Letter to the Editor

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In Vivo Regional Neurochemistry in Stroke: Clinical Applications, Limitations, and Future Directions

To the Editor:

I read with interest the article by Bosche et al and the accompanying editorial comment in the last issue of Stroke.1 The authors should be commended on their elegant work with multi-modality monitoring in predicting “malignant” infarction with large middle cerebral artery ischemia. However, the technique of in vivo cerebral microdialysis utilized in this study deserves several comments that are generally applicable to similar studies.

In vivo cerebral microdialysis is a powerful research technique that has been rapidly adapted in clinical and experimental neurosciences for purposes of analyzing neurochemical dynamics of brain injury. This has resulted in abundant literature from studies in carefully controlled animal models that quantitates neurochemical changes in focal cerebral ischemia. Over the last few years, extension of laboratory-based studies have been reported2-5 in patients with large hemispheric infarctions, traumatic brain injury,6 global cerebral ischemia7 and subarachnoid hemorrhage8,9. Neuroprotective strategies,10 including hypothermia,11-13 and their effects on neurotransmitter release have been well-described using this technique. However, this technique has significant limitations for facilitating new discoveries in the clinical setting that include (a) small sampling volume of brain tissue around the microdialysis probe (at best, a radial distance of a few millimeters around the probe); (b) poor time resolution (collection time of 120 minutes in the study by Bosche et al); (c) the presence of reactive gliosis around the probe with chronic indwelling probes, with subsequent poor recovery of the molecules of interest; (d) a wide intersubject variability in basal neurochemical values and following tissue perturbations; and (e) difficulties in data interpretation as a consequence of tissue trauma following probe placement. Further, large dialysate volumes are often required to optimize neurochemical recovery when slow flow rates of perfusate are used. In the study by Bosche et al, probe positions were accurately localized in relation to infarcted tissue by utilizing CT scan, a confirmation that is frequently lacking in other reports. While some experimental studies have suggested14 that neuropathological changes that occur around the catheter following prolonged (up to 7 days) microdialysis probe placement should not interfere with local brain metabolism, controversy remains concerning this issue.

In addition, a number of issues arise pertaining to data presentation when utilizing microdialysate measurements. First, data generated from microdialysis are often voluminous and many studies present results at selected or “time-averaged values.” One of the distinct advantages of the technique is the ability to follow changes over time. These repeated measurements can be correlated with pathophysiological systemic processes as well as local neurochemical derangements in the injured brain. Thus, it is extremely important to examine individual sample values before subjecting them to averaging and statistical analysis. Second, the data are frequently presented as “trends” of neurochemical change or percentage change from baseline values, in part because of the large sample variability within treatment groups. Furthermore, baseline neurochemical values reported in most studies are from an anatomical area of brain that is already “injured,” and comparison sampling from a distant site or contralateral “uninjured” area is lacking. Third, most studies perform dialysate collections over 60 to 120 minutes and report them as such. However, such time periods are too long if one wishes to initiate therapeutic maneuvers to ameliorate secondary brain injury. Consequently, the majority of reports that utilize microdialysis in clinical paradigms provide data that describes “phenomenology” on injury (eg, excitatory amino acid release in ischemic brain tissue and amelioration with therapeutic maneuvers, such as hypothermia11-13). Unfortunately, this descriptive approach provides limited new information and can be repetitive of other published work.

As noted in the accompanying editorial comment, the study by Bosche et al provides newer insights into regional neurochemistry underlying “malignant” cerebral infarction. However, these results must be validated by other investigators. Furthermore, newer methods must be developed that circumvent current important limitations, including time resolution of regional neurochemistry, and that will allow reasonable study of the effect of therapeutic intervention, not just the disease course. Recent technological advances, comprising continuous neuromonitoring15 of parameters such as brain oxygen, CO2, pH, and temperature and “online” display of relative changes, in conjunction with local neurochemical measures, could prove to be invaluable in the future care of critically ill stroke patients.

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Cerebral Microdialysis in Stroke Patients: Potentials and Limitations of a Method with Longitudinal Information

Response

We have to thank Dr. Bhardwaj for his valuable comments on our microdialysis study on patients suffering from hemispheric stroke,1 and we would like to briefly respond. Cerebral in vivo microdialysis has become a common research technique in neurological studies,2–7 and one example is monitoring in severe stroke patients to predict and evaluate the further clinical course.8

Indeed, in vivo microdialysis has limitations in our study as well as in general. First, the information on neurochemical substances in the extracellular fluid originates from a small tissue volume and deductive conclusions about the metabolic state of larger brain regions cannot be drawn. Second, the time resolution (sampling time) of cerebral microdialysis in our study was 120 minutes. The method, however, allows higher time resolution8,9 or even continuous measurement.10 In our study, we used microdialysis to get information over an 80-hour time period, in which malignant brain edema develops.11 At this stage of an ongoing study, we were searching for neurochemical predictors of malignant MCA infarction. Hence, the analysis of a wide spectrum of substances seemed more important to us rather than to maximize the time resolution. The next step would include improvement of time resolution and we are currently discussing whether nontransmiter amino acids are suitable for this purpose. Third, the presence of reactive gliosis around the microdialysis catheter influences the recovery of substances through the microdialysis membrane, but it is common sense that this gliosis plays a minor role in the first hours after implantation.12–15 To predict malignant MCA infarction, we used dialysate from the first 12 hours measurement. During this time period, recovery remains stable in animal experiments, and even over a time period of 80 hours, tissue alterations like gliosis and/or hematoma are not prominent in the surrounding of the catheter.14 Fourth, the inter-subject variability in basal neurochemical values and the lack of reference values taken, for example, from the contralateral hemisphere as described by other authors,16 is a fundamental problem of our and of other microdialysis studies in humans. But ethical aspects make investigations of basal or reference values delicate or impossible. Finally, variable tissue trauma following probe implantation is also a problem that influences the microdialysis data. Standardized implantations as performed in our study may lower this source of error but cannot eliminate it. However, several experimental studies17–20 have shown that extracellular amino acid and other substance concentrations normalized less than 2 hours after implantation trauma by microdialysis probe.

Finally, we agree with Dr. Bhardwaj and would like to underscore the need to supplement microdialysis with other techniques to overcome limitations of individual methods as shown by other authors.21 In our group we combine multimodal neuromonitoring comprising measurements of ICP, brain tissue oxygen, and cerebral microdialysis with PET22 and currently MRI. However, it seems important to point out again that longitudinal information obtained by multimodal neuromonitoring is essential for understanding dynamics of pathophysiological alteration in brain tissue. This is the crucial advantage over neuroimaging. CT, MRI, or PET provide only snapshot-like information about brain tissue, since sequential imaging of critically ill patients is a medical and logistical problem. Further studies with the combination of imaging and multimodal neuromonitoring are needed to better understand the pathophysiology of hemispheric infarction that may lead to new therapeutic strategies. Known strategies like hemicraniectomy23 should be evaluated with both invasive and noninvasive approaches.

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