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Microdialysis in Abdominal Organ Transplantation and the Potential for Integration with Dynamic Preservation Platforms and Post-Transplant Monitoring

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Keywords
Organ preservation · Viability assessment · Marginal grafts · Microdialysis · Machine perfusion · Transplantation

Abstract
Background: The perpetual organ shortage crisis worldwide has meant a paradigm shift in global thinking with subsequent expansion of the accepted criteria for an organ donor to meet the demand. Robust pre-transplant organ viability assessment is the next great challenge in the field of transplantation today. ***Summary:*** Organ preservation in the nature of static cold storage has reached its limits, and machine perfusion both cold and warm offers theoretically superior preservation and the potential to assess organs. Microdialysis is a novel technique with proven ability to allow remote assessment of tissue biochemistry and metabolism. It has been used in various pre-clinical and clinical models of abdominal organ preservation and transplantation. ***Key Message:*** This review focuses on the use of microdialysis in the assessment of the kidney, liver, and pancreas and where this novel technology is heading in the context of the assessing organ viability prior to and after transplantation.

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Introduction

The perpetual organ shortage crisis worldwide has meant a paradigm shift in global thinking with subsequent expansion of the accepted criteria for an organ donor to meet the demand. The increase in utilization of organs from older donors with more comorbidities in efforts to balance the growth of transplant waiting lists has increased the focus on organ selection and the need for robust pre-transplant organ viability assessment and is the next great challenge in the field of transplantation today.

Kidneys donated after circulatory death (DCD) or from "marginal" expanded criteria donors are more susceptible to ischaemia-reperfusion injury (IRI), with a subsequent higher risk of both delayed and non-functioning grafts and ultimately graft failure [1–3]. Delayed graft function after kidney transplantation is associated with poorer outcomes with an increased risk of acute rejection, longer stay in hospital, higher healthcare economic costs, and lower overall graft survival [4, 5]. Livers from higher risk donors, and in particular after DCD, suffer higher incidences of both primary non-function and intrahepatic cholangiopathy, and graft failure rates are significantly higher compared to livers from donors after brainstem death (DBD) [6].

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These susceptibilities have meant that many kidneys and livers retrieved and offered for transplantation are ultimately declined due to concerns about organ viability, their risk posed to both short- and long-term function [7–9], and impact on patient morbidity and mortality [1, 10].

Latest "non-utilization rate" figures for the UK show 15% of DBD kidneys, 22% of DBD livers, and 86% of DBD pancreases retrieved from all deceased donors are subsequently declined for transplantation. This is higher for DCD organs at 19%, 62%, and 86% for kidneys, livers, and pancreases, respectively [11], and these rates have been generally increasing over time for each organ over the past decade. In the USA, 20% of kidneys and almost 10% of livers that are retrieved are not used [12]. Recent data from the Eurotransplant region show similar figures for kidneys with a considerably higher "non-utilization rate" for livers donated after DCD compared to those from DBD donors [13]. A significant factor in the decline of higher risk organs is the simple fact that organ quality and viability both remain difficult to assess and thus predict clinical outcomes (1).

It is however these discarded organs in particular that would benefit from accurate and reliable pre-transplant viability and quality assessment because it is likely a significant number of these declined organs would be of sufficient viability to provide a risk-to-benefit ratio in favour of transplantation for a proportion of waitlisted individuals [14, 15], where mortality is potentially highest.

Traditional organ preservation via static cold storage (SCS) is felt to have met its full potential in regards to effectiveness of preservation, is insufficient in the current climate of increasing use of expanded criteria donor and DCD donor organs, and has limited options for organ viability assessment.

The pathophysiology of IRI is complicated. Ischaemia causes dysfunction in the cellular machinery related to mitochondrial energy generation with organ parenchymal and endothelial injury; this is exacerbated during reperfusion and oxygen delivery with the resultant milieu encompassing elements of inflammatory and coagulatory processes and cell death [16]. Dynamic machine perfusion (MP) of organs has emerged as a viable and superior alternative to SCS preservation in the kidney and liver. MP offers the potential for assessment of organ viability [17] and organ repair [18].

MP has developed into several entities based on the targeted temperature of preservation. Hypothermic machine perfusion (HMP) at temperatures of 4°C of kidneys has been shown to successfully reduce the risk of delayed graft function compared to SCS [19] and in livers [20] to improve post-transplant outcomes and reduced cholangiopathy rates.

In parallel, normothermic machine perfusion (NMP) at 32–37°C seeks to replicate a near-physiological environment, allowing full cellular metabolism in the organ. In kidney preservation, this has proved viable, safe, and allows such better graft evaluation that kidneys which were initially declined for transplantation were determined to be sufficiently viable and allowed subsequent transplantation with acceptable outcomes [21, 22]. NMP in the liver has demonstrated reduced post-transplant graft injury and increased organ utilization versus livers preserved via SCS [23]. Further differences between described protocols also involve the degree of provision of oxygen, the perfusate employed – whether it is blood-based or acellular.

Critically MP offers the opportunity for assessment of organ viability. Multiple avenues of assessment have been described including [24]: analysis of perfusate biomarkers, histological assessment of tissue, perfusion dynamics, and organ function (e.g., urine production in kidney preservation and bile production in livers during NMP).

A more detailed overview of the assessment methods in kidney, liver, and pancreas preservation described in both research and clinical settings is described in Tables 1 and 2. In general, assessment strategies have focussed on organ function, vascular integrity, tissue metabolism, and tissue damage. No one marker has so proven effective in determination of organ viability, and it is likely a constellation of metrics will be required [25].

