Acta Neurochir (2002) 144: 679–683
DOI 10.1007/s00701-002-0946-1

Acta Neurochirurgica
Printed in Austria

Clinical Article

Local Changes in Cerebral Energy Metabolism due to Brain Retraction During Routine Neurosurgical Procedures

W. Xu[1], **P. Mellergård**[2], **U. Ungerstedt**[3], and **C.-H. Nordström**[2]

[1] Intensive Care Unit, the First Affiliated Hospital of Kunming Medical College, Kunming, Yunnan Province, P.R. of China
[2] Department of Clinical Neuroscience, Lund University Hospital, Lund, Sweden
[3] Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

Published online July 18, 2002

Summary

Patients and Interventions. Tissue damage caused by brain retraction was evaluated utilizing intracerebral microdialysis in six patients operated on subfrontally for pituitary adenoma. The microdialysis probes (membrane length 10 mm, cut-off 20 kDalton) were placed in cerebral cortex beneath the brain retractor and perfused with Ringer solution at 0.3 µl/min. The microdialysis vials were changed at intervals of 30 minutes and analysed for glucose, pyruvate, lactate, glutamate and glycerol.

Results. During brain retraction regional intracerebral glucose was within normal range in cortical tissue and the levels of lactate, glutamate, and glycerol as well as the lactate/pyruvate ratio were considerably above normal range.

Conclusion. The biochemical analysis shows a pronounced incomplete cerebral ischemia due to brain retraction. The increases in glutamate and glycerol indicate tissue damage and degradation of cell membranes. Intracerebral microdialysis may be a valuable tool in the development of optimal techniques for brain retraction during neurosurgical procedures.

Keywords: Cerebral microdialysis; brain retraction; energy metabolism; ischaemia.

Introduction

Brain retraction is often necessary for adequate exposure during intracranial surgery. The retractors produce a certain pressure on the brain surface and secondary brain tissue damage appears to be a frequent complication [1, 2]. This damage is caused either by direct injury to the tissue or ischemia due to reduction of the regional perfusion pressure [3, 4, 5]. Various intra-operative techniques have been suggested to increase the information of the ongoing pathological processes: brain electrical activity monitoring, regional blood flow monitoring, and retractor blade pressure monitoring [2]. Information regarding cerebral energy metabolism within the affected area would be of particular interest and intracerebral microdialysis has been utilized in a preliminary report regarding metabolic changes during cerebrovascular surgery [6]. Recently, the technique of intracerebral microdialysis has been developed for routine clinical use and biochemical analysis can now be performed and monitored bedside [7, 8]. In this study we report on cerebral energy metabolism in cortical tissue compressed by brain retractors during routine subfrontal extirpation of pituitary adenomas.

Patients and Methods

The study was performed in the Department of Neurosurgery, the First Affiliated Hospital of, Kunming, Yunnan Province, Peoples Republic of China. All patients were treated according to the ethical principles at Kunming Medical College. The surgical procedures were performed in accordance with the clinical routines and were not changed because of the microdialysis study. Eight patients treated with resection of non-secreting pituitary adenomas were included in the study. In two of the patients the microdialysis sampling was interrupted due to technical problems. In the six remaining patients the duration of microdialysis was 165 $\pm$ 31 min (range 120–210 min).

All patients were operated on under general anaesthesia via a right-sided subfrontal approach. Anaesthesia was induced with thiopentone and fentanyl and continued with a combination of enfluran and propofol. After exposure of the right frontal lobe the microdialysis catheter was inserted into cortical tissue immediately beneath the brain retractor. The adenoma surgery was performed according to surgical routines and the position of the brain retractor was usually not changed during this period. There were no episodes

Table 1. *Mean Values ± S.D. of Measured Biochemical Variables as well as the Lactate/Pyruvate (la/py) Ratio During Brain Retraction. For Comparison, Data from Normal Human Brain [7], from Human Brain During Manifest Ischemia [8], and from Normal Piglet Brain (Gärdenfors A et al., Personal Communication) are Included in the Table*

