TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

The faster the better: anastomosis time influences patient survival after deceased donor kidney transplantation

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Keywords
anastomosis time, deceased donor, graft survival, kidney transplantation, patient survival.

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Conflicts of interest
There are no conflict of interests to disclose.

Received: 23 September 2014
Revision requested: 17 October 2014
Accepted: 30 December 2014
Published online: 21 January 2015

doi:10.1111/tri.12516

Summary

Despite a continuously growing knowledge of the impact of factors on kidney graft function, such as donor age, body mass index, and cold ischemia time, few data are available regarding anastomosis time (AT) and its impact on long-term results. We investigated whether surgical AT correlates with patient and graft survival after kidney transplantation performing a retrospective analysis of 1245 consecutive deceased donor kidney transplantations between 01/2000 and 12/2010 at Innsbruck Medical University. Kaplan–Meier and log-rank analyses were carried out for 1- and 5-year patient and graft survival. AT was defined as time from anastomosis start until reperfusion. Median AT was 30 min. Five-year survival of allografts with an AT >30 min was 76.6% compared with 80.6% in the group with AT <30 min ($P = 0.027$). Patient survival in the group with higher AT similarly was inferior with 85.7% after 5 years compared with 89.6% ($P < 0.0001$) [*Correction added on February 18, 2015, after first online publication: the percentage value for patient survival was previously incorrect and have now been changed to 89.6%*]. Cox regression analysis revealed AT as an independent significant factor for patient survival (HR 1.021 per minute; 95% CI 1.006–1.037; $P = 0.006$). As longer AT closely correlates with inferior long-term patient survival, it has to be considered as a major risk factor for inferior long-term results after deceased donor kidney transplantation.

Introduction

During the past two decades, short-term results after renal transplantation have improved steadily, what could not be seen for long-term outcomes [1]. There are many possible factors, which may explain the discrepancy between the short and the long-term results, such as the increasing use of expanded criteria donor kidneys (ECD), the increasing age of the recipient population, and the current inability to treat chronic allograft nephropathy in an effective manner [2]. Another growing problem which influences the outcome after transplantation is comorbidities in the recipient and the donor population, such as obesity and diabetes which escalate to a pandemic and have become one of the most serious public health issues worldwide [3]. Due to these mentioned, unchangeable, factors, we have to focus on the analysis and potential influence on modifiable parameters to achieve the best possible long-term results. In the past, cold ischemia time (CIT) has been found to be an important independent risk factor for delayed graft function (DGF) in deceased donor renal transplantation (DDRT) [4–7]. On the contrary, anastomosis time (AT), during which the graft is slowly warming up (sometimes referred to as warm ischemia time), is investigated in few studies only [8–10]. The importance of warm ischemia time has gained relevance, especially as data are available which showed a deleterious influence of prolonged warm ischemia in living donor kidney transplantation [11]. Furthermore, up to

now, there are no sufficient data emphasizing an impact of AT on long-term graft and patient survival after DDRT.

The aim of our study was to evaluate whether there is an influence of AT on renal allograft and patient long-term outcome.

Patients and methods

Patients and data collection

This is a retrospective analysis of all consecutive patients who underwent DDRT at our center between January 2000 and December 2010. Patients with a follow-up <1 year were defined as lost to follow up. Patients with primary nonfunction ($n = 3$) or receiving kidneys from donors deceased after cardiac death ($n = 4$) were excluded from the analysis due to the low numbers. The study was approved by the Institutional Review Board of the Medical University of Innsbruck (UN4358; 300/4.19; April 14th, 2011).

Health information and demographic data for recipients, donors, and the surgical procedure were collected in a digital database. Recipient demographics included BMI, age, gender, history of prior transplant, the cause of renal failure, panel of reactive antibodies (PRA), and recipient comorbidities (hepatitis C). Donor demographics included BMI, age, gender, cause of death, donor comorbidities, serum creatinine, and serum urea.