Microdialysis (MD) is well-established minimally invasive technique that allows the sampling of the interstitial composition of a target organ, enabling monitoring of tissue biochemistry and metabolism [26]. Its use has been validated in both research and clinical scenarios [27] including monitoring in ITU for cerebral ischaemia [28], bowel ischaemia [29], free flap surgery [30], and also transplant surgery [27, 31, 32]. The review will focus on the developments and use of MD in the field of transplantation, focussing on the assessment of organs prior to transplantation, monitoring organs after transplantation, what we have learnt and where the technology is heading.

MD Technology in Clinical Practice

MD was first described in the 1970s and entered clinical use in the 1990s. It is now one of the established modalities to monitor cerebral metabolism in traumatic brain injury in intensive care settings.

MD is achieved by implanting typically a small 600-μm diameter probe with a semipermeable membrane tip into a target tissue – analogous to a blood capillary. The inner aspect of the membrane is perfused at a low flow rate with

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Table 1. Overview of viability parameters used during kidney preservation

Kidney	
Organ function	Primarily during NMP: urine production*, in experimental settings, creatinine clearance, fractional excretion of sodium – are all affected by perfusion parameters and to date, there is no correlation with clinical outcomes
Vascular integrity	HMP – perfusion dynamics and vascular resistance – some association with DGF, however, but not universally applicable due to differences in measurement, and influence of perfusion machines, perfusate NMP – perfusion dynamics, in particular "flow" rate* (can be affected by temperature, viscosity of the perfusate, and target perfusion pressures)
Tissue metabolism	Clinical settings: oxygen consumption during NMP as surrogate for tissue metabolism – however, this may be influenced by degree of oxygen provision Experimental/pre-clinical: Non-Invasive: MRI imaging for graft ATP content, perfusate mRNA profiling for IRI-related gene expression, oxygen consumption, circulating lactate/glucose/glycolytic intermediary levels Invasive: histological assessment of total ATP/ADP ratios, NO, free radical levels. All non-real-time techniques that diminish use for timely determination of organ viability
Tissue damage	Non-invasive: perfusate analysis for biomarkers of specific and non-specific cell injury, e.g., GST, lactate, LDH, AST, KIM-1, FABP, NGAL, FMN. Some isolated reports of correlation with outcome, however, no validation from large clinical cohorts Invasive: histological assessment – e.g., Remuzzi/Karpinski score

*Metrics used in a clinical scoring system in one of the first clinical reports of kidney NMP – including flow rates, urine production, and macroscopic appearance. DGF, delayed graft function.

Table 2. Overview of viability parameters used during liver and pancreas preservation

Liver	
Organ function	During NMP: bile production and composition (alkaline with low glucose levels) are associated with healthy cholangiocytes – specific metrics have yet to be determined in large cohorts
Vascular integrity	Dual arterial and portal perfusion during HMP and NMP demonstrate rapid stability but have not been associated with post-transplant outcomes and are largely dependent of perfusion protocols
Tissue metabolism	During HMP: perfusate ALT, AST, LDH, glucose, and pH have all been shown to have correlation to hepatocyte health and graft outcomes in small studies, with high ALT correlating to poor graft survival. Larger cohorts are needed to establish cut-off levels During NMP: perfusate transaminases, lactate clearance, pH, and glucose trends have been shown to be correlated liver viability and post-op outcomes and are used in clinical NMP protocols. Experimental data suggests ischaemically injured livers have limited capacity to generate coagulation factors during NMP and is being evaluated as another potential marker
Tissue damage	During HMP: perfusate FMN (mitochondrial injury marker) has been shown in small trials to correlate with 3 m graft survival. Larger randomised cohorts investigating liver HMP are needed to determine predictive use of this marker Histological assessment, including steatosis
Pancreas	HMP and NMP of the pancreas have been described in experimental pre-clinical reports. Multiple viability parameters have been suggested
Organ function	Endocrine: insulin release 2nd to a glucose/arginine bolus via histological IHC or perfusate analysis Exocrine: duodenal effluent analysis for amylase/lipase
Vascular integrity	Perfusion dynamics (largely dependent on perfusion protocols, perfusate, temperature)
Tissue metabolism	Invasive: tissue ATP levels, tissue oxygen tension using probe Non-invasive: whole-organ oxygen consumption, perfusate analysis for lactate (energy metabolites)
Tissue damage	Invasive: histological assessment, total cell-free DNA, caspase activation Non-invasive: perfusate LDH

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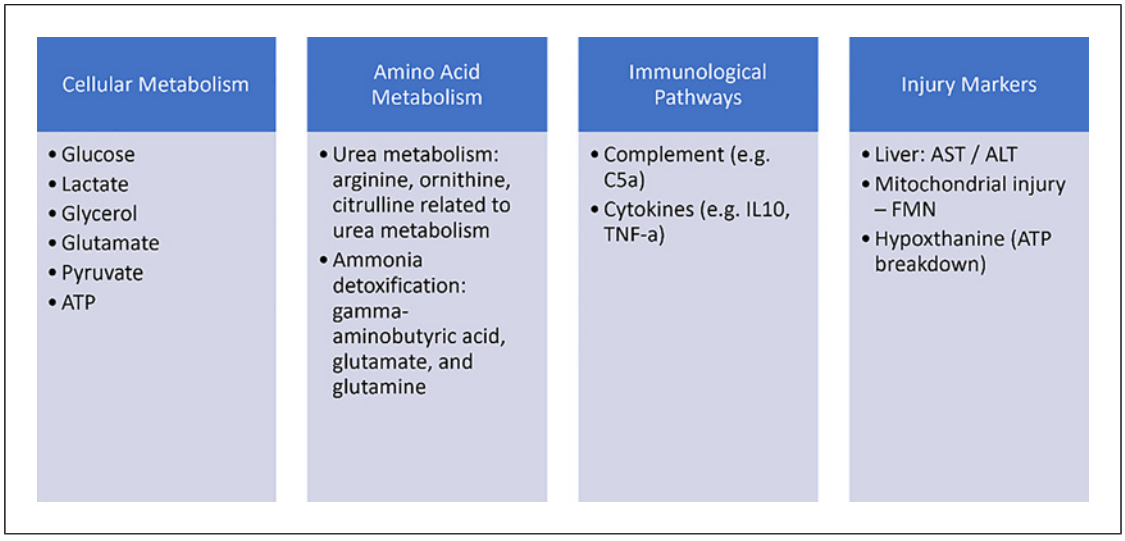


