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Prognostic value of intraoperative renal tissue oxygenation measurement on early renal transplant function

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Conflicts of Interest
All authors declare that they have no conflict of interest that might bias their work.

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Summary

Ischemia time is a prognostic factor in renal transplantation for postoperative graft function and survival. Kidney transplants from living donors have a higher survival rate than deceased donor kidneys probably because of shorter ischemia time. We hypothesized that measurement of intraoperative kidney oxygenation (μHbO_2) and microvascular perfusion predicts postoperative graft function. We measured microvascular hemoglobin oxygen saturation by reflectance spectrophotometry and microcirculatory kidney perfusion by laser Doppler flowmetry 5 and 30 min after kidney reperfusion on the organ surface in 53 renal transplant patients including 19 grafts from living donors. These values were related to systemic hemodynamics, cold ischemia time (cit), early postoperative graft function and length of hospital stay. μHbO_2 improved 30 min after reperfusion compared to 5 min (from 67% to 71%, $P < 0.05$). μHbO_2 correlated with mean arterial blood pressure and central venous pH ($P < 0.01$). Most importantly, μHbO_2 was significantly higher in kidneys from living compared with deceased donors (74% vs. 63%) and in kidneys without vs. with biopsy-proven postoperative rejection (71% vs. 45%, $P < 0.001$). Finally, μHbO_2 correlated positively with cit and postoperative creatinine clearance and negatively with postoperative plasma creatinine, need for hemodialysis and length of hospital stay. Our results suggest higher oxygen extraction and thus oxygen demand of the grafts shortly after reperfusion. The intraoperative measurement of tissue oxygenation in kidney transplants is predictive of early postoperative graft function. Future studies should evaluate the potential effect of intraoperative therapeutic maneuvers to improve organ tissue oxygenation in renal transplantation.

Introduction

Kidney transplantation (KTx) is inevitably associated with a period of graft ischemia. Traditionally, graft ischemia time is calculated as warm (wit) and cold ischemia time (cit). Cit is the period lasting several hours during which the explanted organ is cooled in perfusion solution and is being transported from the explanting hospital to the transplantation centre. Warm ischemia time (wit) is divided into two distinct periods with a first and second warm ischemia time (wit1 vs. wit2). Wit1 relates to the warm ischemia in the donor and is counted from vascular clamping of the kidneys in the donor until organ perfusion with cold solutions is started. Wit2 is the period of time during the transplantation procedure when organ cooling is no longer effective while the vascular anastomoses are being sutured in the recipient. It has been shown that both *wit* and *cit* influence postoperative transplant function [1,2]. The importance of ischemia time is underlined by the fact that postoperative graft function

and survival are better in living donor renal transplantation compared with renal grafts from deceased donors.

In addition, significant alterations in tissue function occur during reperfusion after ischemia, collectively called reperfusion injury. Oxygen free-radical-mediated postischemic reperfusion injury includes the release of proinflammatory cytokines, accumulation of leukocytes and expression of adhesion molecules on endothelial cells all of which affect the microcirculation [3]. Hypoxia-induced endothelial swelling resulting from an intracellular increase in sodium and water results in a decrease in capillary diameter and obstruction to reperfusion (no-reflow phenomenon), even when macrocirculatory hemodynamics are restored [4]. Furthermore, it has been shown that the activity of endothelium derived relaxing factor (EDRF) in the kidney is reduced after ischemia/reperfusion, a mechanism which contributes to postischemic vasoconstriction in the renal microcirculation [5]. Taken together, these factors may contribute to adverse outcomes in renal transplantation such as delayed graft function, acute rejection or graft failure [6]. The relevance of these pathomechanisms become even more important because of the shortage of donor organs leading to an increased use of older and often marginal kidneys for transplantation [7].

Standard anesthesiological hemodynamic management during KTx includes the monitoring and stabilization of global hemodynamics [e.g. blood pressure, heart rate (HR), central venous pressure] and of oxygenation and metabolic variables (e.g. arterial and central venous oxygen saturation, pH). However, it is recognized that an impaired microcirculation and tissue oxygenation are responsible for the morbidity and mortality in several disease states such as sepsis, acute respiratory distress syndrome (ARDS) and multiple organ failure [8]. Consequently, the monitoring of the microcirculation has gained increased interest in recent years, although its clinical application is far from routine. This may be attributed to the fact that anesthesiological measurement of the microcirculation in the intact organism is limited to easily accessible surface areas such as sublingual or nailfold areas, which may not be representative of the microcirculation in visceral organs.