Transplant factors included AT (defined as the time from the start of anastomosis until reperfusion), DGF (defined according to the UNOS data collection convention as the need for dialysis within 1 week after transplantation; cases with dialysis requirement for a different indication, such as hyperkalemia, >5 mmol/l potassium, or volume overload, clinically diagnosed by occurrence of pulmonary edema, were excluded), HLA mismatch at A, B, and DR loci, CIT, and initial immunosuppression (induction treatment).

Statistical analysis

Statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). Graft- and patient survival was calculated using Kaplan–Meier estimates. Graft loss was defined as either loss of the organ or patient death with a functioning organ. Differences between survival curves were tested for significance by the log-rank test. Cox proportional hazards model was performed to determine the hazard ratio (HR) and 95% confidence intervals (CI) for potential predictors of outcome after kidney transplantation. Thereby, the selection of variables was based on univariable comparisons (entry criteria $P < 0.05$) and clinical relevance. Values if not otherwise indicated are means $\pm$ SD. The proportional hazard assumption for the Cox models was tested graphically using log–log plots.

Associations between AT and patient/graft survival were flexibly modeled with the use of penalized splines as additive extensions of the adjusted Cox model [12]. The R2BayesX package in the R 2.15.3 statistical software (BayesX - Bayesian Inference in Structured Additive Regression Models, Version 2.1 (07.05.2012), Munich, Germany) was used for these statistical analysis.

Results

During the observational period, 1245 DDRTs were carried out at our center. The median follow-up time was 5.43 years. Sixty-three (5.06%) patients were lost to follow up. The investigated cohort was divided into two groups according to a median AT of 30 min. Recipient and donor demographics as well as the transplant characteristics are shown in Table 1.

Patient and graft survival

Overall, patient survival at 1 and 5 years after DDRT was 95.4% and 87.5%, respectively. Kidney graft survival at 1 and 5 years after DDRT was 91.6% and 79.0%, respectively (Fig. 1).

Causes of graft loss and death

There were 336 graft losses and 196 deaths of recipients after DDRT during the observational period. One hundred and eighty-four patients died with a functioning graft. Reasons for a graft loss were chronic rejection ($n = 129$), recurrent primary disease ($n = 11$), infection ($n = 7$), and vascular problems ($n = 5$). The most common reason for death after DDRT was cardiac failure ($n = 47$) followed by sepsis ($n = 35$) and malignant diseases ($n = 35$). Other causes of death were pulmonary infection ($n = 5$), cerebrovascular accident ($n = 8$), hemorrhage ($n = 5$), liver failure ($n = 5$), mesenteric infarction ($n = 2$), and an accident ($n = 1$).

Stratified for transplant characteristics, AT was a significant predictive factor for long-term survival. Patient and graft survival in the group with an AT >30 min were dramatically lower than in the <30 min AT-group: 85.7% patient survival vs. 89.6% (log-rank $P < 0.0001$) and 76.6% graft survival vs. 80.6% (log-rank $P = 0.027$), respectively (Fig. 2a and b).

The effects of AT on patient and graft survival, displayed by penalized splines, are shown in Fig. 3a and b. The relation of AT with graft survival was almost linear with higher risk for graft loss with increasing AT. The relation with patient survival showed a nonlinear shape with a reduced risk up to approximately 30 min of AT with an increase of risk between >30 and 80 min.

Because of the small number of events, confidence intervals were relatively wide.

Table 1. Characteristics of 1245 deceased donor kidneys and recipients between 2000 and 2010.