Fig. 1. Overview of MD metabolites used to assess organs during preservation/transplantation.

an isotonic fluid to allow diffusion of analytes from the tissue into the probe to create a dialysate stream that reflects the concentration of analytes in the tissue.

To date, most MD studies use discrete measurements where a vial of dialysate is collected at regular time intervals. The vial represents an average of the analyte concentration in the dialysate, and hence tissue, over the collection period. MD analytes are varied and can include metabolic parameters such as glucose, lactate, pyruvate, glutamate, and glycerol, as well as cytokines and other molecules used as biomarkers. MD allows for assessment of both metabolism and through larger molecules immunological processes in a target tissue (Fig. 1). MD in the field of organ transplantation has focused on assessment of tissue prior to retrieval, during preservation, and after transplantation. The technology used in the majority of reports is commercially available and similar in nature to that use in well-established neuro-intensive care settings. Current commercially available systems have limitations – primarily lacking the time resolution necessary to detect dynamic processes, and a large resource footprint – rendering MD suitable for in laboratory or intensive care settings only.

MD in the Kidney

Kidney Preservation

MD has been used to assess tissue viability in kidney grafts during both SCS and MP organ preservation (Fig. 2). HMP allows the provision of oxygen, nutrients, base metabolites for energy generation, and removal of waste products, the perfusate acting as a sink. At 4°C, cellular metabolism is sufficiently suppressed but not halted completely. Measurements of a variety of analytes have been described including glucose, lactate, glycerol, glutamate, pyruvate, and ATP to assess metabolic activity during HMP. Lactate and glucose metabolism in the kidney is complex, however – differing in nature between the renal cortex and medulla [33, 34].

Pre-Clinical Studies

Keller et al. [35] in a porcine kidney model demonstrated that during 24 h of SCS at 4°C there is an ongoing low level of glycolysis, with progressive increase in lactate, glutamate, and glycerol, compared to 24 h of normothermic ischaemia where analytes increased quickly within 60 min to high levels, with a rapid glucose decline, reflective of the severe effects of warm ischaemia. In an early porcine model of 24 h of HMP, Baicu et al. [36] demonstrated that during perfusion, there is augmented glycolysis, with a progressive increase in tissue pyruvate levels as detected by MD with this increase not reflected in the circulating perfusate – demonstrating the potential value of tissue rather than solely perfusate monitoring of metabolite during HMP.

Using a novel rapid sampling microdialysis (rsMD) system that allowed the collection and measurement of MD analytes every 30 s, we previously demonstrated that real-time assessment of cellular metabolism is feasible during SCS and HMP of porcine and human kidneys [37]. In a series of 22 porcine kidneys, lactate and glucose profiles were monitored in the cortex and medulla during

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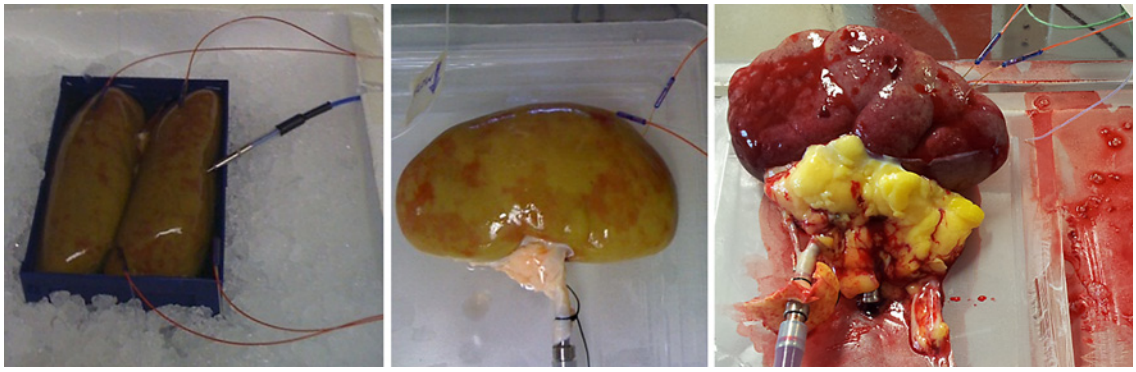


Fig. 2. Photographs of kidneys undergoing MD assessment during SCS, HMP, and NMP in the laboratory (left to right).

24 h of SCS or 10 h of HMP [34]. During SCS, there is a persistent low level metabolic activity reflected by low but static levels of tissue lactate; this is in contrast to HMP where lactate levels increase progressively during perfusion suggesting ongoing and increasing glycolytic activity. At warming, it was noted that SCS kidneys exhibited a rapid peak in cortical lactate followed by a nadir (similar to that seen and described by Keller et al.), while HMP kidneys only demonstrate a slow progressive increase – suggesting HMP kidneys may be more resilient to a secondary warm ischaemic hit (such as during implantation and anastomosis).