		Glucose mmol/L	Lactate mmol/L	Pyruvate μmol/L	La/py ratio	Glycerol μmol/L	Glutamate μmol/L
	Brain retraction	1.2 ± 0.7	5 ± 2.5	45 ± 38	201 ± 148	161 ± 78	65 ± 77
Human brain	Awake normal	1.7 ± 0.9	2.9 ± 0.9	166 ± 47	23 ± 4	82 ± 44	16 ± 16
	Manifest ischemia	0.1 ± 0.2	8.9 ± 0.2	31 ± 0.2	458 ± 563	573 ± 427	381 ± 236
Piglet brain	Normal	1.8 ± 0.7	2.0 ± 0.8	124 ± 93	18 ± 5	35 ± 11	7 ± 6

of arterial hypo- or hypertension during surgery and the blood levels of haemoglobin, sodium, potassium, glucose and creatinine remained within normal range.

The microdialysis catheter (CMA 70, CMA-Microdialysis Stockholm, Sweden) consisted of a 60 mm long shaft and a 10 mm long dialysis membrane (polyamide; 20,000 mol wt cut-off) with an outer diameter of 0.62 mm. The catheter was connected to a 2.5 ml syringe placed in micro-infusion pump (CMA 106; CMA Microdialysis, Stockholm) and perfused with a Ringer solution (Perfusion Fluid, CMA Microdialysis, Stockholm) at a perfusion flow of 0.3 μl/min. The microdialysis samples were collected in capped microvials (CMA, Microdialysis) to prevent evaporation and analysed for glucose, pyruvate, lactate, glutamate, and glycerol using ordinary enzymatic methods on a CMA 600 Microdialysis Analyser (CMA Microdialysis, Stockholm). For technical reasons the microvials were not analysed bedside in the present study but were kept frozen for later biochemical analyses. The first sample after flushing of the catheters was not analysed. The sampling started more than 1 hour after insertion of the catheters and the microvials were afterwards exchanged at intervals of 30 min during the period of surgery.

The reference values for normal piglet brain (Gärdenfors A *et al.*, personal communication) were obtained from anaesthetized (thiopentone, fentanyl), normoventilated, control animals utilizing identical techniques for microdialysis and biochemical analysis as in the present study.

The biochemical data are given as mean ± S.D. in Table 1 and mean ± S.E.M. in the Figs.

Results

Table 1 gives the mean values ± S.D. of measured biochemical variables as well as the lactate/pyruvate (la/py) ratio during brain retraction. For comparison, data from normal human brain [7], from human brain during manifest ischemia [8], and from normal piglet brain (Gärdenfors A *et al.*, personal communication) are included in the table. During brain retraction, the average value for intracerebral glucose concentration was within normal range while the concentrations of glycerol and glutamate were high. The average concentration of lactate was also high and, since the concentration of pyruvate was very low, the lactate/pyruvate ratio was very high.

Figure 1 a–e illustrates the changes in brain interstitial levels of glucose, lactate, la/py ratio, glutamate, and glycerol over time during brain retraction. Brain glucose concentration was initially slightly below baseline but increased to within normal range during the period of brain retraction. The lactate level was normal 1 h after start of brain retraction but increased to high levels during the following two hours. Lactate/pyruvate ratio was very high already at the first measurement and remained at this very high level during the study. Glutamate was within normal range 1 hour after start of brain retraction but increased to very high levels during the following measurements. Glycerol concentration was also within normal range at the first measurement and increased to very high levels during the period of surgery.

Discussion

The biochemical variables obtained by microdialysis show a pronounced disturbance of cerebral energy metabolism and signs of cell membrane degradation. The pattern indicates that the metabolic derangement is caused by severe incomplete cerebral ischemia caused by the brain retractor.

The biochemical variables chosen give a comprehensive view of cerebral energy metabolism and cell membrane degradation. Glucose is under normal conditions the sole substrate for cerebral energy metabolism. The concentration obtained by microdialysis of interstitial fluid reflects the balance between delivery of glucose from the local blood flow and the utilization rate of the tissue. Baseline concentration in human brain is 1.7 ± 0.9 mmol/L [7] and a decrease to a very low or non-detectable level is an early indicator of complete or near-complete ischemia [8, 9]. During the whole period studied cerebral glucose concentration was within normal range (Fig. 1a) indicating that regional cerebral blood flow and delivery of glucose were sufficient for the glucose utilization rate of the tissue.

