual clip time (p=0.001). These preliminary results show that improving tissue oxygenation and reducing acidosis during brain artery occlusion improves outcome, and are more reliable indicators than clip time.

P - 2 - 060

COMPARISON OF THE PARTIAL PRESSURE OF BRAIN TISSUE OXYGEN OF TWO ADJACENT AREAS OF BRAIN TISSUE AFTER SEVERE HEAD INJURY

LMH Kloos, WA van den Brink, AIR Maas, CJJ Avezaat

Department of Neurosurgery, University Hospital Rotterdam, The Netherlands

Introduction:
Continuous monitoring of the partial pressure of brain tissue oxygen ($PbrO_2$) as a parameter of cerebral oxygention has proven to be a clinically applicable monitoring technique. Disadvantage of the technique is that it has a regional character. We investigated the differences and correlation of the values of two $PbrO_2$ catheters which were inserted close to each other.

Material and Methods:
Seven patients with blunt severe head trauma (GCS ≤ 8) were investigated. $PbrO_2$ was measured by two polarographic Clark type catheters, connected with two Licox pO_2 computers. An intracranial bolt with three entries was used for simultaneous ICP monitoring and introduction of two $PbrO_2$ catheters. Measurements started as soon as possible after trauma during 5 days. The patients underwent daily ventilation-provocation tests which induced hyperoxia and moderate hypocapnia. Statistical analysis was performed according to the Altman procedure.

Results:
Although a highly significant correlation between the values measured by both catheters was present considerable variations were noted between the absolute values of the two catheters. In three patients during the hyperoxia tests one of the catheters showed a tendency towards saturation.

Discussion:
Possible explanations for the differences between the two values of the two catheters are a different position in relation to the capillary mesh or possibly the presence of microhemorrhage around the tip of the catheter. Despite the observed differences the technique appears reliable but probably more attention should be focussed on the relative changes than on the absolute value of obtained measurements.

PO - 2 - 061

TIME COURSE OF NEURON SPECIFIC ENOLASE AND PROTEIN S-100 IN JUGULAR VENOUS AND ARTERIAL SERUM FOLLOWING TRAUMATIC BRAIN INJURY

E Grant McKeating *, Luciana Mascia, Peter J D Andrews
Depts. of Anaesthesia and Clin. Neurosciences, University of Edinburgh, UK.

INTRODUCTION: Neuron specific enolase (NSE) and protein S-100 have been described as markers of injury severity following traumatic brain injury (TBI) (1). They originate from neurons and glial cells respectively. Our aim was to study NSE and S-100 in serum over 4 days following injury; our hypothesis was that levels would be elevated with jugular venous (JV) levels greater than arterial.
METHODS: We recruited 24 patients with TBI admitted to the intensive care unit. Paired arterial and JV blood samples were taken on admission, and at 24 h, 48 h and 96 h following injury. Analysis of serum for NSE and S-100 was performed by IRMA. A total of 160 samples (80 pairs) were analysed. Venous serum samples were taken from 12 healthy volunteers to act as controls.
RESULTS: (All units=mcg/l) Median age was 34yrs (range 17-69). Median Glasgow Coma Score was 6.5 (range 3-13). Median time from injury to admission sample was 8h 30 min (range 5-14 h). Mean JV levels of S-100 (1.05, 95%CI [0.58-1.52]) were significantly higher than arterial (0.99, [0.55-1.43], p=0.020) over the 4 days. For NSE, there were no differences between mean JV (11.40, [9.72-13.08] and arterial levels (11.00, [9.65-12.35], p=0.42). The table shows the time course for NSE and S-100 in JV serum (p values from two tailed t test).

Time	NSE (mcg/l)			S-100 (mcg/l)		
	Mean	95% CI	p	Mean	95% CI	p
Controls	6.9	6.3-7.5		ND*	-	
Admiss	14.9	10.7-19.1	<0.001	0.88	0.36-1.39	-
24 h	10.8	8.4 -13.2	0.003	1.30	0.13-2.47	-
48 h	8.8	6.2-11.4	0.140	0.98	0-2.05	-
96 h	9.1	5.7-12.6	0.113	1.04	0-2.24	-

* ND = not detected ; lower limit of detection =0.2mcg/l. Patient samples for S-100 which showed <0.2mcg/l were assigned a level of zero for statistical analysis.
SUMMARY AND CONCLUSIONS: Levels of both NSE and S-100 were elevated in JV and arterial serum following TBI. There was a small, but significant, elevation of S-100 in JV serum, compared to arterial; surprisingly this was not the case for NSE. NSE levels were highest on admission, whereas S-100 levels peaked around 24h after injury.
The next step is to relate the profiles of NSE and S-100 to injury severity, CT findings and outcome - they may be of some predictive value.
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P - 2 - 063

NO INFLUENCE OF IDEBENONE ON CEREBRAL AMYLOIDOSIS AFTER ISCHEMIC BRAIN INJURY

Ryszard Pluta[1,2],Maria Barcikowska[1],Mirosław Ryba[1] and Grzegorz Debicki[1]

[1]Medical Research Centre, PAS, Warsaw; [2]Academy of Physical Education, Biała Podlaska, Poland

Introduction
The two most recognized pathological features of Alzheimer's disease (AD) are amyloid plaques and neurofibrillary tangles. Ischemia has been identified as a risk factor for AD (1). Increased free radicals production may directly contribute to β-amyloid peptide (βA) aggregation and deposition. It has been shown that idebenone prevents oxidative stress mediated cell death and the process of amyloidogenesis. In this study, we examined the effect of idebenone on β-amyloid precursor protein (APP) deposition in ischemic brain.
Methods
Rats (n=15) under ether anaesthesia, were subjected to 7.5 min global cerebral ischemia (GCI) (2). They were treated p.o. one day before and four days after GCI (n=5 on idebenone 100mg/kg/day, n=5 on placebo). At 6 months after GCI, the animals were perfused with phosphate-buffered saline followed by 2% paraformaldehyde. For immunocytochemistry, we used antibodies raised against synthetic peptides corresponding to the aa residues of APP; monoclonal antibody (mAb) 22C11 against N-terminal of APP, mAb 6E10 recognizing 1-17 aa residues of βA, mAb 4G8 recognizing 17-24 aa residues of βA, polyclonal antibodies (pAb) SP 28 recognizing 1-27 aa residues of βA, and pAb RAS 57 against C-terminal of APP (CAPP) (1).
Results
In both groups, treated and placebo we observed extracellular deposits of βA/CAPP ranged from numerous small dots to irregular diffuse plaques. We found the long-term increased βA/CAPP expression in the intracellular space in both groups. In the present study, βA immunoreactivity was found in both unchanged and markedly damaged neurons and in glial cells.
Conclusions
It has been shown that p.o. administration of idebenone did not influence deposition of βA/CAPP after ischemic brain injury. These effects suggest that idebenone is not useful for the preventing and treatment of cerebral amyloidosis and/or AD.
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P - 2 - 064

NITRIC OXIDE DOES NOT AFFECT CEREBROSPINAL FLUID DYNAMICS IN CATS

Shingo SUGIOKA, Junichiro KOTANI, Teruyuki YASUTOME, Yoshihiro MOMOTA*, Alan A ARTRU* and Yutaka UEDA

Department of Anesthesiology, Osaka Dental University, Japan
* Department of Anesthesiology, University of Washington, USA

Introduction
Recent studies of the cerebral vascular effects of nitric oxide (NO) indicate that NO plays a complex role as a cerebral vasodilator. Faraci and Heistad (1) reported that NO had significant effects on blood flow to choroid plexus, the major site of formation of cerebrospinal fluid (CSF). However, the effects of NO on CSF formation (Vf) and reabsorption (Va) rates have not been reported. Because Vf and Va are important determinants of intracranial pressure (ICP), we examined the effect of NO on CSF dynamics in cats using the technique of ventriculo-cisternal perfusion (VCP).

Methods
Six adult cats anesthetized with N_2O/0.5% sevoflurane in O_2 were used for this study. Cannulae were inserted into a radial vein and femoral artery, and the animal was placed in the prone position with its head in a stereotaxic apparatus. VCP was performed using lactated Ringer's solution with 0.5% blue dextran. N^G-nitro-L-arginine methyl estel (L-NAME), an inhibitor of NO synthase (NOS), was given [iv] as a 30 mg/kg bolus and 1 mg/kg/min continuous infusion. Vf, Va, ICP, regional cerebral blood flow (r-CBF), mean arterial pressure (MAP), body temperature, and blood gas tensions, glucose and hematocrit were measured before, during and after discontinuing L-NAME.

Results
MAP increased significantly with L-NAME and then decreased to control values after discontinuing L-NAME. Vf, Va, r-CBF, and other systemic values were not changed with L-NAME.

PO - 2 - 066

RELATIONSHIP OF BRAIN TEMPERATURE TO BRAIN METABOLISM AND CORE TEMPERATURE IN PATIENTS WITH SEVERE HEAD INJURY

Alois Zauner, Egon Doppenberg, Matthias Menzel, Harold Young, Ross Bullock

Neurosurgery, Medical College of Virginia, Virginia, USA

Introduction
Temperature profoundly affects cellular functions. Hypothermia is an important means of protecting brain cells from the deleterious effects of ischemia after severe head injury. There is a linear relationship between temperature and cerebral metabolic rate of oxygen in animal models. However the influence and significance of brain temperature in severely head injured patients on brain oxygenation and metabolism is not well understood.
Methods
We compared continuous measurements of brain oxygen, brain CO_2, brain pH, and hourly brain chemistry (glucose, lactate), to brain temperature and core temperature. A multiparameter sensor (brain oxygen, CO_2, pH and temperature) was inserted into frontal cortex, via a three lumen bolt, along with a standard ventriculostomy catheter and a microdialysis probe in 25 severely head injured patients.
Results
Mean brain temperature was 0.3 to 0.5 ℃ higher than rectal temperature in patients with a brain tissue oxygen of greater than 30 mmHg and a CPP above 70 mmHg. However, for patients with poor outcome (n = 10), and brain tissue oxygen of less than 20 mmHg, brain temperature was more than 1℃ lower than core temperature. Spontaneous hypothermia (5 patients; brain temperature < 36.0°C) correlated with low CBF, low brain tissue oxygen and poor outcome. Brain temperature was in all 25 patients closely related to core temperature, brain oxygen, CPP, brain glucose, and CBF (all $p \leq 0.001$).
Summary and Conclusions
Brain temperature is closely related to core temperature, brain metabolism and CBF in this study. Brain temperature monitoring not only guides therapeutic cooling for ICP management in the future, but it may also indicate brain metabolism, and relate to regional CBF. Clearly further studies are needed.

PO - 2 - 067

REPEATED HYPERBARIC OXYGEN INDUCES ISCHEMIC TOLERANCE IN GERBIL HIPPOCAMPUS

Kojiro Wada, Masataka Ito*, Takahito Miyazawa, Hiroshi Katoh,
Hiroshi Nawashiro and Katsuji Shima
Department of Neurosurgery, National Defense Medical College,
and *Undersea Medical Center, Japan Maritime Self Defense Force, Japan

Introduction

Hyperbaric oxygen (HBO) has been used in humans in the treatment of stroke. The present study was designed to determine whether repeated administration of HBO induces tolerance to a subsequent ischemic insult that would usually be lethal to CA1 neurons.

Methods

Forty-nine gerbils were used. HBO (100% oxygen at 2 atmospheres absolute) was administered for 1 h to gerbils either for a single session or every other day for five sessions. Two days after HBO pretreatment, the gerbils were subjected to 5 min of forebrain ischemia by occlusion of both common carotid arteries under anesthesia.

Results

Seven days after recirculation, neuronal density per 1-mm length of the CA1 sector in the hippocampus was significantly better preserved in the five-session HBO pretreatment group than in the ischemic control group and in the single-session HBO pretreatment group. Immunohistochemical staining for the HSP-72 in the CA1 sector performes 2 days following pretreatment revealed that the five-session HBO pretreatment increased the amount of HSP-72 present compared with that in the ischemic control group and in the single HBO pretreatment group.

Summary and Conclusions

These results suggest that tolerance against ischemic neuronal damage was induced by repeated HBO pretreatment, which is thought to occur through the induction of HSP-72 synthesis.

P - 2 - 071

SIGNIFICANCE OF MANAGEMENT FOR CEREBRAL PERFUSION PRESSURE IN POOR-LEVEL PATIENTS WITH SUBARACHNOID HEMORRHAGE

T, Moriya, N. Hayashi, H. Kushi, T. Saitoh, K. Kinoshita, T. Shibuya
Department of Emergency and Critical Care Medicine, Nihon University School of Medicine,
Tokyo, JAPAN

A surgical treatment in poor-level patients with severe subarachnoid hemorrhage (SAH) is still controversies. In this paper, we present the importance for management of cerebral perfusion pressure (CPP) in the treatment of severe SAH. 【Clinical Material and Methods】 Ten patients with poor-level of SAH (Hunt and Kosnik Grades IV and V: WFNS SAH scale V) have been treated by aggressive combined therapy. The summary of this treatment is as follws, (1) surgical obliteration of the aneurysm within 24 hours, (2) application of spinal or ventricular drainage, (3) large decompressive craniotomy and implantation of intracranial cranial pressure (ICP) sensor into the subdural space, (4) management of hemodynamic changes using Swan-Ganz catheter, (5) maintenance of treatable ICP and systemic blood pressure (SBP) to secure CPP>80 mmHg, (6) measurement of middle cerebral artery (MCA) velocity using Transcranial Doppler (TCD) at 3 times a day and practice of percutaneal transluminal angioplasty (PTA) if nessesary, (7) ealier setting of mild hypothermia, 35 to 36 ℃ of the at the jugular bulb venous temperature, (8) use of authorized kinetic therapy to prevent complications including atelectasis and pneumonia. 【Results】 In eight of 10 patients, CPP was controlled above 80 mmHg by application of large decompressive craniotomy and CSF drainage. Seven of 10 patients (70%) were detected angiospasm by TCD. Moderate disability according to the Glasgow Outcome Scale (GOS) was observed in 3 patients (30%), severe disability in 4 patients (40%), vegetative state in 2 patients (20%) and dead in a patients (10%). 【Conclusion】 We experienced aggressive treatments to decide the therapeutic starategies in poor-level patients with SAH. In this series, the results were suggested that early management for the cerebral ischemia and maintaining the CPP > 80 mmHg were important to the successful outcomes. 【References】 (1) Le Roux PD, J Neurosurg. 85: 39-49, 1996 (2) Nowak G, Acta Neurochir 126: 33-37, 1994 (3) Kassel NF, J Neurosurg. 73: 18-36,1990

P - 2 - 072

Effects of brain surface cooling on cerebral ischemia in cats

Y. Noguchi, N. Ukita, M. Yunoki, M. Kawauchi, S. Asari, T. Ohmoto

Department of Neurological Surgery, Okayama University Medical School

Introduction

The cerebroprotective effets of hypothermia have been extensively studied in various animal models of ischemia. Whole body cooling is the most common method for hypothermia. In order to induce hypothermia during temporal occlusion in anurysm surgery, in this study, we tried brain surface cooling as a new method of selective brain cooling, and evaluated the effects of the method on focal cerebral ischemia using a cat model of transient middle cerebral artery (MCA) occlusion.

Methods

Cats underwent 1 hour of MCA occlusion followed by 5 hours of reperfusion.Brain surface cooling was induced immediately after MCA occlusion for 4 hours in hypothermia group(n=7), but not in normothermia group(n=7). Brain surface cooling was performed with saline perfusion in subdural space. Rectal temperature, brain surface temperature and deep brain temperature were monitored,and regional cerebral blood flow(rCBF)(H_2 clearance) and somatosensory evoked potential(SEP) were continuously measuerd.After reperfusion, water content was also measured by specific gravimetric technique.

Results

During brain surface cooling, although Rectal temperature maintained about 37℃. Brain surface temperature decreased to 33℃ rapidly. The rCBF was lower in hypothermia group than in normothermia group for 3hours from reperfusion. The recovery of SEP amplitude was significantly higher in hypothermia group than in normothermia group at 4and5 hours after reperfusion. In the gray matter, water content was significantly lower in hypothermia group than in normothermia group, there was, however, no significant difference in white matte).

Conclusions

These results demonstrate that brain surface cooling may be useful in avoiding ischemic injury during temporal occlusion in anurysm surgery.

P - 2 - 074

Experimental Study of the Protection Against the Acute Focal Cerebral Ischemia

Kyu-Man Shin, Jun-Hyeok Song, Myung-Hyun Kim, Seoul, Korea
Department of Neurosurgery, Mok-dong Hospital, Ewha Womans University, Seoul, Korea

Introduction : The purpose of this experimental study is to determine the protective effect of pretreatment of mannitol, steroids, thiopental sodium and nimodipine against the acute focal cerebral ischemia.

Methods : The energy metabolism of the brain was measured utilizing the high liquid performance chromatography in the brain tissue of the cats. The experimental animals were separated into three group. In group I (the sham control group) the middle cerebral artery(MCA) was not occluded. In group II (the recirculation group) the MCA was occluded for 5 hours and reperfused for 2 hours. In group III (the treatment group) the combination of mannitol (2gm/kg), steroid (30mg/kg), and thiopental sodium(5mg/kg) were administered intravenously at 30 minutes before occlusion of the MCA. The mannitol and steroids were repeated every one and half hours and thiopental sodium every hours. Nimodipine(3ug/kg/min) was continuously intravenous infused during 7 hours, initiated 30 minutes before induction of ischemia.

Results : 1) Adenosine derivatives : In group III ATP and ADP were very highly significantly increased to 485.35% and 218.45% respectively and the total adenylate to 170.27% of the value of group II. AMP reduced to 62.62% of the group II. 2) Adenylate energy charge(E.C.) : In group III E.C. was increased to 196.67% of the value of group II and recoveried to 78.67% of the group I. 3) GTP and total guanylate : In group III GTP and total guanylate were very highly significantly increased to 351.55% and 241.22% of the value of the group II respectively. 4) UTP and total uridylate : In group III UTP and total uridylate were highly significantly increased to 4296.30% and 222.22% of the value of the group II respectively.

Conclusion : The above results suggest that the pretreatment of this therapeutic combination of the drugs may have an effective means or treating acute focal cerebral infarction and would be applicable in the clinical field in which the ischemia is anticipated during major cerebral artery occlusion.

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P - 2 - 075

CEREBRAL CIRCULATION RESPONSE TO SHOCK FROM INDUCED SEIZURES

Wlodzimierz Lewelt and Russell Hummel III

Department of Anesthesiology, Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia, USA

Introduction
Seizures induce dramatic response in cerebral circulation and physiology, which, when long enough may result in brain damage. Electroconvulsive therapy (ECT) causes similar responses, but of short duration, thus hard to assess by available cerebral blood flow (CBF) techniques (1). Therefore, we continuously evaluated ECT effect on the mean flow velocity (Vm) in a middle cerebral artery using transcranial Doppler (TC-2000 EME) system.

Methods
In patients with depression, ranging in age from 18 to 66 years (45.2 ± 14.8 years), twenty seven ECTs were performed under intravenous anesthesia. The Vm, heart rate (HR), mean arterial blood pressure (MABP), end-tidal CO_2, and electroencephalogram were recorded at rest, during anesthesia and during ECT with five minute recovery.

Results
The VM increased from 37.3 ± 9.5cm/s to 90.5 ± 25.7cm/s ($p < 0.001$) within one minute following ECT stimulus. With termination of seizure activity Vm returned to near-normal value at the fifth minute of recovery. The HR (except for initial bradycardia) and MABP responded to ECT with tachycardia and hypertension that were more persistent than Vm changes.

Summary and Conclusions
We found that Vm, trend of which may reflect CBF changes, increased significantly with ECT stimulus. This reaction seemed to be determined by duration of seizure activity and was accompanied by autonomic response.

References
(1) Lewelt W. et al., Anesth. Analg. 76: S224, 1993

PO - 2 - 077

EXCITATORY NEUROTRANSMITTERS INFLUENCE ENERGY METABOLISM AFTER SEVERE HUMAN HEAD-INJURY: EFFECT OF INJURY TYPE

B. Alessandri, E. Doppenberg, S. Koura, J. Woodward and R. Bullock
Medical College of Virginia, Div. of Neurosurgery, Richmond, VA, 23298, USA

Introduction
Results from animal models of traumatic brain injury have clearly indicated that tissue survival depends upon substrate delivery versus consumption which may be increased by excitatory neurotransmitters. High glutamate has been seen in focal human contusion, especially. Therefore, we investigated the interrelationship between glutamate, lactate and glucose in relation to the type of injury in severely head-injured patients.

Methods and Results
Severely head-injured patients (n=36) were selected in which glutamate, lactate and glucose was analyzed in the same sample. Patients were divided into a group with the probe placed next to the ventriculostomy catheter ("diffuse" injury) and a group with the probe placed adjacent to focal contusions ("contusion" injury). A Spearman rank correlation between glutamate, lactate and glucose was performed over 6-96 hrs for each patient and a one-sample t-test (hypothesis: H_0) was then used to test for significance of mean intra-patient correlation.

TABLE I: Mean intra-patient Spearman rank correlation between dialysate glutamate, lactate and glucose and p-values of one-sample t-tests

Injury type	Glutamate-Lactate		Glutamate-Glucose		Glucose-Lactate	
(n=)	r-value	t-test	r-value	t-test	r-value	t-test
All (36)	0.30	p<0.001	0.17	p<0.02	0.11	p<0.11
"diffuse" (22)	0.33	p<0.01	0.18	p<0.02	0.21	p<0.037
"contusion" (14)	0.24	p<0.05	0.15	p<0.34	-0.02	p<0.80

Summary & Conclusions:
1. A very strong positive correlation between glutamate and lactate was seen in "contusion" and "diffuse" injury; which supports the *concept (Pellerin L and Magistretti PJ. Proc. Natl. Acad. Sci. USA 91: 10625-29, 1994)* that glutamate may 'drive' glycolysis;
2. The expected inverse relationship between glucose and lactate was not seen;
3. In "diffuse" injury, glutamate and glucose appear positively correlated, but not in focal "contusion" injury.

P - 2 - 079

DIFFUSION EFFICIENCY IN CEREBRAL EXTRACELLULAR SPACE: CHANGES INDUCED BY ISCHEMIC CELLULAR SWELLING

T. Kawamata, Y. Katayama, and T. Mori.

Department of Neurological Surgery, Nihon University School of Medicine, Tokyo 173, Japan

Introduction
Cerebral ischemia induces accumulation of toxic substances in the brain tissue. Such toxic substances are released to extracellular space (ECS), diffuse into surrounding tissue, and are removed or detoxicated by glial or other uptake systems. In ischemic brain, however, the diffusion in ECS may be impaired by reduction of extracellular volume due to ischemic cellular swelling. In the present study, ^{14}C-sucrose was perfused into ECS as an ECS marker, and sucrose diffusion in ischemic brain tissue was investigated using microdialysis technique.

Methods
Wistar rat was anesthetized with halothane inhalation, and a pair of microdialysis probe (probe A and B) was placed into the frontal cortex with 1.5 mm distance. Ischemia was induced by decapitation. One probe (A) was then perfused with ^{14}C-sucrose to administer sucrose into ECS, and the other (B) with Ringer solution. Dialysate fractions were collected in probe B to determine level of ^{14}C-sucrose diffused from probe A. The dialysate concentration of sucrose was measured by a scintillation counter. Animals without decapitation were employed as a normal control.

Results
In the normal control, sucrose concentration in probe B progressively increased and reached plateau level within 30-40 min after initiation of sucrose perfusion in probe A. In ischemic brain, in contrast, the increase in sucrose level was less pronounced during first 40 min. The sucrose concentration, however, continuously elevated in ischemic brain even after 40 min, and exceeded normal control level within 60 min.

Summary and Conclusion
Since sucrose is not taken up by either cells or capillaries, above findings suggest that cellular swelling and shrinkage of ECS occurs during cerebral ischemia, and the diffusion efficiency in ECS is impaired. This may enhance accumulation of toxic substances and resultant cellular damage in cerebral ischemia.

PO - 3 - 080

INTRAOPERATIVE IN-VIVO MEASUREMENT OF HEMOGLOBIN, OXY-HEMOGLOBIN, OXYGEN-SATURATION AND CYTOCHROME aa3 WITH THE NIOS MULTISCAN OS 10/30™: A NEW METHOD FOR DETERMINATION OF CEREBRAL BLOOD FLOW AND OXYGEN METABOLISM IN BRAIN TUMORS AND VASCULAR MALFORMATIONS.

H.A. Trost, *K.M. Scheufler, °F. Steinberg, D. Plev and Ch.B. Lumenta

Neurosurgical Departements, KH Bogenhausen München and *University Bonn, °Institute of Radiation Biology, University Essen , Germany

Introduction: A new, NIRS (Near-Infrared Spectroscopy)-based technology (Multiscan OS 10/30™) allows for easy, quick and non-invasive intraoperative measurement of tissue oxygenation in vivo.

Methods: Multiscan OS 10/30™ scans a tissue sector of defined geometry at 400 to 1200 nm with 0.3 nm intervals (2.400 single measurements per scan) and at a scan rate of 400 Hz. Data are visually displayed at 1 Hz, implicating that approximately 10^6 single measurements are contained in one digitally displayed scan. The systems newly developed software is based on the phenomenon of coherence-photons and allows for real time measurement of the absolute values of total hemoglobin (tHb) and oxy-hemoglobin (HbO2) in mg/ml tissue as well as the determination of tissue oxygenation (SO2) from 100% to 0%.

Results: A first series of intraoperative measurements comprising 40 cranial and spinal neoplasms and cerebrovascular malformations has revealed characteristic interindividual differences with respect to intra-tumoral oxygenation and the feasibility of differentiating tumor from unaffected brain tissue as well as monitoring cerebral oxygenation during temporary vessel occlusion.

Summary and Conclusions: With suitable (subcortical or cortical) localisation of an intraaxial neoplasm, certain stimulation dependant alterations of local tissue oxygenation and tissue perfusion within both normal brain tissue and gliomas can be objectively assessed during functional stimulation by means of SSEP and VEP. Thus, even spatially discriminating measurements of local tissue oxygenation within extensive gliomas become feasible before, under and after functional stimulation. Continuous real time characterisation of oxygen metabolism allows for monitoring during temporary occlusion of cerebral arteries, especially in cerebrovascular surgery, provided smaller probes are developed.

PO - 3 - 081

NON CONCORDANCE BETWEEN NEAR INFRA-RED SPECTROSCOPY AND CEREBRAL OXYGEN SATURATION IN BRAIN DEATH

Stephen Lewis[1], John Myburgh[2], Emma Thornton[1], Peter Reilly[1]
[1] Department of Neurosurgery, Royal Adelaide Hospital, Australia.
[2] Department of Intensive Care, Royal Adelaide Hospital, Australia.

Introduction
Near infra-red spectroscopy (NIRS) has been proposed as a non-invasive method of assessing regional cerebral oxygenation. However, clinically significant episodes of global cerebral desaturation, as determined by jugular venous oximetry, have not been detected by NIRS (INVOS 3100) (1). The aim of this study was to compare 2 different NIRS devices in a series of brain dead patients with absent cerebral blood flow.

Methods
2 groups of 4 head injured patients (2 female, 6 male) who fulfilled the clinical criteria for brain death were included in the study. Cerebral oxygen saturation was monitored in Group A by the Somanetics INVOS 3100 and in group B by the Critikon 2020 cerebral oximeter. Transcranial Doppler ultrasonography (TCD) of the middle cerebral arteries (MCA) was performed prior to monitoring. After 10 minutes stabilisation at FIO_2 1.0, cerebral oxygen saturation was recorded continuously for 20 minutes. In addition 4 control subjects for each device were monitored at rest for 20 minutes breathing room air.

Results
TCD assessment of MCA flow velocity in group A and B was consistent with absent cerebral circulation.

	Regional saturation (%)(mean ± sd)	
	Group A	Group B
Device	Somanetics	Critikon
Brain dead	79 ± 4	74 ± 2
Control	71 ± 3	65 ± 3

In one Group A patient a significant fall in regional saturation occurred in association with sustained systemic hypoxia. In addition no signals were detected in the contralateral hemisphere in 2 patients in Group B who had undergone craniectomy.

Conclusion
In the absence of cerebral blood flow, the devices tested in this study detected oxygen saturation values in the upper to normal range. These values can only reflect scalp oxygenation and indicate either a problem in algorithm designed to filter extracranial signals or in the quality of the received signal.

Reference
1. Lewis SB et al, Crit Care Med 24:1334-1338, 1996.

PO - 3 - 082

TRANSCRANIAL CEREBRAL OXIMETRY - NON-INVASIVE MONITORING OF REGIONAL OXYGEN SATURATION AFTER ACUTE BRAIN INJURY

J. Meixensberger, K. Büchner, J. Dings, S. Baunach, K. Roosen

Department of Neurosurgery, University of Würzburg, F.R.G.

Introduction
Transcranial cerebral oximetry offers a method of continuous, non-invasive, real-time monitoring of regional oxygen saturation (rSO_2). Although different studies demonstrated the occurrence of cerebral hemodynamic events reflected by changes in rSO_2 e.g. during carotid endarterectomy, the discussion is still going on, whether this technology is sensitive to detect hemodynamic changes in patients after acute brain injury. Therefore we were interested to study rSO_2 in correlation to invasive regional brain tissue oxygenation ($p(ti)O_2$) after changing $paCO_2$ and administration of mannitol to control intracranial hypertension.

Methods
Simultanous monitoring of rSO_2 and $p(ti)O_2$ of frontal brain tissue was performed continuously in 21 patients after acute brain injury to study hemodynamic changes after change of $paCO_2$ (n = 25) and/or adminstration of mannitol (n = 34) All patients were sedated, ventilated and treated according to a standard protocol (day 0-10 after trauma). Additionally intracranial pressure (ICP) and arterial blood pressure (MAP) were recorded and cerebral perfusion pressure (CPP= MAP - ICP) was calculated using computerized multimodal data storage and analysis. At least before during and after the tests arterial blood gas analyses were made to determine pH, BE, pO_2 and pCO_2.

Results
Depending on baseline conditions three groups with reduced (< 15 mmHg), normal (15 - 30 mmHg) and hyperemic (> 30 mmHg) $p(ti)O_2$ were analyzed after $paCO_2$ change (mean 7.1 +/- 0.4 mmHg):

$p(ti)O_2$	% rSO_2 change /mmHg $paCO_2$	% $p(ti)O_2$ change /mmHg $paCO_2$	CPP change (mmHg)
< 15 mmHg	- 0.7 +/- 0.5 *	- 2.8 +/- 2.3	9.3 +/- 3.4
15-30 mmHg	- 1.3 +/- 1.4	- 2.3 +/- 1.8	7.3 +/- 0.2
> 30 mmHg	- 1.5 +/- 1.0 *	- 0.2 +/- 0.4	8.5 +/- 1.8

Values as mean +/- SD , $p < 0.05$

After mannitol administration (0.5 g/kg body weight) a minimum rSO_2 change of 1.0 +/- 0.4 % could be found, while improvement of p(ti)O2 reached 3.7 +/ - 4.1 mmHg for the whole group.

Conclusion
So far invasive measurement of $p(ti)O_2$ is more sensitive to changes of cerebral blood flow, but continuous non-invasive monitoring of rSO_2 by near infrared spectroscopy can detect hemodynamic changes in patients after acute brain injury.

PO - 3 - 083

RELVEVANT ISCHEMIC THRESHOLDS DETECTED WITH NEAR INFRARED SPECTROSCOPY (NIRS) DURING CAROTID SURGERY ISCHAEMIA

PJ Kirkpatrick, J Lam, P Al-Rawi, P Smielewski, M Czosnyka, JD Pickard.
Dept of Neuorsurgery and the MRC Brain Repair Centre, Cambridge University, UK.

Introduction: Recent experience with mulit-modal monitoring of adults during carotid surgery has indicated that cerebral NIRS contamination due to external carotid attenuation can be corrected.[1] In this study we have explored the hypothesis that corrected NIRS may allow quantification in terms of clinically relevant endpoints, and have attempted to cross calibrate corrected NIRS changes against variables known to warn of severe cerebral ischaemia (SCI).