The same rsMD system was successfully used in successive experiments involving both porcine and declined human kidneys [38–40]. The pre-treatment of porcine and kidneys during HMP with a novel endothelial localising hirudin-based anti-coagulant demonstrated improved perfusion characteristics during subsequent normothermic haemoreperfusion assessment, with less biochemical markers of coagulation, and this correlated with lower detected rsMD levels of cortical lactate versus untreated kidneys – suggesting rsMD was able to demonstrate metabolically less ischaemic injury [38]. A further study looking into the potential for a period of HMP to improve viability in porcine kidneys exposed to lengthy cold ischaemia time (CIT; 72 h) demonstrated that during acellular normothermic reperfusion, rsMD was able to characterise lactate profiles and differentiate trends between kidneys exposed to short versus long initial CIT [40].

Kidney Transplantation

Early identification of vascular and immunological complications post-operatively before established injury has occurred to the graft would allow intervention and potentially prevent graft losses.

Pre-Clinical Studies

Fonouni et al. and the group in Heidelberg, Germany, used MD to observe the metabolic changes in sequential phases of porcine kidney retrieval, SCS CIT of 6 h, and subsequent transplantation into recipient pigs [41]. Similar to the described studies during SCS organ preservation alone, low levels of persistent lactate during the CIT period reflect the low but none the less present ongoing cellular anaerobic metabolism and glycolysis, with a gradual decline in glucose towards the end of SCS. During reperfusion, levels of lactate, glycerol, glutamate, and pyruvate all peaked soon after anastomosis and then decreased towards a steady state by 2 h – reflecting the rapid surge in metabolism and provision of oxygen and normothermia at reperfusion and initial increases in both anaerobic and aerobic metabolic pathways.

Using the same animal model, kidneys were exposed to a different duration of SCS (CIT 6 h vs. 24 h) prior to transplantation [42]. During SCS, glycolytic activity consuming glucose and producing lactate is more pronounced the longer ischaemia is maintained. During warm ischaemia attributed to anastomosis time – kidneys with longer CIT demonstrated a surge and early peak in lactate before falling to a nadir, while a short CIT entailed a slow rise in lactate; similar to our findings during ex vivo SCS versus HMP preservation [34]. During reperfusion, a steady state regardless of duration of CIT was achieved within 2 h.

In a similar porcine transplantation model, where heparin and immunosuppression medication were omitted to instigate microvascular thrombosis [43], MD was used to assess kidneys after reperfusion. Histologically severe venous congestion and macroscopically blue kidneys demonstrated via MD a paucity of cortical glucose compared to controls and significantly higher

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levels of cortical glycerol at 3 h post-reperfusion once the initial surge in metabolism had settled and metabolism stabilised, suggesting glycerol as a potential marker of vascular small vessel thrombosis.

Using the same model, acute rejection was instigated by omitting immunosuppression only versus controls [44]. In the rejection, group biopsy samples taken at 3 h post-reperfusion confirmed "acute borderline rejection." Though trends in profiles for lactate during reperfusion were identified, numbers were likely too small and the degree of rejection too minor to allow sufficient differentiation between kidneys looking at metabolic activity alone, including glycerol and lactate/pyruvate ratios.

Keller et al. in Denmark measured cortical and subcapsular metabolites of porcine kidneys in vivo subjected to either arterial or venous occlusion [45]. Cortical levels of lactate, glutamate, and glycerol increased significantly in both arterial and venous occlusion within 30 min, while changes in glucose took longer. Subcapsular increases in glutamate levels distinguished between ischaemic and control kidneys, suggesting viable alternative anatomical sites for probe placement.

Finally, using the same porcine model, sequential injections of polyvinyl alcohol particles into the renal artery causing a progressive and persistent decline in renal arterial blood flow and thus ischaemia, MD was able to detect significant increases in cortical lactate and glutamate, and subcapsular glutamate, reflecting the varying degrees of ischaemia [46]. The potential for using MD for early identification of complications, especially in high-risk kidney recipients, is compelling from animal studies; however, clinical studies are awaited.

MD in the Liver

Liver Preservation

MD has been used as a tool for graft monitoring in both SCS and HMP of porcine and human livers [47–49]. Direct intrahepatic puncture and insertion of the probes is the preferred method of placement, with a low bleeding risk [31]. Analytes measured included lactate, glucose, glycerol, and pyruvate – key metabolites in cellular energy metabolism, as well as liver-specific entities: AST and ALT, and markers of mitochondrial injury: flavin mononucleotide (FMN).

Pre-Clinical Studies

Puhl et al. [47] compared different SCS flush and preservation solutions in porcine livers – including UW and HTK. MD probes in the parenchyma during SCS detected lower levels of interstitial glycerol in UW flushed livers versus HTK by 12 h, with no difference by 24 h, with similar levels of lactate throughout – suggesting less cellular injury and superior protection with UW for the first 12 h–18 h during SCS versus HTK.

Li et al. [48] designed an early in-house HMP system of dual hypothermic oxygenated perfusion model (D-HOPE – via the portal vein and hepatic artery and HA) of DCD porcine livers. They assessed interstitial metabolites every 3 h using MD compared to SCS for 18 h. Interstitial ALT was initially higher in the D-HOPE livers versus SCS, with levels in both groups declining throughout preservation and lower levels in the perfused livers by 12 h onwards; AST demonstrated a similar trend. Glucose and lactate followed suit with higher initial peaks in SCS livers, followed by a decline to nadir by 12 h, but with levels significantly lower during HOPE throughout, while increasing pyruvic acid levels were significantly lower in D-HOPE livers after 6 h. These metabolic differences correlated with better histological features of apoptosis and necrosis in D-HOPE versus SCS livers.