Lactate and pyruvate are considered to be diffusible through cell membranes, and measurements of ex-

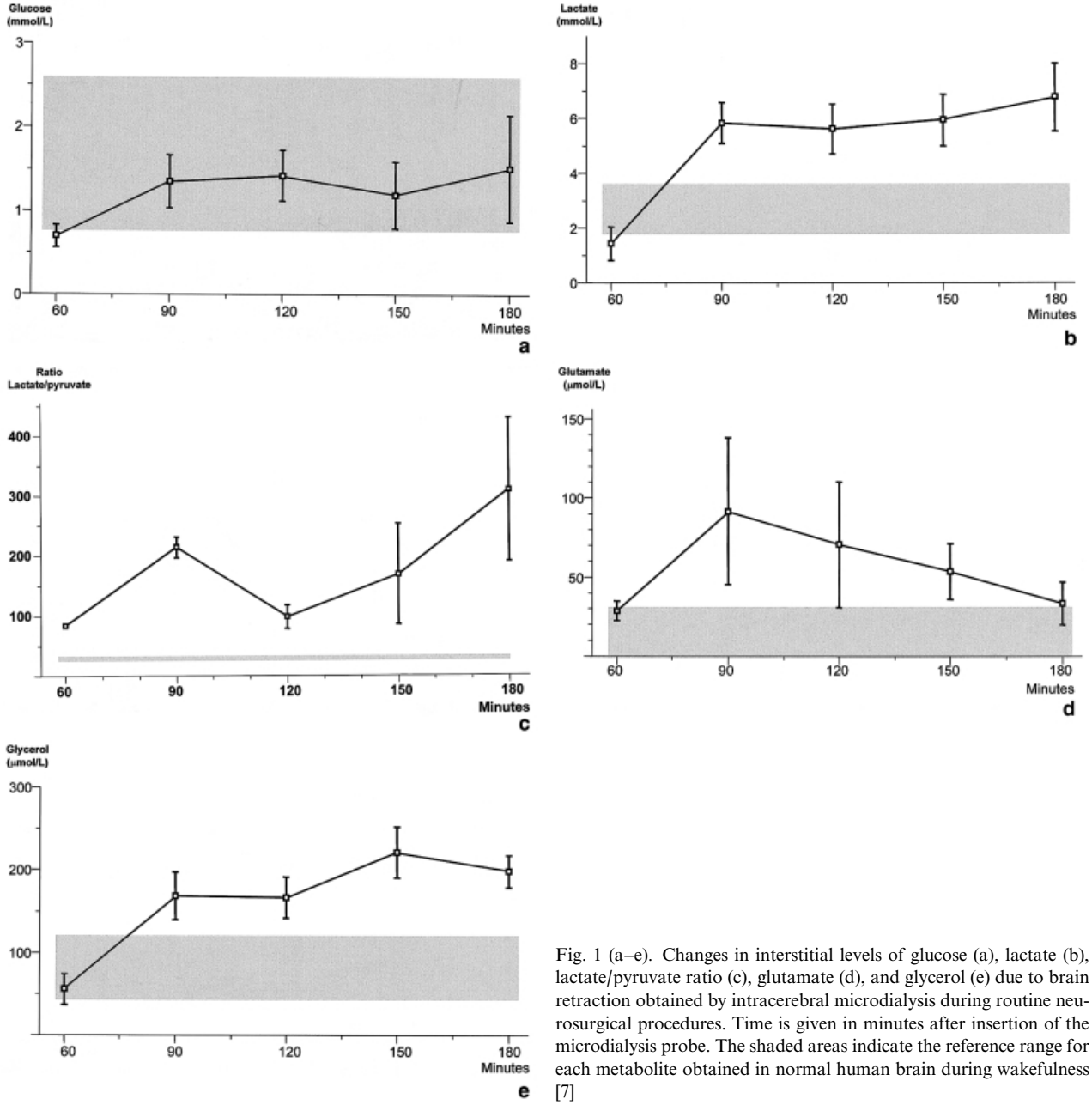

Fig. 1 (a–e). Changes in interstitial levels of glucose (a), lactate (b), lactate/pyruvate ratio (c), glutamate (d), and glycerol (e) due to brain retraction obtained by intracerebral microdialysis during routine neurosurgical procedures. Time is given in minutes after insertion of the microdialysis probe. The shaded areas indicate the reference range for each metabolite obtained in normal human brain during wakefulness [7]

