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Chapter 10

Microdialysis Monitoring of Biomarkers for Early Recognition of Intestinal Ischemia

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Additional information is available at the end of the chapter

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1. Introduction

The intestinal tract is commonly involved in ischemia and reperfusion events, resulting from illness or surgical procedures that might lead to haemorrhage or shock. Ischemia is recognised as a poor blood supply and it is specifically known as intestinal or mesenteric ischemia when the bowel is involved. An ischemic insult can develop further into inflammation and injury. The mechanisms involved are still subject of study, but in general, an increase in intestinal cell membrane permeability provokes bacterial translocation and this in turn results in sepsis and multiple organ failure (MOF). The role of intestinal ischemia in septic shock will be discussed in this chapter as well as techniques commonly used to monitor gastrointestinal (GI) perfusion. However, most of these techniques depend on technical operators thus limiting the diagnosis of intestinal ischemia, which in most surgical departments still relies on clinical symptoms and examination.

Monitoring metabolic biomarkers has allowed not only the study of metabolic rates of tissues and organs, but the rapid detection of life-threatening events. During episodes of low blood flow, metabolic needs of the gastrointestinal tissue are not met. Monitoring this metabolic imbalance has the potential to provide an early diagnosis and prevent the injury from developing further into sepsis. Biosensors have been widely used to study tissue metabolism, proteins and nucleic acids with a wide range of applications. Biosensors as a diagnosis tool for gastrointestinal pathology will be revised in this chapter. The use of biosensors in clinical settings is, however, limited by issues such as biocompatibility, sterilisability and immunoreactivity and despite the extensive studies to overcome the immune-defensive reactions and toxicity effects due to the direct tissue implantation, other techniques have been used as an interface. Microdialysis is an extracting technique widely used to sample extracellular fluid of different human tissues. The use of microdialysis for the monitoring of digestive organs will be revised and intestinal microdialysis to monitor

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ischemia further described. Commonly off-line microdialysis pitfalls such as time lag and misplacement of samples are exposed as well as the use of recent technologies to overcome these issues. The synergetic combination of microdialysis and biosensors is the main reason for the position of this technology in the forefront of invasive monitoring. Biocompatibility issues of biosensors are extremely simplified when coupled with microdialysis and in turn biosensors confer microdialysis with a temporal resolution that it otherwise lacks. Although the combination of these techniques is still in research process, it presents the potential of close monitoring in clinical settings and home care scenarios for early diagnosis of conditions that can lead to sepsis if otherwise missed.

2. Intestinal ischemia and its role in septic shock

A poor blood supply to the intestine, also recognised as intestinal or mesenteric ischemia, generally leads to inflammation and injury (1) and easily develops into hypoxia (deprivation of oxygen supply) causing death of cells and tissue necrosis. This in turn can lead to sepsis and end in shock. Conversely, following haemorrhage or shock, the intestinal tract is the main organ to experience an ischemic/reperfusion injury. Intestinal cell membrane permeability can increase due to mesenteric ischemia (2), provoking bacterial translocation and injury of the gut barrier that in turn leads to sepsis and MOF (3-5). Hence, the measurement of intestinal permeability has been used as a valuable diagnosis of diseases affecting the bowel (6, 7).

The intestinal barrier protects the gastrointestinal tract, which under normal conditions is colonised by the bacterial flora containing enough microorganism, bacteria, and endotoxins to kill the host (8). Epithelial cells covering the surface of the gastrointestinal tract forms this barrier that prevents the absorption of toxins, antigens, proteases and microorganism across the intestinal wall (9). However, bacteria penetrates the intestinal barrier with relative ease and it is a common occurrence in healthy patients. This bacterial translocation can lead to further damage, worsening the health situation in ill patients (8), hence, it is of utmost importance to control this translocation in patients with critical conditions. Some studies have focused their efforts on understanding the function and mechanism of the intestinal barrier (10, 11), however, these are unclear and the correlation between bacterial translocation and intestinal permeability has raised controversies. A correlation between the loss of intestinal barrier function and bacterial translocation was found out in rodents, but not in humans, where bacterial translocation could not be related to the increase of permeability of the atrophied villous (6). Seemingly, no correlation was found after major gastrointestinal surgery between failure of the gut barrier function and septic complication (11). Hence, some studies have proposed a primary mechanism of translocation in the absence of damaged mucosal barrier, where migration of organism across the bowel occurred by pinocytosis in epithelial cells (12-14). Nevertheless, other investigations have identified alterations in intestinal permeability in critically ill patients, where the loss of tight junctions and cells at the villous tip was suggested to be the primary cause of changes in intestinal permeability (15, 16).

During the first stage of the bacterial translocation process, bacteria adhere onto the enterocytes and cross the barrier via transcellular and paracellular mechanisms (12, 17, 18). Disrupted epithelial tight junctions ('leaky gut') are the cause of bacterial translocation in the paracellular route (19, 20). While, intracellular trafficking follows the endocytic uptake during the transcellular route (21) (Figure 1). Nevertheless, regardless of the type of mechanism, bacterial translocation is triggered by common injuries such as ischemia/reperfusion, oxidative stress and bacterial action. Typically, the immune system will attack the bacteria once across the barrier. However, if this fails, sepsis or endotoxemia occurs, and further damage will develop into MOF (8, 22). In fact, the bowel is the main organ involved in MOF and this typically occurs as a consequence of a systemic inflammatory response syndrome (SIRS).

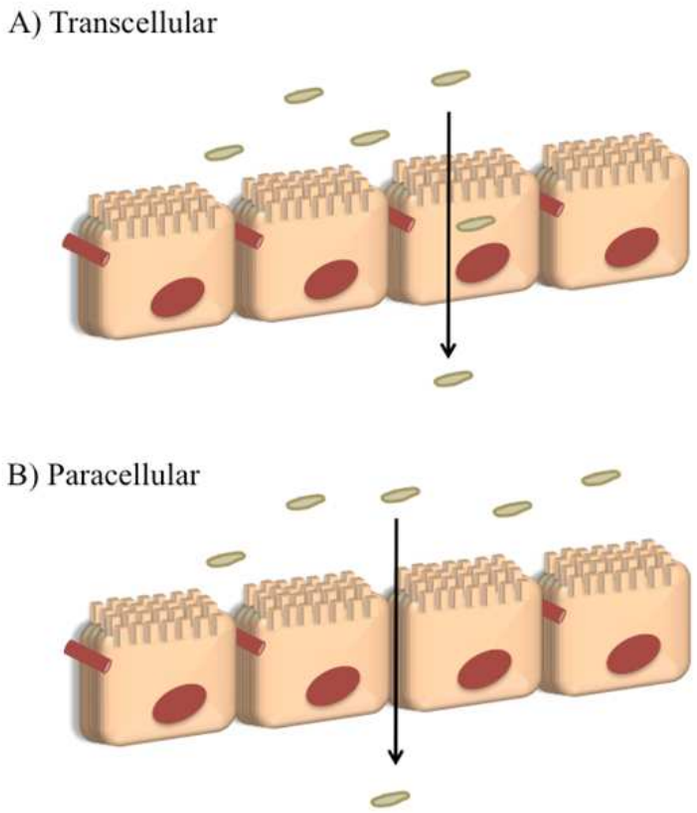

Figure 1. Schematic model of disrupted gut epithelial barrier. Ischemia and infection may be the initial cause of disruption allowing bacteria and other pathogens to cross the barrier and mix with the luminal content. A) Transcellular route occurs by intracellular trafficking; B) Paracellular route occurs due to the disruption of tight junctions.

Insults such as haemorrhage, ischemia/reperfusion, infection or trauma generally lead to an inflammatory response and this further develops into shock, if untreated. Toxins induce the release of cytokines, leukotrienes and platelets-activating factors (PAF), which play a major role in the initiation of shock (23-26). Hence, bacterial and toxin translocation have been suggested to be the main cause of all these intestinal dysfunctions (27, 28). The increase of membrane permeability has been related to bacterial translocation mechanisms and

ischemic process in the intestine. In fact, translocation, vasoconstriction and hypoxic villi are common mechanisms occurring in the bowel due to the proximity of this to luminal bacteria and toxins (29). Reduction in blood flow is also a cause of initiation of shock, as well as activation of endotoxins, which release vasoactive substances and stimulate the formation of oxygen free radicals in the tissue (25, 27, 30, 31). The reduction of blood flow means a loss of plasma volume and hence a reduction of proteins into the interstitium space, which in turn leads to MOF (32-36). The sequence of shock varies with different pathologies (low perfusion, hypotension, hemoconcentration, vasocongestion), but the cause of death initiated due to the inflammatory response is very similar (37).

Certain diseases and common surgical procedures can lead to the weakness of blood vessels that with the continuous passage of blood can dilate forming an aneurysm. As the aneurysm expands, the risk of rupture increases and this can produce severe haemorrhage leading to other complications and ultimately to death. The most common abdominal aneurysm occurs in the aorta, hence the term abdominal aortic aneurysm (AAA). Ischemic colitis is the most common complication after abdominal aortic aneurysm surgery (38, 39) presenting a high impact in mortality rates (40-43). Another high risk postoperative complication is the leakage of a low rectal anastomosis connection, or the site where the two transacted bowel segments are joined again, closing the bowel lumen (44). Anastomosis leaks can easily develop into sepsis increasing the mortality toll. Although other variables contribute to the risk of anastomosis leakage, ischemia is the main factor related to anastomosis leak (45-47). During cardiac surgery with cardiopulmonary bypass (CPB), there is a high risk of patients developing intestinal mucosal ischemia. This may further lead to a disturbed mucosal integrity and increased intestinal permeability due to imbalance between splanchnic oxygen supply and demand which may contribute to systemic inflammation (48). Hence, an early diagnosis and the evaluation of an adequate splanchnic perfusion are crucial to improve outcome rates following surgical procedures such as aneurysm repair, anastomosis connections and CPB.