Clinical Studies

Finally, Patrono et al. [49] used MD in a clinical observational pilot trial of MP via D-HOPE in 10 liver grafts using the Liver Assist perfusion machine. MD assessed tissue biochemistry during back table preparation and for 2 h of HMP. HMP was used in marginal grafts including advancing donor age, high BMI donors, and steatotic graft appearance. 5 of the 10 developed significant complications. Three livers had early graft dysfunction (one required re-transplantation, 2 developed biliary strictures); 2 further grafts developed biliary strictures. MD monitoring took place for approximately 4 h. Probes were placed in segment 6 at a 4 cm depth.

Interstitial glucose and lactate both increased upon the start of D-HOPE and were significantly higher at 2 h in livers that failed. There was an association of 2 h MD interstitial glucose with early graft dysfunction (ROC 0.952) and weak positive correlations between both 2 h glucose and lactate with individualized risk estimation of 3-month graft failure (L-GrAFT), CIT, degree of graft macro-steatosis, and post-op complications. Interstitial FMN – a novel marker of mitochondrial injury – detected by MD significantly dropped after the start of D-HOPE in all livers, while in contrast, levels in the circulating perfusate increased, were higher in dysfunctional grafts, and were highest in the liver requiring re-transplantation. Despite these differences, their explanation is uncertain, as there was no correlation between MD metabolites and biliary complications, nor the histological expression of

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inflammatory cytokines or adhesion molecules suggesting a pathway as of yet not uncovered. Interestingly, there was also no correlation between the perfusate and MD interstitial tissue levels of metabolites, suggesting traditional perfusate analysis would not have detected these trends.

Liver Transplantation

MD has been used in the assessment of the hepatic interstitium in both porcine and clinical liver transplantation. It has been used to look at different nuances of pathology during liver transplantation, specifically: cellular metabolism, IRI, acute rejection, and the immune response. Measured metabolites include those related to cellular energy metabolism (glucose, lactate, glycerol, pyruvate, glutamate), liver-specific entities: AST and ALT, markers of mitochondrial injury/processes: FMN, hypoxanthine (breakdown of ATP).

Pre-Clinical Studies

Nowak et al. [50] used a DCD model of liver transplantation in 14 pigs with the intention to monitor hepatic metabolism via MD catheters placed in segment IV through the process of organ retrieval, SCS, and implantation. At retrieval and SCS flush, glucose, lactate, and glycerol interstitial levels increased, while pyruvate levels declined rapidly. During overnight SCS, glucose and glycerol continued to increase, lactate stabilised, and pyruvate levels were undetectable. After reperfusion, glucose, lactate, and glycerol continued to increase for a further 1 h, while pyruvate levels peaked at 2 h, before settling to a normal nadir. During retrieval and cold preservation, hepatocyte injury occurs with degradation of glycogen, releasing glucose. Lactate production occurs through anaerobic glycolytic pathways that predominate while there is a lack of oxygen, and glycerol reflects damage to cell membrane integrity during this ischaemia.

Another porcine DCD model of liver transplantation [51] used MD to evaluate effects of increasing durations of warm ischaemia. WIT up to 60 min was associated with significant increases in levels of interstitial hypoxanthin, reflecting lower tissue ATP measured by HPLC and correlated with hepatocyte injury via higher levels of serum AST and LDH, histological manifestations of injury, and ultimately poorer graft survival at 7 days.

Gillispie et al., using the same porcine model as Nowak et al., investigated the effect of extended short (5 h) versus long (15 h) of SCS CIT on liver glucose metabolism through retrieval and transplantation [52, 53]. Interstitial MD glycerol levels during CIT correlated with the length of CIT and increased significantly during the 1st hour of reperfusion. After portal reperfusion, there was a more delayed (40 min vs. 20 min) and larger release of cellular glucose after a long CIT, correlating to histological decreases in hepatocyte glycogen. Lactate and pyruvate profiles were similar despite the longer CIT, but lactate to pyruvate ratio showed significant changes over time after long CIT, with significantly higher ratios and with delayed peak levels after portal reperfusion, before settling by 2 h after implantation. Glycerol levels reflect cell membrane damage, and this is more pronounced after long CIT, which may also impact key glycolytic and oxidative enzymes and intermediaries and more time may be needed after reperfusion for resumption of oxidative metabolism, despite optimal provision of oxygen.

Clinical Studies

• *Assessment of Metabolism during Liver Transplantation*

In one of the earliest reports, Nowak et al. [31] used MD to continuously monitor hepatic metabolic changes in 10 patients receiving after transplantation. The point of insertion for the probes was the falciform ligament in segment 4, and a reference probe was placed in pectoral adipose tissue. Samples were collected every 1 h for 3 days and analysed for glucose, lactate, pyruvate, and glycerol.

In general, metabolites were initially high after transplantation, including the lactate:pyruvate ratio and all subsequently declined and stabilised within the 1st 24 h. Perturbations were identified in 2 patients that developed complications: in one with early rejection, there was an isolated spike in lacate:pyruvate ratio at day 3, followed by a rise in glycerol, while in a second patient who developed iliofemoral thrombosis and pericardial tamponade, glycerol and the lactate:pyruvate ratio spiked – rapidly settling after surgical thrombectomy and pericardial aspiration. In both, trends in hepatic metabolites preceded those seen in peripheral blood levels. This report demonstrated the feasibility of using MD in organ monitoring in the post-operative period and the potential to identify evolving complications earlier than with traditional investigations.

Silva et al. [54] assessed energy metabolites in 19 DBD livers after reperfusion for 48 h. There was no incidence of delayed or non-function in these grafts and high lactate, pyruvate, and glycerol levels seen in the immediate post-operative rapidly decreased and to a baseline, with a declining lactate/pyruvate ratio.

