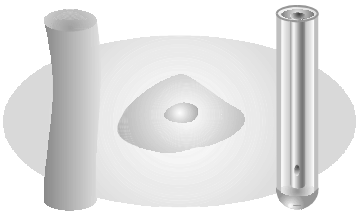
Preface



In Intensive Care diagnostic and therapeutic decisions very often are based on measuring blood concentrations of indicator substances, while it is well known that biochemical reactions take place in the tissues. Measurement of tissue chemistry therefore has been suggested to reveal more valuable data than analysis of systemic parameters in the blood. Microdialysis is a technique that aims to measure the concentrations of various compounds in the extracellular fluid of an organ or in a body fluid. Microdialysis is a way of metabolic monitoring which enables to reveal real-time and continuous information in occurring pathophysiological processes of target organs. This book illucidates the technique of microdialysis and its development from experimental to clinical application in relevant organ systems regarding clinical research, major surgical interventions and critical care.
Intensivists and surgeons, scientists and clinicians, who are interested in biochemical monitoring met in Lübeck/Germany for an interdisciplinary symposium. We are now highly delighted to present a summary of the lectures held at the "1st International Symposium of Monitoring Tissue Chemistry in Intensive Care Medicine" in Lübeck/Germany in December 2003.

PD Dr. med. Stephan Klaus

PD Dr. med. Ludger Bahlmann

Microdialysis in Neurointensive Care – Principles and Interpretations

Urban Ungerstedt[1], Bo-Mikael Bellander[2], Carl-Henrik Nordström[3]

[1]Dept of Physiology and Pharmacology, Karolinska institute, Stockholm; [2]Dept of Neurosurgery, Karolinska institute, Stockholm; [3]Dept of Neurosurgery, University Hospital, Lund, Sweden

Introduction

Today microdialysis is a routine technique for monitoring the chemistry of tissues and organs in physiological and pharmacological research on animals. In more than 8000 papers microdialysis is used to uncover physiological mechanisms and the influence of drugs in almost every organ of the body. Since the first papers describing microdialysis in the human brain and peripheral tissues (1, 2) there are close to 1000 papers published on microdialysis in man and microdialysis has become a technique for routine monitoring of energy metabolism especially in neurointensive care (3, 4). This paper gives an account of the microdialysis technique describing its practical use and interpretation in monitoring energy metabolism and ischemia in human brain and peripheral tissues.

Microdialysis

Microdialysis is a universal technique for sampling the chemistry of individual tissues and organs in the human body (5). It is minimally invasive and simple to perform in a routine clinical setting. A thin microdialysis catheter is introduced into the tissue. A microdialysis pump (Fig. 1) perfuses the interior of the catheter with a physiological fluid, which equilibrates with the interstitial fluid surrounding the catheter. The equilibration takes place by diffusion of chemicals over the dialysis membrane without the need to remove any fluid from

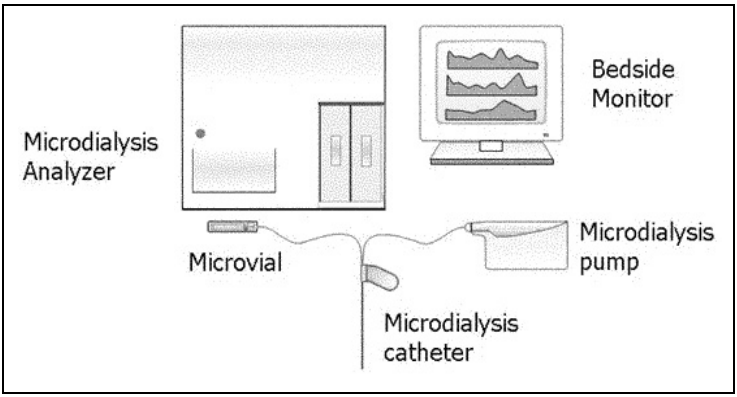


Fig. 1: Microdialysis instrumentation

the body. The samples are continuously collected into microvials and analyzed by a bedside microdialysis analyzer as often as needed, usually every hour. The analysis results are displayed as trend curves on the screen of the analyzer.