3. Gastrointestinal perfusion monitoring

The principal factors in the development of sepsis, systemic inflammatory syndrome and MOF are intestinal ischemia and gut barrier failure. These are also the main causes for the development of anastomosis leak and present a high rate of recurrence after AAA repair. During inadequate blood flow, the metabolic needs of the tissue are not met, leading to tissue injury. Consequently, ensuring both perfusion pressure and blood flow to maintain the necessary metabolic supply and demand are highly important to avoid diseases (49). It is in situations when blood flow has been partially compromised, where an early diagnosis could prevent the injury from developing further into organ dysfunction and death. In order to monitor these perfusion irregularities, several techniques have been used over the years. Human GI perfusion has been monitored by means of tonometry (50-52), laser Doppler flowmetry (53, 54), reflectance spectrophotometry (55), near-infrared spectroscopy (56), orthogonal polarisation spectral imaging, (57, 58), indocyanine green clearance (59), and measurements of plasma D-lactate (60). While the outcome of patients with septic shock can

be predicted, these techniques cannot be compared to each other since they measure different constituents of GI perfusion (61). Alternatively, intestinal bleeding, which is undisputably an indication of organ damage, has been used to diagnose intestinal failure, however this fails to quantify the damage. Absorption markers of increasing permeability have also been extensively studied to assess gut functions, however, as they are highly invasive and require extensive nursing time, they are not appropriate for clinical monitoring in the intensive care unit (ICU). Gastrointestinal tonometry, due to its simplicity, is currently the most commonly used technique. It provides adequate information of GI perfusion and it is highly suitable for use in ICU. The technique consists of a silicone balloon inserted in the stomach that automatically infuses and samples gas every 10 minutes. The gas sample is analysed automatically using an infrared sensor within the measurement instrument (62, 63). However, it has several disadvantages as it does not provide a continuous measurement, presents long response time and leads to potential systematic errors as the gas samples are drawn from the catheter and analysed using an external measurement device. Furthermore, this method depends on the technical operator, compromising its reproducibility, and the effect of perfusion countercurrents changes on its sensitivity is still obscure (64). In addition, improvement of gastrointestinal perfusion has failed to prevent mucosal failure and otherwise, increasing the perfusion might have an effect on the metabolic rate, modifying the balance between oxygen demand and supply (61).

Currently, techniques most commonly used in clinical practices for the diagnosis of leaks are routine blood tests, colonoscopy, ultrasound and abdominal x-rays such as, CT scans, mesenteric angiography and MRIs and as a last resort, an exploratory abdominal surgery. Regardless of all advances in clinical technology, the monitoring of gastrointestinal perfusion is still limited and in most surgical departments, the diagnosis of intestinal ischemia relies on clinical symptoms and examination (65). However, subjectivity, the lack of precision and the delayed manifestation of the symptoms account for the unreliability of this procedure.

Research based on microcirculation and secretion during shock has been broadly explored at cellular and molecular level, however, there is a lack of information at the organ level (66). The mechanism of ischemia before shock and MOF begin, is not only an important area of research but one with plenty of room for exploration. Monitoring organ function and metabolism could be the ultimate mode of measuring gut perfusion (64), since there are evidences of the existence of localised biochemical changes in specific segments of the patient's gut (67).

Splanchnic hypoperfusion is generally associated with a poor outcome in critically ill patients. Moreover, despite presenting a hyperdynamic systemic circulation, the mucosa hypoperfusion in gastric, small intestine and colonic tissue commonly develops into sepsis (68). Gastrointestinal mucosa has been described as one of the highest metabolically active tissues under conditions of sepsis (69, 70) and although no clear association has been found, gut flow and metabolic changes appear to be heterogeneous (71-74). During compromised mucosal tissue, the reaction mechanism has been proposed as an increase of oxygen extraction (75). However, regardless of adequate oxygen delivery, the cells are unable to use

oxygen during sepsis (76). During the initiation of intestinal ischemia, whatever the cause of injury (bowel strangulation, intestinal perforation or impaired blood flow), a rise in intracellular biomarkers occurs due to the increase of intestinal permeability (77). Therefore, metabolic levels are presented as useful measurements for the monitoring of intestinal ischemia.

During ischemia, a change from aerobic to anaerobic tissue metabolism occurs, which results in a decrease of glucose and pyruvate levels and increased lactate and glycerol levels. During anaerobic metabolism, the support of glucose from sphlanchnic circuit is inhibited causing pyruvate to accumulate in the tissue. Due to the lack of oxygen, pyruvate cannot be incorporated into the citric acid cycle, metabolising pyruvate to lactate. Monitoring the gut metabolic markers provides information on the variation from aerobic to anaerobic metabolism, the balance between oxygen supply and demand and therefore the ischemic degree of that tissue. In order to obtain a more accurate assessment of tissue metabolism, determination of lactate/pyruvate or lactate/glucose ratio is preferred compared to lactate alone. In addition, during sustained ischemia, a breakdown of the cellular plasma membrane occurs resulting in the release of phospholipids into the extracellular fluid, which are degraded to free fatty acids and glycerol. Hence, glycerol is another common metabolic product monitored during ischemic studies (78).

4. Biosensors as a diagnosis tool of gastrointestinal pathology

Over the past few decades, a large number of biosensors (a biological sensing element directly interfaced to a signal transducer) have been developed for the detection of various metabolites, proteins and nucleic acids with a wide range of applications, such as for medical diagnosis of gastrointestinal disorders.

Currently, the most common minimally invasive method to monitor the perfusion of the gastrointestinal tract in clinical settings is gastric tonometry. However, the technique only provides discrete measurements. In order to overcome this limitation, an optical fibre sensor was developed (79). This is based on the utilisation of a CO_2 sensing layer fixed at the end of an optical fibre catheter that is connected to an optoelectronic unit. The sensor allows the continous monitoring of the rapid changes in the gastric pCO_2 and hence provides a better understanding of gastrointestinal physiology (Figure 2).

Monitoring tissue adenosine triphosphate (ATP), in addition to other metabolic products, provides a further understanding of the cellular respiration rate. Furthermore, ATP has an important function within the immune system as a clotting signal molecule (80) and it is thought to regulate serotonin (5-HT) release and hence gastrointestinal motility (81-83). An ATP microelectrode biosensor with high long-term stability and selectivity was used to study the regulation of mucosal release mechanisms such as 5-HT based on the long-term in vitro variations of ATP release from isolated ileum and colon tissues (84).

Others have developed a microcapillary immunoassay, the Quantum-dot-Linked Immunosorbent Assay (QLISA), in order to differentiate between inflammatory bowel

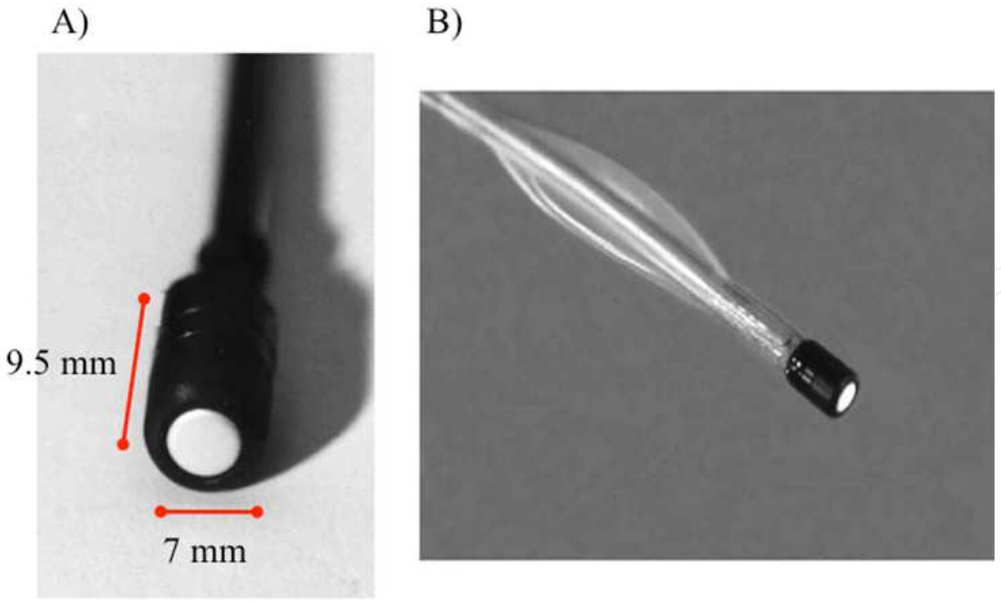

Figure 2. Optical probe for continuous monitoring of gastric carbon dioxide. A) Tip of the optical probe head; B) Optical probe mounted on a Tonocap catheter for gastric tonometry. Modified with permission from Elsevier (79).

diseases such as ulcerative colitis and Crohn's disease and irritable bowel syndrome (IBS). The fecal levels of the gastrointestinal inflammatory disease's biomarkers, myeloperoxidase and lactoferrin, could be quantified using this biosensor (85). In another study, a filter-paper-based strip was used to develop a bacterial whole-cell biosensor that allows optical on-site detection of a chemical signalling molecule in Gram-negative bacteria, which plays an important role in the pathogenesis of several gastrointestinal disorders (86). Differentiation of old blood and new blood for the surveillance of rebleeding occurrence was possible with an endoscopically implantable wireless biosensor designed to detect blood labelled with fluoroscein. This has the potential of immediate, real-time detection of upper gastrointestinal bleeding. Furthermore, the wireless signal can be transmitted to external computers that relay the data to the patient's cell phone or to an emergency response network allowing an early-warning remote surveillance system. In this way, the detection of rebleeding of endoscopically defined sources of GI hemorrhage during periods of high risk is possible (87) (Figure 3).

Studies with biosensors are still commonly performed in animal models or rely on collecting patients' fluids and tissue samples. Implantable biosensors still have problems associated with biocompatibility. Damage of the tissue surrounding the biosensor is believed to affect the measurement levels. In addition, implanted biosensors suffer the reaction of the tissue towards the foreign body, the so-called biofouling. A cascade signal is sent by the immune system that triggers the release of platelets and immune proteins as well as the formation of new blood vessels, which encapsulate the biosensor and hence impair the sensing layer (88-90). Therefore, alternative techniques have been explored to monitor gastrointestinal biomarkers.

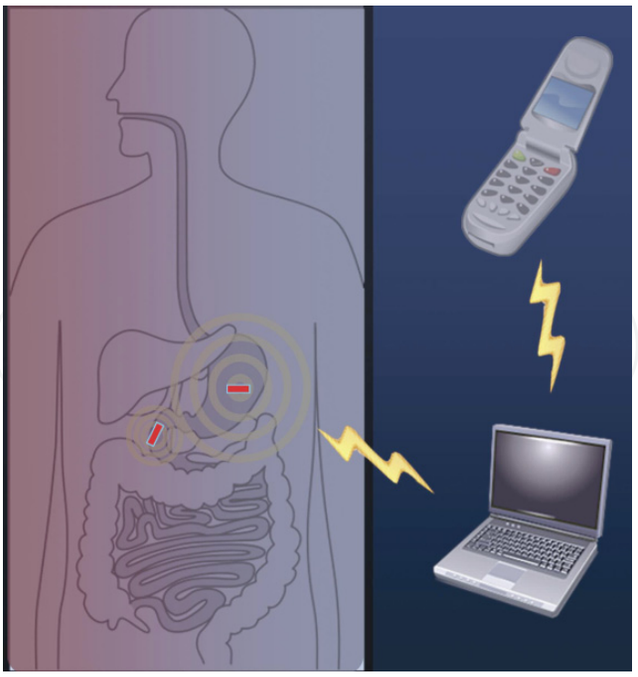

Figure 3. Scheme of wireless communication for gastric bleeding. Optical biosensor implanted endoscopically in the stomach transmits the signal wirelessly to external computers and to the patient's cell phone or other networks. Reprinted with permission from Elsevier (87).

