Review

Bench-to-bedside review: Microdialysis in intensive care medicine

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Abstract

Microdialysis is a technique used to measure the concentrations of various compounds in the extracellular fluid of an organ or in a body fluid. It is a form of metabolic monitoring that provides real-time, continuous information on pathophysiological processes in target organs. It was introduced in the early 1970s, mainly to measure concentrations of neurotransmitters in animal experiments and clinical settings. Using commercial equipment it is now possible to conduct analyses at the bedside by collecting interstitial fluid for measurement of carbohydrate and lipid metabolites. Important research has been reported in the field of neurosurgery in recent decades, but use of metabolic monitoring in critical care medicine is not yet routine. The present review provides an overview of findings from clinical studies using microdialysis in critical care medicine, focusing on possible indications for clinical biochemical monitoring. An important message from the review is that sequential and tissue-specific metabolic monitoring, *in vivo*, is now available.

Keywords critical care, metabolism, microdialysis, monitoring

Introduction

There is not yet any clinically established method for following local biochemical parameters in organs when they are affected by hypoxia or ischemia, or are developing organ failure. In the experimental setting it is possible to follow metabolic parameters such as glucose, lactate, pyruvate and glycerol using microdialysis equipment [1,2]. In the clinical setting, thus far microdialysis has mostly been used in studies of subcutaneous adipose tissue [3], muscle [4] and human brain [5–8].

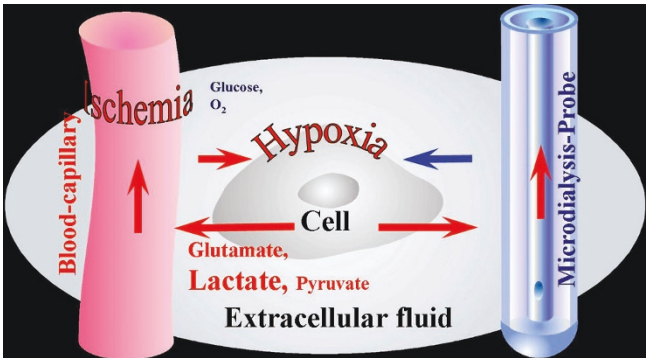
In intensive care medicine, diagnostic and therapeutic decisions are frequently based on measuring blood concentrations of indicator substances, but it is well known that biochemical reactions take place in the tissues. It has therefore been suggested that measurement of tissue chemistry reveals more valuable data than does analysis of systemic parameters in the blood [9]. Furthermore, in the past, detection of tissue concentrations of a substance of interest was hindered by the requirement for tissue harvesting [10], but harvesting is not necessary with microdialysis.

This article reviews the technique of microdialysis and its development from 'bench to bedside' for use in clinical research, major surgical interventions and critical care. We also discuss whether biochemical tissue monitoring has the potential to surpass blood analysis and become the standard technique for certain clinical procedures. Because fundamental research in numerous studies and reviews of the value of biochemical monitoring in the field of neurosurgery have been published, here we focus on the use of microdialysis in general perioperative and intensive care treatment.

Microdialysis

Microdialysis was introduced by Ungerstedt and Pycock [11] and was used primarily in brain research, but it is now increasingly being applied to various tissues in experimental studies dealing with critical illness, and has some applications in the clinical setting [1,2,9]. In theory, the microdialysis catheter acts like a blood capillary [12]. Thereby, it is proposed that microdialysis provides information regarding events that take place in the tissue before any chemical events are reflected by changes in systemic blood levels of

Figure 1



Principle of microdialysis. The microdialysis probe is inserted into the tissue where substances in the extracellular fluid surround the semipermeable membrane at the tip of the catheter. Following equilibration of the tissue metabolites with the perfusion fluid, the dialysate can be analyzed for concentrations of products of energy metabolism (glucose, lactate, pyruvate) as indicators of hypoxia and ischemia. In addition, interstitial glycerol can be determined, which is a parameter of lipolysis and/or cell membrane damage.

indicator substances [13]. Briefly, for those who are less familiar with the technique, the capillaries and the semipermeable membrane are surrounded by substrates and metabolites in the extracellular fluid of the tissue (Fig. 1). These molecules diffuse across the membrane part of the catheter and equilibrate with the perfusion fluid, which is pumped through the probe at very low rates of flow. Changes in the concentration of a substrate in the surrounding milieu are reflected by subsequent changes in the dialysate [14]. Rather than inserting an instrument into the tissue, microdialysate is extracted and later analyzed in the laboratory or clinically at the patient's bedside.