Methods: Established criteria for SCI were applied to 72 consecutative patients undergoing carotid endarterectomy. A relative fall in middle cerebral artery flow velocity (ΔFV) of >60%, and/or a sustained fall in cortical electrical activity (cerebral function monitor) were employed as criteria. NIRS (ipsilateral frontal region) signal changes were computed and configured to calculate the difference (ΔHb_{diff}) in relative concentration in oxy- and deoxy-haemoglobin before and after carotid clamping. Extracranial contributions to the ΔHb_{diff} was corrected by co-monitoring skin blood flow using laser Doppler flowmetry, and by the application of interrupted time series analysis staged clamping of the external and (2 minutes later) the internal carotid vessels.[1]

Results: Data from 54 patients was considered suitable for final analysis. Causes for exclusion were related to instability of blood pressure. There was good correlation between ΔFV and ΔHb_{diff} ($r=0.68$, $p < 0.0001$). Eleven (20%) patients developed SCI in which corrected ΔHb_{diff} was >6.0❍mol/L (median 9.6❍mol/L; range=6.1-12.8) No patient with ΔHb_{diff} <6.0 ❍mol/L showed SCI (median 0.0❍mol/L; range=0.0-5.1). Thus a ΔHb_{diff} threshold of 6.0❍mol/L provided a sensitivity and specificity of 100% for the development of SCI during carotid clamping. Two patients in the series developed postoperative neurological deficits with watershed infarcts on CT scans. Both belonged to the group which showed SCI during surgery.

Conclusion: Quantified NIRS can provide a clinically relevant indication of SCI in the adult brain provided extracranial contamination is corrected.

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PO - 3 - 084

SINUSOIDAL INPUT TEST FOR MEASUREMENT OF CSF PARAMETERS: MATHEMATICAL ANALYSIS

Kischnick B., Brinker T., Beck H., Nguyen B., Samii M.
Dept. of Neurosurgery Nordstadt Hospital Hannover, Germany

Introduction: We present a new method to evaluate intrathecal infusion tests with a sinusoidal variation in the infusion rate („sinusoidal input test"). The method computes efficiently the standard CSF parameters (outflow resistance R and compliance C) as well as their specific nonlinear dependence on the ICP.

Methods and Results: The CSF system is described by R and C, both varying with pressure, by a first-order, nonlinear differential equation: $dP(t)/dt = \left(R(P)(Q(t)+Q_0) - P(t)\right) / \left(R(P)C(P)\right)$ with ICP $P(t)$, infusion volume rate $Q(t)$, physiological CSF production rate Q_0. The infusion volume rate for the sinus input test is given by $Q(t) = \bar{q} + \tilde{q}\sin(2\pi ft)$. The response of a slightly nonlinear system to a sinus input test is nearly sinusoidal itself.

When the ICP response is plotted against the input volume rate after approximation by means of a least-squares fit, the data points form an ellipsoidal curve. The ellipse is geometrically described by its extensions along the $P(t)$ and $Q(t)$ axis, $\tilde{p}$ and $\tilde{q}$ respectively, plus the excentricity (or phase shift) φ of the ellipse. From the excentricity, the time constant τ is calculated as $\tau = \tan(\varphi)/(2\pi f)$.

Thus, the resistance can be assessed as $R = \tilde{p}/\tilde{q}\sqrt{1+4\pi^2 f^2 \tau^2}$ and compliance as $C = \tau / R$.

This numerical ellipse fit technique yields values for R and C over the ICP range covered during the sinus input test (piecewise linear approximation). The ICP range can be selected by the mean infusion rate and the amplitude of the sinus input test. The results of the sinusoidal input test were confirmed experimentally by serial constant rate infusions in 10 rats.

Conclusion: The presented technique of a sinusoidal input test gives reliable results on CSF absorption and intracranial compliance in rats. The test provides the possibility to obtain resistance pressure profile by a single test cycle in contrast to the constant rate infusion technique which needs a series of tests for this purpose.

PO - 3 - 085

COMPUTATIONAL MODELLING OF INTRACRANIAL PRESSURE DYNAMICS IN THE RAT

Terrance J. Malkinson, Quentin J. Pittman and Roland N. Auer

Faculty of Medicine, The University of Calgary. Calgary, Canada.

Adult male Sprague-Dawley rats (290-340 gm)were anesthetized with urethane (1.5 gm/kg) and positioned in a stereotaxic frame in a sphinx posture. Body temperature was maintained at 36.8°C by means of a heating pad. Results represent the mean ±SD. The mean pressure recorded by cannulation of the lateral cerebral ventricle (LCV) was 69.38±17.61 mm/saline (n=250) and the frequency histogram was Gaussian. The mean pressure recorded by cannulation of the subarachnoid space utilizing the subarachnoid screw technique was 46.93±17.80 mm/saline (n=300) and the frequency histogram was non-Gaussian with more observations occurring at the low end of the distribution. The P/V compliance curves obtained from the bolus injection (0-100 ul) of saline into the LCV were also different. The curve for pressures recorded (n=380 observations from 38 animals) from the contra-lateral LCV was exponential in nature increasing to 1430 mm/saline at 100 ul. The curve for pressures recorded (n=380 observations from 38 animals) from the subarachnoid space was identical over the pressure range of 0-80 mm/saline but then became increasingly attenuated at greater volumes reaching a lower level of 806 mm/saline at 100 ul. Pulsation pressure increased in both cases with raised pressure. The P/V compliance curve has been determined for the constant infusion of saline into the LCV over the volume range 0-100 ul and the time range of 0-420 seconds at 60 second intervals (n=1200 observations from 120 animals). A three-dimensional matrix is currently under construction relating infused volume, duration of infusion, and the resulting change in pressure. The application of computational analysis, prediction, modelling, and graphical techniques to this experimentally obtained data will allow the researcher to interactively examine more closely the kinetics of the pressure relationships within the skull.

PO - 3 - 086

THE ICP-DEPENDENCY OF RESISTANCE TO CEREBROSPINAL FLUID OUTFLOW: A NEW MATHEMATICAL METHOD FOR CSF-PARAMETER CALCULATION.

Ullrich Meier, Frank Stefan Zeilinger, Berthold Künzel.

Department of Neurosurgery, Hospital Berlin-Friedrichshain, Germany

Introduction
The international accepted calculation methods concerning the cerebrospinal fluid dynamics proceed from a pressure independent resistance to cerebrospinal fluid outflow. In a new model we focus our attention on pressure dependency of resistance.

Method
In our calculation model we are monitoring the complete pressure course p (t) over the time t during and after the infusion. The comparison of the pressure rise On (p) during the infusion and the descent Off (p) after the infusion in the same pressure level allows to construct all formulas for C (p) and R (p).

Results
For the description of the cerebrospinal fluid dynamics a non linear equation is suitable:

$$C(p) = I_{inf} / [\,On(p) + Off(p)\,]$$

$$R(p) = p / \{I_o + I_{inf}\, Off(p) / [\,On(p) + Off(p)\,]\}$$

Conclusion
The simultaneous measurement of the resistance and compliance during a single investigation allows to minimize the patients exertion. In contrast to the classical methods (1,3) it is not necessary that the ICP reaches a plateau. Our mathematical method (2) diverges with the description of a pressure dependent slope of the function for the resistance from the static examination models. For that we are able to take the non linearity of the cerebrospinal fluid resorption is into consideration.

References
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PO - 3 - 089

Dynamic Interrelation of Spontaneous ICP-Fluctuations to Blood Pressure and Cerebral Oxygenation in Comatose Patients

Steinmeier R, Bauhuf C, Hübner H, Laumer R, and Fahlbusch R
Neurochirurgische Klinik, Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction: Spontaneous slow fluctuations of ICP-waves are supposed to be induced by a decrease of cerebral perfusion pressure or an increase of pCO_2. This theory introduced by Rosner is based upon a descriptive phenomenological approach without the application of specific methods of time series analysis. Modern technical developments now allow the continuous measurement of blood flow velocity and oxygen extraction corresponding to CBF and cerebral metabolism. The analysis of the interrelationship of these signals provides new pathophysiological aspects.

Patients and Methods: ICP, blood pressure (aBP), blood flow velocity in the MCA (FV_{MCA}, by transcranial Doppler sonography), pO_2 (polarographic measurements with Clark-type-electrode) and cerebral oxygen extraction (oximetry in the jugular bulb, SjO_2) were recorded continuously for 30 minutes three times a day in 16 comatose patients with SAH (IV or V Hunt/Hess) or traumatic brain injury (GCS <7), digitalized and stored on a computer disc. Methods of time series analysis with power spectrum for the single signal and cross correlation between each of the signals were applied for 2048 data points (corresponding to 436.9 s).

Results: Classical ICP-B-waves were found in 5 patients. In these cases, signal fluctuations comparable with B-waves (same frequency characteristics) were also found constantly in the aBP, FV_{MCA} and SjO_2-signals.

Cross-correlation revealed a mean time-delay between the aBP and ICP-waves of 6.89 ±1.90s, the correlation being negative in 81%. A positive correlation with much shorter time delay was found in one patient with a disturbed cerebral autoregulation. The mean time delay between FV_{MCA} and ICP was 1.50 ±1.29s, and between ICP and SjO_2 9.47 ±2.21s. The correlation was positive for these two cross-correlations.

Conclusions: These data show that a constant interrelationship exists between the slow fluctuations of aBP, FV_{MCA}, ICP, and oxygen extraction. There is evidence that failure of autoregulation significantly modifies time delay and the correlation between aBP and ICP, and that cross-correlation between aBP and ICP might become a means to *continuously* analyze cerebral autoregulation. Animal experiments are currently performed to validate our hypothesis concerning autoregulation.

PO - 3 - 091

SIGNIFICANCE OF EARLY TRANSIENT POSTASPHYXIC ELEVATION OF ICP IN NEWBORN LAMBS.

Pauline Ting and Paul Wang
Howard University, Washington, D.C., USA

Introduction
Understanding the significance of perturbed neuropathophysio-biochemical profiles associated with asphyxia may unravel mechanisms of neurological morbidity. Thus, we studied changes in brain microcirculation (ICP, BBB, water content), oxidative metabolism, EEG and neurological function in temporarily asphyxiated lambs (LB) of <1 week old.

Methods
Under Chloralose anesthesia 22 LB were asphyxiated (Gp 1) until their arterial MBP was ≤25 torr, and then resuscitated. Arterial pH/gases, epidural ICP, EEG,BBB, MRS^{31}P (4.7T magnet), brain water (SG), and rectal temperature were monitored. Neurological examination was done on 1, 2 and 3 days following the resuscitation (R). Five sham-operated LB without asphyxia served as controls (Gp 2).

Results
Eight asphyxiated LB depicted BBB disruptions (Gp 1A) at 1 and 24 hours after R, but the remaining (Gp 1B) and Gp 2 LB had intact BBB. There was no significant differences in the severity/duration of asphyxia between Gp 1A and B. However, there was a significant transient increase in ICP in Gp 1A within 20 minutes of R (Gp 1A=13; 1B=8 torr, $p<0.05$). The ICP threshold for intact neurological survival and BBB integrity following asphyxia was ≤10 torr. When this threshold was exceeded, 80% of the LB showed BBB disruption ($p < 0.01$), the latter was associated with 100% incidence of severe neurological deficits.In contrast, all those with ICP <10 torr ,or with intact BBB after asphyxia , survived intact ($p < 0.01$). However, the SG values were not significantly different between Gp 1 sacrificed at 1 h R and Gp 2. EEG from 4 LB revealed isoelectric recordings during asphyxia , but, slight recovery at 1h R, despite intact BBB. MRI with and without Gd contrast obtained from 4 asphyxiated LB were normal.Their MRS^{31}P measurements revealed a significant drop in PCr/Pi ratio from preasphyxic level of 3.6 to 0.1, but recovered by 0.5h R. In addition , ATP and brain intracellular pH dropped significantly during asphyxia, but, recovered within 0.5 h R. All these 4 LB survived intact.

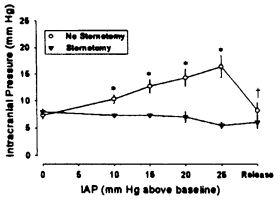
Summary and conclusions
The study showed that the transient postasphyxic increase of ICP to >10 torr within half hour of resuscitation was associated with poor neurological outcome and BBB disruption. In addition, normalization of MRS^{31}P spectrum preceded EEG recovery, and had good outcome.

PO - 3 - 092

INCREASED PLEURAL PRESSURE MEDIATES THE EFFECTS OF ELEVATED INTRA-ABDOMINAL PRESSURE UPON THE CENTRAL NERVOUS AND CARDIOVASCULAR SYSTEMS

Geoffrey L Bloomfield, MD; Philip Ridings, MD; Charles Blocher, BS; Harvey J Sugerman, MD. Div. of General/Trauma Surgery, Medical College of Virginia, Virginia Commonwealth University

Elevated intra-abdominal pressure (IAP) is a serious complication of abdominal trauma that may be even more devastating in patients with combined head and abdominal trauma. It was hypothesized that some of the deleterious effects of increased IAP are mediated by increased pleural pressure (PP) and that these effects include increased intracranial pressure (ICP), altered systemic hemodynamics, and decreased cerebral perfusion pressure (CPP). Methods: Anesthetized, ventilated swine had a balloon inserted into the peritoneal cavity and catheters placed to measure ICP, PP, central venous prossure (CVP), wedge pressure (WP) and systemic arterial pressure (SAP). Following baseline measurements, IAP was increased by incrementally inflating the balloon and parameters were re-measured 30 min after each increase. Group 1 (n=5) had IAP raised to 25 mmHg above baseline, then released. Group 2 (n=3) underwent stemotomy and pleural incision in order to prevent the increased PP with increased IAP. Results: Elevation of IAP to 25 mmHg above baseline caused an increase in PP (9.2±1.5 to 17.2±2.1)*, ICP (6.6±1.1 to 19.6±4.3)*, CVP (4.6±0.6 to 10.4 ±1.5) and WP (7.8±0.9 to 14.0±1.0)*; whereas CI (3.4±0.3 to 1.6±0.1)* and CPP (78.3±4.4 to 62.1±8.2)* decreased. Abdominal decompression returned ICP and all hemodynamic parameters to nearly baseline levels and increased CPP (62.1±8.2 to 73.8±8.0). Stemotomy negated all effects of increased IAP except decreased CI (2.5±0.2 to 1.2±0.1)*. Conclusions: Increased IAP causes increased PP, ICP, CVP and WP; whereas CPP and CI are decreased. Prevention of increased PP negates the effects of elevated IAP. Abdominal decompression restores all parameters towards baseline levels. The mediator of increased IAP's adverse effects upon the central nervous and cardiovascular systems appears to be an increase in PP that is transmitted across the central vasculature, increasing vascular pressures and impeding venous drainage of the cranial compartment. (*p < 0.05, ANOVA. Measurements are mean ± SEM).



PO - 3 - 094

POSTTRAUMATIC WHITE BLOOD CELL ACTIVATION: A PHENOMENON THAT DOES NOT WORSEN ICP WITHIN THE FIRST 6 H AFTER INJURY

Roger Härtl, Max Medary, Max Ruge, Karl E Arfors and Jam Ghajar

The Aitken Neuroscience Institute and Cornell University Medical College, New York, NY, USA

Early inflammatory responses to acute cerebral insults are involved in the pathogenesis of secondary brain damage. The present study was conducted in order to test the hypothesis that white blood cell (WBC) activation after traumatic brain injury (TBI) contributes to increased ICP.

Methods Nineteen anesthetized rabbits had chronic cranial windows implanted three weeks prior to experimentation and were divided into three experimental groups: Group I (n=5) sham-operated animals without injury. Group II (n=7) and Group III (n=7) underwent fluid percussion injury and were given either vehicle (Group II) or 1mg/kg of the anti-adhesion monoclonal antobody (MoAb) "IB4" (Group III) 5 min before injury. Intravital fluorescence videomicroscopy technique was used to visualize WBC trafficking (Rhodamine 6G, i.v.).

Results WBC sticking to pia venules increased significantly over 6 h after TBI (Group II) and was completely abolished by the MoAb (Group III). ICP increased from 4±3 mmHg to 18±13 and 13±9 at 5 min and 8±3 and 7±5 mmHg at 6 h after TBI in Groups II and III, respectively. No significant difference was seen between Groups II and III. WBC accumulation in brain tissue and its inhibition by "IB4" was confirmed by histology.

Conclusion We conclude that increased ICP within the first hours after TBI is not related to WBC activation. Other mechanisms such as early WBC-independent blood-brain barrier disruption leading to vasogenic edema (previously demonstrated by us in the present model) may be responsible for posttraumatic ICP increases.

PO - 3 - 095

THE VASOPRESSIN, PROLACTIN AND ALDOSTERONE INTERACTION IN ICP ELEVATION AND BRAIN EDEMA PATHOGENESIS

V.D.Tenedieva, I.A.Voronina, V.G.Amcheslavsky, E.E.Kalinina, V.P.Kulikovsky, N.D.Tenedieva

Burdenko Neurosurgery Institute, Moscow, Russia

Introduction

ICP elevation is known to result in vasopressin (VP) levels' increase. The mechanism obscurities of brain edema (BE) which is one of the autodestructive tissue damage consequences after operation in patients with brain tumors (BT) are a basis for studing another biological active molecules that can participate in reaction cascades.

Methods

VP, prolactin (Prl), aldosterone (Ald) levels in artery, jugular (Vj) and peripheral vein and CSF dynamics after operation were examined by RIA in 103 patients with different BT localization. ICP was estimated by CT, neurology and ophtalmology data, transcranial Doppler ultrasonography. According to calculated medium values (m) of Vj VP dynamic levels for each patient 3 Groups of patients were distinguished. The extreme difference values (d) of examined parameters were also calculated.

Results

In Vj: The VP levels were up to 6.21 pmol/l (d-6.78), 17.06 (d-15.41) and 53.01 (d-57.58) in 1st, 2nd, 3rd Groups. The Prl levels were normal in 1 and 3 Groups but were increased in Group 2 with significant d value. Ald level' increase were more frequent and pronounced in Groups 1 and 3. **In CSF**: VP and Ald levels were increased in all patients (however, Ald levels were undetectable in 41, 23 and 36% accordingly from 1 to 3 Groups), Prl values were increased in patients of Group 1. **Localizations of BT**: the basal, fossa posterior and hemispheric cerebral tumors were in 60, 30 and 10% of cases in Group 1 in contrast to 0, 64 and 36% in patients of Group 3. In the majority of cases the **pronounced BE and ICP elevation** (especially in Groups 1 and 3) correlated with significantly increased Ald and Prl or VP and Ald and/or Prl levels.

Summary and Conclusion

These findings indicate the considerable VP values increase in fossa posterior and hemispheric cerebral (vs. basal) BT localization. This fact seems to reflect the availability intact VP-secreting neurons and/or other stimulus for VP secretion. The significant magnitudes of blood and CSF Ald typical for patients with marked metabolic and regulatory disturbances (BE, ICP elevation etc.) is of special interest in line with discovery of two brain intracellular steroid receptor populations. Probably in examined patients extreme Ald and its brain receptors (MRs) activation may enhance cellular excitability and Na^+ concentration, thus contributing to neuron damage and Na^+ homeostatic control violation. The obtained data confirm the activation of doubling compensatory body systems; relationship between the extremely high levels of studied biological active molecules and ICP elevation and BE development in BT. This may serve as a basis for modern pharmacological using of VP, Prl and Ald receptor antagonists.

References

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PO - 3 - 096

PEROPERATIVE EXPERIMENCES WITH SUBDURAL ICP MEASUREMENT. REGIONAL ICP DIFFERENCES.

Bundgaard H, Cold G. E, Landsfeldt U.
Department of Neuroanaesthesia, Aarhus University Hospital.
Aarhus, DK-Denmark

Introduction

Regional differences in ICP are important factors influencing cerebral perfusion pressure and consequently regional CBF. However, studies of regional ICP differences during craniotomy are few.
The aim of this study was to investigate regional ICP differences during craniotomy for cerebral tumor.

Material and Methods

After removal of the bone flap and exposure of dura, the ICP was measured subdurally with a 22G cannula connected via a water-filled polyethylene catheter to a pressure transducer. This technique has recently been described (1).
In 26 patients, subjected to supratentorial craniotomies, studies of subdural pressure were performed twice and simultaneously. In 15 patients the two measurements were performed in the same horizontal plane and in 11 patients in the same vertical plane. Right and left differences in subdural pressure were studied in 9 patients with infratentorial cerebral tumor.

Results

In the 15 paired studies of subdural ICP in the horizontal plane, a fairly good correlation was found ($y = 0.809x + 1.223$ $R = 0.9232$, $p < 0.001$). In the study of paired subdural pressure in the vertical plan, a significant correlation was found between the vertical distance of the two measurements and the difference in ICP ($y = 1.91x - 3.25$ $R = 0.902$, $p<0.001$), indicating that the ICP is highest in the most declive part of the brain. In patients with infratentorial cerebral tumor, right/left difference in subdural pressure was only observed in patients with lateral tumor. The ipsilateral subdural pressure was always highest. A difference as great as 16 mmHg was found in these patients.

Conclusion

This study demonstrates differences in regional ICP within the area of the exposed dura. Regional differences might be caused by the influence of the tumor and/or gravity. It is supposed that differences in pressure as well as high pressure might cause cerebral herniation after opening of the dura.

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P - 3 - 099

The influence of PEEP on ICP and CPP.

C. van Velzen[1], A.I.R. Maas[2], W.J. Thijsse[2]
Departments of Anesthesiology[1] and Neurosurgery[2], University Hospital Rotterdam, The Netherlands.

Introduction: In neurosurgical patients with pulmonary complications the use of positive end expiratory pressure (PEEP) is often necessary to ensure adequate arterial oxygenation. The aim of the present study was to investigate in a limited number of patients the influence of PEEP and CPAP on ICP and CPP.
Material and methods: Thirteen patients with severe head injury were studied, nine of these were on artificial ventilation, four intubated but not ventilated. Arterial blood pressure, ICP and CPP were continuously monitored. In the ventilated patients and expiratory airway pressure was changed every 15 minutes to levels of 5, 10, 5, 0, 10 and 0 cm H_2O.
In the non-ventilated patients CPAP was increased at 15 minutes interfalls from 0 to 3, from 3 to 5 cm and back to 0 cm. At the end of each study period arterial bloodgasses were analysed.
Results: The results of the ventilated patients are summarized in table 1. No statistically significant changes of ICP or CPP were noted after changing the PEEP setting. In the patient study with CPAP no changes of ICP were noted In two patients studied a slight increase in mean arterial blood pressure was noted and in one patient a slight decrease.

Table 1: PEEP in cm H_2O

	0	5	10	5	0	10	0
mean ICP +/- SD	19/ 12.2	20/ 11.0	19/ 13.0	19/ 11.1	18/ 12.2	18/ 12.5	19/ 16.8
mean CPP +/- SD	86/ 23	90/ 23	90/ 16.2	85/ 20.0	92/ 23.7	93 21.2	88/ 19.0
mean arterial blood pressure +/- SD	106/ 20.1	109/ 18.5	110/ 16.3	105 16.0	110/ 21.5	111/ 19.9	107/ 19.0
mean arterial pO_2 +/- SD	16.7/ 2.24	17/ 2.61	16.1/ 1.68	16/ 3.05	15/ 3.11	15.8/ 2.26	16.6/ 1.93

Discussion: In this small study in normovolemia we could find no adverse influence of PEEP or CPAP on ICP or CPP. If anything a tendency was noted for an increase of mean arterial blood pressure and CPP after instituting 10 cm of PEEP. Although PEEP appears safe in normovolemic patients careful monitoring is recommended when PEEP is necessary in patients not optimally rehydrated.

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INTRACRANIAL PRESSURE CHANGES FOLLOWING A BOLUS DOSE OF MIVACURIUM.

Tullio Cafiero, Pasquale Mastronardi, Basilio Mazzarella, Lucio Stella*, Antonio Bernardo*.

Institute of Anaesthesiology and Reanimation, University of Napoli-Italy
* Institute of Neurosurgery, University of Napoli- Italy

Introduction

It is well-known that the use of succinylcholine (S) is associated with many side-effects -tachyphylaxis, phase II block, bradydysrhythmias, hyperkalemia and malignant hypertermia. Furthermore S is contraindicated in neurosurgical patients in whom any increase in ICP is deleterious. The purpose of this study was to evaluate effects of Mivacurium (M), a short-acting neuromuscular blocking drug, on ICP during tracheal intubation in neurosurgical patients.

Methods

Ten patients, ASA I or II, aged 40-68 years, undergoing surgery for various intracranial pathology were studied. ICP was monitored via an intraventricular catheter connected to a poligraph (Honeywell). Heart rate, systolic, diastolic and mean arterial pressure were recorded every minute. Following premedication and induction of anesthesia a single bolus dose of M 0.2 mg/kg was injected i.v. and ICP was recorded for 3 minutes and then tracheal intubation was performed.

Results

No significant changes in ICP during neuromuscular blockade were recorded. Tracheal intubation was performed in excellent or good conditions in most of the cases.

Conclusion

Mivacurium provided excellent or good conditions for intubation without increasing ICP. This preliminary study encourages us to use M for maintenance of neuromuscular blockade by continuous infusion in the neurosurgical patient.

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Dynamic hypothalamic-hypophyseal responses to exogenous releasing factors administration:correlation with ICP trends in the severe head injured patients.

Della Corte F., *Mancini A., #Valle D., Gallizzi F., Pennisi M.A., *De Marinis L. Institutes of Anesthesiology & Critical Care and *Endocrinology, #Department of Internal Medicine II; Catholic University School of Medicine, Rome, Italy.

Abnormal responses of hypophyseal hormones (GH, TRH, PRL) to administration of exogenous hypothalamic releasing factors (GHRH and TRH) have been previously described (1). In the present study authors analized the GH, TSH, and PRL responses to synthetic hypothalamic releasing factors in order to evaluate the role of ICP in determining hypothalamus-pituitary function in the acute phase of severe head injured (HI).
Methods. A group of 22 severe head injured patients, all males, aged 18-58 yrs (mean age 29±3 yrs) was retrospectively studied. On admission, all patients had a GCS from 4 to 8 (average GCS=6,09±0,29, motor GCS=4,14 ± 0,25). Outcome was evaluated with the GOS at six months after the trauma. Hormonal tests were performed on 1st (TRH-test) and 2nd day (GHRH-test) after the trauma. On the basis of ICP the pts were divided: pts with normal ICP throughout the time of monitoring (10 pts, 45,5%), pts with episodes of intracranial hypertension (IH) amenable with therapy (10 pts, 45,5%) and pts who showed IH refractory to standard therapies (2 pts, 9%). The last two groups were considered together for statistical evaluation (Mann-Whithney U-test). Results are reported in the following table.

	Group A	Group B	significance
GH after GHRH (µg/L)	477 ± 274	1389± 711	N.S.
PRL after GHRH (µg/L)	241 ± 38	526 ± 168	N.S.
TSH after TRH (µU/ml)	174 ± 60	240 ± 70	N.S.
GH after TRH (µg/L)	389 ± 280	827 ±320	N.S.

Discussion and conclusions. Eventhough Group B showed higher response than Group A, this difference is not significant. High ICP values can modify the hypothalamo-pituitary functions; it is well known that "empty sella syndrome" shows alterations in both the GH, PRL and cortisol 24 hours profile and response to direct stimulations. The data reported here suggest that the hormonal findings in HI could not be strictly dependent from ICP. Conversely, a primitive hypothalamic-pituitary derangement seems occur in these patients.

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THE RELATIONSHIPS BETWEEN PARAMETERS OF CSF DYNAMICS IN THE PATIENTS WITH BENIGN INTRACRANIAL HYPERTENSION SYNDROME CAUSED BY VENOUS OUTFLOW DISORDERS.

Gasparian Sergey S., Shifrin Michial A.
Burdenko Neurosurgical Institute, Moscow, Russia

Introduction
The evolution of clinical signs of benign intracranial hypertension (BIH) syndrome caused by venous outflow disorders is a result of CSF outflow failure and brain swelling. In order to define some compensatory mechanisms in evolution of ICP we have investigated possible relationships between parameters of CSF dynamics in 24 patients, stenosis of jugular vein -2 patients and arterio-sinus fistulas -2 patients).
Methods
All the patients were investigated by standard neurological and ophthalmological examinations, carotid angiography (CA), CT and in 7 patients by MRI and MRI-angiography. In order to estimate the parameters of CSF dynamics we used modified constant pressure infusion test (CPIT), with evaluation of CSF pressure (Po), CSF outflow resistance (R), elasticity of cerebrospinal system (El), intrasinus pressure (Pis), effective pressure (Po-Pis) and CSF production rate (F).
Results
All the patients had a severe papilloedema and fast decrease of VF during a period of 2 to 10 weeks. CT observations were the following : slit syndrome- in 7 patients and alarged optic nerve in 11 patients. We noticed signs of thrombosis of the superior sagittal sinus (3) and one of transversal sinuses (17) by CA and/or MRI-angiography. All patients with signs of thrombosis had a prolongation of venous phase on CA.

As a result of investigation we have determined : the tendency to the increase of R up to 14 mmHg/ml/min-1 with raised Pis up to 11 mmHg, increased Po up to 30 mmHg in accordance with raised P is and R, increase of El up to 0,5 ml-1 in the patients with Pis up to 11 mmHg.

Fast and severe impairment of visual function in the patients with venous outflow disorders confirms the hypothesis about low capacity of compensatory mechanisms of cerebrospinal system. We suppose, that in the patients with BIH syndrome impairment of venous outflow leads to elevation of Pis, R, Po, and is accompanying by increased El. These changes reflect compesatory processes in order to stabilize cerebrospinal system in the process of evolution of intracranial hypertension.

PO - 3 - 103

DUTCH NORMAL PRESSURE HYDROCEPHALUS (NPH) STUDY. Randomised comparison of low and medium pressure shunts

A.J.W.Boon and J.Th.J.Tans on behalf of the Dutch NPH Study Group, Westeinde Hospital, The Hague, The Netherlands.

Introduction
The optimal opening pressure of shunts for the treatment of patients with NPH is a matter of continuing controversy not settled by randomised studies.

Methods
Of 101 NPH patients, fulfilling strict entry criteria, 53 were randomised to low pressure (LP)=4cm H_20, and 48 to medium high pressure (MHP)=10cm Medos Hakim VP shunts. Gait disturbance and dementia were quantified by a NPH scale (NPHS) and handicap by the Modified Rankin scale (MRS). Patients were assessed prior to and 1, 3, 6, 9 and 12 months after surgery. Primary outcome measures were the differences between first and last NPHS and MRS scores.

Results
Using intention to treat analysis of all patients the LP group did better without reaching significance. Mean improvement on NPHS was 30.0 for the LP and 23.2 for the MHP group (p=0.15) and on MRS 1.41 compared to 0.98 (p=0.08). With efficacy analysis excluding serious events and deaths unrelated to NPH in 96 patients the advantage of LP was lost on NPHS. Mean MRS changes were 1.43 for LP and 1.07 for MHP shunts (p=0.13). Mostly transient subdural effusions (SDE) were found in 71% of LP and 34% of MHP shunts (p=0.0002). Both within LP and MHP group outcome was better without than with SDE but none of the differences came near significance.

Summary and conclusions
This study yielded an important trend in favour of LP shunts which was not statistically significant. We advise to treat NPH patients with LP shunts if the occurrence of SDE can be drastically reduced. Otherwise MP shunts are preferable.

PO - 3 - 104

The Evaluation of the prognostic value of a 72 hours prolonged spinal drainage for Normal Pressure Hydrocephalus

T. Yamamoto, A. Marmarou, J. Dunbar, and H. Young

Division of Neurosurgery, Medical College of Virginia, USA

Introduction
Identifying NPH patients who may benefit by shunt diversion remains difficult. At the suggestion of Dan Hanley at Johns Hopkins, we utilized a 72-hour continuous external drainage protocol to help identify which patients should be shunted. The objective of the study was to evaluate the prognostic value of this technique.

Methods
Thirty-five patients (20 male, 15 female) diagnosed as NPH with enlarged ventricles were admitted to MCV for prolonged spinal drainage at a rate 10 cc/hour for 72 hours. Prior to admission, video recordings of patient gait were obtained and neuropsychological tests were measured. Following 72 hours of drainage, both video and neuropsychological measures were repeated. In addition, for 10 days following discharge, a questionnaire was completed by the patient and caregiver to determine the level of improvement. Patients which showed clinical improvement within this time frame, as documented by improved video and neuropsychological scores, were shunted. Those not showing signs of improvement were recommended for continued follow-up.

Results
There were no complications associated with continuous 72-hour external drainage despite the mean age of 70.3 years (range 31 to 89). Prior to drainage, 15 patients showed combined gait disturbance, dementia, and urinary incontinence; 12 patients showed both gait disturbance and dementia; 8 patients showed only one symptom of the classical triad (6, gait disturbance; 2, dementia).
Of the thirty-five drainage patients, 20 (54%) improved clinically by 72 hours. Within these twenty patients, 14 were shunted. Follow-up of these shunted patients at 3 months showed 12 (85.7%) had improved, while 2 (14.3%) showed no change. In those patients that did not improve following 72-hour drainage (n=15), only one of three shunted patients showed improvement.
Of the 18 patients in this study that were not shunted, 16 remained unchanged and 2 were clinically worse.