Only a few studies so far have looked at the microcirculation during KTx by visualizing capillary density and red blood cell (RBC) velocity; they found a positive correlation of early microvascular changes and postoperative plasma creatinine levels suggesting that microcirculatory monitoring might be able to predict early renal graft dysfunction induced by reperfusion injury [9]. In addition, RBC velocity in the early phase after reperfusion deteriorated significantly more in grafts from deceased donors compared with that of living donors [10]. Recently, it has been reported that graft microvascular perfusion in the early reperfusion period was 42% lower in grafts from donors after cardiac death compared with living donor kidneys [11].

We hypothesized that measurement of intraoperative renal graft oxygenation (μHbO_2) and microcirculatory blood flow were higher in grafts from living donors compared with deceased donors and that μHbO_2 predicts early postoperative graft function. For this purpose, we measured μHbO_2 by reflectance spectrophotometry and microcirculatory kidney perfusion by laser Doppler flowmetry on the graft surface intraoperatively and related these values to systemic hemodynamics, cit and early postoperative kidney function.

Patients and methods

The study was approved by the local Ethics Committee of Rostock University (Study No. A 01/2007). After obtaining oral or written consent, renal microcirculation and oxygenation was measured intraoperatively in 53 consecutive renal transplant recipients who underwent transplantation in the Department of Urology at Rostock University Hospital between January 2007 and December 2008. The demographic data of the patients and the kidney origin are given in Table 1.

All patients received a standardized balanced anesthesia technique using propofol and sufentanil for induction and sevoflurane and additional sufentanil for maintenance as clinically required. Muscle relaxation was performed with rocuronium, and the patients were ventilated in a volume-controlled mode with a tidal volume of 7 ml/kg and a respiratory rate between 12 and 18 breath/min to maintain normocapnia.

Measurement of kidney oxygenation and microcirculatory blood flow

Microvascular hemoglobin oxygen saturation (μHbO_2) was measured by reflectance spectrophotometry and

Table 1. Demographic data of recipients of allogenic kidney transplantation.

Demographical description of the recipients (n = 53)	
Age (years; mean ± SD)	46.1 ± 14.4
gender (n; male/female)	31/22
Weight (kg; mean ± SD)	75.6 ± 14.0
BMI (kg/m^2; mean ± SD)	25.4 ± 4.3
ASA classification (n; II/III)	17/36
Time on hemodialysis (years; mean ± SD; Min–Max)	5.5 ± 3.6; 0.2–18.9
Retransplantations (n)	7
Kidney origin (living/deceased donor)	19/34

microcirculatory kidney perfusion by laser Doppler flowmetry (O2C™; Lea, Giessen, Germany). This device combines both optical techniques in one optical fiber without interference because of different wavelengths used. In this study, we used a flat probe with a measurement depth of 4–6 mm for the kidney surface and a microlightguide (measurement depth 0.2 mm) for the reference measurement of the buccal mucosa. This method has briefly been reviewed including a literature overview [12]. Briefly, these probes deliver simultaneously visible light (500–800 nm) and near-infrared laser light (830 nm) to the tissue where part of the light is absorbed. The backscattered light represents the color of hemoglobin, which is a measure of its saturation with oxygen. It is analyzed by the spectrophotometer at a rate of 100 Hz giving the μHbO_2 values, which represent mainly the venous end of the capillaries and thus the lowest oxygen saturation of the tissue. The values are averaged and displayed every 2 s. In addition, the regional amount of hemoglobin in the microvessels (μHb) is determined as a measure of its blood content and capillary density [relative value given in arbitrary units (AU)].

Microvascular perfusion was measured by laser Doppler flowmetry through the same probes. As moving erythrocytes displace the light frequency (Doppler shift), blood flow within the capillary network can be derived by analyzing the power spectra from Doppler frequencies of backscattered laser light. Flow (also in AU) is then related to the velocity multiplied by the number of moving erythrocytes. From these values, local oxygen delivery (DO_{2loc}) was calculated according to the formula:

$$DO_{2loc} = \text{Flow} \times \mu Hb \times \mu HbO_2$$

Measurements were performed 5 and 30 min after the beginning of in-situ graft perfusion on the surface of the transplant. For each kidney, measurements were taken at three sites, i.e. the upper pole of the kidney, the lower pole and the convexity opposite to the renal hilum. Each site was measured for 30 s and the values obtained were averaged for the each kidney. The probe was manually held to the graft surface by the surgeon, which was associated with minimal motion artifacts during the measurements (as exemplified in Fig. 1). Results were taken when stable values (maximum 5% variation between successive readings) of all variables had been recorded for at least 30 s. For aseptic conditions, the probes were wrapped with a sterile transparent cover (Ultracover; Cardinal Health, Zutphen, The Netherland), which did not affect the measurements as shown in pilot investigations with and without cover (data not shown). As the reference, a second probe was placed intraorally to measure microcirculation at the buccal mucosa.