Clinical application of microdialysis was 'catalyzed' by the development of commercially available microdialysis catheters that may be used in humans [9]. Because of modern technical innovations, it is now possible to determine dialysate and tissue concentrations immediately at the bedside during intensive care treatment [15]. The first reported application of microdialysis in humans was a study of interstitial glucose, which was published in 1987 [16]. Since then, microdialysis has been investigated in various human tissues, for example in cancer research [9] and pharmaceutical studies [17,18], and in clinical research [19]. However, particular interest is currently devoted to perioperative biochemical monitoring in the fields of vascular, gastrointestinal and heart surgery, and postoperative observation.

Clinical applications

Microdialysis in vascular surgery

Several studies dealing with tissue vulnerability during ischemia and reperfusion have been reported [20,21]. Previous studies on the consequences of ischemia in skeletal muscle usually involved venous blood sampling or tissue biopsies, but microdialysis has the advantage that metabolite levels can be monitored directly in the interstitial fluid of the tissue, even when blood flow is restricted. Lundberg and coworkers [22] used microdialysis to grade the severity of peripheral vessel disease. Responses of interstitial muscle concentrations of lactate and the lactate–pyruvate ratio to blood flow reduction were variable, whereas glucose concentration subsequently fell. Using microdialysis, Metzsch and coworkers [23] investigated metabolic changes during open and endovascular aortic surgery, and found that stent procedures had a lesser impact on regional tissue metabolism over 24 hours than did open aortic procedures.

In the field of orthopedic surgery, Korth and coworkers [24] demonstrated that interstitial concentrations of glucose, lactate, and hypoxanthine – indicators of tissue ischemia – change more markedly after exsanguination of the extremity than after circulatory occlusion alone. The energy status in muscle tissue was immediately visible after induction of ischemia, when glucose levels decreased and the extracellular concentrations of lactate and hypoxanthine increased.

Our study group clinically monitored patients during abdominal aortic surgery using microdialysis of the subcutaneous tissue. We found the glucose–lactate ratio to be the most sensitive marker for detection of ischemic events (Fig. 2 [25]); in another study we focused on the lactate–pyruvate ratio and interstitial glycerol [26].

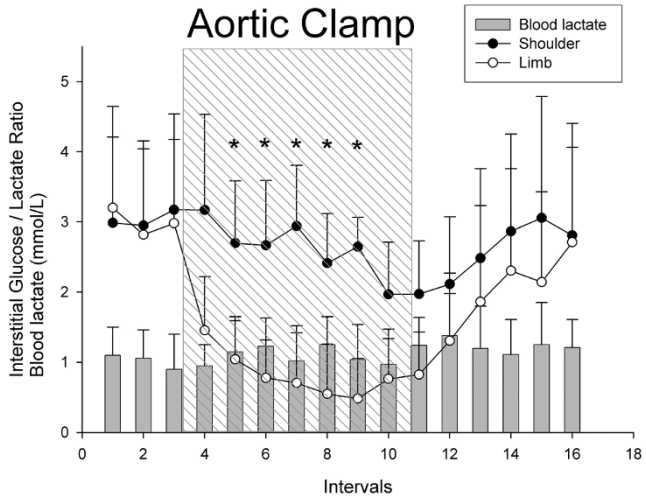
Monitoring in the neonatal intensive care unit

Microdialysis in the neonatal intensive care unit is a new approach to continuous monitoring of newborn patients who are at risk from hypoglycemia (a commonly encountered problem in neonatal intensive care). The objective of the study conducted by Baumeister and coworkers [27] was to evaluate subcutaneous microdialysis in long-term glucose monitoring in the neonatal intensive care unit. By using subcutaneous microdialysis, blood draws and painful stress resulting from diagnostic blood sampling in high-risk neonates were reduced. Subcutaneous microdialysis has been used continuously for up to 4 days in neonates during intensive care, and for 3 and 7 days in adult insulin-dependent diabetic patients [19]. In their clinical study, Baumeister and coworkers [27] continued metabolic monitoring for 4–16 days and found a close correlation ($r \sim 0.97$) between blood and interstitial glucose levels.

Monitoring the gastrointestinal tract in the intensive care unit

Ensuring adequacy of visceral circulation is of high priority in critical illness. However, no clinical instrument has yet been developed to continuously monitor biochemical and circulatory parameters in this compartment [28,29]. Decrease in intestinal blood flow or derangement of visceral oxygen supply is well known to induce local and systemic inflammation. This

Figure 2



Interstitial glucose/lactate ratio in the ischemic and nonischemic region during abdominal aortic surgery. *$P < 0.05$.

could subsequently be responsible for multiple organ dysfunction and/or failure [30]. Many investigators have attempted to measure adequacy of splanchnic circulation either by measuring splanchnic blood flow in global splanchnic blood flow or local tissue perfusion or by evaluating metabolism in one region of the gastrointestinal tissue [28].