Conclusion
We believe the 72-hour extended drainage protocol is safe and may have prognostic value.

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SINUSOIDAL INPUT TEST FOR MEASUREMENT OF CSF OUTFLOW RESISTANCE IN NORMAL VS HYDROCEPHALIC RATS.

Brinker T. , Beck H., Kischnik B., Nguyen B., Oi S.[1], Samii M.

Dept. of Neurosurgery Nordstadt Hospital Hannover, Germany
[1]Dept. of Neurosurgery Tokai University Kanagawa, Japan

Introduction: CSF outflow resistance of normal and hydrocephalic rats was measured by a newly developed intrathecal infusion test with a sinusoidal variation in the infusion rate („sinusoidal input test").

Methods and Results: In 10 adult rats a hydrocephalus was produced by the instillation of kaolin into the cisterna magna. The animals were used for the experiments 6 weeks later, when a high pressure hydrocephalus has been developed. 10 normal rats were used as control. A 1 mm nylon catheter was introduced into the cisterna magna via the occipital bone. In each animal the CSF outflow resistance profile was estimated by a series of constant rate infusions of saline. Then the sinusoidal input test was performed (rate between 0 and 50 µl, frequency =). The sinusoidal input test estimated R(mm Hg / ml/min) in the normal versus the hydrocephalic animals according to the table:

ICP(mm Hg)	10	20	30	40
R normal	1100 ± 835	1003 ± 670	744 ± 566	531 ± 434
R hydroc.	6639 ± 2382	5657 ± 2541	4208 ±2679	2974 ± 2295

(Differences between the groups p< 0.001 , t-test).
The results of the sinusoidal input test corresponded to that obtained by the constant rate infusion technique.
In each animal the time was measured until the sinusoidal input test displayed a pressure equilibrium in which the maximum ICP and the pressure amplitude were stable. This time differed significantly (p<0.001, t-test) with 175 ± 94 sec in the control group versus 520 ± 44.7 sec in the hydrocephalic animals. The different adaptation time was not due to the resistive-capacitive properties of the CSF system.

Conclusion: The sinusoidal input test enables the measurement of the CSF outflow resistance profile of rats by one infusion cycle in contrast to the constant rate infusion technique which requires a time consuming series of infusions. The sinusoidal input test demonstrated in the hydrocephalic rats a delayed adaptation to the rise in ICP.

PO - 3 - 107

Shall patients with asymptomatic and compensated hydrocephalus be operated upon by a ventriculo-peritoneal shunt?

Anders Larsson, Hannes Stephensen and Carsten Wikkelsö

Institution of Clinical Neuroscience, Department of Neurology and Neurosurgery, Göteborg University, Sahlgrenska University Hospital, Sweden.

Between 1984 and 1994 we investigated 350 patients referred for hydrocephalus. Twenty-four of these could be classified as "asymptomatic" or "compensated" hydrocephalus, i.e. patients with ventricular enlargement but no or non-progressive symptoms.

The mean age of the 24 patients was 42 years (range 20-61 years). Thirteen were men, 11 women. All but one had a head circumference exceeding the 95th percentile (57 cm) and most had an massively enlarged ventricular system. Ten patients had no symptoms typical of hydrocephalus. In 15 patients the ventricular enlargement had been a coincidental finding during in the investigation of various cerebral disorders. However, on examination, all patients showed signs of motor or psychometric impairment. All patients were subjected to our standardized diagnostic procedure for NPH patients on admission, if necessary repeatedly, and at regular intervals post-operatively. The following findings in the technical investigations were considered as positive indicators for a favorable outcome after CSF diversion; (a) ventricular reflux and block of convexity flow in communicating hydrocephalus at cisternography; (b) enlarged third ventricle and enlarged temporal horns at CT or enlarged third ventricle, enlarged temporal horns and aqueductal flow-void sign at MRI (c) a reduced basal frontotemporal flow at regional CBF measurement; (d) improvement at CSF-Tap-Test in communicating hydrocephalus.

Eighteen patients underwent surgery (eleven received a Sophy SU8, 4 a Orbis-Sigma Cordis shunt and in 3 patients a Endoscopic third ventriculostomia was performed) and all improved, most of them considerably. Mental function, gait and incontinence improved in all. Five of the patients classed as "asymptomatic" were operated with an excellent result. Six patients with minor symptoms and signs were not operated upon. At follow-up one of these showed deterioration, the remaining were unchanged.

In conclusion we have presented clinical data which has led us to question the entities "arrested" and "compensated" hydrocephalus, by showing that adults with a hydrocephalus since childhood, irrespective of the severity of their symptoms, most often clearly benefits from shunt surgery.

PO - 3 - 108

IN-VIVO ASSESSMENT OF PROGRAMMABLE SHUNTS

PRICE D. J. PINDERFIELDS HOSPITAL WAKEFIELD

INTRODUCTION

The majority of patients requiring shunts are treated for persistent intracranial hypertension. Partial or complete loss of patency almost invariably presents as a recurrence of the symptoms of raised pressure. Partial or even complete shunt failure in patients with normal pressure hydrocephalus is much less easy to recognise as their symptoms are more insidious and they develop over a longer period of time.

RESULTS

Of a series of 230 patients with Normal Pressure Hydrocephalus as defined as an outflow resistance of at least 14mmHg/ml/min., I have shown that the chance of significant clinical improvement is related to the height of outflow resistance above that threshold level. For the last 73 patients, I have taken advantage of the availability of Sophy and Medos programmable valves which have proved ideal for the titration of opening pressure for individual patients with their varying needs. Of the 56 patients who became significantly less disabled as a result of a shunt, 9 subsequently deteriorated and returned to their original condition. To determine as to whether this was due to shunt failure or merely a further progress in the underlying degenerative disease such as cortical infarcts, infusion studies were repeated at two pressure settings of the valve. These demonstrated very graphically the degree of patency and the accuracy of shunt adjustments with external magnetic systems. Only 3 of the 9 patients had shunt obstruction and I was therefore able to conclude that the remaining 6 would not benefit by a shunt revision.

PO - 3 - 109

SLEEP ABNORMALITIES AND INTRACRANIAL PRESSURE FINDINGS IN NOCTURNAL RECORDING IN PATIENTS WITH HYDROCEPHALUS.

M.A. Poca*, M.D. Calzada*, J. Sahuquillo*, M. Busto**, A. Rovira**, E. Rubio*.

Departments of Neurosurgery(*), Neurophysiology(*) and Magnetic Resonance Unit (IDI)**. Vall d'Hebron University Hospitals. Barcelona. Spain.

Introduction: Intracranial pressure (ICP) monitoring is a useful method in selecting candidates for surgical treatment in some types of hydrocephalus. Most of the important abnormal findings are found during overnight recording. Moreover, in some patients with hydrocephalus abnormalities in sleep structure have been reported. These sleep abnormalities may be important in justifying shunting in patients who are olygosymptomatic or asymptomatic, specially children and adolescents. The aim of this study was to investigate sleep abnormalities and ICP findings during overnight recording in different types of hydrocephalus.

Patients and Methods: Simultaneous extradural ICP and polysomnographic recordings were done on 32 patients with hydrocephalus of different etiologies. According to ICP recording, patients were included in one of the following categories[1]: *Active Hydrocephalus*: mean ICP > 12 mm Hg; 2) *Compensated Hydrocephalus*: mean ICP≤12 mm Hg with abnormal ICP waves; 3) *Arrested Hydrocephalus*: mean ICP≤12 mm Hg, normal ICP recording and no pathological waves. According to these categories, 12 patients had an active, 12 a compensated and 8 an arrested hydrocephalus. Besides ICP, electroencephalogram (C3-A2), chin electromyogram, right and left electro-oculogram, chest and abdominal movements and airflow were monitored overnight. Mean ICP and the percentage of A and B waves were evaluated in the global nocturnal recording and different sleep stages.

Results: In active and compensated hydrocephalus, patients who presented sleep apneas showed high and low amplitude B waves during stages 1 and 2 and REM sleep. In these cases, ICP increases were related to apneas or hypoapneas and a reduction in arterial oxygen saturation. In those patients without breathing disorders, ICP increases were only observed during REM sleep. Sleep and ICP abnormalities were more frequent in active than in compensated hydrocephalus. In both types of hydrocephalus, fragmented sleep, a very low proportion of stages 3 and 4 and a decrease in the proportion of sigma rhythms were observed. In arrested hydrocephalus only irrelevant ICP irregularities during REM sleep were found.

Conclusions: In the work-up of patients with hydrocephalus, continuous ICP monitoring must always include one overnight recording. In active and compensated hydrocephalus, the highest mean ICPs and greatest amount of abnormal waves appear mainly in specific sleep stages. In these cases, sleep abnormalities are frequently observed. The clinical significance of these abnormalities are discussed.

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PO - 3 - 112

CLINICAL APPLICATION OF PHYSICAL MODELLING OF CSF PRESSURE-VOLUME COMPENSATION : COMPUTERISED INFUSION TEST

Marek Czosnyka, Stefan Piechnik , Jo Copeman , Wojciech Maksymowicz, Piotr Smielewski, John D. Pickard

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, U.K.

Background: The mathematical model of CSF pressure volume-compensation introduced by Marmarou et al. (J. Neurosurg 1978, 48:332-344) and modified in later studies, provides a theoretical basis for the differential diagnosis of hydrocephalus. The Computerised Infusion Test was designed to compensate for the disadvantages of Katzman's lumbar infusion method: inadequate accuracy of estimation of the resistance to cerebrospinal fluid outflow and poor predictive value in normal pressure hydrocephalus.

Method: Accuracy was improved by intracranial pressure signal processing and model analysis for measurement of cerebrospinal compensatory parameters. These include the CSF outflow resistance, brain compliance, pressure-volume index, estimated sagittal sinus pressure, CSF formation rate and other variables. Infusion may be made into the lumbar space, ventricles or, when assessing shunt function in-vivo, the shunt antechamber.

Results: The computerised test has been used for five years in a multi-centre study (UK, Poland, Denmark) in 350 hydrocephalic patients of various ages (n=136 in children), aetiologies and states of cerebrospinal compensation. The principles of using the test to characterise different types of CSF circulatory disorders in patients presenting with ventricular dilatation, including brain atrophy, normal- and high-pressure hydrocephalus are presented. Our studies showed a positive correlation between cerebrospinal compensatory parameters and the results of shunting (group analysis of n=53 patients, Poland), but such a prediction remains difficult in idiopathic normal pressure hydrocephalus, particularly in the elderly.

Conclusion: Although not all patients presenting with abnormal CSF circulation may improve after shunting, computerised infusion test is an important element of diagnosis in hydrocephalus. When considered in conjunction with the hydrodynamic properties of hydrocephalus shunt, it provides a valuable method for the testing of shunt function in vivo.

PO - 3 - 113

SLEEP ASSOCIATED ARTERIAL OXYGEN DESATURATION IN PATIENTS WITH HYDROCEPHALUS

Marc D. Malkoff, Alexander Y. Razumovsky, Michael A. Williams, Michael N. Diringer, Cecil O. Borel, Daniel F. Hanley

The Johns Hopkins University, Baltimore, MD, USA

Introduction

The purpose of this prospective study was to describe the P_{csf} changes, appearance of B-waves, and systemic arterial oxygen saturation (SaO_2) changes in a group of patients with occult communicating hydrocephalus.

Methods

Eight patients with hydrocephalus were admitted for elective lumbar P_{csf} monitoring. Respiratory function was monitored continuously. Chest plethysmography was performed using the electrical impedance method with a Marquette respiratory rate monitor. SaO_2 was recorded by a pulse oximeter (Nellcor Inc.). P_{csf}, respiratory pattern and SaO_2 were recorded continuously for 24-72 hours. Sleep-wake pattern was divided into three stages: a) wakefulness; b) normal sleep, identified on the basis of visual monitoring and regular respiratory rhythm; c) abnormal sleep, defined as sleep with an irregular breathing pattern such as sleep apnea, hypopnea, or Cheyne-Stokes respirations.

Results

We had 16 days of P_{csf}, SaO_2 , and chest plethysmography tracings suitable for evaluation. There were 8775 minutes of monitored sleep. P_{csf} was elevated during 29% of the sleep period. In six patients P_{csf} elevations and B-waves occurred only in sleep and always in association with altered pattern of respiration. In the two other patients B-wave activity occurred during the awake state. During periods of P_{csf} elevation B-wave became more prominent. B-waves were usually associated with systemic arterial oxygen desaturation, however, the peak of P_{csf} usually preceded the low point of O_2 desaturation.

Summary and Conclusions

The association of elevated P_{csf}, B-waves and arterial O_2 desaturation represents increased CSF outflow resistance in patients with occult communicating hydrocephalus. This may be due to the limited ability of the cerebrospinal fluid system to compensate for increases in cerebral blood flow or cerebrospinal fluid volumes. We propose that B-wave activity in our group of patients is initiated by respiratory irregularity and may be explained by cerebral blood volume changes resulting from variation in SaO_2 or arterial CO_2 pressure.

PO-3-114

CEREBRAL HEMODYNAMICS IN PATIENTS WITH NORMAL PRESSURE HYDROCEPHALUS.

Adnan I. Qureshi, Alexander Y. Razumovsky, Michael A. Williams, John A. Ulatowski, Daniel F. Hanley.

Neurosciences Critical Care Division, Johns Hopkins Medical Institutions, Baltimore, MD 21287-7840, USA.

Introduction
Chronic cerebral ischemia is one of the possible mechanisms of cerebral injury in normal pressure hydrocephalus (NPH) (1). We evaluated cerebral hemodynamics before and after cerebrospinal fluid (CSF) drainage in patients with presumed NPH and their relationship with clinical outcome.
Methods
We measured mean cerebral blood flow velocity (mCBFV) by transcranial Doppler ultrasound in the right middle cerebral artery (MCA) before and after 3 days of controlled CSF drainage (10 cc/hour) in 13 patients with presumed NPH. Patients were clinically evaluated before and after CSF drainage. The change in neurological function was scored according to a standard scale (range -3 to +3). Patients were divided into those with clinical improvement (total score > 0) or without clinical improvement (total score ≤ 0) after CSF drainage.
Results
Patients with clinical improvement after CSF drainage had lower baseline MCA-mCBFV (30.2±7.5 cm/sec [mean±SD]) compared to those without improvement (MCA-mCBFV 38.0±6.4 cm/sec, p=0.06). Compared with baseline MCA-mCBFV, there were no significant changes in MCA-mCBFV after CSF drainage in patients with clinical improvement (34.3±10.2 cm/sec, p=0.3) and without clinical improvement (39.2±10.2 cm/sec, p=0.8).
Summary and Conclusions
Low resting MCA-mCBFV in patients who improve after CSF drainage is consistent with the mechanism of partial ischemia in NPH. However, lack of change in MCA-mCBFV in patients who improve with CSF drainage suggests that early improvement may occur by other mechanisms.

References
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P-3-115

BEHAVIOUR OF THE CEREBROSPINAL FLUID AND DISSOLVED SUBSTANCES

Darko Orešković, Marijan Klarica[1] and Velimir Lupret[2]

Department of Organic Chemistry and Biochemistry, "Ruđer Bošković" Institute, [1]Department of Pharmacology, Medical Faculty, [2]Department of Neurosurgery, University Hospital "Sisters of Mercy", Zagreb, Croatia

INTRODUCTION
According to the classical hypothesis the cerebrospinal fluid (CSF) flows unindirectionally as a river carrying dissolved substances from brain ventricles through subarachnoid spaces and it is absorbed into cerebral venous sinuses. Since, we have recently questioned this hypothesis we wanted to investigate does one way bulk flow of CSF and dissolved substances exist inside CSF spaces.

METHODS
Distribution of substances through CSF spaces was investigated by monitoring of ^{3}H-inulin and ^{3}H-water distribution in cats CSF. The samples were taken from different part of CSF system and radioactivity was measured by Beckman LS 100 C counter. The way of CSF bulk flow was studied in cats by cannulated aqueduct of Sylvius and measuring outflow rate of CSF under physiological pressure.

RESULTS
Behaviour of labelled substances after application into different part of CSF spaces in cats (n=20) showed multidirectional distribution of substances in CSF. Following cannulation of aqueduct of Sylvius in cats it was not observed escape of CSF (at physiological pressure) throughout the open cannula during two hours (n=4).

SUMMARY AND CONCLUSION
The obtained results indicate that the CSF does not behave as a slow river, and that is necessary to abandon the classical framework of thinking in CSF physiology in order to explain distribution of dissolved substances and dynamics of CSF.

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P-3-116

MAY ASSISTED OR AUTO REGULATED SHUNT VALVES ADDRESS THE SHUNT RELATED COMPLICATIONS EFFECTIVELY?

Hassan M, Higashi S, Yamashita J

Department of Neurosurgery, Kanazawa University School of Medicine Kanazawa, Japan

Introduction:
There had been differences in selecting the shunt valve systems in spite of much development in diagnostic procedures and selection of patients. Auto regulation of shunt flow by implanted valves like siphon reducing devices (ASD, SCD) and self regulating flow regulatory (SRFR) valves as well as assisted regulation of programmable valves are the latest valves available. Optimum in vitro pressure -flow study may reveal the efficacy and limitations of these valves.

Methods:
Pressure-flow relationship was examined with a complete shunt systems of Delta, Phoenix CRX (medium pressure) and Codman-Medos valves, where the variable factors affecting the valve performance were considered. These included postural hydrostatic differential pressure changes with variable head and valve positions, abdominal back pressure, temperature, choroid plexus pulsation, external pressure upon valves.

Results:
Closing pressure of valves changes with alteration of posture bringing different flow patterns with different valves. Shunt flow in Delta valve was found dependent on the implantation site and was susceptible to external pressure. Phoenix CRX valves responded to alteration of hydrostatic pressure and found moderately resistant to negative pressure and flow was unaffected by external pressure. Programming in Codman-Medos valve was dependable but ineffective in controlling posture related flow change as observed in a conventional valve.

Summary and Conclusion:
The concept of controlling the siphon effect with postural changes introduced newer expensive devices, not proved superior yet as it is reported that some are affected adversely by external pressure and others are susceptible to diagnostic procedures. Self adjusting flow regulating valves should be less expensive and its greater resistance to negative pressure may prove more acceptable to the hydrocephalic patients. Further in vivo studies should prove the efficacy of these valves and acceptability of such studies.

P-3-117

CSF Dynamics during Lidocaine-Induced Seizure Activity in Rabbits; Effect of Treatment with Midazolam and Propofol

Yoshihiro Momota*#, Alan A. Artru*, Karen M Powers*, Yutaka Ueda#

*Department of Anesthesiology, University of Washington School of Medicine, Seattle, WA
#Department of Anesthesiology, Osaka Dental University, Japan

Introduction
This study was designed to determine a) CSF dynamics and BBB permiability during lidocaine (L)-induced seizures, and b) whether post treatment with propofol abolishes L-induced seizures as effectively as midazolam.

Methods
With institutional approval, rabbits were anesthetized with fentanyl and nitrous oxide in oxygen for surgical preparation and ventriculocisternal perfusion. They were divided into midazolam (n=6) and propofol (n=6) groups. CSF dynamics were determined at each of four experimental conditions: baseline, L-induced seizures, treatment with midazolam or propofol, and return to baseline. At the end of study, L again was given to induce seizures, Evans blue was injected iv, and brains were removed and sectioned to assess BBB permiability.

Results
CSF formation rate (6 ± 1 to 7 ± 1 $\mu l \cdot min^{-1}$, mean ±SE) and resistance to reabsorption of CSF (428 ± 160 to 763 ± 160 $cmH_2O \cdot ml^{-1} \cdot min$) were not significantly different between conditions or groups. Propofol (3.8 ± 1.3 $mg \cdot kg^{-1}$) stopped seizure activity, as did midazolam (2.0 ± 1.7 $mg \cdot kg^{-1}$). Evans blue staining of the 84 brain sections was grade 0 (no staining) =48%, grade 1 (gray only) =45%, grade 2 (gray and some white) =7%, and grade 3 (extensive gray and white) = 0%, with no significant difference between groups.

The Summary and Conclusions
These findings indicate that L-induced seizure activity does not affect CSF dynamics. Propofol and midazolam both treat seizures without changing CSF dynamics. BBB breakdown following seizures was modest and not different with propofol than with midazolam.

PO - 4 - 118

INCREASED INTRA-ABDOMINAL PRESSURES AND CARDIAC FILLING PRESSURES IN OBESITY ASSOCIATED PSEUDOTUMOR CEREBRI

Harvey Sugerman, Geoffrey Bloomfield, Warren Felton III, Michael Nakatsuka

Division of General/Trauma Surgery, Department of Surgery and Department of Neuro-ophthalmology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Introduction
We have previously documented a significant decrease in cerebrospinal fluid (CSF) pressures and correction of headache and pulsatile auditory tinnitus in 8 morbidly obese patients at 3 years following gastric bypass induced weight loss. We hypothesized that intra-abdominal pressure (IAP), as estimated from urinary bladder pressures (UBP), are elevated in patients with pseudotumor cerebri and central obesity, as measured by sagittal abdominal diameter (SAD), and this leads to an increased pleural pressure (PP), measured by a transesophageal pressure transducer, which raises central venous (CVP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressures (PCWP), increasing the resistance to venous return from the brain.

Methods
5 women with pseudotumor cerebri, including 1 with a CSF leak and 1 with a patent lumboperitoneal shunt, were studied prior to gastric bypass (4 patients) and adjustable laparoscopic gastric banding (1 patient) for obesity with measurement of CSF pressure, SAD, UBP, PP, CVP, PAP and PCWP.

Results
UBP (21 ± 4 cm H_2O) and SAD (29 ± 3 cm) were significantly ($p < 0.001$) elevated in these patients with an elevated CSF pressure (314 ± 82 mm H_2O) when compared to a previous data base of non-obese patients. The trans-esophageal PP (15 ± 10 mm Hg), CVP (20 ± 6 mm Hg), PAP (32 ± 4 mm Hg) and PCWP (23 ± 7 mm Hg) were all markedly elevated ($p < 0.001$) when compared to previous obese patients without pseudotumor cerebri.

Summary and Conclusions
These data support the hypothesis that central obesity raises IAP which increases PP and cardiac filling pressures impeding venous return from the brain leading to increased intracranial venous pressure and increased intracranial pressure associated with pseudotumor cerebri. The patient with the CSF leak ceased to leak 4 months after gastric bypass induced loss of 30 kg. Headaches and pulsatile tinnitus resolved in all patients including the patient with a patent lumboperitoneal shunt.

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Combination of ICP monitoring and repeat CT scanning in initial non surgical management of acute subdural hematomas: a prospective study of 14 patients in a consecutive series of 65 cases.

Franco Servadei, Maria Teresa Nasi, Andrea Nanni, Gilberto Vergoni, Patrizia Cenni and Giuliano Giuliani, from the Division of Neurosurgery, Intensive Care Unit , Service of Neuroradiology , Ospedale M.Bufalini, Cesena, Italy

INTRODUCTION
In 1993 we identified retrospectively, in a published series of 412 comatose patients, 12 cases of acute subdural hematomas initially managed conservatively with a combination of ICP monitoring and repeat CT scan with good results.

METHODS AND RESULTS
From January 1 , 1994 to May 31, 1996, we admitted 65 comatose (GCS<8) patients harbouring acute subdural hematomas 5 mm thick or more. There were 45 males and 20 females, average age was 54 yrs and the cause of trauma was RTA in 45 (70%) cases. On the basis of the conclusion of our previous work , we have prospectively decided to initially conservatively treat the following cases : a) GCS stable or improving from the scene of accident b)The first CT scan was always obtained within 3 hrs of injury. The examination was repeated within 12 hours from injury and showed either initial hematoma reabsorption or hematoma stability c) Hematoma thickness of less than 10 mm and midline shift of less than 5 mm d) ICP of less than 20 mm Hg . In the case of conservative management the ICP monitoring was deliberatly inserted in the subdural space (with a fluid filled catheter at the beginning of the study and later with a strain gauge catheter tip , Codman Man.). Out of 65 cases , 14 patients fullfilled these criteria and were initally managed non surgically. We compared all the clinical and radiological parameters between the two groups : patients with immediate surgical indication and patients with initial non surgical treatement. No statistically significant differences were seen concerning average age, causes of trauma, GCS on admission and worst GCS, presence of pupillary abnormalities and time from injury to admission. As obvious, hematoma thickness ($p<0.0001$) , midline shift ($p<0.05$) and mean ICP ($p<0.05$) were reduced in the conservatively treated patients . Hematoma reabsorption was visibile on repeat of CT in all of the cases within 48 hrs and in 6 cases already within 6 hours from injury. Two patients were operated after an initial non surgical management only because of increased ICP . An other CT scan showed in both cases an enlarging parenchymal contusion whereas the subdural clot was either unchanged or even reduced. The outcome of the non surgical group was 9 cases of functional recovery (GR+MD) out of 14 patients whereas in the surgical group there were only 14 cases of functional recovery out of 51 patients ($p<0.02$) . **In conclusion** initial non surgical management of a selected subgroup of subdural hematoma patients using a combination of ICP monitoring and repeat of CT seems to be reasonably safe.

PO - 4 - 124

FACTORS INFLUECING THE INCRESE IN INTRACRANIAL PRESSURE AFTER THE RUPTURE OF CEREBRAL ANEURYSM

Thomas Brinker and Madjid Samii
Department of Neurosurgery, Nordstadt Hospital, Hannover, Germany

Introduction:
It was investigated whether the increase in intracranial pressure (ICP) after aneurysmal rupture could be explained by acute changes of the dynamics of the cerebrospinal fluid system. Particularly two factors were considered: the space occupying effect of blood released into the subarachnoid space and the synchronous acute impairment of cerebrospinal fluid absorption.

Methods and Results: the resistance to cerebrospinal fluid outflow (R) was determined after subarachnoid hemorrhage (SAH) which was produced by constant rate infusions of different volumes of blood (2.4 ml) injected under different pressure conditions (mean ICP 8-80 mm Hg) into the cisterns magna of 21 cats. Based on the experimental results an exponential equation predicting the R after SAH was derived in terms of the following parameters: R before SAH, the volume of blood infused, the mean ICP during the infusion and a constant k (k was calculated by a curve fitting procedure). The equation for R was implemented into a mathematical model of CSF dynamics (Marmarou et al 1978). Assuming that the bleeding rate after aneurysmal rupture depends physically on the gradient between the arterial blood and the intracranial pressure, the model was used to calculate the bleeding rate during SAH. Two different flow curves were calculated and experimentally tested by computer controlled cistern infusions of blood. During the infusion ICP rised within seconds up to 56.5 ± 7.8 (n=3. Mean $\pm$ SD) or 81.5 ± 2.9 mm Hg (n=5). This pressure range was maintained over the period of infusion (5 minutes), although the infusion rate decreased according to the computations exponentially from 3.2 ml/min or 3.8 ml/min to approx. 0.2 ml/min. The volume of the infused blood was less than 1 ml/kg body weight (2.9 or 3.2 ml).

Conclusion: The typical increase in ICP, as recorded after aneurysmal rupture in man, depends on acute changes of the CSF dynamics. It can be reproduced by an experimental computer controlled cisternal infusion of blood.

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PO - 4 - 125

Lumboperitoneal Shunting in Patients with Benign Intracranial Hypertension Syndrome

Gasparian Sergey S., Serova Nataliya K, Scherbakova Evgeniya Ya.
(Burdenko Neurosurgical Institute, Moscow, Russia)

Introduction:
The evolution of benign intracranial hypertension syndrome (BIH) leads to impairment of vision. In patients with CSF dynamic disorders conservative therapy is not always effective. The aim of current study was to analyze the efficacy of lumbo-perioneal shunting (LPS) in treatment of patients with BIH syndrome.

Methods:
In 37 patients (from our clinical series in 133 patients with BIH syndrome) LPS procedure was performed (James, Codman) . The indications to operation were failure of conservative therapy, low visual function with constricted vision fields, promination of optic discs to more than 2D decrease of draining function of subarachnoid spaces revealed at radioisternomiolography, increased outflow resistance (more than 12 mmHg/ml/min.-1) at CSF infusion test.

Results:
We observed improvement of vision in 65% of cases partial or complete regression of papillocccdema in 72% of patients in period from 2 to 12 months. Twenty percent of patients returned to normal activity. LPS was not effective in two patients who presented secondary atrophy of optic nerve. Radicular pain was noted in three cases and intestinal paresis at first week after surgery in one case. Clinical manifestations of hypotensive syndrome were present in nine patients but regressed in two weeks, five patients were reoperated on for adhesive process around abdominal catheter in period from 6 months to one year after surgery.

Conclusions:
We suppose that the patients with BIH syndrome caused by CSF and venous outflow disorders may be treated by LP shunting, which can be one of the effective methods for prevention of blindness in patients with BIH syndrome.

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EFFECTS OF MIVACURIUM ON CEREBROSPINAL FLUID PRESSURE IN PATIENTS WITH AND WITHOUT INTRACRANIAL HYPERTENSION.

Tullio Caficro*, Salvatore Razzino*, Pasquale Mastronardi, Basilio Mazzarella

*Department of Anaesthesia and Reanimation-S.Rocco Hospital, Sessa Aurunca, Italy
Institute of Anaesthesiology and Reanimation, University of Napoli, Italy

Introduction

Mivacurium(M) is a non-depolarizing neuromuscular blocking drug with a duration of action shorter than that of other neuromuscular blocking agents. The availability of a non-depolarizing drug with a short onset and rapid recovery without deleterious effects on cerebrospinal fluid pressure (CSFP) is desired in neurological ICU. The aim of this study was to evaluate the effects on CSFP of M in patients with cerebrovascular insult and requiring muscle relaxation to facilitate mechanical ventilation.

Methods

Twelve patients, aged 45-75 years, wheighing 60-85 Kg, suffering from intracranial haemorrhage or ischaemic stroke were studied. CSFP was monitored via a catheter in lumbar subarachnoid space connected to a Statham transducer and to a monitor (Sirecust-Siemens). M was administered as a single bolus dose of 0.2 mg/Kg i.v. .Heart rate, systolic, diastolic and mean arterial pressure were recorded every minute after M injection .

Results

In all patients no significant changes in CSFP were recorded. The cardiovascular parameters were stable in all cases.

Conclusion

M rapresents a valid and manageable non-depolarizing neuromuscular blocking drug in management of comatose patients with decreased intracranial compliance and requiring muscle relaxation for satisfactory ventilation.

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P - 4 - 128

Hemicranicctomy in patient with "malignant" middle cerebral artery infarction - the influence of timing.

Thorsten Steiner, Stefan Schwab, Alfred Aschoff and Werner Hacke

Department of Neurology, Department of Neurosurgery, Ruprecht-Karls University of Heidelber, Germany

Introduction

Fatality rates of patients with malignant middle cerebral artery infarction (MMCAI) were found to be between 40 and 80% (1). Rieke et al. Have shown that decompressive surgery (DS) can improve the unfavourable outcome in a well defined group of patients with MMCAI (2). Still, the influence of timing surgery remains unclear.

Methods

Ongoing, open prospective trial on patients with MMCAI (2). We studied different time periods between onset of symptoms to admission (OAT), clinical deterioration (ADT), intubation (OIT), and DS (ADST). Outcome of survivors was assessed by Barthel Index (BI) and Rankin Scale (RS).

Results

DS has been performed in 52 patients with MMCAI. The majority of operated patients had BI scores between 60 and 70 points, and RS scores of 3.

Time	Death (n=14)	Survivors (n=38)
OAT (hrs)	10.1	17.3
ADT (hrs)	25.5	42.
OIT (hrs)	27.1	29.5
ADST (hrs)	32.4	44.1

Summary and Conclusion

Clinical development before surgery seems to influence outcome of patients whith MMCAI. Our data suggest that those patients who clinically deterioratic slower, take profit from DS. Optimal timing of surgery is difficult to assess in individual patients with MMCAI. Most important is a reliable, clinical observations. Once clinical deterioration occurs and CCT reveals midline shift, we would perform DS.

References

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PO - 4 - 131

Monitoring Intracranial Pressure outside the Intensive Care Unit

IR Chambers, K Bingham, A Clark, S Praharaj*, H. Fernandes* and AD Mendelow*
Regional Medical Physics Department, Newcastle General Hospital and *Department of Surgery (Neurosurgery), University of Newcastle upon Tyne.

