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Original research

Is microdialysis useful for early detection of acute rejection after kidney transplantation?

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HIGHLIGHTS

- Kidney transplantation (KTx) is a curative treatment for patients with end-stage renal diseases.
- Acute rejection is still one of the challenging complications of KTx.
- The gold standard for diagnosis of acute rejection is renal biopsy which is invasive and time-consuming.
- Microdialysis (MD) has the capability in monitoring the graft function during the stages of KTx.
- MD may help to identify the need to immunosuppression adjustment in the early KTx phase.

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ABSTRACT

Introduction: Acute rejection following kidney transplantation (KTx) is still one of the challenging complications leading to chronic allograft failure. The aim of this study was to investigate the role of microdialysis (MD) in the early detection of acute graft rejection factor following KTx in porcine model.
Methods: Sixteen pigs were randomized after KTx into case (n = 8, without immunosuppressant) and control groups (n = 8, with immunosuppressant). The rejection diagnosis in our groups was confirmed by histopathological evidences as "acute borderline rejection". Using MD, we monitored the interstitial concentrations of glucose, lactate, pyruvate, glutamate and glycerol in the transplanted grafts after reperfusion.
Results: In the early post-reperfusion phase the lactate level in our case group was significantly higher comparing to the control group and remained in higher levels until the end of monitoring. The lactate to pyruvate ratio showed a considerable increase in the case group during the post-reperfusion phase. The other metabolites (glucose, glycerol, glutamate) were nearly at the same levels at the end of our monitoring in both study groups.
Conclusion: The increase in lactate and lactate to pyruvate ratios seems to be an indicator for early detection of acute rejection after KTx. Therefore, MD as a minimally invasive measurement tool may help to identify the need to immunosuppression adjustment in the early KTx phase before the clinical manifestation of the rejection.
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1. Introduction

Kidney transplantation (KTx) has nowadays been considered as a curative treatment for patients with end-stage renal diseases. Despite the improvements in histocompatibility testing methods including cross-match as well as progression in

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immunosuppressive agents and induction therapy, acute rejection is still one of the challenging complications of KTx [1]. The incidence of acute rejection of kidney allograft is approximately 10% [2] which has consistently been reported as the most important risk factor leading to chronic allograft failure [3,4]. Therefore, early detection and immediate treatment can prevent irreversible graft damage and deterioration of long-term graft survival [5,6]. An important, routine and diagnostic sign of acute rejection is the increase in serum creatinine over baseline in an asymptomatic patient but it is a delayed rejection marker [7]. The gold standard for the diagnosis of acute rejection is renal biopsy. This method is an invasive and time-consuming diagnostic method which may delay the initiation of the treatment. Thus, developing of a minimally invasive on-line and on-time method for early detection of rejection seems mandatory for decreasing the risk of graft loss as well as for improving the long term results.

Microdialysis (MD) is a technique based on the passive diffusion of substances according to their concentration gradients from the extracellular fluid to the dialysate, by which the biochemical composition of the interstitial fluid in all parenchymatous organs (central nervous system, livers, kidney, etc.) can be detected [8]. It was initially developed in experimental studies, but over the past years found the way to the clinic as well [7,9]. Today, MD is applied almost everywhere in research and clinic and there are several clinical and experimental studies about the application of microdialysis in neurosurgery, reconstructive surgery and liver transplantation [10,11]. It is a safe and easy sampling tool which has been used in pre-clinical as well as clinical studies for continuous monitoring of free, protein-unbound concentrations in extracellular fluids by means of a microdialysis catheter [12–14]. We have reported its capability in monitoring the kidney graft function during the different stages of KTx [15]. The aim of this experimental study is to investigate, if MD could be used for early detection of the acute graft rejection in KTx in porcine model.