Perera et al. [55] then used MD to examine the differences in energy metabolism between DCD and DBD

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liver grafts in a series of 30 patients. Assessment ran from back table benching what amounts to the end of formal SCS to 48 h after reperfusion. MD catheters were placed near the falciform ligament towards segment 4. Samples were taken and analysed during SCS and after reperfusion.

At the end of SCS, lactate levels and the lactate:pyruvate ratio were significantly higher in DCD versus DBD livers, with similar levels of pyruvate, and in addition, there were higher but not significant levels of glycerol in DCD livers, suggesting an impact of the additional WIT during retrieval sustained by these organs.

After reperfusion, lactate levels quickly declined and normalised, with rising pyruvate levels decreasing the lactate:pyruvate ratio, and rapid clearance of interstitial glycerol and normalisation by 12 h. 2 DCD and 1 DBD livers experienced PNF. There was a higher parenchymal lactate:pyruvate ratio during SCS in these 3 grafts, but the small numbers negated statistical analysis. Histology revealed worse glycogen storage in DCD versus DBD livers during SCS, with moderate to severe depletion in the three grafts that failed and severe depletion after reperfusion. The link between the severity of deficit in metabolic energy reserves and graft failure was one of the driving forces behind the optimism for oxygenated HMP or NMP in improving and evaluating organs prior to transplantation.

The same group then used MD to assess amino acid metabolism in DBD livers through retrieval, back table bench preparation (SCS), and after reperfusion for 48 h [54, 56, 57]. MD samples were analysed for arginine, ornithine, citrulline related to urea metabolism; and gamma-aminobutyric acid, glutamate, and glutamine which are AAs related to ammonia transport, into hepatic ureagenesis pathways and detoxification. They demonstrated dynamic changes and a flux in the interstitial levels of urea cycle and ammonia transport intermediaries between the different phases of retrieval and transplantation. Metabolism was suppressed during SCS and increased rapidly during reperfusion, without any significant differences between identified between immediately functioning and delayed functioning liver grafts.

• *Assessment of IRI during Liver Transplantation*

Silva et al. [58] in another study showed that levels of key metabolites in glucose metabolism are altered in DBD livers with delayed function (AST >2,000) post-transplantation compared to those with immediate good function. MD probes inserted into segment 4 via the falciform were used to measure lactate, pyruvate, glucose, and glycerol during donor retrieval, back bench, and after reperfusion for 48 h. Interstitial lactate levels during the donor procedure and the back table were higher and took longer to normalise after reperfusion in those livers with delayed function, with higher lactate/pyruvate levels in these livers. The MD profiles correlated with histological injury. They found hepatocyte rounding in zone III, necrosis, and C4d staining during retrieval and sinusoidal endothelial injury after reperfusion, with delays in resumption of normal aerobic energy pathways – both through glycolysis and oxidative phosphorylation – likely playing a dominant role [59].

Haugaa et al. prospectively measured interstitial levels of glucose, lactate, pyruvate, and glycerol in 66 consecutive adult liver transplant [60] and then 20 paediatric liver transplants [61] after reperfusion every 1–2 h for 10 days post-op. They compared MD metabolite profiles measured in grafts that were treated for ischaemic complications to grafts with an uneventful post-operative course. MD probes were inserted into both the right and left lobes of each graft via the falciform ligament.

Higher lactate levels, the lactate/pyruvate ratio, and glycerol levels were evident in ischaemic grafts. Using ROC curves, a lactate cut-off of 3.0 nM, a lactate/pyruvate ratio of >20, and a glycerol level of 29 μm, we predicted ischaemia with AUCs of 1, 0.99 and 0.85, respectively. Using a lactate >3.0 nM and lactate/pyruvate ratio of >20, a single timepoint predicted ischaemia with 100% sensitivity and at two timepoints (1 h apart), 90% specificity for graft ischaemia. MD changes preceded systemic markers of ischaemia and predicted ischaemia prior to radiological detection.

Von Platen et al. re-evaluated the usefulness of the interstitial lactate/pyruvate ratio in the prediction and detection of ischaemic complications in a series of 45 liver transplants. MD probes were inserted after reperfusion into segment 4 via the falciform ligament, as well as in the subcutaneous tissue. Levels for glucose, lactate, and pyruvate were measured every hour for 6 days post-operatively. There was one ischaemic complication – hepatic artery thrombosis. The low incidence of ischaemia does limit interpretation of results; however, interestingly in this cohort, the lactate:pyruvate ratio did not predict ischaemia. In particular, using surrogate cut-off values suggested by Haugaa et al., 17% of patients had metrics suggested of ischaemia which were excluded on subsequent imaging, and the 1 case of thrombosis did not exhibit a sustained rise in lactate or the lactate:pyruvate ratio. The contrasting conclusions from this study demonstrate both the complexity and nuance in

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interpretation of levels and profiles of energy metabolites after liver transplantation and need for further research in identifying robust interstitial markers for complications [62].

- *Assessment and Detection of Rejection and Immune Responses during Liver Transplantation*

Traditional metabolites measured by MD are relatively small simple molecules of <20 kDA in size, in part limited by the size of the pores in the MD probes that allow diffusion from the interstitium. Using probes with larger pores, molecules up to 100 kDa may be sampled – such as cytokines, chemokines, inflammatory mediators, and cell signalling proteins. This has allowed the assessment of interstitial levels of immune mediators and actors in liver grafts – and may provide insight into rejection processes rather than biopsies in the immediate post-operative period.