5. Microdialysis monitoring

In the early seventies, Ungertstedt and Pycock (91) developed microdialysis, an extraction technique to measure interstitial substance in the brain without causing extensive tissue damage. The original concept for microdialysis was to mimic a blood capillary (92). Microdialysis is based on the passive diffusion of the molecules through a hollow fibre membrane (93). A sterile physiological solution (perfusate) is infused by a syringe pump at very low flow rates (typically 0.3-2 μl/min). Molecules present in the extracellular fluid diffuse to the lumen of the microdialysis (dialysate) and this is sampled through the outlet (Figure 4). The membrane cut-off confers selectivity to the technique, limiting the size of molecules diffusing through it. In clinical situation, this prevents the passage of virus into the dialysate and it eliminates problems associated with instability of metabolites due to sample preparation. Since the dialysate is free of proteins, this can be directly injected into analytical systems for analysis.

Since its beginning, microdialysis applications have broadened to the sampling of extracellular fluid of different human tissues including ear fluid (94), brain (95, 96), liver (97), heart (98), lungs, muscle (99) and bowel (78). The reader is directed to some of the reviews on microdialysis found in the literature (92, 100-103). Extensive studies have been carried out using microdialysis in the digestive system organs. This section describes some of the work published in stomach tissue, liver, pancreas and intestine.

Gastric microdialysis has been used to continuously monitor gastrin release to determine the response to food, acid blockage and acute vagal excitation (104). Microdialysis monitoring of

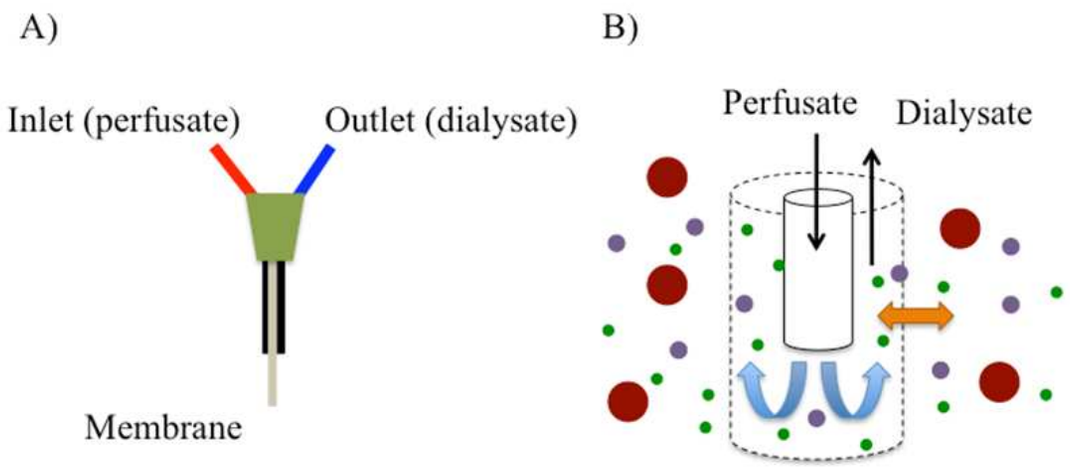

Figure 4. Scheme of a Microdialysis probe. A) Microdialysis membrane is depicted as a tip, which is connected via a shaft to the inlet and outlet tubings; B) The semipermeable membrane limits the diffusion of large molecules such as red blood cells, large proteins and virus.

gastric ischemia during temporary celiac artery occlusion in anesthetised rats showed a more remarkable response to ischemia in the relative changes of metabolic ratios of lactate/pyruvate and lactate/glucose compared to changes in the flow indicator of H_2O efflux and glycerol (105). Histamine release from enterochromaffin-like (ECL) cells during ischemia has been commonly sampled from the stomach submucosa with a single microdialysis probe (106-109). However, submucosal microdialysis sampling has been suggested to be unrepresentative of histamine levels released from ECL cells, since these are located in the mucosa layer, requiring a diffusion of histamine from the mucosa to the submucosa and finally to the probe (110). A more accurate sampling of stomach analytes was introduced using a multiple probe approach in which the probes were implanted in the stomach lumen, mucosa, submucosa and in the blood of a rat (111) (Figure 5). This four-probe microdialysis sampling was used to directly compare drug absorption between gastric ulcerated and healthy tissue in the same animal, where the dialysate was analysed using high performance liquid chromatography ultraviolet (HPLC-UV). The study showed a higher drug concentration in ulcer tissue, which was a function of ulcer size and thickness and probe location within the tissues when compared to healthy tissue (112). The reconstructed oesophagus of patients undergoing resection of carcinoma was monitored with microdialysis to investigate the risk of postoperative complications caused by ischemia. This study showed lactate/glucose ratio to be the most reliable parameter and sets microdialysis as a promising method for examination of free jejunal flaps (113).

Liver metabolism has also been studied using microdialysis sampling. A study in anaesthetised rats showed that of the stimulation of hepatic nerves result in glycogenesis via α-adrenergic mechanism and eicosanoids mediators (114). Other metabolites typically measured in the liver are glucose, lactate, pyruvate and glycerol. Dialysate concentrations of these analytes were measured in swine models during and after liver transplantation. The samples were collected and analysed at 20 minute intervals during both the donor operation and cold preservation, and 7 hours after reperfusion in the recipient (115).

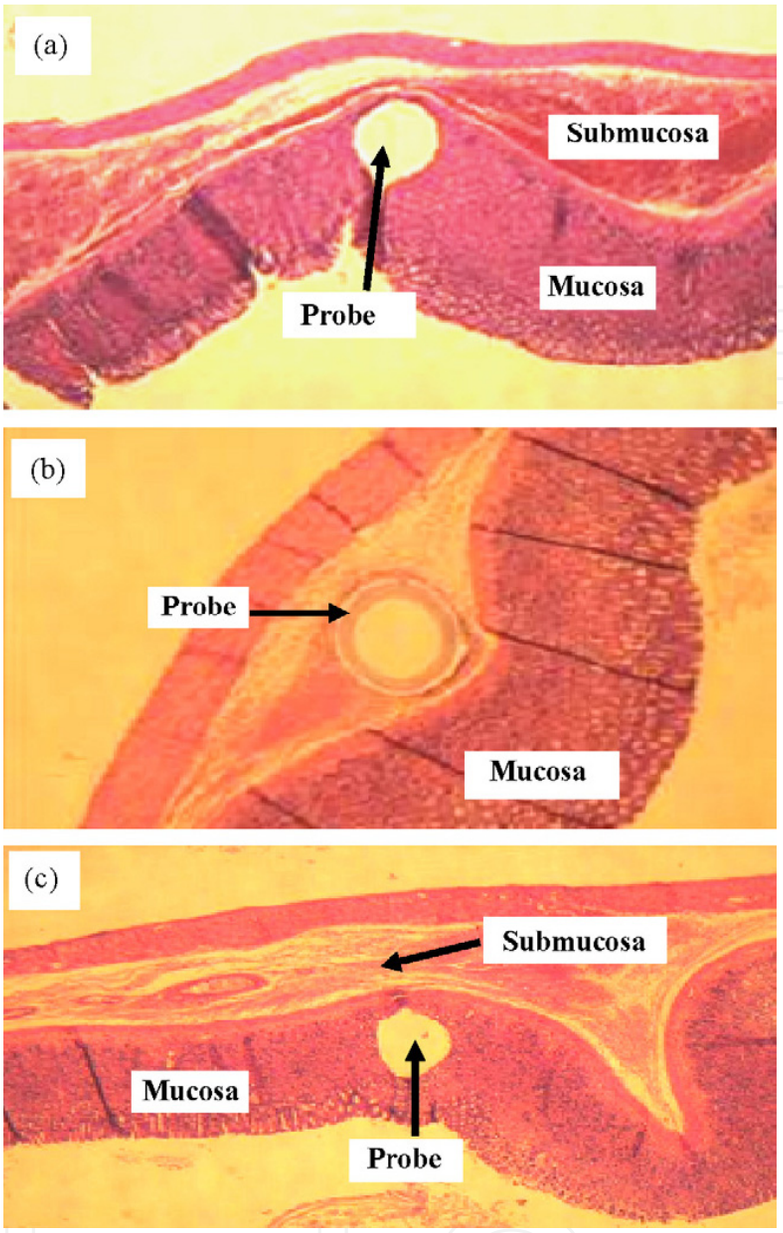

Figure 5. Histology images of microdialysis probe implantation (a) in the mucosa right after implantation, (b) in the submucosa 2 h post implantation and (c) in the mucosa 12 h post implantation (20x magnification). Reprinted with permission from Elsevier (111).

This led to the monitoring of metabolic changes in liver grafts in a clinical pilot study with 10 patients (116). Metabolic products were also monitored during ischemia-reperfusion injury in the rat liver using microdialysis and commercially available bedside kits (117). This study proved that microdialysis is applicable for human liver surgery by continuous intraoperative monitoring of intrahepatic metabolism (118). Alternatively, liver slices and microsomes have been used to carry out in vitro microdialysis studies of hypoxia (119), steroid enzymes activity (120) and drug metabolic processes (121).

As microdialysis collects only the unbound fraction (the pharmacologically active fraction) of the drug, it eliminates the need for unnecessary extensive sample preparation and

enzyme degradation processes. This is highly advantageous during pharmacokinetic studies, such as the intraperitoneal monitoring of a drug active concentration in freely moving rodents (122). Other studies have used microdialysis to investigate the pathophysiology of brain activity among irritable bowel syndrome (IBS) patients and brain-gut interactions. In vivo brain microdialysis monitoring during colorectal distention in rats showed that noradrenaline is released in the hippocampus during the distention thus suggesting a possible correlation with behavioural changes (123).

5.1. Intestinal microdialysis

Microdialysis possesses the advantage of its applicability to other organs in which needle puncturing is possible including the stomach and intestines. On the other hand, the puncturing performed by the probe implantation, as seen in Figure 5, can inflict an acute inflammatory response that may influence the measurement levels and interpretation (124). A common solution has been to establish equilibration periods after probe implantation. Nevertheless, there is a critical need for smaller microdialysis probes to reduce the damage in surrounding tissue and local blood supply. This trauma caused by the implantation of the microdialysis probe is one of the main controversial issues when deciding the probe placement in gastrointestinal tissue.