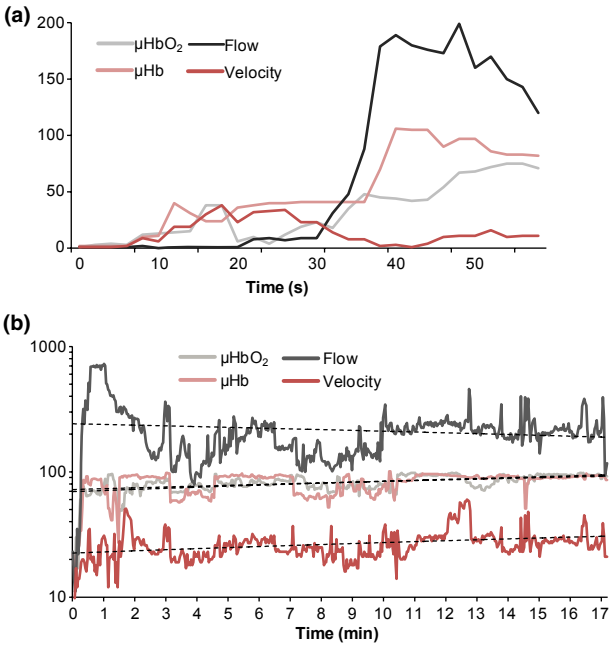

Figure 1 Representative example of the time course of microvascular hemoglobin oxygen saturation (μHbO_2), microvascular hemoglobin concentration (μHb), and microcirculatory kidney perfusion (flow and velocity) in a patient undergoing allogenic kidney transplantation immediately after start of reperfusion. Shown is the first minute after start of reperfusion (a) and the time course over the following 17 min (b). Note the trend lines for each variable in (b) and the fluctuations caused by measurement probe movement during surgery.

Routine systemic hemodynamic and metabolic measurements during transplantation surgery include mean arterial pressure (MAP), HR, arterial (SpO_2) and central venous oxygen saturation ($ScvO_2$) as well as central venous pH, and these were recorded. In addition, the need for vasoactive medication was recorded and central venous blood was taken (for blood gas analysis including pH and hemoglobin) at 5 and 30 min after reperfusion. Oxygen extraction was estimated for the whole organism ($SpO_2 - ScvO_2$), the kidney ($SpO_2 - \mu HbO_2$) and the buccal mucosa.

Postoperatively, clinical parameters of graft function were recorded: plasma creatinine, creatinine clearance (MDRD) and urea on postoperative days 1,2,3,4,5,10, and 15, the number of postoperative hemodialyses needed, and biopsy-proven graft rejection. For comparison, the postoperative blood chemistry values were described as changes referred to the last preoperative values. In addition, length of hospital stay (LOS) was also recorded.

Data analyses

Data were analyzed using a standard software package (SPSS 15.0; SPSS Inc., Chicago, IL, USA). Normal data distribution was tested using Kolmogorow–Smirnow test. With normal distribution, data are presented as means ± SD and further analysis was performed with Student's *t*-test or ANOVA. Otherwise, data are presented as medians ± range and analysis was performed by Mann–Whitney *U*-test and Wilcoxon test. Correlation analysis was performed according to Pearson (normal data distribution) or Spearman. A multivariate analysis was performed according to the equation: $y = (ß_i x_i) + \xi + \alpha$. Receiver operating characteristic (ROC) analysis was performed to determine the ability of μHbO_2 to predict postoperative hemodialysis requirement and graft rejection. A *P*-value <0.05 was considered statistically significant.

Results

Figure 1 shows an example of the development of the microcirculatory variables during reperfusion in one graft kidney. Before reperfusion, all values were around zero, increased shortly after start of reperfusion (Fig. 1a) and reached a stable plateau after about 2 min for the remaining observation period. This pattern was observed in all grafts.

