Acta Neurochir (2005) [Suppl] 95: 113–116

Printed in Austria

Monitoring of autoregulation using intracerebral microdialysis in patients with severe head injury

M. T. V. Chan[1], **S. C. P. Ng**[2], **J. M. K. Lam**[2], **W. S. Poon**[2], and **T. Gin**[1]

[1] Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
[2] Division of Neurosurgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Summary

We evaluated the performance of continuous intracerebral microdialysis to indicate the autoregulatory reserve in 36 severely head-injured patients. All patients received standard treatment with intracranial pressure (ICP) monitoring. A microdialysis probe was placed in the frontal cortex anterior to the ICP catheter. Perfusate was collected frequently and extracellular concentration of glutamate was measured online using enzymatic method. Autoregulatory index was calculated by comparing glutamate concentration with CPP using Pearson's correlation. A correlation coefficient $(r) < -0.5$ is considered as loss of autoregulation, whereas r values approach 0 indicate preserved autoregulation. The change of autoregulatory status over time was correlated with outcome at 6 months.

Three patterns of autoregulatory profiles were identified. Patients with intact autoregulation had satisfactory outcome. Transient impairment of autoregulation may result in favorable outcome if patients responded to treatment. However, persistent loss of autoregulation was associated with poor outcome ($P < 0.001$).

The correlation between extracellular glutamate concentration (by microdialysis) and CPP is a useful index of autoregulation in head-injured patients. It predicts clinical outcome and may be used to guide therapy.

Keywords: Cerebral ischemia; jugular venous oxygen saturation; head injury; intracerebral microdialysis.

Introduction

The ability for the brain to maintain a constant cerebral blood flow (CBF) over a wide range of cerebral perfusion pressure (CPP) provides effective protection against ischemia. This mechanism, known as cerebral autoregulation, is frequently impaired in patients with severe head injury [3, 6, 7, 9]. Therefore, the head injured patient with deranged autoregulation is more susceptible to ischemic insult despite a small decrease in arterial pressure. In this regard, a loss of cerebral autoregulation was associated with unfavorable outcome [7, 9]. Furthermore, the choice of treatment depends largely on an accurate assessment of cerebral autoregulatory reserve. Thus, it is important to monitor cerebral autoregulation during the management of severe head injury.

A number of methods have been used to determine cerebral autoregulation. Common techniques include carbon dioxide reactivity [4], and pressure autoregulation with manipulations of systemic or regional arterial pressure [1, 5]. All these tests require a measure of dynamic CBF response. Glutamate, an excitatory neurotransmitter, is released during cerebral ischemia. The concentration is inversely proportional to cerebral perfusion and can be regarded as a surrogate marker of CBF [10]. Currently, extracellular glutamate can be measured by intracerebral microdialysis. We hypothesized that a change in glutamate concentration in response to spontaneous fluctuation of CPP is an index of autoregulatory reserve. We correlated this autoregulatory index with clinical outcome in patients with severe head injury.

Materials and methods

The present study involved a subgroup of patients from a large ongoing trial investigating the metabolic disturbances after head injury [11]. Patients were eligible for the study if they were 18 years or older, suffering from severe head injury. Patients were excluded if they had predominantly extracranial trauma, were pregnant or known to have a serious premorbid illness. We also excluded patients who are moribund on admission, to whom further active management was not considered. This study was approved by the Clinical Research Ethics Committee, and written informed consent was obtained from patients' relatives.

All patients were treated according to standard protocols targeting control of intracranial pressure (ICP). During episodes of intracranial hypertension, patients receive a treatment cascade that included sedation, muscle relaxation, mannitol administration, cerebrospinal

fluid (CSF) drainage, moderate hyperventilation, mild-to-moderate hypothermia and finally barbiturate-induced coma. Mass lesions with pressure effects were removed promptly with surgery. Invasive arterial pressure was monitored continuously by arterial cannulation whereas ICP was monitored using ventricular catheter. CPP was defined as the difference between mean arterial pressure and ICP.