Characteristics	*n* = 1245
Recipient BMI kg/m^2 (mean, SD)	23.67 ± 3.74
Recipient age in years (median)	51.02
Recipient male gender (*n*, %)	830 (66.67%)
Prior kidney transplantation (*n*, %)	231 (18.55%)
Cause of renal failure (*n*, %)	
Immune-mediated disease	396 (31.81%)
Diabetes mellitus	316 (25.38%)
Polycystic kidney disease	114 (9.16%)
Others	320 (25.70%)
PRA at NTx (in %, mean, SD)	4.99 ± 16
Donor BMI in kg/m^2 (mean, SD)	24.81 ± 3.52
Donor age in years (median)	45
Donor male gender (*n*, %)	738 (59.28%)
Cause of death (*n*, %)	
Cerebrovascular accident	587 (47.15%)
Trauma	358 (28.76%)
Others	301 (24.17%)
ECD (*n*, %)	308 (24.74%)
Serum creatinine in mg/dl (mean, SD)	0.95 ± 1.37
Serum urea in mg/dl (mean, SD)	33.4 ± 30.6
HLA A mismatches (*n* = recipients with mismatch)	865
HLA B mismatches (*n* = recipients with mismatch)	986
HLA DR mismatches (*n* = recipients with mismatch)	969
Cold ischemia time in hours (mean, SD)	14.53 ± 5.69
Anastomoses time in min (mean, SD)	30.95 ± 9.6
Delayed graft function (*n*, %)	412 (33.09%)
Acute rejection (*n*, %)	181 (14.54%)

ECD, expanded criteria donor.

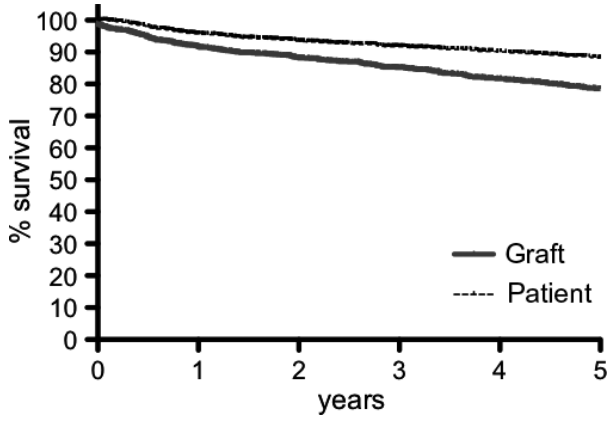

Figure 1 Patient survival after 1 and 5 years was 95.4% and 87.5%; graft survival 91.6% and 79% at the 2 time points. Graft loss was defined as either loss of the organ or patient death with functioning allograft.

Further, univariable analysis for long-term patient survival revealed AT, donor BMI, donor age, hypertension of the donor, the fact that the kidney is from an ECD, recipient gender, recipient age, HLA A mismatch, the occurrence of DGF and receiving induction treatment as significant factors. These results (HR, 95% CI, *P*-values) are displayed in Table 2. Donor BMI, donor age, cerebrovascular accident and hypertension of the donor, ECD, recipient age, retransplantation, the maximal count of PRAs prior to transplantation, mismatches in HLA A, receiving induction treatment, developing DGF, the occurrence of an acute rejection (AR) and AT were univariable significant risk factors for long-term kidney allograft survival (Table 3).