On average, 30 min after the start of reperfusion all parameters of microcirculatory oxygenation and flow had increased significantly compared with the values obtained after 5 min (Table 2). In detail, by 30 min μHbO_2 had increased in 66% of all patients, µHb in 62%, flow in 60%, and DO_{2loc} in 65%. Recipients with an American Society of Anesthesiologists (ASA) physical status of II ($n = 17$) had a higher μHbO_2 of their kidney grafts than those with an ASA III status ($n = 36$): 74 ± 13.6 vs. 64 ± 17.5%, $P < 0.05$).

Systemic hemodynamic and metabolic variables are given in Table 2. There was a significant increase in MAP between 5 and 30 min after start of reperfusion, while gas exchange and ventilation remained constant. Furthermore, there was a significant positive correlation between MAP and μHbO_2 ($r = 0.66$, $P < 0.001$) and DO_{2loc} ($r = 0.43$, $P = 0.002$), respectively.

Central venous pH ($R^2 = 0.47$, $P < 0{,}001$), but not $ScvO_2$ correlated with the μHbO_2 of the graft kidney. Comparing microcirculatory values between those patients with normal (7.35–7.45) versus those with low central venous pH (<7.35) revealed significant differences

Table 2. Intraoperative values of regional and systemic hemodynamic oxygenation data obtained 5 and 30 min after start of reperfusion.

	5 min reperfusion			30 min reperfusion			
	n	mean	SD	*n*	mean	SD	*P*
μHbO_2	53	67.1	16.8	49	70.8	14.4	0.042
µHb	52	66.4	16.9	49	70.9	17.7	0.049
Flow	53	108	76	50	127	85.5	0.048
DO_{2loc}	52	5719	4576	49	7131	6044	0.035
MAP [mmHg]	53	80	7.7	53	85	9.1	<0.001
Heart rate [1/min]	53	76	14.6	53	78	16.5	0.047
SpO_2 [%]	53	98.4	1.0	53	98.6	0.7	0.115
FiO_2 [%]	53	46.9	0.09	53	47.0	0.07	0.898
$etCO_2$ [kPa][h]	53	4.84	0.4	53	4.83	0.4	0.885

μHbO_2, kidney oxygenation; µHb, microvascular hemoglobin concentration; Flow, microvascular blood flow; DO_{2loc}, local oxygen delivery; MAP, mean arterial pressure; SpO_2, arterial oxygen saturation obtained by pulse oximetry; FiO_2, inspired oxygen concentration; $etCO_2$, end-tidal carbon dioxide pressure.

Table 3. Comparison of intraoperative kidney oxygenation and microvascular flow of renal grafts depending on underlying pH.

	pH < 7.35			pH = 7.35–7.45			
	n	mean	SD	*n*	mean	SD	*P*
μHbO_2	28	63.0	15.2	19	77.0	9.4	0.001
µHb	27	60.3	15.6	19	74.4	16.3	0.005
Flow	28	89	75.1	19	141	75.4	0.025
DO_{2loc}	27	4286	5189.9	19	8618	5647.5	0.01

μHbO_2, kidney oxygenation; µHb, microvascular hemoglobin concentration; Flow, microvascular blood flow; DO_{2loc}, local oxygen delivery.

for all variables (Table 3). Oxygen extraction of the graft kidney (31.4 ± 16.7%) was significantly higher than that of the whole organism (13.5 ± 5.1) or that at the buccal mucosa (19.8 ± 11.5).

Median cold ischemic time (Cit) of all transplanted kidneys was 10 h 55 min (range: 2 h 02 min to 22 h 35 min). Grafts with a shorter Cit (≤10 h 55 min) had significantly higher μHbO_2, flow and DO_{2loc} than those with a longer Cit (>10 h 55 min)(Fig. 2). Similarly, these variables were significantly higher in grafts originating from living donors ($n = 19$, median Cit 2 h 31 min, range: 2 h 02 min to 4 h 11 min) compared with those from deceased donors ($n = 34$, median Cit 14 h 06 min, range: 4 h 48 min to 22 h 35 min) ($P < 0.05$; data not shown).

The duration of the transplant procedure was on average 181 min (range 115–365 min) from skin incision to skin closure. The period from skin incision to graft reperfusion was 108 min on average (range 67–365 min) and correlated negatively with μHbO_2 ($r = -0.41$, $P < 0.002$) and DO_{2loc} ($r = -0.41$, $P < 0.002$).

