Intracerebral microdialysis in severe brain trauma: the importance of catheter location

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Object. Intracerebral microdialysis has attracted increasing interest as a monitoring technique during neurological/neurosurgical intensive care. The purpose of this study was to compare cerebral energy metabolism, an indicator of secondary excitotoxic injury and cell membrane degradation close to focal traumatic lesions (“penumbra zones”) and in remote and apparently intact brain regions of the ipsilateral and contralateral hemispheres.

Methods. The study included 22 consecutive patients with a mean age 44 ± 17 years and an estimated postresuscitation Glasgow Coma Scale motor score less than 5. Altogether 40 microdialysis catheters with radiopaque tips were inserted. Two catheters could not be localized on postoperative computerized tomography (CT) scans and were excluded from the analysis. The perfusates were analyzed at the patient’s bedside for levels of glucose, pyruvate, lactate, glutamate, and glycerol with the aid of a CMA 600 Analyzer. The positions of eight (22%) of the 36 catheters were reclassified after a review of findings on CT scans. Except for pyruvate the values of all biochemical variables and the lactate/pyruvate (L/P) ratio were significantly different in the penumbra zone when compared with mean values found in “normal” tissue ipsilateral to the parenchymal damage and in contralateral normal tissue (p < 0.001). In the penumbra zone a slow normalization of the L/P ratio and levels of glutamate and glycerol were observed. In normal tissue these parameters remained within normal limits.

Conclusions. Data obtained from intracerebral microdialysis can be correctly interpreted only if the locations of the catheters as they relate to focal brain lesions are visualized. A “biochemical penumbra zone” surrounds focal traumatic brain lesions. It remains to be proven whether therapeutic interventions can protect the penumbra zone from permanent damage.

**KEY WORDS • microdialysis • brain trauma • penumbra zone**

**Abbreviations used in this paper:** ASDH = acute subdural hematoma; CBF = cerebral blood flow; CT = computerized tomography; L/P = lactate/pyruvate; rCBF = regional CBF; SD = standard deviation; SEM = standard error of the mean; TBI = traumatic brain injury.
and indicators of secondary excitotoxic injury as well as cell membrane degradation in relation to focal traumatic brain lesions (penumbra zones) and in remote and apparently intact brain regions of the ipsilateral and contralateral hemispheres by performing intracerebral microdialysis and bedside biochemical analyses. Twenty-two consecutive patients with severe TBI and one or more focal intracranial mass lesions were included. The study was designed to test the hypothesis that cerebral metabolism is more affected and more vulnerable in the penumbra zone surrounding focal lesions. In all patients we used probes with radiopaque gold tips, enabling us to determine the positions of the intracerebral microdialysis catheters in relation to focal brain lesions during postoperative CT scanning.

**Clinical Material and Methods**

**Patient Enrollment and Ethical Considerations**

The Department of Neurosurgery, Lund University Hospital is the only neurosurgical department in a geographic area containing 1.6 million inhabitants. Patients with severe TBIs are either directly admitted to the Emergency Department at Lund University Hospital or transferred from 11 local hospitals following initial treatment (resuscitation, endotracheal intubation, controlled ventilation, blood volume substitution, and CT scanning). Annually 60 to 80 patients with severe brain trauma are admitted to our facility. This study only includes patients with focal traumatic brain lesions treated with surgical evacuation. In accordance with routine clinical care, all patients also received an intraventricular catheter for continuous monitoring of intracranial pressure and one or more intracerebral microdialysis catheters for bedside monitoring of cerebral metabolism. Since 1991 the Ethical Committee of Lund University Medical Faculty has approved microdialysis with multiple intracerebral catheters for routine clinical use.

**Patient Characteristics and Clinical Treatment**

The study included 22 consecutive patients with a mean age of 44 ± 17 years and an estimated postresuscitation total Glasgow Coma Scale score less than 8 (motor score < 5). Some basic data regarding the patients are given in Table 1. Fourteen patients presented with a focal, intracerebral hemorrhagic contusion that was evacuated surgically. In several cases this lesion was combined with an ASDH. Altogether, 40 microdialysis catheters were inserted. Two catheters could not be identified on the postoperative CT scan, probably because they had been placed too close to the skull bone, and these are not included in Table 1. All patients were treated according to the principles developed and evaluated at the Department of Neurosurgery, Lund University Hospital (“Lund concept”).1,7,10,18,28 One patient died during the period of intensive care.