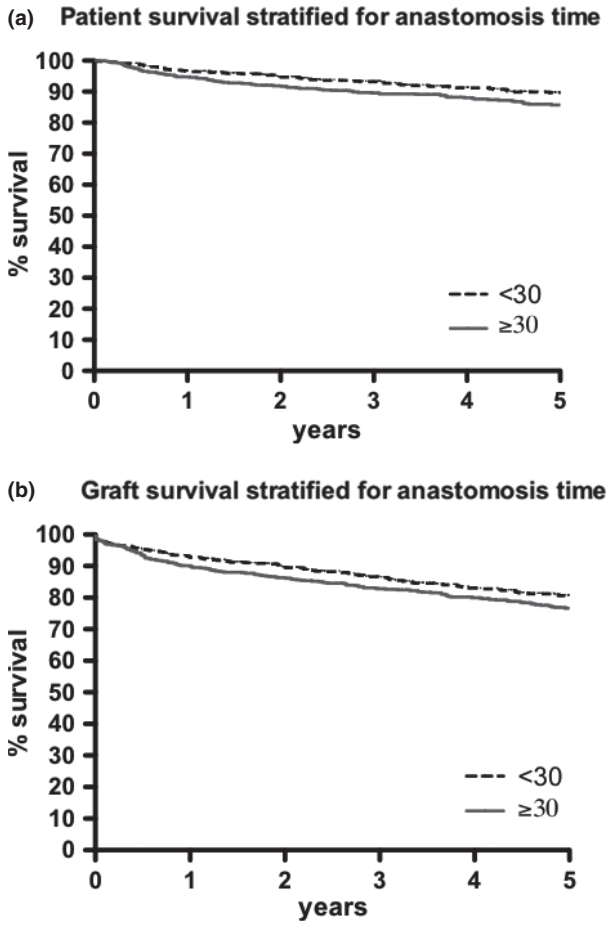

Figure 2 Patient survival stratified for anastomosis time (AT) above 30 min (a): 5-year patient survival of recipients in the group with an AT longer than 30 min was significantly lower, 85.7%, than in the group with an AT less than 30 min, 89.6%; log rank $P < 0.0001$. Graft survival stratified for AT above 30 min (b): 5-year graft survival of deceased donor renal transplantations (DDRTs) in the group with an AT longer than 30 min was significantly lower, 76.6%, than in the group with an AT less than 30 min, 80.6%; log rank $P = 0.027$.

Factors influencing AT

Recipient and donor factors, which could be indirect markers displaying arteriosclerosis, were subanalyzed in

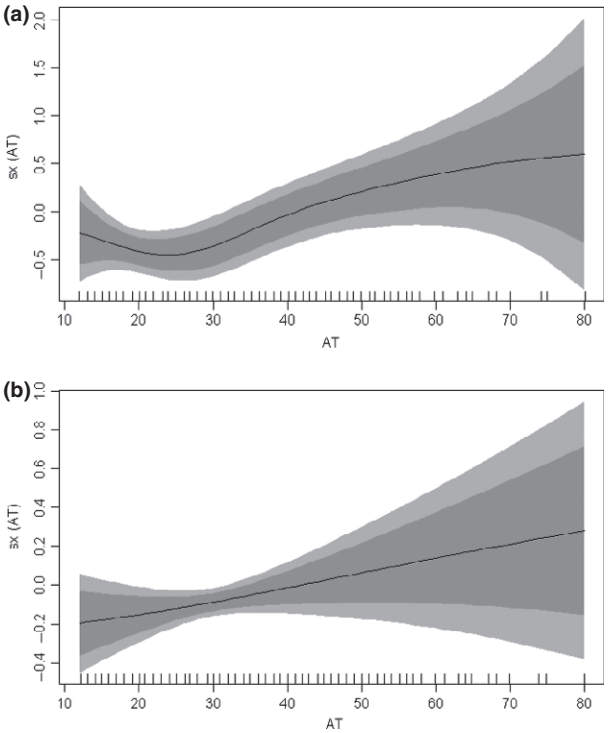

Figure 3 Relationship of anastomosis time (AT) with patient survival in the fully adjusted Cox model, displayed by penalized splines (a): light gray shaded areas indicate 95% confidence limits, dark shaded areas 80% confidence limits, estimated regression coefficients are denoted by sx(AT), a value of 0 equivalents a relative risk of 1, a value of 0.5 a risk of 1.65, a value of −0.5 a risk of 0.61. Relationship of AT with graft survival in the fully adjusted Cox model, displayed by penalized splines (b): light gray shaded areas indicate 95% confidence limits, dark shaded areas 80% confidence limits, estimated regression coefficients are denoted by sx(AT), a value of 0 equivalents a relative risk of 1, a value of 0.4 a risk of 1.49, a value of −0.4 a risk of 0.67.

