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Neuromonitoring in Brain Injury

Edited by
R. Bullock, A. Marmarou, B. Alessandri, J. Watson

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R. Bullock
Department of Neurosurgery, Medical College of Virginia,
Virginia Commonwealth University Richmond, U.S.A.

A. Marmarou
Department of Neurosurgery, Medical College of Virginia,
Virginia Commonwealth University Richmond, U.S.A.

B. Alessandri
Department of Neurosurgery, Medical College of Virginia,
Virginia Commonwealth University Richmond, U.S.A.

J. Watson
Neurological Surgery, UC Davis Medical Center,
Sacramento, CA, U.S.A.

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Preface

Proceedings of the Second International Conference on Neurochemical Monitoring in the intensive care unit

In this volume, we have compiled a selected series of manuscript generated from the proceedings of the Second International Conference on Neurochemical Monitoring in the Intensive Care Unit. This was held as a satellite symposium at the time of the Tenth International Meeting on Intracranial Pressure held in Williamsburg, Virginia in May 1997.

Since the first such symposium was held in Tokyo in 1994, much progress has been made in the field of neurochemical monitoring for the acutely injured human brain. The development of safe, continuous microdialysis techniques, which are suitable for human use in over several days, coupled with microanalytical methodology such as High Performance Liquid Chromatography and Enzyme-Linked Voltametric methods can generate semi-continuous time profiles of the changes in numerous brain analytes. These include lactate, glucose, pyruvate, excitatory amino acids, structural amino acids, indicators of free radical generation, cytokines, adenosine, and neuroprotective drugs.

More recently, continuous micro-sensors of cerebral oxygen tension have become available, and the proceedings of this conference, and others now clearly document altered patterns of regional oxygen delivery and consumption in acutely brain injured patients.

These research endeavors are now poised to enter a new and exciting phase. Descriptive studies have shown profound, prolonged, and severe abnormalities in many of the analytes measured: the next phase is to determine the effects of therapeutic interventions upon these parameters in order to determine whether we can continuously determine the neurochemical milieu of the brain, and alter it by therapeutic interventions. Therapeutic possibilities include increasing oxygen delivery, augmenting cerebral blood flow, hypothermia (which may modify the rate of substrate consumption), and augmenting delivery of substrates such as lactate and glucose. 'Neuroprotectant' drugs may also alter these biochemical indicators.

About 25 neuro-intensive care units worldwide are now engaged in neurochemical monitoring, and enthusiasms for these techniques is increasing. Already, this field of research has contributed tremendously to our understanding of pathomechanisms in acute human brain damage. It remains to be seen whether these insights can be translated into tangible benefit for patients with acute brain injury in the future.

Ross Bullock
Richmond, VA, USA

Contents

Methodology and Animal Studies

Hillered, L., Persson, L.:
Theory and Practice of Microdialysis – Prospect for Future Clinical Use 3

Hinton, J. P., Hudson, G.:
Unbound Plasma Concentrations May Predict Neuroprotective Brain Concentrations:
A Brain Microdialysis and Pharmacokinetic Study of Enadoline in Rats 7

Kawamata, T., Katayama, Y., Satoh, M., Mori, T., Maeda, T.:
Intraoperative Enzyme-Amperometric Monitoring of Extracellular Glutamate Concentration
with a Dialysis Electrode in Ischemic Human Brain 11

Glutamate and Energy Metabolities in Severe Human Head Injury

Yamamoto, T., Rossi, S., Stiefel, M., Doppenberg, E., Zauner, A., Bullock, R., Marmarou, A.:
CSF and ECF Glutamate Concentrations in Elead Injured Patients 17

Alessandri, B., Doppenberg, E., Bullock, R., Woodward, J., Choi, S., Koura, S., Young, H. F.:
Glucose and Lactate Metabolism after Severe Human Head Injury: Influence of Excitatory
Neurotransmitters and Injury Type 21

Alessandri, B., Doppenberg, E., Zauner, A., Woodward, J., Choi, S., Bullock, R.:
Evidence for Time-Dependent Glutamate-Mediated Glycolysis in Head-Injured Patients:
A Microdialysis Study 25

Ionic Changes in Severe Human Head Injury

Doppenberg, E. M. R., Reinert, M., Zauner, A., Massie, T. S., Bullock, R.:
Determinants of Cerebral Extracellular Potassium After Severe Human Head Injury 31

Goodman, J. C., Valadka, A. B., Gopinath, S. P., Uzura, M., Grossman, R. G., Robertson, C. S.:
Simultaneous Measurement of Cortical Potassium, Calcium, and Magnesium Levels Measured
in Head Injured Patients Using Microdialysis with Ion Chromatography 35

Oxygen, Carbondioxide and pH in Severe Human Head Injury

Charbel, F. T., Hoffman, W. E., Misra, M., Nabhani, T., Ausman, J. I.:
What Does Measurement of Brain Tissue pO_2, pCO_2 & pH Add to Neuromonitoring? 41

Letarte, P. B., Puccio, A. M., Brown, S. D., Marion, D. W.:
Effect of Hypocapnea on CBF and Extracellular Intermediates of Secondary Brain Injury 45

Shiogai, T., Nara, I., Saruta, K., Hara, M., Saito, I.:
Continuous Monitoring of Cerebrospinal Fluid Acid-Base Balance and Oxygen Metabolism in Patients with Severe Head Injury: Pathophysiology and Treatments for Cerebral Acidosis and Ischemia 49

Hutchinson, P. J. A., O'Connell, M. T., Maskell, L. B., Pickard, J. D.:
Monitoring by Subcutaneous Microdialysis in Neurosurgical Intensive Care 57

Multiparametric Systems in Severe Human Head Injury

Mayevsky, A., Doron, A., Meilin, S., Manor, T., Ornstein, E., Ouaknine, G. E.:
Brain Viability and Function Analyzer: Multiparametric Real-Time Monitoring in Neurosurgical Patients . 63

Kushi, H., Moriya, T., Saito, T., Kinoshita, K., Shibuya, T., Hayashi, N.:
Importance of Metabolic Monitoring Systems as an Early Prognostic Indicator in Severe Head Injured Patients 67

Author Index .....

Index of Keywords .....

Listed in Current Contents

Methodology and Animal Studies

Acta Neurochir (1999) [Suppl] 75: 3–6
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Theory and Practice of Microdialysis – Prospect for Future Clinical Use

L. Hillered[1,2] and **L. Persson**[1]

[1] Department of Clinical Chemistry, Uppsala University Hospital, Uppsala, Sweden
[2] Department of Neurosurgery, Uppsala University Hospital, Uppsala, Sweden

Summary

The application of microdialysis for neurochemical monitoring in neurosurgery and neurointensive care is rapidly expanding in a number of clinical centers around the world. In order for microdialysis to become a future routine method in these clinical settings a number of problems, outlined in this communication, must be solved by the clinical researchers and the commercial companies. Regardless of the future success as a routine method, it is already obvious that microdialysis will be an important clinical research tool for years to come, providing new important insights into the pathophysiology of acute human brain injury.

Keywords: Microdialysis; neurochemical monitoring; brain injury.

Introduction

Microdialysis (MD) is currently the most widely used method for sampling of chemical substances from the neuronal microenvironment, i.e. the interstitial fluid of the brain. Over 3600 publications have been published with this technique in basic science. The first reports on the use of this method in the human brain appeared in 1990. These studies employed MD for neurochemical sampling in conjunction with neurosurgical operative procedures [11, 18]. The first reports on the use of MD in epilepsy patients appeared in 1991–1992 [4, 5, 8, 24]. In 1992 the first report on the use of MD for neurochemical monitoring of the human brain in neurointensive care was published [19]. Since then, there has been a remarkable development in the use of MD in many neurosurgical centers around the world. The current number of original papers describing MD in human brain is over 35. A couple of review articles have recently appeared [10, 16, 26].

Prospects for Future Clinical Use

The following discussion will focus on some methodological aspects that appear to be important for the future development and utility of MD as a routine method in clinical neuroscience.

Biochemical Markers

The value of MD for neurochemical monitoring is heavily depending on the availability of biochemical markers that reliably reflect the phenomenon that one wishes to monitor. It should be recalled that MD provides samples from the interstitial fluid of the brain. Therefore, previous knowledge of biochemical markers based on studies in whole brain homogenate, CSF or blood may not be readily applicable for the interpretation of MD data. The interstitial markers thus need validation, sometimes in experimental models before they can be regarded as reliable. Table 1 is a listing of interstitial markers that our group has been focusing on. Additional markers used by other groups comprise potassium as a marker for membrane depolarization and pH for monitoring of lactic acidosis [7, 15]. Many groups have used lactate and glutamate as markers for ischemia and excitotoxicity [3, 9, 11, 13, 19, 22, 25]. Based on the extensive studies in experimental models of CNS injury by numerous investigators we have come to the conclusion that particularly the markers for energy metabolic disturbances (glucose, lactate, pyruvate, hypoxanthine) and excitotoxicity (glutamate) can be regarded as reliable interstitial markers, whereas others such as glycerol, urea

Table 1. *Some Biochemical Markers in Brain Interstitial Fluid*

Energy metabolism	glucose lactate/pyruvate ratio lactate/glucose ratio
Excitotoxicity	hypoxanthine glutamate aspartate
Membrane degradation	glycerol
Oxygen radicals	hypoxanthine, xanthine uric acid and its oxidation products (e.g. allantoin)

Biochemical markers with potential value for clinical use in neurosurgical patients with intracerebral microdialysis. The left column indicates the phenomenon the markers are reflecting.

and allantoin need further validation. For the future we envision that many new markers reflecting clinically important phenomena will emerge based on basic neuroscience research.

Invasiveness

MD is no doubt an invasive technique causing adverse tissue reactions that may influence the measurements and interpretation of the data. The biochemical effects of the implantation trauma is well known from basic studies [2, 23]. The data from clinical studies suggest that the implantation trauma is less of a problem in the human brain with a normalization of dialysate metabolite levels within approximately 30 minutes [11]. The implication of this phenomenon is that the results obtained immediately after implantation must be interpreted cautiously.

Bleeding and infection are other possible adverse effects following implantation. According to the current experience with clinical MD in many centers, discussed at the recent "2nd International Symposium on Clinical Microdialysis" in Uppsala, Sweden (1997) these side-effects do not seem to present much of a problem, although they need to be considered.

What about gliosis? Theoretically, gliosis around the MD probe could cause a diffusion barrier and blunt neuronal chemical responses. To our knowledge there is no hard data on gliosis following MD probe implantation in the human brain available. Our own experience from long-term measurements suggest that there is no general problem with a diffusion barrier occurring at a certain time-point following implantation since we see marked fluctuations in the dialysate levels also several days (up to 11 days) following implantation [12, 19, 21]. Admittedly, more knowledge is required before the importance of gliosis around the MD probe can be determined. Until such data is available, some colleagues prefer to perform short-term measurements, hoping to avoid this problem.

In Vivo Calibration

The relative in vivo recovery of an MD system is defined as the ratio of the dialysate concentration to the interstitial concentration of a certain metabolite [23]. The in vivo recovery is dependent upon several factors including perfusion flow, membrane surface of the probe, the interstitial diffusion characteristics, the interstitial volume fraction, temperature and the turnover rate for the particular substance [2]. The clinically important implication of this dependency is that the in vivo recovery may vary during the course of the disease process in the brain. This may be caused by changes in blood brain barrier permeability, edema formation and intracranial pressure, as well as episodes of secondary ischemia, temperature fluctuations and gliosis. Based on this line of reasoning, two major questions arise: 1) How do we control for variations in blood brain barrier permeability and 2) How do we control for variations of in vivo recovery? Since there is a blood-to-brain gradient for many substances that are being harvested by MD in the brain (e.g. glycerol) it may sometimes be necessary to do parallel measurements of such substances in blood and CSF to exclude the possibility that leakage over an injured barrier is influencing the MD measurements [12].

The problem of controlling for variations of in vivo recovery may in principle be approached in different ways. The available methods for in vivo calibration of MD probes, e.g. the so-called no-net-flux method described by Lönnroth *et al.* [17], is reliable but not suitable for repeated calibrations in the neurointensive care setting. An alternative approach is to use reference compounds, either endogenous (e.g. urea, which is equally distributed in the body fluid compartments) or exogenous compounds administered systemically [14]. Our group has taken the approach to use ratios such as the lactate/pyruvate ratio or the lactate/glucose ratio. This is based on the theoretical assumption that these molecules by being structurally and electrically similar should be equally affected by fluctuations of the interstitial diffusion characteristics and thereby independent of in vivo recovery. By varying the perfusion flow (and thereby the in vivo recovery) in a patient with a stable condition without sings of secondary en-

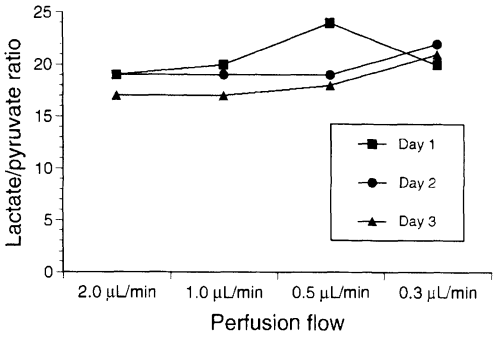

Fig. 1. The effect of changes of in vivo probe recovery on the MD lactate/pyruvate ratio. In a subarachnoid hemorrhage patient with a stable condition and no signs of secondary energy metabolic disturbances or structural changes in the probe region of the frontal lobe, the in vivo probe recovery was varied by stepwise changing the perfusion flow through the probe (allowing a 1 h equilibration without sampling between the changes). This procedure was repeated on three consecutive days. Note the stability of the ratio in spite of a 6.7-fold change in perfusion flow. The lactate/pyruvate ratio in normal brain is thought to be 15–20 [19, 21]

ergy perturbations, we obtained data supporting the notion that the lactate/pyruvate ratio is independent of changes in probe recovery in vivo (Fig. 1; 20).

Standardization

It appears to be of fundamental importance for the future success of clinical MD that data from different centers can be directly compared. To achieve this goal it is highly desired that calibration methods become available allowing repeated or continuous estimation of in vivo probe recovery and thereby estimation of the true interstitial concentration. Until such methods are available, further evaluation of recovery independent measures such as the lactate/pyruvate ratio and the use of endogenous reference compounds are warranted.

Equipment Designed for Clinical Use

Much of the early work with MD in the human brain has been done with equipment originally designed for experimental work but modified and sterilized to allow human use. It is obviously important that new equipment designed for clinical use become available on the market. One of the major advantages with MD is the possibility of high frequency or continuous measurements. A key aspect for the future success of MD in neurointensive care is that optimized bedside or on-line analytical instruments will be available. We have tried two instruments, the YSI 2700 Select (Yellow Springs Instruments Co, Inc, Yellow Springs, OH, USA), measuring glucose and lactate [21], and recently the CMA/600 Analyzer (CMA/Microdialysis AB, Stockholm, Sweden), measuring glucose, lactate, glycerol and urea [12]. Although both devices are accurate and can be used bed-side, they are not yet designed to measure some of the most important markers previously mentioned.

Future Clinical Use in Neurointensive Care

We are currently focusing our efforts on clinical evaluation of the MD method. An important part of this evaluation are feasibility studies. One way of doing this is to measure "time of good quality data acquisition" i.e. for how long is chemical data actually acquired by MD during the clinical course of a patient. Evaluation also includes the definition of a standard set-up of analytes that should be routinely used. Previous research has demonstrated the potential value of the lactate/pyruvate ratio, the lactate/glucose ratio and glutamate; three markers that deserve further evaluation.

The relationship between the MD levels and important clinical events such as neurological deterioration, increased ICP or decreased CPP, desaturations measured by jugular bulb oximetry or brain tissue PO_2, are crucial parts of the clinical evaluation. In this respect the calculation of specificity and sensitivity of the MD markers [6] are necessary for establishing MD for routine use. Comparison of the MD data to clinical outcome such as GOS is also important. Furthermore, we have tried to establish so-called "structural outcome", as a surrogate end point for assessment of the fate of the brain tissue harboring the probe. For this, CT and MR obtained in the late phase after acute brain injury has been used [21].

Finally, since MD is a focal sampling method, it is in many cases important that the tissue at risk of developing secondary injury processes can be defined before probe implantation. In this regard several neuroimaging techniques such as CT, MR and PET [6] may become important tools in combination with MD.

Conclusions

The application of MD for neurochemical monitoring in neurosurgery and neurointensive care is rapidly expanding in a number of clinical centers around the

world. In order for MD to become a routine method in these clinical settings a number of problems, outlined above, must be solved by the clinical researchers and the commercial companies. Regardless of the future success as a routine method, it is already obvious that MD is and will be an important clinical research tool for years to come, providing new important information on the pathophysiology of acute human brain injury.

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Correspondence: Lars Hillered, M.D., Department of Neurosurgery, Uppsala University Hospital, S-751 85 Uppsala, Sweden.

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Unbound Plasma Concentrations May Predict Neuroprotective Brain Concentrations: A Brain Microdialysis and Pharmacokinetic Study of Enadoline in Rats

J. P. Hinton and **G. Hudson**

Department of Pharmacokinetics, Dynamics, and Metabolism, Parke-Davis Pharmaceutical Research, Ann Arbor, MI

Summary

A rat brain microdialysis study of enadoline (CI-977), a k-opioid agonist, was conducted in nonanesthetized healthy rats to determine brain extracellular fluid (ECF) concentrations of CI-977 associated with neuroprotective subcutaneous (SC) doses. Three groups of 3 to 4 nonanesthetized yet restrained Sprague-Dawley rats with jugular cannulas and implanted brain (striatum) microdialysis probes received single SC doses of 0.3, 1.0, or 3.0 mg/kg CI-977. Blood and microdialysate samples were collected over a 12-hour period. Extent of rat plasma protein binding was 77.5%. Unbound plasma concentrations associated with neuroprotection were 10–50 ng eq/mL. At each dose, brain ECF concentration-time profiles (corrected for probe recovery) were nearly coincident with enadoline plasma unbound concentration-time profiles. Consequently, at each dose the ratio of $AUC_{ecf}/AUC_{ffplasma}$, (AUC = Area Under the concentration-time Curve; ffplasma = free fraction in plasma = unbound plasma) which represents the distribution of drug between plasma and brain, was determined to be unity within experimental error. These results suggest that unbound plasma concentrations may predict brain ECF concentrations of CI-977. Further, our findings allow us to postulate enadoline unbound brain ECF concentrations necessary for neuroprotection.

Keywords: Brain microdialysis; enadoline; neuroprotection.

Introduction

Enadoline hydrochloride (CI-977•HCl) is a potent centrally-mediated k-opioid receptor agonist that was originally developed for use as an analgesic in human patients [8, 9]. At present CI-977 is being evaluated as a neuroprotective agent in patients with head trauma.

In preclinical models of ischemia, CI-977 is found to be neuroprotective when administered subcutaneously (SC) or intravenously (IV) to rodents [1, 7, 10] or IV to cats [12] with associated plasma concentrations of 50 to 200 ng eq/mL. CI-977 at SC doses of 0.3 and 1.0 mg/kg administered 30 minutes prior to middle cerebral artery occlusion (MCAO) significantly reduced the volume of ischemic damage within the hemisphere and cortex when compared with control animals in a nonrecovery model of focal cerebral ischemia in rats [7]. Cerebral microdialysis studies in rats and cats further demonstrated that the neuroprotective effects of CI-977 were associated with significant reductions in cerebral ECF glutamate concentrations [6, 13].

Our interest was to obtain quantitative and kinetic information on the brain concentrations of CI-977 associated with glutamate inhibition and neuroprotection. An additional objective was to use this information to postulate brain ECF concentrations of CI-977 necessary to be neuroprotective and thus to guide clinical development.

Materials and Methods

Three groups of 3 to 4 nonanesthetized yet restrained Sprague-Dawley rats (weighing 266–356 g) with jugular cannulas and implanted brain (striatum) microdialysis probes received single SC doses of 0.3, 1.0, or 3.0 mg/kg CI-977. Microdialysis surgery occurred at least 3 days prior to dosing, and jugular cannulas were implanted the day before dosing. On day of dosing, microdialysis probes (CMA/12, 14-mm shaft length, 4-mm membrane length, 0.5-mm membrane diameter, 20,000 dalton molecular weight cutoff, BAS, West Lafayette, Indiana) were then implanted 2 hours before dose administration. The probe was perfused with artificial cerebrospinal fluid (CSF) at 2 μL/min by a syringe pump (Harvard Apparatus, Boston, Massachusetts). Throughout the study, animals were given free access to food and water. Blood and microdialysate samples were collected over a 12-hour period. Plasma and dialysate samples were assayed for CI-977 with a validated radioimmunoassay (RIA) [15].

In-vitro probe recovery of CI-977 was determined at the end of each experiment. Recovery was used to correct brain dialysate concentrations to reflect brain ECF concentrations. Rat plasma protein binding was determined in vitro by ultrafiltration. Total measured

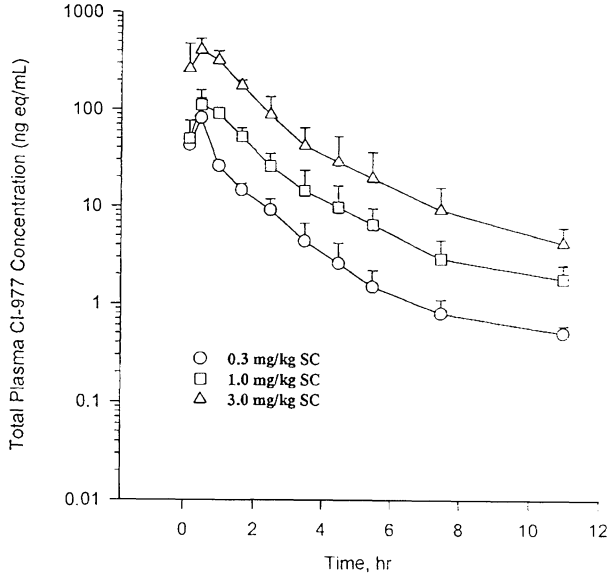

Fig. 1. Mean (+SD) total plasma CI-977 concentration-time profiles following SC doses of 0.3, 1.0, and 3.0 mg/kg CI-977 to healthy non-anesthetized rats

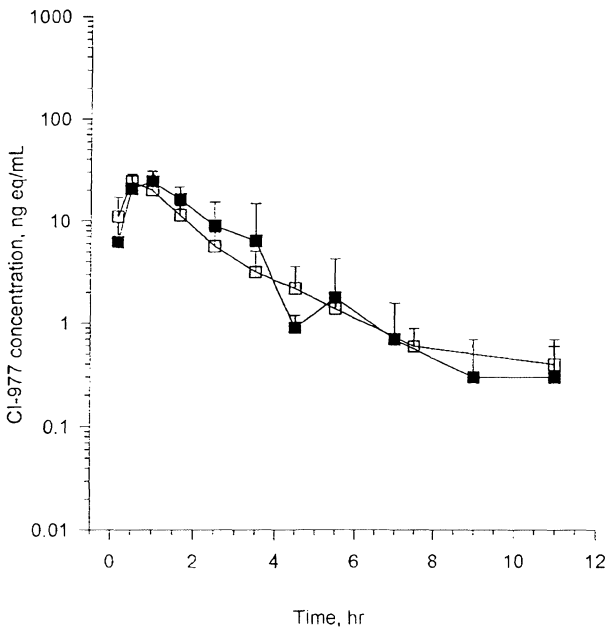

Fig. 2. Unbound plasma (open symbol) and brain ECF (closed symbol) concentration-time profiles after 1.0 mg/kg SC CI-977 dose to healthy non-anesthetized rats

plasma concentrations were then corrected by the percent protein bound to obtain the corresponding free concentration or unbound concentration CI-977 in plasma. Plasma and ECF pharmacokinetic parameters were calculated by standard non-compartmental methods.