**Positioning of the Microdialysis Catheters and the Microdialysis Technique**

The goal of this study was to insert one or more microdialysis catheters into the penumbra zone surrounding a focal lesion, one catheter outside the penumbra zone, and, in

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TABLE 1

Basic data regarding 22 patients with severe traumatic brain lesions*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Lesion</th>
<th>Penumbra Zone</th>
<th>Ipsilat Normal Tissue†</th>
<th>Contralat Normal Tissue</th>
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<tbody>
<tr>
<td>1</td>
<td>7, F</td>
<td>ICH</td>
<td>1</td>
<td></td>
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<td>3</td>
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<tr>
<td>4</td>
<td>26, F</td>
<td>ASDH</td>
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<td>75, M</td>
<td>ICH</td>
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</table>

* EDH = extradural hematoma; ICH = intracerebral hemorrhagic contusion (sometimes combined with ASDH).
† Penumbra indicates that the probe was located close to a focal lesion in an area that displayed a pathological appearance on CT scans. Ipsilateral indicates that the probe was located outside the penumbra zone ipsilateral to a focal lesion but in an area with a normal CT appearance. Contralateral indicates that the probe was placed in an area with a normal CT appearance in the contralateral hemisphere.
‡ Numbers within parentheses indicate that the data were excluded due to interrupted monitoring caused by technical problems.
§ Patient died during the period of intensive care.
In some cases, one catheter in the contralateral normal hemisphere, close to the intraventricular catheter. The surgeon’s judgment on catheter position was recorded. All catheters were CMA 70 catheters with radiopaque gold tips (CMA Microdialysis, Stockholm, Sweden). The actual positions of the catheters, as disclosed by postoperative CT scanning, are given in Table 1.

The microdialysis technique that we developed for routine clinical use has been described previously. Briefly, the microdialysis catheters (CMA 70; CMA Microdialysis) were perfused (Perfusion Fluid; CMA Microdialysis) at a rate of 0.3 μL/minute and the perfusates were collected in capped microvials at 1-hour intervals. The samples were immediately analyzed using conventional enzymatic techniques (CMA 600 Microdialysis Analyzer) and the results were displayed on a bedside monitor.

The perfusates were analyzed for glucose, pyruvate, lactate, glutamate, and glycerol. Because the CMA 600 Analyzer allows the simultaneous analysis of a maximum of four substances, glutamate was analyzed using a separate analyzer unit. The data obtained from cerebral microdialysis were integrated with all other biochemical and online physiological data by using a specially developed computer program (ICU-Pilot; CMA Microdialysis) and included in clinical decision making. No complications or adverse effects caused by the microdialysis catheters were noted.

**Statistical Analysis**

Statistical analysis was performed using a factorial repeated-measures analysis of variance. A post hoc analysis with the Student t-test was performed when this analysis indicated significance. A probability value less than 0.05 was considered statistically significant.

### TABLE 2

**Cerebral interstitial concentrations of chemical metabolites in the normal human brain and in patients with severe brain trauma***

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Penumbra Zone</th>
<th>Ipsilateral Normal Tissue</th>
<th>Contralateral Normal Tissue</th>
<th>Normal Brain (baseline)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose (mmol/L)</td>
<td>1.2 ± 0.1‡§</td>
<td>2.2 ± 0.1‡</td>
<td>3.1 ± 0.1</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>lactate (mmol/L)</td>
<td>6.3 ± 0.1‡§</td>
<td>3.2 ± 0.1</td>
<td>2.9 ± 0.1</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>pyruvate (μmol/L)</td>
<td>170 ± 80</td>
<td>160 ± 50</td>
<td>160 ± 50</td>
<td>170 ± 20</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>45 ± 11‡§</td>
<td>19 ± 0.2</td>
<td>20 ± 0.3</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>glutamate (μmol/L)</td>
<td>63 ± 21‡§</td>
<td>13 ± 1</td>
<td>17 ± 1</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>glycerol (μmol/L)</td>
<td>175 ± 61‡§</td>
<td>53 ± 2</td>
<td>38 ± 1</td>
<td>82 ± 15</td>
</tr>
</tbody>
</table>