Introduction

Intracranial pressure is an important parameter in the management of the acutely brain injured patient. The Camino fibre-optic transducer-tipped catheter system has greatly facilitated the use of ICP monitoring. Outside the ITU physiological monitors may not be readily available and their cost prohibits them being routinely available in other clinical areas. There are several conditions where it may be desirable to both monitor and record the ICP over protracted intervals and it has already been established that computerised recordings are better at detecting secondary insults[1]

Methods

The Camino 420V monitor does provide a chart recorder option. However this does not allow the precise recording of ICP data for subsequent analysis. The Camino transducer system provides an analogue output signal of approximately 10mv/mmHg. This signal is level shifted to allow for negative pressures and connected to the input of a 12-bit Maxim Analogue to Digital converter. The whole circuit was fabricated inside a 25-way 'D plug' shell and connected directly to the parallel printer port of a laptop computer.
A software package was developed which displays both the real-time ICP input waveform and a long term chart recorder style trend graph and the data is stored in a spreadsheet-compatible data file. It will also record non-invasive blood pressure readings, if such a machine is connected to the laptop's serial interface.

Discussion

The vast majority of recordings that we have obtained have been from patients who have suffered either a subarachnoid haemorrhage or an intracerebral haemorrhage The system has proven to be reliable and easy to use. It has greatly helped several research projects which have been set up to investigate the physiological effects after brain injury.

Jones et al Computer monitoring of secondary insults. J Neurosurgical Anaesthesiology 6:4-14, 1994

PO - 4 - 134

ICP CHANGES AFTER EXPERIMENTAL SAH OF RATS USING NEWLY DEVELOPED EDP SENSOR

Ken Kamiya, Shigenori Harada, Nobuko Yamashita, Kazuo Yamada, Hajime Nagai*

Department of Neurosurgery, Nagoya City University
* Nagoya Rehabilitation Center
Nagoya, JAPAN

Introduction

Several experimental SAH models of rat have been advocated from many institutes. In order to clarify ICP changes after SAH, cisternal measurement or other methods were employed. However, CSF space and cranium of rats are very small and these measurements have a lot of difficulty and inaccuracy.
We developped newly formed EDP sensor for small animals with Toyota central institutes and Tokai Rika Denki.

Methods

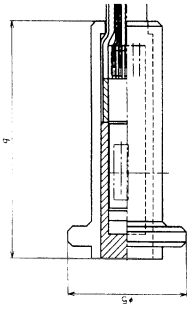
In Sprague-Dawley rats, a burr hole 3 - 4 mm in diameter was made and the EDP sensor(fig. 1) was fixed on the skull with cyano-acrylates glue. Experimental SAH was produced in modified Sheffield method. We examined immediate early gene expression(HSP 70, c-fos, c-jun) and pathological changes in chronic stage.

Results

We separated these animals into two groups according to ICP changes after SAH (High and Low ICP group. The low ICP group revealed early gene expression especially in the cortex and other regions exposed to CSF. The high ICP group also revealed early gene expression and delayed neuronal death in th ipsilateral hippocamus(CA1 and 2).

Summary and Conclusions

Our precise ICP measurement for rat experimental model clarified that initial brain damage due to SAH caused delayed neuronal death in the high ICP group. This result might explain the onset of severe ischemic damage secondary to cerebral vasospasm. On the other hand, the low ICP group might explain the occurrenceoccurrence of ischemic tolerance by the initial brain damage due to SAH.



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ABSTRACT

NON - INVASIVE REGISTRATION OF ICP

Firsching R*, Schütze M*, Motschmann M**, Behrens-Baumann W**

*Klinik für Neurochirurgie, ** Klinik für Augenheilkunde
O.-v. Guericke-Universität
Leipziger Str. 44
39120 Magdeburg
Germany
Tel: 0391-6715534 Fax: 0391-6715544

The pressure within the veins of the retina is equal to or higher than the ICP, as the drainage of the central retinal vein passes through the optic nerve, which is engulfed by CSF. In 21 patients it was attempted to register the pressure of the retinal veins and the findings were compared with conventional ICP measurements.

Methods: There were 18 patients with hydrocephalus and 3 patients with head injury. Pressure of the retinal veins were determined with oculodynamometry. ICP was measured with intraventricular catheters or at operation of the underlying cause in 18 patients and 3 patients with epidural registation.

Results: The pressure of the retinal veins correlated well with the intracranial pressure.

Discussion: Oculodynamometry requires some cooperation from the non comatose patient. In comatose patients it is possible to perform oculodynamometry as long as the eyelids can be retracted. Usually, however, pupils need to be dilated with a mydriatic agent, which may be hazardous in comatose patients. In papilledema venous outflow pressure is markedly higher than ICP. Altogether, registration of the pressure of the retinal veins seems to be useful as a non-invasive screening method and in some cases of head injury.

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THE RELATIONSHIP BETWEEN THREE-DIMENSIONAL VIBRATIONS IN BRAIN AND BRAIN DYSFUNCTION BY CHANGES IN EPIDURAL MECHANICAL PRESSURE ON HEAD INJURY MODEL IN THE CAT

Kazuo Yoshida M.D., Hiroji Kuchiwaki M.D., Suguru Inao M.D., Takayuki Tanaka M.D.,Yoshihisa Kida M.D., Tatsuya Kobayashi M.D.
Department of Neurosurgery Komaki City Hospital , Japan

Introduction

The mechanism of the brain injury by an impact has still not satisfactorily clarified. In the present study, we measured 3-dimensional acceleration on the intact dura when the impact (20 msec) was done from the dura to determine relationship between the degree of impact to brain and the brain dysfunction.

Methods

Anesthetized adult cats, which vibration waves were measured on the dura matter in left parietal region, were stimulated from the right temporal dura or the frontal dura using a mechanical stimulator (1 to 4 mm). These waves were analyzed using the fast Fourier transform (FFT). Also partial FFT was used for estimating sequential changes in vibration. Furthermore, we differentiated the velocity of the waves toward the 3 dimensions, using cross correlation. Auditory evoked responses (ABR) and somatosensory evoked potentials (SEP) was measured to assess the brain function until 15 minutes after injury.

Results

The bigger the impact is, the longer conduction time of the wave are measured on the neuronal axis on the both impact directions. However, in comparison with temporal impact, the frontal impact gave rise to higher frequency with large amplitudes and longer duration of vibration, especially to the neuronal axis. Although the amplitude and the conduction time of SEP were unchanged in every cases, the ABR 3rd-5th interpeak latency was prolonged until 10 minutes especially in the frontal impact group.

Conclusions

We speculated that high frequency with large amplitude and long duration time of vibration, especially to the neuronal axis, concerned the brain destruction when head injury was occurred. So it is suggested that frontal impact leads to more severe brain dysfunction than the temporal impact.

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ANALYSIS OF INTRACRANIAL PRESSURE MONITORING IN 60 PATIENTS WITH CLOSED HEAD INJURY

S.H. Khan, H.C. Onyiuke

Department of Neurosurgery, Hartford Hospital/University of Connecticut

Introduction

The current methods of intracranial pressure (ICP) monitoring and management in closed head injury (CHI) include intraventricular and intraparenchymal fiberoptic catheters (IPC). Intraventricular method has previously been shown to result in higher complications (1).

Materials and Methods

At a level I trauma center, 60 consecutive patients with CHI who either underwent a ventriculostomy (n=14), or IPC insertion (n=46), were selected.The age, Glasgow coma score (GCS) at admission and discharge from neurosurgical intensive care unit as well as hospital, computed tomography (CT) findings, opening pressure (OP), course of ICP, duration of monitoring, changes of monitoring device, complications and outcome of these patients were noted. They were categorized into mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 13-15) groups. A retrospective, comparative, analysis between the two methods was done. We applied the Kruskal-Wallis one way analysis of variance with chi square and Mann-Whitney U tests for statistical significance.

Results

In this cohort, with a median age of 29 years (range 13-79 years), the use of IPCs at 78.4% and 83.3% dominated in GCS 3-8 and 9-12; ventriculostomies at 66.6% prevailed in GCS 13-15 (p=0.375). 50% of ventriculostomies were used for more than 10 days and 28.5% for 1-3 days; IPCs were used more in 1-3 and 4-6 days categories (p=0.009), respectively. 64.2% ventriculostomies and 76% IPCs (p=0.000) had normal OP. In both methods, there were increased CT findings, especially loss of basal cisterns (p=0.02) and enlarged ventricles (p=0.001) with normal OP. 14.2% of ventriculostomies and 5% IPCs had a complication. There was one case of intracerebral hemorrhage and 2 of inadvertent monitor removal with the IPCs, but no infection with either technique.

Conclusion

Intraventricular monitors are comparable to IPCs in terms of complications and outcome in this patient population.

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A NEW DEVICE FOR MEASURING THE INTRACANIAL PRESSURE.
Development, Properties and Animal Tests.

Reihsner R.[1], Beer R.J.[2], Prosquill E.[3], Schlag G.[4], Hofbauer B.[5]

1) Ludwig Boltzmann Institute for Experimental Plasic Surgery, 2) Institute for Strength of Material, University Vienna, 3) Social Medical Center SMZ-Ost Vienna, 4) Ludwig Boltzmann Institute for Clinical ans Experimental Traumatology Vienna. 5) Vienna Donau-Hospital

The intracranial pressure can be measured either intraventricularly, intracerebraly or using an epidural measurment device. From the viewpoint of the reliability of the reading the first mentiond method is often prefered. However from the viewpoint of the medical care a suitable epidural technique seems to be more convenient. In addition a intracranial measurement is for technical reason not always possible. But it is well known that the measurements using the commerically available epidural devices are either sometime artificially and with some devices always systematically wrong. That was the reason the analyses the know defects of the different epidural devices. There are two main reasons to be found. The first one is coming up from the roughness of the cranial bone and from the structure of the dura influencing the loadtransfer into the sensor, especially with sensors sensitity to changing boundary conditions. The second reason is caused by the influence of the thickness of the measurement device itself, causing membran-stresses and an additional rheological process in the dura which varies from patient to patient and can therefore not be removed by compensation. That means that a new epidural measurment device must be able to integrate over area large enough compared to the roughness of the cranial bone and should be insensitive to the boundary conditions and in addition it must be as flat as possible. Furthermore it should be made by dispossable materials, must be cheap and easy applicable. In spite of the fact that from the pressure-signal relationship remains constant after the first sterilisation, proofed by additional sterilisation experiments.

In this paper the new ICP-sensor and its application is described in detail. The signal-pressure relationship shows a long-time stability (no rheology within the demended accuracy up to about 100 mmHg), the thermal properties (reaction to fever or with lower temperature when cooling down the patient for therapeutic reasons) are tested using a specially developed calibration device, a dura-cranial bone model and finally in animal tests in which the signal of the new epidural sensor was compared with an accompaning intracranial measurement. It could be shown that the aggreement between these two measurements is excelent and the handling is quite simple and time saving. The necessary sterilisation prodedures were done using gas-sterilisation.

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A Multi-Centre Database for Multimodality Clinical Monitoring

T. Howells, D.F.. Signorini, P. Jones, P. Andrews
Clinical Neurosciences, Western General Hospital, Edinburgh, UK
I. Piper, G. Teasdale
Department of Neurosurgery, Southern General Hospital, Glasgow, UK
C. Contant, C. Robertson
Department of Neurosurgery, Baylor College of Medicine, Houston, USA
M. Czosnyka, S. Piechnik, J. Pickard
Academic Neurosurgical Unit, Addenbrookes Hospital, Cambridge, UK.

Introduction: Recent advances in computerized clinical monitoring have enabled the collection of databases containing minute by minute samples of physiological parameters for head-injured patients in intensive care. It has been demonstrated that these detailed records reveal significant clinical events missed in nurses' charts [1]. They also present the data in a form readily accessible for later inspection and analysis. Despite this progress, serious problems remain regarding the collection, validation and interpretation of clinical monitoring data [2, 3]. We are currently establishing common standards for collecting and sharing data, which will allow us to develop and maintain a joint database. In addition to producing an expanded dataset, this will allow us to share more readily and to validate theoretical concepts and pratical results.

Methods: We have developed software for collecting data in the intensive care unit and for displaying and accessing the data offline [4]. Data collection modules have been developed for the Marquette 7000, Baxter Explorer, and Kontron Kolormon 7250. We are developing interfaces for the Marquette Transcom, Eagle and Solar monitors, and for the HP Merlin, which incorporates its own data collection system. We are in the process of defining a core set of demographic and clinical data fields which we will share in an ASCII format. Similarly, an ASCII format will be agreeed upon for sharing the monitoring data. This will allow easy translation to any database or data analysis system.

Discussion: As it becomes more easy to collect clinical monitoring data, it becomes more important to decide how best to manage the data. Without the appropriate demographic and clinical data, or proper data validation and sufficient sample sizes, these databases will be of little use. The development of this joint database will be a step towards a world-wide consensus on how best to manage this important resource.

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MULTIMODAL NEUROMONITORING AND STATISTICAL ANALYSIS IN PATIENTS AFTER ACUTE BRAIN INJURY

A. Jäger, J. Meixensberger, J. Dings, S. Baunach, K. Roosen

Department of Neurosurgery, University of Würzburg, Germany

Introduction

Multimodal monitoring of different cerebral parameters seems to be of important value in the treatment of severely ill patients after acute brain damage. While data storage is routinely possible, data handling to study the pathophysiological interaction (e.g. between ICP and various hemodynamic parameters) as well as statistical analysis are unsolved problems. Therefore the issue of our study is to demonstrate possibilities, which allow data management and analysis.

Methods

Multimodal neuromonitoring including intracranial pressure (ICP), mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP), endtidal CO_2 ($etCO_2$), regional tissue pO_2 ($p(ti)O_2$), regional oxygen saturation (rSO_2), and jugular venous oxygen saturation (SjO_2) was performed in 35 patients after acute brain injury. The average monitoring time was about 4 days (range from 2 days to 8 days). After detecting and elminating artifacts (by several independant physicians according to a clinical protocol) data were statistically evaluated with an self developed program based on Mathematica running on an UNIX workstation. Only nonparametric statistical methods were used.

Results

Storing 6 parameters every ten seconds resulted in ASCII data files with a size of about 500 kByte each day or about 2 Mbyte in 4 days, respectively. Handling and statistical analysis of these large data sets was made possible by use of Mathematica on a UNIX workstation. After data conversion we performed non-parametric time series analysis (e.g. cross correlation with respect to time-shift, frequency analysis, trend analysis) to search for interactions between the parameters mentioned above. Critical changes and critical changes per time in these parameters were defined and finally an automatic event detection has been introduced. All results were displayed graphically.

Conclusions

The data handling and statistical analysis as described above may improve our knowledge of pathophysiological reactions after acute brain injury and my help us to optimize treatment in severly ill patients after acute brain damage.

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Comparison of Volume Flow and Waveform Analysis Derived Parameters of the MCA flow Velocity Signal in Patients with Subarachnoid Haemorrhage

I. Piper, L. Mascia, J. Wardlaw, P. Andrews
Clinical Neurosciences, Western General Hospital, University of Edinburgh

Introduction: There is published work suggesting that in head injured patients the shape of the MCA flow velocity waveform is different between patients with high flow velocity (> 120 cm/sec) compared with those with lower velocity[1]. The aim of this pilot study was to define how specific TCD waveform derived indices relate to volume cerebral flow (CBF) and jugular saturation levels (SjO2) in patients with subarachnoid haemorrhage (SAH).

Methods: Ten patients with SAH were monitored for SjO2, CBF (nitrous oxide method) and TCD waveform analysis of the MCA flow velocity signal. Twenty two recordings were made of the TCD waveform during measurement of the CBF simultaneously to recording of SjO2. Measurements were categorised by mean MCA flow velocity into those below 120 cm/sec (range 51->118, median 95 cm/sec) or those above 120 cm/sec (126->160, median 142 cm/sec).

Results: There were no significant differences between the normal velocity and high velocity (> 120 cm/sec) groups in terms of SjO2 (67 ± 9 vs 62 ± 19) or CBF (113 ± 77 vs 80 ± 33 ml/100g/min respectively.). Similarly there were no differences in the high frequency components of the Doppler waveform as measured by the derived indices "k" (distortion factor) or the HFC (high frequency centroid). Pulsatility index (PI) was significantly lower ($p < 0.001$) in the high flow velocity group (0.5 ± .15) compared with the normal velocity group (0.8 ± 0.1) despite there being no significant differences in CPP between the groups (69.4 ± 14 (normal velocity) vs 73 ± 25 mmHg (high velocity)).

Conclusions: Although PI is lower in the high flow velocity group, this may reflect only the increase in mean velocity in the PI equation and does not indicate any difference in pathophysiology (e.g.: vasospasm) between patients. This is supported by a lack of difference in CBF, oxygen extraction or high frequency waveform component change between the groups. Further work is planned, using bilateral MCA monitoring in order to detect potential side to side differences.

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CEREBRAL AUTOREGULATION AFTER HEAD INJURY ASSESSED USING TRANSCRANIAL DOPPLER ULTRASONOGRAPHY.

StefanPiechnik, Marek Czosnyka, Piotr Smielewski, Peter Kirkpatrick, John D. Pickard

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hopital, Cambridge, U.K.

Introduction:Disturbed cerebral autoregulation has been reported to be associated with an unfavourable outcome following head injury. Using transcranial Doppler ultrasonography, we investigated whether haemodynamic responses to spontaneous variations of cerebral perfusion pressure (CPP) provides reliable information on cerebral autoregulatory reserve.

Methods:82 severe head injured patients were studied daily. Waveforms of intracranial pressure (ICP), arterial pressure and transcranial Doppler flow velocity (FV) were captured over two hour periods. Time averaged mean FV (FVm), and the FV during cardiac systole (FVs) were resolved. The correlation coefficient indices between FVm and CPP (Mx), and between FVs and CPP (Sx) during spontaneous fluctuations of CPP were calculated over 3 minutes epochs, and averaged for each investigation. A further 12 patients were monitored continuously using these indices.

Results: Mx and Sx correlated significantly with CPP ($r=-0.34$, $p<0.002$; $r=-0.38$, $p<0.0008$ respectively), with ICP ($r=0.46$, $p<0.0001$; $r=0.34$, $p<0.003$respectively), the admission Glasgow Coma Score ($r=-0.34$, $p<0.0025$; $r=-0.38$, $p<0.0008$ respectively), and with outcome following head injury ($r=0.41$, $p<0.0002$; $r = 0.48$, $p<0.00009$ respectively). In patients who died, cerebral autoregulation was severely disturbed during the first two days following injury. Continuous monitoring of autoregulatory indices demonstrated good sensitivity to critical changes in CPP caused either by intracranial hypertension or arterial hypotension, changes in anaesthesia regime and ventilation parameters.

Conclusion: Indices derived from spontaneous fluctuations of FV waveform and CPP describe cerebral vascular pressure-reactivity. They correlate with outcome and therefore may be used for guiding autoregulation-oriented intensive therapy.

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UNIVERSAL SOFTWARE FOR DATA-ACQUISITION AND ANALYSIS OF CEREBROVASCULAR REACTIVITY TESTS IN CLINICAL AND EXPERIMENTAL CONDITIONS

Peter Smielewski PhD, Marek Czosnyka PhD, Wojciech Zabolotny MSc, Peter Kirkpatrick FRCS (SN), John D. Pickard FRCS,

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, University of Cambridge (UK)

A computing system for the recording and on-line analysis of analogue signals derived from bed-side cerebrovascular monitors in different pathophysiological conditions was created and veryfied in clinical practice. The monitored signals include arterial blood pressure and oxygen saturation, end-tidal carbon dioxide concentration, cerebral blood flow velocities using transcranial Doppler ultrasonography (TCD), and concentration changes in cerebral oxy- and deoxyhaemoglobin from near infrared spectroscopy. The structure of the system is build around a client/server model with server application encapsulating analogue to digital (A/D) converter interface. The program has been designed to provide a flexible tool for cerebrovascular dynamics investigations. It enables the user to monitor and record raw signals, calculate time trends of complex parameters, provides calculation 'wizards' supporting various tests of cerebrovascular reactivity and automatically updates patients data bases. Configuration and analysis adopts arithmetic expressions of different signal processing functions, various statistical properties for each signal, frequency spectrum analysis using fast Fourier transformation, and correlation/cross-correlation. The software offers off-line analysis of non-invasive tests of cerebrovascular reactivity including stress tests which employ carbon dioxide, acetazolamide, the breath holding test, leg cuff inflation and deflation, and transient carotid artery compression. The software has been used for examination of 58 patients with carotid artery disease (age range 48 to 87 years), in 22 normal volunteers (age range 20 to 30 years) for TCD studies on cerebral haemodynamics, and for data analysis of recordings from 47 head injured patients (age 16 to 63 years). The system provides a universal tool for clinical and academic purposes. Its flexibility and advanced signal processing is suitable for research based applications. By providing a user-friendly interface, use of pre-set configuration files, and 'wizard' based calculations, the software enables non-computer technicians to perform routinely complex tests of cerebrovascular reactivity.

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NONINVASIVE MULTIMODAL CEREBRAL MONITORING IN THE INTENSIVE CARE UNIT.

Valery Amcheslavski, Grigory Toma, Gajne Margishvili, Sergey Madorski, Alexander Parfenov, Emil Gaitur, Alexander Ostrovski, Ivan Savin.

Department of Intensive Care, Burdenko Neurosurgical Institute, Moscow, Russia.

Introduction

One of the goals of noninvasive multimodal cerebral monitoring (NMCM) in critically ill patients is the early detection and prevention of secondary brain damage due to ischemia.

Methods

NMCM was used in 21 patients with severe HI and in 10 patients with subarachnoid hemorrhage (SAH). We preferred the bedside and non-invasive methods:1)TCD for measurement of CBF velocity (Transpect Medasonics, Germany; Sonas 2500 HP, USA): 2) NIRS (Cerebral Oximeter Invos 3100 Somanetics, USA) for investigation of cerebral oxygenation (CO); 3) registration of SSEP (Phasis, ESAOTE Biomedica, Italy) that provide definite information to integrity of neural pathways. This combination of methods in addition to detailed neurological examination allowed us to receive more complete information about functional, anatomical and metabolic state of brain.

Results

The patients were divided into 3 groups according to GOS: -patients with fatal outcome; -patients with severe disability or vegetative state; -patients with good recovery or moderate disability. In the 1-st group bilateral high values of CBF velocity (227±7 sm\sec), bilateral absence of SSEP, bilateral changes of CO unresponsive to therapeutic measures were revealed. In the 2-nd group -high values of CBF velocity (211±15 sm\sek), predominantly on one side and disturbances of CO on the side of vasospasm were observed. SSEP were persistent asymmetric with improvement in 2 cases. In the 3-rd group -moderate bilateral increase of CBF velocity (140±8 sm\sec), normal values of CO, asymmetrical mild and reversible changes of SSEP were observed.

Summary and Conclusion

NMCM in acute period of severe head injury and subarachnoid hemorrhage revealed different disturbances of central conductivity and of cerebral hemodynamic. NMCM turned out to be of great importance for patient's clinical evaluation, for choice of optimum treatment as well as for outcome prognosis.

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EFFECTS OF HYPERVENTILATION AND INDOMETHACIN ON CPP, SjO2 AND BRAIN TISSUE PO2 IN PATIENTS WITH SEVERE HEAD INJURY

Imberti R, Bellinzona G, Ilardi M, Bruzzone P, Dionigi RV, Raimondi M, Campagna G

IRCCS Policlinico S. Matteo - 27100 Pavia, Italy

Purpose of this study was to investigate the effects of hyperventilation and indomethacin administration on CPP, SjO2 and brain tissue PO2 (PbrO2) in 10 patients with severe head injury (GCS $\leq$8).

ICP was measured by an intraparenchymal fiberoptic transducer (Camino Laboratories), PbrO2 by a Clark-type electrode (Licox GMS), SjO2 by intermittent blood sampling. In all patients PaO2 was > 100 mmHg.

The effects of *hyperventilation* were evaluated on 11 occasions. Hyperventilation decreased ICP from a mean value of 26.1±2.6 to 14±8.6 mmHg ($p<0.05$), but in 3 cases it was ineffective. In all cases hyperventilation decreased SjO2 (from 76±10.9 to 68.5±12.1%, $p<0.001$). PbrO2 decreased in 8 cases, while in 3 cases an increase of PbrO2 was observed. On these occasions SjO2 was $\geq$ 82%.

Indomethacin determined a decrease of ICP in all cases (27) from 49.3±14.5 to 18.4±7.6 mmHg ($p<0.001$). After indomethacin SjO2 decreased in 15 cases (from 70.6±8.1 to 64.5±8.4%, $p<0.001$)). In these cases CPP ranged from 38 to 75 mmHg. In 12 other cases indomethacin determined an increase of SjO2. In these cases CPP ranged from 30 to 48 mmHg. When SjO2 was >78%, indomethacin determined an increase of PbrO2. Indomethacin increased PbrO2 also in 7 cases in which CPP ranged from 34 to 57 mmHg and SjO2 was normal or low, while in 2 cases PbrO2 decreased (CPP was 52 and 75 mmHg, respectively).

This study suggests that SjO2 and PbrO2 are two complementary parameters useful for the treatment of patients with severe head injury. Vasoconstriction by either hyperventilation or indomethacin can be useful to treat intracranial hypertension when SjO2 is >75%. The effects of indomethacin on SjO2 (an index of global cerebral perfusion) and on PbrO2 (an index of regional perfusion) seem to be dependent on the levels of CPP. Indomethacin can be useful to treat episodes of uncontrollable intracranial hypertension associated with severely compromised CPP.

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CLINICAL IMPACT OF A CEREBRAL PERFUSION PRESSURE BASED ALGORITHM ON JUGULAR VENOUS DESATURATION IN ACUTE HEAD INJURY.

Stephen Lewis[1], John Myburgh[2]

[1] Department of Neurosurgery, Royal Adelaide Hospital, Australia.

[2] Intensive care unit, Royal Adelaide Hospital, Australia.

Introduction

Episodes of jugular venous oxygen (SjO_2) desaturation correlate directly with adverse outcome following acute head injury (1). The aim of this study was to determine the impact of a cerebral perfusion pressure algorithm directed at maintaining euvolaemia, $PaCO_2$ 35 - 40 mmHg, osmolality < 300 mosmol/l, SjO_2 > 55% and cerebral perfusion (CPP) > 70 mmHg, on the incidence, duration and associations of SjO_2 desaturation.

Methods

20 consecutive patients with severe closed head injury GCS $\leq$ 8 were studied and compared to 20 patients monitored prior to the institution of the CPP algorithm. All patients had mean arterial blood pressure, intracranial pressure, SjO_2, and end-tidal CO_2, monitored. Jugular venous desaturation was defined as a SjO_2 < 55% for 10 or more minutes and confirmed as described previously (2).

Results

Demographics and presenting GCS were similar in both groups.

	Pre algorithm (n = 20)	Post algorithm (n = 20)
Number of desat. episodes	42	7
Mean duration (mins)	84	48
Occurrence after injury (%)		
0 - 24 hours	46	85
24 - 48 hours	38	0
> 48 hours	16	15
Associations (%)		
Hypocapnia	45	0
Cerebral hypoperfusion	22	85
Intracranial hypertension	9	15
Combination of above	24	0

Conclusions

All episodes of desaturation in the post algorithm group responded to treatment. Lower moderate and severe disability Glasgow Outcome Scores at 6 months were demonstrated in the post algorithm group. In conclusion, therapies directed at maintaining CPP > 70 mmHg are associated with a reduced incidence in cerebral venous desaturation and potentially an improvement in overall outcome.

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DESIGN OF A CLINICAL TRIAL FOR COMPARISON OF TWO INTENSIVE CARE UNIT TREATMENT PROTOCOLS

Charles F. Contant, Jr., Claudia S. Robertson, Alex B. Valadka, Shankar P. Gopinath, Manuela Cormio, Masahiko Uzura

Department of Neurosurgery, Baylor College of Medicine

Introduction

Standard clinical trial designs are difficult to apply to the comparison of two treatment protocols in the neurosurgical intensive care unit(NICU). Unlike a drug trial in which the only difference in treatment is the drug, treatment protocols may be different in multiple treatment goals. When the individual clinicians must be aware of all these aspects of the the patient's treatment protocol, having both protocols running at the same time in the NICU may lead to many protocol violations. For this reason, we have explored alternatives to designs in which the patients are individually randomized to each treatment.

Methods

The design chosen was one of the so-called incomplete block designs, and is well-described in the statistical literature. The year was divided into three four-month periods, corresponding to the rotations of the residents through the NICU. Each four-month period was divided into two month blocks of time so that both treatment types will be given in each four-month interval. All patients entering the ICU during each two-month time period received the same treatment. The order in which the treatments were given was randomly selected for each four-month period. This design allows for the estimation of the treatment effect, the effect of different resident groups, and the effect of the order of treatment. It is assumed that the patients arrive in a random manner over time. It is also assumed that there is no bias in selection of the patients who are included in the trial. Selection bias may tested by maintaining a careful log of all patients who are admitted to the NICU during the trial and by comparing those selected for inclusion to those who are not selected.

Results

We will present the comparisons of selected to non-selected patients.

Summary and Conclusions

We believe this design best fits the practical limitations of performing a comparison of treatment modalities.

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CHANGES IN mRNA OF VASOACTIVE SUBSTANCE-PRODUCING ENZYMES IN A RAT MODEL OF TRAUMATIC BRAIN INJURY

Kenneth I. Strauss and Raj K. Narayan
Department of Neurosurgery, Temple University, Philadelphia, USA

Introduction

The pathological sequelae of traumatic brain injury may be exacerbated by vasoactive substances (e.g. nitric oxide, prostanoids) which can cause local vasoconstriction, lot of autoregulation or vasospasm. The processes result ir hypoxic/ischemic injury and contribute to free radical mediated tissue damage (lipid peroxidation). Such secondary post-traumatic insults are associated with worse clinical outcomes. Enzymes that produce such vasoactive substances (e.g nitric oxide synthases or prostanoid synthases) are potential targets for pharmacologic therapy. We have measured changes in mRNA expression of several of these genes in a lateral cortical contusion model of traumatic brain injury in the rat.

Materials and Methods

Sprague-Dawley rats (300-400g) were preanstherized with isofluorane and maintained with a mask-cone using a mix of oxygen and isofluorane (2-4%). A 6mm lett craniectomy was performed animals were randomly assigned to sham or moderate injury groups (n=6), and subjected to a cortical contusion using a 4mm piston (4 m/s) to a depth of 0mm (SHAM) or 3mm (INJURED). Postinjury neurological and behavioral assessments were performed at 1 and 3d just prior to decapitation. Brains were rapidly removed, frozen on powdered dry ice and stored at -80°C until use. Lysate Rnase protection assays were performed to quantitate mRNA using species-specific radiolabled probes (1).

Results

Prostanoid synthase genes were observed to rise early after injury. Prostaglandin H2 synthase (COX2) mRNA doubled by Id postinjury and by 3d had not returned to control levels. Inducible nitric oxide synthase mRNA was also upregulated though to a lower extent than COX2. We are evaluating postinjury mRNA levels from comparable enzymes and the vasoactive substances that they produce.

Conclusions

Modulation of gene expression has been demonstrated for genes that affec vascular tone. Modulation of these enzymatic activities may be a rationa strategy for improving outcome after phase of neurotrauma.

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PRELIMINARY PHARMACOKINETIC PROFILE OF ENADOLINE, A POTENTIAL NEUROPROTECTIVE AGENT.

Joanna P. Hinton* and G. Hudson, Department of Pharmacokinetics and Drug Metabolism, Parke-Davis Pharmaceutical Research, Division of the Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105.

Introduction.

An increasing-dose study of the tolerance, safety, and pharmacokinetics (PK) of intravenous enadoline compared with placebo in patients with head injury was initiated in November 1995. Enadoline has been shown to be neuroprotective in rat, cat, and gerbil models of acute focal ischemia with associated total plasma concentrations of 50 - 200 ng eq/mL. Further, these neuroprotective effects were associated with significant reductions in brain extracellular fluid glutamate. In this first clinical study of intravenous enadoline in head trauma patients, the objectives were to determine the safety and tolerability of increasing intravenous doses and to determine the plasma and cerebrospinal fluid (CSF) concentrations and PK during treatment. The study was to end when either the maximum tolerated dose had been determined or a mean maximum plasma concentration of 150 ng eq/mL had been reached.

Study Design and Methods.

The study is an increasing-dose, double-blind, placebo controlled, parallel group, multicenter design for 56 patients with head injury. In each of 7 blocks of 8 patients, 4 patients were randomized to receive study drug and 4 were to receive placebo. Patients on drug were to receive a 12-hour continuous IV infusion at the following treatment rates starting between 24 and 72 hours of head injury: 0.06, 0.20, 0.60, 2.0, 6.0, 18, and 35 μg/kg/hr. In addition to the extensive safety and clinical measures, blood and CSF samples were collected serially before, during the infusion and out to 192 hours post initiation of infusion. Enadoline equivalent concentrations were determined with a validated radioimmunoassay. Plasma and CSF pharmacokinetic parameters were calculated by standard non-compartmental methods.