Results

Mean (%*RSD*) probe recoveries at a flow rate of 2 μL/min were 27.0% (34%), 31.1% (11%), and 24.0% (32%) for the 3 different probes used. Mean (%RSD) protein binding was 77.5% (8.4%) and independent of concentration across the range of 10 to 400 ng/mL.

All rats survived the microdialysis procedure. CI-977 was rapidly absorbed after SC administration as given by plasma tmax $\leq$0.5 hr. Plasma AUC values increased in a dose-proportional manner, which supports linear pharmacokinetics of CI-977 across this dose range. Figure 1 shows semilogarithmic plots of mean (+SD) total plasma CI-977 concentrations versus time for all doses. Plasma concentration-time profile and pharmacokinetic parameters were similar to after IM adminstration. [5] Interstudy comparisons thus suggest that CI-977 is also completely bioavailable after SC administration.

Figure 2 (representative of all doses) shows that brain ECF concentration-time profiles were essentially coincident with unbound plasma concentration-time profiles at 1 mg/kg. Coincident profiles were also observed for each individual animal. This result suggests rapid equilibration between plasma and brain compartments. Brain extracellular fluid AUC values were linearly related to dose, as were plasma (total and unbound) AUC values. Table 1 summarizes individual and mean AUC_{ecf} and $AUC_{ffplasma}$ values for each dose and the ratio $AUC_{ecf}/AUC_{ffplasma}$, which represents the distribution of the drug between the plasma and brain. At all doses, ratio was unity within experimental error.

Table 1. *Mean (%RSD) Brain ECF and Plasma CI-977 AUC Values and Ratios*

SC Dose (mg/kg)	N	AUC_{ecf} (ng eq · hr/mL)	$AUC_{ffplasma}$ (ng eq · hr/mL)	Ratio
0.3	4	15.2 (31%)	20.1 (30%)	0.81 (42%)
1.0	3	58.8 (56%)	48.1 (22%)	1.2 (38%)
3.0	3	166 (46%)	174 (30%)	0.93 (18%)

Discussion

Microdialysis, which has been an important preclinical technique for the neurosciences in the study of neurotransmitters and neuropeptides [16] and is gaining popularity for the study of brain pharmacokinetics of drugs [4, 17], is now playing an increasingly important role in neuromonitoring in the clinical setting.

CI-977 is k-opioid receptor agonist with high affinity (Ki = 0.11 nM) and selectivity (mu/kappa ratio = 905) [9]. Although extensively ionized at physiological pH, the lipophilicity of CI-977 (log P = 1.15) is such that transfer across the blood brain barrier (BBB) might be expected to be rapid and rate limited by the local blood flow. The superimposability of the ECF concentration-time profile with that of the plasma unbound concentration-time profile is consistent for the predicted high permeability-surface area product and transport by non-facilitated diffusion [3].

Maximum observed brain ECF concentration at low dose was 9.9 ng eq/mL (mean 9.3 ng eq/mL), which equals approximately 25 nanomolar concentration. Based on the equilibrium inhibition constant, Ki, receptors should be essentially fully occupied by CI-977 (assuming radioequivalent concentrations correspond fully to CI-977) [9]. Although CI-977 is demonstrated to be neuroprotective in models of cerebral ischemia [1, 7, 10, 12] and shown to inhibit glutamate release and accumulation in ECF [6, 11, 12], exact contribution to these effects by the kappa receptor is still unclear. Cellular neuroprotective mechanism studies suggest that CI-977's effect on glutamate release and accumulation is the result of not only its action on kappa opioid receptors but also on voltage-dependent sodium channels [2, 11, 14].

The present finding that unbound plasma concentrations may predict brain ECF concentrations of CI-977 is currently being tested in the clinic in head trauma subjects. In preclinical models of ischemia, CI-977 is found to be neuroprotective with associated total plasma concentrations of 50 to 200 ng eq/mL [6, 16, 20, 22]. With protein binding of 77.5% in rat, this corresponds to unbound plasma and brain ECF concentrations on the order of 10–50 ng eq/mL. Consequently, we would predict that for CI-977 to be neuroprotective in head trauma patients, brain ECF concentrations should also approach 10–50 ng eq/mL. Total plasma concentrations would likely need to be higher (200–1000 ng eq/mL) in humans since CI-977 is more highly protein bound in human plasma (95%).

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Correspondence: Dr. Joanna P. Hinton, Department of Pharmacokinetics, Dynamics and Metabolism, Parke-Davis Pharmaceutical Research, Division of the Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105.

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Intraoperative Enzyme-Amperometric Monitoring of Extracellular Glutamate Concentration with a Dialysis Electrode in Ischemic Human Brain

T. Kawamata, Y. Katayama, M. Satoh, T. Mori, and **T. Maeda**

Department of Neurological Surgery, Nihon University, School of Medicine, Tokyo, Japan

Summary

Changes in the extracellular concentration of glutamate in the brain ([Glu]e) were monitored continously by an enzyme-amperometric technique employing a dialysis electrode during ischemia caused by isolation of the brain tissue in rats and human patients. In the rat (n = 10), the dialysis electrode was placed in the frontal cortex and the frontal lobe was transected. A transient sharp increase in [Glu]e was frequently observed during the transection. A biphasic elevation (a rapid increase followed by a slowly continuing increase) subsequently occurred with a latent period of 1–3 min after the transection of the rat frontal lobe. In patients (n = 7), the dialysis electrode was placed in tumor-free cortical areas which were planned to be resected together with gliomas. Progressive increases in [Glu]e were observed in all of the patients as the isolation of the brain tissue progressed. A biphasic increase, similar to that seen in the rat, was identified in 2 patients in whom the cortical area surrounding the dialysis electrode was rapidly isolated. The present enzyme-amperometric technique employing a dialysis electrode appears to be useful for detecting the occurrence of potentially harmful ischemia and for securing minimal metabolic stress caused during various surgical manipulations.

Keywords: Microdialysis; brain ischemia glutamate.

Introduction

There is a substantial body of evidence to suggest that glutamate plays an important role in developing neuronal damage after cerebral ischemia as well as trauma [2, 6]. Ischemia elicits a rapid increase in extracellular concentration of glutamate within the brain ([Glu]e) [7]. Intraoperative monitoring of [Glu]e should thus be useful for detecting the occurrence of potentially harmful ischemia during various neurosurgical procedures, such as temporary occlusion of the cerebral arteries. The microdialysis technique has been widely employed for determining dynamic changes of [Glu]e in experimental animals as well as in patients under neurosurgical intensive care. However, this technique does not provide a sufficiently high time resolution to detect intraoperative ischemic episodes and to take steps to neuronal damage.

Hydrogen peroxide produced by glutamate oxidation with glutamate oxidase can be detected amperometrically using a platinum electrode. Enzyme-amperometry has been applied for the real-time measurement of [Glu]e [1, 4, 9, 10, 11, 12]. Obrenovitch and his co-workers [9, 11] reported a microdialysis technique in which a small sized enzyme-amperometric detector cell is employed for continuous analysis of glutamate in dialysate emerging from a microdialysis probe. Glutamate oxidase is immobilized by glutaraldehyde on surfaces adjacent to the platinum electrodes within the detector cell. Such an on-line enzyme-amperometric microdialysis technique enables the detection or rapid changes in [Glu]e to be made with 90% of maximum response within 30 s [11]. Walker *et al.* [12] have described another technique in which a platinum electrode for measurement of [Glu]e was placed within a microdialysis probe. The probe is filled with glutamate oxidase and not perfused. This dialysis electrode technique provides 90% maximum response within 15 s [1]. Asai and his co-workers, including the authors of the present study [1, 10], have applied the dialysis electrode technique with some modifications to the determination of dynamic changes in [Glu]e during cerebral ischemia; the probe is perfused with phosphate buffered saline (PBS) containing glutamate oxidase. Such perfusion with fresh PBS provides a stable oxygen supply which may be critical to support the enzymatic oxidation reaction in experimental situations such as cerebral ischemia [11]. Furthermore, the above modification improves the

response time; 90% of maximum response is reached within 5 s [1]. Measurement of [Glu]e with such a high time resolution is regarded, for practical purposees, as real-time monitoring and should therefore be appropriate for detecting intraoperative ischemic episodes.

Surgical excision of gliomas, contused brain tissue or epileptogenic foci in patients causes isolation ischemia in the resected part of the brain. This provides a model of focal ischemia in humans. We [8], like other investigators [3, 5], have carried out intracerebral microdialysis intraoperatively in such patients to validate that the microdialysis technique is capable of detecting ischemic episodes in patients similarly as in laboratory animals. In the present study, we again employed this model of focal ischemia to examine the performance of enzyme-amperometric monitoring using a dialysis electrode [1, 10], and the effect of ischemia induction on [Glu]e in the human brain. Before undertaking clinical application of this technique to patients, we also tested the response of the dialysis electrode in the rat to similar isolation ischemia induced by transection of the frontal cortex.

Methods

A dialysis electrode (Sycopel International, UK), consisting of a microdialysis probe with a built-in platinum electrode, was used for the monitoring of [Glu]e. The structure and principle of the dialysis electrode for determining glutamate were as described elsewhere [1, 12]. All the materials employed in the present study were sterilized by irradiation before preparation of the dialysis electrode. The electrode was filled with PBS and immersed in 5 mM *O*-phenylenediamine in PBS bubbled with 100% N_2 for 15 min while constantly stirring the PBS. The dialysis electrode was then electropolymerized at +650 mV for 15 min and stored in PBS. Before application of the dialysis electrode, it was perfused with fresh PBS and the current at +650 mV was allowed to stabilize. An ascorbate calibration was performed in order to assure *O*-phenylenediamine coverage for avoiding such compounds from being oxidized at the electrode. The dialysis electrode was then perfused at a flow rate of 0.5 µl/min with PBS containing glutamate oxidase (0.1 U/µl; Yamasa Co. Ltd., Chiba, Japan) and calcium ions, and calibrated in vitro with glutamate solution bubbled with 100% N_2 while stirring was continued at 34 °C.

In the rat, the dialysis electrode was placed in the frontal cortex at a depth of 3 mm. The frontal lobe was then transected. Data from a total of 10 rats were analyzed. In patients, the dialysis electrode was placed in various tumor-free cortical areas at depths of 0.5–1 cm which were planned to be resected together with gliomas. These cortical areas were then surgically isolated during the process of *en bloc* lobectomy, or rapidly by a circumscribing incision around the dialysis electrode during the process of piece by piece resection. Before the procedures causing isolation ischemia were initiated, approximately 30 min were allowed to elapse in order to stabilize the baseline value. Surgical manipulations of the brain tissue were kept at a minimum during the measurement of [Glu]e. Data from a total of 7 patients with gliomas (glioblastomas and grade III astrocytomas) were analyzed. All patients gave their consent for the procedure employed in the present study to be performed.

Table 1. *In vitro Calibration of the Dialysis Electrode*

Glutamate concentration (µmol/l)	Current (nA)
10	0.9 + 0.1
100	9.6 + 1.0
200	18.5 + 2.2
300	27.0 + 2.9

Data are for successive increases in glutamate in the calibration solution bubbled with 100% N_2 at 34 °C. Perfusion was at 0.5 µl/min. Slope of regression line, 0.09 nA/µmol/l.

Results

The in vitro calibration of the dialysis electrode with glutamate solution bubbled with 100% N_2 demonstrated that the current increased linearly with glutamate concentration up to 300 µmol/l while stirring was continued at 34 °C, indicating that the enzymatic oxidation reaction can be well maintained in experimental situations such as cerebral ischemia in which the tissue oxygen tension falls and the brain temperature decreases (Table 1). Consistent with previous studies [1, 10], the electrode sensitivity was approximately 0.09 nA/µmol/l. When the calibration solution contained 100 µmol/l, 90% of maximum response was reached within 5 s.

In the rat, a dialysis electrode perfused without glutamate oxidase revealed no changes in the current before and after ischemia induction. In contrast, a distinct biphasic elevation was detected after ischemia induction when the dialysis electrode was perfused with glutamate oxidase. During transection of the frontal lobe, the current often sharply increased but returned to the baseline level within a minute (Fig. 1). A rapid increase then occurred suddenly to a level in the range of 5–7 nA with a latent period of 1–3 min after the transection (Fig. 1). This rapid increase (first phase) was followed by a slowly continuing increase (second phase).

Progressive increases in the current were observed in all patients as the isolation of the cortical areas surrounding the dialysis electrode progressed, although the time course was variable (Table 2). A biphasic increase was identified in 2 patients in whom the cortical area surrounding the dialysis electrode was rapidly isolated by a circumscribing incision (Table 2, Fig. 2). Similarly to the rat, this response was characterized by

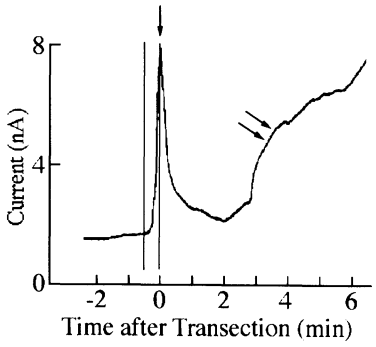

Fig. 1. Representative example of enzyme-amperometric monitoring of [Glu]e using a dialysis electrode during ischemia caused by isolation of brain tissue. The dialysis electrode was placed in the frontal cortex of a rat and the frontal lobe was transected. A transient sharp increase (arrow) was observed during the transection. A biphasic elevation (a rapid increase followed by a slowly continuing increase; double arrow) subsequently occurred with a latent period of 4 min after the transection

Table 2. *Changes in Current Produced by Glutamate Oxidase Perfusion After Isolation Ischemia in Human Patients*

Procedure	n	Progressive increase	
		distinct biphasic	mono/ multiphasic
En bloc lobectomy	3	–	3
Cicumscribing incision around the probe	4	2	2

the sudden onset of a rapid increase with a latent period and a subsequent slowly continuing increase.

Discussion

Employing the microdialysis technique with dialysate sampling at 1-min intervals, a biphasic increase in [Glu]e with a latent period has been shown to occur during ischemia in the rat [7]. Simultaneous measurements of the extracellular concentration of K^+ and [Glu]e have suggested that the sudden onset of the initial rapid increase is concomitant with the onset of anoxic depolarization [7]. The results of on-line enzyme-amperometric microdialysis [9, 11] and dialysis electrode techniques [1, 10] have clearly confirmed these earlier findings. The present study demonstrated that such a biphasic increase in [Glu]e can also occur in humans.

The high time resolution of enzyme-amperometric monitoring using a dialysis electrode provides valuable information intraoperatively. The sudden and rapid

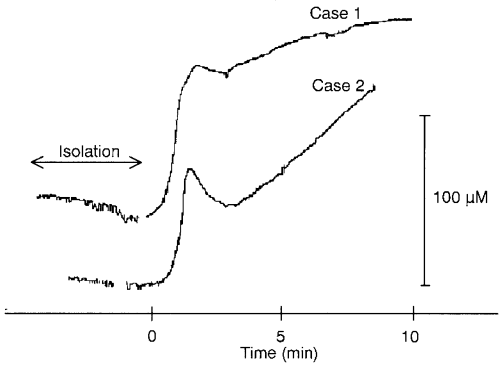

Fig. 2. In 2 patients, a biphasic increase was identified following the isolation of the cortical area surrounding the dialysis electrode, characterized by the sudden onset of a rapid increase with a latent period and a subsequent slowly continuing increase

increase in [Glu]e can be regarded as an indicator of the occurrence of potentially harmful ischemia. The distinct biphasic increase is observed when isolation ischemia is induced rapidly. Temporary occlusion of the cerebral arteries, which is sometimes employed during various neurosurgical procedures, may elicit similar changes in [Glu]e if the ischemia is sufficiently severe to cause typical anoxic depolarization.

A clear biphasic increase was not seen in patients who underwent *en bloc* lobectomy which may give rise to a gradual reduction of blood supply to the brain area to be isolated. The failure to detect a biphasic increase in such patients could be related to movement of the brain during surgical manipulations which may cause damage to the brain tissue around the dialysis electrode, although definite conclusions must await further research. Nevertheless, a progressive increase in [Glu]e was consistently observed in all patients, indicating that such a change in [Glu]e can be regarded as an indicator of persistent ischemia. The transient sharp increase in [Glu]e occurring during transection of the frontal lobe in the rat may be caused by massive neuronal discharges or induction of traumatic depolarization [6]. It remains uncertain whether surgical manipulations in patients can induce similar changes or not. However, monitoring of [Glu]e with such a high time resolution could possibly be useful for securing minimal metabolic stress caused during surgical manipulations.

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Correspondence: Dr. Tatsuro Kawamata, Department of Neurological Surgery, Nihon University, School of Medicine, Tokyo 173-8610, Japan.

Glutamate and Energy Metabolites in Severe Human Head Injury

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CSF and ECF Glutamate Concentrations in Head Injured Patients

T. Yamamoto, S. Rossi, M. Stiefel, E. Doppenberg, A. Zauner, R. Bullock, and **A. Marmarou**

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, USA

Summary

Excitatory Amino Acids (EAAs) release has been considered to be neurotoxic in traumatic brain injury patients. Microdialysis samples of extracellular space (ECS) and high glutamate concentrations in cerebrospinal fluid (CSF) following Traumatic Brain Injury (TBI) have been documented. The objective of this study was to determine the correlation between EAA release in ECS and CSF in focal and diffuse injury.

Head injury patients (GCS $\leq$ 8, n = 16) admitted to Medical College of Virginia Hospital were instrumented for microdialysis collection of ECS samples. CSF samples were collected through the external ventricular drainage catheter at four hour intervals for the first four days following injury. As a control group, CSF was collected from normal pressure hydrocephalus patients (n = 6).

Elevated glutamate levels were observed in both CSF and ECS following head injury. The average glutamate concentration in CSF (3.20 $\pm$ 3.62 μmol/l) was significantly increased from control levels (1.13 $\pm$ 0.49 μmol/l, $p < 0.05$). Comparison of CSF and extracellular fluid (ECF) samples showed that the glutamate concentrations were maximal on the first and second days and gradually decreased on days 3 and 4. On days 4, the level of the glutamate had remained elevated above the normal level.

Keywords: Microdialysis; excitatory amino acids; glutamate; head injury.

Introduction

Excessive Excitatory Amino Acids glutamate and aspartate are considered to be neurotoxic in both brain injury patients and ischemic disease. In the experimental traumatic brain injury (TBI) model, EAAs have been shown to be related to neuronal death. High glutamate concentration in extracellular space (ECS) or cerebrospinal fluid (CSF) following TBI have been documented in recent human studies [1–3, 5]. However, the relationship and the transport mechanisms between ECF and CSF have still not been determined. It was hypothesized that the dialysate from microdialysis probes placed distal to a lesion site may not reflect the high EAA release seen proximal to the lesion, whereas CSF levels are more likely to reflect a global measure of EAA release in diffuse injury. The objective of this study was to determine the correlation between EAA release in CSF and ECS in focal and diffuse injury.

Methods

Head injury patients (mean age = 36.7 y.o., range 25 to 75) admitted to the Medical College of Virginia Hospital with a severe closed head injury (Glasgow Coma Scale $\leq$ 8) were utilized in this study. All of the patients had been treated for raised intracranial pressure by mechanical hyperventilation, osmotherapy, and the insertion of an external ventricular drain. Intracranial hematomas were surgically removed, if the cases needed. Seven patients were instrumented for microdialysis collection of ECS samples. The microdialysis probe with a 10 mm dialysis membrane was placed into the brain cortex, which was perfused with 0.9% saline at rate 2 μl/min. CSF samples were collected through the external ventricular drain at four-hour intervals for the four days following injury. As a control group, CSF was collected from normal pressure hydrocephalus (NPH) patients (n = 6) by lumbar puncture which was indicated for the CSF dynamic study. Prior to assay, the CSF sample was deproteinized as follows; 1) diluted with 99.9% Acetonitrile (CH_3CN) in a ratio CSF/CH_3CN equal at 1/5, 2) *solution was centrifuged and the supernatant filters*, 3) heated to 54°C for four hours. 4) dried and stored in refrigerator for long-term storage. The concentration of both glutamate and aspartate were analyzed by high performance liquid chromatography (HPLC). CSF was also used for measurement of the sodium and potassium concentration in CSF, which was determined via flame photometer.

Results

In the control subjects, the concentrations (mean $\pm$ s.d) of glutamate (1.13 μmol/l $\pm$ 0.49) and aspartate (1.44 $\pm$ 0.98 μM) in CSF were similar to previous reports 5. The CSF sodium (155.2 $\pm$ 6.46 mEq/L) and potassium (3.06 $\pm$ 0.16 mEq/L) concentrations in CSF were also within normal limits.