However, Tenhunen and coworkers have forwarded a theory, supported by several studies conducted in various experimental and clinical settings [31–36], that changes in tissue perfusion and metabolism in response to different drug interventions vary. That research group is by far the most experienced with respect to experimental biochemical monitoring of the gastrointestinal tract in the critical care setting. They identified intestinal histamine release in a selective regional intestinal ischemia–reperfusion model, not during ischemia but only during the reperfusion phase [33].

Following short-term endotoxin challenge, Oldner and coworkers [37] observed early increases in microdialysate lactate and hypoxanthine in ileum, as opposed to systemically detectable changes. However, insertion of a microdialysis probe into the intestinal wall is not feasible for clinical application. Subsequently, intraluminal [34] and intraperitoneal [38] applications were evaluated in experimental ischemia and hypoxia. Using microdialysis, Ungerstedt and colleagues [39] investigated local and regional gastrointestinal ischemia caused by vascular occlusion. Also in the setting of gastrointestinal ischemia caused by vascular occlusion, Jansson and coworkers [40] were the first to apply intraperitoneal microdialysis in clinical pilot studies of patients undergoing abdominal surgery. Intraperitoneal microdialysis appears to represent a very promising clinical tool for continuous monitoring of metabolic status in visceral tissues. It is minimally invasive; for example, the probe may be left *in situ* after laparotomy.

Liver monitoring in the intensive care unit

Despite improvements in liver preservation and surgery, a significant incidence of graft dysfunction following liver transplantation persists. Microdialysis offers the possibility to monitor the liver during and after transplantation. Nowak and coworkers, who are pioneers in this field, investigated this application both experimentally [41] and clinically [42]. In their studies they investigated ischemia–reperfusion injury and post-transplant vascular complications, with apparent impact on hepatic metabolism, using microdialysis. They characterized the course of normalization in biochemical markers during the 72-hour postoperative period following liver transplantation. Nowak and coworkers concluded that the procedure is easy to perform and safe for the patient. They stated that the detection of specific pathologic changes (e.g. arterial and portal vein thrombosis, early graft rejection) might be possible using microdialysis, and that this should be addressed in further studies.

Monitoring sepsis

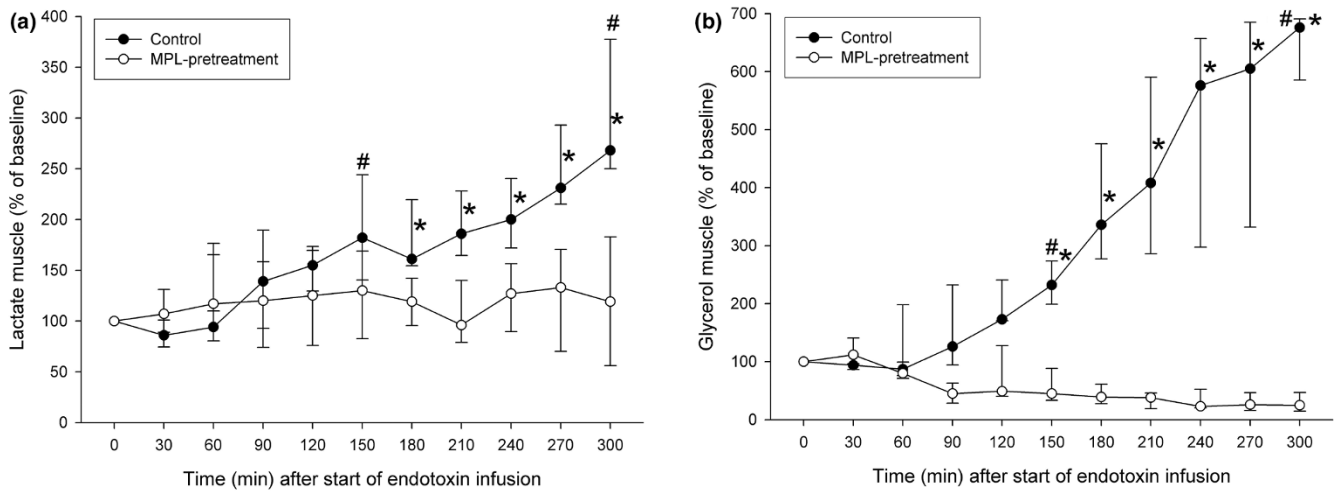
Increasing interest has been devoted to metabolic changes that occur in the tissue during sepsis and endotoxemia. In their animal experiments, Tenhunen and coworkers [36] induced a biphasic endotoxic shock lasting 12 hours and measured regional blood flows. Endotoxin shock *per se* had heterogeneous effects on tissue perfusion, and it was observed that blood flow changes did not correlate with metabolic events. We performed endotoxin [43] and monophosphoryl-lipid A [44] vaccination before induction of endotoxemia in animal experiments. Despite nonsignificant differences in hemodynamic parameters, lower interstitial lactate and glycerol accumulation (Fig. 3) were clearly associated with prolonged survival.