Intraluminal probe placement could be a good approach, because the injury that occurs in the bowel causes a bigger damage to the mucosa than to the seromuscular layer, and therefore, biomarkers in the lumen rise early during the injury period (125). However, intraluminal metabolites measurements have been found to be extremely low and the detection is not feasible due to the resting phase of the intestine and to the high volume of contents in the lumen (126). A common approach is to place the microdialysis probe in the human peritoneal cavity (127-129). The assumption is that due to the high amount of intestinal anaerobic products metabolised by the liver, the metabolic markers of an impaired circulation are greater in the peritoneum than in blood (77). However, the ischemic biomarkers are diluted by non-ischemic markers and by the systemic circulation supplied to the peritoneum (78). Sommer et al. compared results from microdialysis probes inserted intraperitoneally, intramurally and intraluminally in the bowel of a swine model (126) (Figure 6). Insertion of the probe intramurally provides faster detection of metabolic changes than intraluminal and peritoneal microdialysis due to the proximity of the probe to the damaged tissue and the lack of dilution artifacts (130). However, this is more invasive and presents a difficult challenge for the clinician thus requiring intensive training. A recent approach has been to evaluate the insertion of the microdialysis probe in pancreatic tissue guided by an endoscopic ultrasound device (131), which has the potential to be used in other tissues. In addition, the microdialysis probe has a fragile tip, which can be broken during the probe implantation. It is increasingly recognised the need for the production of less fragile probes and alternative geometries.

Microdialysis monitoring can be divided into off-line and on-line microdialysis depending on the coupling method between the microdialysis outlet and the detection technique.

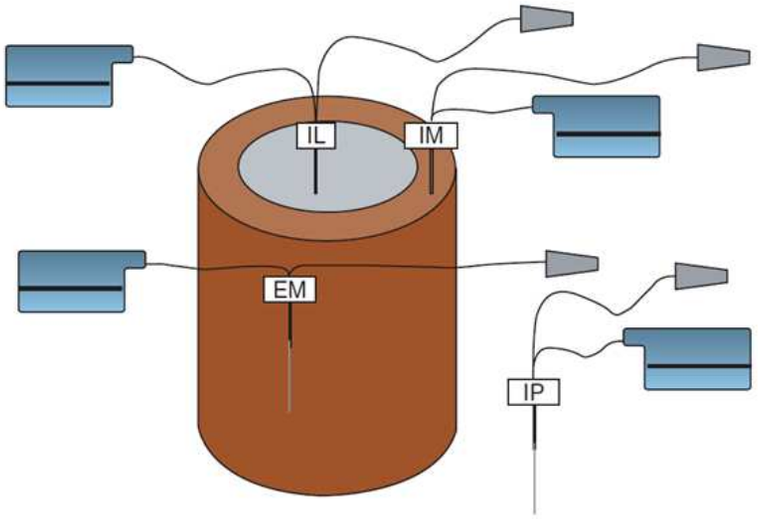

Figure 6. Microdialysis probe placement in the bowel. IL, intraluminal; IM, intramural; EM, extramural; IP, intraperitoneal. Reprinted with permission from John Wiley & Sons (126).

Off-line Microdialysis

Several studies have used in vivo microdialysis monitoring in animal models to investigate splanchnic metabolic disorders by measuring glucose, lactate/pyruvate ratio and glycerol both intraluminally (132-134) and in the intraperitoneal space (128). From these studies, microdialysis was suggested as a valuable tool for surgeons to detect early signs of mesenteric ischemia and the postoperative complications associated with this. In another study, microdialysis was used to monitor several episodes of ischemia in the pig intestine. The results showed lower dialysate levels of lactate during the second ischemic event compared with the first. This suggested that extended periods of ischemia triggered a mechanism of protection against hyperpermeability for later ischemic events (135).

Few have translated this technology to human subjects. Some pilot studies have used microdialysis for intraoperative monitoring. Intestinal luminal microdialysis and tonometry was used to monitor the rectal mucosa of patients undergoing elective cardiac surgery with cardiopulmonary bypass. This combination allowed the monitoring of both circulation and metabolism to indicate the adequacy of splanchnic perfusion in the colon (136). Others have used blood, urine and interstitial fluid microdialysis samples to investigate the phamacokinetic effect of antibiotic concentrations at the sites of infection during AAA open repair surgery (137). But, in general, studies in patients are carried out postoperatively. The safety of intraperitoneal microdialysis was evaluated to monitor metabolic and inflammatory changes in infants after surgery for necrotising enterocolitis (138). Peritoneal microdialysis was used postoperatively to assess the anastomosis leak rate in patients undergoing a low rectal resection due to cancer. In a medical trial for defunction stoma procedure, where patients were randomised, results showed that showed that defunctioning loop stoma decreased the probability of anastomosis leak (139). Another study distinguished a higher lactate/pyruvate ratio postoperatively in patients presenting anastomosis leakage before evidences of clinical symptom compared with those without (140).

From these clinical studies, scientists have agreed on the advantages of microdialysis as an early indication of intraoperative and postoperative complications compared with customary devices for the monitoring of splanchnic circulation. However, most of the microdialysis studies presented here used either bulky laboratory techniques such as liquid chromatography and electrophoresis or the commercially available bedside kit analyser from CMA/Microdialysis (141). Since the detection is off-line, samples are required to be collected in vials and manually stored in ice by a trained technician or the ward nurse. This time lag and the problem associated with sample misplacement are serious pitfalls of off-line microdialysis.

On-line Microdialysis

In order to have an early diagnosis, a tight monitoring is required. Metabolic events are rapid so a continuous monitoring is necessary. In recent years, compact instrumentation and microfluidic devices are being coupled online with microdialysis probes to overcome the temporal resolution of microdialysis. Lab-on-chip technology, such as microchip electrophoresis and liquid chromatography (142, 143) and microfluidic devices that increase temporal resolution by creating segmented nanolitres dialysate samples (144) are increasingly being investigated. However, the synergetic combination of microdialysis and biosensors has put this technology to the forefront of invasive monitoring. Sensitivity and biocompatibility of the biosensors increased when coupled to microdialysis and in turn biosensors enhance the temporal resolution of microdialysis to the millisecond scale (145, 146). This technology plays an important role in both point-of-care testing and home care (147).

Some studies placed the biosensors inside the microdialysis tubing (148-150), while others use connectors (151-153) or flow injection analysis systems (95, 154, 155). Alternatively, miniaturised flow-through biosensors have been fabricated for the connection with microdialysis (156).

An on-line rapid sampling microdialysis biosensor system has been used to monitor ischemia at the bowel level. The system couples selectively glucose and lactate electrochemical biosensors on-line with the microdialysis probe using a flow injection analysis (FIA) system. This allows in vivo monitoring of metabolic substrates changes in the colon at a high time resolution, every 30 seconds, without the need for extensive manipulation, running by itself during 24 hours up to 5 days (Figure 7).

Rapid sampling microdialysis was used to monitor rapid changes of glucose and lactate levels in patients undergoing an elective colectomy, most typically due to cancer. The microdialysis probe was inserted in the seromuscular layer of the colon and sutured to ensure fixation and allow the surgeon to proceed with the resection. A stabilisation period of 10-15 minutes was allowed before the transection of the main feeding artery, where glucose and lactate levels decrease and increase, respectively. These metabolic changes were not immediate as expected, but after an average interval of 12 minutes, attributed to the colon collateral flow, however, these agreed with the mechanism of blood flow reduction

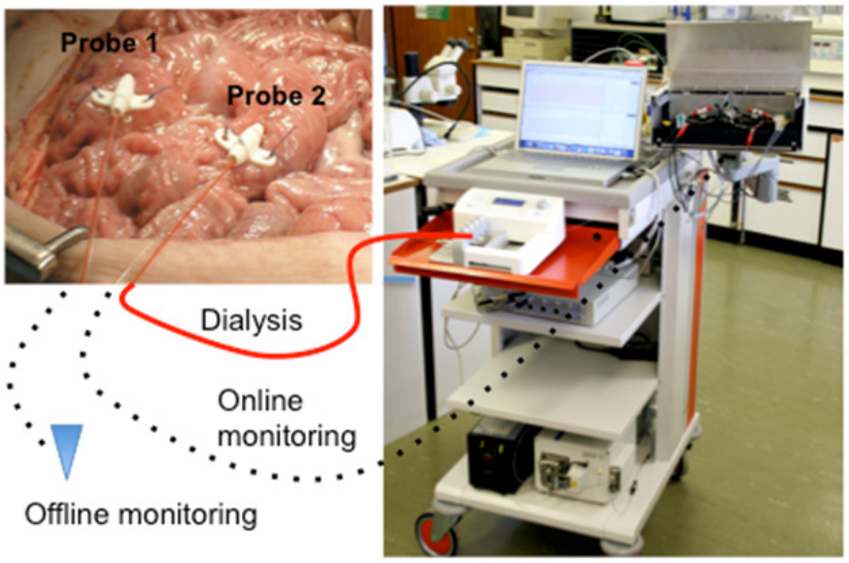

Figure 7. On-line rapid sampling intestinal microdialysis monitoring system. Two probes are implanted in the bowel wall, one as a control (off-line) and one as a test (on-line). The system parts are placed in a laparoscopy trolley allowing the transport of the system from the lab to clinical settings. Reproduced by permission of The Royal Society of Chemistry (157), http://pubs.rsc.org/en/Content/ArticleLanding/2011/AY/c1ay05306j

(158). A preliminary work in animal models was carried out to understand the mechanism of ischemia in compromised bowel, such as that after an anastomosis procedure. Here, the microdialysis was also tunnelled in the seromuscular layer, but in parallel with the site of the anastomosis construction, within a distance of a few millimeters. In this case, glucose and lactate changes occurred almost immediately after the feeding artery transection, which reveals that the tissue cannot rely on the same collateral flow once it has been compromised (by the resection previous to the anastomosis) (157). This has been further illustrated when comparing both data, where a therapeutical window is clearly observed in healthy patients but not in compromised tissue (159) (Figure 8).

The system was recognised as a potential candidate for monitoring early diagnosis of ischemia after AAA repair surgery. A set of data was obtained during the monitoring of aneurysm repair elective surgery patients for up to 2 days in ICU. The probe was implanted in the bowel of seven subjects in the mesenteric border of the sigmoid colon just at the junction of the mesentery with the colon. Although changes in plasma values were observed, dialysate levels for both glucose and lactate were steady. This confirms the fact that microdialysis levels are a good indicator of local changes, but it does not reflect systemic conditions. The lactate/glucose ratio was observed to be constant for all patients for up to 2 days after probe implantation, which strongly indicates the lack of acute ischemic events. Some episodes of transient metabolic ischemia were observed due to a compromised blood supply, which allows for pattern recognition during further studies (160).