In the head-injury patients, the glutamate concentration and ions concentration in microdialysis sam-

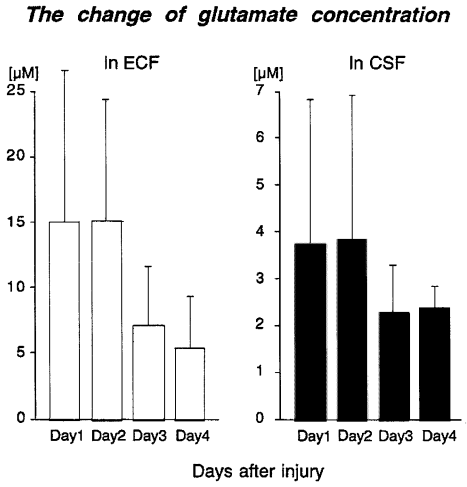

Fig. 1. Comparison of CSF and ECF in glutamate concentration
The daily glutamate concentration changes in both ECF and CSF. The glutamate concentrations were maximal on the first and second days and gradually decreased during day 3 and day 4. By day 4 glutamate levels in ECF and CSF were 35% and 65%, respectively, of levels observed during day 1 and 2

ples were calibrated by the in-vitro recovery rate [2]. The mean amino acid concentrations and the mean electrolyte concentrations were obtained every 12 hours; 1–12, 13–24, 25–36, 37–48, 49–60, 61–72, 73–84, 85–96 hours after the injury via repeated CSF sampling (Table 1). The daily concentrations are summarized in Table 2. The elevated glutamate levels were observed in both CSF and ESF samples. The CSF glutamate concentration while our time frame was significantly increased from control levels ($p < 0.05$). In the ECF glutamate concentration, the elevation was confirmed on the first and second days after the injury.

Comparison of CSF and ECF samples showed that the glutamate concentrations were maximal on the first and second days and gradually decreased during days 3 and 4. By day 4, glutamate levels in ECF and CSF were 35% and 50%, respectively, of levels observed during day 1 and 2 (Fig. 1).

In the electrolyte, the potassium concentration in CSF had been regulated within normal range for four days after the injury as well as ECF. There was no correlation between the potassium concentration in ECF and in CSF. Similarly, the significant changes of sodium concentration were not observed in ECF and CSF.

The concentration of glutamate in ECF nor CSF was not correlated with initial GCS score. However, the peak value of CSF glutamate concentration measured over four days after the injury was correlated with GOS in 6 month and 12 month follow-up ($p < 0.05$).

Discussion

The contribution of EEA to neuronal injury has been well documented in both the laboratory and clinical setting. In an experimental TBI model, the ECF concentrations of EAA were significantly increased immediately after the insults, as well as potassium. These experimental changes which were related with NMDA Ca channel disruption and cell death, have been reported in literature [3]. On the other hand, brain injury patients also have been examined with regard to EEA release with the microdialysis technique [2]. Moreover, in the recent studies, the EEA concentration of CSF was measured with traumatic brain injury, seizure and specific neurological deficits [1, 4, 5]. However, the transport mechanisms and relationship between CSF and ECF have not been clarified in the injured brain.

This study was designed to compare the concentrations of amino acids in CSF and ECF in traumatic brain injury patients. We observed that the glutamate concentrations in both ECF and CSF were elevated in patients following traumatic brain injury. In addition, the glutamate concentration in CSF followed a trend similar to that seen with extracellular glutamate. As an explanation for the elevated glutamate concentrations in CSF, Palmer *et al.* [5] described the following 1) CSF reflects a high ECF glutamate concentration, 2) glutamate may influx from plasm through the broken blood-brain barrier, 3) it could originate from the cytosol of dead cells.

In our study, the adjusted ECF glutamate concentration, using the in-vitro recovery rate, was higher than the CSF glutamate concentration. This concentration gradient favors the movement of glutamate from the ECF into CSF. Furthermore, the accumulation of glutamate in the ECF following brain injury provides an even greater driving force for the movement of glutamate into CSF. Previous studies have shown the rate of turn-over of glutamte in CSF to be longer than that observed in ECF [1, 5]. The extended half-life compounded by possible failure of up-take mechanism may also contribute to the accumulation of glutamate in the CSF. This could also explain why CSF glutamate is elevated for a longer period of time following a transient increase of glutamate in the ECF.

Influx of glutamate from plasma or brain paren-

chyma may also help to contribute to the elevated glutamate observed in CSF. The glutamate concentration in plasma is 10 times greater than CSF. Most of the patients in this study had a subarachnoid hemorrhage, intracranial hematoma, or damaged blood brain barrier. A large hematoma will contain high concentrations of glutamate while the damaged blood brain barrier allows for the influx of blood and could cause brain edema or additional ischemic injury. Glutamate may also have originated from the brain parenchyma, entering the CSF via ruptured cell membranes. In traumatic brain injury, the neuronal cell death associated with EAA release or mechanical breaking of cell membranes could provide a route of glutamate release from brain cells. In the present study, the leaking from the cystol of death cell may be a one of the causes. These secondary factors might exacerbate the brain injury and as a result, the ECF glutamate concentration would be further increased.

Conclusion

Monitoring CSF glutamate may be useful for predicting patient outcome. The results of this study showed that the glutamate concentration in CSF was elevated following severe traumatic brain injury. The glutamate in CSF may reflect the changes occurring in the extracellular space. Further studies are needed to determine the source and mechanism of accumulation in the CSF.

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Correspondence: Dr. Anthony Marmarou, Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, 23298 USA.

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Glucose and Lactate Metabolism After Severe Human Head Injury: Influence of Excitatory Neurotransmitters and Injury Type

B. Alessandri, E. Doppenberg, R. Bullock, J. Woodward, S. Choi, S. Koura, and **H. F. Young**

Department of Neurosurgery, Virginia Commonwealth University, Medical College of Virginia, Department Neurosurgery, Richmond, USA

Summary

The survival of traumatized brain tissue depends on energy substrate delivery and consumption. Excitatory amino acids produce a disturbance of ion homeostasis and thus, increase energy demand. In head-injured patients, massive release of glutamate has been reported, especially in patients with focal contusions. Therefore, we studied the interrelationship between glutamate, glucose and lactate in relation to the type of injury. We investigated 37 severely head-injured patients in which a microdialysis probe was placed next to a focal contusion ($n = 14$) or together with a ventricular catheter in diffusely injured tissue ($n = 23$). Within-subject Spearman-rank correlation revealed an overall strong relationship between glutamate and lactate ($p < 0.001$) and glutamate and glucose ($p < 0.01$), but not between glucose and lactate (n.s.). The interrelationship was more pronounced in diffusely injured brain (normal CT appearance) compared to the contused tissue.

The results demonstrate that glutamate clearly influences the release of lactate following injury, supporting the hypothesis that glutamate "drives" glycolysis in astrocytes. The strong positive correlation between glutamate and glucose might indicate an effect of glutamate upon glucose uptake by cells which differs according to the type of injury.

Keywords: Microdialysis; head-injury; glutamate; lactate; glucose; head injury.

Introduction

Glucose is the main energy source of the brain. About 40% of brain glucose is used to maintain ionic homeostasis [11]. In animal models of traumatic brain injury (TBI) and in severely head-injured patients, dynamic studies have shown massive *hyperglycolysis* early after impact which is then followed by a hypometabolic state [10]. This early increase in energy demand may be exacerbated by derangement of ion homeostasis due to glutamate which affects agonist-operated channels [11]. TBI is also accompanied by high tissue lactate levels, the cause of which is not clear. It may be produced by either hypoxic/ischemic episodes, blockage of mitochondrial function or glutamate induced glycolysis in astrocytes [3, 13, 15]. Microdialysis studies have also shown a dramatic decrease of extracellular glucose following ischemia which is already normalized 24 hours after insult [1].

Using microdialysis in severely head-injured patients, we have reported high extracellular glutamate levels [4, 5, 16] which correlated with lactate, but not with glucose levels during a selected time-window [7]. Massive glutamate increase has especially been seen in patients with focal contusions, indicating effects of injury type on neurochemical processes. In the present study we wanted to test the hypothesis 1) that increases in glutamate cause reproducibly linked changes in the metabolic markers lactate and glucose, i.e. a fall in glucose and a rise in lactate.; 2) that the injury type (focal contusion versus diffusely injured tissue) will influence the above relationship.

Materials and Methods

Patients

A total of 37 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 a ventriculostomy (usually right-frontal), or through a craniotomy adjacent to a cerebral contusion. According to the placement of the probe, patients were divided into a group in which the probe was in diffuse injured tissue (DIFFUSE, $n = 23$) and a group with the probe next to contused tissue (CONTUSION, $n = 14$). Outcome was assessed by Glasgow outcome scale (GOS). GOS of 0–2 was considered as good outcome and GOS 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

Table 1. *Patient Characteristics of 37 Severely Head-Injured Patients, Divided by Type of Injured Tissue Into a DIFFUSE* ($n = 23$) *and CONTUSION* ($n = 14$) *Group*

	Age (years)	Sex (n)		Outcome (GOS)		ICP** (mmHg)	CPP** (mmHg)
		female	male	good	poor		
Diffuse	36.4 ± 3.9	6	18	65.2%	34.8%	16.5 ± 1.5	81.0 ± 3.2
Contusion	44.4 ± 4.5	8	6	57.1%	42.9%	14.8 ± 0.9	84.6 ± 2.8

CPP Cerebral perfusion pressure; *GOS* Glasgow Outcome Scale; *ICP* intracerebral pressure; **mean value over the entire monitoring period.

saline at a flow rate of 2 μL/min. Half-hourly samples (60 μL) were collected in sealed glass vials by means of a refrigerated (4 °C) autosampler (CMA/170). Vials were frozen at −70 °C for later analysis. In vitro probe recoveries for glutamate, lactate and glucose were 43 ± 3%, 49 ± 2% and 42 ± 2%, respectively.

Glutamate

Glutamate was analyzed in 15 μL dialysates using HPLC with pre-column derivatisation by OPA and electrochemical detection (LC-4B detector) [17].

Lactate

Lactate was analyzed in 10 μL dialysate samples (1 : 5 diluted in saline) using a HPLC system consisting of an ion-exclusion column (Hamilton PRP-X300) and ultraviolet detector (BAS UV116A; detection wavelength 214 nm).

Glucose

Glucose was analyzed using a BAS glucose assay kit (# MF-8925; Bioanalytical System Inc. IN, USA). Briefly, dialysate (5 μL) was diluted in 20 μL saline and injected into a reverse-phase HPLC system, consisting of a pre-column separating glucose from ascorbate, uric acid and other electrochemically active molecules, and a ready-to-use immobilized enzyme column (glucose oxidase). The generated hydrogen peroxide was oxidized at a Pt electrode and electrochemically detected.

Statistics

In order not to loose the dynamic extracellular changes which occur during the course of microdialytic monitoring, a Spearman rank correlation was performed to compare glutamate, lactate and glucose for each single patient. The mean of all derived correlation coefficients was tested for significant difference from zero (0) by a one-sample t-test (H_0 hypothesis). The distribution of the correlation coefficients was approximately normal. Difference from zero was considered to be significant at a p-level < 0.05. Mean values of glutamate, lactate and glucose of both groups were compared by non-parametric Mann-Whitney U-tests ($p < 0.05$).

Results

Dialysate Concentrations for Glutamate, Lactate and Glucose

The microdialysis findings from one patient of each group for glutamate, lactate and glucose are depicted in Figs. 1, 2. The mean (±s.e.m) dialysate glutamate, lactate and glucose for all patients was 26.3 ± 9.0 μM, 1404 ± 152 μM and 463 ± 78 μM, respectively (normal ranges: Glu < 2 μM, Lac ~ 500 μM, Gluc ~ 1000 μM). The levels in the DIFFUSE group were 24.6 ± 13.8 μM, 1284 ± 168 μM and 561 ± 113 μM, whereas 29.1 ± 8.1 μM, 1602 ± 291 μM and 301 ± 79 μM

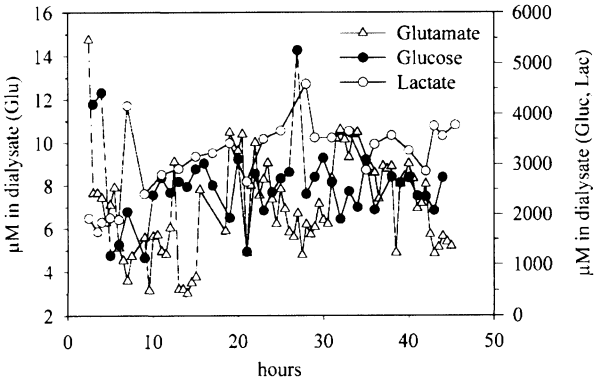

Fig. 1. Patient E.G. with a diffuse injury (DIFFUSE group): 33-year old male, severely head-injured patient with initial Glasgow Coma Score (*GCS*) of 8, and 3-month Glasgow Outcome Scale of 1. The MD probe was placed next to the ventriculostomy

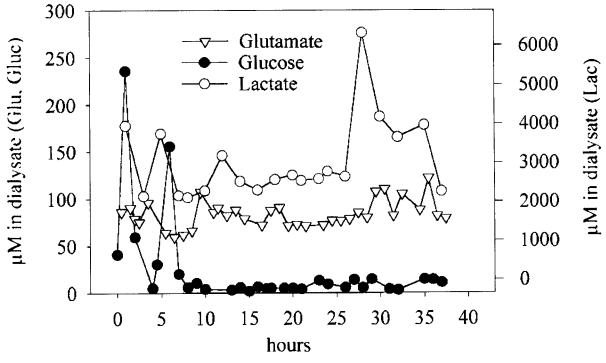

Fig. 2. Patient T.C. with a right frontal and temporal contusion (CONTUSION group): 44-year old male, severely head-injured patient with initial GCS = 4, who died (GOS = 4). The MD probe was placed next to the contusion

were measured for the CONTUSION group. The CONTUSION group had significantly higher glutamate ($p < 0.05$) and lower glucose ($p < 0.05$) concentrations in dialysate than the DIFFUSE group.

Relationship Between Glutamate and Lactate

The results of the statistical analysis of the interrelationship between glutamate, lactate, and glucose in severely head-injured patients are listed in Table 2. Overall, lactate was strongly correlated with glutamate. This effect was, however, more pronounced in diffusely injured tissue than in contused brain tissue. In both groups only about 15% of the patients had negative correlation between glutamate and lactate, indicating a *robust coupling* between these two neurochemicals.

Relationship Between Lactate and Glucose

On the other hand, a relationship between lactate and glucose could not be seen with the analyzed data for the entire group as well as for the CONTUSION group. In diffusely injured brain tissue, however, lactate correlated positively with glucose.

Relationship Between Glutamate and Glucose

The results show a positive relationship between glutamate and glucose for all patients, and the DIFFUSE group in particular (Table 2). In both groups about 30% of all within-subject correlations were *negative*.

Table 2. *Mean within-subject Spearman rank correlation coefficients for glutamate vs. lactate and glucose as well as glucose vs. lactate for the entire patient group and the DIFFUSE and CONTUSION group*

Spearman rank correlation Mean (±s.e.m) within-subject correlation coefficient	Glutamate versus		Glucose vs.
	lactate	glucose	lactate
All patients (n = 37)	0.320 ±0.07	0.176 ±0.06	0.110 ±0.07
One-sample t-test (H_0):	$p < 0.001$	$p < 0.01$	*n.s.*
Diffuse (n = 23)	0.334 ±0.09	0.181 ±0.07	0.206 ±0.09
One-sample t-test (H_0):	$p < 0.001$	$p < 0.05$	$p < 0.05$
Contusion (n = 14)	0.298 ±0.11	0.168 ±0.13	−0.03 ±0.09
One-sample t-test (H_0):	$p < 0.05$	*n.s.*	*n.s.*

n.s. Not significant.

Discussion

Substrate delivery and consumption play a key role in the survival of brain cells. Following traumatic brain injury, there is a massive increase of energy demand lasting from minutes to many days after the initial trauma [10]. Glutamate is markedly increased following TBI in patients and animal models, and contributes to this increased metabolic demand by disturbing the ion homeostasis via agonist-opened channels [4, 5, 16]. The re-uptake of glutamate into glial cells has recently been found to induce glycolysis in astrocytes and this produces lactate. There is evidence that locate then acts as a major energy substrate for neurons, following activation by ionic disequilibrium [2, 6, 13, 15]. A cerebral blood flow study (CBF) using the non-radioactive stable Xenon computer tomography technique has indicated that in more than 50% of patients with elevated lactate, CBF was *higher than the ischemic threshold of 22 ml/100 g/min blood flow* [7]. This human study clearly supports the concept of glutamate-induced lactate production by astrocytes. Under pathophysiological conditions, this energy source may thus help to provide lactate for Krebs cycle metabolism in neuronal mitochondria. This will then yield sufficient energy for glutamate uptake, and ion pumping. However, effects on energy metabolism following TBI may depend on the type of injury. Therefore, we studied two patient populations, in which we monitored in the diffusely injured brain (no surgical intervention) or focally contused tissue, after craniotomy to remove a hematoma. Thus, the placement of the MD probe was either in a diffusely injured area or next to more damaged and contused tissue, which was typically of "low density" by CT scanning. The goal of this study was to determine if glutamate stimulates lactate production in severely head-injured patients and if this relationship depends on injury type.

The analysis of the interrelationship between glutamate, lactate and glucose in severely head-injured patients showed that increased lactate correlates strongly and robustly with increased glutamate. This supports the concept of glutamate "driven" lactate production in patients with traumatic brain injury [13]. The effect was, however, more pronounced in diffusely injured tissue than in severely contused tissue, indicating possible *overshadowing* of this relationship, by other pathological mechanisms generating lactate such as local ischemia, edema or non-specific tissue destruction.

The hypothesis that glucose decreases due to glutamate-induced increased energy demand, thus providing a source of lactate production, could not be proven by this study [2]. In severely contused tissue, there was neither a correlation between glutamate and glucose nor between lactate and glucose. It might be speculated that other mechanisms, such as cerebral blood flow reduction or impairment of glucose transporters, may have influenced the extracellular glucose content and that normal uptake and metabolic processes were extremely disturbed next to severely contused brain tissue. It is also possible that severely contused tissue was metabolically inert, allowing all neurochemicals and substrates to regress adjacent ECF.

In conclusion, these results clearly indicate a coupling between glutamate and lactate, supporting the concept that glutamate "drives" lactate production to provide lactate as an energy substrate to neurons. The type of injury can clearly influence neurochemical parameters measured by microdialysis, indicating that the production of lactate as a neuronal energy substrate, however, could be disturbed by secondary insults. Since lactate may not only indicate severe neuropathological events, lactate might not be useful as a sole marker for such processes. It should be combined with other markers of energy metabolism such as glucose, pyruvate or others [8, 9, 12, 14].

Acknowledgments

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Correspondence: Dr. B. Alessandri, Virginia Commonwealth University, Medical College of Virginia, Department of Neurosurgery, P.O. Box 693, Richmond, 23298, USA.

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Evidence for Time-Dependent Glutamate-Mediated Glycolysis in Head-Injured Patients: A Microdialysis Study

B. Alessandri, E. Doppenberg, A. Zauner, J. Woodward, S. Choi, and **R. Bullock**

Department of Neurosurgery, Virginia Commonwealth University, Medical College of Virginia, Richmond, USA

Summary

In the brain, lactate is not only a marker of anaerobic glycolysis due to hypoxia/ischemia, but also a neuronal energy source which is provided by glutamate-induced astrocytic glycolysis. In the present study we wanted to investigate the relationship between glutamate release and lactate production during the entire time-course and during three time periods of microdialytic monitoring in 54 severely head injured patients. Within-subject Spearman rank correlations were calculated in each period for glutamate and lactate, for each patient and the mean of all correlation coefficients were analyzed for difference from zero by a one-sample t-test. The results show a strong overall positive relationship between glutamate and lactate. However, during the first 12 hours after injury, there was no significant correlation. Thereafter, good correlation was seen. The splitting of patients into groups with good (Glasgow Outcome Scale; GOS 0–2) and poor outcome (GOS 3–4) showed a similar strong correlation for patients with good outcome, but this was lost for patients with poor outcome. The results clearly indicate that glutamate "drives" astrocytic lactate production in head-injured patients. The contribution of glutamate to overall lactate release is thus time-dependent. During the first 12 hours after injury, factors such as hypoxia, ischemia or edema overshadowed glutamate-induced glycolysis in astrocytes. In addition, the effect of glutamate is more pronounced in patients with good outcome.

Keywords: Microdialysis; head-injury; glutamate; lactate; head injury.

Introduction

Lactic acid has widely been accepted as an indication of anaerobic metabolism caused by hypoxia/ischemia. Lactic acidosis also disturbs ionic homeostasis and might have its own adverse effects on the development of secondary brain damage. Microdialysis studies in head-injured patients have shown a good correlation between peak lactate concentrations and pathophysiological events, such as high ICP, low CPP or MABP, and high jugular $AVDO_2$ values [7, 8]. However, lactate is also massively released at non-ischemic blood flow levels during spreading depression [12], physiological activation or glutamate application [5], and ischemic [2] or traumatic brain injury [6]. Recently, glutamate-induced, non-ischemic glycolysis has been reported in cultured astrocytes [10]. It was thus hypothesized that after release, glutamate uptake induces astrocytic glycolysis, leading to lactate production which then becomes the preferred energy substrate for neurons, undergoing "excitotoxic" or transmitter-induced ionic stress. In head-injured patients, high and long-lasting glutamate and lactate levels have been shown and astrocytic glycolysis might predominantly contribute to this high lactate after head-injury. Thus, we tested the hypothesis that glutamate "drives" lactate production in astrocytes by analyzing the time-dependency of the relationship between glutamate and lactate in severely head-injured patients which were monitored by microdialysis.

Materials and Methods

Patients

A total of 54 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 a ventriculostomy (usually right-frontal), or during surgery, next to a cerebral contusion. Outcome was assessed by dichotomized Glasgow outcome scale (GOS). GOS of 0–2 was considered as good outcome and GOS 3–4 as poor outcome.

ICP and CPP Management

Ventriculostomy ICP (mmHg) data, and mean arterial blood pressure (MABP, mmHg), were continuously acquired by a VAX mainframe computer system. For analysis, time points of microdialysis and physiological parameters were matched.