reference to AT. Univariable analysis revealed that recipient BMI >25 kg/m^2 significantly leads to a longer AT ($P = 0.0004$); 30.39 ± 0.34 min in the group of BMI <25 kg/m^2 vs. 32.32 ± 0.51 min in the recipient group with a BMI >25 kg/m^2. Similarly, donor hypertension resulted in a significantly longer AT of 32.23 ± 0.63 min compared with the AT in the normotensive donor group; 30.71 ± 0.34 min ($P = 0.0152$). Other factors causing longer AT without reaching statistical significance were donor diabetes mellitus (31.83 ± 0.37 min in the diabetes group vs. 30.52 ± 1.59 min; $P = 0.459$), donor BMI (31.29 ± 0.44 min in the BMI-group >25 kg/m^2 vs. 30.90 ± 0.37 min; $P = 0.496$), donor CVA (31.25 ± 0.39 min in the CVA group vs. 30.57 ± 0.40 min; $P = 0.219$), and ECD (31.59 ± 0.55 min in the ECD group vs. 30.74 ± 0.32 min; $P = 0.146$).

Anastomosis time in the donor age group above the median of 45 years was 31.38 ± 0.41 min vs. 30.52 ± 0.38 min in the <45 years donor group; $P = 0.123$. Higher recipient age ended up in a longer AT as well, 31.29 ± 0.39 min vs. 30.61 ± 0.40 ($P = 0.223$) in the recipient age group below the median of 51.02 years.

Renal transplant recipients in which DGF occurred, the duration of AT was significantly longer than in those with an excellent initial kidney function; 32.63 ± 0.54 min in the DGF-group vs. 30.15 ± 0.32 min, $P < 0.0001$.

Multivariable analysis for factors influencing long-term patient and graft survival

Recipient, donor, and transplant factors, which reached level of significance in the univariable analysis, were examined for their independent, predictive values using Cox proportional hazards model; the results are summarized in Table 4 (patient survival) and Table 5 (allograft survival).

Anastomosis time, recipient gender, recipient age, recipient BMI< 18.5 kg/m^2, HLA A mismatches, and developing DGF were independent significant predictors for mortality (Table 4). Donor age, donor hypertension, recipient BMI between <18.5 and 25 kg/m^2, recipient age, retransplantation, mismatches in HLA A, occurrence of DGF, and an episode of AR significantly predict graft loss after DDRT (Table 5). Furthermore, we could figure out a significant interaction of AT with graft loss by the variable retransplantation. When analyzing kidney-first-transplants ($n = 1014$) separately, AT showed a significant effect on graft survival ($P = 0.005$, HR 1.018, 95% CI 1.006–1.031). This impact could not be found in retransplantations ($P = 0.707$, HR 0.995, 95% CI 0.971–1.02).

Discussion

The major issues affecting outcomes after renal transplantation these days are ischemia reperfusion injury (IRI) [13] and chronic graft deterioration, which inevitably is related to IRI. While T-cell mediated graft losses have become scarce, the sequelae of DGF resulting in chronic rejection have to be encountered to improve long-term results, especially as the numbers of ECD kidneys being transplanted are increasing [14]. No pharmacological treatment, except the conditioning of the donor with steroids, has found its way into clinical routine for the treatment and/or prevention of IRI and/or DGF [15]. Further, the unfulfilled need for donor organs forces us to use kidneys for transplantation that may not have been considered therefore a decade ago. Even transplant departments are trying to increase the numbers of living donor kidney transplantations, it is a matter of fact that certain variables cannot be modified (donor age, donor hypertension, donor diabetes, donor arteriosclerosis, reci-

Table 2. Results of the univariable Cox regression analysis to evaluate predictors for patient survival.