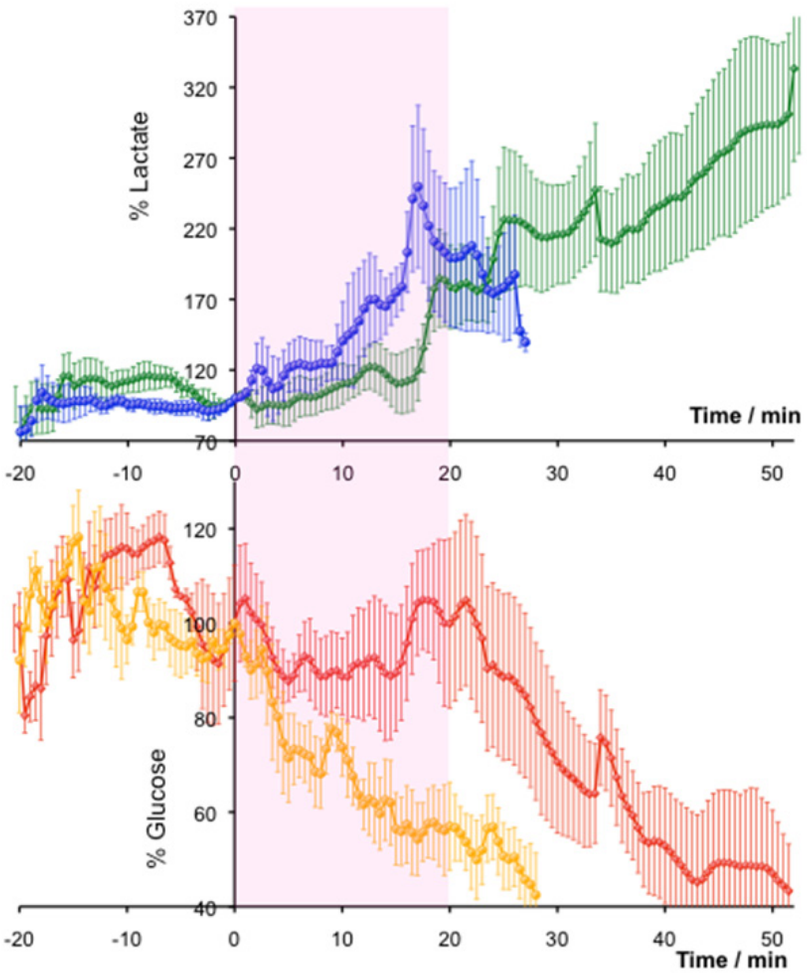

Figure 8. Microdialysis monitoring of healthy tissue in patients versus compromised anastomotic porcine tissue. Percentage of metabolites levels (mean ± sem) monitored during colorectal surgery in patients (red & green traces) and in the anastomosis site of porcine bowel wall models (orange & blue traces). Glucose traces drop from baseline values, while lactate traces rise. Alignment at the transection of main feeding artery (t=0). Reprinted with kind permission from Springer Science & Business Media (159).

6. Conclusion and future trends

Mesenteric ischemia has been known to increase intestinal cell membrane permeability, provoking bacterial translocation and ultimately leading to sepsis and multiple organ failure. An adequate splanchnic perfusion and evaluation of intestinal permeability are crucial to improve outcome rates following surgical procedures. However, current techniques for the diagnosis of leaks are unreliable due to the subjectivity, lack of precision and the delayed manifestation of the symptoms.

Microdialysis has been used to monitor biomarkers in a range of tissues and organs. Clinical studies using intestinal microdialysis have agreed on the advantages of the technique as an early indication of intraoperative and postoperative complications compared with common monitoring of splanchnic circulation. However, off-line detection carries a limitation for the

early diagnosis of ischemic insults, since metabolic events are rapid. On-line rapid microdialysis technology takes advantage of the synergetic combination of microdialysis and biosensors, which plays an important role in both point-of-care testing and home care.

Microdialysis has recently been evaluated as a tool to assess the metabolic changes during liver resection, stomach ischemia and for the diagnosis of novel biomarkers of the pancreas that are undetectable in plasma. Preliminary work has been done with microdialysis to monitor key metabolites during and after organ transplantation. Although still in early stage, this presents the potential of monitoring the organ's condition during the transportation. This will allow not only the determination of the suitability of the organ for transplantation, but will also decrease the possibility of occurrence of an ischemic insult by perfusing the organ when it reaches a certain predetermined threshold.

Among some limitations of microdialysis is the trauma caused by the implantation of the probe, which causes an inflammatory response and compromises the results of the investigation. A common solution has been to establish equilibration periods after probe implantation and to develop miniature probes. Since smaller sized probes present high back-pressure, a droplet microdialysis probe has been designed to overcome this issue (161). Alternatively, flat microdialysis geometries can be envisioned, for those tissues where tunnelling of the probe is not necessary. Temporal resolution also limits microdialysis use, hence microfluidic and lab-on-chip devices have been investigated to directly connect the microdialysis with biosensors (162-164). As the microfabrication technology advances, more chips and miniaturised devices will be seen such as micropumps to be implanted in line with the microdialysis inlet and wireless detection systems embedded in the probe design, reducing in this way bulky instrumentation, otherwise required. One of the paramount targets of biomedical research is to be able to create close-loop systems that combine sensing devices with drug delivery systems. Microdialysis probes are currently used for drug delivery and fluid sampling for diagnosis. Hence, it can be envisioned a device where microdialysis is coupled with biosensors for diagnosis and depending on the levels recorded, the mechanism switches to a reverse mode delivering the drug required.

Most microdialysis publications focus on the monitoring of neurochemicals, however, general reviews and book chapters are helpful to understand the fundamentals of the technique and learn how to handle the probes and perform calibration experiments (165-167). Originally, microdialysis probes were fabricated from dialysis fibres connected to an inlet and outlet tubing. With the expansion of microdialysis, few major trades are handling the commercialisation of microdialysis products, producing CE approved sterile probes for human use (141) and for in vitro and animal studies (168, 169).

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7. References

[1] Brandt LJ, Boley SJ. AGA Technical Review on Intestinal Ischemia. Gastroenterology. 2000;118(5):954-68.

[2] Loganathan A, Linley JE, Rajput I, Hunter M, Lodge JPA, Sandle GI. Basolateral potassium (IKCa) channel inhibition prevents increased colonic permeability induced by chemical hypoxia. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2011;300(1):G146-G53.

[3] Alexander C, Rietschel ET. Bacterial lipopolysaccharides and innate immunity. J Endotoxin Res. 2001;7(3):167-202.

[4] Davidson MT, Deitch EA, Lu Q, Osband A, Feketeova E, Nemeth ZH, et al. A study of the biologic activity of trauma-hemorrhagic shock mesenteric lymph over time and the relative role of cytokines. Surgery. 2004;136(1):32-41.

[5] Deitch EA, Forsythe R, Anjaria D, Livingston DH, Lu Q, Xu DZ, et al. The Role of Lymph Factors in Lung Injury, Bone Marrow Suppression, and Endothelial Cell Dysfunction in a Primate Model of Trauma-Hemorrhagic Shock. Shock. 2004;22(3):221-8.

[6] Sugi K, Musch MW, Di A, Nelson DJ, Chang EB. Oxidants Potentiate C^2^+- and cAMP-Stimulated Cl^- Secretion in Intestinal Epithelial T84 Cells. Gastroenterol. 2001;120(1):89-98.

[7] Thanou M, Verhoef JC, Marbach P, Junginger HE. Intestinal Absorption of Octreotide: N-Trimethyl Chitosan Chloride (TMC) Ameliorates the Permeability and Absorption Properties of the Somatostatin Analogue In Vitro and In Vivo. J Pharm Sci. 2000;89(7):951-7.

[8] Wiest R, Rath HC. Gastrointestinal disorders of the critically ill. Bacterial translocation in the gut. Best Pract Res Clin Gastroenterol. 2003;17(3):397-425.

[9] Chang JX, Chen S, Ma LP, Jiang LY, Chen JW, chang RM, et al. Functional and morphological changes of the gut barrier during the restitution process after hemorrhagic shock. World J Gastroentero. 2005 Numb 35;11:5485-91.

[10] Ackland G, Grocott MP, Mythen MG. Understanding gastrointestinal perfusion in critical care: so near, and yet so far. Crit Care. 2000;4(5):269-81.

[11] Kanwar S, Windsor AC, Welsh F, Barclay GR, Guillou PJ, Reynolds JV. Lack of Correlation Between Failure of Gut Barrier Function and Septic Complications After Major Upper Gastrointestinal Surgery. Annals Surg. 2000;231(1):88-95.

[12] Alexander JW, Boyce ST, Babcock GF, Gianotti L, Pack MD, Dunn DL. The process of microbial translocation. Ann Surg. 1990;212:496-510.

[13] Berg RD. Bacterial trasnlocation from the gastrointestinal tract. Trends Microbiol. 1995;3(4):149-54.

[14] Tsokos M. Pathology of Sepsis Essentials of Autopsy Practice. 2006:39-85.
[15] Freter R, Abrams GD. Function of Various Intestinal Bacteria in Converting Germfree fice to the Normal State. Infect Immun. 1972;6(2):119-26.
[16] Teshima C, Meddings J. The measurement and clinical significance of intestinal permeability. Current Gastroenterology Reports. 2008;10(5):443-9.
[17] MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut. 1999;45(2):223-8.
[18] Porras M, Martín MT, Yang PC, Jury J, Perdue MH, Vergara P. Correlation between cyclical epithelial barrier dysfunction and bacterial translocation in the relapses of intestinal inflammation. Inflammatory Bowel Diseases. 2006;12(9):843-52.
[19] Clayburgh DR, Shen L, Turner JR. A porous defense: The leaky epithelial barrier in intestinal disease. Laboratory Investigation. 2004;84(3):282-91.
[20] Liu Z, Li N, Neu J. Tight junctions, leaky intestines, and pediatric diseases. Acta Paediatr. 2005 Numb 4;94:386-93.
[21] Swidsinski A, Ladhoff A, Pernthaler A, Swidsinski S, Loening-Baucke V, Ortner M, et al. Mucosal flora in inflammatory bowel disease. Gastroenterology. [doi: 10.1053/gast.2002.30294]. 2002;122(1):44-54.
[22] Swank GM, Deitch EA. Role of the Gut in Multiple Organ Failure: Bacterial Translocation and Permeability Changes. World J Surg. 1996;20(4):411-7.
[23] Caplan MS, Kely A, Hsueh W. Endotoxin and hypoxia-induced intestinal necrosis in rats: the role of platelets activating factor. Pediatr Res. 1992;31:428.
[24] Kubes P, Arfors KE, Granger DN. Platelet-activating factor-induced mucosal dysfunction: role of oxidant and granulocytes. Am J Physiol. 1991;260:G965.
[25] Kubes P, Suzuki M, Granger DN. Modulation of PAF-induced leukocyte adherence and increased microvascular permeability. Am J Physiol. 1990;259:G859.
[26] Redl H. Cytokines in severe sepsis and septic shock: Birkhäuser Basel; 1999.
[27] Adams RB, Planchon SM, Roche JK. IFN-gamma Modulation of Epithelial Barrier Function: Time Course, Reversibility, and Site of Cytokine Binding. J Immunology. 1993;150(6):2356.
[28] De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: Effect of glutamine *. Critical Care Medicine. 2005;33(5):1125-35 10.097/01.CCM.0000162680.52397.97.
[29] Ceppa EP, Fuh KC, Bulkley GB. Mesenteric hemodynamic response to circulatory shock. Curr Opin Crit Care. 2003;9(2):127-32.
[30] Andriantsitohaina R, Suprenant A. Acetylcholine release from guine-pig submucosal neurones dilate arterioles by releasing nitric oxide from endothelium. J Physiol. 1992;453:493.
[31] Falcone JC, Bohlen HG. EDRF from rat intestine and skeletal muscle venules causes dilation of arterioles. Am J Physiol. 1990;258:h1515.