Table 1. *Patient Characteristics of 54 Severely Head-Injured Patients*

Age (years)		38.4 ± 17.6
Sex	female	24%
	male	76%
Outcome (GOS)	good	44%
	poor	56%
ICP (mmHg)**		16.8 ± 9.1
CPP (mmHg)**		80.7 ± 15.6
MABP (mmHg)**		97.3 ± 12.5
Contusion		15
Diffuse injury		9
Subdural, subarachnoid, epidural, intracerebral hemorrhage		9
Multiple mechanisms		19
Normal CT		2

CPP Cerebral perfusion pressure; *CT* computer tomography; *GOS* Glasgow Outcome Score; *ICP* intracerebral pressure; *MABP* mean arterial blood pressure.
** Mean values over the entire monitoring period.

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 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). Vials were frozen at −70 °C for later analysis. In vitro probe recoveries for glutamate, lactate and glucose were 43 ± 3%, 49 ± 2% and 42 ± 2%, respectively.

Glutamate

Glutamate was analyzed in 15 μL dialysates using HPLC with pre-column derivatisation by 0-phthalic dicarboxyaldehyde and electrochemical detection (LC-4B detector) [15].

Lactate

Lactate was analyzed in 10 μL dialysate samples (1 : 5 diluted in saline) using a HPLC system consisting of an ion-exclusion column (Hamilton PRP-X300) and ultraviolet detector (BAS UV116A; detection wavelength 214 nm).

Glucose

Glucose was analyzed using a BAS glucose assay kit (#MF-8925; Bioanalytical System Inc. IN, USA). Briefly, dialysate (5 μL) was diluted in 20 μL saline and injected into a reverse-phase HPLC system, consisting of a pre-column separating glucose from ascorbate, uric acid and other electrochemically active molecules and a ready-to-use immobilized enzyme column (glucose oxidase). The generated hydrogen peroxide was oxidized at a Pt electrode and electrochemically detected.

Statistics

In order not to lose the dynamic extracellular changes which occur during the course of microdialytic monitoring, a Spearman rank correlation was performed to compare glutamate, lactate and glucose for each single patient, at each time point of microdialysis monitoring. The mean of all derived correlation coefficients was then tested for significant difference from zero (0) by a one-sample t-test (H_0 hypothesis). The distribution of the correlation coefficients was approximately normal. Difference from zero was considered to be significant when a p-level of < 0.05 was achieved.

Results

Time-Dependent Glutamate–Lactate Relationship

Two patients are depicted in Figs. 1 and 2. Overall, there was a positive correlation between glutamate and lactate in 77% of all cases, whereas during the first 12 hours after injury 40% of the within-subject correlations were positive. The mean correlation coefficients from the within-subject Spearman rank correlations are shown in Table 2. As it can be seen, there was a relatively poor relationship during the first 12 hours after head-injury. A positive correlation, however, de-

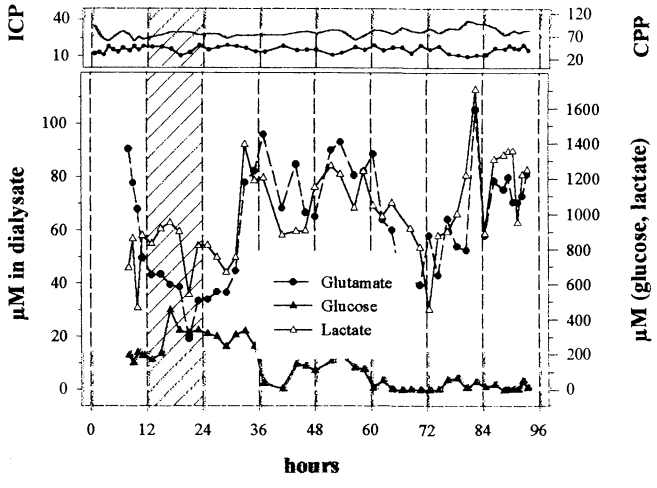

Fig. 1. Patient P.D. 33-year old male severely head-injured patient with initial GCS = 7; diffuse injury; and 3-month COS = 1 (moderate disability). MD probe was placed next to the ventriculostomy. CBF measurement at admission and on day 4 showed global (39.7; 37.8 ml/100 g/min) and regional (36.1; 37.8 ml/100 g/min) cerebral blood flows above ischemic threshold (22 ml/100 g/min). Spearman rank correlation coefficients for glutamate vs. lactate were 0.63 (overall), −0.30 (0–12 hrs after injury), 0.94 (12–24 hrs.), and 0.69 (>24 hrs). The analyzed time periods are separated by the shaded bar

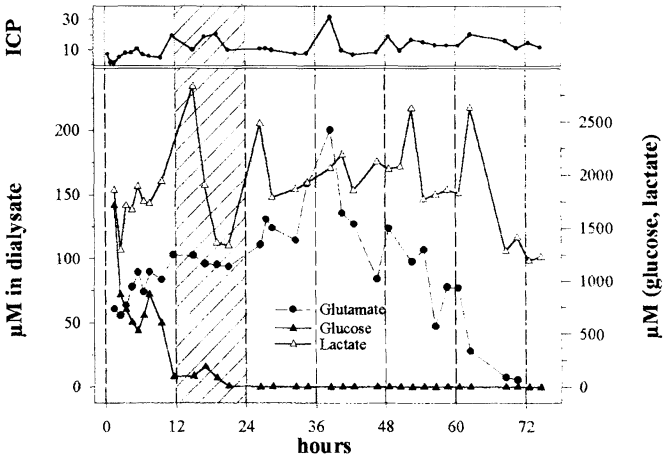

Fig. 2. Patient B.D.: 44-year old female severely head-injured patient with initial GCS = 7; right frontal contusion; and 6-month GOS = 4 (dead). MD probe was placed next to the contusion. CBF measurement at admission showed hemispheric CBF of 31.3 ml/100 g/min and regional CBF of 20.9 ml/100 g/min. The regional CBF (around MD probe) was below ischemic threshold (22 ml/100 g/min). Spearman rank correlation coefficients for glutamate vs. lactate were 0.51 (overall), 0.76 (0–12 hrs. after injury), 0.46 (12–24 hrs.) and 0.90 (>24 hrs). The analyzed time periods are separated by the shaded bar

veloped during the second 12 hours (12–24 hrs.) and later (>24 hrs.) after initial injury.

Outcome and Glutamate–Lactate Relationship

The Spearman rank correlation coefficients were analyzed in a group of patients with good (GOS 0–2) and one with poor outcome (GOS 3–4). As shown in Table 2, there was a good overall relationship between glutamate and lactate in patients with good outcome. The results indicate that there was no initial significant relationship between glutamate and lactate if patients had a good outcome. During the second 12 hours after injury, however, there was again a good correlation between the two parameters. If the outcome is poor, the overall out come as well as the relationship during the three time periods were not significant.

Discussion

The goal of this study was to determine if glutamate stimulates lactate production in severely head-injured patients. The results strongly suggest that glutamate "drives" lactate production in patients with traumatic brain injury, supporting the concept of glutamate-induced glycolysis in astrocytes. It seems, however, that this relationship is *overshadowed* by other mechanisms during a first period after the initial injury and is affected by the severity and type of injury.

In animal models of ischemia or trauma as well as in human head-injury, high glutamate [3, 4, 14] and lactate [8] levels were found. Lactate was normally considered to be a product of anaerobic glycolysis and therefore a good marker for neuropathological events. The development of lactic acidosis may also have adverse effects on pH and ion homeostasis. Goodman and coworkers [7] found lactate elevation of which

Table 2. *Mean Within-Subject Spearman Rank Correlation Coefficients for Glutamate vs. Lactate for the Entire Time-Course of Microdialytic Monitoring and for Three Different Time Periods After Initial Injury*

Spearman rank correlation Mean (±S.D) within-subject correlation coefficient	Time period after initial injury			
	total	0–12 hrs.	12–24 hrs.	> 24 hrs.
All patients	0.250 ±0.44	0.128 ±0.63	0.210 ±0.55	0.184 ±0.38
One-sample t-test (H_0): p-values	*< 0.001*	*n.s.*	*< 0.05*	*< 0.01*
Patients with good outcome (GOS 0–2)	0.285 ±0.43	0.101 ±0.66	0.255 ±0.45	0.178 ±0.41
One-sample t-test (H_0): p-values	*< 0.01*	*n.s.*	*< 0.05*	*< 0.077*
Patients with poor outcome (GOS 3–4)	0.194 ±0.49	0.126 ±0.59	0.145 ±0.70	0.162 ±0.35
One-sample t-test (H_0): p-values	*n.s.*	*n.s.*	*n.s.*	*n.s.*

n.s. Not significant.

78% were accompanied by pathophysiological events, such as increased ICP, jugular venous desaturation or brain death. A correlation between outcome and peak lactate levels was found [8].

Recently, Magistretti and coworkers [10, 13] showed that astrocytic glycolysis is stimulated by glutamate uptake and that lactate is produced as an energy substrate for neurons. In vivo elevation of lactate levels can be induced by physiological stimulation, such as tail pinch or grooming in rats. The application of glutamate through microdialysis probes was also effective in producing increased extracellular lactate levels without causing noxious decrease of blood flow [1, 5]. A cerebral blood flow study (CBF), using the non-radioactive stable Xenon computer tomography technique [6], indicated that in more than 50% of elevated lactate, CBF was higher than the ischemic threshold of 22 ml/100 g/min blood flow. These studies clearly support the concept of glutamate-induced lactate production by astrocytes.

The present investigation also showed a good positive correlation between glutamate release and lactate in severe head-injured patients. In an early phase following injury, however, this relationship was not apparent. Secondary insults such as hypotension, increased ICP due to edema or hypoxic episodes which are common in head-injured patients may induce neuropathological mechanisms which overshadowed the glutamate-lactate relationship. A lack of relationship was additionally found in patients with poor outcome, indicating massive disturbance of lactate production, in those with the most severe brain damage.

In summary, changes in extracellular lactate levels are positively correlated with glutamate levels, supporting the concept of glutamate-induced glycolysis in astrocytes [10]. The production of lactate as a neuronal energy substrate, however, could be augmented by its origin due to secondary insults. Since lactate may not only indicate severe neuropathological events, such as dense ischemia, but also non-specific cellular poration adjacent to contusions, lactate might not be useful as the sole marker for such ischemic processes. It should be combined with other markers of energy metabolism, such as glucose, pyruvate or others (e.g. lactate/glucose ratio, lactate/pyruvate ratio) [9, 11].

Acknowledgments

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Correspondence: Dr. B. Alessandri, Department of Neurosurgery, Virginia Commonwealth University, Medical College of Virginia, P.O. Box 693, Richmond, 23298, USA.

Ionic Changes in Severe Human Head Injury

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Determinants of Cerebral Extracellular Potassium After Severe Human Head Injury

E. M. R. Doppenberg[1], **M. Reinert**[1], **A. Zauner**[1], **T. S. Massie**[2], and **R. Bullock**[1]

[1] Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia
[2] Department of Biostatistics, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Abstract

The key role players of brain swelling seen after severe human head injury have only been partly determined. We used our human head injury data base to determine relationships between potassium, glutamate, lactate and cerebral blood flow (CBF). A total of 70 severely head injured patients (GCS $\leq$ 8) were studied using intracerebral microdialysis to measure extracellular glutamate, potassium and lactate. Xenon CT was used to determine regional cerebral blood flow (rCBF).

The mean $\pm$ SEM of the r value of all patients, between potassium and glutamate, and potassium and lactate was 0.25 ± 0.04 ($p < 0.0001$) and 0.17 ± 0.06 ($p = 0.006$), respectively, demonstrating in both cases a positive relationship. rCBF was negatively correlated with potassium with marginal significance ($r = -0.35$, $p = 0.08$). When separated into two groups, patients with contusion had higher potassium levels than patients without contusion (1.55 ± 0.03 mmol/l versus 1.26 ± 0.02 mmol/l, respectively). These results in severely head injured patients confirm previous in vitro and animal studies in which relationships between potassium, glutamate, lactate and CBF were found. Potassium efflux is a major determinant of cell swelling leading to clinically significant cytotoxic edema due to increased glutamate release during reduced cerebral blood flow.

Keywords: Potassium; glutamate; lactate; cerebral blood flow; severe human head injury.

Introduction

Massive cell swelling is the major determinant of morbidity and mortality of patients following severe head injury [7]. The key events of this pathophysiological process have only been partly unraveled. Recently, the role of potassium efflux from the intracellular compartment to the extracellular space after traumatic brain injury has become a focus of increased interest [2–6]. The leakage of potassium into the extracellular space is followed by intracellular influx of sodium influx and calcium, resulting in the breakdown of essential intracellular components [8]. In addition, extracellular potassium is buffered by rapid uptake into astrocytes, to maintain extracellular fluid homeostasis. Astrocytes may swell to 5–6 times normal volume, by this mechanism, which is probably a major cause of cytotoxic post-injury cell swelling [11]. Data from different groups including our own have shown that in the early phase after traumatic brain injury, cerebral blood flow (CBF) is reduced in up to one-third of the patients [3]. At the same time we have shown recently that glutamate release is massively increased in certain subgroups of patients with contusions, mass lesions and ischemic events [4]. This increase is closely related to the severity of CBF reduction [20]. The increase in glutamate then results in "agonist driven" ion channel opening, leading to further potassium efflux and sodium influx. This is then countered by the sodium-potassium dependent ATPase pump, which requires an increased metabolic rate, and therefore increased substrate delivery. Katayama *et al.* showed a decade ago, that increased glutamate release after fluid percussion injury was accompanied by potassium efflux into the extracellular space [10]. Furthermore, massive potassium efflux has been shown to increase aerobic metabolism, demonstrating the coupling between neuroexcitation and ATP production [16].

Classically, an increase in lactate production seen after traumatic brain injury is explained by a flow-metabolism mismatch; the increase in substrate demand cannot be met by CBF, resulting in anaerobic glycolysis and lactate generation. However, Andersen and Marmarou have shown that lactate generation is increased, following TBI in the cat, as measured by MRS, even when CBF was adequate to ensure sub-

strate delivery [2]. This implies that factors other than ischemia can cause lactate generation after TBI. This increase in lactate generation may be a consequence of the massive glutamate release, in accordance with the hypothesis of Pellerin *et al.* They showed under physiological conditions in an in vitro study, that glutamate release due to physiological stimulation results in increased lactate generation [15].

We have therefore used our human brain microdialysis TBI data base to study the interrelationships between CBF, potassium, glutamate and lactate after severe human head injury.

Methods

These studies were approved by the Committee for conduct of Human Research, at the Virginia Commonwealth University.

Patients

A total of 70 patients, admitted to the Neuroscience Intensive Care Unit at the Medical College of Virginia (MCV), older than 16 years, with severe head injury, and a Glasgow Coma Score of 8 or less, were studied. All patients received intensive intracranial pressure (ICP)-directed management, according to a standard protocol at MCV. In the following analysis there were no significant differences found regarding distribution of sex or age. Patients who were brain dead or close to brain death on admission or for whom informed consent could not be obtained, were excluded from this study.

Cerebral Blood Flow Measurements

Stable (non radioactive) xenon enhanced computed tomography (CT) was used for measuring cerebral blood flow in all patients. This was performed by repeated CT scanning during the inhalation of a gas mixture containing 30% xenon, 30–60% oxygen and room air. Regional CBF (rCBF) was calculated, using a 20 mm^2 region of interest, at the site where the microdialysis probe was placed.

Microdialysis

A custom-built 10 mm flexible microdialysis probe (CMA Microdialysis, Acton, MA) with an external diameter of 0.5 mm, and a molecular weight cutoff of 20,000 Dalton was used to monitor extracellular cortical levels of glutamate and lactate. The probe was placed in a standard fashion through a custom-built triple lumen bolt in the right frontal cortex or alongside a ventriculostomy catheter. The microdialysis probe was perfused at two microliters per minute using sterile 0.9% saline. Sixty microliter dialysates were collected every half hour into sealed glass tubes using a refrigerated (4 °C) automated collector system (CMA 170 System, CMA-Microdialysis system Acton, MA). The time between the start of collection of dialysate or performance CBF measurements was at least one hour in each patient. The microdialysis probe was saved after removal for in vitro calibration. Glutamate and lactate were measured using high performance liquid chromatography (HPLC).

Statistical Analysis

Microdialysis measurements for potassium, obtained 6 hours before until 6 hours after the actual cerebral blood flow study, were averaged and compared with the rCBF results. Regression analysis and Spearman Rank tests were used to test the inter-relationships between these parameters.

To study the relationships between glutamate-potassium, and lactate-potassium, the regression coefficients ("r-values") *for each patient* were calculated. In this way the "nature" (positive or negative) of the relationship could be determined. This was followed by a one sample *t*-test over these r-values to test the significance of these regression results. Results are given with in mean ± SEM unless otherwise specified.

Results

Potassium and its Relationship with Glutamate and Lactate

The mean r value, in 70 patients, between potassium and glutamate was 0.25 ± 0.04, demonstrating a positive correlation between glutamate and potassium. A histogram of the distribution of the r-values is shown in Fig. 1a. A highly significant association was shown

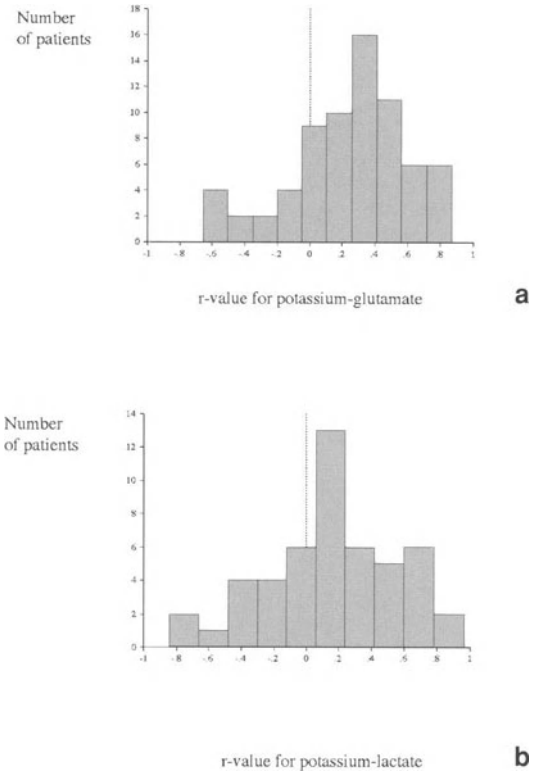

Fig. 1. (a) Histogram showing the distribution of the r-values derived from Spearman rank correlation between extracellular potassium and glutamate in each patient (n = 70). The mean of the r-values is 0.25 ± 0.04 (P < 0.0001, one sample *t*-test). (b) Histogram showing the r values derived from Spearman rank correlation between extracellular potassium and lactate in each patient (n = 49). The mean of the r-values is 0.17 ± 0.06 (P = 0.006, one sample *t*-test)

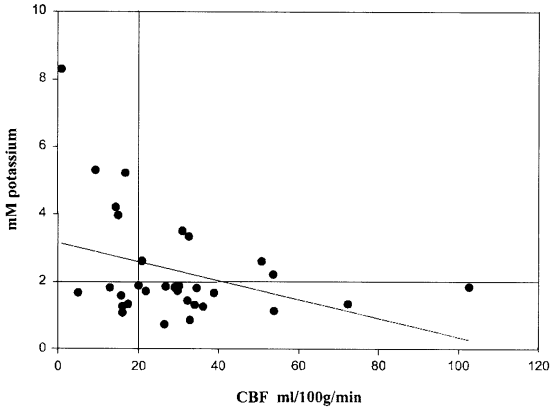

Fig. 2. Regression plot showing the correlation between rCBF and extracellular potassium of the mean values of each patient (n = 32). r = −0.35, p = 0.08

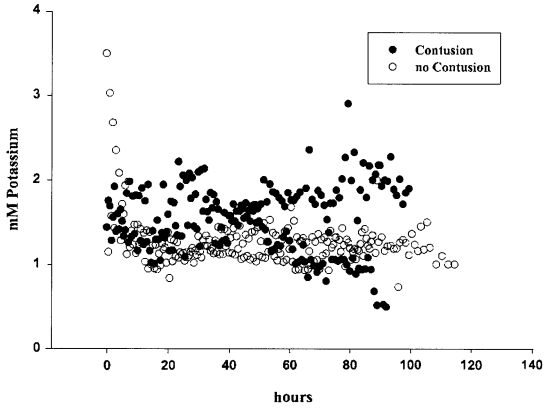

Fig. 3. Mean values for all extracellular potassium measurements at each timepoint for all patients. Contused tissue demonstrated rising extracellular potassium values over time, while non-contused brain showed a decreasing extracellular potassium (n.s)

by a one sample *t*-test over the group as a whole ($p < 0.0001$).

In 49 patients, potassium and lactate were measured during the recording time and were similarly analyzed. The mean r-value was 0.17 ± 0.06, demonstrating a positive correlation between lactate and potassium. The distribution of the r-values is shown in Fig. 1b. A strong significance was shown with a one sample *t*-test ($p = 0.006$).

Potassium and rCBF and Type of Injury

In 32 patients rCBF was compared with the mean of the potassium values of each patient. The r-value of the regression analysis was −0.35. The Spearman Rank Correlation was $p = 0.08$, demonstrating an inverse relationship between potassium and cerebral blood flow (Fig. 2). Patients with contusion had higher dialysate potassium levels than patients without contusion as seen from Fig. 3. (1.55 ± 0.03 mmol/l versus 1.26 ± 0.02 mmol/l). Thus, contused tissue demonstrated increased potassium values, when compared to non-contusion tissue. Moreover, in contused tissue dialysate potassium was increasing over the period of monitoring, in contrast to those with diffuse injury, in whom dialysate potassium was progressively falling (Fig. 3).

Discussion

This study demonstrates a clear link between increased glutamate and (failed) ionic homeostasis after human TBI. This positive correlation between glutamate and potassium has already been shown in different animal models [5, 9, 10, 12, 14, 17]. This is to our knowledge the first study to show this relationship in humans after severe traumatic brain injury. However, it is not yet clear whether this increased glutamate leads to the increased potassium or vice versa. The classically proposed mechanism for this linkage is the (over)stimulation of the NMDA receptor by the massively released glutamate after traumatic brain injury, which then in turn releases the intracellular potassium, followed by influx sodium and calcium, leading to cytotoxic edema. However, non specific cell poration could lead both to potassium and EAA efflux. We showed earlier that glutamate is particularly elevated in patients with contusions and that the structural amino acid threonine was also increased, in parallel with the EAA's [4]. This suggests that non-vesicular EAA release may be a major factor in these patients and we are therefore cautious about the assumption that this causes potassium efflux into the extracellular space.