Characteristic	Wald	HR	95% CI	*P* value
Donor BMI (kg/m^2)	4.206	1.221	1.009–1.478	**0.040**
Donor gender	0.001	1.005	0.756–1.336	0.974
Donor age (years)	16.084	1.018	1.009–1.027	**<0.0001**
Donor hypertension	5.973	1.517	1.086–2.120	**0.015**
Donor diabetes mellitus	0.251	1.431	0.353–5.809	0.616
Donor CVA	0.510	0.475	0.835–1.472	0.475
ECD	17.772	1.891	1.406–2.543	**<0.0001**
Donor serum creatinine (mg/dl)	0.148	0.969	0.828–1.135	0.700
Donor serum urea (mg/dl)	3.725	1.004	1.000–1.007	0.054
Recipient BMI (kg/m^2)	0.009	1.002	0.963–1.042	*0.924*
Recipient gender	7.094	1.547	1.122–2.134	**0.008**
Recipient age (years)	80.010	1.059	1.046–1.073	**<0.0001**
Time on dialysis (months)	1.293	1.002	0.998–1.006	0.256
Retransplantation	0.426	1.127	0.787–1.612	0.514
CMV mismatch (recipient −/donor +)	1.110	1.201	0.854–1.691	0.292
PRA at Tx (%)	1.632	1.005	0.997–1.013	0.201
PRA max (%)	1.480	1.003	0.998–1.008	0.224
HLA A mm (0)	7.822			**0.020**
HLA A mm (1 mm vs. 0)	3.640	1.412	0.991–2.012	0.056
HLA A mm (2 mm vs. 0)	7.737	1.787	1.187–2.691	**0.005**
HLA B mm (0)	3.947			0.267
HLA B mm (1 mm vs. 0)	0.712	1.192	0.792–1.795	0.399
HLA B mm (2 mm vs. 0)	3.459	1.477	0.979–2.227	0.063
HLA DR mm (0)	2.978			0.226
HLA DR mm (1 mm vs. 0)	0.934	1.212	0.820–1.793	0.334
HLA DR mm (2 mm vs. 0)	2.892	1.436	0.946–2.179	0.089
CIT (hours)	0.022	1.000	1.000–1.001	0.881
AT (min)	13.469	1.025	1.012–1.039	**<0.0001**
Induction treatment	9.536	1.650	1.201–2.268	**0.002**
DGF	29.856	2.191	1.654–2.904	**<0.0001**
AR	2.186	1.302	0.918–1.846	0.139
HCV	6.257	1.923	1.152–3.209	**0.012**
Tx year	0.410	0.982	0.929–1.038	0.522
Tx median (05.06.2005)	1.078	0.838	0.601–1.170	0.299

AT, anastomosis time; CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor. Bold values mark significant parameters.

pient age, and recipient arteriosclerosis) or modifying of them would neither improve outcomes nor increase the organ pool. In contrast, CIT can be drastically reduced by logistic measures and has been shown to have a significant impact on short- and long-term results after kidney transplantation [16–18].

We herein demonstrate for the first time the negative impact of increased AT on the 5-year outcome in a DDRT-cohort. Our analysis revealed that AT >30 min significantly impacts long-term graft outcome and leads to inferior patient survival.

The overall 5-year graft survival of 79% is comparable and even better to what has been published earlier [19]. Improvements in immunosuppression, management of infections, and comorbidities have helped to sustain and even improve the results [20,21] while the number of organs from ECDs are increasing, a factor that is related to inferior outcomes after renal transplantation [14,22,23]. However, not much room for improvements in these aspects is left. Certainly, immune tolerance leading to independence of immunosuppression would cause a dramatic change, still, factors primarily related to the innate immune system inevitably related to the transplant procedure itself are of eminent relevance, as has been shown in animal models [24]. Among them, the arousal of the immune system in brain dead donors, the necessity of interrupting the blood supply and the sequelae of reperfusion. In particular, in brain dead donor renal transplantation, the kidney is retrieved after cold perfusion of the donor and stored at 4° until vascular anastomosis is begun. At the moment, the preferred methods of storage to improve transplant outcomes, static cold storage, or hypothermic machine perfusion remain controversial. A systematic review and

Table 3. Results of the univariable Cox regression analysis to evaluate predictors for graft survival.