Results.

To date 4 of the 7 blocks have been completed. Enrollment in block 5 (6.0 μg/kg/hr for 12 hr) is ongoing. Neither the maximum tolerated dose nor the threshold plasma concentration has been reached. Mean (%RSD) plasma Cmax values after the first 4 treatments were 0.73 (200), 0.83 (50), 0.98 (10), and 8.2 (56) ng eq/mL, respectively. Individual elimination t1/2 values ranged from <1 to 6 hr. Preliminary plasma and CSF PK results will be discussed for treatments completed and compared to therapeutic expectations.

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PREDICTION OF AXONAL INJURY BY A PHYSIOLOGICAL SCORING SYSTEM IN A HEAD IMPACT MODEL.

Stephen Lewis[1], Michael Wong[1], John Finnie[2], Peter Blumbergs[2], Jim Manavis[2], Corinna Van Den Heuvel[2], Peter Reilly[1], Nigel Jones[1].
[1] Department of Neurosurgery, Royal Adelaide Hospital, Australia.
[2] Neuropathology Laboratory, Institute of Medical & Veterinary Science, Australia.

Introduction

Quantifying the effect of head injury in laboratory models is difficult. Axonal injury has been semi-quantitatively measured in a laboratory model of head injury by a sector scoring method utilising amyloid precursor protein (APP) as a marker of axonal injury (1). Recently we described a physiological scoring system (PIIS) which correlated with the degree of axonal injury as determined by the APP sector score (APPS) (r^2=0.81, p<0.001) (1). The aim of this study was to further investigate the correlation between physiology (PIIS) and pathology (APPS) scores in a model of axonal injury.

Methods

10 merino sheep were studied. 8 were impacted in the left temporal region using a variable impact force and 2 served as controls (no impact). All sheep survived for 2 hours following the insult. Arterial blood pressure, intracranial pressure, cerebral blood flow and heart rate were monitored continuously. Arterial blood gases were measured every 10 minutes. All brains were perfused fixed with formaldehyde. Immunostaining with APP was used as the marker of axonal damage and the distribution of APP positive axons scored according to a sector scoring method (APPS) (1). The PIIS was calculated by weighting the percentage shift from preinjury values for each monitored parameter over the first hour after injury.

Results

In all impacted animals widespread axonal injury was identified. All monitored physiological parameters were shifted 20% or more from preinjury values. Peak responses were recorded within the first minute after injury. The correlation between APPS and PIIS was significant (r^2=0.87, p<0.001).

Conclusions

Quantifying the physiological effect of a head impact model of axonal injury has been shown to correlate with APP positive axonal damage. This physiological score may offer a guide to severity of injury and degree of axonal damage.

Reference

1. Lewis SB et al, J Neurotrauma 13: 505-514, 1996.

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LOSS OF MYOGENIC RESPONSE IN THE MIDDLE CEREBRAL ARTERY FOLLOWING SEVERE HEAD INJURY IN THE RAT

Elke M. Golding, Claudia S. Robertson, and Robert M. Bryan, Jr.
Dept. of Neurosurgery, Baylor College of Medicine, Houston, TX 77030 USA

Introduction
Loss of autoregulation is a common observation in patients with severe head injury. A component of autoregulation is the myogenic response which is defined as the characteristic of blood vessels to constrict with increasing and dilate with lowering of transmural pressure. The aim of the present study was to examine the effect of traumatic brain injury (TBI) on the myogenic response in the rat middle cerebral artery (MCA).

Methods
The right hemisphere was injured in twelve male rats (2.5% isoflurane anesthesia) using controlled cortical impact (CCI, 5 m/sec, 3 mm deformation) (1). The left hemisphere was used as control. At 24 hours postinjury, segments of MCA ipsilateral (immediately outside the hemorrhagic zone) and corresponding contralateral segments were harvested, mounted in a vessel chamber, and pressurized (2). After a one hour equilibration period, pressure was increased over a given range in the presence and absence of extracellular Ca^{2+}. Removal of Ca^{2+} eliminates the myogenic response and provides the passive properties of the vessel to changing pressure.

Results
Lumen diameters of MCAs contralateral and ipsilateral to the injury were not significantly different at 20 mm Hg [145 ± 11 μm (mean ± se, n=12) and 136 ± 11 μm (n=10), respectively]. Contralateral vessels constricted 11.5% in a pressure dependent manner when the lumen pressure was increased from 20 to 100 mm Hg in increments ($p=0.002$). In contrast, ipsilateral vessels dilated 5.6% ($p=0.01$). In the absence of Ca^{2+}, contralateral MCAs dilated 20.5% ($p<0.001$ compared to contralateral MCAs with Ca^{2+}). The dilation in the ipsilateral MCAs was the same regardless of the presence or absence of Ca^{2+}.

Summary and Conclusions
We conclude that following severe CCI injury in the rat, MCAs contralateral to the injury maintained a myogenic response while the ipsilateral MCAs showed complete abolition of the myogenic response. The loss of a myogenic response may be the primary cause of autoregulatory dysfunction after TBI.

References
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(2) Bryan Jr RM, et al., Am. J. Physiol. 269: H1171-H1174, 1995
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CONTROLLED CORTICAL IMPACT (CCI) IN MICE: EFFECT OF INSULT SEVERITY AND ASSESSMENT OF FUNCTIONAL OUTCOME

EH Sinz, CE Dixon, JK Schiding, RSB Clark, PM Kochanek

Safar Center for Resuscitation Research and Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

Introduction
Transgenic and knockout strategies in mice should facilitate investigation of mechanisms of secondary injury after traumatic brain injury (TBI), but reports of TBI models in mice are limited.[1,2] We sought to more fully characterize the CCI model of TBI in mice including: 1) monitoring/control of brain temperature (Temp), 2) evaluation of effects of insult severity, and 3) assessment of motor and cognitive dysfunction.

Material and Methods
C57BL/6 mice (n=24) were anesthetized with isoflurane in N_2O/O_2, brain Temp was controlled, and craniotomy performed over the left parietal cortex. CCI parameters were 3 mm flat tip, 6 m/s velocity. To assess effect of injury severity on histology, depth was varied (1.0, 1.5, or 2.0 mm). For studies of functional outcome, a 1.0 mm insult was chosen and compared to shams (n=8, craniotomy). Motor function was assessed 1-7 d after TBI (beam balance). Cognitive function (spatial memory acquisition) was assessed 7-21 d after TBI using Morris water maze (MWM) modified for mice. At 21 d, contusion and hemispheric volumes were determined from serial brain sections.

Results
There was no mortality. In pilot studies, brain Temp decreased to 32°C during anesthesia, but was readily controlled. After a 1.0 mm insult, beam balance latency decreased for the initial 3 d vs sham ($p<0.05$). Latency to find the hidden platform in the MWM was increased (injured vs sham, $p<0.05$). Brain loss in injured vs non-injured hemisphere was related to injury severity (10.7±3.5, 16.6±6.7, 19.9±4.0% in 1.0, 1.5, and 2.0 mm depth, respectively). Contusion volume increased between 1.0 and 1.5 mm insult (8.4±0.6 vs 10.4±1.6% of injured hemisphere); but 2.0 mm did not further augment contusion volume. Contusion was limited to cortex only after a 1.0 mm insult.

Summary
CCI is feasible in mice. A 1.0 mm depth with a 6.0 m/s velocity produces a contusion involving > 8% of the injured hemisphere with significant motor and cognitive deficits. Brain Temp monitoring in mice is necessary. This model should be useful to assess secondary mechanisms of injury after TBI.

[1]Smith et al, J *Neurotrauma*, 1995; [2]Chen et al, *J Neurotrauma*, 1996. *Support:* American Heart Assoc., PA Affiliate, NINDS 2P50 NS30318-04A1, and Dept. of Anesthesiology/CCM.

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Introduction: Delayed post-traumatic hemorrhage into underlying contusion can cause significant mass effect. The authors identified a subgroup of young patients with initial mild/moderate head injury, who presented with orbito-frontal punctate contusions, which within 24 hours, expanded into dramatically larger non-coalesced hemorrhagic contusions.
Methods: Four consecutive patients within a 17 months period admitted to our institution with the above radiographic picture were presented and their clinical and treatment courses compared.
Results: After observing the relentless downhill course of the two earlier patients treated expectantly for control of intracranial pressure (ICP), our treatment protocol changed to early prophylactic intubation and moderate hyperventilation, insertion of intraventricular catheter for ICP monitoring, hyper-osmolar therapy with mannitol, sedation, chemical paralysis, and eventually pentobarbital for control of increased ICP. These interventions were taken more rapidly, and mostly prior to dramatic clinical and radiographic deterioration. These two subsequent patients had a prolonged course of ICP elevation and intubation, requiring tracheostomy placement. However, the clinical outcome was excellent, with both patients decanulated from the tracheostomy in 6 weeks, and both patients returned to relatively normal functions.
Conclusion: Though this series consisted of only 4 patients with similar radiographic and clinical courses, the authors advocate early aggressive medical treatment for this subgroup of patients prior to deterioration. The outcome difference can be great if the lesion is not recognized early.

DELAYED ORBITO-FRONTAL CONTUSION: EARLY TREATMENT PROTOCOL

Thomas T. Lee and Philip A. Villanueva
Dept of Neurological Surgery
Univ of Miami School of Medicine

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MANAGEMENT OF TRAUMATIC CEREBELLAR HEMORRHAGIC CONTUSIONS AND HEMATOMAS (TCHC)

Domenico d'Avella, Francesco M. Salpietro, Filippo F. Angileri, Fabio Cacciola, Massimo Cardali, Antonino Germanò, Giovanni la Rosa, Francesco Tomasello

Neurosurgical Clinic, University of Messina Medical School, Messina, Italy

Introduction
TCHC are unusual lesions and their surgical management is still controversial: some advocate early evacuation of all traumatic intracerebellar clots, while others emphasize the possible "benign" behavior of traumatic cerebellar hematomas and suggest, in selected cases, an expectant policy.

Methods
From 1990 to 1996, 2350 patients underwent CT scan for moderate or severe head injury at our Institution. Thirteen patients (0.55%) were retrospectively identified as harboring TCHC. There were 9 male and 4 female patients (mean age, 42 yr, range 4-88 yr).

Results
Patients were divided into two groups. In Group I (n = 7) G.C.S. at admission was ≤ 5. Five of these patients had concomitant supratentorial lesions which was the cause of neurological deterioration and evacuated in 2 cases. Surgery was not performed in the others because of the moribund status. All these patients died or survived in vegetative state. In Group II patients (n = 6), all with "isolated" intracerebellar clots, C.G.S. was ≥ 8. The initial clot size was < 3 cm in 3 cases and > 3 cm in the others. Five patients were managed conservatively and one was operated on, and all recovered completely. Three patients, aged 4, 9 and 12 yr, exhibited an evolving clinico-radiological course.

Summary and Conclusions
The "isolated" intracerebellar traumatic hemorrhages appear to be relatively benign lesions. We do not recommend immediate surgery in all cases. Indication for surgery emerges from a combination of both serial CT monitoring and careful clinical surveillance, since in the case of "pure" posterior fossa lesions the role of ICP monitoring in assessing the need for surgical evacuation before deterioration is still to be established. Finally, although based on a limited number of cases, our results suggest that a significant proportion of TCHC are prone to evolve. As recently emphasized for the supratentorial compartment, hemorrhagic contusions on initial CT examination should be considered at risk for early development of evolving intracerebellar hemorrhage.

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INTRAHOSPITAL TRANSPORT IN THE ACUTE PHASE AFTER HEAD INJURY

C Mattioli, A De Vitis, M Gemma, MR Calvi, L Beretta.

Neurosurgical ICU-Scientific Inst. Hosp. S. Raffaele-Via Olgettina 60, 20132 Milano, Italy.

Introduction
In the first hours following acute head injury, uncoupling between CBF and CMRO2 can occur and desaturation phenomena (low SjO2) are often present.
The purpose of this study is to evaluate our transport modality and ensure no further brain insults.

Method
We studied 16 transfers from ICU to the neuroradiological department on 10 head injury patients admitted to our Hospital between April 1996 to the present time. Transports were carried out within the first 36 hours of the head injury. The patients were transported by a neurointensivist and a porter, the GCS was 6.37± 1.58 on admission and 6± 1.12 on the first day, medium age 27.9 yrs (min 19, max 51), the admission CT disclosed 2 epidural hematomas, 2 subdural hematomas, 6 brain contusions. Observations were performed both before and after transportation: we measured Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), jugular hemoglobin saturation, arterial hemoglobin saturation, PaO2, PaCO2, pH, PvO2, PvCO2, internal temperature. Continuous infusion of sedatives, analgesics and eventually amines were unchanged during transport. The patients were previously ventilated in CPPV. Immediately prior to transport they were curarized and connected to Oxylog (a portable ventilator) in IPPV maintaining unvariated minute volume and respiratory rate. There was also continuous monitoring of blood pressure, cardiac rate, and O2 saturation. During the diagnostic process the patient were ventilated in CPPV using the Drager Ventilator with the same values as previously stated.

Results
Outcome on discharge from ICU was 1 death and 9 survivors. Medium time span for transport was 63 minutes. No significant differences were found in the ICP,CPP and %HbSaO2 before and after transp.: ICPm pre-transp. was 20, ICPm post-transp. 23, CPPm pre-transp. 74, CPPm post-transp. 77, HbSaO2 pre-transp. 97.9, HbSaO2 post-transp. 98. Significant differences were found in the PaCO2 pre-and post-transportation and %HbjO2 pre- and post-transport. PaCO2 pre = 33.0±5.6 vs. PaCO2 post = 30.5±.7 (p = 0.036) HbjO2 pre = 67.6±8.7 vs. HbjO2 post = 61.6±8.1 (p = 0.028) (Wilcoxon test).

Conclusions
Our prelimnary study points out that, having used all our possible resources in order to maintain patient stability, transport caused cerebral desaturation probably attributed to a decreased PaCO2.

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CEREBRAL PERFUSION AND INTRACRANIAL PRESSURE DYNAMICS IN A CLOSED-HEAD DIFFUSE BRAIN INJURY MODEL IN THE RAT

Paul Tompkins, F.A. Stevens, Greg Halko, and L. Philip Carter

Department of Neurosurgery, University of Oklahoma, HSC, Oklahoma City, OK

INTRODUCTION
Diffuse brain injury is an important component of human closed-head injury. A model of diffuse brain injury in rats has recently been reported (1). We have extended this model to include measurement of laser Doppler cerebral perfusion (CP), intracranial pressure (ICP), pressure volume index (PVI) and compliance (C) in control and injury groups, pre- and post trauma.

METHODS
Sprague-Dawley rats anesthetized with pentobarbital (40mg/kg, IP) were prepared for closed-head injury as described in the literature (1). Bilateral laser Doppler fibers were placed on the lateral parietal cerebral cortex. The cisterna magna was cannulated for ICP and C measurements. Blood gas, pH, mean arterial blood pressure (MBP) and respiration rate were monitored throughout the experimental time (-30 pre- to 120 min post-injury).

RESULTS
Control animals showed no significant change in any measured parameter throughout the experiment. Spontaneously breathing animals that died (50%, within 7 min post-injury) had respiratory failure with concomitant decreases in CP and MBP. Spontaneously breathing animals that lived showed an immediate bilateral increase (150% above pre-injury levels) in CP followed by a gradual decline over the next 30 min post injury (25% below pre-injury values). From 30 min to 120 min post injury, CP increased toward pre-injury levels. Animals that were artificially ventilated showed an immediate increase in CP (+100%) with a decrease to -13% at 3 min post-injury, increasing to +50% at 120 min post-injury. ICP, PVI and C remained stable in all groups pre- to post-injury.

SUMMARY and CONCLUSIONS
In agreement with the literature (1), 50% of the head injured animals without respiratory assistance die within a few minutes of impact due to respiratory failure. Animals that survive the initial injury experience a period of reduced cerebral perfusion that may lead to long term problems. While this diffuse head injury model results in significant alterations in CP, there are no significant changes in ICP,PVI or C from 2 to 120 minutes post injury.

(1) Marmarou A, Foda MAA, van den Brink W, Campbell J, Kita H, and Demetriadou K, J. Neurosurg. 80:291-300, 1994.

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Diffuse Axonal Injury (DAI) Is Not Associated With Elevated Intracranial Pressure

Thomas T. Lee, MD, Marcelo Galarza, MS, and Phillip A. Villanueva, MD
Department of Neurological Surgery, University of Miami School of Medicine

Introduction. Traditionally, intracranial pressure (ICP) monitoring has been utilized in all patients with severe head injury (Glasgow coma score of 3-8). Ventriculostomy placement, however, does carry a 4 to 10 percent complication rate consisting mostly of hematoma and infection. The authors propose that a subgroup of patients presenting with severe head trauma and diffuse axonal injury without associated mass lesion, do not need ICP monitoring.
Materials & Methods. Twenty-two patients sustaining blunt head trauma and fitting our strict clinical and radiographic diagnosis of DAI were enrolled in our study. Inclusion criteria were severe head injury patients who did not regain consciousness after the initial impact, and whose CT scan demonstrated characteristic punctate hemorrhages of < 10 mm diameter at the grey-white junction, basal ganglia, corpus callosum, upper brainstem, or a combination of the above. Patients with significant mass lesions and documented anoxia were excluded.
Results. Twelve (54.5%), three (13.6%), and seven (31.8%) patients had types I, II, and III DAI, respectively. The admission Glasgow Coma Score (GCS) was higher for types I and II than for type III DAI. ICP was monitored from 24 to 165 hours, with a mean ICP for 22 patients of 11.70 mmHg (SEM=0.75) and a range from 4.27 to 17.26 mmHg. Types I , II, and III DAI had a mean ICP of 11.53mmHg (SEM=1.06), 13.10mmHg (SEM=2.32), and 11.16mmHg (SEM=1.31). Of all ICP recordings, 89.5% (1583/1768) were ≤ 20mmHg, 9.3% (164/1768) were between 21 and 30 mmHg, 1.0% (17/1768) were between 31 and 40mmHg, and 0.2% (4/1768) were greater than 40mmHg. Average mean arterial pressure(MAP) was 95.64mmHg (SEM=2.27), and 94.5% (1401/1483) of all MAP readings were greater than 80mmHg. Average cerebral perfusion pressure (CPP) was 84.72 mmHg (SEM=2.07), and 90.22% (1338/1483) of all CPP readings were greater than 70mmHg. Interestingly, patients with type III DAI presented with higher MAP, and consequently CPP, than Types I and II patients. No treatment for sustained elevated ICP >20mmHg was needed except in one patient with extensive intraventricular and subarachnoid hemorrhage who developed communicating hydrocephalus, necessitating the subsequent placement of a ventriculoperitoneal shunt. One complication from a catheter tract hematoma was encountered.
All patients, except type III DAI, generally demonstrated clinical improvement with time. The outcome, as measured by Glasgow Coma Score (GCS) and Glasgow Outcome Score (GOS) was similarly better with types I and II than type III DAI.
Conclusion. The authors conclude that ICP elevation in DAI patients without associated mass lesions is not as prevalent as other severe head injured patients, therefore ICP monitoring may not be as critical. The presence of an ICP monitoring device may contribute to increased morbidity. Of key importance, however, is an accurate clinical history and interpretation of the CT scan.

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THE BRAIN PARENCHYMA-PO_2 CATHETER INTERFACE, A HISTOPATHOLOGICAL STUDY IN THE RAT.

W.A. van den Brink[1], I.K. Haitsma[1], A.B. Houtsmuller[2], J.M. Kros[2], A.I.R. Maas[1], C.J.J. Avezaat[1]
Dept. of Neurosurgery[1], Dept. of Pathology[2], University Hospital Rotterdam, The Netherlands

Cerebral ischemia is the main factor in secondary brain damage.
We have investigated the value of local tissue pO_2 monitoring as parameter for cerebral oxygenation in patients with severe head injury. Reliability of such measurements is dependant on catheter characteristics and on the brain parenchyma-pO_2 catheter interface. Characteristics of this interface were evaluated in the experimental situation.
Histopathological and morphometrical examination was performed on the brains of 19 rats in whom catheters had been introduced for measuring of $pBrO_2$. In each animal two catheters were inserted: one for actual measurement, one as reference. Twelve animals were studied for a period of one hour (group 1); seven others for 24 hours (group 2).
The measured $pBrO_2$ varied considerably among the experiments. The catheter caused a central bore with a surrounding zone of edema. In several experiments blood in or surrounding this bore, or blood in the ventricles, was found. These findings were similar in both measuring and reference catheters. The presence of blood was associated with lower $pBrO_2$ values.

	group 1		group 2	
	measured	sham	measured	sham
$pBrO_2$ mean (sd)	28 (20)	--	33 (18)	--
radius bore (μm)	157 (51)	156 (44)	184 (39)	191 (59)
zone edema (μm)	118 (60)	134 (45)	123 (44)	121 (45)
blood (10^{-3} μm²)	83 (143)	12 (13)	70 (121)	83 (114)

The quantative damage to the tissue is very small and of no clinical importance. The zone of tissue damage and surrounding edema around the catheter is small enough to permit fast diffusion of oxygen over the brain parenchyma catheter interface. Local micro hemorrhages around the tip of the catheter were shown to be of some influence on measurement results. This observation should be taken into account when interpreting results in clinical studies.

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Can We Improve Brain Tissue Oxygenation with Increased Inspired Oxygen Concentration?

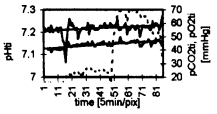
M Menzel, MD, E Doppenberg, MD, A Zauner, MD, R Bullock, MD, PhD, JD Ward, MD, HF Young, MD, A Marmarou, PhD, P Brockenborugh R.R.T.
Department of Neurosurgery, MCV, Commonwealth University, Richmond, Virginia

Continuous brain tissue oximetry is a newly clinical monitoring method, after severe head injury (SHI). With a new multisensor probe it is now possible to continuously measure pO_2, pCO_2, pH and temperature in brain tissue. Our early studies of brain pO_2 have shown brain O_2 tension < 20 mmHg in most patients who do badly after SHI, and > 30 mmHG in most who do well (1,2).
The aim of this study was to explore the dynamics of brain *pO_2 (PO_2ti), pCO_2 (PCO_2ti), pH and temperature* related to standardized increases in inspired oxygen concentrations. We also assessed the effect of increased FiO_2 upon glucose and lactate as measured by collecting extracellular dialysate in brain tissue.

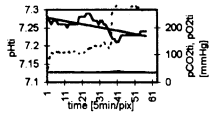
Methods

We measured PO_2ti, PCO_2ti, pH and temperature simultaneously in the frontal cortex of 8 patients after SHI, using the Paratrend 7® probe (Malvern, PA, USA). Additionally we performed brain tissue microdialysis in the frontal cortex with samples every 30 minutes. The inspired oxygen was increased stepwise from 30% to 60% to 100% over a period of 6 hours.

Results



Graph 1: Course of pCO_{2ti}, pH_{ti} and pO_{2ti} during stepwise increase of inspired oxygen in brain tissue (with linear trend line) related to a **starting brain tissue oxygen level of 16 mmHG**



Graph 2: Course of pCO_{2ti}, pH_{ti} and pO_{2ti} during stepwise increase of inspired oxygen in brain tissue (with linear trend line) related to a **starting brain tissue oxygen level of 45 mmHG**

We found PO_2ti increased by 100% to 500% in response to changes in FiO_2 from 30% to 100%. The relation between pH_{ti} and pCO_2ti depends on the metabolic situation in the injured brain (graph 1,2).

Summary and Conclusions

The additional information by measuring pH_{ti} and pCO_2ti will provide a better understanding of the pathology after SHI and extend the benefit of brain tissue monitoring. Potentially, the simple measure of increasing FiO_2 may improve local brain oxygenation and metabolism.

Literature: [1] Neurosurg (1996) 37,6: 1168-1177
[2] Acta Neurochir (1996) Suppl. 67: 40-44

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DISTRIBUTION OF BRAIN TISSUE PO_2 IN CORRELATION WITH OUTCOME AFTER SEVERE HEAD INJURY

J. Dings, A. Jäger, J. Meixensberger, K. Roosen

Department of Neurosurgery, University of Würzburg, Germany

Introduction

Monitoring of brain tissue pO_2 ($p(ti)O_2$) after severe head injury (SHI), to detect secondary ischemia, becomes more and more routine. Although the critical value is accepted at 10 - 15 mm Hg, still there is no proof that low $p(ti)O_2$ values over a certain period influence outcome negatively. Therefore distribution of brain $p(ti)O_2$ was correlated to outcome 1 year after SHI

Methods

Brain $p(ti)O_2$ monitoring is performed with a flexible, polarographic microcatheter (diameter 0.5 mm, pO_2-sensitive surface 8 mm^2, position 2.5 cm in the frontal white matter). Depending on the Glasgow outcome score (GOS) 1 year after SHI patients were grouped into bad outcome (GOS 1 - 3, n = 17) and good outcome (GOS 4 + 5, n = 20). $P(ti)O_2$-values from day 0 - 6 were analyzed.

Results

	age (yrs)	interval trauma to $p(ti)O_2$-monitoring (hrs.)	initial GCS	duration of monitoring (hrs.)	artificial readings (hrs.)	lesiontype (focal/ diffuse)
good (n=20)	28.9+/-9.6	27.5+/-7.5	5.8+/-1.7	141	3.5	8/12
bad (n=17)	34.3+/-10.5	22.6+/-8.6	4.8+/-2.1	146	5.8	6/11

Values as mean +/- sd. or absolute.

Brain $p(ti)O_2$-histogram of the bad outcome group shows a left-shift with more values below 15 mm Hg (20 %) compared to the good outcome group (12 % below 15 mm Hg).

Summary and Conclusions

Although brain $p(ti)O_2$-monitoring was initiated 5 hours earlier in the bad outcome group, this period might not influence the histogram significantly as it is only 3.4 % of the total mean monitoring time. The same holds true for the greater period of artificial readings in the bad outcome group (4 % to 2,5 % in the good outcome group). There is evidence that brain $p(ti)O_2$ values below the critical level of 15 mm Hg might have an adverse effect on outcome 1 year after SHI.

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AN OBSERVATIONAL STUDY OF BRAIN TISSUE pO_2, pCO_2 AND pH IN HEAD INJURED PATIENTS.

Al-Rawi P.G., Piechnik S., Harland S., Datta A., Gupta A.K., Kirkpatrick P.J.
University Dept. of Neurosurgery, Addenbrooke's Hospital, Cambridge. U.K.

Introduction: Continuous monitoring of brain tissue pH, pCO_2 and pO_2 may give valuable information on the condition of cerebral tissues. Such information may help the targeting and timing of therapeutic interventions. The Paratrend 7 (Biomedical Sensors Ltd.) sensor is a single, compact, multiparameter sensor that uses combined electrochemical and fibreoptic technology to monitor pH, pCO_2, pO_2 and temperature. This sensor has been validated for continuous intra-arterial monitoring of blood gases. The principles of the sensor should also be valid for direct tissue measurements and therefore we have set out to evaluate its use as a monitor of brain tissue pO_2, pCO_2, pH and temperature in adult head injured patients.

Method: The Paratrend 7 (P7) was inserted into the brain tissue of 13 head injured patients and incorporated into an established multimodality monitoring system. Ethical approval and informed consent were obtained. A P7 sensor was also placed into the femoral artery, for continuous monitoring of blood gases. CT scanning was used to confirm the position of the intracranial sensor. Data signals from all the monitored parameters were digitised and collected at the bedside on a laptop computer. Sensors remained in place for up to 7 days.

Results: No complications were associated with the use of the P7 sensor in the brain. Excluded from the data analysis were those periods where P7 channels may have failed or when artefact was detected. Brain temperature was consistently 0.25°C $\pm$ 0.18 higher than the temperature detected with the arterial sensor. Pooling the data for all patients gave a mean brain pO_2 of 3.56kPa (sd=0.67) and a mean arterial pO_2 of 16kPa (sd=2.0). The mean brain pCO_2 was 5.85kPa (sd=0.68) with a mean arterial pCO_2 of 4.36kPa (sd=0.82), whilst the mean brain pH was recorded as 7.22 kPa (sd=0.12) and arterial pH as 7.6kPa (sd=0.19). For individual patients the changes in brain and arterial pO_2 showed large variations during any 24 hour period. In many cases short time analysis of trends revealed a reproducible pattern of changes related to clear periods of arterial desaturation and cerebral hypoperfusion.

Discussion: Our studies have shown that the P7 sensor can be inserted into brain tissue safely, that they are reliable for up to 7 days and can provide continuous quantitative information about the metabolic status of the injured brain. Such technology may enable the early detection and correction of potentially damaging secondary insults.

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BRAIN TISSUE PO_2, PCO_2, PH AND BLOOD FLOW DURING AVM RESECTION

Fady T. Charbel, William E. Hoffman, Mukesh Misra, James I. Ausman
University of Illinois at Chicago, Chicago, Illinois

Introduction: It has been reported that an AVM is associated with a decrease in cerebral perfusion pressure and blood flow which produces tissue ischemia. During AVM resection it is suggested that the sudden restoration of cerebral perfusion pressure may produce hyperemic related injury.

Material and Methods: We evaluated whether brain tissue PO_2 $PCO_2$and pH showed signs of ischemia before AVM resection and monitored changes during AVM resection. Anesthesia was induced with thiopental and Fentanyl and maintained with 1% Isoflurane and oxygen in air. Following a craniotomy, a Paratrend tissue sensor which measures PO_2 PCO_2 pH and temperature was inserted into the brain tissue. A laser Doppler sensor was placed on the cortex surface in the same region. After equilibration, MAP, tissue gases and pH were measured continuously from the start to the end of AVM resection in 13 patients. Eight non-ischemic patients undergoing aneurysm clipping served as time based controls for this study. These patients were maintained at steady state conditions over a similar time period as the AVM resection. MAP, blood gases and brain temperature were similar between the two experimental groups.

Results: Under baseline conditions, brain tissue $PO_2$was 14 ± 5 mmHg in AVM and 32 ± 15 mmHg in control patients ($P < 0.05$). Tissue $PCO_2$and pH were 51 ± 7 mmHg and 7.09 ± 0.03 in AVM, not different from the controls (50 ± 9 mmHg, 7.13 ± 0.02). During AVM resection (115 ± 33 min) PO_2increased to 50 ± 33 mmHg (<0.05), PCO_2decreased to 46 ± 7 mmHg ($p < 0.05$) and pH increased to 7.43 ± 0.02 ($p < 0.05$). These variables did not change in controls over the same time period. Surges in PO_2were observed in AVM patients at times when a large AVM feeder was occluded and were associated with the decrease in PCO_2an increase in laser Doppler flow.

Conclusions: These results show that tissue hypoxia is present in AVM patients under baseline conditions. Increase in tissue blood flow are seen during AVM resection when tissue perfusion pressure is restored and this is associated with tissue hyperoxygenation and CO_2clearance.

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EXPANDING POSTERIOR FOSSA MASSES DO NOT CAUSE REGIONAL BRAIN TISSUE PRESSURE GRADIENTS

Christopher E. Wolfla and Thomas G. Luerssen

Division of Neurosurgery, Indiana University Medical Center, Indianapolis, Indiana USA

Introduction: Previous work in our laboratory has shown that expanding supratentorial masses produce regional brain tissue pressure gradients (RBTP) in a pattern that is dependent upon the location of the mass (1,2). This study was undertaken to determine the RBTP response to an expanding posterior fossa mass (PFM).
Methods: RBTP was monitored in both frontal and temporal lobes, midbrain, and cerebellum of 15 domestic swine. Posterior fossa epidural masses were expanded incrementally adjacent the right cerebellar hemisphere. Lumbar spinal fluid pressure (LSFP) was measured in three animals. Ventricular and cisterna magna drainage was undertaken in two animals.
Results: With mass expansion, no consistent significant RBTP gradients were detected ($p>0.05$), even after observation for 60 minutes. During mass expansion, LSFP became less than ($p<0.05$) RBTP, returning to near-normal values at maximum mass volumes. Drainage of CSF from the ventricles or the cisterna magna did not change the findings.
Conclusions: 1. Unlike supratentorial masses, an expanding PFM does not create reproducible RBTP gradients. 2. The pressure differential that develops between the intracranial RBTP monitors and LSFP suggests that lack of RBTP gradient formation may be due to trapping of subarachnoid cerebrospinal fluid (CSF) in the intracranial compartment. 3. Unlike expanding supratentorial masses, where the location of the parenchymal ICP monitor may be critical for making management decisions, an expanding PFM which produces elevated cerebellar RBTP may be detected with a frontal parenchymal monitor. 4. This finding is not apparently affected by continuous ventricular drainage of CSF.
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HISTOPATHOLOGICAL FINDINGS FOLLOWING FOCAL MASS LESION AND INSERTION OF PO2 SENSORS IN BALLOON EXPANSION MODEL IN RATS.