Glutamate has been shown to increase lactate during physiological and pathological brain activation. Pellerin and Magistretti showed in an in vitro study that glutamate release induces glycolysis in astrocytes, resulting in increased extracellular lactate [15]. Lactate then in turn can be preferentially used as a fuel for the neuron to restore ionic homeostasis. Previously, we have shown the clear correlation between glutamate and lactate, supporting this hypothesis [1, 6]. The positive correlation between lactate and potassium fits this theory. In summary, we conclude that extracellular glutamate increases are correlated closely with ex-

tracellular potassium, and this may cause an increase in lactate, by preferentially stimulating glycolysis, especially in astrocytes.

Previously we have shown the clear inverse correlation between glutamate and CBF [20]. The interplay between CBF, glutamate and potasssium can be explained using different mechanisms. First, Bouma showed previously that reduced CBF early after severe human head injury, was present in at least 35% of patients. We speculate that this may result in increased release of glutamate, leading to increased extracellular potassium, and thus cell swelling [3]. Alternatively, it may be that the direct impact of shearing forces on cell membranes can result in ion channel changes and in glutamate release, leading to cell swelling and a secondary reduced CBF, due to astrocyte swelling and compression of micro vessels [18]. The relatively close inverse relationship between potassium and CBF is in accordance with these theories.

Whichever mechanism starts this cascade of events, our results indicate that glutamate release, ionic homeostasis and lactate production (and use) are closely intertwined. Their role in pathophysiological mechanisms after traumatic brain injury is clearly important. However, it remains to be determined to what extent, and at which time after injury, each individual parameter contributes to derangements in cerebral function and metabolism after severe human head injury.

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Correspondence: Egon M. R. Doppenberg, M.D., Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.

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Simultaneous Measurement of Cortical Potassium, Calcium, and Magnesium Levels Measured in Head Injured Patients Using Microdialysis with Ion Chromatography

J. C. Goodman[1], A. B. Valadka[2], S. P. Gopinath[2], M. Uzura[2], R. G. Grossman[2], and C. S. Robertson[2]

[1] Department of Pathology, Baylor College of Medicine, Houston, Texas
[2] Department of Neurosurgery, Baylor College of Medicine, Houston, Texas

Abstract

Potassium, calcium and magnesium were measured in 3717 microdialysate samples in 43 patients with head injury experiencing refractory increased ICP, episodes of jugular venous oxygen desaturation and brain death. Cation analysis was performed with 'ion chromatography'.

Potassium levels remained stable until severe physiological deterioration occurred, whereupon they increased 100–400%, usually associated with release of amino-acids including glutamate, aspartate, and taurine into the extracellular space. The magnesium and calcium levels remained unchanged, regardless of the severity of physiological deterioration.

Keywords: Head injury; microdialysis; cortical potassium and calciumlevels; ion chromatography.

Introduction

Ionic shifts between the intracellular and extracellular space may indicate loss of cellular membrane integrity or altered membrane cation channel function following head injury. Ion selective electrodes or atomic absorption spectroscopy have traditionally been used to study ionic alterations following head injury, but these methods permit measurement of only one cation at a time. In contrast, high-pressure liquid chromatography (HPLC) with conductometric detection – ion chromatography – permits the concurrent measurement of multiple cations in microdialysate samples. We used this technique to measure potassium, calcium, and magnesium levels in microdialysate samples from head injured patients.

Materials and Methods

Potassium, calcium and magnesium were measured in 3717 microdialysate samples in 43 patients with head injury experiencing refractory increased intracranial pressure, episodes of jugular venous oxygen desaturation, and brain death. In addition, neurochemical data including glucose, lactate and amino acids was available for these samples. The cortical microdialysis probes were perfused at 2 µl/min with normal saline and 30-minute samples were collected. Cation analysis was performed using HPLC with ion suppression conductimetric detection (DX-100 chromatography system, Dionex Corporation, Sunnyvale CA). Microdialysate samples (10 µl) were diluted 50-fold in deionized water and 25 µl of the diluate was directly injected into the system. The dilution was performed to optimize detection of potassium, magnesium and calcium in the presence of the high levels of sodium introduced by the use of normal saline (NaCl) as the microdialysis perfusate. The mobile phase consised of diluted sulfuric acid. Cation recovery varied inversely with dialysate sodium composition, and was 3–5% under our conditions. This technique permits measurement of sodium, lithium, and ammonium in addition to potassium, calcium and magnesium with separation requiring a 12-minute chromatography period.

Results

Potassium levels remained stable until severe physiological deterioration occurred whereupon they increased 100–400% (mean 10.49 µM baseline; 33.15 µM during deterioration, $p < 0.001$), usually associated with release of amino acids including glutamate, aspartate, and taurine into the extracellular space. The magnesium (mean 1.52 µM baseline; 1.72 µM during deterioration) and calcium (mean 3.16 µM baseline; 3.08 µM during deterioration)

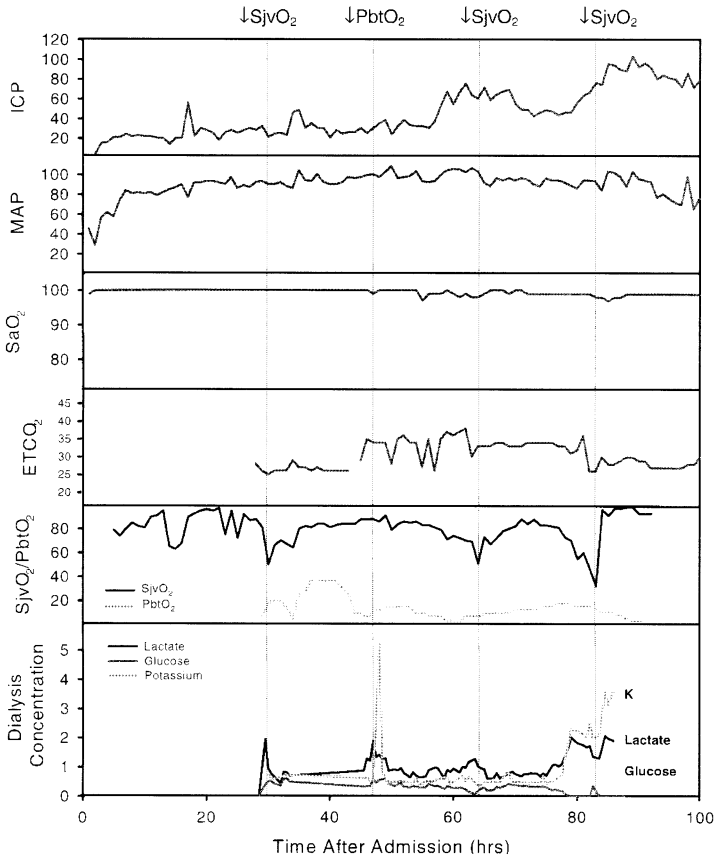

Fig. 1. This composite graph of physiological and microdialysate data demonstrates that jugular venous oxygen desaturations or brain tissue oxygen reductions are associated with elevations in microdialysate potassium levels. The cation alterations are associated with elevations of lactate and reductions in glucose indicative of accelerated glycolysis

levels remained unchanged throughout the course regardless of the severity of physiological deterioration. Neither lithium or ammonium was detected, nor could sodium be measured with accuracy because of the high concentrations of sodium in the perfusate.

Discussion

The physiological cations potassium, calcium and magnesium have differing physical-chemical properties which confer different physiological and potential pathophysiological properties on this ions.

Potassium normally exists at high 155 mM levels intracellularly and accounts for the resting membrane potential due to conductance through leak channels. Extracellular efflux of potassium occurs during membrane depolarization. Potassium alterations have been studied extensively in experimental head injury and stroke. Following either type of injury a massive increase in extracellular potassium and the magnitude of increase correlates with the severity of the injury. Normal levels of potassium in the extracellular space are 6–10 mM while levels of 80 mM or more are seen following trauma, ischemia and during spreading depression.

Extracellular calcium levels are very tightly controlled and are normally maintained at very low levels (1 μM). Fluctuations of calcium are used physiologically in intracellular signaling. Calcium in has been less completely studied in experimental head injury. There appears to be a shift from extracellular to intracellular space by ^{45}Ca isotope studies. Such a shift may raise intracellular levels of calcium sufficiently to activate proteases leading to enzymatic degradation of cellular components and possibly to collapse of the mitochondrial proton gradient which leads to energy production shutdown. The movement of cations is interdependent since the increase of extracellular potassium can be partially blocked by calcium channel blockade.

Magnesium, like calcium, is maintained at low levels intracellularly where it participates in the activity of at least 300 enzymes including many of those involved in anaerobic and aerobic metabolism. The divalent cation stabilizes membranes and competes with calcium. Magnesium has also been studied moderately in experimental head injury and ischemia. Following either

traumatic or ischemic damage, there is a marked decrease in intracellular magnesium measured by nuclear magnetic resonance. Reduced total tissue levels following injury reflect this decrease in intracellular magnesium stores. Under these circumstances, the degree of reduction of magnesium correlates with severity of motor dysfunction.

Conclusions

During pathophysiological deterioration following head injury, potassium egress from cells occurs through cation channels during cellular membrane potential collapse and also occurs with the release of taurine as a counter-regulatory response to cellular swelling. This shift of potassium from the intracellular to extracellular space is reflected in the potassium elevations we observed. If any entry of calcium and magnesium into the cells occurred, it did not result in measurable changes in levels of these cations in the extracellular space by microdialysis. Ion-selective probes may help to elucidate rapid and subtle changes in the studied ions in head-injured patients.

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Correspondence: J. Clay Goodman, M.D., Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Oxygen, Carbondioxide and pH in Severe Human Head Injury

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What does Measurement of Brain Tissue pO_2, pCO_2 & pH add to Neuromonitoring?

F. T. Charbel, W. E. Hoffman, M. Misra, T. Nabhani, and **J. I. Ausman**

Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL

Summary

In this paper the rationale behind utilizing the brain tissue measurements of oxygen, carbon dioxide, pH and temperature is evaluated in the context of ischemia. These parameters were measured using an intraparenchymal multi-parametric brain tissue monitor (Paratrend 7). The need to establish the relevance of this type of monitoring becomes acute as further experience is gained using this kind of technology. Our experience with such a device is presented and is illustrated with two clinical cases. The potential caveats and areas of possible future work are also delineated.

Keywords: Brain tissue monitoring; pO_2; pCO_2; pH; brain ischemia.

Introduction

Traditionally, even a brief interruption of cerebral blood flow was thought to cause permanent neurological damage. Recent research suggests that the brain can survive prolonged periods of incomplete ischemia [3]. Cerebral protective agents, such as pentobarbital, reduce cerebral metabolism [9, 18]. The use of neuroprotective measures can help the brain to tolerate ischemic events [4, 7]. These advances make possible the use of temporary clipping in cerebral aneurysm and tumor surgery. The most serious risk inherent to temporary clipping is a persistent neurological deficit secondary to excessive clip time [15]. The risks associated with the use of hypertensive hypervolemia, cerebral angioplasty, and intra-arterial papaverine for cerebral vasospasm make the need for an instrument that allows continuous and direct assessment of cerebral perfusion even more urgent. Jugular bulb oxygen saturation and cerebral perfusion pressure are global measurements and cannot identify regions of focal ischemia. In an effort to better assess cerebral perfusion, we have begun using a sensor that measures interstitial pH, carbon dioxide, and oxygen tension [1]. We will first provide our rationale for using these parameters as measures of cerebral perfusion, and then outline ways to employ this device via two case histories.

Rationale

Much evidence suggests that neuronal injury in ischemia and trauma share a common mechanism. Activation of lytic enzymes by cytosolic calcium is thought to be the final common pathway of primary neuronal cell death. Acidosis and calcium ions promote free radical formation during reperfusion. Secondary damage to neurons and endothelial cells is promoted by acidosis and calcium influx during ischemia [21]. Glucose and oxygen deprivation secondary to ischemia is the initial step in this process [22]. Oxygen deprivation causes a shift from aerobic to anaerobic metabolism. This greatly increases intracellular lactate concentration, causing cell swelling by an osmotic mechanism [10]. Intracellular accumulation of sodium and chloride secondary to intracellular acidosis and energy failure prevents mitochondrial recovery and proton extrusion [20] Glutamate is removed from the synapse via a sodium-glutamate exchanger [15]. During ischemia, high intracellular sodium concentrations might reverse this transporter, catalyzing the net release of glutamate [19]. Additionally, protons displace calcium from intracellular binding sites, enhancing calcium-catalyzed proteolysis, lipolysis and free radical formation [19]. Finally, acidosis promotes free radical formation which can degrade proteins and damage lipid membranes [16]. Carbon dioxide buffers changes in proton concentration via the carbonic an-

hydrase reaction [2]. Tissue carbon dioxide tension rises during ischemia as bicarbonate is converted to carbon dioxide and water to eliminate excess hydrogen ions [12]. These processes suggest the value of using tissue pH, carbon dioxide, and oxygen tension as measures of cerebral perfusion in neurosurgical patients. The use of this technology in other various clinical procedures further highlights the importance of these parameters [5, 6, 8, 11, 13, 14].

Methods

In our experience at the University of Illinois at Chicago (UIC) from September 1995 to April 1997 we have used the Paratrend 7 (P^7) intraparenchymal multi-parametric brain tissue monitor in patients under an IRB informed consent [1]. The Paratrend 7 probe (Biomedical Instruments, Malvern, PA) measures PO_2, PCO_2, pH and temperature simultaneously. In each case the P^7 was inserted in brain tissue at risk for ischemia by the attending neurosurgeon. The probe is 0.5 mm in diameter and must be inserted 4 cm for all of the sensors to be in brain tissue. The PO_2, PCO_2 and pH sensors are calibrated using precision gases before insertion into the tissue and a 30 min equilibration period is allowed after insertion before recording baseline values.

Case 1

This patient presented with internal carotid artery stenosis TIAs (transient ischemi attack) and impaired cerebrovascular reactivity. The decision was made to perform an EC-IC bypass. Cerebral protection with 9% desflurane was used. Following craniotomy and dural reflection, a P^7 and a Vasamedics laser Doppler blood flow probe were placed to monitor cerebral perfusion. During temporary MCA (middle cerebral artery) occlusion, tissue hypoxia was not accompanied by acidosis and hypercapnia (Fig. 1). Tissue perfusion and PO_2 increased above baseline when the bypass was opened. Postoperatively, the patient tolerated temporary occlusion very well. Recovery was complete, and the patient experienced no further TIAs.

Case 2

61 year old female with an anterior communicating aneurysm. This patient presented several hours after subarachnoid hemorrhage. She was a Fisher grade 3, Hunt-Hess grade 3. An attempt to coil the aneurysm was unsuccessful. While the patient was still sedated in the angiography suite, a burr hole was made, and a Codman ICP sensor and a P^7 were placed to continuously assess cerebral perfusion. This patient received daily Xenon CT scans to measure cerebral blood flow. After waking up from angiography, the patient was abulic. Although not hydrocephalic, the patient was very hypoxic, acidotic and hypercapnic, with PO_2 ranging from 3 to 24 mm Hg, pH ranging from 6.4 to 7.1 and pCO_2 ranging from 89 to 168 mm Hg (Fig. 2). Approximately 24 hours after the bleed, Xenon-CT showed global hypoperfusion, CBF was 15 to 35 ml/100 gr-min. Her neurological status gradually improved, but she remained abulic with little capacity for spontaneous actions.

Discussion

The promise of an intraparenchymal multiparametric brain tissue monitor lays in the neurochemical monitoring of cerebral tissue ischemia. It is fairly safe to state that the Paratrend 7 allows the detection of the onset of ischemia which is best defined as

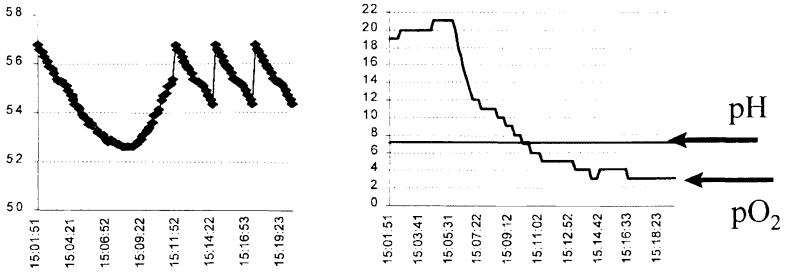

Fig. 1. Graphs show brain tissue PCO_2 (mm Hg; left graph), PO_2 (mm HG) and pH changes (both right graph) following temporary MCA occlusion during EC-IC bypass operation in case 1. Note that tissue hypoxia was not accompanied by acidosis and hypercapnia

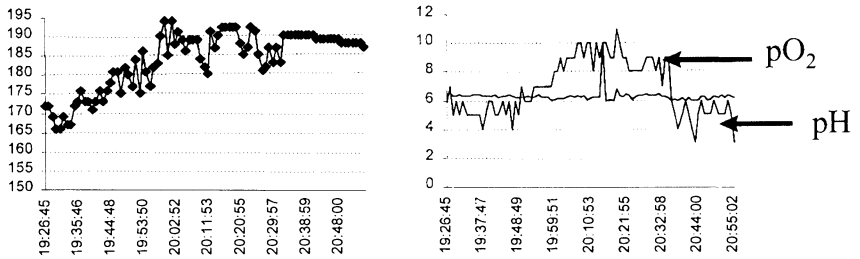

Fig. 2. Graphs show brain tissue PCO_2 (mm Hg; left graph), PO_2 (mm Hg) and pH changes (both on right graph) during acute stage of aneurysmal subarachnoid hemorrhage

a combined decrease in brain tissue pO_2 elevation of CO_2 and a decrease in pH. This detection occurs in real time. In addition to the onset of ischemia, its resolution can be monitored with this technology.

These findings related to brain tissue parameter changes are consistent whether monitoring is performed in the setting of acute ischemia, such as temporary clipping, a sub-acute situation such as in vasospasm or more chronic ischemia as in AVMs or atherosclerosis and in other clinical conditions [5, 6, 7, 8, 9, 11, 13, 14]. Perhaps just as important will be the potential use of this technology for monitoring and modulation of various cerebral protective therapies. Whereby, if one were to accept the above mentioned parameters as indicative of ischemia, then therapeutic efforts aimed at preserving a homeostatic range for these parameters might be valuable. The caveats of this technology consist primarily at this point of its early stages and the questions that remain to be answered pertain to the validity of brain oxygen monitoring alone and to the potential effect of systemic changes on the cerebral monitored values. Finally, although of great promise at this stage, the effect of using this technology on improving outcome has yet to be determined in prospective appropriately scaled studies.

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Correspondence: Fady T. Charbel, M.D., Department of Neurosurgery (M/C 799), 912 South Wood Street, Chicago, Illinois, Illinois 60612, USA.

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Effect of Hypocapnea on CBF and Extracellular Intermediates of Secondary Brain Injury

P. B. Letarte, A. M. Puccio, S. D. Brown, and **D. W. Marion**

Department of Neurological Surgery, Maywood, Illinois

Summary

We examined the metabolic response of the brain underlying subdural hematomas or surrounding contusions to hyperventilation and looked for evidence of ischemia.

Twelve consecutive patients with severe traumatic brain injury (TBI) (GCS < 8) who required surgery for evacuation of subdural hematoma or hemorrhagic contusion were studied. At surgery, a microdialysis catheter was placed into the cortex in a gyrus adjacent to the contusion or underlying the subdural hematoma. A thermal diffusion flow probe was placed on the cortex directly above the dialysis catheter.

On days 1 and 3 post injury, two trials of hyperventilation were performed which dropped the patients' pCO_2 10 mm Hg for 30 minutes. Monitoring of CBF and collection of dialysis fluid continued throughout each hyperventilation trial. Data was analyzed for a three hour window surrounding each hyperventilation.

Brief periods of hyperventilation did not cause a significant elevation of the extracellular lactate/pyruvate ratio or glutamate level in areas of the brain likely to be the most vulnerable to secondary injury. In spite of hyperventilation leading to a significant decline in local CBF in 20% of the trials, there was no evidence of ischemia or excitatory amino acid release associated with hyperventilation.

Keywords: Brain injury; microdialysis; thermal diffusion flow: effect of hyocapnea on CBF; extracellular metabolite.

Introduction

Cerebral blood flow (CBF) is typically less than 50% of normal early after severe traumatic brain injury, and is lowest underlying subdural hematomas or surrounding contusions [2, 6, 8, 10, 11]. It has been suggested that low CBF values indicate ischemia and that hypocapnic therapy should therefore be avoided. We examined the metabolic response of injured brain to hyperventilation and looked for evidence of ischemia.

Hyperventilation induced hypocapnia has been central to the treatment of elevated intracranial pressure (ICP) for many years. Hypocapnia reduces ICP by reducing CBF via vasoconstriction. Studies on the effects of hypocapnia on CBF, however, have demonstrated that hypocapnia may well induce ischemia.

After TBI, CBF can drop to less than 30 mL/100 gm/min during the first 8 hours and may be less than 20 mL/100 gm/min during the first four hours [1, 2, 3, 10, 11]. These levels are near traditionally accepted ischemic thresholds. It is feared that further reductions in CBF resulting from hypocapnia could result in further secondary injury.

Using jugular venous oxygen saturations, Cruz (1991) found a mean SjO_2 of $45 \pm 8\%$ with an arterial $pCO_2 < 22$ mmHg as opposed to a SjO_2 of $59 \pm 3.2\%$ with a pCO_2 of 32 mmHg [4]. Jugular venous oxygen saturations of less than 50% are considered desaturations. Desaturations are most common with low CBF and prolonged or profound episodes of desaturation are associated with a poor outcome [3, 12]. Sheinberg (1992) found desaturation in 10 of 33 patients in association with a $pCO_2 < 28$ mmHg [12].

Obrist and coworkers (1984) found that 15 of 31 patients in one study had decreases in ICP in response to hyperventilation but that 29 of 31 had declines in CBF [9]. They also found that aggressive hyperventilation to pCO_2 of 23.2 ± 2.8 caused 10 patients to have AVO_2 of 10.5 ± 0.7 and CBF of 18.6 ± 4.4 at or near the ischemic threshold for both measurements [9].

Unfortunately, the CBF threshold for irreversible ischemia or infarction in TBI is not clearly established. Obrist *et al.* (1984) has suggested that TBI causes a depression of cerebral metabolism and that the reduced CBF that occurs following TBI may be appropriate for the metabolic needs of the brain [9]. Ultimately, CBF studies alone cannot prove the existence

of ischemia because they do not define the metabolic demands of the tissue, and ischemia is defined as blood supply insufficient to meet the metabolic demands of the brain.