The median LOS was 22 days (range 10–57 days). The higher μHbO_2 and DO_{2loc} were intraoperatively, the shorter this LOS was ($r = -0.52$, $P < 0.001$, and $r = -0.47$. $P < 0.007$, respectively).

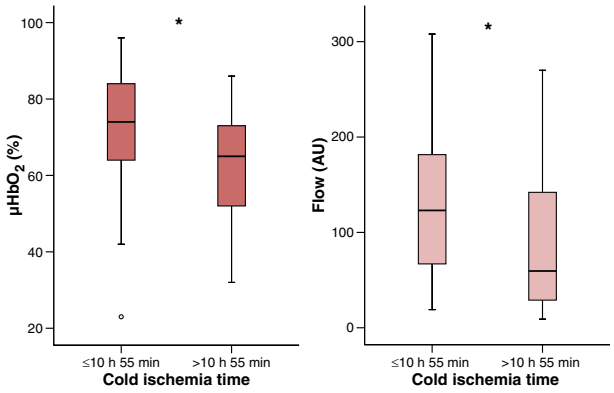

Figure 2 Tissue oxygenation (μHbO_2) and Flow in grafts with cit ≤10 h 55 min and >10 h 55 min, respectively. * = $P < 0.05$ between groups.

Postoperative kidney function

Of all patients, 54% required at least one postoperative hemodialysis (median 1, range 1–17). Grafts with delayed function had a longer Cit (mean 11 h 36 min) compared with those not requiring any postoperative hemodialysis (mean 7 h 45 min)($P < 0.05$). High intraoperative graft μHbO_2 ($r = 0.73$, $P < 0.001$) and microcirculatory variables corresponded to low postoperative hemodialysis requirements (Fig. 3). Multivariate analysis showed the following independent predictors of postoperative hemodialysis requirement: μHbO_2 (ß = −0.39, $P < 0.05$), surgical time to reperfusion (ß = 0.31, $P < 0.05$) and recipient ASA status (ß = 0.24, $P < 0.05$). ROC analysis revealed a highly predictive value of μHbO_2 to predict the absence of postoperative hemodialysis requirement (area under the curve 0.864, $P < 0.0001$)(Fig. 4a) with a cut-off μHbO_2 of 67.5% (sensitivity 0.773 and specifity 1.0).

Also the postoperative plasma creatinine development correlated significantly with μHbO_2. Fig. 5 shows the results of postoperative days 1 and 15. While on day 1 about half of the patients presented with increased creatinine levels compared with the last preoperative value, most patients had lower values on day 15. In summary, the higher the intraoperative μHbO_2 was, the more pronounced was the postoperative decrease in creatinine levels. Similar results were found for BUN and creatinine clearance (data not shown).

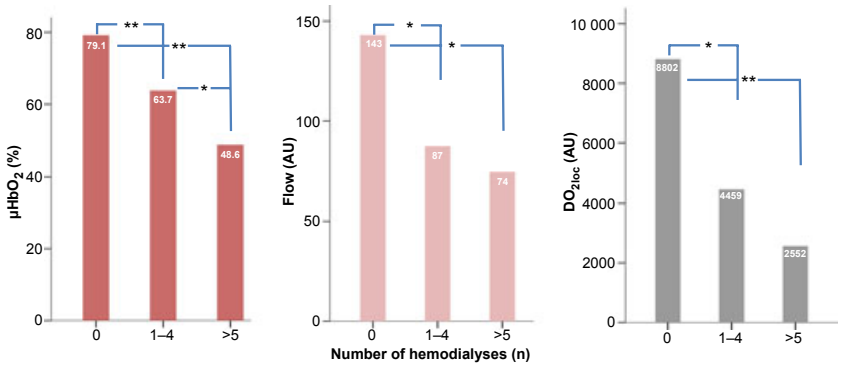

Figure 3 Intraoperative values of tissue oxygenation (μHbO_2), microvascular blood flow (flow), and local oxygen delivery (DO_{2loc}) depicted to the postoperative number of hemodialyses required. * = $P < 0.05$; ** = $P < 0.01$ between groups.