Wælgaard et al. [63, 64] in several reports described the use of 100 kDa MD probes to measure the levels of inflammatory mediators in 34 liver grafts post-transplantation and their potential to discriminate between ischaemia and rejection. Probes were placed in the left and right lobes of each liver post-reperfusion and samples were taken regularly for 7 days. Interestingly in cases of ischaemia, interstitial levels of C5a increased significantly compared to livers with uncomplicated post-operative progress – with an AUC of 0.99 and high specificity of 1.0 and sensitivity of 0.8, reiterating the strong correlation between ischaemic injury and development of an inflammatory milieu in the graft. Similarly in proven cases of rejection, IP10 (an inducible pro-inflammatory protein stimulated by interferon-gamma and tumour necrosis factor alpha) was increased with an AUC of 0.81, specificity of 0.94, and sensitivity of 0.83, occurring between 2 and 5 days before detectable increases in AST and bilirubin levels. In parallel, IL-6 and IL-8 increased significantly in both ischaemia and rejection.

Amin et al. [65] used similar 100-kDa probes to monitor interstitial inflammatory cytokines in 15 livers post-operatively for 7 days. Patients transplanted for HCV-related liver failure demonstrated higher levels of interstitial cytokines than the non-HCV recipients. Censoring for HCV – 4 recipients who developed biopsy-proven rejection had low interstitial levels of IL-10 compared to the recipients who had no rejection. Suggesting a low level of inherent IL-10-related immunosuppression may have been one factor.

Most recently, Von Platen et al. [66] looked at traditional MD metabolites of energy metabolism in a series of 71 liver grafts. Of them, 33 (46%) grafts that developed proven rejection analysis of the MD profiles demonstrated the lactate/pyruvate ratio in the 1st 12 h post reperfusion, and lactate levels at 60–72 h were two independent risk factors for rejection within 30 days after transplantation. Demonstrating a possible relationship between IR injury and the development of rejection and highlighting that such patients may be readily identified via MD early in the post-operative course.

MD in the Pancreas

MP is not clinically used in pancreas preservation. There are only limited reports in the use of MD in organ assessment in the setting of pancreas transplantation specifically preservation and in the detection of vascular complications.

Assessment during Pancreas Preservation

We have previously described a hypothermic machine preservation model of the pancreas using porcine grafts. In this setting, during HMP and normothermic reperfusion, viability assessment using online rsMD was used to successfully monitor tissue lactate in real time [67]. Lactate during HMP remained low and stable suggesting cold suppression of metabolism, while during reperfusion, levels progressively increased. Lactate metabolism in the pancreas is specific and different from that encountered in the kidney or liver – with lactate believed to be a key mediator and signalling molecule for insulin release in response to glucose [68].

Assessment in the Detection of Pancreatic Thrombosis and Ischaemia

In the clinical context of pancreas transplantation, graft thrombosis is considered to be the Achille's heel and is the leading cause of early graft loss. Systemic markers of graft thrombosis are non-specific, and the diagnosis of graft thrombosis is usually too late with operative salvage unsuccessful and ultimately leading to graft loss. MD assessment of pancreatic interstitium may help identify graft thrombosis and ischaemia early and allow timely and successful intervention.

Blind et al. [69] used an in vivo porcine model of pancreatic ischaemia to investigate the ability of MD probes to detect changes in pancreatic perfusion measuring lactate, pyruvate, and glucose. MD probes were inserted into the head or tail of the porcine pancreas. Pancreatic arterial inflow was isolated to both the head and tail of the pancreas – the pancreas itself was divided along the line of the portal vein. Clamping of arterial inflow to the tail occurred for 40 min followed by 3 h of

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reperfusion. The pancreatic head served as an in animal control. MD interstitial lactate increased, while pyruvate and glucose levels decreased by 20 min after arterial clamping, continuing until the end of ischaemia. Following reperfusion, levels rapidly returned to baseline. Concurrent analysis of plasma levels of lactate, amylase, and tumour necrosis factor alpha were normal during and after induced ischaemia. MD in this setting was successfully able to identify pancreatic ischaemia in the absence of systemic markers of ischaemia or inflammation.

Rydenfelt et al. used a similar porcine model [70]. They induced sequential arterial and then venous pancreatic ischaemia for 45 min followed by 2 h of reperfusion. MD probes were both inserted within the pancreatic parenchyma, and specialist unidirectional probes were placed on the pancreatic surface. Sequential ischaemia resulted in increase in parenchymal and surface lactate, without changes in systemic plasma levels, with the AUCs 0.97 and 0.9, respectively, in detecting ischaemia. The parenchymal and surface levels were closely correlated $Q = 0.9$, suggesting penetration of the pancreatic parenchyma can be avoided due to the theoretical risk of parenchymal disruption and instigating pancreatitis.

Finally Kjøsen et al. [71] monitored 34 consecutive pancreas transplants post-op with MD probes placed within and on the anterior and posterior pancreatic surfaces. Glucose, lactate, pyruvate, and glycerol were measured regularly for approximately 7 days post-op. Post-op graft-related complications occurred in 19 grafts, the remaining 15 grafts served as controls. Nine grafts developed venous thrombosis with significant increases detected in parenchymal lactate and the lactate/pyruvate ratio, without any rise in systemic plasma levels or clinical symptoms. Of these nine grafts, angiographic salvage was successful in 4, 1 graft did not warrant intervention, and the remaining 4 grafts were lost. In 4 patients with enteric anastomotic leakages, higher levels of interstitial glycerol were observed, and in 6 patients with bleeding and graft haematomas, lactate and lactate/pyruvate rations were elevated, compared to controls. Despite that MD allowed earlier diagnosis of thrombotic complications, MD profiles themselves did not allow graft salvage in almost half of the grafts with venous thrombosis. Nor help discriminate between the various types of complications. In the post-operative setting, the use of MD may lie in close local interrogation of the organ in question, rather than relying on systemic markers, and potentially late markers to suggest a perfusion-related complication. Which markers to detect and at what timepoint still remain to be elucidated.