G.H.Vince, R.Burger, K.Roosen
Dept. of Neurosurgery, University of Würzburg, Germany

Introduction
With the aim of estimating the degree of damage caused by the inflation of a parietal epidural balloon and the insertion of bifrontal pO2 sensors in a rat model, thus determining the validity of the model and its comparability to the epidural hematoma encountered in humans, we histologically examined the immersion fixed brains of 8 Sprague Dawley rats after inflation on an epidural balloon. Additional 10 rats served as controls.
Methods
The epidural balloon was placed in a left parietal burr hole on the skull of the rat and slowly inflated using a microsyringe until pupillaries dilated and EEG read a flat signal. Maximum inflation was sustained for 10 minutes. Reperfusion lasted on average 178 minutes. The animals were then sacrifced and the brains removed for 5 day immersion fixation in 3.7 % paraformaldehyde. We prepared paraffin sections through the frontal lobe, the parietal lobe and mesencephalon, cerebellum and medulla oblongata. Tissue sections were stained with hematoxylin, Cresyl Violet and Luxol Fast Blue.
Results
In all 8 animals we detected diffuse brain swelling pronounced on the side of the balloon and typical findings associated with raised intracranial pressure with distortion of the brain, supracallosal, central and uncal herniation and caudal shift induced elongated thalamic neurons. We found compressed and obliterated arteries and consecutive temporal, occipital and superior cerebellar infarction also typically seen in humans following supratentorial mass lesions. Tissue edema is currently being determined using a computerized stereological approach. Hypoxic alterations were detected in the hippocampus, particularly in the CA1 fields, in 6 animals unilaterally and in 2 animals bilaterally. The pO2 sensors lay above the cingulum, usually within the thin line of white matter, but always deeper than 3 mm. From 36 pO2 sensor injuries 32 were found during histopathological work up and measured under a microscope using a recticle eyepiece. Diameters ranged from 0.37 to 1.0 mm (mean 0.62mm). Statistical analysis proved no correlation between the yielded pO2 values and the degree of sensor induced injury.
Conclusion
Histological changes found in the epidural balloon expansion model in rats are consistent and morphologically comparable to the human epidural hematoma. The pO2 sensors used in this model cause only slight tissue disruption which does not interfere with the measurement itself.

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THE INFLUENCE OF ICU PROCEDURES ON BRAIN OXYGEN TENSION

C. Hogesteeger, J. Vermeulen, W.A. van den Brink, A.I.R. Maas
Department of Neurosurgery, University Hospital Rotterdam, The Netherlands

Introduction:
In our neurosurgical intensive care brain tissue oxygen tension is routinely measured as parameter for cerebral oxygenation in patients with severe head injury. The reliability of the technique and its clinical value have been previously reported. In this presentation the influence of various intensive care procedures on cerebral oxygenation as measured by brain tissue pO_2 is illustrated in individual patients. Tracheal suctioning procedures without prior preoxygenation can induce a decrease in $PbrO_2$, probably secondary to inadvertent hyperventiation. Sedation in a not completely volume resuscitated patient can induce a decrease in $PbrO_2$ secondary to a fall in cerebral perfusion pressure. The effect of cerebral perfusion pressure on $PbrO_2$ is further illustrated in a number of recording and subsequent analysis performed. Changing the head position from 0 degrees to 30 degrees elevation induced only minor changes in $PbrO_2$ in the majority of patients.

Based on the illustrative recordings presented we conclude that $PbrO_2$ is a sensitive parameter for cerebral oxygenation. Continuous monitoring can detect possible ischemic secondary insults, following inadvertent hyperventilation during tracheal suctioning procedures or unwanted decreases in cerebral perfusion pressure, resulting from sedation. Careful analysis of the results permits recognition of unwanted adverse insults following routine ICU procedures.

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MANNITOL THERAPY VS. CONTROLLED VENTILATION DURING1 HOUR OF TEMPORARY MIDDLE CEREBRAL ARTERY (MCA) OCCLUSION IN THE RAT

Eckhard Rickels, Kathrin König, Stefan Krömer, Hans E. Heissler, Petra Klinge-Xhemajli, Madjid Samii
Medizinische Hochschule Hannover, Neurochirurgische Klinik, D-30623 Hannover, FRG

Background: The pharmacological influence on infarction size is still under investigation. Controlled ventilation might be a determining factor.

Methods and Results: In two independent studies the efficacy of mannitol on cerebral infarction after 1 hour of ischemia and reperfusion was investigated. 73 male rats (study I, $n_I=50$ and study II, $n_{II}=23$) were anaesthetized and intubated. Animals in study I breathed spontaneously and those in study II were controlled ventilated. Infarction was induced by reversible clipping of the left MCA for 1 hour. The blood pressure, heart rate, extracellular ion activities, and cortical DC potential were monitored throughout the experiments. In both studies animals were randomly assigned to receive isovolumetric infusions of 20% mannitol ($n_I=29$, $n_{II}=11$, 1.7 ml/h) or saline ($n_I=21$, $n_{II}=12$). Infusion started 10 min prior to ischemia and was maintained for 1 hour. For histological examination the brains were cut into serial slices and infarction was calculated morphometrically. Animals treated with mannitol showed a percentual infarction of 11.5±2.2 % (mean ± SD) and 11.2±4.1 %, whereas in the controls it was 20.6±4.1 % and 10.4±2.7 % in study I and II, respectively. In the control animals of study I infarction was twice as big ($p<0.05$) as in the mannitol groups and the ventilated controls.

Conclusion: Our results suggest that untreated animals benefit from sufficient artificial respiration. Mannitol treatment alone reduces infarction size considerably but in combination with controlled ventilation no further reduction was accomplished. We conclude that in this study mannitol does not contribute to the reduction in infarction but its therapeutical effect is overlayed by the benefits of sufficient controlled ventilation.

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BRAIN INJURY IMPAIRS ATP-SENSITIVE K^+ CHANNEL FUNCTION IN PIGLET CEREBRAL ARTERIES

William M. Armstead, University of Pennsylvania and The Children's Hospital of Philadelphia, Philadelphia, PA 19104

Introduction: Traumatic injury is the leading cause of death for infants and children and mortality is increased with head injury. Previous studies have shown that pial arteries constricted and responses to several nitric oxide (NO) dependent dilator stimuli were blunted after fluid percussion injury (FPI) in newborn pigs. Membrane potential of vascular muscle is a major determinant of vascular tone and activity of K^+ channels is a major regulator of membrane potential. Recent data show that the NO releasers SNP and SNAP as well as 8-Bromo cGMP elicit dilation via ATP sensitive K^+ channel (K_{ATP}) activation. The present study was designed to investigate the effect of FPI on K_{ATP} channel function.

Methods: Chloralose anesthetized newborn pigs equipped with a closed cranial window were connected to a percussion device consisting of a saline-filled cylindrical reservoir and a metal pendulum. Brain injury of moderate severity (1.9-2.1 atm) was produced by allowing the pendulum to strike a piston on the cylinder. Data were analyzed by repeated measures analysis of variance. An α level of $p<0.05$ was considered significant.

Results: FPI blunted dilation to cromakalim (10^{-8}, 10^{-6}M), a K_{ATP} agonist (10±1 and 27±2 vs 3±1 and 7±2% before and after FPI, respectively, n=8). Similarly, FPI blunted dilation to calcitonin gene related peptide, an endogenous K_{ATP} activator. FPI also blunted dilator responses to SNP, SNAP, and 8-Bromo cGMP (10^{-8}, 10^{-6}M) (10±1 and 20±1 vs 2±1 and 8±2% for SNP before and after FPI; 9±1 and 16±1 vs 2±1 and 4±1% for 8-Bromo cGMP before and after FPI, respectively, n=8). In contrast, responses to papaverine and brain natriuretic peptide (10^{-8}, 10^{-6}M) were unchanged after FPI (9±1, and 18±1 vs 11±1 and 20±1% for papervine before and after FPI, respectively, n=8).

Conclusions: These data show that K_{ATP} channel function is impaired after FPI. Furthermore, these data suggest that impaired function of mechanisms distal to NO synthase contribute to altered cerebral hemodynamics following FPI.

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EFFECT OF HYPOTHERMIA AND REWARMING ON CEREBRAL ELECTROPHYSIOLOGICAL FUNCTION IN TRANSIENT ISCHEMIA

M. Kawauchi, S. Nishio, Y. Noguchi, S. Asari, T. Ohmoto

Department of Neurological Surgery, Okayama University Medical School

Introduction

The protective effects of mild hypothermia have been demonstrated in cerebral ischemia and traumatic brain injury. Meanwhile, somotosensory evoked potential(SEP) has been utilized to monitor electrophysiological function in experimental cerebral ischemia and clinical circumstances. However, little has been known about functional recovery during mild hypothermia and rewarming. We investigated the protective effects of hypothermia on functional recovery using SEPs as a quantitative measurement of electorphysiological function in experimental transient focal ischemia, and the effects of different speed of rewarming.

Materials and Methods

Nineteen cats underwent one hour of left middle cerebral artery occlusion under normothermic (36-37°C, n=6) or hypothermic (30-31°C) conditions followed by five hours of reperfusion with slow(n=6) or rapid rewarming(n=7). Whole body hypothermia was induced during ischemia and first three hours of reperfusion. The rewarming to 36°C was done in two hours (slow) or 30 minutes (rapid). SEPs and regional cerebral blood flow (rCBF, hydrogen clearance) were monitored before and during ischemia and reperfusion in all animals. The specific gravity of gray and white matter was examined as an indicator of edema formation.

Results

Hypothermia reduced postischemic hyperperfusion, which was observed in normothermic animals. During rewarming, SEP amplitudes have recovered gradually. After rewarming, SEPs in the normothermic and rapid rewarming groups remained partially depressed (20-40% of preocclusion values), however, SEP recovery was significantly enhanced in the slow rewarming group ($p<0.05$). Hypothermia followed by slow rewarming reduced brain edema in gray and white matter, while rapid rewarming did not reduce edema in white matter.

Conclusion

These results demonstrate that mild hypothermia may improve electrophysiological function in transient focal ischemia, and rapid rewarming appears to reduce the protective effect of mild hypothermia.

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POSTINJURY HYPERGLYCEMIA INCREASES MORTALITY AND HISTOLOGICAL DAMAGE FROM SECONDARY ISCHEMIC INSULTS

Leela Cherian, J. Clay Goodman, Claudia S. Robertson. Departments of Neurosurgery and Pathology, Baylor College of Medicine.

Introduction

In a previous study, preinjury hyperglycemia increased the damage caused by a secondary insult after cortical impact injury in rats. The purpose of this study was to examine the effect of postinjury glucose administration, which would better mimic the clinical situation of patients being administered glucose containing fluids during the early postinjury period.

Methods

Long Evans rats fasted overnight and anesthetized with isoflurane were subjected to a 4 m/sec, 2.5 mm deformation impact injury, followed in 1 hr by 40 minutes of bilateral carotid occlusion. Forty minutes before the carotid occlusion, either 2 gm/kg glucose in 4 ml saline or saline was infused over 20 minutes. To control for the temperature effects of glucose infusion observed in the previous study, half of the saline infused animals had their brain temperature kept at 37°C throughout the impact/ischemia experiment by external heating. The brains were examined at 2 weeks after injury for contusion volume and neuronal loss in CA1 and CA3 areas of the hippocampus.

Results

The significant results are summarized in the table below, as median (25^{th} percentile, 75^{th} percentile). Postinjury infusion of glucose resulted in a higher mortality rate, and worse histological indices of brain damage than either saline control group.

Infusion	Saline		Glucose
Brain Temperature Kept at 37°C	No	Yes	No
Number of animals	16	18	20
Preischemia blood glucose (mg%)	102(86, 112)	104(94, 111)	346(277, 388)*
Ischemia brain temperature (°C)	35.5(35.1, 36.5)	37.0(37.0, 37.0)*	36.6(35.4, 37.1)*
Mortality rate	0	4/18(22%)	11/20(55%)
Contusion Volume (mm^3)	7.9(4.4, 10.0)	18.3(6.6, 49.4)	64.2(30.8, 192.0)*
Viable CA1 Neurons ($cells/mm^2$)	211(194, 217)	182(57, 208)	127(22, 197)*
Viable CA3 Neurons ($cells/mm^2$)	115(113, 118)	107(35, 113)	87(14, 114)

Conclusions

Infusion of glucose after the impact injury had adverse effects on the consequences of a secondary ischemic insult that were similar to the effects of preinjury glucose infusion. Although the postinjury glucose infusion was associated with higher brain temperatures during the ischemia period, simply keeping the brain temperature constant with external heating did not duplicate the severity of the adverse effects of glucose infusion. Other metabolic or vascular effects of glucose are probably involved.

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MORPHOLOGICAL STUDY OF THE MICROCIRCULATIONIN NORMAL BRAINS AND IN PATIENTS AFTER A SEVERE HEAD INJURY.

A.Rodríguez-Baeza [1], F.Reina [1], J.Sahuquillo [2], A.Poca [2], A. Garnacho [3] and J.González-Olivan [4].

Department of Morphological Sciences of the UAB [1], Departments of Neurosurgery [2], Neurotraumatology Intensive Care Unit. Vall d'Hebron University Hospitals. Anatomical Forensic Institute [4]. Barcelona. Spain.

Introduction

The mechanisms involved in the cerebral blood flow (CBF) control are not fully understood yet. Alterations on these mechanisms may play an important role in the increase of the intracranial pressure found after a severe head injury, specially when there is a difusse brain swelling. However, etiological factors and anatomical structures involved in these abnormalities have not been defined yet. Our purpose is to study the cortical microcirculation both in normal brains and in patients who died after a severe head injury, in order to elucidate the morphological structures involved in the CBF control, as well as to define the microcirculatory patterns of normality and their modifications after a severe head trauma [1].

Methods

We have studied twenty human normal brains and ten brains corresponding to patients who died after a severe head trauma, and who had been previously monitorized in the Neurotraumatology Intensive Care Unit. The study was carried out by means of the analysis with scanning electron microscopy and confocal laser scanning microscopy, after intravascular injection of Mercox® and immunocitochemistry staining of endothelium.

Results

Cortical vessels are distributed in four main vascular layers. Along their initial traject, we have observed the presence of arterial anastomosis. Plastic strips and vascular constrictions were common on the surface of those vessels. Occasionally, plastic strips were associated to corrugated endothelium, mainly in patients who died after a severe head injury.

The capillary network is continuous. On its surface, it was frequent the presence of images similar to pericytes. Patients who died after a severe head trauma frequently showed images of blind endings and corrugated surface of the cast.

Summary and Conclusions

Our data suggest that both endothelium-plastic strips unions and endothelium-pericyte unions may be important in the local control of the CBF. In patients who suffer a severe head injury, frequent abnormalities as arteriolar constrictions and blind capillary endings suggest the presence of a local control of the CBF. Although the etiology of these findings in the angioarchitecture could be multifactorial it is feasible that they may play an important role in the alterations of the CBF found in these patients.

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The role of the endothelin system in pressure autoregulation of the cerebral vessels

L Mascia [1], D Webb[2], I Piper[2], M Souter[2], P Andrews[2].

[1] University of Bari, Italy, University of Edinburgh, UK[2]

INTRODUCTION The role of the endothelin system, as a potent vasoconstrictive peptide (1) in the development of cerebral vasospasm after subarachnoid hemorrhage (2; 3) and in focal cerebral ischemia (4) has been shown. Its influence on pressure autoregulation is poorly characterised. Using the non selective receptor antagonist (Bosentan), we have investigated the effect of the endothelin system on the pressure autoregulation of the cerebrovascular bed in normal rats.

METHODS: 10 Sprague - Dowley rats were studied, each animal being its own control. All the animals received Chloralose - Urethane anaesthesia and were intubated and ventilated (PaC02 40 - 45 mmHg). Mean arterial pressure (MAP) and intraventricular intracranial pressure (ICP) were measured continuously. Cerebral perfusion pressure (CPP) was calculated, blood gas samples taken through a femoral cannula with regional cerebral blood flow (CBF) measured using the hydrogen - clearance technique.

STEP 1, control: ICP, MAP and CBF were measured before and during noradrenaline infusion (0.06-0.1 γ/Kg/min) to increase CPP up to 20% baseline.

STEP 2 , bosentan: STEP 1 protocol was repeated after a slow intravenous bolus of bosentan (10 mg/Kg over 5 min; Hoffman- LaRoche LTD, Switzerland).

RESULTS: there was a significant difference (ANOVA $p<0.01$) between STEP 1 and STEP 2 CBF response to noradrenaline infusion (see table 1) although the blood pressure was similar on the two occasions and not affected by bosentan. The result was not affected when CBF was normalised for PaC02 = 34 mmHg

TABLE 1: CBF (ml/100 gr/min) change (not corrected for PaC02)

	CBF baseline	CBF pressure up	p value
STEP 1	37± 6	42±15	N.S.
STEP 2	33±4	45±16	< 0.01

DISCUSSION: these data show that after inhibition of the endothelin system, the pressure autoregulation is impaired. This indicates that blood flow autoregulation could be mediated, in part, by endothelium-dependent contraction through endothelin-1 generation. The role of the increased expression of the endothelin system after vasospasm (SAH) remains to be defined.

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APPLICATION OF THE TRANSIENT HYPERAEMIC RESPONSE TEST FOR ASSESSMENT OF AUTOREGULATION IN HEAD INJURED PATIENTS

Peter Smielewski PhD, Marek Czosnyka PhD, Peter Kirkpatrick FRCS (SN), John D. Pickard FRCS.

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, University of Cambridge (UK)

Introduction

The transient hyperaemic response test has been shown to provide an index of cerebral autoregulation in normal individuals, and in patients following a subarachnoid haemorrhage. In this study, the test was applied to patients who have suffered a severe head injury, and the value of the test was assessed by comparing its result with the individual's clinical condition (Glasgow Coma Score), cerebral perfusion pressure (CPP), transcranial Doppler wave form derived index for cerebral autoregulation (relationship between the CPP and the middle cerebral artery flow velocity - FV), and outcome (Glasgow Outcome Score).

Methods

Forty seven patients (age 16 to 63 years) with head injuries have been included. Signals of intracranial pressure, arterial blood pressure, FV, and cortical microcirculatory flux were digitised and recorded using special software for a period of 30 minutes. Two carotid compressions were performed at the beginning of each recording. The ratio of the hyperaemic FV seen after carotid release and the pre-compression baseline FV (THRR) was calculated, as was the correlation coefficient (Sx) describing the relation between slow fluctuations in the systolic FV and CPP for the period of recording.

Results

No significant changes in CPP during compression were found. There was a significant correlation between the THRR and the Sx ($r = 0.49$, $p < 0.0001$). The hyperaemic response proved to be lower in patients with poor clinical grade at presentation (GCS <6, $p=0.01$), and lower in patients achieving a poor outcome (GOS 3,4&5, $p=0.003$). Loss of post-compression hyperaemia occurred when the CPP fell below 50 mmHg.

Conclusion

The carotid compression test provides a simple index of cerebral autoregulation which is relevant to the clinical condition and outcome of the severely head injured patient.

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Cerebral Arterio-venous Difference of Blood Gases in the Assessment of Brain Energetic State Following Human Brain Injury

Ehud Shalmon, David A. Hovda, Daniel F. Kelly, Thomas C. Glenn, Marvin Bergsneider, Michael Caron, Neil A. Martin and Donald P. Becker. *Division of Neurosurgery, University of California School of Medicine, Los Angeles*

Introduction: Jugular bulb (JB) catheterization is used for determination of arterio-venous difference (AVD) of various cerebral metabolites. Increased cerebral AVD of oxygen ($AVDO_2$) and lactate production had been found to be sensitive indicators of brain ischemia. Recent experimental and clinical studies suggest that post-traumatic cerebral lactic acidosis is associated with cerebral hyperglycolysis rather then ischemia. This study evaluates the value of cerebral AVD of blood gases (BG) and their molecular ratios as indicators of energy metabolism of the brain and as a prognostic factor.

Methods: 25 severe head-injured patients who had JB catheters were included in this study. 362 pairs of arterial and JB blood samples were simultaneously obtained every 6-8 hours for determination of BG during the first 10 post-injury days. The molecular concentrations of oxygen, CO_2, and H^+ (driven from pH), in each sample were calculated, and their AVD was determined. The daily AVD of these metabolites and their molecular relationships were plotted.

Results: JB saturation ($SjbO_2$) ranged 43.7-94.6% (average 71.1% ±8.7%). Average $AVDO_2$, $AVDCO_2$, and $AVDH^+$ were 1.82±0.61; 2.42±1.55; and 4.13±1.90 μ mol/ml, respectively. Production of H^+ was higher on days 4-7, and decreased on days 8-10 post-injury. No daily changes in other BG values were observed. The average calculated molecular ratios between CO_2 production and oxygen utilization, between H^+ production and oxygen utilization, and between H^+ and CO_2 production were 1.36±0.88, 2.36±1.21, and 3.79±1.07, respectively. In a subgroup of all 104 samples (9 patients) who expired during the acute post-injury period, a slightly high production of CO_2 and H^+ (2.56±1.52 and 4.65± 2.41μ mol/ml, respectively) was found. A subgroup of 93 (26%) samples with $SjbO_2$ below 65.0%, had higher $AVDO_2$ (per definition) and $AVDCO_2$ (2.49±0.42; and 2.97±1.41μ mol/ml, respectively), and H^+ production was 22% higher (5.03±2.2μ mol/ml).

Conclusions: This analysis suggests an association between increased cerebral production of H^+ and low $SjbO_2$ (high $AVDO_2$) state. It is postulated that post-traumatic production of H^+ represents cerebral hyperglycolysis which contributes to the acidemia via lactate production; although analysis of $AVDO_2$ may potentially indicate cerebral ischemia as the etiology of cerebral lactate production. Increased $AVDH^+$ was found in association with fatality, but this method poorly indicate outcome following severe head injury.

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Early signs of brain edema in acute infarcts of the brain

A.Hartmann, L.Solymosi
Neurologische Univ.-Klinik, 53105 Bonn, FRG

Introducion: Early therapeutic regimens in acute cerebral ischemia aim at early reperfusion. This might provoke certain side effects, even increase of intracranial pressure (ICP) due to development of reperfusion edema. The consequence is that early reperfusion should not be performed in patients with already existing signs of brain edema (BE).

Patients and Method: In 147 patients with acute infarcts of the supratentorial brain tissue CCT have been done on day 1 or 2 of the disease course. Development of (vasogenic) BE have been estimated by indicators such as hypodensity, midline shift, narrowing of the sulci, enlargement of the gyri and clinical symptoms of increased ICP. Their frequency has been compared to risk factors of stroke, etiology of stroke and side of vascular affection. CCT have been controlled between day 3 and 7 in most of the cases.

Results: In 62% of the patients with acute complete occlusion of the middle cerebral artery one or several indicators of BE could be observed on day 1, in 40% within 4 hours after onset of symptoms. Patients with complete occlusion of the MCA trunk developed signs of BE more than patients with branch occlusion. Only a few patients with hemodynmaic infarcts did develop signs of BE. Patients with anterior cer.art. infarcts had less BE than patients with posterior cer.art. infarcts. Stroke risk factors and age did not influence the risk of early BE.

BE have been observed more in patients with territorial than with lacunar stroke. Several patients who were subjected to early intraarterial thrombolysis had to be excluded due to the early development of BE.

Conclusion: Vasogenic brain edema may occur very early in cerebral infarcts. Infarcts of the MCA and PCA and territorial infarcts are more affected than those of the ACA or lacunar or hemodynamic strokes. Early BE is one critical contraindication for thrombolyis.

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EFFICACY OF CEREBRAL PERFUSION PRESSURE THERAPY IN OPTIMIZING CEREBRAL BLOOD FLOW FOLLOWING TRAUMATIC BRAIN INJURY

Jae Hong Lee, Daniel F. Kelly, Thomas C. Glenn, George Counelis, and Neil A. Martin
UCLA Cerebral Blood Flow Laboratory and UCLA Division of Neurosurgery, Los Angeles, CA, USA

Introduction Low Cerebral Blood Flow (CBF) has been associated with poor outcome following traumatic brain injury (TBI) (1). Therapy aimed at elevating cerebral perfusion pressure (CPP) has been advocated to optimize CBF (2). The study presented here examines the relative importance of CPP compared to $PaCO_2$ in determining CBF when CPP has already reached a specific threshold (70mmHg).
Methods *Relative* changes in CBF were monitored using continuous transcranial Doppler ultrasonography (TCD) in 13 head-injured patients (12male,1female; median initial GCS 6, range 3-12; mean age 32.4 ± 10.3 yrs). Sixteen studies were performed (median post-injury day 2.5, range 0-18; 2 patients had multiple studies) with simultaneous recording of the following parameters: left and right middle cerebral artery flow velocities (V_{MCA}), mean arterial pressure (MAP), intracranial pressure (ICP), and end-tidal CO_2 ($ETCO_2$). At least 25 sets of recordings were made manually or by computerized data acquisition in each study. Multiple linear regression analysis was performed with left and right V_{MCA} as dependent variables; CPP and $ETCO_2$ served as independent variables. Statistical significance was defined as $p<.05$.
Results In 15 out of 16 studies, mean CPP was maintained at or above 70 mmHg (range for mean CPP: 69.1-103.3 mmHg). High ICP (>20 mmHg) was noted in 10 of 16 studies. In 12 out of 16 studies (11 of 13 patients), a statistically significant positive correlation was found bilaterally between $ETCO_2$ and V_{MCA} (in 2 additional patients, a significant correlation was seen on one side only). In contrast, a significant positive correlation between CPP and V_{MCA} was seen bilaterally in only 5 of 16 studies (4 of 13 patients; 2 patients showed a significant correlation on one side only). Furthermore, multiple regression analysis demonstrated $ETCO_2$ to have a greater influence on V_{MCA} than CPP in 14 out of 16 studies (12 of 13 patients): the mean beta coefficient for $ETCO_2$ was .54 ± .26 versus .19 ± .30 for CPP.
Conclusions In patients with TBI whose CPP is already maintained above a threshold of 70 mmHg, further elevating CPP appears to have little influence on CBF. In these patients, greater emphasis should be placed on optimizing $PaCO_2$.
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The role of the endothelin system in pressure autoregulation in head injured patients

L Mascia [(1)], G E Mc Keating[(2)], M Souter[(2)], D Webb[(2)], P Andrews[(2)].

[(1)] University of Bari, Italy, University of Edinburgh, UK[(2)]

INTRODUCTION Pressure autoregulation in head injured patients is frequently deranged (1). Furthermore, the endothelin system (ETS), comprising potent vasoconstrictive peptides, has been implicated in the development of cerebral vasospasm after subarachnoid hemorrhage (2) and in focal cerebral ischemia (3). ETS influence on pressure autoregulation is poorly characterised. We have investigated the effect of endothelin 1 (ET1) on pressure autoregulation in head injured patients.
METHODS: we tested pressure autoregulation in 8 haed injury patients (mean GCS = 7) admitted to the ITU. Mean arterial pressure (MAP) and intracranial pressure (ICP) were measured continuously. Cerebral perfusion pressure (CPP) was calculated and regional cerebral blood flow (CBF) measured by inhalation Xe133 clearance technique. CBF was measured before and during norepinephrine infusion (0.06 - 0.1 γ/Kg/min) used to increase CPP by 30% above baseline. During each CBF measurement, paired arterial and jugular samples were taken. Analysis of plasma for endothelin 1 was performed by ELISA. (4).
RESULTS: According to Muizelaar formula, pressure autoregulation was preserved (index < 2) in this population. An arterio-jugular gradient for endothelin 1 (0.23 ±0.4 pg/ml) was not found (reference range 1-6 pg/ml). The absolute values for arterial and jugular samples were in the normal range (arterial (3.1±0.7, jugular 2.9 ±0.7 pg/ml).
DISCUSSION: these data show that plasma level for ET 1 was in the normal range and not influenced by our challenge to pressure autoregulation in this patient population. However it has been hypothesised that, due to the blood brain barrier, endothelin 1 in cerebral circulation acts from the abluminal side rather than the luminal aspect of the endothelium (5). Therefore, before to exclude the role of this paracrine system from intact pressure autoregulation, we must assess endothelin cerebrospinal fluid level.
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BLOOD PRESSURE REACTIVITY TO MENTAL STRESS IS ASSOCIATED WITH LEARNED DISTRESS

S. Porter, C.P. McGraw, and M.W. Herrmann

Department of Neurosurgery
University of Louisville School of Medicine

Introduction
The purpose of this study was to determine whether the variation in blood pressure (BP) reactivity to mental stress was associated with the concept we have identified as learned distress (LD).

Methods and Materials
Thirty-six volunteers completed an in-depth self evaluation developed to measure their perceptions and beliefs of being out of control. Through the use of a stethoscope and sphygmanometer, each had their BP non-invasively measured and recorded before, during and after administration of a mental stress to yield pretest, test, and post-test BP, respectively. The Stroop color test, computerized color interference task, was used as the stressor.

Results
Statistical analysis of the survey responses and BP readings by the SPSS computer program computed a correlation between systolic reactivity and Competitive Drive ($p=0.006$) and between diastolic reactivity and Career Progress ($p=0.021$), Social Presentation ($p=0.044$) and Internal Control ($p=0.031$). Multiple regression indicates that three variables ("Personal Achievement", "Competitive Drive", and "Sufficient Money") account for 39.4% of the variation in systolic difference. Whereas seven variables ("Career Progress", "Physical Discomfort", "Internal Control", "Self Perception", "Intestinal Normality", "Work Quality", and "Life Optimism") account for 72.4% of the diastolic reactivity variation.

Conclusion
These results suggest that what we consider learned distress plays more of a role in diastolic BP reactivity than systolic BP reactivity.

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MODEL OF CEREBRAL VASCULAR DILATION AND CORRESPONDING VARIATION OF RESISTANCE OF VENOUS DRAINAGE PATHWAYS

Michael L. Daley[1], Jin Ye[1], and Charles W. Leffler[2]

[1]Department of Electrical Engineering, University of Memphis and
[2]Department of Physiology and Biophysics, University of Tennessee-Memphis

Introduction
Increases of PCO_2 induce dilation of the cerebral arterial vasculature and a systematic change in the ICP recording. As the physiologic state progresses from normocapnia to deep hypercapnia, ICP and arterial pressure recordings become more similar and exhibit a high correlation during deep hypercapnia (1). The purpose of this study was to develop an analytical model which might provide a further understanding of the mechanisms during cerebral vascular dilation.

Methods
The venous drainage pathways of the model proposed by Ursino (2) were modified to be pressure dependent and time-varying. These pathways represent the resistance of bridging veins into the lateral lacuna and the resistance of valve-like elements of chordae Willisii along the walls of the sagittal sinus and resistance of the anastomotic venous vasculature. The model simulates increasing dilation from a progressive increase in PCO_2 by decreasing flow through bridging veins and increasing flow through the other pathways of venous drainage. Also, arterial resistance is decreased progressively.

Results
The model simulates a monotonic increase of the correlation value between ICP and arterial pressure with increasing PCO_2 that is consistent with experimental observations.

Summary and Conclusions
The model suggests a decrease of arterial resistance and a variation in the venous drainage pathway resistance might underlie the observed increase in similarity between ICP and arterial pressure recordings with progressive states of hypercapnia.

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AN ICP MODEL FOR A HUMAN PATIENT SIMULATOR

W. James Thoman, Samsun Lampotang, Dietrich Gravenstein, Jan van der Aa and Edward Walsh

Department of Anesthesiology and College of Engineering University of Florida, USA

Introduction

The Department of Anesthesiology has developed a Human Patien Simulator (HPS) that is a full scale, fully interactive, life-lik simulator that meets the needs of educators and learners in all healt care professions. Clinical features and monitored parameters includ items such as palpable pulses, self-regulating control of breathing heart and breath sounds, electrocardiograms, invasive and non invasive blood pressures, and others. Further, physiological an pharmacological models direct simulated patient responses to drugs mechanical ventilation, and other medical therapies.

Now an ICP model has been developed to incorporate th physiological parameters of the HPS to generate a dynamic displa of intracranial events such as intracranial pressure (ICP), cerebra blood flow (CBF), and cerebral blood volume (CBV), which are no normally evident to the physicians. The model accounts for th interplay between the volume elements in the intracranial system an incorporates an elastance curve which determines the ICP. I addition, the ICP model can operate in a stand alone mod independent of the HPS using clinical patient data.