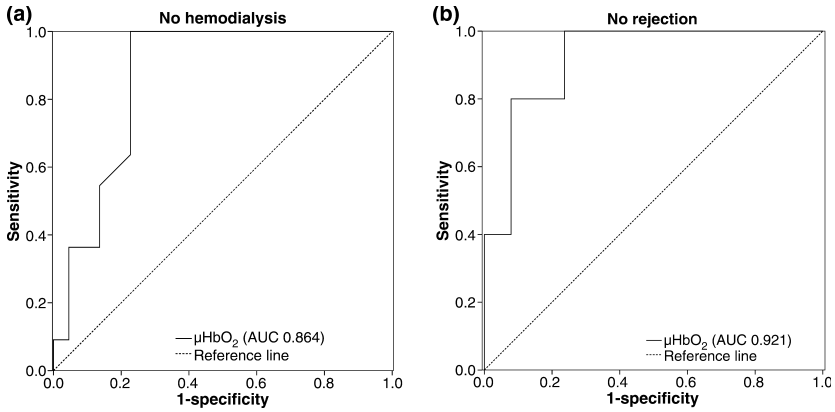

Figure 4 Receiver operating characteristic curves for μHbO_2 to predict no hemodialysis requirement (a) and no graft rejection (b), respectively. AUC is area under the curve.

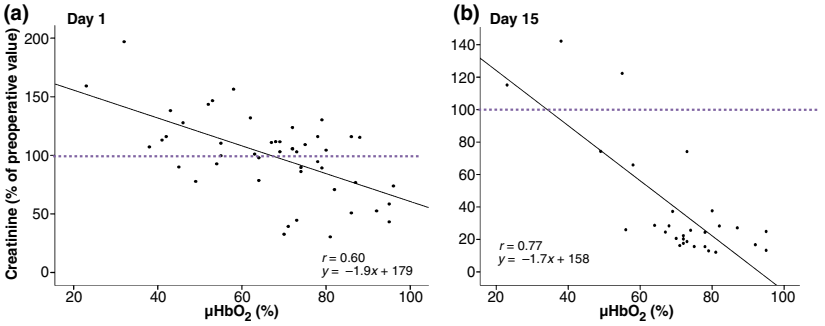

Figure 5 Correlation between plasma creatinine (in % of the preoperative value) at first (a) and 15th postoperative day (b) and kidney oxygenation (μHbO_2) 5 min after start of reperfusion. $P < 0.01$.

Nine patients had biopsy-proven postoperative graft rejection. In those grafts with an episode of postoperative rejection, intraoperative μHbO_2, flow and DO_{2loc} had been significantly lower than in grafts that had not early postoperative rejection (Fig. 6). ROC analysis revealed a highly predictive value of μHbO_2 to predict absence of acute graft rejection (area under the curve 0.921, $P < 0.01$)(Fig. 4b) with a cut-off μHbO_2 of 63.5% (sensitivity 1.0 and specifity 0.763).

Discussion

The main findings of this study are that intraoperative graft oxygenation during allogenic renal transplantation is

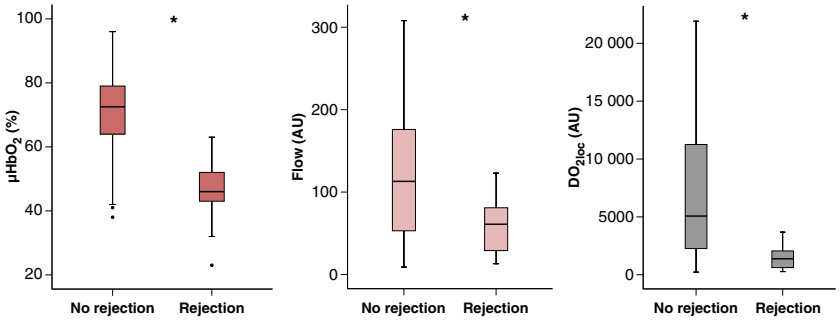

Figure 6 Intraoperative values of tissue oxygenation (μHbO_2), microvascular blood flow (flow), and local oxygen delivery (DO_{2loc}) in grafts without ($n = 42$) and with ($n = 9$) biopsy-confirmed rejection. * = $P < 0.05$ between groups.

affected by several recipient and graft parameters and influences postoperative graft function. Factors that significantly influenced intraoperative graft oxygenation were kidney origin, mean arterial blood pressure, systemic acidosis, recipient ASA physical status, and ischemia time of the graft. Intraoperative graft oxygenation was predictive of early transplant function, as indicated by postoperative hemodialysis requirements and the postoperative development of plasma creatinine values, and of acute graft rejection.