Developments in MD Technology

A key limitation to conventional MD is the offline aspect of measurements, of targets that are innately dynamic – cellular metabolism and biochemical pathways. At Imperial College London, the development of rsMD offers both direct interrogation of a target tissue at a cellular level and coupled with high-resolution analytical techniques provides real-time monitoring with measurements up to every minute [37, 72]. Work is continuing to address the challenge of making MD more mobile, timely, and clinically applicable in transplantation.

Similar to conventional MD, the equipment for rapid sampling measurements required a large clinical trolley and hence were limited to a laboratory setting. As a result, it was not possible to use this system to track the organ health from donation all the way through to transplantation. The possibility to track the health of the organ in real time and to investigate how it responds to preservation methods and interventions could revolutionise organ transplantation; continuous organ assessment would allow a more measurement-based acceptance criteria and hence reduce organ discard. In addition, it would allow the possibility to improve the organ health during preservation and to assess this in real time. With developments in measurement technology, organs could continue to be monitored after transplantation in order to monitor organ perfusion [30] and to assess functionality.

A key step towards this goal was to miniaturise the analysis technology and instrumentation to create a portable system [72]. The portable analysis system consists of enzyme-based microelectrode biosensors for glucose and lactate housed in a 3D printed microfluidic chip (Lab chip paper), designed to couple directly with the MD probe for high temporal resolution continuous analysis. The biosensors connect to wireless custom-made electronics, which transmit the biosensor measurements in real time over Bluetooth to an app running on a tablet for real-time visualisation of the organ health. We successfully demonstrated the potential of this miniaturised analysis system for continuous monitoring of porcine kidneys from organ retrieval, during transport back to the laboratory and during preservation methods.

Until recently, studies have used implantable MD probes; however, with the rapid development of microfabrication and processing technologies, it is possible to imagine 2D probes that could sample from the organ surface non-invasively. Singh et al. [73] developed a conformal microfluidic sampling device, which was 3D printed to interface with the surface of a kidney. Microfabrication techniques, such as thin film approaches, femtosecond laser micromachining, and laser

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cutting, can be combined with modelling (manuscript currently submitted to ACS Chemical Neuroscience) to produce sterile and specialised MD probes for specific clinical applications. For example, a sampling probe that allows for measurement of functional markers in the vein and artery could allow quantification of kidney function over time. In addition to this, we are currently looking at ways to probe tissue metabolism from the tissue surface.

The Role of MD in the Spectrum of Organ Evaluation

Both HMP and NMP through the provision of oxygen are thought to improve the functional capacity of the metabolic energy architecture and potentially mitigate against IR injury. We see MD as a technique that could provide accurate and real-time (using a system such as rsMD) information on cellular metabolism, and hence the effectiveness of dynamic preservation. Combined with allied aspects of viability – endothelial integrity, tissue damage, and organ function, it would allow a metric on total graft viability to be calculated that would ultimately rule on the risk of primary non-function and delayed graft function. This would help aid decision to transplant, recipient choice, and guide peri-operative care. However, the use of MD as a method of graft evaluation requires further iteration and refinement through preclinical and clinical studies. These would allow us to select the most discriminating markers, the most predictive cut-off values, and accurately profile their chronology during preservation (via SCS, HMP, and NMP), correlated to graft outcomes.

Extended into the post-operative setting – it could also allow continued monitoring of a graft, its metabolism during the reperfusion phase of IR injury, as well as immune responses in the first few days after transplantation. Proponents of MD will argue that such monitoring is minimally invasive and allows interrogation of the tissue in question, potentially alerting clinicians to changes and disturbances locally indicative of a developing complication within the graft before these manifest by systemically. Others will be cautioned by concerns of iatrogenic complications (bleeding/injury) and look to advocates of the "liquid biopsy" and support identification of (for example, circulating DNA) specific markers of graft injury in the systemic circulation that reflect processes occurring in the graft. As with any test, the preference towards using each modality will depend on the predictive value of the markers in question and the risk appetite of the attending clinicians.

Conclusion

Accurate assessment of organ viability prior to transplantation combined with novel platforms of organ preservation in the form of cold or warm MP has the potential to expand the donor pool to more marginal and extended criteria organs. This notion is exemplified by the national project in the UK to establish Assessment and Recovery Centres (ARCs) and a national service for organ assessment and recovery using machine preservation. Numerous metrics have been described for organ assessment including perfusion dynamics (flow rates, pressures), functional markers (urine output and creatinine clearance in kidneys, bile production in livers, insulin release in the pancreas), organ-specific biomarkers (e.g., KIM-1 in kidneys, ALT in livers), and analysis of cellular metabolism (histologically, functional imaging/MRI, and perfusate interrogation). No one marker has emerged to be truly indicative of organ viability, and it is likely a constellation of different metrics will be used to assess and determine organ quality. Combining MP platforms with real-time analysis of organ bioenergetics and metabolism via MD has the potential to improve the determination of organ viability, and with the introduction of therapeutics targeting IR injury and cellular damage, potentially demonstrate tissue repair and recovery prior to considering an organ for transplantation. While the use of MD in the post-operative period after transplantation has the potential to identify complications before they manifest via traditional metrics. The next phase of MD integration in both settings would seek to define and unify viability profiles and incorporate newer iterations of MD technology, allowing more timely, accurate, and portable generation of data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Karim Hamaoui and Vassilios Papalois developed the concept for the review. Karim Hamaoui, Sally Gowers, Martyn Boutelle, and Vassilios Papalois drafted the manuscript and critically reviewed it for publication.

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