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SPECTRAL ANALYSIS OF ARTERIAL PRESSURE, AND BLOOD FLOW VELOCITY IN BRACHIAL AND MIDDLE CEREBRAL ARTERIES

A. Ter Minassian, L. Beydon, F. Bonnet, M. Simon, P. Peronneau.
Surgical Intensive Care Unit H. Mondor Hospital. Créteil, and INSERM U256. Paris, France.

Introduction

Blood flow velocity in middle cerebral artery (MCAV) is known to oscillate within a 0.008-0.033 Hz frequency band as does ICP pressure in the form of Lundberg's B waves. ICP would oscillate through the autoregulatory response to cyclic changes in cerebral blood volume and vascular resistance. This study aimed to further study in the frequency domain, the relationship between arterial pressure (AP), MCAV and brachial blood flow velocity (BV).

Material and Methods

19 volunteers who gave written informed consent were studied at rest. We simultaneously recorded MCAV at left arm (2 MHz pulsed Doppler, Angiodyne, France), BV (8 MHz pulsed Doppler Alvar, France) and digital AP (Finappress, Ohmeda). Two 30 min periods have been recorded : one at complete rest during which signals oscillated in most subjects with a 30-120 s period frequency range studied (B state). The other recording period (named NB-state) was performed when the subject was kept fully awake by verbal stimulation. Spectral analysis was performed on 512 s of B and NB state in all subjects who showed both states.

Results

10 subjects (40.7 ± 3.6 years) showed B and NB states. Verbal stimulation suppressed the oscillatory pattern in MCAV in all subjects. MCAV was higher and AP lower in B than in NB state ($p=0.046$ and $p=0.03$, respectively). Spectral power of MCAV, BV, and PA in the 0.008-0.033 Hz frequency decreased from B to NB state (-76%, $p<10^{-3}$; -54%, $p<10^{-4}$; - 36%, $p=0.02$). Signal coherence between MCAV and BV and between MCAV and AP was greater in B state compared to NB state ($p<10^{-5}$, $p<10^{-3}$, respectively), but similar between BV and AP. The phase-amplitude diagram in B state showed a normal distribution of phase (Kolmogorov test). Mean phase shift between MCAV and AP was 1.31 ± 0.67 radian and differed from that between BV and AP (2.21 ± 0.5 radian, $p<10^{-4}$).

Summary and conclusions

In B state, an oscillatory pattern appears and MCAV amplitude is increased despite a decrease in mean AP. Moreover, MCAV variability increases more than the variability of AP, as compared to NB state. In B state, the change in signal profile, in the frequency domain, suggests a change in autoregulation. Values of amplitude and phase we obtained in normal subjects during B state could serve as reference for the assessment of autoregulation in pathology.

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VENOUS BLOOD FLOW PULSATILITY AND IMPEDANCE INCREASES AS COMPARTMENT COMPLIANCE DECREASES

Marvin Bergsneider, Abeer Alwan, Eduardo H. Rubinstein
Division of Neurosurgery, Department of Electrical Engineering, Department of Physiology, UCLA School of Medicine, USA

Introduction: The amount of work necessary to drive blood through the venous system, which constitutes 80% of the total blood volume, is reduced secondary to nonpulsatile venous flow (lowering inductive reactance). This nonpulsatile flow occurs as a result of low-pass filtering in the elastic arterial system (capacitance). Within the cranium, pulsatile trans-foramen magnum movement of CSF is an essential facilitator of arterial capacitance. The hypothesis of this study was: the pulsatility of venous blood flow will increase as compartment compliance decreases secondary to inhibition of arterial capacitance.

Methods: The intracranial compartment was simulated by utilizing a rigid, hermetically-sealed, saline-filled container surrounding the leg of an adult New-Zealand white rabbit (N=5). Endotracheal mechanical ventilation with halothane (0.8%) and neuromuscular blockade was used. The leg preparation preserved the intact femoral artery and vein, with denervation and osteo-muscular disarticulation of the thigh and foot. Container compliance was changed by opening or closing a release valve atop the container. Blood flow profiles in the femoral artery and vein were determined by Doppler 20 MHz probes. Blood pressure was monitored in the contralateral femoral artery. All data was digitized, stored, and analyzed by signal averaging techniques.

Results: Baseline blood flow profiles with the container open to air demonstrated completely nonpulsatile venous blood flow (pulsatility index PI=(systolic-diastolic)/mean of 0.12). Closure of the container resulted in an immediate transition to pulsatile venous flow with a pulsatility index of 0.64 ± 0.20. Blood pressure and container temperature remained constant throughout the experiment. Reopening the container resulted in immediate return to nonpulsatile flow. Intermediate restriction of the container opening resulted in a graded venous pulsatility.

Summary and Conclusions: Compartment compliance has a direct influence on venous blood flow pulsatility. The inertial mass of the venous blood pool, which is normally masked by the conversion of pulsatile-to-nonpulsatile flow by the arterial system, will become an important additive component to total cerebrovascular impedance as arterial compliance decreases. This finding supports a concept that in high intracranial pressure - low compliance states, cerebral blood flow will be a function of total cerebrovascular impedance, not solely arteriolar resistance. Future studies will be necessary to determine if the increase in venous reactance leads to a compensatory dilatation of arterioles to maintain cerebral blood flow.

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Correlation of High Extracellular Potassium and Glutamate with Intracranial Pressure in the Severely Head Injury Patient: A Human Microdialysis Study

J.C. Watson, MD; E.M.R. Doppenberg, MD; C.J. Winters, MD; S.C. Choi, Ph.D.; A. Marmarou, Ph.D.; S.S. Koura; M.R. Bullock, MD, Ph.D.

Introduction: Brain swelling and elevated intracranial pressure (ICP) is a well-known cause of neurological deterioration and secondary injury in severe head trauma. Excitotoxic damage is involved in secondary injury, and human microdialysis studies have shown correlation with ICP and elevated extracellular glutamate[1,2]. Elevated extracellular potassium has been shown to correspond to glutamate release in experimental brain injury[3], either through channel activation and/or cell toxicity. We hypothesized that in severe head injury, secondary excitotoxic damage will lead to increased extracellular potassium which correlates with extracellular glutamate in human subjects.

Patients and Methods: 45 human subjects with severe head injury (GCS<8) were studied after obtaining institutional informed consent. Continuous brain microdialysis was performed using a 10mm flexible probe (CMA) at a rate of 2(l/min and collected in 30 min intervals with a closed, refrigerated collecting system. The probes were placed via a transcranial bolt, routinely placed in the frontal region. Simultaneous ventriculostomy ICP data were collected. Potassium levels were obtained using flame photometry, and glutamate levels were measured using HPLC.

Results and Data Analysis: Data were analyzed using Spearman's rank correlation coefficients in each individual patient, and the strengths of the correlation were tested across all patients, using a t-test of the "r" values. A significant positive correlation between potassium and glutamate ($P<0.001$) was demonstrated. Furthermore, a significant correlation between elevated glutamate and elevated ICP (ICP>20mmHg) ($P<0.05$) was seen.

Conclusions: Our data support the hypothesis that an increase in extracellular potassium is a glutamate-mediated response. This is further evidence that excitotoxic mechanisms, rather than non-specific mechanisms of cell damage, contribute to elevated ICP after severe human head injury.

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LONGTIME MONITORING OF REGIONAL OXYGEN SATURATION USING NEAR INFRARED SPECTROSCOPY

J. Meixensberger, E. Barcsay, E. Kunze, J. Dings, K. Roosen

Department of Neurosurgery, University of Würzburg, F.R.G.

Introduction

Near infrared spectroscopy allows non - invasively monitoring of regional hemoglobin oxygen saturation (rSO_2). On the other hand continuous monitoring of cerebral hemodynamics is demanded to detect ischemic episodes in the time course after acute brain injury. Therefore the issue of our study was to evaluate the quality and sensitivity of this technology in the longtime course after acute brain injury. Especially we were interested in a correlation between rSO_2 and invasively measured regional brain tissue oxygenation ($p(ti)O_2$).

Methods

Multimodal neuromonitoring including intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), endtidal CO_2 as well as rSO_2 and $p(ti)O_2$ (frontal brain tissue) was performed continously in 23 patients after acute brain injury (day 0 -9). All patients were sedated, intubated and ventilated as well as treated after a protocol to control raised ICP. Data sampling and analysis was performed using computerized programs. After manual artifact elimination and calculating the time of good data quality , the time course of CPP as well as rSO_2 and $p(ti)O_2$ was analyzed. As „significant event" we defined a 10 % increase/decrease from the averaged hourly value of rSO_2. A significant $p(ti)O_2$ episode was recognized when $p(ti)O_2$ decreased or increased by more than 20 % over the hourly average.

Results

Analyzing a total of 2425 hours the $p(ti)O_2$ good data quality reached 93.5 %. In contrast to $p(ti)O_2$, good data reading of rSO_2 was only 70.5 % in mostly unoperated patients over time. In the acute phase after trauma rSO_2 ranged between 60 - 80 % within narrow limits (∓ 5 %), while $p(ti)O_2$ often revealed a critical decrease of $p(ti)O_2$ (< 15 mmHg) in the first days and an increase to 15 - 30 mmHg with a plateau on day 3 to 6. Totally 208 episodes of decrease and 131 of rSO_2 - increase could be detected, while in the same time period 511/442 significant events of $p(ti)O_2$ (decrease/increase) were observed. Only in 25 %, respectively 40 % of the rSO_2 episodes (decrease/increase) a simultanous change of regional cerebral microcirculation ($p(ti)O_2$) could be found.

Conclusion

In clinical routine regional oxygen saturation alone is not reliable and sensitive enough to provide sufficient information about cerebral hemodynamics over a longtime period. Further improvements of the technology are neccessary to give the physician a useful and powerful non - invasive tool in monitoring and treating ischemic episodes in the time course after acute brain injury.

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NEAR INFRARED SPECTROSCOPY (NIRS) AS AN EARLY DETECTOR OF LATE INTRACRANIAL HEMATOMAS

S.P. Gopinath, C.S. Robertson, B.C. Chance. Department of Neurosurgery, Baylor College of Medicine; Department of Biochemistry and Biophysics, University of Pennsylvania

Introduction

Delayed intracranial hematomas are a treatable cause of secondary injury if identified early. Current monitoring techniques include measurement of ICP, and neurological examination with Glasgow Coma Scale (GCS) score. The purpose of this study was to determine if NIRS would detect hematomas earlier than would be indicated either by a change in the ICP or the neurologic status.

Methods

Three hundred and five patients with head injury were studied with serial NIRS examination in the intensive care unit. The NIRS probe of a dual reflectance spectrometer (RunMan, NIM, Inc., Philadelphia) was placed successively in various regions of the scalp to record the intensity of reflected light at 760nm. The difference in optical density in the different areas was calculated from the formula: $\Delta OD = \log_{10}(I_L/I_R)$ where I_L = the intensity of reflected light on left side, I_R= intensity of reflected light on right side. An increase in ΔOD to > .10 was considered abnormal.

The patients were also followed with the usual clinical monitoring that consisted of periodic measurement of GCS and ICP. An increase in ICP to >30mmHg and/or a decrease in the GCS score of at least 2 points or signs of tentorial herniation were considered indicators of a intracranial hematoma.

Results

A comparison of the various clinical indicators in the 59 patients who developed late hematomas are shown in the table below. In 55 of the 59 patients, an increase in the ΔOD to >0.10 occurred prior to an increase in ICP or a change in the neurological examination. In 31 of the 33 who required surgery the ΔOD was at least 0.3, compared to only 17/26 in the patients with the late hematoma managed non-surgically.

Type of Late Hematoma	Earliest Indicator of Late Hematoma				Number with ΔOD > .3
	NIRS (ΔOD>.10)	ICP (>30 mmHg)	GCS (- 2 points)	Routine CT scan	
Large hematoma, requiring surgery	30	3	0	0	31/33(94%)
Small hematoma, treated medically	25	0	0	1	17/26(65%)

Conclusion

The NIRS detected the presence of the hematoma earlier than ICP or neurological examination in 93% of the cases. Early diagnosis using NIRS may allow early treatment and reduce secondary injury caused by late hematomas.

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IS NIRS A SUITABLE DEVICE TO STUDY HEMODYNAMIC EFFECTS OF REPETITIVE MAGNETIC STIMULATION ?

O. Piazza, F. Gallizzi, M.A. Pennisi, F. Della Corte, A. Oliviero*, V. Di Lazzaro*.Institute of Anesthesiology and *Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy.

Introduction: The hemodynamic effects of repetitive magnetic stimulation (RMS) of the human brain were investigated by several authors who reported an increase of cerebral blood flow (CBF). Authors evaluated if CBF changes induced by RMS were associated to metabolic activation and if they could be detected by Near Infrared Spectroscopy (NIRS).

Methods: Cerebral variations in HHb, HbO_2, and Cit aa3 due to magnetic stimulation were studied in 10 healthy volunteers. The NIRS probe (Critikon Cerebral Research Monitor 2001) was placed on motor and premotor areas. Magnetic stimulation was performed using a Magstim 200 (Novametrix, UK). Thirty stimuli (100% of the maximal stimulator output; 0.25 Hz) were delivered through a figure of 8 coil over the premotor and motor cortex. The data averaging of 10 minutes recording before and of 5 minutes after the magnetic stimulation were analized.

Results: Immediately after the stimulation a significant increase in HbO_2 and a decrease in Cit aa3 was observed ($p<0.05$). The increase in HHb was not statistically significant (Tab 1).

Before RMS				After RMS			
HHb	HbO2	THb	Citaa3	HHb	HbO2	THb	Citaa3
-1,071	-0,198	-0,15	-0,626	-0,126	4,138	3,31	-2.237
p				0,06	0,03	0,019	0,021

Tab 1 Influence of frontal RMS on NIRS parameters. The medium NIRS parameters are given in μM of difference from the starting baseline considered as zero.

Conclusions: The NIRS data suggest that RMS induces metabolic activation of the cerebral cortex together with an increase of CBF.

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COMPARISON OF THE NIRO500 AND INVOS 3100A CEREBRAL OXIMETERS IN NORMAL SUBJECTS

Edwin M. Nemoto, Mark Sanders,* Karl Fernandes,* and Howard Yonas

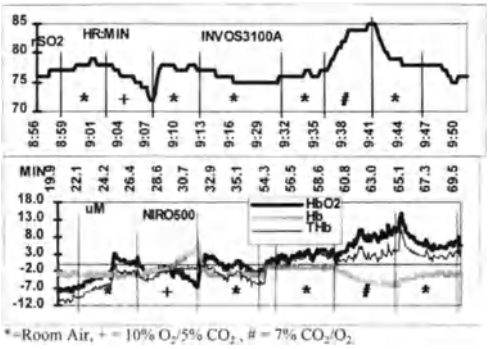
Departments of Neurological Surgery and Pulmonary Medicine*, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

Introduction: Two of the commercially produced cerebral oximeters using near-infrared to monitor cerebral oxygenation are the INVOS3100A (Somanetics, Inc.) and the NIRO500 (Hamamatsu Photonics, Inc.). This study compares these instruments in normal subjects subjected to mild hypoxia and hypercapnia.

Methods: Following an IRB approved protocol, the NIRO500 and INVOS3100A optodes were placed bilaterally on the foreheads of 12 healthy, normal subjects. They breathed randomly, either a hypoxic gas mixture to lower arterial saturation to a minimum of 85% with 5% CO_2 or a hypercapnic (7% CO_2/O_2) mixture for a period of 5 min preceded by or followed by breathing with room air.

Results: Typical responses of the INVOS3100A (Fig.,top) and the NIRO500 (Fig.,bottom) are shown below.

Conclusions: Both the NIRO500 and the INVOS3100A reliably detect changes in cerebral oxygenation during hypoxia and hypercapnia.



*=Room Air, + = 10% O_2/5% CO_2, # = 7% CO_2/O_2

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TRAUMATIC-ISCHEMIC BRAIN INJURY AS STUDIED IN THI ISOLATED-PERFUSED RAT BRAIN PREPARATION

D. Scheller[1], G. Clincke[2] and F. Tegtmeier[1]

Janssen Research Foundation, [1]Neuss, Germany, [2]Beerse, Belgium

Introduction
The isolated-perfused rat brain preparation (1) allows to perform in vitr investigations using a completely defined blood substitute as perfusate. In orde to develop the preparation as model for brain edema, we induced a traumatic ischemic injury and measured the rise of intracranial pressure (ICP) and th corresponding decline of cerebral blood flow. Clinically used compounds, DMS(or mannitol, were tested to validate the model.

Methods
The art. carotis internae of male Wistar rats (200 to 220 g) were cannulated unde anaesthesia. The blood was washed out by the perfusate - a fluorocarbon emulsio consisting of 16 % fluorocarbon as oxygen carrier and the typical electrolyte bloo constituents (in mM: NaCl (110), KCl (3.5), $NaHCO_3$ (26.2), $NaHPO_4$ (1.7), CaC (1.5), Mg_2SO_4 (0.7), pH 7.4, CO_2 40 mmHg, O_2 600 mmHg, Glucose (11.5), Lactat (2), Pyruvate (0.4) and Cysteate (0.17)). Subsequently, the art. vertebralis wer compressed and a tip catheter (Millar type, 1 mm diameter, 2.5 mm length; membran size about 1.0 x 1.0 mm) for intracranial pressure (ICP) recording was inserted int the cortex. Cerebral blood flow was measured continuously by monitoring venou outflow. After a control period of 30 min, complete ischemia was induced for 10 mi Reperfusion was then started and maintained for 45 min with DMSO (1, 5, 10 c 20 %), mannitol (40 or 100 mM) or equal amounts of isotonic NaCl in the perfusate.

Results
Post-ischemic reperfusion with a solution containing 1, 10 or 20 % DMSO had n effect on venous outflow. However, a solution containing 5 % DMSO reduced th post-ischemic flow-decline. All concentrations of DMSO delayed the onset of the ris of the ICP and slowed it down. The 5 % solution of DMSO was the most effective. I contrast, mannitol at a concentration of 100 mM had only a transient effect.

Conclusion
The data show that DMSO had a beneficial effect on ICP rise and flow declin However, DMSO delayed the onset of ICP rise but could not completely prevent i This effect was more pronounced than that of mannitol that only induced a transie reduction of ICP. The observations are in line with clinical experience using DMSO c mannitol as standard treatments to control critical ICP rise. Thus, the induction of traumatic-ischemic brain injury in the isolated rat brain preparation seems to be valuable model to investigate potential treatment strategies for critical ICP rise.

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SUPERIOR SAGITTAL SINUS PRESSURE AND CONFLUENCE PRESSURE DURING INCREASED ICP IN YOUNG PIGS: SIGNS OF CEREBRAL VENOUS SINUS COMPRESSION

Mads Rasmussen , Bo Bergholt , Pang Qi , Gorm von Oettingen and Jens Astrup

Department of Neurosurgery , Århus University Hospital , Denmark.

Introduction
Cerebral venous outflow is assumed to be obstructed in conditions of high ICP, due to the "waterfall" phenomenon at the bridging vein-superior sagittal sinus junction[1]. Compression of the dural venous sinuses may occur in infancy and thus may further aggravate venous outflow obstruction. We have studied this possibility in young pigs.

Purpose of study
To measure an increase in venous superior sagittal sinus pressure(SSSP) and confluence pressure(CP) during stepwise increasements in ICP between 0-40 mmHg.

Methods
8 young pigs , aged approx. 4-5 months were anesthetized using fentanyl and halothane. SSSP and CP were measured by a 2.0 F catheter. ICP was increased stepwise to approx. 40 mmHg by infusion of mock CSF into the cisterna magna. In 6 pigs the catheter was retracted from the confluence to the anterior part of the superior sagittal sinus.

Results
A positive correlation was observed between CP and ICP , indicating progressive venous obstruction in the posterior fossa. SSSP increased progessively from the confluence towards its frontal part indicating compression of the superior sagittal sinus.

Conclusion
The dural venous sinuses are compressed by increased ICP in young pigs. This may aggravate venous outflow obstruction in conditions of high ICP

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Early Response to Hypercapnia Following Traumatic Brain Injury

M. Sheinberg, X. Wang, L. Dickinson, and B. Zink

Introduction: Metabolic coupling ensures that in non-pathologic states CO2, or more precisely, hydrogen ion concentration, is closely linked to cerebral blood flow (CBF). Previous studies have shown early alterations in CBF following traumatic brain injury (TBI), and suggested changes in responsiveness to PCO2 associated with this pathologic state (1). We undertook a controlled study to determine ultra-early changes in response to a hypercapnic stimulus following TBI in an animal model.

Methods: A porcine fluid percussion injury model was used for this experiment. There were 6 animals in the control group and 8 in the experimental group. Animals were anesthesized with 1% halothane and instrumented in an identical manner. Injured animals received a 3.0 atm injury which produced a diffuse brain injury on pathologic examination. Continuous measure was made of ICP, CPP, MAP, EtCO2, PAP, saggital sinus O2 saturation, brain and blood temperature. Intermittent measure was made of regional CBF, global CBF, CO, arterial and cerebral venous blood gases, lactate and glucose concentrations. At 6 timepoints during the experiment (15 min, 30 min, 60 min, 90 min, 120 min,and 180 min) a 6% CO2 stimulus was administered and response recorded.

Results: There were no significant differences between control and experimental animals in weight or any pre-injury physiologic parameter measured. Following injury, there was a significant and sustained increase in ICP (mean diff. @ 15 min=47 mmHg) and decrease in CPP (mean diff @ 15 min=45 mmHg), most pronounced at the earliest timepoints. Hypercapnic stimulus pre-injury and in the control animals resulted in consistent elevation of ICP (mean 5.5 mmHg;SD-3.3) and decrease in CPP (mean 5.3 mmHg; SD-3.7). There was a trend towards diminished ICP response to hypercapnia at the 15 min timepoint, and a statistically significant loss of CPP response to hypercapnia in injured animals at this point (mean diff= -1.75 mmHg; SD-4.8; p<.02). There was no difference in baseline PCO2 at 15 min or in EtCO2 after the CO2 stimulus. By 30 minutes, and for the remainder of the experiment, there was no difference in response between the two groups.

Conclusion: Very early after a severe diffuse brain injury there is loss of cerebrovascular response to a hypercapnic stimulus. By 30 minutes post-injury, normal CO2 responsiveness is restored in this model. Initial loss of chemoregulation is likely related to a vascular bed that is maximally vasodilated and unresponsive to further vasodilatory stimulus. Further studies will attempt to better characterize early changes in vascular regulation and their underlyng biochemical mechanisms.

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METHOD OF ESTIMATING CEREBRAL DILATION FROM CLINICAL RECORDINGS OF ICP AND ARTERIAL PRESSURE

Michael L. Daley[1], Sarah Patterson[2], Anthony Marmarou[3], Charles W. Leffler[4], and Gregory Stidham[5]

[1]Dept. Electrical Engineering, University of Memphis, [2]Dept. Anesthesiology, University of Tennessee, [3]Dept. Neurosurgery, Richmond College of Medicine, Richmond VA, [4]Dept. Physiology and Biophysics, Univ. of Tennessee, [5]Dept. Pediatrics, University of Tennessee, Memphis, TN

Introduction
Laboratory studies have shown that correlation analysis applied to the ICP and arterial pressure signals provides a means for detecting loss of vascular tone during massive vasodilation induced by deep hypercapnia [1]. In this preliminary clinical study, the same correlation analysis technique was used to evaluate changes of ICP and arterial pressure in 6 pediatric patients with brain injury.

Methods
Entrance criteria for the study were admission to the ICU for management of closed head-injury from trauma, and implementation of ICP and arterial pressure monitoring. GCS assessments were made by neurosurgical/ICU staff. Digitized recordings of ICP and arterial pressure were obtained from 6 patients.

Results
Four patients with a mean (± S.D.) monitoring period of 2.75 ± 2.2 days demonstrated: mean GCS (± S.D.) of 6 ± 0.8 upon admission; mean ICP generally < 20 mmHg; and a positive CO_2 response. The remaining 2 patients were monitored 2 and 5 days and demonstrated: a GCS of 3 and 5 upon admission; mean ICP generally > 50 mmHg; and a negative CO_2 response. In 2 of the 4 patients with mild ICP a high mean correlation value (+ S.D.) indicative of maximal cerebral vasodilation was found. Both patients in the group with high ICP demonstrated an mean r-value of xxxx + xxxx.

Summary and Conclusions
Correlation analysis applied to pediatric clinical recordings of ICP and arterial pressure indicates massive dilation of the cerebral vasculature and cerebral hyperemia can in exist in cases exhibiting only a mild elevation of ICP.

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HOMEOSTATIC ROLE OF ACTIVE TRANSPORT IN DISTRIBUTION OF SUBSTANCES ALONG CEREBROSPINAL FLUID

Anton Vladić, Marijan Klarica, Marin Bulat

Department of Pharmacology, Medical Faculty, University of Zagreb, Zagreb, Croatia

Introduction
Whether brain metabolites of neurotransmitters such as 5-HIAA (metabolite of serotonin) and HVA (metabolite of dopamine) can reach lumbar CSF is not clear, because they are removed from CSF to bloodstream by active transport. This active transport can be blocked by probenecid which also inhibits transport of benzylpenicillin (BP) out of CSF (1). Since labeled BP is commercially available we studied its distribution from cisterna magna to lumbar CSF in dogs.

Methods
^{3}H-BP was applied into cisterna magna by direct puncture under short ether anesthesia in control dogs and those pretreated with probenecid (150 mg/kg i.p.). At different time intervals thereafter (90, 180 or 300 min) dogs were anesthetized by thiopenton (50 mg/kg i.p.) and samples of CSF (0.2 ml) from both cisterna magna and lumbar subarachnoid space were taken for analysis.

Results
^{3}H-BP from cisterna magna reaches lumbar CSF only in traces in control dogs, while in dogs pretreated with probenecid ^{3}H-BP in lumbar CSF reaches concentration similar to that in cisterna magna at 300 min after its application. Furthermore, half-life of ^{3}H-BP in cisterna magna is short under control condition (30 min), while it is several times longer after blockade of transport by probenecid.

Summary and Conclusions
It appears that active transport prevents accumulation of potentially toxic substances in the CSF and diminishes their distribution between CSF compartments, and in this way it plays a homeostatic role. In addition, our results suggest that after blockade of active transport in patients distribution of cerebral metabolites to lumbar CSF should be enhanced.

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PO_2 - MONITORING IN TRAUMATIC BRAIN INJURY: ARE ICP AND CPP INDICATORS OF BRAIN TISSUE HYPOXIA?

Roger Härtl, Tillman F. Bardt, Andreas Unterberg, Asita Sarrafzadeh, Karl Kiening, Gerd-Helge Schneider, Wolfgang Lanksch

Department of Neurosurgery, Virchow Medical Center, Humboldt University, Berlin, Germany

We previously described a correlation between CPP and brain tissue PO_2 ($PtiO_2$) in severe traumatic brain injury (TBI) during spontaneous drops of blood pressure and identified a CPP of 60 as the lower threshold of cerebral autoregulation. A $PtiO_2$ of 10 mmHg was found to be indicative of cerebral ischemia. In a larger patient group we now investigated the relationship between $PtiO_2$, ICP and CPP over the total monitoring time (MT) after severe TBI.
Methods 35 comatose patients with severe TBI and abnormal CT findings indicative of increased ICP underwent multimodal cerebral monitoring in our neurosurgical ICU. ICP was measured using an intraparenchymal Camino device. $PtiO_2$ was monitored in vital brain tissue with a Licox PO_2 catheter inserted into the white matter of the hemisphere contralateral to the main lesion.
Results Average MT per patient was 123 ± 68 h. ICP was > 20 mmHg in 41% of total MT, CPP < 60 and $PtiO_2$ < 10 mmHg in 12.5% and 12% of MT, respectively. No correlation was found between ICP > 25 (> 20) mmHg, CPP < 60 (< 70) mmHg and $PtiO_2$ < 10 (<15) mmHg. When ICP was > 25 mmHg, $PtiO_2$ was < 10 mmHg in only 10% of MT. When CPP was < 60 mmHg $PtiO_2$ was < 10mmHg in only 11.3 % of MT. For a CPP > 60 mmHg the likelihood of $PtiO_2$ being < 10 mmHg was still 0.12.
Conclusion Randomly picked critical ICP and CPP values do not always predict a low $PtiO_2$. CPP values above 60 or 70 mmHg, conversely, do not always guarantee adequate $PtiO_2$. These findings expand our previous reports and show that $PtiO_2$ monitoring provides critical and unique information about the status of the brain that cannot be derived from other monitoring parameters such as ICP and CPP. The role of arterial hypoxia, anemia, hyperventilation and vasospasm in causing cerebral hypoxia is currently under investigation.

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DYNAMIC MEASUREMENT OF ICP DURING CRANIOTOMY.

Cold GE, Bundgaard H.
Department of Neuroanaesthesia, Aarhus University Hospital, Aarhus, DK-8000 , Denmark.

Introduction
During craniotomy opening of dura occasionally may be followed by herniation of cerebral tissue. In some patients this process is self-limiting, where decompression (suction of CSF) balances the development of brain herniation. In other patients herniation develops so rapidly that ischemia of cerebral tissue develops. To our knowledge studies of dynamic regional ICP measurement during the opening of dura are not available.
The aim of this study was to measure the regional ICP during the opening of dura.

Material and method
In 21 patients with supratentorial cerebral tumor, subdural ICP was measured continuously 2 min before opening of the dura and 3-5 min after opening. The technique has recently been described (1). Subdural pressure was measured in a distance of about 1 cm from the dural incision.

Results
In 8 patients with median ICP 6 mmHg (range 2-9 mmHg) herniation never occurred. Opening of dura was followed by a rapid decrease in ICP over 2-3 min. In 9 patients with median ICP 10 mmHg (range 8-17 mmHg), cerebral swelling was observed but cerebral herniation did not occur. In these patients ICP decreased slowly, but steadily over 3-5 min. In 4 patients with median ICP 16 mmHg (range 12-32 mmHg) severe herniation developed. An initial decrease in ICP after opening of dura was followed by a secondary increase occurring 2-3 min after the opening. In these patients cerebral herniation was only controlled by evacuation of cerebral tissue.

Conclusion
Risk of cerebral herniation is ICP dependant. Severe cerebral herniation was only observed at ICP > 12 mmHg. In these patients a secondary ICP increase was observed after opening of dura, suggesting venous congestion of cerebral tissue.

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WAVEFORM PREDICTORS: ADVERSE RESPONSE TO NURSING CARE

P.H. Mitchell, C. Kirkness, R. Burr, K.S. March, D. W. Newell. Departments of Biobehavioral Nursing & Health Systems, Psychosocial and Community Health, and Neurosurgery, University of Washington, Seattle WA, USA (Funded by the National Institutes of Health, RO3 NR03386)

Introduction A subset of patients being treated for actual or potential intracranial hypertension respond to care procedures, such as being turned or suctioned, with sharp and sustained increases in ICP that threaten cerebral perfusion pressure (CPP), threatening secondary injury in the already insulted brain. While elevated P_2 of the ICP waveform (ICPWF) has been suggested to reflect altered compliance and thus to predict these adverse responses,[1] transcranial doppler ultrasonography (TCDU) and ICP waveform analysis have not been examined simultaneously for their ability to predict this subset of patients and their outcomes. **Methods**. ICP, ABP, CPP and TCDU recordings of middle cerebral artery blood flow velocity (MCBFV) were simultaneously and continuously monitored for one hour in 37 critically ill persons with traumatic brain injury, SAH, tumor and aneurysm repair. Disproportionate increases in ICP (DIICP), defined as ICP increases >10 mm Hg above baseline for > 5 minutes, were counted from 24 hour trend recordings. Autoregulatory index (ARI) was derived from rate of return analyses of MABP and CBFV data with spontaneous blood pressure changes.[2] Spectral properties of ICP and ABP waveforms were characterized by fast fourier transform, with Karhunen-Loeve (K-L) expansion; joint spectral properties were described by the coherence function.. Outcome at hospital discharge was categorized by the Glasgow Outcome Scale (GOS). **Results**. Incidence of DIICP, abnormal ARI or elevated P_2 ICPWF did not differ by diagnostic category. Elevated P_2 ICPWF was predictive of increased frequency of DIICP (Odds Ratio 7.2, sensitivity 99%, specificity 20%, PPV 75%).Patients accounting for the low specificity of the elevated P2 predictor had significantly lower frequency of DIICP as well as significantly lower mean ICP, ICP amplitude, greater low frequency spectral mean, greater high frequency centroid (HFC), and greater coherence at low frequency than those with more DIICP. K-L ICPWF factors representing level, amplitude of P_{1-3} accounted for 30% of the variance in DIICP. DIICP frequency was moderately related to GOS (r= -.33), with ICP HFC, low frequency spectral mean, and mean ICP explaining 56% of the variance in GOS. 79% of the sample had abnormally low or high ARI, but this index did not predict either DIICP frequency or discharge outcome. **Summary and Conclusions**. Elevated P_2 ICPWF is easily determined visually. It was validated as a rough estimate of patient risk for care-related ICP increases sufficient to compromise CPP, and was related to discharge outcome. "Normal" ICP values in a substantial percent of patient who had abnormal waveforms and increased frequency of DIICP suggests clinicians should not rely on low ICP values as evidence of low risk for untoward responses. Although abnormal ARI did not distinguish those with low frequency DIICP or poorer outcome, several indices derived from ICP and ABP spectra did, including pattern recognition techniques not previously reported. Further study is indicated to determine if protection from these care induced episodes of DIICP alters longer term outcome. **References**: 1. Cardoso ER, Rowan JO, Galbraith S. J Neurosurg. 59: 817-821, 1983. 2. Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard KF. Stroke 22: 1148-1154, 1991.