Critique of methods

Graft μHbO_2 was measured by reflectance spectrophotometry, a method validated *in vitro* and *in vivo* using pO_2 electrodes [13] and shown to detect splanchnic ischemia with similar precision as laser Doppler flowmetry [14]. The O2C device combines these techniques in one probe, allowing assessing tissue oxygenation and microvascular blood flow simultaneously. It has been shown to provide reproducible intraoperative evaluations of the hepatic microcirculation [15], to quantify tissue ischemia in diabetic foot ulcers [16], and to evaluate the sublingual microcirculatory effects of vasopressors applied in patients during constant flow cardiopulmonary bypass [17].

The tissue penetration depth of the signals is restricted to a maximum of 8 mm. Thus it may be argued that our measurements apply to superficial areas of the kidney grafts only and cannot be representative of the whole organ. We speculate that tissue oxygenation and microvascular perfusion in the kidney medulla might even be lower than in the cortical areas we could monitor. Moreover, in renal function the cortical areas are those of most functional importance where tubular necrosis occurs [18]. This is supported by our finding of delayed function in grafts with low intraoperative μHbO_2 and microvascular perfusion. It should be noted in this context that μHbO_2 measurements did not correlate with the macroscopic impression of reperfusion of the surgical team (e.g. patchy perfusion).

A limitation of our study is the short observation time limited by the intraoperative period where we had access to the kidney surface. It would be interesting to assess μHbO_2 also in the donor prior to recovery to predict graft quality and to follow the postoperative course of μHbO_2 and microvascular flow with the availability of implantable measurement probes. This would also allow evaluating the potential influence of anatomical and vascular differences between donors and recipients on graft oxygenation and microvascular perfusion.

Interpretation of results

Intraoperative kidney oxygenation and microvascular graft perfusion increased during reperfusion with time. This might be caused by an increased oxygen demand after the ischemic period and a reperfusion injury causing a no-reflow phenomenon in some microvessels [9]. Consistently, Hattori *et al.* reported that the diameter of peritubular capillaries is decreased to two-thirds of its baseline diameter 20 min after the start of reperfusion and is not restored until 120 min thereafter [10]. Snoeijs *et al.* found a significantly lower microvascular blood flow in grafts from deceased compared with living donors 5 min after start of reperfusion, whereas this difference was attenuated at 30 min after start of reperfusion [11]. Accordingly, we found that all parameters of microvascular blood flow and kidney oxygenation measured with the O2C were lower in grafts from deceased donors (long *cit*) compared with living donors (short *cit*).

The decreased μHbO_2 may also be the result of mitochondrial dysfunction [19], causing impaired oxygen utilization and thus tissue hypoxia. The decreased micovascular blood flow within the grafts might be the result of endothelial cell injury with subsequent vascular stasis and loss of capillaries [20].

We found a linear correlation between MAP and μHbO_2 shortly after the start of reperfusion indicating that the autoregulation of kidney perfusion might be impaired during this period. We also observed that μHbO_2 was significantly lower (63% vs. 77%) when central venous pH was low (< 7.35). This might be the result of the so-called Bohr-effect [21], which stipulates that tissue acidosis improves oxygen release from hemoglobin to that tissue, causing the observed decrease in μHbO_2. Similar results were found in cremaster microvessels of the rat where tissue oxygen saturation fell from 98.6% to 64.2% when pH decreased from 7.39 to 7.26 in microvessels [22]. Consistently, acidosis is a common finding during reperfusion in kidney transplantation [23], and this may inhibit endothelium-dependent vascular relaxation [24]. Thus, our findings support the importance of maintaining a normal pH during reperfusion to achieve sufficient kidney oxygenation as a prerequisite for early transplant function. Furthermore, our findings also support the importance of maintaining a high MAP during reperfusion for the same reason.

We estimated oxygen extraction of the grafts by subtracting μHbO_2 from systemic oxygen saturation, thus neglecting regional and systemic pO_2. This simplification seems to be justified since the contribution of oxygen partial pressures to oxygen delivery is negligible under normal conditions. Unfortunately, there are no values for graft oxygen extraction during transplantation reported in the literature. One can imagine that both high oxygen extraction (suggesting low oxygen availability) and low oxygen extraction of the graft (suggesting the presence of nonrespiring tissue) are unfavorable findings.