Intracerebral microdialysis was performed in the frontal cerebral cortex of maximal injury. In patients with diffuse injury, a right frontal catheter was placed. Technically, we used a single burr hole, where a ventricular drain was first inserted. This was followed by the placement of a microdialysis catheter (CMA70; shaft length 60 mm; membrane length 10 mm) anterior to the ventricular drain. The catheter was then perfused with lactate free Ringer's solution using a microinfusion pump (CMA 106, CMA Microdialysis, Stockholm, Sweden). Microdialysates were collected regularly. Extracellular glutamate concentration was measured by enzymatic colorimetry (CMA600 analyzer, CMA Microdialysis, Stockholm, Sweden).

Physiologic data including arterial pressure, ICP and CPP were captured on a personal computer using a purposely designed data acquisition program. Since microdialysis measured the average glutamate concentration over a specific period of time, we calculated the average CPP value over the same period using an interrupted time series technique [2, 8]. Data were divided into segments of 10 data points. An index of autoregulation was then calculated by comparing glutamate concentration with CPP in the epoch using Pearson linear regression. This index, derived from the correlation coefficient (r), varies from -1 to $+1$. An increase in glutamate concentration with decreasing CPP produces an index of high negative value that indicates loss of autoregulation. Conversely, preserved autoregulation maintains glutamate concentration with changes in CPP. This results in an index approaching zero. We defined a loss of autoregulation as the index less than -0.5 [10]. The changes of autoregulation over time was determined using a moving average technique, where new data point was added to the segment as old one was removed (Figure 1).

Patient outcome was evaluated independently at 6 months according to the Glassgow outcome scale. Autoregulatory status was correlated with outcome using Mantel-Haenzsel test. A P value < 0.05 was considered as statistically significant.

Results

We recruited thirty-six patients with severe head injury in the study. There were 22 males and 14 females. The median (range) age was 28 (18–67) years. The median (range) Glasgow coma scale score recorded on admission was 5 (4–8). At six months after injury, seven (19.4%) patients died, 15 (41.7%) were classified as severely disabled. The remaining 17 patients (47.2%) had a satisfactory outcome with good recovery ($n = 6$) or moderate disability ($n = 11$).

Intracerebral microdialysis was started within 12 hours after head injury. The median (range) duration of microdialysis monitoring was 5 (2–9) days. A total of 1,507 hours of data were recorded. After exclusion of artifacts, 1,428 segments of data were available for analysis.

Autoregulation, expressed as the correlation between glutamate concentrations and CPP, changed with time. Longitudinal analysis identified three patterns of autoregulatory profiles. 17 patients had no autoregulatory response despite treatment, seven (41.2%) of these patients died during the first month after injury. At six months follow up, six (35.3%) patients were classified as vegetative and another four (23.5%) patients were severely disabled. On the contrary, four patients demonstrated intact autoregulation throughout the course of treatment. All of these patients had favorable outcome. The remaining 15 patients had fluctuating course of autoregulatory response. 13 of these patients had responded to treatment (craniectomy $n = 3$; barbiturate coma, $n = 5$; others, $n = 5$) and resulted in favorable outcome. In the other two patients, autoregulation was lost for a considerable period of time with transient improvement after treatment. Both patients had poor outcome. The autoregulatory index correlated well with clinical outcome ($P < 0.001$, Table 1).

There was no complication associated with the placement and removal of micodialysis catheter.

Discussion

This study demonstrates that a change of intracerebral extracellular glutamate concentration in relation to CPP is a useful index of the state of cerebral pressure autoregulation. This autoregulatory index changed with time as the patients' conditions improved or deteriorated. Impairment of autoregulation may be caused by the primary brain injury or by secondary insults. In the present study, we have shown that a deterioration in the autoregulatory response is a good predicator of impending secondary insult. Therefore, timely resuscitation guided by the autoregulatory index should prevent further brain damage [7]. We found the overall progress of the autoregulatory responses correlated with the clinical outcome 6 months after injury.