Characteristic	Wald	HR	95% CI	*P* value
Donor BMI (kg/m^2)	5.606	1.196	1.031–1.387	**0.018**
Donor gender	0.631	0.916	0.738–1.137	0.427
Donor age (years)	33.887	1.020	1.013–1.027	**<0.0001**
Donor hypertension	26.818	1.938	1.509–2.490	**<0.0001**
Donor diabetes mellitus	0.399	1.446	0.461–4.537	0.527
Donor CVA	6.934	1.342	1.078–1.671	**0.008**
ECD	28.732	1.874	1.489–2.358	**<0.0001**
Donor serum creatinine (mg/dl)	0.247	0.972	0.871–1.086	0.619
Donor serum urea (mg/dl)	3.608	1.003	1.000–1.006	0.057
Recipient BMI (kg/m^2)	0.586	0.988	0.959–1.019	0.444
Recipient gender	1.367	0.872	0.692–1.097	0.242
Recipient age (years)	20.185	1.019	1.011–1.028	**<0.0001**
Time on dialysis (months)	1.551	1.002	0.999–1.005	0.213
Retransplantation	15.218	1.650	1.283–2.123	**<0.0001**
CMV mismatch (recipient −/donor +)	0.004	1.009	0.768–1.325	0.949
PRA at Tx (%)	2.574	1.005	0.999–1.011	0.109
PRA max (%)	4.341	1.004	1.000–1.008	**0.037**
HLA A mm (0)	7.110			**0.029**
HLA A mm (1 mm vs. 0)	4.217	1.316	1.013–1.711	**0.040**
HLA A mm (2 mm vs. 0)	6.605	1.506	1.102–2.058	**0.010**
HLA B mm (0)	1.823			0.610
HLA B mm (1 mm vs. 0)	1.211	1.184	0.876–1.601	0.271
HLA B mm (2 mm vs. 0)	1.758	1.234	0.905–1.682	0.185
HLA DR mm (0)	3.810			0.149
HLA DR mm (1 mm vs. 0)	1.183	1.177	0.878–1.578	0.277
HLA DR mm (2 mm vs. 0)	3.716	1.363	0.995–1.878	0.054
CIT (hours)	1.401	1.000	0.999–1.000	0.237
AT (min)	4.542	1.012	1.001–1.023	**0.033**
Induction treatment	9.829	1.460	1.152–1.849	**0.002**
DGF	43.568	2.069	1.667. 2.567	**<0.0001**
AR	14.297	1.640	1.269–2.120	**<0.0001**
HCV	15.179	2.162	1.467–3.186	**<0.0001**
Tx year	0.90	0.994	0.953–1.036	0.765
Tx median (05.06.2005)	0.850	0.888	0.690–1.143	0.356

AT, anastomosis time; CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor. Bold values mark significant parameters.

meta-analysis suggests that hypothermic machine perfusion reduces DGF compared with static cold storage and did not result in a different long-term renal function or patient survival [25].

The surgical AT, equivalent to warm ischemia time, was pointed out as a very important significant factor influencing kidney function and patient survival after DDRT in our investigation. According to the analysis stratified for AT, it was shown that the time for the vascular anastomosis was significantly longer in recipients who developed DGF, which is a tremendous influencing factor affecting long-term outcome.

Beside one clinical publication from Marzouk *et al.* [10] and an outcome report of experimental research in rats in form of a medline search [26], nothing can be found in the literature concerning the impact of vascular AT on kidney transplant outcomes in the setting of deceased donor kidney transplantation. An urological nontransplant study, examining the effect of warm ischemia time in patients undergoing partial nephrectomy of a solitary kidney, showed that each minute of warm ischemia counts, because it was associated with a 6% increased risk of acute kidney injury and 4% increased risk of new onset end stage renal disease [27]. During AT, a continuous global warming of the kidney takes place unavoidable. Reinstitution of blood flow in the ischemically damaged kidneys will activate a complex sequence of events that sustain renal injury and play a pivotal role for the initial allograft function [28]. Explanations for the interaction between AT and the outcome after DDRT may be immune system related. Activation of the innate immune response initiated during organ recovery and IRI might be a potential mechanism that triggers such processes and contributes to DGF or graft dysfunction [29]. Pathogenesis of IRI is complex and even

Table 4. Results of the multivariable Cox regression analysis to evaluate independent predictors for patient long-term survival.