* Values are given as the means ± SEMs.
† Data for comparison from Reinstrup, et al.
‡ Value is significantly different from that of contralateral catheter position.
§ Value is significantly different from that of ipsilateral catheter position.
Results

The positions of 38 of 40 microdialysis catheters were observed on postoperative CT scans (Table 1). Two catheters did not function throughout the entire study period and were excluded from the analysis. The microdialysis data were referred to the time of injury, and data obtained between 24 and 96 hours after injury were included in the study. In figures illustrating changes in the various markers, the presentations are limited to 24 to 72 hours after injury to focus on the most variable period.

The positions of eight (22%) of the 36 catheters were reclassified after a review of the CT scans. In two cases the neurosurgeon originally believed that the catheter had been placed in an uninjured hemisphere, whereas the CT scan revealed that the catheter had been placed ipsilateral to minor contusions in tissue that appeared normal radiologically. In six patients the surgeons had intended to insert the catheter outside the penumbra zone but the CT scan revealed that the catheter had been placed close to the contusion area in tissue deemed pathological on neuroimaging studies.

All patients underwent postoperative CT scanning the day after surgery. Subsequent CT scanning was performed only when there was a clinical indication. In no case did the pericontusional edema increase and include the ipsilateral catheter.

Figure 1 shows postoperative CT scans used in the evaluation of probe locations in two cases. In Fig. 1A (obtained in Case 17) two microdialysis probes were placed in the left frontal penumbra zone after evacuation of a hemorrhagic contusion. In Fig. 1B (obtained in Case 3) bilateral epidural hematomas were evacuated and the bone flaps were not replaced. Microdialysis Probe 1 was placed in the penumbra zone below the evacuated epidural hematoma, and Probe 2 was placed in ipsilateral normal brain tissue (the patient had bilateral lesions). In both patients the ventricular catheter used for intracranial pressure monitoring can be seen.

Table 2 presents mean ± SEM values for all biochemical markers during the period 24 to 96 hours after injury. With the exception of pyruvate, all the biochemical variables and the L/P ratio were significantly different in the penumbra zone when compared with mean values in both normal tissue found ipsilateral to the parenchymal damage and contralateral to the site of injury (p < 0.001). Glucose was the only substance demonstrating a difference between ipsilateral normal and contralateral normal tissue; in the latter location the level of glucose was significantly higher (p < 0.001).

Figure 2 shows glucose levels in the three locations during the period 24 to 72 hours after injury. In the penumbra zone and in ipsilateral normal tissue, the mean glucose levels were close to the level found in the normal human brain during wakefulness. In contralateral normal tissue the level of glucose was significantly higher (see also Table 2).

Figure 3 demonstrates lactate levels 24 to 72 hours after injury. The lactate levels were close to normal in ipsilateral normal and contralateral normal tissue during most of the study period. In the penumbra zone, on the other hand, the mean level of lactate remained high with no obvious trend toward normalization. Figure 4 shows that the intracerebral pyruvate level was close to normal limits in all three catheter positions.
The calculated L/P ratios are shown in Fig. 5. In ipsilateral normal and contralateral normal tissue the L/P ratio was very close to the level found in the normal human brain. In the penumbra zone the L/P ratio was high 24 hours after injury and continued to increase during the following 10 hours. A trend toward normalization was observed during the latter part of the study (see also Table 2). A prolonged elevation in the L/P ratio was observed in some patients and was most pronounced in the patient in Case 8.

Glutamate levels were within normal limits in ipsilateral normal and contralateral normal tissue but remained very high in the penumbra zone (Fig. 6). A slow decrease in the mean levels of glutamate was observed during the second half of the study. A prolonged elevation of the glutamate level was observed in some patients and was most pronounced in the patient in Case 8.