We believe, therefore, that the accurate determination of local cerebral ischemia must combine local CBF monitoring with measurements of neurochemical mediators of secondary injury/ischemia. We sought to define the prevalence of local cerebral ischemia and secondary injury during hyperventilation by directly measuring local CBF using a thermodiffusion probe and extracellular markers of ischemia and secondary injury using in vivo microdialysis.

Materials and Methods

Twelve patients with severe traumatic brain injury (TBI) (GCS < 8) who required surgery for evacuation of subdural hematoma or hemorrhagic contusion were studied.

At surgery, after evacuation of the mass lesion a microdialysis probe (CMA 20, 10 mm active end, 20 kD MW cutoff) was placed 1.5 cm into the cortex in a gyrus adjacent to the contusion or underlying the subdural hematoma.

A thermal diffusion flow probe (Flowtronics, Phoenix, AZ) was then placed on the cortex directly above the dialysis catheter.

The thermal diffusion flow probe provided continuous real time monitoring of the cortical blood flow over the dialysis catheter. The interstitial fluid was assayed by the continuous infusion of saline through the dialysis catheter at a rate of 2 microliters/minute. Samples were collected in a refrigerated fraction collector in 30 minute aliquots (60 microliters).

Once collected the samples were stored at -80° until analysis. Lactate and pyruvate levels were measured using High Pressure Liquid Chromatography (HPLC) followed by UV detection. Glutamate levels were obtained via HPLC with fluorescence detection.

On day 1 post injury, two trials of hyperventilation were performed. Two trials of hyperventilation were again performed on day 3. To perform the study, a pre-hyperventilation arterial blood gas (ABG) was obtained. Patients on the study were routinely maintained at pCO_2 of 35 ± 2 mm Hg. Hyperventilation was begun and continued for 30 minutes. At the end of this period a second ABG was obtained to confirm a drop in pCO_2 of approximately 10 mmHg. The ventilator was returned to its previous setting and a third ABG was obtained at 60 minutes from the start of hyperventilation to confirm a return to baseline pCO_2.

Continuous monitoring of CBF and collection of dialysis fluid continued throughout the hyperventilation trial. Data is reported for the hour preceding hyperventilation, the hour of hyperventilation and recovery and the hour after hyperventilation.

Statistical analysis was done by regression analysis using general estimating equations. Correlations were sought between metabolite levels as a function of CBF and metabolite levels as a function of hyperventilation.

Results

Local CBF ranged from 7–120 ml/100 g/min. The highest levels of glutamate, lactate and lactate/pyr-

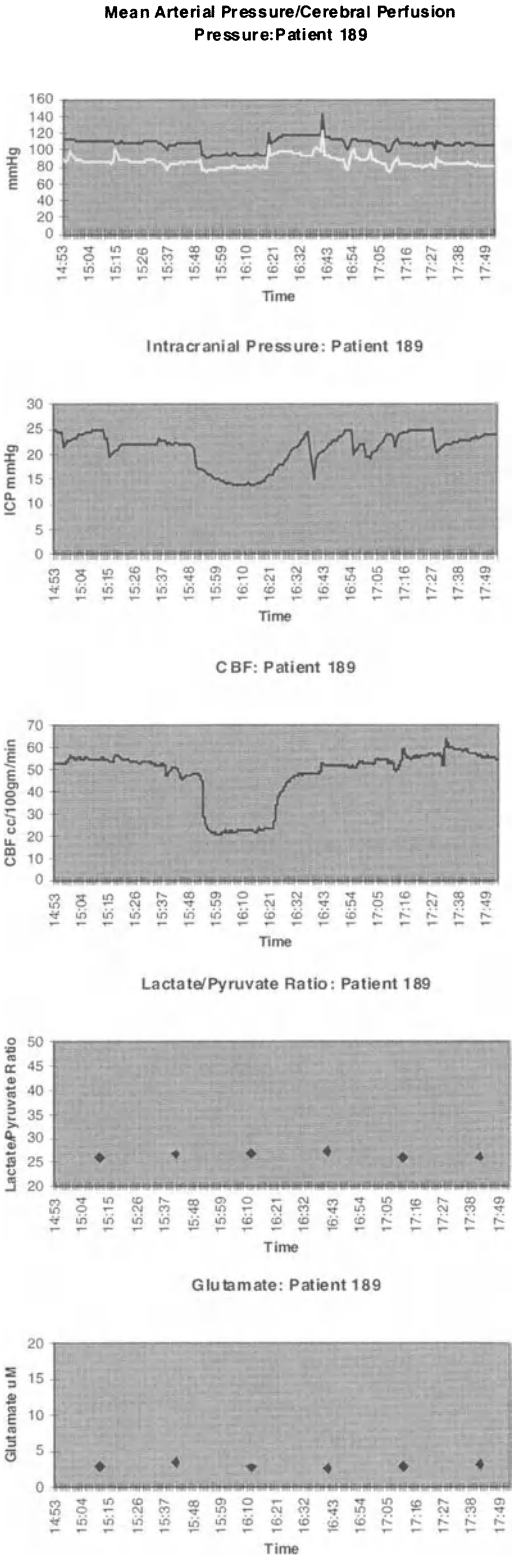

Fig. 1. The results of one hyperventilation trial for patient 189. Note the dip in ICP during the hyperventilation period. Note also the simultaneous dip in CBF. The bottom two panels depict the lactate pyruvate levels and the glutamate levels for the dialysis samples collected during this period. No elevation in these levels can be seen

Table 1. *Regression Analysis Using General Estimating Equations*

Metabolite levels as a function of CBF	
Metabolite	p
Lactate/pyruvate	.14
Glutamate	.21
Metabolite levels as a function of hyperventilation	
Metabolite	p
Lactate/pyruvate	.10
Glutamate	.20

uvate ratios were associated with the lowest of local CBF.

Hypocapnia was associated with a decrease in local CBF in 20% of our patients. In these patients, a decline in ICP from 5–20% was observed. A change in ICP was not observed in the absence of a change in local CBF.

Hypocapnia for 30 minutes was not associated with significant changes in glutamate, lactate, or pyruvate levels or in the lactate/pyruvate ratio in any of our patients. Even when there was a decrease of local CBF by more than 50%, elevations of these levels were not observed.

Discussion

Brief periods of hyperventilation did not cause a significant elevation of the extracellular lactate/pyruvate ratio or glutamate level in areas of the brain likely to be the most vulnerable to secondary injury. In spite of hyperventilation leading to a significant decline in local CBF in 20% of the trials, there was no evidence of ischemia or excitatory amino acid release associated with hyperventilation in any of our trials.

It is important to note that only brief periods of hyperventilation were used in this study. No conclusions can be drawn about more severe or prolonged episodes of hypocapnia. Muizelaar *et al.* (1991) have shown that patients with TBI treated with chronic prophylactic hyperventilation have significantly worse outcomes than patients who are not hyperventilated [7]. We do not see our results to be in conflict with these findings. The practice of prolonged hyperventilation for long term ICP control is still to be avoided.

Our data does help to clarify the role of hyperventilation in the emergent management of intracranial hypertension (ICH). The growing evidence of risk for ischemic damage by hypocapnia has perhaps created some confusion about the emergent management of ICH and impending herniation. Guided by the Guidelines for the Management of Severe Head Injury [5], prehospital providers, emergency room physicians and others faced with emergent ICH have continued to hyperventilate their patients on the valid assumption that the consequences of acute, uncontrolled ICH are far more disastrous than the consequences of brief periods of hypocapnia. Our data now supports this view. It suggests that in the face of impending herniation, hyperventilation can be used as a temporizing life saving maneuver, without causing ischemia, even in the most vulnerable brain regions.

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Correspondence: Peter B. Letarte, M.D., Department of Neurological Surgery, 2106 South First Avenue, Maywood, Illinois 60153.

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Continuous Monitoring of Cerebrospinal Fluid Acid-Base Balance and Oxygen Metabolism in Patients with Severe Head Injury: Pathophysiology and Treatments for Cerebral Acidosis and Ischemia

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

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

Summary

Introduction. Continuous monitoring of cerebral acid-base balance and oxygen metabolism has been introduced in neurointensive care settings. The hypothesis of this study utilizing multimodal neuromonitoring modalities is that hyperventilation and hypothermia improve cerebral acidosis through prevention of cerebral ischemia aggravation in patients with severe head injury.

Patients and Methods. Continuous monitoring of cerebrospinal fluid (CSF) pH, PCO_2, HCO_3^-, base excess (BE), PO_2, SO_2, temperature, lactate and pyruvate (La and Py) measurements were conducted in 8 patients with severe head injury. Temperature-corrected CSF parameters were correlated with those in the jugular blood including oxygen saturation (SjO_2), regional oxygen saturation (rSO_2), intracranial pressure (ICP) and cerebral perfusion pressure (CPP), jugular blood temperature (Tjb), and endtidal PCO_2 ($PetCO_2$). Therapeutic significance of hyperventilation and hypothermia was evaluated.

Results. 1) CSF acidosis was observed in all cases (minimum pH 6.59–7.17) due to increased CSF PCO_2 and/or decreased CSF HCO_3^- and tended to associate with abnormal ICP and/or CPP or ischemic episodes indicated by CSF PO_2 and SO_2, rSO_2, and/or SjO_2 during monitoring. 2) It was more obvious in CSF than in jugular blood that increased PCO_2, La and Py, and/or decreased HCO_3^- resulted in decreased BE and pH. 3) Decreased CSF PO_2 and SO_2 only correlated with severe CSF acidosis. 4) Hyperventilation: Decreased $PetCO_2$ did not always closely correlate with CSF PCO_2 decrease and CSFpH increase. 5) Hypothermia: There were negative correlations of Tjb with CSF pH and SO_2 in all cases, though correlation coefficients were not always high.

Conclusions. CSF acidosis caused by increased CSF PCO_2, La and Py, and/or decreased HCO_3^- tended to associate with abnormal ICP and CPP, and desaturation indicated by CSF SO_2, rSO_2, and/or SjO_2. Hypothermia rather than hyperventilation tends to improve cerebral acidosis and ischemia.

Keywords: Head injury; CSF acid-base balance; oxygen metabolism; cerebral acidosis.

Introduction

It is well-known that cerebral acidosis aggravates ischemic cell injury [24, 25] that is regulated by physicochemical buffering, consumption of metabolic acids, and transmembrane transport of H^+ and HCO_3^- [24]. The ischemic cell damage is caused by several adverse effects of a raised H^+ activity: inhibition of Na^+/H^+ exchange and lactate$^-$ oxidation, inhibition of mitochondrial respiration, and acceleration of coupled Na^+/H^+ and Cl^-/HCO_3^- exchange. The cell damage is secondary to a reduction in intra- and extracellular pH [25].

Cerebrospinal fluid (CSF) pH mainly is determined on the basis of CSF CO_2 and HCO_3^- balance [19], reflects changes in extracellular fluid pH in brain parenchyma [23], and is important in relation to intracellular acidosis of the brain. When respiratory alterations were studied, there was a very close temporal correlation between CSF pH and extracellular pH [4]. However, intravenous HCO_3^- caused a rapid rise in plasma pH and a much slower rise in exracellular pH [4]. CSF pH, or extracellular pH, mainly is regulated by pulmonary ventilation and cerebral blood flow [23].

Old experimental works and clinical observations indicated that not only CSF PO_2 but also brain tissue PO_2 reflect changes in cerebral oxygenation [2, 12, 20, 32]. Furthermore, brain tissue PO_2 monitoring recently has been introduced in clinical settings [10, 15, 28].

Based on previous literature, normal values of CSF parameters were as follows: pH, 7.307–7.439; PCO_2, 45.05–50.5 mmHg; HCO_3^-, 22.5–24.8 mmol/l; PO_2, 41.0–41.2 mmHg; lactate (La), 2.03 mEq/l; pyruvate (Py), 0.079 mEq/l [4, 6, 32].

Continuous monitoring of acid-base balance and oxygen metabolism in CSF as well as in brain paren-

chyma has recently been introduced both experimentally [1, 30] and clinically [3, 5, 8, 31].

Attempts to treat cerebral acidosis in cerebral ischemia have been made in cases of head injury [14, 21], but the lack of a monitoring modality in neurointensive care settings previously has been responsible for insufficient evaluation of therapeutic effects. The hypothesis of our study is that hyperventilation and hypothermia improve cerebral acidosis through the prevention of cerebral ischemia aggravation in patients with severe head injury.

In order to clarify the pathophysiology of, and to establish treatments for, cerebral acidosis and ischemia in patients with severe head injury, continuous monitoring of CSF pH, PCO_2, HCO_3^-, base excess (BE), PO_2, SO_2, temperature, La and Py measurements were correlated with those in the jugular blood, including oxygen saturation (SjO_2), regional oxygen saturation (rSO_2), intracranial pressure (ICP), cerebral perfusion pressure (CPP), jugular blood temperature (Tjb), and endtidal CO_2 partial pressure ($PetCO_2$). Therapeutic significance of hyperventilation and hypothermia was evaluated.

Patients and Methods

The subjects were 8 patients with severe head injury (6 focal, 2 diffuse injuries; age 17–55). Glasgow coma scale scores at admission were 8 or less. CSF parameters were continuously monitored by a multiparameter sensor (Biomedical Sensors) connected to an intraventricular catheter for ICP monitoring (Camino) for 38–288 hours during the two initial weeks of injury. Data were stored in a computer every 10–30 minutes. CSF parameters were mathematically corrected by Tjb after the monitoring because CSF temperature was affected by room temperature if the multiparameter sensor was located in the ventricular catheter. rSO_2 in the bifrontal cerebral cortex was monitored by near-infrared spectroscopy (Invos 3100 or TOS-96), SjO_2 and Tjb were monitored with a jugular catheter (Opticath, Abott). ICP, CPP, and $PetCO_2$ were also evaluated during monitoring. Patient characteristics for age, type of injury, Glasgow coma scale scores (GCS) at admission, monitoring days, analyzed data, special treatments (hypothermia and decompressive craniectomy), and 3-month Glasgow outcome scale (GOS), are shown in Table 1. All data obtained during monitoring, except that considered insufficient due to artifacts, such as suctioning, change in body position, are presented in Table 2. CSF and jugular blood La and Py values were measured 1–4 times during monitoring. CSF parameters at those times are compared with those of jugular blood in Table 3. To evaluate the therapeutic effects of hyperventilation (minimum $PetCO_2$ 12 mmHg) and hypothermia (minimum Tjb 31.7 °C), Pearson's correlation coefficients of CSF parameters with $PetCO_2$ (Table 4) and Tjb (Table 5) were analyzed.

Principal therapies based on ICP (<20 mmHg) and CPP (>70 mmHg), SjO_2 (55–75%), rSO_2 (60–80%) [18] were sedation with midazolam or propofol, hyperventilation, osmotherapy with glycerol or mannitol, and ventricular CSF drainage. Decompressive craniectomy in 6 cases of focal injuries and hypothermia (n = 5) were performed as special treatments.

Results

CSF Parameters During Monitoring (Table 2)

CSF acidosis was observed in all cases (minimum CSF pH 6.59–7.17) during monitoring. Based on mean CSF pH (7.13–7.34), CSF acidosis could be graded as mild 7.2–7.3 (n = 3) and severe ≤7.2 (n = 2). Decreased mean pH (n = 5) is due to increased mean PCO_2 (n = 1) (Fig. 1) or decreased mean HCO_3^- (n = 4). Decreased HCO_3^- or increased PCO_2 was compensated for by decreased PCO_2 or increased HCO_3^-, which resulted in normal pH (n = 2).

Extremely increased mean PO_2 was observed in all cases. However, decreased PO_2 (minimum 17–28 mmHg) and mean SO_2 (<90%) were identified in two cases of severe acidosis.

Table 1. *Background Characteristics of Patients*

Case	Age	Injury	GCS	Monitoring		Treatments		GOS
				injury days	data analyzed (n)	hypothermia	DC	
KB	17	diffuse	8	2–6	38	+	–	GR
AY	39	focal	8	1–5	26	–	+	SD
TM	44	focal	5	1–3	29	–	+	MD
SK	25	diffuse	5	0–8	125	+	–	GR
MK	55	focal	8	0–12	84	+	+	MD
MF	39	focal	8	0–5	33	–	+	MD
MW	44	focal	3	0–2	13	+	+	D
SM	29	focal	8	3–11	68	+	+	SD

* *GCS* Glasgow Coma Score at admission; *DC* decompressive craniectomy; *GOS* Glasgow Outcome Scale at three months after injury; (*GR* good recovery; *MD* moderate disability; *SD* severe disability; *D* dead).

Table 2. *Cerebrospinal Fluid and Associated (SjO₂, rSO₂, ICP, CPP, PetCO₂, and Tjb) Parameters During Monitoring**

Case	N		Cerebrospinal fluid					SjO₂	rSO₂(L)	rSO₂(R)	ICP	CPP	PetCO₂	Tjb
			pH	PCO_2	HCO_3^-	PO_2	SO_2							
KB	38	mean	7.34	40.2	22.1	139	98	72	77	77	10	76	30	35.6
		SD	0.17	17.9	3.7	27.3	1.5	10	14	15	4	13	6	1.6
		range	7.13–7.61	16–64	19–38	91–183	95–99	54–87	50–94	47–95	5–17	45–99	18–41	32.3–38.3
AY	26	mean	7.34	29.3	17	145	98.5	76	80	75	14	91	32	38
		SD	0.08	8.36	1.54	9.2	0.64	15	6	3	2	9	4	0.6
		range	7.2–7.43	21–44	15–19	127–154	97–99	55–98	73–98	71–80	13–17	78–108	28–38	36.9–38.9
TM	29	mean	7.31	56.5	32.7	122	97.8	69	73	72	12	83	41	37.7
		SD	0.04	14.1	8.4	18.5	0.8	7	4	2	6	8	4	0.3
		range	7.17–7.36	38–89	24–51	106–197	94–99	56–80	67–82	67–76	4–25	69–101	35–48	37–38.4
SK	125	mean	7.23	ND	ND	86.4	93.4	79	64	64	15	74	32	35.6
		SD	0.1	ND	ND	21.5	13.5	8	4	6	8	9	6	1.7
		range	7.03–7.32	ND	ND	32–138	19–99	60–96	57–73	53–82	4–59	52–94	15–60	31.7–38.3
MK	84	mean	7.23	50.1	22.8	57.6	84.4	62	72	60	17	103	26	35.3
		SD	0.07	8.1	2.8	14.4	8.4	14	4	14	4	14	3	2
		range	7.13–7.52	18–64	13–28	37–86	63–99	32–99	18–97	16–81	2–16	72–129	21–33	32.3–38.5
MF	33	mean	7.21	35.7	14.5	165	97	68	81	62	8	82	33	37.5
		SD	0.15	19.1	4.5	26.5	7.6	14	6	18	5	10	7	0.2
		range	6.93–7.43	16–75	11–25	86–190	55–99	38–82	74–87	35–96	2–18	58–99	22–42	36.9–37.8
MW	13	mean	7.2	43	18.5	72.7	87.9	73	81	70	48	58	17	33.9
		SD	0.07	5.2	2.4	28.5	14	12	10	2	14	12	2	0.8
		range	7.04–7.31	38–53	13–21	28–116	46–98	54–95	55–92	66–73	19–63	43–76	13–19	32.9–35.1
SM	68	mean	7.13	48	17.4	82	79.6	67	69	69	15	101	20	36.1
		SD	0.11	11.7	3.17	52.5	22	15	9	12	8	13	6	1.5
		range	6.59–7.36	16–88	2–22	17–242	21–99	31–88	55–86	51–95	1–36	55–138	12–30	32.3–38.4
Zupping 1970	39	mean	7.34	46.3	23.5	41.2								
		SD	0.01	0.6	0.3	1.4								

* PCO_2 (mmHg); HCO_3^- (mmol/l); PO_2 (mmHg); SO_2 (%); *SjO_2* jugular bulb oxygen saturation (%); *rSO_2* regional oxygen saturation (%); *L* left; *R* right; *ICP* intracranial pressure (mmHg); *CPP* cerebral perfusion pressure (mmHg); *$PetCO_2$* end-tidal pCO_2 (mmHg); *Tjb* jugular bulb blood temperature (°C); *ND* no data.

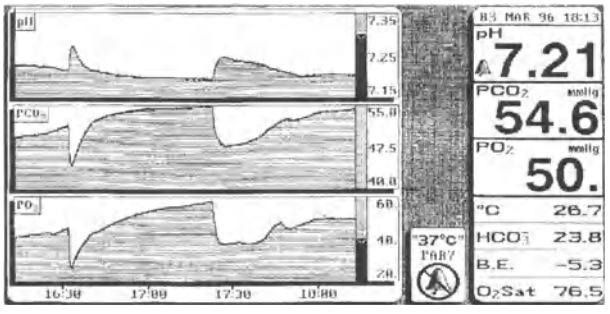

Fig. 1. Case MK, 55-year-old male with right acute subdural hematoma.

Two-hour postoperative monitoring of CSF records changes of pH, PCO_2, PO_2. At 18:30, temperature-corrected (37°C) pH of 7.21, PCO_2 54.6 mmHg, PO_2 50 mmHg, and 26.7°C of CSF temperature, 23.8 mmol/l of HCO3-, −5.3 of base excess (*BE*), and O_2 saturation (*SO_2*) of 76.5 are shown. CSF pH, PCO_2, and PO_2 changes are parallel. Around 17:30, a simultaneous decrease of PCO_2 and PO_2 due to hyperventilation had resulted in pH increase

Comparisons of CSF and Jugular Blood Parameters (Table 3)

Higher PCO_2, lower HCO_3^-, and higher La and Py resulting in lower BE and pH were characteristics of CSF in comparison with jugular blood. There also was a tendency to observe higher PO_2 and SO_2 in CSF, except for two cases of severe acidosis (MW and SM).

