# On-line monitoring in neurointensive care using rapid sampling microdialysis

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**Abstract – the use of a novel instrument for rapid sampling of an on-line clinical microdialysis stream is described. Microdialysis probes and electrocortical electrode were placed in peri-lesional tissue during brain surgery. The 2 µl / min dialysate stream was fed via a 1m low volume connection tube directly into a bed side analysis system. A flow-injection analysis biosensor records the level of glucose and lacate in the dialysate at 6s to 30s intervals. The system runs continuously over the 5 day period of monitoring in the intensive care unit. Additional data channels record brain electrocortical activity, arterial blood pressure, intercranial blood pressure and tissue oxygen saturation at high time resolution. An interface box records time stamps nursing activity. The advantages of rapid monitoring are discussed together with recent results from on-line patients. These are interpreted in terms of the role of spreading depression in the maturation of cortical brain injury.**

*Key words – brain, clinical microdialysis, on-line, biosensor, EcoG, spreading depression*

## I. Introduction

Clinical microdialysis is of increasing importance for monitoring a wide range of head trauma cases in the intensive care unit (ICU). Key target analytes are energy metabolites (glucose, lactate, pyruvate) as they give sensitive information about local energy delivery and utilization (**1**). The goal of such measurements of cerebral metabolism is to provide intensive care unit staff with diagnostic information leading to improved patient management and outcome. Much work in this area has concentrated on monitoring trends in baseline values over the lengthy time periods that patients can remain in the ICU. Such measurements have been achieved by off-line assays such as the CMA/600 analyser. These are sophisticated instruments but they require the manual transfer of samples from patient to the instrument. This is invariable carried out by ICU nursing staff. In our own measurements of metabolism in animals we have demonstrated the dynamic nature of cerebral metabolism, with levels of glucose and lactate fluctuating rapidly in response to both physiological and adverse stimuli(**1**). To achieve this we developeda rapid sampling on-line assay for monitoring glucose and lactate in a microdialysate flow stream. We have now developed (**2**) a clinical version of this system providing even greater time resolution and sensitivity that can be used in the intensive care environment. We have used this instrumentation to look at the metabolic consequences of the passage of peri-infarct depolarisations (PIDs.). These are rapid events resembling the spreading depression of Leão that we have recently shown to occur spontaneously in peri-lesional brain tissue (**3**) The availability of fast sampling in our clinical assay system now allows us to search for evidence for PIDs in head trauma patients

## II. Material and Methods

*Microdialysis probe placement* – A sterile, flexible CMA 70 microdialysis probe (CMA Microdialysis, Stockholm, Sweden) with a 10mm membrane and a 60mm probe shaft length was inserted obliquely (under direct vision) so as to lie within cerebral cortex. The catheter was sited so as to be in any 'traumatic penumbra'.

*Electrocorticography* – Full details are given elsewhere (**3**). Briefly, four active channels were acquired from a linear six electrode array (5 mm Pt disks separated by 10 mm, Adtech medical). In each patent an ECoG strip was placed on mildly contused cortex above the microdialysis probe. The strip was connected in a bipolar montage to two dual bioamplifiers (ADInstruments).

*On-line microdialysis* – The probe was perfused with sterile artificial cerebral spinal fluid (aCSF)(CMA Microdialysis) at 2µl/min using a CMA 107 mini pump (CMA Microdialysis). The outlet tubing of the probe, which normally has a sample vial holder, was adapted for use to connect to a dual on-line assay system. The electrical impedance and mains leakage of 0.5 m of microdialysis tubing from the probe outlet to the assay inlet was tested and found sufficient to isolate the patient from the assay equipment. Typically a 1m length was used resulting in a delay of 9 minutes between sample dialysis and readout.

*Rapid sampling analysis* – For clinical analysis we have developed a novel dual on-line assay system. Full details are given elsewhere (**2**). Briefly, the assay comprised of a custom built valve (Valco Inc, Ch) that allowed rapid flow injection of small volumes of dialysate into two separate enzyme bed systems. The valve injected glucose and lactate samples sequentially each 15 seconds. A buffer contaning a ferrocene compound was pumped at high flow rates through the enzyme bed system using an HPLC pump. At each injection the flow carried the dialysate into the enzyme bed, mediated the enzyme turnover within the bed, then carried the resulting ferrocinium species to a downstream radial flow electrode (BAS, USA) giving a current peak related to concentration in the dialysate.