Stjernstrom and coworkers [15] were the first to report on the use of microdialysis in sepsis; they described case reports of microdialysis monitoring in patients with septic shock. Clinically, Martinez and coworkers [45] evaluated adipose tissue metabolism in severely ill patients. The aim of the latter investigation was to study whole body substrate utilization and adipose tissue lactate and glycerol release in healthy human volunteers and in two groups of critically ill patients: one group of patients with severe sepsis or septic shock and another with circulatory failure after cardiac surgery. Differences in tissue metabolic response were found between sepsis/septic shock and cardiac failure patients using microdialysis. The observations summarized above, along with Fink's theory of 'cytopathic hypoxia' [46] in septic states, add weight to a recommendation to introduce biochemical tissue monitoring into critical care practice.

Monitoring pharmacological concentrations

Achievement of appropriate concentrations of antibiotics at target sites is associated with clinical outcome [47] and

Figure 3



Interstitial muscle concentrations of **(a)** lactate and **(b)** glycerol during continuous endotoxin infusion with (black) or without (white) pretreatment with monophosphoryl lipid A (MPL). *$P < 0.05$, between groups; #$P < 0.05$, versus baseline (only assessed at 150 and 300 min).

therefore is of particular importance. Recent data, however, strongly suggest that concentrations of antibiotics reached in the interstitium of soft tissues might be ineffective in critically ill patients, despite achievement of adequate plasma concentrations [18]. Fundamental experimental research in the field of drug monitoring using microdialysis has been reported [48]; this was recently reviewed by Joukhadar and coworkers [17].

Monitoring myocardial metabolism

Several experimental approaches such as biochemical analysis of coronary sinus blood, myocardial biopsy and magnetic resonance imaging have been taken in order to describe the metabolic changes that occur during and after cardiopulmonary bypass [49]. With the exception of septic conditions [46], the interstitial concentration of lactate has been shown to be closely related to variations in tissue perfusion [1] and may thus be used as a surrogate marker of myocardial ischemia. Following experimental evaluation by Kennergren and coworkers [49], Habicht and colleagues [50] were the first to introduce this concept into the clinic by inserting microdialysis probes into the interventricular septum of the human heart. Kennergren and colleagues [51] then focused on changes in troponin T and aspartate transferase in patients undergoing coronary artery bypass grafting and valve surgery.

We investigated the course of myocardial metabolism in patients undergoing standard coronary artery bypass grafting [52]. In contrast to blood levels, myocardial lactate–pyruvate ratio exhibited marked changes during the period of observation; pyruvate was found to be a promising indicator of tissue reperfusion. In a recent study of myocardial microdialysis (unpublished data), we categorized patients by lactate concentration at baseline into a high lactate group and a low lactate group. We found an association between increased myocardial lactate levels – as determined by microdialysis – and reduced myocardial performance with difficult weaning from cardiopulmonary bypass during coronary artery bypass grafting. This suggests that myocardial microdialysis may be a useful adjunct for stratifying treatment in these interventions (unpublished data). Microdialysis may reveal promising diagnostic and therapeutic options by permitting analysis of the effects of different treatment strategies on myocardial metabolism (i.e. the 'target tissue' of therapeutic interventions) in cardiac surgical patients.

Conclusion

Microdialysis has been introduced into several sectors of critical care medicine. The precise role and cost-effectiveness of microdialysis, in comparison with well established technologies, in developing strategies to improve organ function in intensive care remain to be determined. However, even in the well established field of neurosurgery, clinical use of microdialysis has not yet been found to improve outcome. Current data support a recommendation to introduce this new technique to evaluate the adequacy of regional tissue metabolism; it may even permit monitoring of the effects of therapeutic interventions. Further studies of various approaches are needed to conclude which seems clinically most feasible, which is sufficiently non-invasive, and which supplies the clinician with the most physiologically relevant information. Whether clinicians will be able to monitor their 'tissues of interest' directly, with microdialysis playing a key role, will be determined by the results of further evaluation.

Competing interests

The authors declare that they have no competing interests.

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