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COMPREHENSIVE ASSESSEMENT OF CEREBRAL CO2 REACTIVITY IN SEVERE HEAD INJURY.

A. Ter Minassian, E. Melon, C. Le Guerinel, F. Bonnet, M. Ursino, L. Beydon. Surgical Intensive Care Unit & Dept of Neurosurgery. H. Mondor Hospital. Créteil, France. Dept of biomathematics University of Bologna, Italy.

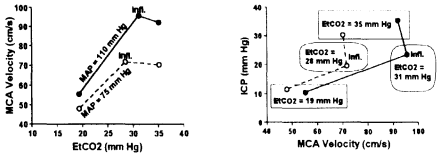
Introduction

Altering CO_2 allows modulation of both cerebral blood flow (CBF) and ICP. By optimizing cerebral vascular resistance (CVR) one should avoid either an excessive CBF reduction or a rise in cerebral blood volume which would increase ICP. The ICP/CBF relationship is expected to be non-linear. Moreover, mean arterial pressure (MAP) is a major determinant of CBF reactivity to CO_2. The aim of this study was to systematically assess the interdependence between ICP, CBF and MAP during primitive variation of CVR in order to characterize some inflection points of the specific ICP/CBF relationship which may have physiopathological significance.

Material and Methods

We studied 14 head injured patients (GCS<8). We simultaneously recorded MAP, ICP, middle cerebral artery blood velocity (MCAV) during standardized CO_2 rebreathing at two steady levels of MAP (using Norepinephrine). We assessed the inflection point (Infl.) on continuous recording during CO_2 rebreathing as the point at which maximal MCAV was achieved.

Results



Left figure: increasing CO_2 leads to a plateau level of MCAV starting at Infl. Increasing MAP increases MCAV reactivity to CO_2 before Infl. ($p<0.05$) and Infl. Is reached at higher end-tidal CO_2 ($EtCO_2$) ($p<0.05$). *Right figure:* ICP at Infl. is higher at high MAP ($p=0.05$). After Infl. increasing $EtCO_2$ leads to a significant rise in ICP ($p<0.05$) without change in MCAV. Maximal ICP reached at the same $EtCO_2$ is higher at high MAP ($p=0.01$).

Summary and conclusions

After Infl., CO_2 induced decrease in CVR is compensated by a decrease in CPP

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RELATION OF INTRACRANIAL PRESSURE FLUCTUATIONS AND BRAIN BLOOD VOLUME

Yuri Moskalenko, Boris Gaidar, Tomara Kravchenko, Gustav Weinstein.

Sechenov Institute of Evolutionary Physiolology and Biochemistry, Russiar Academy of Sciences; M.Thorez pr. 44, Sankt-Petersburg 194223, Russia

Introduction

Within the cranio-spinal cavity ICP, CSF volume, and blood volume are interrelated. Changes in these parameters initiate regulatory responses in brain blood vessels that are important for maintenance of cerebral blood flow. The objective of the present study to evaluate fluctuations in ICP and BBV in relation to cerebral circulation.

Methods

Subjects were 12 cats anesthesthetized with urethane 1g/kg and 8 patients after intracranial surgery. Changes of BBV were measured by a high frequency (60kHz) electrical impedance method and ICP by pressure transducers; conditions were resting states and during specially selected functional tests, directed to change BBV or ICP (1). Data were analyzed by mathematical modeling (2).

Results

ICP and BBV were closely correlated. (R^2=0.8-0.9) at rest and during functional tests. CSF volume changes were always reciprocal to BBV. Regional redistributions of CSF and BBV were rapid (within 2s), while redistributions of CSF between cranial and and spinal cavities were slower (longer than 5s). Mathematical modeling of data indicated that in addition to main perfusion pressure, about 30% of energy for maintance CBF is a result of transforming brain arterial pulsation to venous outflow by ICP changes. Slow ICP fluctuations with compensating adaptative reactions occurred practically without energy losses.

Summary and Conclusion

Close correlation between ICP and BBV is a basis for an important role of ICP fluctuations in process of maintance of optimal level of cerebral circulation under different living conditions.

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MULTIMODAL MONITORING OF REFRACTORY INTRACRANIAL HYPERTENSION

John D. Pickard, Marek Czosnyka, Peter Kirkpatrick

MRC Cambridge Centre for Brain Repair and Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, UK

Introduction : Measures to manage refractory intracranial hypertension are limited. Consensus classification of refractory hypertension is lack of response to classical attempts (CSF drainage, anaesthesia, hyperventilation, osmotherapy) to reduce ICP increasing above 40 mmHg over a period longer than 3 hours. High dosage barbiturate is nonproven . Decompressive surgery may induce local herniation, when ICP is already grossly elevated but has a role. Methods of monitoring of cerebral dynamics to anticipate terminal ICP rises would be helpful.

Methods: Our own experience is based on continuous multi-modal monitoring of 200 consecutive patients suffering from head injury. 18 deaths were associated with severe intracranial hypertension.

Results: Computer supported data analysis demonstrated examples of deranged cerebrovascular pressure responses seen when cerebral perfusion pressure was declining below 50 mmHg. A positive association of slow waves in arterial pressure and ICP and also pressure-passive behaviour of transcranial Doppler waveform have been selected as particularly useful for anticipating death from severe intracranial hypertension by several hours. Also derangement of relationship between pulse amplitude of ICP and mean ICP level was found to be a good predictor of fatal termination. Impending intracranial hypertension should normally be accompanied by a rise in pulse amplitude of ICP. Where the increase in ICP (>30 mmHg) is associated with a distorted amplitude-pressure relationship the critical threshold of intracranial hypertension has been reached with limited time for large decompressive craniotomy to reduce ICP.

Conclusion: Multimodal monitoring supported by computer on-line data analysis may be useful for anticipating terminal rises in ICP.

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ENDOTOXIN FEVER AND INTRACRANIAL PRESSURE

Terrance J. Malkinson, Roland N. Auer and Quentin J. Pittman

Faculty of Medicine, The University of Calgary. Calgary, Canada. T2N 4N1

Previously we introduced the hypothesis of vasopressin's involvement in limiting or reducing intracranial pressure during experimentally induced fever (1). We have now investigated further this question. Adult (290-300 gm) male Sprague-Dawley rats were anesthetized with urethane (1.5 gm/kg). With this preparation the thermoregulatory inter-threshold range is widened. The animals body temperature can however be stabilized for long periods of time by providing a constant supply of external heat to the animal via an electrically heated pad and a fever will result following administration of pyrogenic agents (2,3). Results represent the mean ±SEM from groups of 12 animals each. 50 ug/kg of *Escherichia coli* endotoxin i.p. was selected from a febrile dose-response relationship. This produced a biphasic fever rising from a baseline of 36.83±0.10°C to a first peak of 37.54±0.16°C at 160 min to a second peak of 37.73±0.18°C after 340 min. Carotid mean arterial blood pressure significantly increased from a baseline of 85.3±2.4 mm/Hg to a peak of 97.8±2.8 mm/Hg after 120 min. Heart rate increased from a baseline of 367±8.7 beats/min to a first peak of 405±12.12 beats/min after 120 min to a second peak of 420±9.8 beats/minute after 340 min. Vasoconstriction and vasodilatation occurred at appropriate phases of the fever. Central venous pressure recorded in the superior vena cava increased slightly during the "chill" phase of the fever as did the venous pulsation pressure amplitude. A significant increase in intracranial pressure measured from the subarachnoid space from a baseline of 44.2 ±4.04 mm/saline to a peak of 59.9±4.90 mm/saline occurred only during the initial period of the first "chill" phase of the fever. Investigations in our laboratory have shown a release of vasopressin into brain tissue during experimentally induced fever. AVP has been implicated in the regulation of ICP. The bolus administration of AVP (0.1 ug) into the LCV of intracranially hypertensive (68.8±7.04 mm/saline) rats significantly reduced ICP to 54.6±6.7mm/saline. This suggests that in addition to it's proven action as an antipyretic modulator limiting the increase of body temperature during fever that it may also act as a protective mechanism to reduce or limit increasing ICP which occurs during fever. These results were all significantly different $p<0.05$ from control experiments. Experiments are currently in progress which will extend this work to the complex relationship of intracranial hypertension, elevated body temperature, and vasopressin during experimentally induced cerebral ischemia.

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INTRACRANIAL PRESSURE FLUCTUATIONS AND SKULL BONE MOTIONS.

Yuri Moskalenko, Boris Gaidar, Tomara Kravchenko

Institute of Evolutionary Physiology and Biochemistry,. Russian Academy of Sciences, M.Thorez pr. 44, Sankt-Petersburg 194223, Russia.

Introduction

The recognition of periodic motions of human skull bones, correlated with slow fluctuations of ICP, is important for understanding of mechanisms of relationships between volumes and pressures of blood and CSF in the closed cranio-spinal cavity. Presence of skull bone motions is based on some experimental observations and on personal experience of specialists in osteopathic medicine (1,2). The objective of the present study to demonstrate the presence of continuous periodic fluctuations of human skull bones, similar to ICP fluctuations, with X-Ray and MRI images analyzed by modern computer technique.

Method

Serial MRI and X-Ray images of human skull were taken from 12 patients 20-43 years old, who were indicated for routine MRI scanning or angiography. Both X-Ray and MRI pictures were taken during 60s with 2-5 frames per second in resting conditions; 8 recordings were taken during angiographic procedures. Image analysis was performed on Macintosh IIsi running NIH Image 1.49 software. ICP fluctuations were monitored by intracranial implanted miniature pressure transducer in 6 patients afterintracranial surgery.

Results

Serial images from both MRI and X-Ray demonstrated periodic fluctuations of human skull bones with amplitude 250 - 400μm and maximal changes up to 1mm. Frequency ranges (0.2-0.6Hz) and pattern of these fluctuations were similar to ICP fluctuations. During angiographic procedure, which is accompanied by moderate transient (1-3s) increase of ICP, skull size increased also with peak up to 1 mm during this time period.

Summary and Conclusions

Periodic human skull motions were monitored by serial MRI or X-Ray methods and computer-aided image analysis. We interpret the covariation of ICP fluctuations and bone movements as initiated by the ICP fluctuations.

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SOME QUESTIONS OF BRAIN SWELLING PATHOGENESIS

Svadovsky A.I.
Department of Neurosurgery, Institute of Neurology, Moscow, Russia.

Introduction

Well known from the literature about one of the specific form of head injury - brain swelling (BS) in your patients. This pathology as considered connect with increasing cerebral blood flow (CBF) because of cerebral vesels dilatation (vasoparalysis) and hyperemia. Therefore, many questions of the pathogenesis of this form are not well understood.
Aim of investigation. Study CT picture of BS in dynamics in compare with dynamical changes lipid peroxidation (LP) in a blood and consciousness level.

Material and Methods

We analysed 8 patients with BS after sever head in jury. Age 2-18 years old.3 patients were woman and 5 - men. Time of admissions first 1-3 days after trauma. GCS was 4-7. Malone dyaldehyde (MDA) one of the stable end product of the LP was investigate in all patients but not less 3 times in periferical venous blood. We also study LP patterns in patientss with focal head injury (6 patients) as control group. Age was 10-18.

Results

Maximal values of MDA in blood in acute period trauma accompanied by the pick CT picture of BS and bilateral slite ventricle syndrom. All patients in this were in comatose status. Then, in dynamics we seen parallel picture dilatation the size of ventricular system on the CT significant decrease MDA level in blood and restoration consciousness level till GCS 8 - 10 Another patterns observed in patients with focal injury (brain contusions) as in absolute values as in dynamics.

Conclusions.

1. Reason of high level MDA in the blood in patients with BS is disturbances the brain metabolism during vasodilatation and hyperemia.
2. Systemic changes in blood such as a high level MDA in BS not reflect focal brain destruction of the paranchima but discirculation cerebral blood flow and brain parenchima disfunction after head injury.

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In vivo function of the PS Medical Delta valve

Bo Lundqvist[1], Anders Eklund[2], Bo Kristensen[1], Lars Ove Koskinen[3], Markku Fagerlund[4], Jan Malm[1].

Departments of Neurology[1], Biomedical engineering[2], Neurosurgery[3] and Radiology[4], University Hosptial, S-901 85 Umeå, SWEDEN.

Introduction: shunt dysfunction is of major concern in patients with idiopathic adult hydrocephalus syndrome (IAHS). Using a CSF infusion technique, it is possible to assess whether CSF dynamics have been normalized postoperatively together with the properties of the shunt system, including the degree of gravity induced CSF flow. The objective of this prospective study, was to compare the in vivo function of a traditional differential pressure device (Cordis Hakim valve) with a standard shunt with a "modified" antisiphon device (PS Medical Delta valve).

Subjects and methods: eight IHAS patients had recieved a PS Medical Delta valve in September 1996. Clinical testing, MRI and a CSF infusion investigation were performed before surgery and three respectively twelve months after shunt placement. CSF pressure pre- and postoperatively, gravity effect and a pressure-flow curve of the shunt were estimated. 28 patients with a Cordis Hakim valve were used as controls[1]. The following conversion factor is given: 1 kPa = 7.5 mmHg.

Results: seven patients have passed through the three month follow-up. Six were clincial improved. No shunts have been revised. In patients with the Delta valve, the mean CSF pressure preoperatively was 2.2 kPa (95% CI 1.8-2.6). At follow-up, the corresponding CSF pressure was 1.9 kPa (95% CI 1.6-2.3) and 1.8 kPa (95% CI 1.4-2.1) after sitting for 10 minutes. The hydrostatic effect was more pronounced in patients with a Hakim valve compared to Delta shunts (0.6 kPa (95% CI 0.5-0.7) vs 0.2 kPa (95% CI 0-0.3). The Delta valve patient who exhibited the most pronounced gravity effect developed a subdural haemorrhage nine months after the operation. According to the postoperative pressure-flow curves, one shunt did not function properly.

Conclusions: preliminary results indicated that most of the Delta valves do behave according to the specifications provided by the manufacturer. The gravity effect was significantly lower compared to the Hakim shunt. However, there may be a risk of overdrainage in spite of the siphon control mechanism.

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Analysis of hearing loss after shunting for normal pressure hydrocephalus

E Delwel, M van Veelen, R Teeuw, E Kurt, D de Jong, M Brocaar, B Pauw, C Avezaat, G van Zanten

We decided to analyse hearing in shunt-treated patients with Normal Pressure Hydrocephalus (NPH) after complaints about their hearing, postoperatively. An effect of shunting on hearing may be expected as the cerebrospinal fluid system can affect cochlear physiology.
Sixteen patients with the classical triad of NPH and hydrocephalus on CT were treated with a shunt. Hearing was assessed by pure tone audiometry before operation, 3 days, 1, 6 and 12 weeks after operation. We only analysed bone conduction because air conduction may be influenced by intubation and consequent temporary eustachian tube dysfunction. Audiometry showed a preoperative hearing loss in most of the patients in the higher frequencies, due to presbyacusis. At frequencies of 1000Hz and higher we did not see significant postoperative hearing losses, and therefore decided to analyse hearing only at 250Hz and 500Hz. We also measured transient evoked oto-acoustic emissions (TE OAE). We discarded the results because we obtained emissions only in 8 of 32 tested ears. This low yield is due to the high incidence of preoperative hearing loss.
Fourteen of 16 patients had a postoperative increased hearing loss of more than 10dB, 7 of them in both ears and for both frequencies, 3 in one ear for both frequencies and 4 in one ear for one frequency. Only two patients did not suffer from any additional postoperative hearing loss. Remarkably, 54% of all affected ears recovered partially or completely after 6 to 12 weeks. The ears that did not recover showed a mean loss of 25dB (range 20-35dB). The incidence of hearing loss after shunting was higher in patients who had a low pressure valve implanted, subdural effusions on follow-up CT scans or clinical improvement in the first week after shunting. Therefore, there seems to be a relationship between the rate of drainage and the extent of hearing loss.
The etiology of this hearing loss after shunting and its recovery in 6-12 weeks remains hypothetical. It is known that a balance exists between the pressure in the perilymphatic and endolymphatic space in the cochlea as well as mechanisms to maintain this balance. If the cochlear aquaduct is patent, an intracranial pressure drop will be conducted to the perilymphatic space, consequently causing overpressure in the endolymphatic space with subsequent dysfunction of the basilar membrane and hearing loss. Recovery of the hearing loss may then be owed to the usual mechanisms involved in maintaining or restoring the pressure balance in the cochlea. Persistant hearing loss could be explained by irreversible damage to the basilar membrane duc to severe pressure drops or fluctuating intracranial pressure, as in effusions or drain dysfunction, thereby preventing restoration of the pressure balance in the inner ear.

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Quantitative Measurement of CSF Flow Velocity in the Aqueduct using MRI --- Experimental Study and Clinical Application

Departments of Neurosurgery and *Radiology, Nagoya City University Medical School, Nagoya, Japan

Mitsuhito Mase, *Tatsuo Banno, Kazuo Yamada, *Toshiaki Miyachi, Shigeki Ohara and Takashi Matsumoto

Background and Purpose

Several authors reported cerebrospinal fluid (CSF) flow velocity measured using MRI in the aqueduct in normal volunteers, but the values were widely different between the papers (1,2,3). To establish the reliability of the CSF flow study by MRI and clarify the exact flow velocity, we made a model of CSF flow in the aqueduct and measured the velocity by electromagnetic flow-metry and cine MRI simultaneously and compared them.

Materials and Methods

CSF flow in the aqueduct consists of to-and-fro flow by brain pulsation and bulk flow by CSF production. The flow pattern was simulated by the flow of lactate Ringer's solution generated by a pulsatile flow pump and a continuous flow pump in a phantom. The flow velocity was measured by electromagnetic flow-metry and cine MRI simultaneously. On a 1.5T MR system (Philips ACS II), the quantitative flow data were obtained from two-dimensional phase contrast images with retrospective cardiac triggering techniques. This sequence was used with parameters of 20-23 / 12-15 msec (TR / TE), flip angle of 20 degrees. Velocity encoding gradient was set to 5-20 cm/sec in parallel with the aqueduct. We also applied this MRI technique for healthy volunteers and patient with various intracranial pathologies.

Results

The flow velocity by electromagnetic flow-metry corresponded to the velocity by cine MRI completely within a range of the velocity from 0 to 20 cm/sec in the phantom . The volunteers were divided into 3 groups ; young (≤39 y.o., n=9), middle (≥40, ≤59, n=4), and old (≥60, n=6) groups. The maximum CSF flow velocity (Vmax) in the aqueduct in the young, middle, and old groups were 4.97±1.51, 4.26±1.80 and 6.39±1.78 (cm/sec,mean±SD), respectively. Hypercapnia increased the Vmax and hypocapnia reduced it. In NPH patients, the Vmax became smaller after the shunt operations.

Conclusion

CSF flow study using MRI in our methods is useful to estimate the intracranial CSF flow dynamics, which is quantitatively reliable and accurate. There was no age-dependent difference of the maximum CSF flow velocity in the aqueduct.

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THE INTRATHECAL INFUSION TEST AS AN INVESTIGATIVE METHOD IN NORMAL PRESSURE HYDROCEPHALUS: - WHEN SHOULD A SHUNT BE INSERTED ?

Frank Stefan Zeilinger; Ullrich Meier, Dieter Kintzel.

Department of Neurosurgery, Hospital Berlin-Friedrichshain, Germany

Introduction

Normal pressure hydrocephalus (NPH) should be diagnosed at the early stages when therapy is likely to be successful.

Method

We investigated 150 patients suspected for a NPH during a period of 13 years. In 111 patients we used the lumbar and in 56 patients the ventricular infusion test in constant-flow-technique.

Results

In 81 patients (54%) the diagnosis of a NPH could be confirmed; 78 patients (96%) unterwent a shunt-operation. A graduation of the NPH after the results of the infusion test into an early and late stage allows to make a prognostic evaluation of the course of disease. Patients with a NPH in early stage are reporting in the follow up about an improvement of their symptoms after shunt operation in 60 percent and those with late stage NPH in 50 percent.

Conclusion

While presenting the pressure dependent resistance to outflow R (p) we could obtain more informations in comparison with the international used method which provides only one resistance value per infusion test. The computer assisted infusion test enables a definite differentiation between patients suffering from a normal pressure hydrocephalus and those with a cererbal atrophy.

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The temporal profile of intracranial pressure and clinical changes in relation to lumbar spinal tap test in patients with normal pressure hydrocephalus.

M. Tisell*, H. Stephensen*, M. Tullberg** E. Blomsterwall** and C. Wikkelsö**.
Institute of Clinical Neuroscience, Department of Neurosurgery* and Neurology**, Sahlgrenska University Hospital, Göteborg, Sweden.

Introduction: It is well established that patients with normal pressure hydrocepalus(NPH) improve temporarly after a lumbar spinal tap. The relationship to changes in ICP is however unknown. To investigate this we measuared the changes in ICP, pulse pressure amplitude and the clinical response to a spinal tap of 50cc CSF.

Material and methods: Thirteen paitents with NPH were included. The ICP was measured simultaneously in the right lateral ventricle (ICP**iv**) and in the subarachnoidal space over the cerebral convexity (ICP**sub**), using microsensor ICP transducers (MicroSensor™ Codman). The study was appproved by the local ethical committee and informed consent was obtained from the patients and their relatives. The sensors were inserted in general anaesthesia through a right sided frontal burr hole near the coronal suture. The following morning a spinal tap of 50cc was performed. Prior to and one, two and three hours after the tap the patients were tested using reaction time test, figure identification test and finger and arm motoric tests. All patients could not perform all tests due to their clinical condition. All ICP measurements refers to the actual testing situation with the patient in sitting position.

Results: The ICP was lowest one hour after the tap nearly reaching pretap level after three hours. The changes in ICP**iv** and ICP**sub** were parallel and subsequently, the transmantle pressure didnt change. The pulse pressure amplitude was identical in both compartments and was lowest after one hour.
Two patients were excluded from the clinical tests. One had convulsions after the tap and one could not cooperate at all. Of the remaining eleven patients the first five did not improve as expected (although some of them had shown improvement after previous spinal taps). The reasons seemed to be lack of sleep and suboptimal test conditions. After improving the test protocol the next six patients all showed improvements The greatest improvements were seen after three hours.

Conclusion: In all patients the ICP and pulse pressure amplitude reached theirs minimum values directly after the tap. In the last six patients where we observed clinical improvment, it reached its maximum after three hours. We can not show that the clinical performance is directly linked to either the ICP, pulse amplitude or transmantle pressure. Some changes in the cerebral functions are mediated by the lumbar tap but the clinical response is postponed and culminates after three hours in spite of steadily rising ICP and pressure amplitude.

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PERSONAL EXPERIENCE IN NORMAL-PRESSURE HYDROCEPHALUS (NPH) SYNDROME

Osamu Hirai, MD.

Department of Neurosurgery, Shinko Hospital, Kobe, Japan.

INTRODUCTION

Over a 15-year period, 63 cases with NPH were treated by CSF shunting. Among them, clinical factors affecting surgical outcome were reviewed.

MATERIALS AND METHODS

Etiology was unknown in 18 cases (idiopathic NPH), 30 cases wee secondary to aneurysmal subarachnoid hemorrhage (post-SAH NPH) and 15 cases developed after head trauma or brain tumor surgery (secondary NPH). Continuous CSF pressure monitoring, single photon emission computed tomography (SPECT) and cisternography were carried out as diagnostic tests.

RESULTS

Marked improvement was obtained in 25 patients (39.7%), slight improvement was seen in 21 patients (33.3%), and 17 patients (30.0%) did not benefit from shunting. Later deterioration without shunt malfunction was noted in 10 patients in idiopathic NPH, 6 patients with secondary NPH, while only 4 patients with post-SAH NPH showed slight decrease in activity during follow-up period. Favorable factors in idiopathic NPH were some elevation in CSF pressure and frontal dominant slight reduction of CBF on SPECT. Unfavorable factors in post-SAH and secondary NPH were profound neurological deficit lasting after brain pathology, and abnormal CT or MRI findings suggestive of parenchymal damage.

CONCLUSION

Diagnostic tests were important for idiopathic NPH to predict favorable shunt response, however lasting improvement would not be anticipated. Shunting will be effective for post-SAH NPH unless severe brain damage had not occurred. Generally speaking, CSF shunting is not indicated for secondary NPH where ventricular dilatation is not significant factor than in other etiologies. Based on the results, our recent option of treatment is to be reported.

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THE IMPORTANCE OF XENON-COMPUTED-TOMOGRAPHY IN THE DIAGNOSIS OF NORMAL PRESSURE HYDROCEPHALUS.

Ullrich Meier*, Bernd Reichmuth**, Frank Stefan Zeilinger*.

Department of Neurosurgery, Hospital Berlin-Friedrichshain*, Practice of Neuroradiology Berlin-Köpenick**, Germany.

Introduction
Patients with normal pressure hydrocephalus (NPH) exhibit disturbances of regional cerebral blood flow (rCBF). This report describes the different features of cerebral autoregulation at different stages in the course of NPH in contrast to atrophy.

Method
In 35 patients with possible NPH, the regional cerebral blood flow was investigated by xenon computed tomography (Xenon-CT) before and during a standardized intrathecal infusion test with constant flow technique.

Results
Xenon inhalation alone increases the intracranial pressure (ICP) an average of 3 mm Hg. This investigation documents that patients in different stages of NPH, and of atrophy, exhibit different responses of rCBF when challenged with additional, larger increases in ICP, deliberately induced by intrathecal infusion of mock cerebrospinal fluid (CBF) during the standardized infusion test.

Conclusion
These results suggest the hypothesis that disturbance of cerebral autoregulation and ischemic processes are important in the pathogenesis of NPH. Examination of CSF dynamics is essential for the diagnosis and staging of patients with possible NPH.

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Bench-Test of 383 Hydrocephalus Valves

A. Aschoff, P. Kremer, B. Hashemu, C. Schulte and St. Kunze

University of Heidelberg, Department of Neurosurgery, Germany

Shunts should keep the ICP in the physiological ranges unaffected by body position, subcutaneous pressure, vasogenic intracranial volume changes or crying babies. In addition they should be reflux-safe, durable for 20 years, optimum biocompatible and able, to restore potentially a shunt-independence step-by-step.
Material: We have tested in vitro 52 difference valve constructions, of them 238 new and 145 explanted probes (max. 21 years). The accuracy was measured conform to ASTM/ISO, in 146 specimen repeatedly during non- stop tests up to one year. Max 35 sub-tests were dedicated to the hysteresis, flow dependent on pressure, reflux, susceptibility to external fluid pressure, vectorial forces, flection (e.g. on curved head), temperature, CSF-protein (500 mg/ml), air bubbles, pulsations, pumping manoeuvre and sterilization. "Programmable" valves were exposed to common magnetic fields, MRI (1.0 - 4.0 T.) and test of the adjustment (linearity, tolerance of decentration). Gravitational valves were checked varying the angle of verticalization and simulating common body movements.
Results: Only 36% of all valves met to specifications of the producer (± 20 mm H_2O). 24% showed deviations of ± 21-50 mmH_2O, 15% of ± 51-80 mm H_2O and 15% of ± 81-135 mmH_2O . 13% had massive failures up to 1446 mm H_2O. Ball valves were superior with 61% good and 21% fair results. After 90 days driftet 72%, after 365 days 89%. 32% of the valves were not reflux-safe, 29% irritable by external fluid pressure (e.g. 30 mmHg increased the resistance up to 3000%!), 50 % susceptible to vectorial forces and 56% to flections, common on an infant's head. - In upright body position 81% showed overdrainage (>100 ml/h),9% had an insufficient flow (<15 ml/h). A few valves only offered physiological flow-rates in horizontal *and* upright position, but most of them had problems either with safety. The optimum for adults were gravitational valves combined with ball valves (± adjustable) and low-flow catheters (ø 0.8 mm).
Conclusion: 1. The vast majority of valves showed deficits in accuracy, long-term stability, safety and adequate flow-rates either in upright or in horizontal position. 2. The ASTM- test and analoga are too short, ignore potential disturbing factors, and include failures of the test methods. 3. The evident clinical success in 80% of cases in spite of a poor shunt technology may be caused by the enormous adaptability of the patients, not by the valves. 4. Intelligent shunts are not a "Mission Impossible".

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EFFECT OF ACUTE AQUEDUCTAL BLOCKAGE ON INTRACRANIAL PRESSURE AND DEVELOPMENT OF HYDROCEPHALUS IN CATS

Marijan Klarica, Miroslav Vukić[1], Boris Božić[1], Darko Orešković[2], Vladimir Butković[3], Branko Miše, Marin Bulat

Department of Pharmacology, Medical Faculty, [1]Department of Neurosurgery, University Hospital "Sisters of Mercy", [2]Institute "Ruđer Bošković", [3]School of Veterinary Medicine, Zagreb, Croatia

Introduction
It is generally assumed that obstruction of aqueduct of Sylvius leads to acute increase of CSF pressure and dilatation of brain ventricles (acute obstructive hydrocephalus). We wanted to test this hypothesis in our new experimental model in cats.

Methods
Blockage of aqueduct was performed by implatation of plastic cannula in aqueduct of Sylvius through the small tunnel in vermis of the cerebellum in chloralose anesthetized cats. After reconstitution of occipital bone CSF pressure was measured both in lateral venricle and cisterna magna. In additional experiments changes of brain ventricles size were monitored by radiography.

Results
CSF pressure in lateral ventricle gradually increased from control value of 8.7 ± 0.4 cm H_2O to 12.2 ± 1.7 cm H_2O (n=11) during two hours of aqueductal obstruction. However, development of pressure gradient between lateral ventricles and cisterna magna was not observed. Ventriculograms in 5 cats did not disclose dilatation of ventricles two hours after blockage of aqueduct except a slight enlargement of body and temporal horn of lateral ventricle in one cat.

Summary and Conclusions
This results suggests that acute blockage of aqueduct of Sylvius durnig two hours does not produce either intracranial hypertension or significant ventricular dilatation. According to our chronic experiments (1) it seems that impairement of systolic-diastolic to-and-fro displacemets of CSF along aqueduct can lead to ischemia and damage of brain parenchyma and development of hydrocephalus. Thus, we suggest that more than two hours of aqueductal obstruction is needed for manifestation of such damage and development of hydrocephalus.

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Index of Keywords

H. E. James, L. F. Marshall, H.J. Reulen, A. Baethmann, A. Marmarou,
U. Ito, J. T. Hoff, T. Kuroiwa, Z. Czernicki (eds.)

Brain Edema X

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This volume is a selection of papers presented at the Tenth International Symposium on Brain Edema. As in previous volumes, brain edema and disturbances of metabolism arising from acute insults of any etiology, are the central issues of research. The supportive role of biochemically activated mediators, changes in blood-brain barrier, spread of the edema process, always elicit great scientific as well as clinical interest. Therapeutic interventions can only be effectively directed to these problems once the understanding of the underlying biochemical disturbances, disturbances in cerebral perfusion and parallel events, are mastered. This volume presents a comprehensive survey of the present state of the art and gives the directions for further research.

A. Baethmann, O.S. Kempski, N. Plesnila, F. Staub (eds.)

Mechanisms of Secondary Brain Damage in Cerebral Ischemia and Trauma

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The publication is a progress report of the understanding of secondary brain damage from head injury and cerebral ischemia. The spectrum reaches from the molecular- and cell biological level up to the complex issues of clinical management. Specific topics on cerebral ischemia are concerned with apoptosis, inflammation, acidosis, cellular Ca^{2+}-overflow, the role of the stimulatory input for maintenance of functional competence in stroke, effects of brain grafting in infarction, and the current state of glutamate antagonization or reestablishment of cerebral blood flow by thrombolysis, among others.

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