Intracerebral glycerol levels were within normal limits in both ipsilateral normal and contralateral normal tissue (Fig. 7). Glycerol was increased in the penumbra zone 24 hours after injury and a further marked increase was observed during the following 10 hours. Normalization of intracerebral glycerol occurred during the latter part of the study period.

The time course of simultaneous changes in L/P ratio, glutamate, and glycerol in the penumbra zone are shown in Fig. 8 for two illustrative cases (Cases 11 and 17). The interruption of data collection between 44 and 52 hours after injury in Case 11 was caused by sampling for pharmacokinetic measurements.

Discussion

To be of direct importance for clinical decision making during neurological/neurosurgical intensive care, the microdialysis technique must fulfill several demands: 1) the microdialysis technique should be standardized to allow a comparison of data between centers; 2) the biochemical variables should be analyzed and displayed at the bedside; 3) the data should be quantitative and the biochemical variables should cover important aspects of cerebral metabolism; and 4) because each microdialysis probe reflects interstitial biochemical values in a small surrounding volume, the locations of the probes in relation to focal lesions must be documented and defined. The introduction of the CMA Microdialysis system in 1995 fulfilled the first three demands. This is the first systematic study to approach the fourth demand and to relate cerebral biochemistry to documented locations of the microdialysis catheters. As shown in Fig. 1, probes with radiopaque tips are usually easy to identify on routine CT scans. Their positions may then be defined in relation to observed focal lesions. It is notable that 22% of the catheters were not located in the sites expected, although these catheters had been inserted during open surgery. In this study we did not try to insert microdialysis catheters into pericontusional tissue in patients in whom open surgery was not performed. In that case it would probably have been necessary to use image-guided surgery to confirm that the probe was placed in the tissue of interest. We assume that, if catheters had been correctly positioned in such an instance, the biochemical data obtained would have been similar to those in the present study.

Studies of rCBF have revealed a pericontusional zone of low rCBF, which often corresponds to hypodensity on plain CT scans. Normal findings on a CT scan do not ensure that the rCBF is normal (or vice versa), but a low-density
pericontusional area has been described to be consistently associated with low rCBF, which contrasts with findings in patients with cerebral infarction. The focus of the present study was to compare cerebral biochemistry in this penumbra zone to that in areas of the brain that display a normal appearance on CT scans. As shown in Table 2 cerebral energy metabolism was severely deranged in the penumbra zone, whereas it was close to normal outside the pericontusional area. Certainly biochemical deterioration may also occur in these “normal” brain areas if severe complications are not effectively treated and the cerebral metabolic perturbation becomes generalized. Nevertheless, the study supports the hypothesis that a biochemical penumbra zone surrounds a focal traumatic brain lesion.

In the present study glucose, pyruvate, and lactate were monitored to reflect cerebral energy metabolism. Under normal conditions glucose is the sole substrate for cerebral energy metabolism. The baseline concentration in the human brain is 1.7 ± 0.9 (mmol/L, mean ± SD) and a decrease to a very low or nondetectable level is an early indicator of complete or near-complete cerebral ischemia. The L/P ratio reflects a cytoplasmatic redox state, which can be expressed in terms of the lactate dehydrogenase equilibrium: (NADH)/(NAD+)** = (lactate)/(pyruvate) × K_{L/P},** where NAD is nicotinamide adenine dinucleotide, NADH is its reduced form, and LDH is lactate dehydrogenase.

The L/P ratio accordingly provides information on tissue oxygenation. Using the present technique the baseline L/P ratio of the normal human brain was found to be 23 ± 4 (mean ± SD) during wakefulness, and the variations observed during changes in physiological parameters (for example, hyper- and hypoventilation) are limited.