tracellular la/py ratio should therefore reflect cytoplasmatic redox changes [10], which can be expressed in terms of the lactate dehydrogenase equilibrium:

$$\frac{[\mathrm{NADH}][\mathrm{H}^+]}{[\mathrm{NAD}]} = \frac{[\mathrm{Lactate}]}{[\mathrm{Pyruvate}]} \times K_{\mathrm{LDH}}$$

With the present technique baseline la/py ratio has been found to be 23 ± 4 in the normal human brain during wakefulness [7]. The very high la/py ratio obtained already at the 1-hour measurement indicates that brain retraction caused an incomplete cerebral ischemia with insufficient delivery of oxygen. During the following hours the hypoxic conditions were reflected in the continued elevation of the lactate level.

The finding that glucose concentration was within normal limits (Fig. 1a), indicating sufficient supply of substrate, although the la/py ratio was very high (Fig. 1c), indicating insufficient supply of oxygen, is not contradictory. At a normal haemoglobin concentration of 150 g $\times$ l^{-1} and 95% saturation, human arterial blood contains about 9 µmole of oxygen per ml and arterio-venous oxygen difference is about 3 µmole $\times$

ml^{-1} [10]. Thus if CBF is reduced to about 1/3 theoretically all oxygen will be extracted. For glucose the following approximate levels have been described for humans [10]: arterial concentration 5.1 μmole × ml^{-1}; venous concentration 4.6 μmole × ml^{-1}; arterio-venous glucose difference 0.5 μmole × ml^{-1}. Accordingly, during incomplete ischaemia with a gradual decrease in CBF oxygen supply to the brain will be insufficient before the supply of substrate is seriously decreased.

Excitatory amino acids are generally considered to play an improtant role in the development of cell damage in cerebral ischemia and trauma [11, 12, 13, 14]. An increase in interstitial glutamate has been described in patients with spontaneous intracranial haemhorrhages [15, 16] and has also been confirmed in a variety of pathological conditions utilizing different techniques for intracerebral microdialysis and biochemical analysis. In the present study we compared the glutamate levels during brain retraction to those obtained with identical techniques in normal human brain and in human brain with near-complete ischaemia [8, 9, 17]. The interstitial glutamate level was high but within normal range at the 1-hour measurement and the pronounced increase during the following two hours indicates that excitotoxic mechanisms may be of importance also during brain retraction.

Experimental studies with biochemical analyses of rat brain homogenates originally suggested that glycerol might be an indicator of cell membrane degradation [18, 19]. When intracerebral microdialysis was introduced in clinical practice glycerol was proposed as a clinically useful indicator of cell membrane degradation [7, 8, 9, 17] and this variable has been described to increase to very high levels during severe ischemia [8, 17, 20, 21]. In brain tissue, glycerol can be derived primarily from two sources: from the glycoltic chain via glycerol-3-phosphate and from a phospholipase activated degradation of the glycerophospholipids of the cell membranes [7]. It is well established that the latter pathway is rapidly activated in ischemia and other conditions associated with energy failure, which leads to the accumulation of large concentrations of various free fatty acids [22]. In the present study the progressive increase in glycerol is interpreted as caused by membrane degradation due to the hypoxic/ischaemic conditions in combination with the high extracellular levels of glutamate.

The incidence of brain retraction injury is difficult to determine. In a recent review it was summarized that brain injury secondary to retraction occurred in 10% of major cranial base tumour procedures and in 5% of intracranial aneurysm and other tumour surgery [2]. High-resolution CT or magnetic resonance imaging performed after surgery can visualize the lesion but during the surgical procedures the possibilities for detecting imminent tissue damage has been limited to two kinds of measurements: brain electrical activity monitoring, and regional blood flow monitoring.