The dialysis membrane at the distal end of the microdialysis catheter functions like a blood capillary. Chemical substances from the interstitial fluid diffuse across the membrane into the perfusion fluid inside the catheter. The recovery of a particular substance is defined as the concentration in the dialysate collected from the catheter expressed as percent of the concentration in the interstitial fluid.

A low perfusion flow and a long membrane result in a high recovery. If the membrane is long enough and the perfusion flow low enough the concentration in the dialysate will be close to the concentration in the interstitial fluid i.e. recovery will be 100% (6). However, in the brain where the length of the membrane is kept short (10mm) to allow for exact positioning in relation to the lesion the recovery is in the order of 70% at a flow of 0.3µl/min (7).

The concentration in the dialysate depends upon the length of the membrane, the perfusion flow, the properties of the membrane and the diffusion coefficient in the tissue, which is often the limiting factor. However, it is important to realize that the concentration of a particular substance in the dialysate, for example glucose, also depends upon the supply of glucose from blood capillaries and the uptake and release of substances from cells. For example, the concentration of glucose in the dialysate can decrease due to a decrease in the capillary blood flow or due to an increase in the cellular uptake of glucose.

Biochemical Markers

The composition of the interstitial fluid reflects the biochemistry of neurons and glia in the brain. During neurointensive care microdialysis is used to evaluate how seriously brain cells are affected by ischemia, trauma, haemorrhage, vasospasm and various physiological, pharmacological and surgical interventions. Microdialysis tells us how the cells react to a decrease in the supply of oxygen and glucose. Cells in normal brain tissue may not be affected by a decrease in oxygen supply while vulnerable cells in the penumbra surrounding a lesion may turn severely ischemic. This is displayed as an increase in the lactate/pyruvate ratio and an increase in glycerol due to beginning decomposition of cell membranes (see below).

Lactate/pyruvate ratio

The lactate/pyruvate ratio is a well-known marker of cell ischemia (8). During normal glycolysis (Fig. 2) pyruvate enters the citric acid cycle provided that oxygen is available. The citric acid cycle is the dominant producer of energy in the form of ATP. If the tissue is exposed to ischemia (a decrease in blood flow causing an inadequate supply of oxygen and glucose) the cells take up as much glucose as possible in order to produce ATP from the anaerobic part of the glycolysis.
The decrease in glucose delivery from the capillaries together with the increase in glucose uptake leads to a fall in the glucose concentration in the dialysate. More lactate is formed in order to regenerate NAD+ which is necessary for maintaining anaerobic glycolysis. The result will be an increase in lactate and a decrease in pyruvate resulting in an increase in the lactate/pyruvate ratio. The use of a ratio has the additional advantage of abolishing the influence of changes in recovery over the dialysis membrane.
Lactate alone is not a good marker of ischemia as an increase in lactate may be due to hypoxia, ischemia or hyper-metabolism.

Glycerol

Glycerol is a marker of how severely the brain cells are affected by the ongoing pathology (9, 10). Glycerol is an integral component of the cell membrane. Loss of energy leads to an influx of calcium and activation of phospholipases, which split away glycerol from cell membranes (Fig. 3).

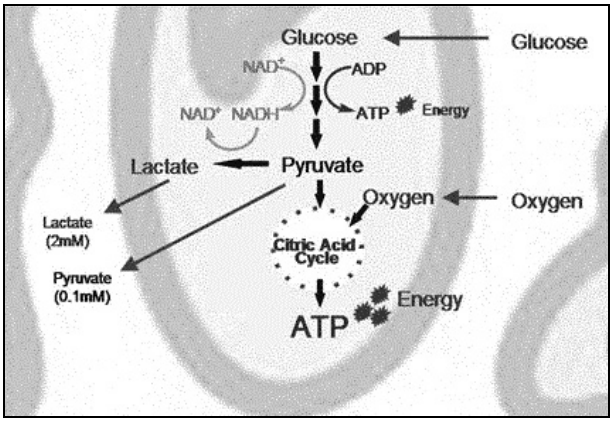


Fig. 2: A cell surrounded by interstitial fluid. The anaerobic glycolysis leads to the production of lactate and pyruvate that enters the surrounding fluid where it can be taken up by the microdialysis catheter. The aerobic part of the glycolysis utilizes the citric acid cycle to produce the majority of energy in the form of ATP.