The interstitial glucose concentration reflects the balance between capillary delivery and cellular uptake. The significant increase in glucose level in contralateral normal tissue is accordingly interpreted as caused by an rCBF that exceeds metabolic demands. In the penumbra as well as in ipsilateral normal tissue the level of glucose was close to the normal baseline value (Fig. 2 and Table 2). This observation indicates that although rCBF is probably compromised in the penumbra zone, rCBF was sufficient to cover the regional supply of glucose. In contrast, tissue oxygenation was simultaneously and severely jeopardized, as revealed by the significant increase in the L/P ratio (Fig. 5 and Table 2). The observation that the glucose concentration was normal, although tissue oxygenation appeared to be compromised, is not contradictory. At a normal hemoglobin concentration of 150 g/L and 95% saturation, human arterial blood contains approximately 9 μmol O2/ml and the arteriovenous O2 difference is approximately 3 μmol/ml. Thus if CBF is reduced to approximately one third of its normal value, theoretically all O2 will be extracted. In practice such a reduction in CBF cannot maintain a normal O2 supply because the reduction in PO2 will also decrease the O2 diffusion gradient. For glucose the following approximate levels have been described for humans: arterial concentration 5.1 μmol/ml; venous concentration 4.6 μmol/ml; and arteriovenous glucose difference 0.5 μmol/ml. Accordingly, during ischemia induced by a gradual decrease in rCBF, the O2 supply to the brain will be insufficient before the supply of substrate is seriously jeopardized.

As shown in Fig. 5 an increase in the interstitial L/P ratio was obtained in the penumbra zone 24 to 44 hours after injury. An increase of the L/P ratio close to a focal brain lesion has been described after systemic adverse events and pro-
If the cerebral O\textsubscript{2} supply was suddenly severely compromised, an almost instantaneous increase in the L/P ratio would occur, and if the event were transient, the L/P ratio would rapidly return to nearly the normal level.\textsuperscript{16} The protracted increase in the L/P ratio shown in Fig. 5 was caused by transient adverse episodes in several patients, although in some patients prolonged secondary insults contributed to this (Case 8). In contrast to

FIG. 5. Graph showing the intracerebral L/P ratio (mean ± SEM) 24 to 72 hours after injury in the penumbra zone and in ipsilateral and contralateral normal tissue. The value of the L/P ratio in the normal human brain (mean ± SD) is shaded in gray. Circles represent 21 microdialysis catheters in the penumbra zone; triangles, nine catheters in ipsilateral normal tissue; and squares, six catheters in contralateral normal tissue.

FIG. 6. Graph demonstrating intracerebral glutamate levels (mean ± SEM) 24 to 72 hours after injury in the penumbra zone and in ipsilateral and contralateral normal tissue. The level of glutamate in the normal human brain (mean ± SD) is shaded in gray. Circles represent 19 microcatheters in the penumbra zone; triangles, nine catheters in ipsilateral normal tissue; and squares, six catheters in contralateral normal tissue.
Intracerebral microdialysis: the importance of catheter location

![Graph depicting intracerebral glycerol levels (mean ± SEM) 24 to 72 hours after injury in the penumbra zone and in ipsilateral and contralateral normal tissue. The level of glycerol in the normal human brain (mean ± SD) is shaded in gray. Circles represent 21 microcatheters in the penumbra zone; triangles, eight catheters in ipsilateral normal tissue; and squares, six catheters in contralateral normal tissue.](image-url)

FIG. 7. Graph depicting intracerebral glycerol levels (mean ± SEM) 24 to 72 hours after injury in the penumbra zone and in ipsilateral and contralateral normal tissue. The level of glycerol in the normal human brain (mean ± SD) is shaded in gray. Circles represent 21 microcatheters in the penumbra zone; triangles, eight catheters in ipsilateral normal tissue; and squares, six catheters in contralateral normal tissue.

the L/P ratio the average lactate level remained elevated in the penumbra zone, with no obvious tendency toward a decrease (Fig. 3 and Table 2). A discrepancy between a continued increase in the lactate level and a near normalization of the L/P ratio has previously been described after transient ischemia,16,17 but the explanation remains obscure. Given that various forms of cytochrome oxidase deficiencies are known to be associated with increased levels of lactate,23 we may tentatively assume that there is a contribution by mitochondrial damage. Following experimental brain trauma mitochondrial swelling has been described as more pronounced if the primary injury was followed by transient hypoxia.33

Excitatory amino acids are considered to play an important role in the development of cell damage in cerebral ischemia and trauma13,24 and an increase in interstitial glutamate has been described during various pathological conditions in the human brain.3,20,26,31 Although excitotoxic mechanisms may play an important part in TBI, their role is presently unclear. As illustrated in Figs. 5 though 7, the time course of changes in glutamate levels was often similar to changes in the L/P ratio and in the glycerol level, although exceptions were also observed (see Fig. 8).