Brain electrical activity monitoring is usually performed with evoked potentials (EP). For extensive cranial base surgery spontaneous EEG as well as brain stem auditory EP and somatosensory EP have been used concurrently [23, 24]. These techniques are valuable in particular since they can be performed with little operative delay. However, the changes in EEG during anaesthesia limit the usefulness of this technique and monitoring by EP can only be performed in certain regions of the brain [2]. Intra-operative measurements of regional cerebral blood flow (CBF) can be performed by two techniques: laser-Doppler [25] and thermal diffusion [26]. However, both techniques have been considered to have insufficient accuracy for practical routine intra-operative use [2].

Various types of retractor blade pressure monitoring have been used in the laboratory as well as intra-operatively [2]. In a series of experimental studies Andrews *et al.* studied the effects of controlled brain retraction and evaluated tissue damage as well as the protective effects of various treatment protocols utilizing recording of EP and measurements of regional CBF by needle-point laser-Doppler [27, 28, 29]. They concluded that brain retraction should be limited to 15 minutes maximum at a pressure of less than 40 mm Hg, with a 5-min recovery period between retractions [2].

The present study shows that intracerebral microdialysis gives important information regarding tissue damage during brain retraction. The technique can be used intra-operatively but is presumably too complicated and laborious for routine use. However, the microdialysis technique is well suited for experimental evaluation of optimal techniques for brain retraction and the results may later be verified during clinical conditions.

Acknowledgments

We are grateful to our neurosurgical colleagues of the Department of Neurosurgery, the Affiliated Hospital of Kunming Medical College, China, who made this study possible. The study was supported by grants from the Segerfalk Foundation, The Laerdal Foundation,

the Swedish Medical Research Council (14X-003574-28D), and Lund University Hospital. We thank Katarina Nielsen for help with the microdialysis equipment and biochemical analyses.