Associated Parameters (SjO₂, rSO₂, ICP, CPP, PetCO₂, and Tjb) During Monitoring (Table 2)

Ischemic episodes indicated by decreased SjO_2 (<55%) and/or rSO_2 (<60%) were observed in 6 out of the 8 cases. Five of the six ischemic cases demonstrated CSF acidosis. Mean SjO_2 and rSO_2 values during monitoring, however, tended to stay within normal ranges (SjO_2 55–75%, rSO_2 60–80%) or in-

Table 3. *Comparisons Between Cerebrospinal Fluid (CSF) and Jugular Blood (JB) Parameters**

Case	Day**	pH		PCO_2 (mmHg)		HCO_3^- (mmol/l)		Base excess		PO_2 (mmHg)		SO_2 (%)		Lactate (mg/dl)		Pyruvate (mg/dl)	
		CSF	JB	CSF	JB	CSF	JB	CSF	JB	CSF	JB	CSF	JB	CSF	JB	CSF	JB
KB	3	7.49	7.4	22.1	50.6	19.4	31.1	−2	6.3	157.6	36.1	99.2	65				
AY	1	7.19	7.41	47.9	37.5	18.9	23.4	−9.4	0.3	125.4	57.6	97.3	87.6				
	3	7.4	7.43	21.6	39.9	15.2	26.1	−6.5	2.6	150.8	31.2	99	63.7				
TM	3	7.47	7.39	42.6	49.5	23.5	29.3	−3.1	4.6	136.8	42.8	98.3	73.4				
SK	3	7.29	7.43	ND	46.2	ND	31.6	ND	6.6	94.5	32.4	97.3	79.9				
MK	1	7.19	7.38	51.4	43.9	22.3	26.6	−7.7	1.3	152.4	38.8	98.3	77.1				
	2	7.26	7.42	49.9	39.5	25.7	26.8	−3.8	1.5	64.1	34.7	93.3	81.1				
	7	7.19	7.38	57.2	42	23.6	24.6	−5.6	0.3	74.9	32.3	89.9	47.1				
	9	7.18	7.4	56.7	44.8	22.8	27.6	−6.3	3.6	73	41.2	87.7	72	30.1	13.7	2.96	1.5
MF	0	7.18	7.32	60.8	29.3	25.4	15.2	−4.5	−9.3	111	44.6	96.6	85.8				
MW	0	7.13	7.23	52.7	48	19.3	20	−11.9	−7.2	27.6	58.8	46	84.2	117	67	7.5	4.95
SM	3	7.15	7.46	58	31.1	22.4	22	−8	−0.7	38.1	33.2	57.2	66.8				
	13	7.08	7.42	58.8	34	18.8	22	−12.2	−0.9	49.1	41.1	64.2	71.1	43.6	8.9	2.66	1.02
Zupping	mean	7.34	7.36	46.3	48.4	23.5	26.2			41.2	43			18.5	13.8	0.71	0.78
(1970)	SD	0.01	0.01	0.6	0.7	0.3	0.5			1.4	1			1.27	0.82	0.05	0.06

* *Tjb* Jugular bulb venous blood temperature; *$PetCO_2$* end-tidal PCO_2; *CSF* cerebrospinal fluid; *JB* jugular blood; *ND* no data.
** Days after injury.

dicated hyperemia ($SjO_2 > 75\%$, n = 2; $rSO_2 > 80\%$, n = 2).

Episodes of increased ICP (>20 mmHg) and/or decreased CPP (<70 mmHg) were observed in 6 of the 8 cases. Five of the six abnormal cases demonstrated CSF acidosis. Mean ICP and CPP values during monitoring, however, did not demonstrate abnormalities except in one case (outcome, death).

Hyperventilation ($PetCO_2 < 40$ mmHg) was utilized in all cases. Mean $PetCO_2$ values below 35 mmHg during monitoring were observed in all but one case. Hypothermia (Tjb < 35 °C) was utilized in 5 cases where the mean Tjb values during monitoring were 33.9–36.1 °C. Hyperventilation and hypothermia were utilized in all cases indicating CSF acidosis.

Table 4. *Correlation Coefficients of $PetCO_2$ with pH, PCO_2, HCO_3^-, PO_2, SO_2 in Cerebrospinal Fluid (CSF)**

	N	$PetCO_2$ vs CSF parameters				
		pH	PCO_2	HCO_3^-	PO_2	SO_2
KB	38	−0.89	0.85	0.74	−0.49	−0.69
AY	26	0.16	−0.08	0.11	0.07	0.08
TM	29	0.2	0.42	0.55	−0.1	0.09
SK	125	0.22	ND	ND	−0.22	−0.04
MK	84	−0.3	0.34	−0.14	0.14	0.05
MF	33	0.84	−0.92	−0.52	0.54	0.52
MW	13	−0.33	0.66	0.06	−0.34	−0.54
SM	68	−0.12	0.6	0.47	−0.26	−0.28

* *$PetCO_2$* End-tidal pCO_2; *ND* no data.

Correlation Coefficients of $PetCO_2$ with CSF Parameters (Table 4)

Negative correlations between $PetCO_2$ and CSF pH were observed in four cases (50%). Positive correlations of $PetCO_2$ with CSF PCO_2 and HCO_3^- were identified in 5 of 7 cases. Negative correlations between $PetCO_2$ and PO_2 were identified in 5 cases (63%). However, these correlation coefficients were not close, except in one case each of $PetCO_2$ correlation with CSFpH ($r = -0.89$) and CSF SO_2 ($r = -0.69$) and two cases of correlation with CSF PCO_2 ($r > 0.6$).

Correlation Coefficients of Tjb with CSF Parameters (Table 5)

There were negative correlations of Tjb with CSF pH and SO_2 in all cases. Positive correlation coefficients between Tjb and PCO_2 were observed in 6 of 7 cases. High correlation coefficients ($r > 0.6$) between these parameters, however, were identified in only two cases (KB and MK).

Table 5. *Correlation Coefficients of Tjb with pH, PCO_2, HCO_3^-, PO_2, SO_2 in Cerebrospinal Fluid (CSF)**

Case	N	Tjb vs CSF parameters				
		pH	PCO_2	HCO_3^-	PO_2	SO_2
KB	38	−0.82	0.82	0.54	−0.42	−0.6
AY	26	−0.44	0.51	0.57	−0.17	−0.44
TM	29	−0.1	−0.18	−0.18	−0.3	−0.45
SK	125	−0.36	ND	ND	0.14	−0.18
MK	84	−0.69	0.75	−0.14	0.72	−0.44
MF	33	−0.28	0.13	−0.04	0.01	−0.09
MW	13	−0.09	0.46	0.05	−0.22	−0.31
SM	68	−0.13	0.45	0.38	0.05	−0.16

* *Tjb* Jugular bulb venous blood temperature; *ND* no data.

Discussion

CSF, Jugular Blood, and Associated Parameters in Terms of Acid-Base Balance, La and Py

CSF pH mainly is determined on the basis of CSF CO_2 and HCO_3^- balance [19], reflects changes in extracellular fluid pH in brain parenchyma [23], and is important in relation to intracellular acidosis of the brain.

It is known that, in patients with severe head injury, decreased HCO_3^-, PCO_2, pH with a concomitant increase in both La and Py concentrations were observed in CSF [6, 11, 32]. Decreased PCO_2 is more obvious than decreased HCO_3^- which results in increased pH or respiratory alkalosis in jugular blood [32]. In our preliminary series, the same tendency was confirmed in CSF and jugular blood. However, despite decreased $PetCO_2$ and/or jugular blood PCO_2, there was increased CSF PCO_2 with or without decreased HCO_3^- resulting in severe CSF acidosis during monitoring. CSF PCO_2 changes have been known to mainly be effected by respiratory conditions [23]. Decreased CSF PCO_2 coincided with decreased jugular blood PCO_2 [32] or arterial PCO_2 [6]. Discrepancy between CSF PCO_2 and jugular blood PCO_2 and/or $PetCO_2$ in our series may be caused by disturbance of gas exchange in the brain capillary bed resulting from decreased cerebral circulation. Our data supported the speculation that severe CSF acidosis tended to associate with cerebral ischemic episodes based on SjO_2, rSO_2, ICP, and CPP abnormality.

Recently, acid-base balance in brain parenchyma has been continuously evaluated [8, 30, 31]. The results demonstrated correlation of brain tissue pH decrease with PCO_2 increase [30] and with HCO_3^- decrease [8]. Brain tissue pH monitoring is a more direct evaluation of acid-base balance in extracellular space of the brain than CSF. In reality, brain tissue pH in a contused brain was lower than CSF pH [5]. These evaluations, however, are restricted to very focal region of the brain. CSF monitoring, therefore, may be suitable for control of acid-base balance in the global brain. Further comparative studies are essential for evaluation of the usefulness of these methodologies.

CSF, Jugular Blood, and Associated Parameters in Terms of Oxygen Metabolism

In evaluating cerebral oxygen metabolism, CSF PO_2 has been studied [6, 20, 32], and brain tissue PO_2 has also been introduced in clinical settings recently [12, 15, 28, 30]. In our series, CSF PO_2 values were higher than reported lumber CSF data [6, 20, 32]. The following factors affecting measured PO_2 data should be taken into account: differences of investigated site [20], effects of respiratory oxygen [12], or direct effect of oxygen in air passing to the monitoring catheter through the ventricular tube. In our series, we inserted a multiparameter catheter into the ventricular tube, mean CSF PO_2 data were extremely high in all cases, and therefore the last factor may have the greatest influence.

In our series, there was a tendency for decreased CSF PO_2 and SO_2 to associate with not only severe CSF acidosis but also with episodes of SjO_2 and rSO_2 decrease and ICP and CPP abnormality. It has been concluded that both CSF PO_2 and brain tissue PO_2 reflect changes in cerebral oxygenation [12]. Parallel changes of SjO_2 and brain tissue PO_2 have recently been found [10]. However, there was no clear correlation between brain tissue PO_2 and ICP or CPP [28]. Brain tissue PO_2 can only demonstrate focal changes of oxygenation, and therefore CSF PO_2 probably reflects more global changes that should have a closer relationship with SjO_2 or ICP and CPP.

Hyperventilation for Cerebral Acidosis

Cerebral acidosis caused by accumulation of CO_2 aggravates ischemic brain injury [9]. Hyperventilation is an effective method, with a 24-hour limit, of ameliorating cerebral acidosis [17]. Additionally, prolonged hyperventilation induced intracellular lactate accumulation resulting in the risk of cerebral ischemia [29]. In our series, decreased $PetCO_2$ by hyperventilation did

not correlate with decreased CSF PCO_2 and increased CSF pH. CSF acidosis also was caused by decreased CSF HCO_3^-. Previously, intrathecal administration of $NaHCO_3^-$ for CSF acidosis was attempted, and improvement of CSF pH, cerebral blood flow and both oxygen and glucose metabolism has been reported [21].

On the one hand, recent studies have pointed out that slight extracellular acidosis ameliorates ischemic cell injury [27]. Taking these results into account, the administration of HCO_3^- or tromethamine (THAM) to avoid alkalosis is probably suitable for cerebral acidosis.

Hypothermia for Cerebral Acidosis and Ischemia

Increased intracellular pH caused by hypothermia was confirmed in experimental and clinical studies [7, 26]. The rise in intracellular pH with hypothermia may prevent deleterious effects, caused by ischemia-induced acidosis, on enzyme function, ion permeability, and cellular function. Ischemic neurons at 38 °C, when compared with those at 34 or 36 °C, had a lower periischemic intracellular pH [7]. In our head injury series, there were negative correlations of Tjb with CSF pH. However, interrelations among CSF, extracellular, and intracellular pH should be taken into account.

In head injury series, hypothermia reduces cerebral metabolic rate of oxygen ($CMRO_2$) [16, 22]. However, cerebral blood flow data during hypothermia were not consistent, such as reduction [13, 22] or no change [16]. Therefore, arteriojugular venous oxygen content ($AJDO_2$) also was inconsistent, such as reduction [16, 22] or no change [13]. In our hypothermia cases, SjO_2 or rSO_2 tended to stay within normal range or indicated hyperemia. Furthermore, CSF PO_2 and SO_2 increased and there were negative correlations of Tjb with CSF SO_2 in all cases. These results implied that hypothermia can ameliorate cerebral acidosis and oxygen metabolism or ischemia.

Conclusions

In patients with severe head injury, CSF acidosis caused by decreased HCO_3^-, increased La and Py, and/or increased PCO_2 tended to associate with increased ICP, decreased CPP, and cerebral ischemia based on $CSFSO_2$, rSO_2, and/or SjO_2. The therapeutic effects of hyperventilation and hypothermia were not always satisfactory. However, hypothermia rather than hyperventilation tends to improve cerebral acidosis and ischemia.

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Correspondence: Toshiyuki Shiogai, M.D., Ph.D., Department of Clinical Neurosciences, Kyoto Takeda Hospital, Minamikinuta-cho 11, Nishinanajo, Shimogyo-ku, Kyoto 600-8884, Japan.

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Monitoring by Subcutaneous Microdialysis in Neurosurgical Intensive Care

P. J. A. Hutchinson, M. T. O'Connell, L. B. Maskell, and **J. D. Pickard**

University Department of Neurosurgery and Medical Research Council for Brain Repair, Addenbrooke's Hospital, Cambridge, UK

Summary

Microdialysis is an in vivo sampling technique which provides a powerful approach to monitoring metabolic events. We have performed a study to determine the feasibility and effectiveness of subcutaneous microdialysis in monitoring patients on the Neurosurgical Intensive Care Unit (NICU). A microdialysis probe was placed in the subcutaneous fat of the anterior abdominal wall and perfused with Ringer's solution. Collecting vials were changed every 30 minutes and monitoring continued for 2–6 days. Biochemical analysis of glucose, lactate, and glutamate was correlated with clinical events. The normal ranges of glucose, lactate and glutamate were 3–6 mM, 1–2.5 mM and 5–20 μM, respectively. Periods of low tissue glucose were detected by microdialysis which were not detected by routine plasma sampling. In one patient, following an apparently brief period of hypoxia, there was a prolonged disturbance of tissue chemistry. Another patient with obesity had significantly higher concentrations of dialysate glucose, lactate and glutamate. Monitoring by subcutaneous microdialysis on intensive care units is feasible, reveals unexpected changes in tissue metabolism and might be an important adjunct for the interpretation of intracerebral data.

Keywords: Neurosurgical patients; subcutaneous microdialysis; comparison with plasma sampling.

Introduction

Microdialysis is an in vivo sampling technique which measures the concentration of substances in the extracellular fluid [4, 5, 9]. The principle is based on the passive transfer of substances across a dialysis membrane due to concentration gradients. Pioneered in the laboratory, it has now entered the clinical arena, being applied peripherally [1, 7] and in the brain [3, 6]. We have designed a study to assess whether subcutaneous microdialysis is effective in monitoring biochemical events within the intensive care unit.

Materials and Methods

Ethical approval for the study was obtained from the Local Research Ethics Committee and consent obtained from the patients' relatives. We selected the CMA 60 probe which has a 30 mm dialysis membrane. By using the CMA 106 pump which perfuses at 0.3 μl/min, an in vivo recovery rate approaching 100% is achieved such that the dialysate concentration equates to the true extracellular concentration. Under sterile conditions, a CMA 60 microdialysis probe (CMA Microdialysis, Stockholm, Sweden) was inserted through the skin to lie in the subcutaneous fat of the anterior abdominal wall. The probe was perfused with Ringer's solution (K^+ 4 mM, Na^+ 147 mM, Ca^{++} 2 mM, Cl^- 155 mM) and collecting vials were changed manually every 30 minutes and placed on dry ice. The vial number, time of vial change, and clinical events were recorded on data sheets in order to correlate the clinical and biochemical data.

Off-line analysis was performed using enzymatic spectrophotometry to measure glucose and lactate and high performance liquid chromatography (HPLC) to measure glutamate.

Results

5 patients were studied for a period of 2–6 days. The overall results showed normal ranges of glucose 3–6 mM, lactate 1–2.5 mM and glutamate 5–20 μM. A good correlation was observed between plasma and dialysate concentrations except in patient 5 who suffered from obesity.

Patient 1 was a 59 year old female who presented with poor grade subarachnoid haemorrhage requiring ventilation. The major findings from this patient were that periods of low tissue glucose (1 mM) were detected by microdialysis that were not detected by routine plasma sampling (Fig. 1).

Patient 2 was a 50 year old female who presented with poor grade subarachnoid haemorrhage requiring ventilation. Microdialysis monitoring was performed for 6 days. During bronchoscopy, there were brief periods of hypoxia. This was associated with a prolonged rise in the dialysate concentration of the glucose and lactate (Fig. 2).

Patient 3 was a 51 year old female who also presented with subarachnoid haemorrhage. Her condition

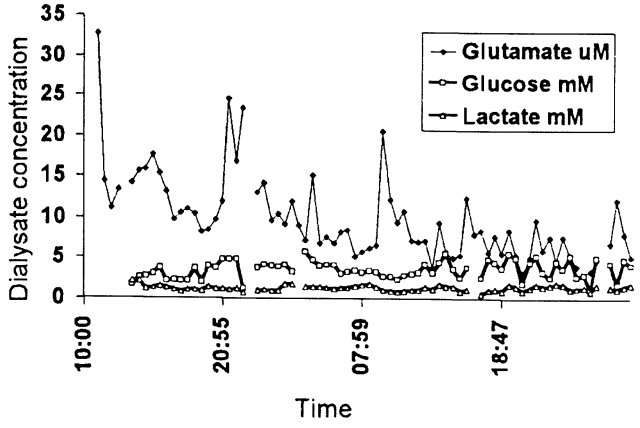

Fig. 1. Dialysate levels of glucose, lactate and glutamate in patient 1. Note the periods of low tissue glucose

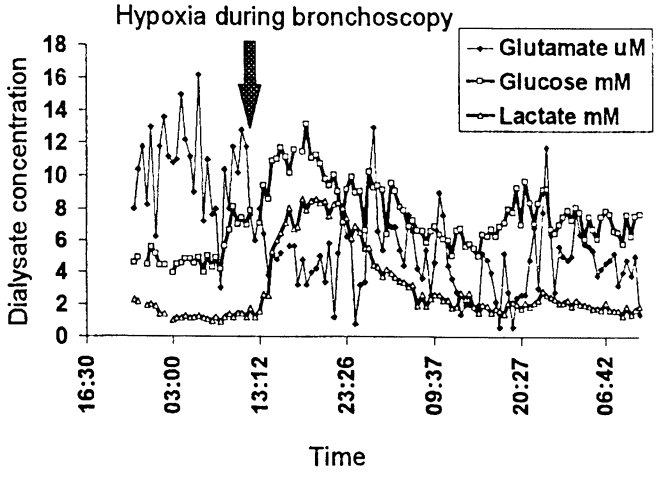

Fig. 2. Dialysate levels of glucose, lactate and glutamate for patient 2. Note the prolonged increase in glucose and lactate concentrations following episode of hypoxia

was complicated by gross obesity. This patient had significantly higher concentrations of dialysate glucose (6–15 mM), lactate (8–15 mM) and glutamate (50–100 μM).

Patient 4 was a 17 year old male with a severe head injury. The glucose and lactate levels were stable but with periods of high glutamate concentrations (up to 30 μM).

Patient 5 was a 68 year old female undergoing surgery for subluxation of the atlas due to rheumatoid arthritis. The probe was placed prior to induction of anaesthesia, monitoring performed during the operation and continued during her elective admission to the NICU until she was awake and extubated. During surgery and on initial admission to the NICU there were no significant changes in the concentrations of the monitored substances. However, during the period of weaning there was a gradual rise in the concentration of glucose and large peaks in the glutamate levels (up to 25 μM).

Discussion

Current biochemical monitoring in intensive care relies on plasma sampling which is intermittent and may miss important changes in tissue metabolism. Microdialysis provides a means of continuous monitoring. We have performed this study to determine whether microdialysis can be effectively utilised for monitoring states of tissue metabolism on the NICU.

The detection of low tissue glucose may have important metabolic implications. Currently glucose monitoring is performed by blood sampling by venepuncture or finger prick, which may not detect periods of low or high glucose concentrations. Microdialysis has been applied to diabetic patients in other situations [2] and our study demonstrates that it may also be useful for monitoring diabetic patients in intensive care. The hypoxic episode during bronchoscopy demonstrated the medium term consequences of apparently brief periods of hypoxia. It is possible that the

rise in tissue glucose and lactate may not represent genuine changes in tissue metabolism but be due to variations in local blood flow. However, other studies have demonstrated that blood flow has very little or no influence on the probe recovery rate of glucose and lactate in human subcutaneous abdominal adipose tissue [8]. The rise in glutamate during the period of weaning from the ventilator is difficult to explain. In comparison with intracerebral microdialysis, there is little data on the relevance of peripheral glutamate levels.

This study demonstrates that subcutaneous microdialysis can be applied as a monitoring method in intensive care units and is effective in detecting changes in tissue metabolism. It may be particularly useful in patients who are metabolically unstable e.g. diabetics and in patients in whom repeated blood sampling is not desirable e.g. neonates. During the study, the biochemical analysis was performed off-line, but for the technique to be applied clinically, on-line analysis will be required.

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Correspondence: Mr. P. J. A. Hutchinson, F.R.C.S., University Department of Neurosurgery and Medical Research Council for Brain Repair, Box 167, Addenbrooke's Hospital, Cambridge, UK.

Multiparametric Systems in Severe Human Head Injury

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Brain Viability and Function Analyzer: Multiparametric Real-Time Monitoring in Neurosurgical Patients

A. Mayevsky[1], A. Doron[2], S. Meilin[1], T. Manor[1], E. Ornstein[3], and G. E. Ouaknine[2]

[1] Department of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel
[2] Department of Neurosurgery, Tel-Aviv Med. Center, Tel-Aviv, Israel
[3] Department of Anesthesiology, Columbia Presbyterian Med. Center, New York, USA

Summary

We have developed the Brain Viability (BVA) and Brain Function (BFA) Analyzers for monitoring the following parameters from the human cerebral cortex cerebral blood flow: (CBF), NADH redox state, Electro corticography (ECoG), brain temperature, extracellular K^+, DC potential and intracranial pressure (ICP). The BVA monitors the first 4 parameters only. The Brain viability probe (BVP) and Brain function multiprobe (BFM) were used during 11 operations and in 18 ICU patients, respectively. Preliminary results from the OR showed that 5 patients exhibited a typical increase in CBF in response to changes in end-tidal CO_2 without a significant change in the NADH redox state. In 4 other patients no changes in CBF and NADH were observed. Two patients exhibited a "steeling response", i.e., a decrease in CBF and an increase in NADH. In 18 comatose patients monitored in the ICU, the ICP, CBF and ECoG were measured correctly in most patients, whereas NADH and K^+ were more problematic. One patient exhibited a typical response, may be due to repeated cortical spreading depression cycles and an ischemic depolarization event. Continuous realtime multiparametric monitoring in neurosurgical patients is feasible and practical in the OR and the ICU. The information provided could be used as a diagnostic tool to guide the procedures or treatment given to the patients.