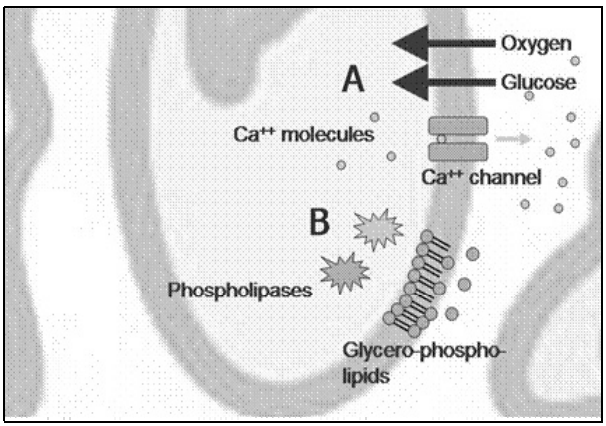


*Fig. 3: **A**: If the supply of oxygen and glucose is sufficient there is energy enough to activate the calcium channels transporting calcium out of the cell. **B**: In case of energy failure calcium leaks into the cell and activates the phospholipases. Glycerol molecules are split from the fatty acids and released into the interstitial fluid where they are taken up by the microdialysis catheter as a sign of cell damage.*

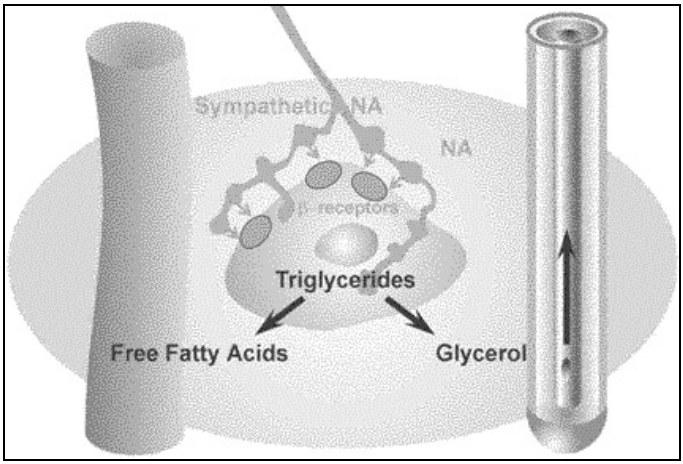


Fig. 4: Lipolysis is controlled by the release of noradrenaline from nerve terminals in the adipose tissue splitting fat into free fatty acids and glycerol. Glycerol, which is water soluble, is easily taken up into the microdialysis catheter.

In subcutaneous adipose tissue, on the other hand, glycerol originates from the splitting of fat (triglycerides) into free fatty acids and glycerol. This process is controlled by the sympathetic nerves in the tissue and their release of noradrenaline. Glycerol therefore becomes an indirect marker of sympathetic tone, which may be considered synonymous with sympathetic "stress" (Fig. 4).

Glucose

The level of glucose is somewhat complicated to interpret as it is affected by changes in glucose supply to the microdialysis catheter. This supply changes with alterations in local capillary flow and with changes in peripheral blood glucose concentration. The interstitial concentration is also affected by brain cell uptake due to changes in demand e.g. a shift from aerobic to anaerobic metabolism (11). A decrease in glucose level is often parallel to a decrease in tissue pO2 and an indicator of decreased blood capillary perfusion of the brain.

Microdialysis during Neurointensive Care

Microdialysis monitors the local chemistry of the brain. The interpretation of microdialysis data therefore depends upon the position of the catheter in relation to the existing pathology. It is important to adopt a consistent clinical strategy of where to place catheters e.g. in the penumbra of a lesion and/or in "normal" brain tissue. The fact that the penumbra tissue is more vulnerable than "normal" tissue makes it more liable to suffer secondary damage (12). A general consensus is therefore emerging that placing the catheters in the penumbra will provide a much earlier warning of secondary damage than placing the catheter in normal tisue.

When implanted during surgery the catheter is tunnelated under the scalp with the help of a steel cannula (Fig. 5). The protective tube of the brain catheter is removed. A small incision is made through all meninges and the dialysis membrane of the catheter is positioned in the penumbra region, usually 1 cm from the border of the lesion. A special forceps makes it easy to hold the catheter firmly during introduction into the brain tissue. The cuff, which slides on the in- and outflow tubing, is sutured tightly to the skin.