References

1. Rosenorn J (1987) Self-retaining brain retractor pressure during intracranial procedures. Acta Neurochir (Wien) 85: 17–22
2. Andrews RJ, Bringas JR (1993) A review of brain retraction and recommendations for minimizing intraoperative brain injury. Neurosurgery 33: 1052–1064
3. Rosenorn J, Diemer NH (1982) Reduction of regional cerebral blood flow during brain retraction pressure in the rat. J Neurosurg 56: 826–829
4. Rosenorn J, Diemer NH (1985) The risk of cerebral damage during graded brain retractor pressure in the rat. J Neurosurg 63: 608–611
5. Rosenorn J, Diemer NH (1987) The influence of the profile of brain retractors on regional cerebral blood flow in the rat. Acta Neurochir (Wien) 87: 140–143
6. Bächli H, Langemann H, Mendelowitsch A, Alessandri B, Landolt H, Gratzl O (1996) Microdialytic monitoring during cerebrovascular surgery. Neurol Res 18: 370–376
7. Reinstrup P, Ståhl N, Mellergård P, Uski T, Ungerstedt U, Nordström CH (2000) Intracerebral microdialysis in clinical practice. Normal values and variations during anaesthesia and neurosurgical operations. Neurosurgery 47: 701–710
8. Ståhl N, Mellergård P, Hallström Å, Ungerstedt U, Nordström CH (2001) Intracerebral microdialysis and bedside biochemical analysis in patients with fatal traumatic brain lesions. Acta Anaesth Scand 45: 977–985
9. Nilsson OG, Brandt L, Ungerstedt U, Saveland H (1999) Bedside detection of brain ischemia using intracerebral microdialysis: subarachnoid hemorrhage and delayed ischemic deterioration. Neurosurgery 45: 1176–1184
10. Siesjö BK (1978) Brain energy metabolism. John Wiley & Sons, New York
11. Jorgensen MB, Diemer NH (1982) Selective neuronal loss after cerebral ischemia in the rat: possible role of transmitter glutamate. Acta Neurol Scand 66: 536–546
12. Rothman SM (1983) Synaptic activity mediates death of hypoxic neurons. Science 220: 536–537
13. Simon RP, Swan JH, Griffiths T, Meldrum BS (1984) Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. Science 226: 850–852
14. Wieloch T (1985) Hypoglycemia-induced neuronal damage prevented by an N-methyl-D-aspartate antagonist. Science 230: 681–683
15. Persson L, Hillered L (1992) Chemical monitoring of neurosurgical intensive care patients using intracerebral microdialysis. J Neurosurg 76: 72–80
16. Säveland H, Nilsson OG, Boris-Möller F, Wieloch T, Brandt L (1996) Intracerebral microdialysis of glutamate and aspartate in two vascular territories after aneurysmal subarachnoid hemorrhage. Neurosurgery 38: 12–19
17. Ungerstedt U, Bäckström T, Hallström Å, Grände PO, Mellergård P, Nordström CH (1997) Microdialysis in normal and injured human brain. In: Kinney JM *et al* (eds) Physiology, stress, and malnutrition: functional correlates, nutritional intervention. Lippincott-Raven Publishers, Philadelphia, pp 361–374
18. Gercken G, Bräuning C (1973) Quantitative determination of hydrolysis products of phospholipids in the ischaemic rat brain. Pflügers Arch 344: 207–215
19. Paschen W, van den Kerckhoff W, Hossmann K-A (1986) Glycerol as an indicator of lipid degradation in bicuculline-induced seizures and experimental brain ischemia. Metab Brain Dis 1: 37–44
20. Nordström C-H, Ungerstedt U (1996) Intracerebral microdialysis with bedside analysis of lactate, glucose, glycerol and urea. In: Diemath HE *et al* (eds) Brain protection in severe head injury. W Zuckswerdt Verlag, München, pp 117–119
21. Hillered L, Valtysson J, Enblad P, Persson L (1998) Interstitial glycerol as a marker for membrane phospholipid degradation in the acutely injured human brain. J Neurol Neurosurg Psychiatry 64: 486–491
22. Rehncrona S, Westerberg E, Akesson B, Siesjo Bk (1982) Brain cortical fatty acids and phospholipids during and following complete and severe incomplete ischemia. J Neurochem 38: 84–93
23. Sekhar LN, Nanda A, Sen CN, Snyderman CN, Janecka IP (1992) The extended frontal approach to tumors of the anterior, middle, and posterior skull base. J Neurosurg 76: 198–206
24. Spetzler RF, Hadley MN, Rigamonti D, Carter LP, Raudens PA, Shedd SA, Wilkinson E (1988) Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. J Neurosurg 68: 868–879
25. Fasano VA, Urciuoli R, Bolognese P, Mostert M (1988) Intraoperative use of laser Doppler in the study of cerebral microvascular circulation. Acta Neurochir (Wien) 95: 40–48
26. Carter LP, Erspamer RJ, White WL, Yamagata S (1982) Cortical blood flow during craniotomy for aneurysm. Surg Neurol 17: 204–208
27. Andrews RJ, Knight RT, Kirby RP (1990) Evoked potential mapping of auditory and somatosensory cortices in the miniature swine. Neurosci Lett 114: 27–31
28. Andrews RJ, Muto RP (1992) Retraction brain ischemia: Cerebral blood flow, evoked potentials, hypotension, and hyperventilation in a new animal model. Neurol Res 14: 12–18
29. Andrews RJ, Muto RP (1992) Retraction brain ischemia: Mannitol and nimodipine preserves both cerebral blood flow and evoked potentials during normoventilation and hyperventilation. Neurol Res 14: 19–25

Comment

The authors describe the use of microdialysis to establish the local energy metabolism changes during brain retraction. They describe in detail the microdialysis method and these are correct for the purpose of this study. It might have been interesting to demonstrate that the metabolism level was at a constant value after 1 hour of microdialysis.

In my experience some metabolites require 110 min. to reach the steady state level. The choice of the products that have been analysed (glucose, lactate, pyruvate, lactate/pyruvate ratio, glycerol and glutamate) are an interesting and very justified choice to illustrate the tissue damage due to retraction.

The method of microdialysis is well compared to the advantages and limits of others methods of brain monitoring.

In conclusion the authors wonder if the technique is presumably too complicated for routing use, but in experienced hands the technique is actually simple and very reproducible

J. Caemaert

Correspondence: Carl-Henrik Nordström, Department of Neurosurgery, University Hospital, S-221 85 Lund, Sweden.