[32] Boughton-Smith NK, Deakin AM, Whittle BJR. Actions of nitric oxide on the acute gastrointestinal damaged induced by PAF in the cat. Agents Actions. 1992;Specs No:C3-9.

[33] Deitch EA. Multiple Organ Failure: Pathophysiology and Potential Future Therapy. Ann Surg. 1992;216(2):117-34.

[34] Kubes P. Nitric oxide modulates epithelial permeability in the feline small intestine. Am J Physiol. 1992;262:G1138.

[35] Kubes P, Granger DN. Nitric oxide modulates microvascular permeability. Am J Physiol. 1992;262(H611).

[36] MacHiedo GW, Zaets SB, Berezina TL, Xu DZ, Feketova E, Spolarics Z, et al. Trauma-hemorrhagic shock-induced red blood cell damage leads to decreased microcirculatory blood flow. Critical Care Medicine. 2009;37(3):1000-10.

[37] Landry D, Oliver J. The ATP-sensitive K^+ channels mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog. J Clin Invest. 1992;89:2071.

[38] Green BT, Tendler DA. Ischemic Colitis: A Clinical Review. South Med J. 2005 Numb 2;98:217-22.

[39] Perry RJ, Martin MJ, Eckert MJ, Sohn VY, Steele SR. Colonic ischemia complicating open vs endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2008;48(2):272-7.

[40] Bauer EP, Redaelli C, Von Segesser LK, Turina MI. Ruptured abdominal aortic aneurysms: Predictors for early complications and death. Surgery. 1993;114(1):31.

[41] Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of Hospital Volume on Postoperative Morbidity and Mortality Following a Colectomy for Ulcerative Colitis. Gastroenterology. [doi: 10.1053/j.gastro.2008.01.004]. 2008;134(3):680-7.e1.

[42] Meissner MH, Johanson KH. Colon infarction after ruptured abdominal aortic aneurysm. Arch Surg. 1992;127:979.

[43] Tollefson DF, Ernst CB. Colon ischemia following aortic reconstruction. Ann Vasc Surg. 1991;5:485.

[44] Karanjia ND, Corder AP, Bearn P, Heald RI. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. Brit J Surg. 1994;81(8):1224.

[45] Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors Associated with Clinically Significant Anastomotic Leakage after Large Bowel Resection: Multivariate Analysis of 707 Patients. World J Surg. 2002;26(4):499-502.

[46] Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KGM. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Brit J Surg. 2001;88(9):1157-68.

[47] Law Wl, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg. 2000;179(2):92-6.

[48] Ascione R, Talpahewa S, Rajakaruna C, Reeves BC, Lovell AT, Cohen A, et al. Splanchnic Organ Injury During Coronary Surgery With or Without Cardiopulmonary Bypass: A Randomized, Controlled Trial. The Annals of Thoracic Surgery. [doi: 10.1016/j.athoracsur.2005.06.038]. 2006;81(1):97-103.

[49] Pinsky MR. Both Perfusion Pressure and Flow are Essential for Adequate Resuscitation. Sepsis. 2001;4(2):143-6.
[50] Cancio LC, Kuwa T, Matsui K, Drew GA, Galvez E, Sandoval LL, et al. Intestinal and gastric tonometry during experimental burn shock. Burns. 2007;33(7):879-84.
[51] Cerny V, Cvachovec K. Gastric tonometry and intramucosal pH - theoretical principles and clinical application. Physiol Res. 2000;49(3):289-98.
[52] Marshall AP, West SH. Gastric tonometry and monitoring gastrointestinal perfusion: using research to support nursing practice. Nursing in Critical Care. 2004;9(3):123-33.
[53] Oltean M, Aneman A, Dindelegan G, x00F, lne J, Olausson M, et al. Monitoring of the Intestinal Mucosal Perfusion Using Laser Doppler Flowmetry After Multivisceral Transplantation. Transplantation Proceedings. 2005;37(8):3323-4.
[54] Boyle NH, Manifold D, Jordan MH, Mason RC. Intraoperative assessment of colonic perfusion using scanning laser doppler flowmetry during colonic resection. Journal of the American College of Surgeons. [doi: 10.1016/S1072-7515(00)00709-2]. 2000; 191(5):504-10.
[55] Ramirez FC, Padda S, Medlin S, Tarbell H, Leung FW. Reflectance Spectrophotometry in the Gastrointestinal Tract: Limitations and New Applications. Am J Gastroenterol. 2002;97(11):2780-4.
[56] Hirano Y, Omura K, Yoshiba H, Ohta N, Hiranuma C, Nitta K, et al. Near-Infrared Spectroscopy for Assessment of Tissue Oxygen Saturation of Transplanted Jejunal Autografts in Cervical Esophageal Reconstruction. Surg Today. 2005 Numb 1;35:67-72.
[57] Cautero N, Gelmini R, Villa E, Bagni A, Merighi A, Masetti M, et al. Orthogonal polarization spectral imaging: a new tool in morphologic surveillance in intestinal transplant recipients. Transplantation Proceedings. 2002;34(3):922-3.
[58] Turek Z, Cerny V, Parizkova R. Noninvasive in vivo assessment of the skeletal muscle and small intestine serous surface microcirculation in rat: sidestream dark-field (SDF) imaging. Physiol Res. 2008;57(3):365-72.
[59] Behrendt FF, Tolba RH, Overhaus M, Hirner A, Minor T, Kalff JC. Indocyanine Green Fluorescence Measurement of Intestinal Transit and Gut Perfusion after Intestinal Manipulation. Eur Surg Res. 2004;36(4):210-8.
[60] Assadian A, Assadian O, Senekowitsch C, Rotter R, Bahrami S, Furst W, et al. Plasma d-Lactate as a Potential Early Marker for Colon Ischaemia After Open Aortic Reconstruction. Eur J Vasc Endovasc. 2006;31(5):470-4.
[61] van Haren FMP, Sleigh JW, Pickkers P, van der Hoeven JG. Gastrointestinal perfusion in septic shock. Anaesth Intensive Care. 2007 Numb 5;35:679-94.
[62] Heinonen PO, Jousela IT, Blomqvist KA, Olkkola KT, Takkunen OS. Validation of air tonometric measurement of gastric regional concentrations of CO2 in critically ill septic patients. Intensive Care Medicine. 1997;23(5):524-9.
[63] Salzman AL, Strong KE, Wang H, Wollert PS, Vandermeer TJ, Fink MP. Intraluminal "balloonless" air tonometry: a new method for determination of gastrointestinal mucosal carbon dioxide tension. Critical Care Medicine. 1994;22(1):126-34.

[64] Rombeau JL, Takala J. Summary of round table conference: gut dysfunction in critical illness. Intensive Care Med. 1997;23(4):476-9.

[65] Ballard JL, Stone WM, Hallett JW, Pairolero PC. A Critical Analysis of Adjuvant Techniques Used To Assess Bowel Viability in Acute Mesenteric Ischemia. Am Surg. 1993;59(5):309.

[66] Gaginella TS, editor. Regulatory Mechanisms in Gastrointestinal Function. Florida: CRC Press, Inc; 1995.

[67] Knichwitz G, Brussel T, Reinhold P, Schaumann F, Richter KD, Van Aken H. Early Onset of Regional Intestinal Ischemia Can Be Detected with Carbon Dioxide Tension Measurement Inside the Peritoneal Cavity. Anesth Analg. 2000;91(5):1182-7.

[68] Tenhunen JJ, Uusaro A, Karja V, Oksala N, Jakob SM, Ruokonen E. Apparent Heterogeneity of Regional Blood Flow and Metabolic Changes Within Splanchnic Tissues During Experimental Endotoxin Shock. Anesth Analg. 2003;97(2):555-63.

[69] Hiltebrand LB, Krejci V, tenHoevel ME, Banic A, Sigurdsson GH. Redistribution of Microcirculatory Blood Flow within the Intestinal Wall during Sepsis and General Anesthesia. Anesthesiology. 2003;98(3):658-69.

[70] Krejci V, Hiltebrand L, Banic A, Erni D, Wheatley AM, Sigurdsson GH. Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage. Brit J Anaesth. 2000;84(4):468-75.

[71] Hiltebrand LB, Krejci V, Banic A, Erni D, Wheatley AM, Sigurdsson GH. Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. Crit Care Med. 2000;28(9):3233-41.

[72] Krejci V, Hiltebrand L, Buchi C, Ali SZ, Contaldo C, Takala J, et al. Decreasing gut wall glucose as an early marker of impaired intestinal perfusion. Crit Care Med. 2006 Numb 9;34:2406-14.

[73] Tugtekin IF, Radermacher P, Theisen M, Matejovic M, Stehr A, Ploner F, et al. Increased ileal-mucosal-arterial PCO~2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med. 2001;27(4):757-66.

[74] Uusaro A, Russell JA, Walley KR, Takala J. Gastric-Arterial PCO~2 Gradient Does Not Reflect Systemic and Splanchnic Hemodynamics or Oxygen Transport After Cardiac Surgery. Shock. 2000;14(1):13-7.

[75] VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. Crit Care Med. 1995;23(7):1217.

[76] Trager K, Radermacher P, Rieger KM, Grover R, Vlatten A, Iber T, et al. Norepinephrine and N^G-monomethyl-L-arginine in hyperdynamic septic shock in pigs: Effects on intestinal oxygen exchange and energy balance. Crit Care Med. 2000;28(6):2007-14.

[77] Liao XP, She YX, Shi CR, Li M. Changes in Body Fluid Markers in Intestinal Ischemia. J Pediatr Surg. 1995;30(10):1412.

[78] Sommer T, Larsen JF. Validation of intramural intestinal microdialysis as a detector of intestinal ischaemia. Scandinavian Journal of Gastroenterology. 2004;39(5):493-9.