The microdialysis catheter may be connected to the microdialysis pump during surgery in order to follow the condition of the brain tissue intra-operatively. The non-sterile pump is usually dropped into a sterile glove, which is closed by a suture. In this way the pump may remain within the sterile field. However, in most cases the Microdialysis catheter is connected to the microdialysis pump by the nursing staff when the patient has arrived in the ICU. The microdialysis syringe should be filled with artificial cerebrospinal fluid. It is not advisable to use saline (NaCl). Animal experiments have shown that perfusion with saline

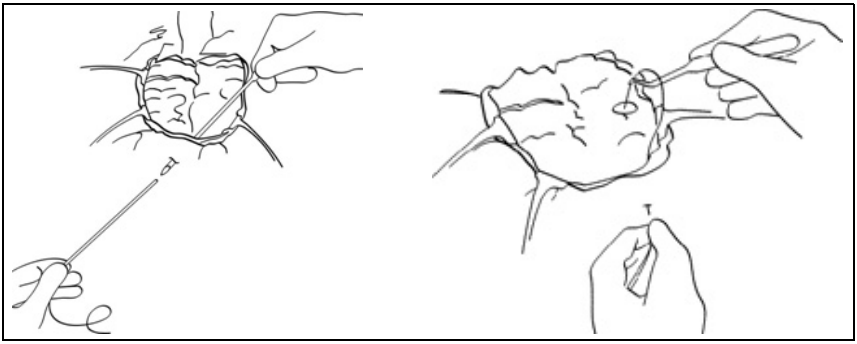


Fig. 5: Tunnelation and implantation of the brain catheter.

depletes calcium and potassium and alters neurotransmission in the vicinity of the catheter.
The flow of the standard CMA106 Microdialysis pump is 0.3 µl /min, which gives approximately 70 % recovery when using a 10 mm dialysis membrane. The CMA107 Microdialysis pump offers a flow range of 0.1–5 µl/min. A higher flow is motivated when sampling is so frequent that the 0.3 µl/min does not give enough volume for analysis, for example, during intra-operative microdialysis when samples are changed frequently. The nursing staff normally takes care of the microdialysis procedures in the ICU which includes staring the analyzer, connecting the catheter to the pump and changing microvials regularly every hour.
In order to make effective use of microdialysis data it is essential to relate them to other data collected bedside. This can be done with software, which allows "multimodal monitoring". The ICU monitor, the ventilator, oxygen analyzers, infusion pumps etc, can be displayed as trend curves on the same screen as the microdialysis data allowing the interpretation of microdialysis data in relation to brain chemistry.
The trend curves make it possible to evaluate the gradual improvement or deterioration in the patient's condition. Data from other patients or from statistical averages of large groups of patients can be dragged and dropped into the graphs of the patient under treatment in order to compare and predict outcome.

Interpreting Microdialysis Data

During intensive care brain chemistry often changes profoundly in the patient. At our present state of knowledge it is impossible to interpret every change, however, major pathological states manifest themselves in dramatic increases or decreases of the chemical markers.
Many changes cannot be interpreted in retrospect but are easily related to therapeutic events when they are observed bedside. In the following we will give examples of lactate/ pyruvate ratio as well as glucose, lactate, and glycerol levels from patients, which illustrate the practical use of bedside microdialysis monitoring. Our examples are drawn from a population of about 300 patients.
The predictive value of tissue chemistry depends to a large extent on the positioning of the microdialysis catheters in the brain. It is, by now, well known that after Traumatic Brain Injury (TBI) or Subarachnoid Hemorrhage (SAH) the sensitivity of brain tissue to secondary damage varies greatly. A minor drop in

blood pressure may have devastating effects on cells in the penumbra of the lesion while normal cells in the contralateral hemisphere are not affected at all. It is therefore of great importance that catheters are placed strategically. If there is a localized trauma one catheter should be placed in the penumbra of the lesion and one may be placed in apparently non damaged tissue to serve as a reference. The localization of the catheters should be verified during the first post surgical CT.
The first hours of microdialysis data give an indication of how severely the brain tissue is affected in the "worse" location (the penumbra). The range from normal to pathological levels of the different analytes are well known from normal brain tissue in patients with posterior fossa tumors (4) and from damaged as well as "normal" brain tissue in TBI (13) and SAH patients (14). The normal levels of the various chemical markers when using 10 mm membrane and 0.3 µl /min flow in sedated patients are: Glucose 2 mM, Lactate 2 mM, Pyruvate 120 µM, Lactate/pyruvate ratio 20, Glycerol 50 µM, Glutamate 10 µM.