The advantage of using intracerebral microdialysis as a surrogate measure of regional CBF is that the readings are unaffected by routine activities in the intensive care unit. This is in contrast to transcranial Doppler ultrasonography, jugular venous oximetry or laser Doppler flowmetry, for which recordings are often lost during chest physiotherapy, tracheal suction, and cerebrospinal fluid drainage [1, 3, 4, 6, 7]. Microdialysis is also resistant to brain shift and noises related to physiologic phenomena, including arterial pulsation and respiratory cycling. In the present study, only

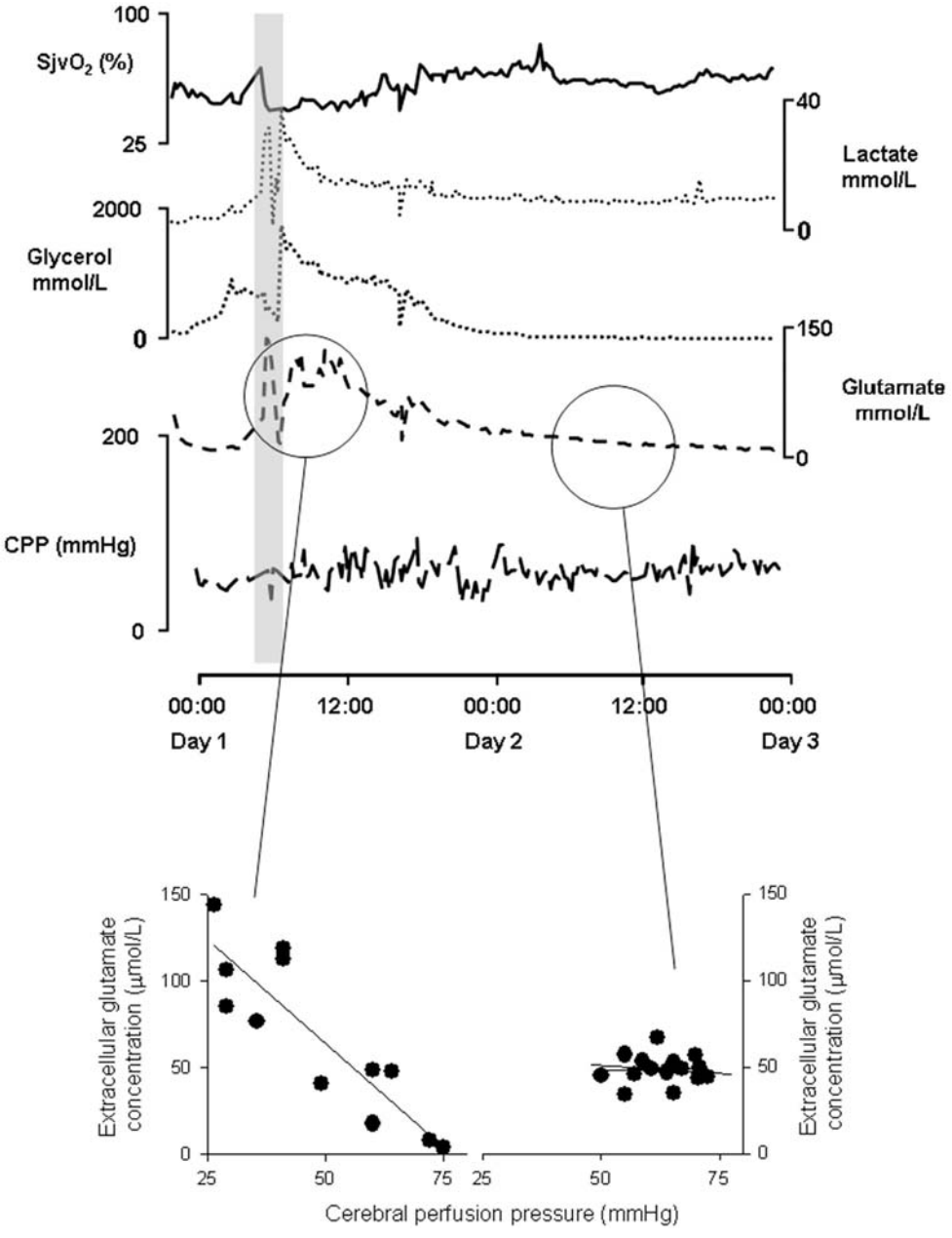

Fig. 1. Changes of intracerebral extracellular concentrations of glutamate, lactate and glycerol, jugular venous oxygen saturation ($SjvO_2$) and cerebral perfusion pressure (CPP) before and after evacuation of intracerebral hematoma in a 67 year-old male after road traffic accident (indicated by the gray rectangle). The correlation between extracellular concentrations of glutamate during absence of autoregulation is shown in the bottom left panel $r = 0.88$, whereas the period with restored autoregulation is shown in the bottom right panel, $r = 10$

5.2% of the data were excluded from analysis. This is due to a partially dislodged catheter and was readily identified as the volume of microdialysate became diminished.