Increasing amounts of evidence support the hypothesis that glycerol is a clinically useful indicator of cell membrane degradation3,20,26 and may increase to very high levels during severe ischemia.26 With few exceptions, the level of glycerol was very high in the penumbra zone (Table 2 and Fig. 7), indicating a degradation of cellular membranes. In all patients a gradual normalization was observed (Figs. 7 and 8). This normalization probably indicates that cellular degradation has come to an end. Nevertheless, it cannot be excluded that in some cases a large number of cells has succumbed and the normalization of cerebral energy metabolism indicates that the supply of O₂ and substrate is sufficient for the limited demands of the tissue. In ipsilateral as well as contralateral normal tissue the interstitial glycerol level decreased below baseline level in the normal human brain during the latter part of the study. This low level was probably a result of the data having been obtained in patients who were in a state of general anesthesia. Glycerol is related to glycolysis, and a reduction in the glycolytic rate has been described to decrease the interstitial concentration of glycerol in the normal human brain.32

During microdialysis levels of the measured chemical substances correspond to their absolute interstitial concentrations only if a complete equilibration has occurred over the dialysis membrane. The degree of equilibration for a permeable substance (relative recovery) is mainly dependent on the perfusion rate, the length of the dialysis membrane, and the diffusion of the substance in tissue. With the use of clinical microdialysis equipment the estimated recovery for the substances we have described is approximately 70% of the true interstitial level at a perfusion rate of 0.3 μl/minute.12 The recovery may vary during pathophysiological conditions due to changed conditions for diffusion in the tissue, but this variability is of relevance mainly when performing studies of absolute concentration levels (for example, pharmacokinetic studies).9 We have no reason to suspect that pericontusional edema significantly affected the levels of biochemical variables in the penumbra zone. If the interstitial diffusion in this area had influenced our data a decrease in relative recovery would have been expected,6 and in that case, the true interstitial levels of glutamate and
glycerol would have been even higher than those observed. During intensive care, however, the changes caused by perturbation of energy metabolism are so profound that minor changes in relative recovery are of limited importance. In addition, when the L/P ratio is used the problem of recovery is completely eliminated because these two substances are biochemically similar and may be expected to have identical recoveries.

The concept of “biochemical penumbra” is of particular clinical importance if this zone is more susceptible to secondary adverse events. An increased metabolic perturbation in the penumbra zone may be observed in individual patients during adverse events and is demonstrated in Figs. 5 through 7. In contrast to the ipsi- and contralateral locations, an increase in the average L/P ratio was obtained in the penumbra 28 to 36 hours after injury, reflecting a secondary deterioration in individual patients (Fig. 5). The parallel changes in the levels of glutamate and glycerol indicate that secondary tissue injuries also occurred (Figs. 6 and 7). A structured follow-up study relating the ultimate fate of the biochemical penumbra to findings on CT or magnetic resonance images was not performed. It is up to future studies to define the biochemical pattern of irreversibly damaged tissue.

Conclusions

In summary, the technique of microdialysis allows bedside monitoring of biochemical variables that reflect important aspects of cerebral energy metabolism. Because CT scans and rCBF measurements reveal profound regional differences in most severe cerebral disorders, the technique appears to be of clinical interest, provided the positioning of the catheters is verified in relation to the lesions. In this study we have shown that a biochemical penumbra zone surrounds focal traumatic brain lesions. Cerebral metabolism is more affected in the penumbra zone than in tissue that appears normal on CT scans. Based on the data provided in this study we infer that this zone is more susceptible to secondary adverse events. It remains to be proven whether adequate therapeutic interventions can protect the penumbra zone from permanent damage and prevent further extension of the focal brain lesion.

Disclosure

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References

Intracerebral microdialysis: the importance of catheter location