[79] Baldini F, Falai A, De Gaudio AR, Landi D, Lueger A, Mencaglia A, et al. Continuous monitoring of gastric carbon dioxide with optical fibres. Sensors and Actuators B: Chemical. [doi: 10.1016/S0925-4005(03)00042-X]. 2003;90(1–3):132-8.

[80] Bours MJL, Swennen ELR, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5′-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacology & Therapeutics. [doi: 10.1016/j.pharmthera.2005.04.013]. 2006;112(2):358-404.

[81] Burnstock G. The journey to establish purinergic signalling in the gut. Neurogastroenterology and Motility. 2008;20(SUPPL. 1):8-19.

[82] Christofi FL, Kim M, Wunderlich JE, Xue J, Suntres Z, Cardounel A, et al. Endogenous adenosine differentially modulates 5-hydroxytryptamine release from a human enterochromaffin cell model. Gastroenterology. 2004;127(1):188-202.

[83] Cooke HJ, Wunderlich J, Christofi FL. "The force be with you": ATP in gut mechanosensory transduction. News in Physiological Sciences. 2003;18(2):43-9.

[84] Patel BA, Rogers M, Wieder T, O'Hare D, Boutelle MG. ATP microelectrode biosensor for stable long-term in vitro monitoring from gastrointestinal tissue. Biosensors and Bioelectronics. [doi: 10.1016/j.bios.2010.11.033]. 2011;26(6):2890-6.

[85] Hansberry DR. A Quantum Dot -- Based Diagnostic Immunoassay for Biomarker Detection in Gastrointestinal Inflammatory Diseases: Drexel University; 2011.

[86] Kumari A, Pasini P, Deo Sapna K, Flomenhoft D, Shashidhar H, Daunert S. Biosensors for Quorum Chemical Signaling Molecules: Implications of Bacterial Communication in Gastrointestinal Disorders. Microbial Surfaces: American Chemical Society; 2008. p. 13-27.

[87] Ryou M, Nemiroski A, Azagury D, Shaikh SN, Ryan MB, Westervelt RM, et al. An implantable wireless biosensor for the immediate detection of upper GI bleeding: a new fluorescein-based tool for diagnosis and surveillance (with video). Gastrointestinal Endoscopy. [doi: 10.1016/j.gie.2011.03.1182]. 2011;74(1):189-94.e1.

[88] Frost M, Meyerhoff ME. In vivo chemical sensors: Tackling biocompatibility. Analytical Chemistry. 2006;78(21):7370-7.

[89] Vadgama P. Sensor biocompatibility: Final frontier in bioanalytical measurement. Analyst. 2007;132(6):495-9.

[90] Wisniewski N, Reichert M. Methods for reducing biosensor membrane biofouling. Colloids and Surfaces B: Biointerfaces. 2000;18(3-4):197-219.

[91] Ungerstedt U, Pycock C. Functional correlates of dopamine neurotransmission. Bull Schweiz Akad Med Wiss. 1974 Jul;30(1-3):44-55.

[92] Benveniste H. Brain microdialysis. J Neurochem. 1989 Jun;52(6):1667-79.

[93] Klaus S, Heringlake M, Bahlmann L. Bench-to-bedside review: Microdialysis in intensive care medicine. Crit Care. 2004;8(5):363-8.

[94] Hahn H, Kammerer B, DiMauro A, Salt AN, Plontke SK. Cochlear microdialysis for quantification of dexamethasone and fluorescein entry into scala tympani during round window administration. Hearing Research. [doi: 10.1016/j.heares.2005.12.001]. 2006;212(1–2):236-44.

[95] Jones DA, Parkin MC, Langemann H, Landolt H, Hopwood SE, Strong AJ, et al. On-line monitoring in neurointensive care - Enzyme-based electrochemical assay for simultaneous, continuous monitoring of glucose and lactate from critical care patients. J Electroanal Chem. 2002 DEC 13;538:243-52.

[96] Parkin MC, Hopwood SE, Strong AJ, Boutelle MG. Resolving dynamic changes in brain metabolism using biosensors and on-line microdialysis. Trends Anal Chem. 2003 SEP;22(9):487-97.

[97] Battezzati A, Bertoli S. Methods of measuring metabolism during surgery in humans: focus on the liver-brain relationship. Curr Opin Clin Nutr Metab Care. 2004 Sep;7(5):523-30.

[98] Kennergren C, Mantovani V, Lonnroth P, Nystrom B, Berglin E, Hamberger A. Extracellular amino acids as markers of myocardial ischemia during cardioplegic heart arrest. Cardiology. 1999;91(1):31-40.

[99] Henriksson J. Microdialysis of skeletal muscle at rest. Proceedings- Nutrition Society of London. 1999;58(4):919-23.

[100] Dawson LA. Capillary electrophoresis and microdialysis: current technology and applications. Journal of Chromatography B: Biomedical Sciences and Applications. [doi: 10.1016/S0378-4347(96)00533-6]. 1997;697(1–2):89-99.

[101] Binnert C, Tappy L. Microdialysis in the intensive care unit: a novel tool for clinical investigation or monitoring? Curr Opin Clin Nutr Metab Care. 2002 Numb 2;5:185-8.

[102] Plock N, Kloft C. Microdialysis—theoretical background and recent implementation in applied life-sciences. European Journal of Pharmaceutical Sciences. [doi: 10.1016/j.ejps.2005.01.017]. 2005;25(1):1-24.

[103] Nandi P, Lunte SM. Recent trends in microdialysis sampling integrated with conventional and microanalytical systems for monitoring biological events: A review. Analytica Chimica Acta. [doi: 10.1016/j.aca.2009.07.064]. 2009;651(1):1-14.

[104] Ericsson P, Håkanson R, Rehfeld JF, Norlén P. Gastrin release: Antrum microdialysis reveals a complex neural control. Regulatory Peptides. [doi: 10.1016/j.regpep.2010.01.004]. 2010;161(1–3):22-32.

[105] Cibicek N, Zivna H, Vrublova E, Cibicek J, Cermakova E, Palicka V. Gastric submucosal Microdialysis in the detection of rat stomach ischemia-a comparison of the3H2O efflux technique with metabolic monitoring. Physiological Measurement. 2010;31(10):1355-68.

[106] Bernsand M, Håkanson R, Norlén P. Tachyphylaxis of the ECL-cell response to PACAP: Receptor desensitization and/or depletion of secretory products. British Journal of Pharmacology. 2007;152(2):240-8.

[107] Ericsson P, Norlén P, Bernsand M, Alm P, Höglund P, Håkanson R. ECL cell histamine mobilization studied by gastric submucosal microdialysis in awake rats: Methodological considerations. Pharmacology and Toxicology. 2003;93(2):57-65.

[108] Fykse V, Solligård E, Bendheim MØ, Chen D, Grønbech JE, Sandvik AK, et al. ECL cell histamine mobilization and parietal cell stimulation in the rat stomach studied by microdialysis and electron microscopy. Acta Physiologica. 2006;186(1):37-43.

[109] Kitano M, Bernsand M, Kishimoto Y, Norlén P, Håkanson R, Haenuki Y, et al. Ischemia of rat stomach mobilizes ECL cell histamine. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2005;288(5 51-5):G1084-G90.

[110] Kitano M, Norlén P, Håkanson R. Gastric submucosal microdialysis: a method to study gastrin- and food-evoked mobilization of ECL-cell histamine in conscious rats. Regulatory Peptides. 2000;86(1-3):113-23.

[111] Woo KL, Lunte CE. The development of multiple probe microdialysis sampling in the stomach. Journal of Pharmaceutical and Biomedical Analysis. [doi: 10.1016/j.jpba.2008.04.019]. 2008;48(1):20-6.

[112] Woo KL, Lunte CE. The direct comparison of health and ulcerated stomach tissue: A multiple probe microdialysis sampling approach. Journal of Pharmaceutical and Biomedical Analysis. [doi: 10.1016/j.jpba.2008.05.014]. 2008;48(1):85-91.

[113] Sorensen H. Free Jejunal Flaps Can Be Monitored by Use of Microdialysis. J Reconstr Microsurg. 2008;24(6):443-8.

[114] Takahashi A, Ishimaru H, Ikarashi Y, Kishi E, Maruyama Y. Effects of hepatic nerve stimulation on blood glucose and glycogenolysis in rat liver: Studies with in vivo microdialysis. Journal of the Autonomic Nervous System. [doi: 10.1016/S0165-1838(96)00082-3]. 1996;61(2):181-5.

[115] Nowak G, Ungerstedt J, Wernerman J, Ungerstedt U, Ericzon B-G. Metabolic changes in the liver graft monitored continuously with microdialysis during liver transplantation in a pig model. Liver Transplantation. 2002;8(5):424-32.

[116] Nowak G, Ungerstedt J, Wernerman J, Ungerstedt U, Ericzon BG. Clinical experience in continuous graft monitoring with microdialysis early after liver transplantation. British Journal of Surgery. 2002;89(9):1169-75.

[117] Björnsson B, Winbladh A, Bojmar L, Trulsson LM, Olsson H, Sundqvist T, et al. Remote or Conventional Ischemic Preconditioning –Local Liver Metabolism in Rats Studied with Microdialysis. Journal of Surgical Research. [doi: 10.1016/j.jss.2011.07.038]. (0).

[118] Isaksson B, D'Souza MA, Jerseniuss U, Ungerstedt J, Lundell L, Permert J, et al. Continuous assessment of intrahepatic metabolism by microdialysis during and after portal triad clamping. Journal of Surgical Research. 2011;169(2):214-9.

[119] Wu Y-S, Tsai T-H, Wu T-F, Cheng F-C. Determination of pyruvate and lactate in primary liver cell culture medium during hypoxia by on-line microdialysis–liquid chromatography. Journal of Chromatography A. [doi: 10.1016/S0021-9673(00)01265-6]. 2001;913(1–2):341-7.

[120] Sun L, Stenken JA, Yang AY, Zhao JJ, Musson DG. An in vitro microdialysis methodology to study 11β-hydroxysteroid dehydrogenase type 1 enzyme activity in liver microsomes. Analytical Biochemistry. [doi: 10.1016/j.ab.2007.06.038]. 2007;370(1):26-37.

[121] Gunaratna C, Kissinger PT. Application of microdialysis to study the in vitro metabolism of drugs in liver microsomes. Journal of Pharmaceutical and Biomedical Analysis. [doi: 10.1016/S0731-7085(97)00042-3]. 1997;16(2):239-48.

[122] Beier H, Kaiser K, Langhans M, Malmendier K, Sluijsmans I, Weiher J. Peritoneal microdialysis in freely moving rodents: An alternative to blood sampling for pharmacokinetic studies in the rat and the mouse. European Journal of Pharmaceutical Sciences. [doi: 10.1016/j.ejps.2006.10.005]. 2007;30(1):75-83.