One reason for the better microvascular variables in grafts from living donors compared with those from deceased donors will obviously be the shorter Cit resulting in less energy deficit and damage to the tissue. Cit is a significant risk factor for acute tubular necrosis and delayed graft function in kidney transplant recipients [25] and its duration [26]. In addition, in our study recipients of grafts from living donors were on average 11 years younger, had been 5 years less on chronic hemodialysis and had an average waiting time which was 5 years shorter. Burns *et al.* found significantly more apoptosis in post reperfusion biopsy specimens from deceased donors compared with living-related renal transplants [27]. Similarly, it has been shown that living-related donor grafts show less microcirculatory alteration than deceased donor kidneys. [10,28] Moreover, a long Cit is related to reduced renal blood flow and delayed onset of graft function as evidenced by the need for post-transplant dialysis [29].

Our results clearly indicate that with better μHbO_2, microvascular flow and DO_{2loc} in the grafts during early reperfusion up to 30 min postoperative renal function will likely be better as evidenced by the postoperative decrease in creatinine levels and need for postoperative hemodialysis. Similar findings have been reported from a pilot study using the same methodology: μHbO_2 (42% vs. 52%) as well as flow (177 vs. 253 AU) was lower in patients who required postoperative hemodialysis [30]. A positive correlation between graft perfusion and postoperative function has also been shown in other studies using different methods of monitoring microcirculatory function, too [9,10,28].

Our multivariate analysis indicated factors other than microcirculatory-derived variables to be important for postoperative graft function, such as the ASA physical status of the recipient. A higher ASA score has previously been described as a risk factor for ischemic tubular necrosis and delayed graft function [25]. In our cohort, we have shown for the first time that an ASA II status of the recipient was associated with higher values of μHbO_2 and regional hemoglobin concentration (μHb). The reason for that remains unclear, the more so as the ASA score of the deceased donors was unknown.

Postoperative graft function by necessity had an impact on the LOS and this has obvious economic relevance. Moreover, from this point of view, it is remarkable that intraoperative measurements of μHbO_2 and microvascular perfusion were able to predict postoperative graft function and therefore indirectly LOS. Most interestingly, however, μHbO_2 and microvascular perfusion were significantly lower in grafts with biopsy-proven rejection within the 2-month observation period after transplantation. Although we did not perform any immunological tests, we speculate that an impaired microcirculation and oxygenation during reperfusion might have contributed to graft rejection by causing more cellular damage and thus increase antigenicity of the graft. In addition, this finding underscores the predictive abilities of our method.

Perspective

The shortage of kidneys for transplantation in relation to the large number of patients with terminal renal failure has led to an enlargement of the donor inclusion criteria (i.e. marginal donors, European Senior Program). As a consequence, increasingly kidneys with marginal quality are being transplanted. In general, these marginal organs have similar 5-year graft survival (70.4% vs. 76.7%) and patient survival rates (88.2% vs. 88.9%) compared with renal grafts not considered marginal than inconspicuous kidney transplants [31]. So far, there is no monitoring method available which can predict the likely postoperative course of a donor kidney in the recipient. The measurement of tissue oxygenation and microcirculatory blood flow in grafts early after reperfusion may be helpful for this purpose. In this respect, the O2C may offer a useful enlargement of the diagnostic armature, and it has to be shown whether this can be of general clinical benefit.

Delayed graft function is associated with lower graft survival [32] and increased mortality [33]. Our results indicate that high values of μHbO_2 and microvascular flow are good prognostic factors for postoperative graft function. Low values may be indicative of delayed graft function and/or later graft rejection. This is of potential benefit indicating increased risks in recipients with poor intraoperative microperfusion parameters who might therefore benefit from additional surveillance or treatment.

Moreover, the intraoperative measurement of reperfusion parameters might be used to evaluate intraoperative measures likely to improve microperfusion. Despite the limitations of our study (measurements primarily restricted to cortex and short observation time), our results clearly show the necessity of maintaining a high MAP during reperfusion. Further work is required to evaluate the potential effects of therapeutic maneuvers in cases with impaired μHbO_2 during reperfusion. Theoretically, these might consist of pharmacological interventions, e.g. the use of vasodilators for recruiting microcirculatory units [34], or inotropes for increasing microvascular flow and oxygen delivery [35,36]. Finally, additional studies should address the correlation between oxygenation and organ antigenicity.

Authorship

TWLS: designed the study, carried out the research and contributed to the writing of the paper. KM: carried out

the research, contributed to the data analysis and the writing of the paper. MM: carried out the research. OWH: carried out the research and contributed to the writing of the paper.

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