2. Materials and methods

2.1. Study design

In our study, a group of 16 Landrace pigs with a mean body weight of 29.06 kg (27–32 kg, SD = ±1.97) was used. The animals were divided into two groups based on receiving or not receiving immunosuppressive treatment with methylprednisolone (Urbason, Sanofi-Aventis, Frankfurt, Germany) with the dosage of 250 mg i.v. intraoperatively, which was administrated in our control group (n = 8) before reperfusion but not in the case group (n = 8). During the explantation the organs were perfused with the standard histidine–tryptophan–ketoglutarate (HTK) solution (Custodiol, Dr. F. Kohler Chemie GmbH, Alsbach-Hahnlein, Germany). After a cold ischaemia time (CIT) of 24 h, the grafts were implanted using a standardized KTx technique as previously published [15,16]. The metabolic changes were monitored within 180 min after reperfusion, using MD (Fig. 1).

2.2. Collecting and analysing of the microdialysis samples

The MD method has been described completely by the authors [15]. Briefly, A CMA 20 microdialysis catheter (CMA microdialysis, Sweden) was used to collect the samples. The dialysing membrane was 10 mm in length and the catheter membrane cut-off was 20,000 Da. Insertion into the tissue was achieved with the help of a unique slit cannula introducer that left the catheter in place when it was withdrawn. This catheter was connected to a CMA 102 pump (CMA microdialysis, Sweden) by inlet tubes perfused with isotonic, sterile solution T1 (Na: 147 mmol/L, K: 4 mmol/L, Ca: 2.3 mmol/L, Cl: 156 mmol/L) at a flow rate of 2 μl per minute into the catheter. The outlet tube extends to a microdialysis collector CMA 142 (CMA microdialysis, Sweden) holding the microvials. After collecting the samples, our microvials were stored at −80 °C for further assessment. The samples were then analysed by a CMA 600 microdialysis analyser. The measured parameters included: Glucose (mmol/l), Lactate (mmol/l), Pyruvate (μmol/l), Glycerol (μmol/l) and Glutamate (μmol/l).

2.3. Measurement protocol

Different samples were collected from both case and control groups during the monitoring period. The Microdialysis samples were collected in 20 min intervals during the 3 h post-reperfusion phase. In each group, in order to standardize our experimental study, blood samples were obtained from donors (1 sample during procurement), and recipients (1 sample before and another sample at the end of the reperfusion phase) to determine haemoglobin, haematocrit, glucose, blood urea nitrogen and creatinine values. This analysis was performed in the central laboratory of our clinic.

2.4. Histopathological evaluations

Biopsy samples were taken before and 180 min after reperfusion to discriminate the tissue injury. All biopsy samples were fixed in formaldehyde 5% and analysed by one experienced nephropathologist who was blinded to the randomization. The samples were evaluated to detect the histopathological evidences of “acute rejection” in the grafts based on the Banff classification [17]. Special emphasis was placed on detection of “rejection” in early stages with patchy interstitial infiltration, with or without tubulitis in less than 3 tubular cross-sections [18].

2.5. Animal rights

The Study protocol was approved by the German Committee for Animal Care, Karlsruhe, Germany (AZ: 35-9185.81/G-113/05). Animals received human care according to the institutional guidelines established for the Animal Care Facility at the University of Heidelberg. Following completion of the experimental protocol, the animals were sacrificed with an intravenous injection of kalium-chloride (2 mmol/kg), in deep anaesthesia.

2.6. Statistics

The statistical analysis was performed using SPSS 14.0 (Stata Corp, College Station, Texas, USA) for windows. The variable analysis was performed using T-test when needed. All metabolic parameters were expressed as mean ± standard error of mean (SEM). The laboratory results were expressed as mean ± standard deviation (SD). The P-value of less than 0.05 was considered statistically significant.

3. Results

In both study groups the monitored cardiovascular parameters during the implantation and post-reperfusion phase including MAP, CVP heart rate, and body temperature did not show any significant differences. The mean values of the laboratory results are summarized in Table 1. As it is shown, in both study groups during different phases [explantation, warm ischaemia time (WIT) and post-reperfusion] no significant fluctuations could be seen in any of the above mentioned variables.

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