The major problem of microdialysis is that it only measures regional metabolic changes. Therefore, regional ischemia at a distance from the catheter tip may have been missed [13]. We inserted the catheter in the hemisphere with maximal injury because this is the area that is most vulnerable to secondary insult. Sampling from multiple sites will improve the spatial resolution of microdialysis monitoring. However, this will increase the risk of brain hemorrhage and infection.

The safety of microdialysis monitoring has been a concern to clinicians. Animal report indicated a lack

Table 1. *Clinical outcome at 6 months after severe head injury in patients with transient or persistent loss of autoregulation*

Glasgow outcome score		Autoregulatory profile		
		Intact	Transient loss	Persistent loss
Favorable outcome	good recovery	3	3	0
	moderately disabled	1	10	0
Unfavorable outcome	severely disabled	0	1	4
	vegetative state	0	1	6
	death	0	0	7

of pathological changes around the insertion site following implantation of a microdialysis catheter for 7 days [12]. More recent human data suggested that long term monitoring is not associated with complications [13].

In summary, neurochemical monitoring with intracerebral microdialysis is a safe and feasible technique. Its correlation with CPP provides a useful index of cerebral autoregulation that predicts clinical outcome.

Acknowledgments

The study was supported in part by a Competitive Earmarked Research Grant, CUHK4223/98M, from the Research Grant Council, Hong Kong.

References

1. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H (1989) Cerebral autoregulation dynamics in humans. Stroke 20: 45–52
2. Chan MTV, Ng SCP, Lam JMK, Poon WS, Gin T (2005) Re-defining the ischemic threshold for jugular venous oxygen saturation – a microdialysis study in patients with severe head injury. Acta Neurochir [Suppl] (in press)
3. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD (1996) Monitoring of cerebral autoregulation in head-injured patients. Stroke 27: 1829–1834
4. Enevoldsen EM, Jensen FT (1978) Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 48: 689–703
5. Giller CA (1991) A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. Acta Neurochir (Wien) 108: 7–14.
6. Hlatky R, Furuya Y, Valadka AB, Gonzalez J, Chacko A, Mizutani Y, Contant CF, Robertson CS (2002) Dynamic autoregulatory response after severe head injury. J Neurosurg 97: 1054–1061
7. Lam JMK, Hsiang JNK, Poon WS (1997) Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. J Neurosurg 86: 438–445
8. Lam JMK, Smielewski P, al-Rawi P, Griffiths P, Pickard JD, Kirkpatrick PJ (1997) Internal and external carotid contributions to near-infrared spectroscopy during carotid endarterectomy. Stroke 28: 906–911
9. Overgaard J, Tweed WA (1974) Cerebral circulation after head injury, 1: cerebral blood flow and its regulation after closed head injury with emphasis on clinical correlations. J Neurosurg 41: 531–541
10. Peerdeman SM, Girbes AR, Vandertop WP (2000) Cerebral microdialysis as a new tool for neurometabolic monitoring. Intensive Care Med 26: 662–669
11. Poon WS, Ng SC, Chan MT, Leung CH, Lam JM (2002) Neurochemical changes in ventilated head-injured patients with cerebral perfusion pressure treatment failure. Acta Neurochir [Suppl] 81: 335–338
12. Whittle IR, Glasby M, Lammie A, Bell H, Ungerstedt U (1998) Neuropathological findings after intracerebral implantation of microdialysis catheter. NeuroReport 9: 2821–2825
13. Siddiqui MM, Shuaib A (2001) Intracerebral microdialysis and its clinical application: a review. Methods 23: 83–94

Correspondence: Matthew Chan FANZCA, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China. e-mail: mtvchan@cuhk.edu.hk