Using Reference Data to Estimate Outcome

When summarizing a large number of patients it is possible to extract a "typical" change in tissue chemistry during the course of intensive care. This is characterized by a gradual decline in, for example, glycerol levels. This "typical" course of events, extracted from a large patient database, may be used to predict outcome in the patient presently undergoing treatment (Fig. 6).

Ischemia and Herniation due to Severe Brain Edema

Brain edema may lead to increased ICP, ischemia and eventually herniation and death. These events usually affect the two hemispheres very differently. The trauma and edema often give rise to early, severe and profound changes in the catheter on the worse side, while the biochemistry on the better side may show pathological signs very late when the outcome is already severe.
A 74-year old man was admitted to hospital after motorcycle accident. After the evacuation of an acute subdural haematoma and temporal contusion on the right side a microdialysis catheter was inserted into the biochemical penumbra zone surrounding the evacuated contusion (worse position). An intraventricular catheter was placed in the left ventricle for continuous recording of ICP and a second microdialysis catheter was introduced into the frontal grey

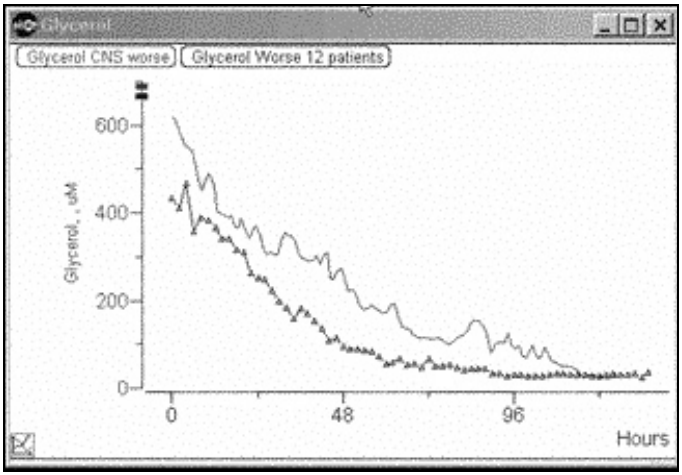


Fig. 6: The glycerol level from the patient under treatment (light grey) is very high and stays well above the reference value (dark grey) during five days. It reaches acceptable levels two days after the reference group (12 patients), which is an indication of worse outcome.

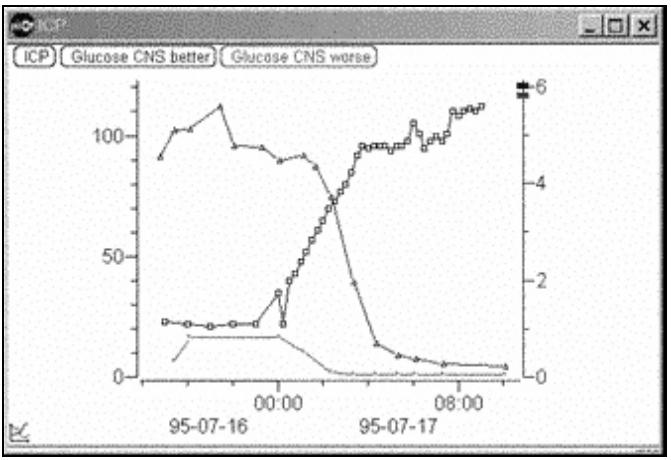


Fig. 7: Patient herniating after TBI. ICP (black) increases to blood pressure levels. Glucose levels are initially high on the better side (dark grey) but decline as cerebral blood decreases and the supply of glucose decreases. On the worse side (light grey) glucose levels are low even before the rise in ICP.