[123] Saito K, Kanazawa M, Fukudo S. Colorectal distention induces hippocampal noradrenaline release in rats: an in vivo microdialysis study. Brain Research. [doi: 10.1016/S0006-8993(02)03007-X]. 2002;947(1):146-9.

[124] Zhou Q, Gallo JM. In vivo microdialysis for PK and PD studies of anticancer drugs. AAPS Journal. 2005;7(3):E659-E67.

[125] Solligård E, Juel IS, Bakkelund K, Johnsen H, Saether OD, Gronbech JE, et al. Gut barrier dysfunction as detected by intestinal luminal microdialysis. Intensive Care Med. 2004 Jun;30(6):1188-94.

[126] Sommer T, Larsen JF. Intraperitoneal and intraluminal microdialysis in the detection of experimental regional intestinal ischaemia. Br J Surg. 2004 Jul;91(7):855-61.

[127] Jansson K, Ungerstedt J, Jonsson T, Redler B, Andersson M, Ungerstedt U, et al. Human intraperitoneal microdialysis: increased lactate/pyruvate ratio suggests early visceral ischaemia. A pilot study. Scand J Gastroenter. 2003 Sep;38(9):1007-11.

[128] Klaus S, Heringlake M, Gliemroth J, Bruch H-P, Bahlmann L. Intraperitoneal microdialysis for detection of splanchnic metabolic disorders. Langenbeck's Archives of Surgery. 2002;387(7):276-80.

[129] Ungerstedt J, Nowak G, Ericzon BG, Ungerstedt U. Intraperitoneal microdialysis (IPM): a new technique for monitoring intestinal ischemia studied in a porcine model. Shock. 2003 Jul;20(1):91-6.

[130] Sommer T, Larsen JF. Detection of intestinal ischemia using a microdialysis technique in an animal model. World J Surg. 2003 Apr;27(4):416-20.

[131] Kitano M, Sakamoto H, Das K, Komaki T, Kudo M. EUS-guided in vivo microdialysis of the pancreas: a novel technique with potential diagnostic and therapeutic application. Gastrointestinal Endoscopy. [doi: 10.1016/j.gie.2009.05.040]. 2010;71(1):176-9.

[132] Tenhunen JJ, Kosunen H, Alhava E, Tuomisto L, Takala JA. Intestinal Luminal Microdialysis: A New Approach to Assess Gut Mucosal Ischemia. Anaesthesiology. 1999;91(6):1807-15.

[133] Tenhunen JJ, Jakob SM, Takala JA. Gut luminal lactate release during gradual intestinal ischemia. Intensive Care Med. 2001;27(12):1916-22.

[134] Högberg N, Carlsson PO, Hillered L, Meurling S, Stenbäck A. Intestinal ischemia measured by intraluminal microdialysis. Scandinavian Journal of Clinical and Laboratory Investigation. 2012;72(1):59-66.

[135] Solligård E, Juel IS, Spigset O, Romundstad P, Grønbech JE, Aadahl P. Gut luminal lactate measured by microdialysis mirrors permeability of the intestinal mucosa after ischemia. Shock. 2008;29(2):245-51.

[136] Solligård E, Wahba A, Skogvoll E, Stenseth R, Grønbech JE, Aadahl P. Rectal lactate levels in endoluminal microdialysate during routine coronary surgery. Anaesthesia. 2007;62(3):250-8.

[137] Douglas A, Udy AA, Wallis SC, Jarrett P, Stuart J, Lassig-Smith M, et al. Plasma and tissue pharmacokinetics of cefazolin in patients undergoing elective and semielective abdominal aortic aneurysm open repair surgery. Antimicrobial Agents and Chemotherapy. 2011;55(11):5238-42.

[138] Pedersen ME, Dahl M, Qvist N. Intraperitoneal microdialysis in the postoperative surveillance after surgery for necrotizing enterocolitis: A preliminary report. Journal of Pediatric Surgery. 2011;46(2):352-6.

[139] Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning Stoma Reduces Symptomatic Anastomotic Leakage After Low Anterior Resection of the Rectum for Cancer: A Randomized Multicenter Trial. Ann Surg. 2007 Numb 2;246:207-14.

[140] Matthiessen P, Strand I, Jansson K, TÃ¶rnquist C, Andersson M, RutegÃ¥rd Jr, et al. Is Early Detection of Anastomotic Leakage Possible by Intraperitoneal Microdialysis and Intraperitoneal Cytokines After Anterior Resection of the Rectum for Cancer? Dis Colon Rectum. 2007;50(11):1918-27.

[141] CMA-Microdialysis. [Feb 2012]; Available from: www.microdialysis.se/.

[142] Seo JH, Leow PL, Cho SH, Lim HW, Kim JY, Patel BA, et al. Development of inlaid electrodes for whole column electrochemical detection in HPLC. Lab on a Chip - Miniaturisation for Chemistry and Biology. 2009;9(15):2238-44.

[143] Wang M, Roman GT, Perry ML, Kennedy RT. Microfluidic chip for high efficiency electrophoretic analysis of segmented flow from a microdialysis probe and in vivo chemical monitoring. Analytical Chemistry. 2009;81(21):9072-8.

[144] Wang M, Slaney T, Mabrouk O, Kennedy RT. Collection of nanoliter microdialysate fractions in plugs for off-line in vivo chemical monitoring with up to 2s temporal resolution. Journal of Neuroscience Methods. 2010;190(1):39-48.

[145] Chaurasia C, Müller M, Bashaw E, Benfeldt E, Bolinder J, Bullock R, et al. AAPS-FDA workshop white paper: Microdialysis principles, application, and regulatory perspectives report from the Joint AAPS-FDA Workshop, November 4–5, 2005, Nashville, TN. The AAPS Journal. 2007;9(1):E48-E59.

[146] Müller M. Microdialysis. British Medical Journal. 2002; 324:588–91.

[147] Baldini F. Microdialysis-based sensing in clinical applications. Analytical and Bioanalytical Chemistry. 2010;397(3):909-16.

[148] Blazkiewicz P, Blazkiewicz K, Verhaege A, Anissimov YG, Roberts MS, Zvyagin AV. Dialysis-assited fiber optic spectroscopy for in situ biomedical sensing. Journal of Biomedical Optics. 2006;11(1).

[149] Pasic A, Koehler H, Klimant I, Schaupp L. Miniaturized fiber-optic hybrid sensor for continuous glucose monitoring in subcutaneous tissue. Sensors and Actuators, B: Chemical. 2007;122(1):60-8.

[150] Zahn JD, Trebotich D, Liepmann D. Microdialysis microneedles for continuous medical monitoring. Biomedical Microdevices. 2005;7(1):59-69.

[151] Böhm S, Olthuis W, Bergveld P. Micromachined double lumen microdialysis probe connector with incorporated sensor for on-line sampling. Sensors and Actuators, B: Chemical. 2000;63(3):201-8.

[152] Pasic A, Koehler H, Schaupp L, Pieber TR, Klimant I. Fiber-optic flow-through sensor for online monitoring of glucose. Analytical and Bioanalytical Chemistry. 2006;386(5):1293-302.

[153] Ricci F, Caprio F, Poscia A, Valgimigli F, Messeri D, Lepori E, et al. Toward continuous glucose monitoring with planar modified biosensors and microdialysis: Study of temperature, oxygen dependence and in vivo experiment. Biosensors and Bioelectronics. 2007;22(9–10):2032-9.

[154] Gramsbergen JB, Cumming P. Serotonin mediates rapid changes of striatal glucose and lactate metabolism after systemic 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") administration in awake rats. Neurochemistry International. 2007;51(1):8-15.

[155] Yao T, Okano G. Simultaneous determination of L-glutamate, acetylcholine and dopamine in rat brain by a flow-injection biosensor system with microdialysis sampling. Analytical Sciences. 2008;24(11):1469-73.

[156] Rhemrev-Boom RM, Tiessen RG, Jonker AA, Venema K, Vadgama P, Korf J. A lightweight measuring device for the continuous in vivo monitoring of glucose by means of ultraslow microdialysis in combination with a miniaturised flow-through biosensor. Clinica Chimica Acta. [doi: 10.1016/S0009-8981(01)00574-5]. 2002;316(1–2):1-10.

[157] Córcoles EP, Deeba S, Hanna GB, Paraskeva P, Boutelle MG, Darzi A. Use of online rapid sampling microdialysis electrochemical biosensor for bowel anastomosis monitoring in swine model. Analytical Methods. 2011;3(9):2010-6.

[158] Deeba S, Corcoles EP, Hanna BG, Pareskevas P, Aziz O, Boutelle MG, et al. Use of rapid sampling microdialysis for intraoperative monitoring of bowel ischemia. Diseases of the Colon and Rectum. 2008;51(9):1408-13.

[159] Córcoles EP, Deeba S, Hanna GB, Paraskeva P, Boutelle MG, Darzi A, editors. Bowel ischemia monitoring using rapid sampling microdialysis biosensor system2011.

[160] Corcoles EP, Deeba S, Damji S, Hanna GB, Boutelle MG, Cheshire N, et al. Rapid sampling microdialysis monitorign of post aortic repair intestinal ischemia. J Gastroenterol Hepatol. [Meeting Abstract]. 2011 Oct;26:192-3.

[161] Chen Cf, Drew KL. Droplet-based microdialysis-Concept, theory, and design considerations. Journal of Chromatography A. 2008;1209(1-2):29-36.

[162] Tseng YT, Yang CS, Tseng FG. A perfusion-based micro opto-fluidic system (PMOFS) for continuously in-situ immune sensing. Lab on a Chip - Miniaturisation for Chemistry and Biology. 2009;9(18):2673-82.

[163] Malecha K, Pijanowska DG, Golonka LJ, Kurek P. Low temperature co-fired ceramic (LTCC)-based biosensor for continuous glucose monitoring. Sensors and Actuators, B: Chemical. 2011;155(2):923-9.

[164] Rogers M, Leong C, Niu X, De Mello A, Parker KH, Boutelle MG. Optimisation of a microfluidic analysis chamber for the placement of microelectrodes. Physical Chemistry Chemical Physics. 2011;13(12):5298-303.

[165] Nordström CH. Lessons we have learnt from microdialysis in animals and humans Anaesthesia, Pain, Intensive Care and Emergency Medicine — A.P.I.C.E. 2005:125-38.

[166] Nordström CH, Ungerstedt U. Microdialysis: principles and techniques Anaesthesia, Pain, Intensive Care and Emergency A.P.I.C.E. 2006:61-77.

[167] Ungerstedt U. Continuous Monitoring of Organ Chemistry — a Paradigm Shift in Management of Intensive Care Anaesthesia, Pain, Intensive Care and Emergency A.P.I.C.E. 2008:29-44.

[168] Microbiotech. [Feb 2012]; Available from: www.microbiotech.se/.

[169] Brainlink. [cited Feb 2012]; Available from: www.brainlink.nl

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