Keywords: Brain multiparametric function analyzer; real time monitoring; neurosurgical patients.

Introduction

Various technologies have been developed and applied to neurotrauma patients in order to assess the functional state of the brain in vivo and in real-time. The main disadvantage of the existing technology is the single modality of the monitoring instrument. The most commonly used technique in the intensive care units is the intracranial pressure probe inserted into the brain [10]. Other techniques used to directly monitor brain tissue are the EEG and evoked potentials [11]. In the neurosurgical operating room the EEG is very useful and is used, while other techniques, such as CBF monitoring by Laser Doppler flowmetry [6] or blood oxygenation by reflectometry [3], are available and slowly penetrating the field.

The development of multimodality monitoring systems for neurotrauma patients is an ongoing process but most of the parameters used in those systems are related to body or cerebral hemodynamics [2, 5].

We have developed a device measuring simultaneously several brain functions from the same brain location: Relative CBF is monitored by laser Doppler flowmetry; mitochondrial redox state is measured by monitoring NADH fluorescence; surface mini-electrodes are used for monitoring extracellular levels of K^+; the functional state of the brain is evaluated by monitoring electrical activities (ECoG and DC steady potential); brain temperature and ICP [8, 9] were also monitored.

Our approach was to monitor the brain at the "tissue level" rather than the "cellular level". We believe that the various elements of the brain: neurons, glial cell and capillaries, act as an integrated system. Therefore, we monitor brain functions using "mini"-probes rather than the "micro"-probes commonly used by other investigators for monitoring ionic homeostasis. The evaluation of other parameters, such as CBF and NADH redox state, were also adapted to the "tissue" level rather than to the "cellular" level. Our strategy was therefore to develop a multiparametric monitoring assembly in which all the probes have the same type of contact with the sampled tissue volume. The probes do not penetrate the tissue itself, thus

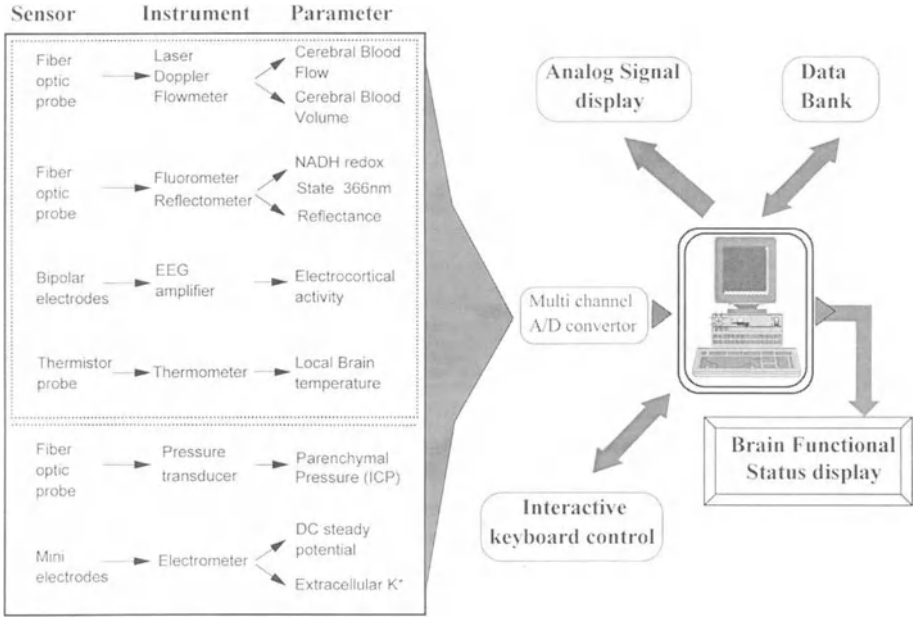

Fig. 1. Schematic presentation of the 2 multiparametric monitoring systems used in the operating room or in the Intensive Care Unit (*ICU*). The Brain Viability Analyzer (*BVA*) is based on the upper 4 sensors while by the addition of the other 3 (lower part) a total of 8 parameters were monitored

avoiding severe damage to the brain or formation of an artificial environment around the sensor, as is created around a penetrating microelectrode [4] or microdialysis probe [1, 12]. The surface monitoring approach is also more acceptable for clinical applications and may provide on-line "physiological mapping" of the brain tissue.

Methods

The multiparametric monitoring system developed for neurosurgical patients includes two kinds of instruments. The basic unit Brain Viability Analyzer – BVA includes 4 sensors (upper 4 in Fig. 1) providing 5 different parameters. By the addition of 3 more sensors a total of 8 signals could be monitored by the BFA (Brain Function Analyzer). Details on the construction of the individual sensors and the BFM have been described previously (7–9). The BVP (Brain Viability Probe) used during operations was held above the brain in such a way that movement of the brain did not affect the constant contact required for reliable monitoring. The BFM was connected to the surface of the brain of head injured patients, using the procedure described recently [7].

Results

The results presented in Fig. 2 were recorded during an STA-MCA anastomosis operation. Gradual occlusion of the internal carotid artery (Occl) while the aneurysmal area was temporarily occluded led to a

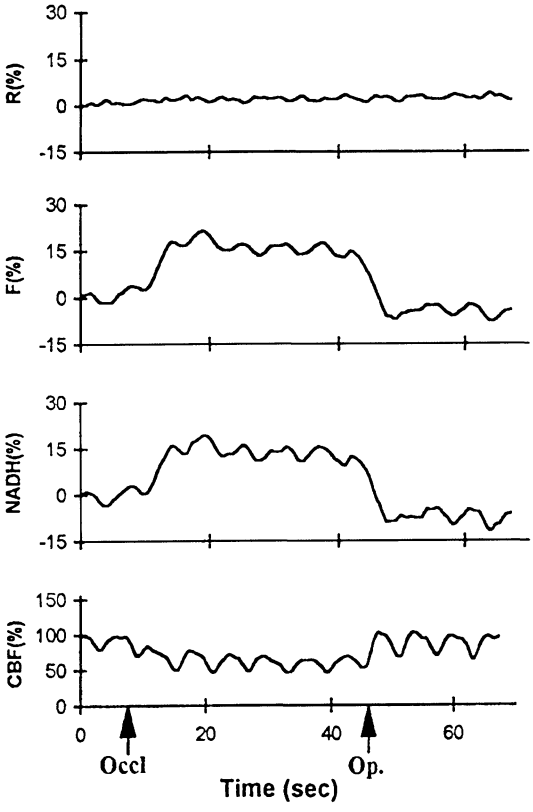

Fig. 2. The metabolic and hemodynamic responses to a brief occlusion of the internal carotid artery during an STA-MCA by-pass operation. R-reflected light at 366 mm. F-fluorescence at 450 nm

large decrease in CBF whereas NADH increased significantly. The recovery of the signals to baseline levels after reperfusion was very fast, indicating that the microcirculation was intact and responsive.

In this patient the reflectance trace was quite stable during the manipulation. In this preliminary study, the EEG and temperature signals are not shown, but will be integrated in the near future. Another perturbation used in other patients was the change in the end-tidal CO_2 levels. The expected increase in CBF under hypercapnia was recorded in only 5 (superficial temporal artery-middle cerebral artery) out of 11 patients while in the other 4 the signal was stable during this episode. In two patients exposed to hypercapnia the CBF began increasing followed by a sharp decrease at higher CO_2 levels. NADH correlated significantly to the CBF and exhibited a large increase during the hypoperfusion caused by high CO_2.

Discussion

The development of the multiparametric monitoring systems for the diagnosis of the neurosurgical patients may increase the efficiency of the treatment given to the patients.

The changes in the individual parameters as well as the inter-relation between the various parameters will serve as an indicator for the responses monitored under drug or other kinds of treatment. The changes in CBF may identify a vascular event alone, namely an increase or a decrease without direct connection to the utilization of this blood by the tissue. If the coupling between the flow and O_2 consumption is intact, a decrease in CBF will be accompanied by an increase in the NADH redox state indicating metabolic stress. On the other hand, when uncoupling occurs between CBF and O_2 consumption, a change in CBF will not have any complementary change in the NADH redox state. Determination of critical values of flow decrease is not simple, and therefore the combination with the NADH redox state data and K^+ levels will enable the identification of critical transition points in the development of a pathological state or the deterioration to brain death [13]. The extracellular K^+ level under normal conditions is in the range of 3–4 mM. Any change in the intactness of the energy supply systems will be reflected in an increase in K^+ due to an inhibition of the Na^+-K^+-ATPase activity. The degree of K^+ increase during pathological states will enable the determination of the degree of brain damage as well as the recovery from such damage (decrease in K^+ levels).

Animal experiments have shown that it is necessary to monitor as many parameters as possible simultaneously and in real time. The combination of ICP, ECoG with multi-functional probes (Multiparametric Analyses MPA) will enable better diagnosis of the functional state of the brain, since the correlation between ICP and ECoG to the prognosis is quite well established in the literature. Also, it is well accepted that brain temperature is correlated to the metabolic usage of energy resources, therefore, temperature monitoring has significant value in directing the treatment to avoid an increase in brain temperature and brain damage.

The monitoring system suggested here has been in use with experimental animals for the last 10–20 years with various probe combinations. The connection between the patient and the monitoring system is performed by an optical fiber probe and passive electrodes which collect information from the surface of the brain. No electrical current flows to the brain and the system is isolated electrically. We want to emphasize that this MPA system was tested in many hundreds of animal experiments including control untreated animals monitored continuously for up to 24 hours. It was found that all signals remained within the normal range during the entire monitoring period. None of the sensors penetrate the brain itself. Therefore, damage to the tissue is minimal and complete recovery is expected after the end of the monitoring period and removal of the MPA and the holder.

In conclusion, we have good reasons to believe that the introduction of the MPA system into routine ICU usage will contribute significantly to the better understanding and treatment of head-injured patients.

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Correspondence: A. Mayevsky, Department of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel.

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Importance of Metabolic Monitoring Systems as an Early Prognostic Indicator in Severe Head Injured Patients

H. Kushi, T. Moriya, T. Saito, K. Kinoshita, T. Shibuya, and **N. Hayashi**

Department of Emergency and Critical Care Medicine, Nihon University School of Medicine, Tokyo, Japan

Summary

We have analyzed and evaluated what is the best metabolic monitoring system to determine the prognosis for maintenance of neurological function in severe head injured patients. Acute subdural hematoma (ASDH) was recognized in fifteen of 22 patients and cerebral contusion in seven in this series. Intracranial pressure (ICP), jugular venous pH and jugular bulb venous oxygen saturation (SjO_2) were continuously monitored as soon as possible following stabilization. The measurement of cerebral blood flow (CBF) was carried out using a stable Xenon-computerized tomography (Xe-CT). After measuring CBF, 3% carbon dioxide (CO_2) loading was conducted to determine CO_2 responses ($\Delta CBF/\Delta CO_2$). In patients who died (D), jugular venous pH showed evidence of acidosis (6.3–7.2) with $\Delta CBF/\Delta CO_2 < 1$ and cerebral metabolic rate of oxygen ($CMRO_2$) < 1.21 within several hours of the trauma. On the other hand, arterial pH was shown to be within the normal range. In vegetative state (VS) and severe disability (SD) patients, jugular venous pH was shown to be within normal range, with $\Delta CBF/\Delta CO_2 < 1$ and $1.44 < CMRO_2 < 1.79$. In all of moderate disability (MD) and good recovery (GR) patients, jugular venous pH was shown to be within the normal range, with $\Delta CBF/\Delta CO_2 > 1$ and $1.65 < CMRO_2 < 1.85$. These results suggest that jugular venous pH, CO_2 response and $CMRO_2$, were useful as early prognostic indicators in the maintenance of neurological function.

Keywords: Head injury; metabolic monitoring; jugular venous pH; jugular venous oxygen saturation.

Introduction

Recently, there have been large number of reports about the treatment of severe head injured patients in intensive care unit due to the development of physiologic monitoring systems. In our institution, we utilized the measurements of ICP, SjO_2, electroencephalography (EEG) mapping and auditory brainstem response (ABR), in a continuous monitoring system, also cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) using Xe-CT. There is an established early prognostic indicator in severe head injured. We have evaluated what we believe to be the optimal parameters to establish critical limits in severely head injured patients. Further, critical levels of hemometabolic parameters have been proposed which may provide a prognosis for maintenance of neurological function.

Methods

Randomly twenty-two patients, 18–52 years of age, including 15 males and 7 females, with severe head injury but no complicated injuries, Glasgow Coma Score (GCS) of 3 to 7, were included in the study. They were admitted to the Nihon University, Emergency and Critical Care Center from January 1994 to December 1996. It took an average of 35 ± 12 minutes from the scene of the accident to arrive at our facility. All patients underwent computerized tomography (CT) scan within 1 hour of traumatic insult. Acute subdural hematoma was recognized on their initial CT scan in fifteen (60%) of 25 patients and cerebral contusion in seven (28%). If the mass effect showed compression of the brain stem, evacuation of hematoma, external decompression, and ventricular drainage were performed to control ICP. The ICP was measured by a catheter placed within the anterior horn of the lateral ventricle, ipsilateral to the injured side. Jugular venous pH (normal range 7.3–7.4), SjO_2 (normal range 65–75%), end-tidal carbon dioxide ($ETCO_2$) and transcutaneus oxygen (TCO_2) were also continuously monitored. A blood gas monitoring system, Paratrend 7^{TM} (Sensors Limited, UK: tube measuring 0.5 mm in diameter with built-in pH, PCO_2, PO_2 and temperature sensors) was used to continuously determine jugular venous pH and SjO_2, after the position of Paratrend 7^{TM} probe was identified with neck X-ray. The measurement of CBF was carried out using a stable Xe-CT within 12 hours and 72 hours following head trauma. Just after measuring CBF, 3% CO_2 loading was conducted to determine CO_2 responses which were visualized using a subtraction technique. Using these values, ΔCBF (post 3% CO_2 loading CBF minus pre 3% CO_2 loading CBF)/ΔCO_2 (post CO_2 concentration minus pre CO_2 concentration) and $CMRO_2$ were calculated. The outcome at a three-month follow-up was determined by GOS, and divided into five grades: good recovery (GR), moderate disability (MD), severe disability (SD), vegetative state (VS) and dead (D).

Table 1. *The Relationship Between Three Parameters and Prognosis in Neurological Function and Mortality*

GOS	No	pH	$CMRO_2$	$\Delta CBF/\Delta CO_2$
D	6	6.30 < 7.20	< 1.21	< 1
VS & SD	8	7.33 <	1.44 < 1.79	< 1
MD % GR	11	7.36 <	1.65 < 1.85	> 1

D Dead; *VS* vegetative state; *SD* severe disability; *MD* moderate disability; *GR* good recovery; *pH* jugular venous pH; $CMRO_2$ cerebral metabolic rate of oxygen; $\Delta CBF/\Delta CO_2$ CO_2 response.

Results

Good recovery (GR) according to the GOS was observed in 6 patients (24%), MD in 5 patients (20%), SD in 5 patients (20%), VS in 3 patients (12%) and D in 6 patients (24%) at 3-month follow-up. In the dead patients, jugular venous pH showed evidence of acidosis (6.3–7.2) with $\Delta CBF/\Delta CO_2 < 1$ and $CMRO_2 < 1.21$ within several hours of the trauma. Death of the 6 patients was caused by cerebellum tonsillar herniation due to an intractable intracranial hypertension within a week. Most of the arterial blood gases in the 6 dead patients showed from 7.30 to 7.45 within 48 hours following head trauma. On the other hand, jugular venous pH decreased to 7.30 and under. In VS and SD patients, jugular venous pH was shown to be within normal range, with $\Delta CBF/\Delta CO_2 < 1$ and $1.44 < CMRO_2 < 1.79$. In all of MD and GR patients, jugular venous pH was shown to be within the normal range, with $\Delta CBF/\Delta CO_2 > 1$ and $1.65 < CMRO_2 < 1.85$ (Table 1).

Discussion

It is well known that arterial pH is controlled by bicarbonate ion, hemoglobin, serum proteins and phosphate as buffer systems. Consequently, unexpectedly decreased jugular venous pH indicates that an excess hydrogen ion concentration could not be compensated by all of the buffer systems. For these severe conditions, we expected that a cerebral hypothermia would be more effective in regulating dearrangements of the buffer systems including glia and neuron. Furthermore, it has become clear that the jugular pH was correlated with jugular lactic acid. These results suggested that a decreased jugular pH indicates a severe ischemic condition. In all patients who went on to die of their trauma, the jugular venous pH decreased to 7.30 and under. On the other hand, in all of the survivors the jugular venous pH was constantly above 7.30. These facts indicated that the critical level of jugular venous pH related to the prognosis was 7.30. We checked CO_2 response ($\Delta CBF/\Delta CO_2$) for 3% CO_2 loading in severe head injury patients, because of reports that CO_2 response to hypercapnia is more sensitive than that for hypocapnia [4]. Decreased CO_2 response suggested the existence of hypoperfusion, and may be an early prognostic indicator, when the values of CO_2 response ($\Delta CBF/\Delta CO_2$) are under or 1. Shalit *et al.* [2] emphasized that it was impossible to recover consciousness in the condition of $CMRO_2 < 1.4$. Tabaddor [3] and Jaggi [1] suggested that the prognosis in severe head injury was correlated with $CMRO_2$ in the acute phase. Our clinical evaluations have indicated similar results.

These results suggest that jugular venous pH, CO_2 response ($\Delta CBF/\Delta CO_2$) and $CMRO_2$, are useful as early prognostic indicators in the maintenance of neurological function. Although it could not be compared statistically it is possible that venous pH and $CMRO_2$ might be identified as prognostic indicators related to mortality, $\Delta CBF/\Delta CO_2$ as that related to morbidity. We have correlated the critical levels of these parameters with the outcome. We think that regional brain pH, PO_2 and PCO_2, directly measured from brain tissue, should be considered to confirm our results.

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Correspondence: Takashi Moriya, M.D., Ph.D., 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo, Japan 173-8610.

Author Index

Alessandri, B. 21, 25
Ausman, J. I. 41

Brown, S. D. 45
Bullock, R. 17, 21, 25, 31

Charbel, F. T. 41
Choi, S. 21, 25

Doppenberg, E. 17, 21, 25, 31
Doron, A. 63

Goodman, J. C. 35
Gopinath, S. P. 35
Grossman, R. G. 35

Hara, M. 49
Hayashi, N. 67
Hillered, L. 3
Hinton, J. P. 7
Hoffman, W. E. 41
Hudson, G. 7
Hutchinson, P. J. A. 57

Katayama, Y. 11
Kawamata, T. 11
Kinoshita, K. 67
Koura, S. 21
Kushi, H. 67

Letarte, P. B. 45

Maeda, T. 11
Manor, T. 63
Marion, D. W. 45
Marmarou, A. 17
Maskell, L. B. 57
Massie, T. S. 31
Mayevsky, A. 63
Meilin, S. 63
Misra, M. 41
Mori, T. 11
Moriya, T. 67

Nabhani, T. 41
Nara, I. 49

O'Connell, M. T. 57
Ornstein, E. 63
Ouaknine, G. E. 63

Persson, L. 3
Pickard, J. D. 57
Puccio, A. M. 45

Reinert, M. 31
Robertson, C. S. 35
Rossi, S. 17

Saito, I. 49
Saito, T. 67
Saruta, K. 49
Satoh, M. 11
Shibuya, T. 67
Shiogai, T. 49
Stiefel, M. 17

Uzura, M. 35

Valadka, A. B. 35

Woodward, J. 21, 25

Yamamoto, T. 17
Young, H. F. 21

Zauner, A. 17, 25, 31

Index of Keywords

Brain injury 3, 45
Brain ischemia 11, 41
Brain microdialysis 7
Brain multiparametric function analyzer 63
Brain tissue monitoring 41

Cerebral acidosis 49
Cerebral blood flow 31
Comparison with plasma sampling 57
Cortical potassium and calcium levels 35
CSF acid-base balance 49

Effect of hyocapnea on CBF 45
Enadoline 7
Excitatory amino acids 17

Extracellular metabolite 45

Glucose 21
Glutamate 11, 17, 21, 25, 31

Head injury 17, 21, 25, 35, 49, 67

Ion chromatography 35

Jugular venous oxygen saturation 67
Jugular venous pH 67

Lactate 21, 25, 31

Metabolic monitoring 67
Microdialysis 3, 11, 17, 21, 25, 35, 45
Neurochemical monitoring 3

Neuroprotection 7
Neurosurgical patients 57, 63

Oxygen metabolism 49

pCO_2 41
pH 41
PO_2 41
Potassium 31

Real time monitoring 63

Severe human head injury 31
Subcutaneous microdialysis 57

Thermal diffusion flow 45

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Intracranial Pressure and Neuromonitoring in Brain Injury

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Information is provided from the basic and clinical sciences on the mechanisms damaging the brain from trauma or ischemia. New aspects involve the endoplasmic reticulum, mitochondrial failure, pathobiology of axonal injury, molecular signals activating glial elements, or the emerging therapeutical role of neurotrophins. Experimental issues involve a better analysis of the ischemic penumbra, the salvagable tissue.

Therapeutic contributions reach from the environmental influence to gene expression, including neuroprotection, such as hibernation – mother nature's experiment – or hypothermia which is reported to induce cell swelling. Treatment issues deal also with thrombolysis and combination therapies, or with the clearance of adverse blood components – LDL/fibrinogen – by a novel procedure using heparin.

Other highlights are discussing the specificities of pediatric vs. adult brain trauma, or the evolving role of the Apolipoprotein-E e4 gene in severe head injury. An update is also provided on an online assessment of the patient management during the pre- and early hospital phase in Southern Bavaria.

The empirical observation of neuroworsening is analyzed in further details, whether this is a specificity autonomously driving the posttraumatic course. Finally, the unsolved question why drug trials in severe head injury have failed so far in view of the promising evidence from the laboratory is subjected to an expert analysis.

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Sachsenplatz 4–6. P.O.Box 89. A-1201 Wien. Fax +43-1-330 24 26. e-mail: books@springer.at. **Internet: www.springer.at**
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