The assay was calibrated at daily with standards in an appropriate range (typically 50 x $10^{-6}$ mol dm-3 to 2 x $10^{-3}$ mol dm-$^3$ ). A nonlinear regression of the resulting peak current concentration data was then obtained using the Hill equation (**2**)

*Data collection* – All Data collection was with a Powerlab A/D convertor (16 S/P ADInstruments, Australia), controlled by a portable computer (Apple G4 Powerbook) running Chart 5.02 software (ADInstruments). Collected channels were dialysate glucose, dialysate lactate, systemic pulsatile (invasive) arterial blood pressure, pulsatile intracranial pressure, 4 channels of ECoG, % arterial oxygen saturation (pulse oximeter). Most channels were digitised at 200 Hz. To improve data quality and interpretationa simple push-button box was constructed in house to our specification and was used by nursing staff to record specified nursing actions such as suction and sedation changes during the period of monitoring. Each of 8 labelled buttons fed a separate bit on the digital input of the Powerlab. When pushed a corresponding text comment was time stamped, added to the data set, and displayed in real time on the display screen.

All research procedures were approved by the local Research Ethics Committee

## III. Results and Discussion

To date we have monitored some 24 patients at King's College Hospital, with monitoring times varying from 1 to 5 days. Figure 1 shows a typical snap shot of the computer screen available to the assay team and clinical staff during patient monitoring.

**Figure 1**. Screen from monitoring system seen in the ICU. Channels are from top: Glucose, Lactate, Blood pressure, Intracranial pressure, 4 Channels of ECoG, %Tissue oxygen Glucose and lactate peaks at 30s intervals.

This screen updates continuously but data from the past 24h can be reviewed without stopping data collection. Consequently, it is possible for clinical staff to assess both the levels of glucose and lactate and the directions of any changes in these metabolites in the ICU before a more formal of-line analysis of the data takes place.

The Nurse action box is a vital addition as it allows the consequences of nursing actions on measured variables to be determined on the timescale of the measurements, estabilishing likely causality. An example of this is shown in figure 2, where routine turning of the patient causes a parallel transient increase in glucose and lactate. Rather than merely trapping intervention artifacts, this offers the exciting possibility of using such routine parts of patient care as a dynamic challenge to energy availability within compromised 'at risk' tissue.

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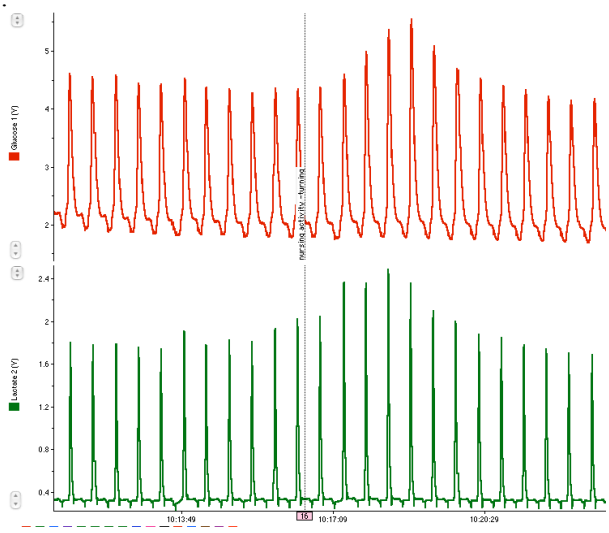


**Figure 1**. Screen trace showing glucose (upper) and lactate (lower) FIA peaks. The dotted vertical line is an automatically entered comment indicating 'nursing activity – turning'. For convenience the timescales are adjusted by 9 min time lag. Peaks at 30s intervals.

We also see spontaneous dynamic changes in glucose and lactate that can be charcterised as

- Transient changes
- Step changes
- Oscillations

These generally are not associated with changes in ICP and typically occur in one metabolite, This is particularly helpful as the constant level in the other metabolite acts as a control for the microdialysis (**2**).

In separate experimental models of brain injury we believe that these dynamic changes are associated with the development of pathology, reflecting the conversion of 'at risk tissue to core damaged tissue.

We wish to thank EPSRC, GSK, Golden-Rosetree, Wellcome Trust for finacial support

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