Characteristic	Wald	HR	95% CI	*P* value
Donor BMI 18.5–25 kg/m^2	3.448			0.486
don BMI <18.5 kg/m^2	0.802	0.514	0.120–2.206	0.371
don BMI 25.01–30 kg/m^2	1.225	0.815	0.567–1.171	0.268
don BMI 30.01–35 kg/m^2	0.873	1.432	0.674–3.041	0.350
don BMI >35 kg/m^2	0.005	1.041	0.321–3.376	0.946
Donor age (years)	0.076	1.002	0.987–1.017	0.783
Donor hypertension	0.180	1.096	0.718–1.674	0.672
ECD	0.002	1.011	0.573–1.784	0.969
Recipient BMI 18.5–25 kg/m^2	9.228			0.056
rec BMI <18.5 kg/m^2	7.087	2.466	1.269–4.792	**0.008**
rec BMI 25.01–30 kg/m^2	0.936	0.837	0.584–1.200	0.333
rec BMI 30.01–35 kg/m^2	0.377	0.794	0.379–1.660	0.539
rec BMI >35 kg/m^2	Too few cases	Too few cases	Too few cases	Too few cases
Recipient gender	7.047	1.673	1.144–2.445	**0.008**
Recipient age (years)	53.911	1.061	1.044–1.078	**<0.0001**
HLA A mm (0)	7.898			**0.019**
HLA A mm (1 mm vs. 0)	4.478	1.558	1.033–2.350	**0.034**
HLA A mm (2 mm vs. 0)	7.702	1.943	1.215–3.105	**0.006**
AT (min)	7.666	1.021	1.006–1.037	**0.006**
Induction treatment	0.777	1.178	0.819–1.694	0.378
DGF	7.055	1.560	1.124–2.166	**0.008**
HCV	9.427	2.565	1.406–4.681	**0.002**

AT, anastomosis time; DGF, delayed graft function; ECD, expanded criteria donor. Bold values mark significant parameters.

Table 5. Results of the multivariable Cox regression analysis to evaluate independent predictors for long-term graft survival.

Characteristic	Wald	HR	95% CI	*P* value
Donor BMI 18.5–25 kg/m^2	3.371			0.498
don BMI <18.5 kg/m^2	0.010	1.055	0.374–2.979	0.919
don BMI 25.01–30 kg/m^2	1.880	0.819	0.617–1.089	0.170
don BMI 30.01–35 kg/m^2	0.001	1.011	0.504–2.026	0.976
don BMI >35 kg/m^2	0.941	1.516	0.654–3.516	0.332
Donor age (years)	3.943	1.012	1.000–1.024	**0.047**
Donor hypertension	4.321	1.407	1.020–1.942	**0.038**
Donor CVA	3.473	1.274	0.988–1.644	0.062
ECD	0.087	1.065	0.700–1.622	0.768
Recipient BMI 18.5–25 kg/m^2	11.633			**0.020**
rec BMI <18.5 kg/m^2	10.315	2.076	1.329–3.242	**0.001**
rec BMI 25.01–30 kg/m^2	0.120	0.950	0.711–1.269	0.729
rec BMI 30.01–35 kg/m^2	0.358	0.837	0.467–1.500	0.550
rec BMI >35 kg/m^2	Too few cases	Too few cases	Too few cases	Too few cases
Recipient age (years)	10.706	1.018	1.007–1.029	**0.001**
Retransplantation	11.100	1.773	1.266–2.483	**0.001**
PRA max (%)	1.245	0.997	0.991–1.002	0.265
HLA A mm (0)	8.481			**0.014**
HLA A mm (1 mm vs. 0)	7.352	1.544	1.128–2.114	**0.007**
HLA A mm (2 mm vs. 0)	6.249	1.606	1.108–2.329	**0.012**
AT (min)	1.337	1.007	0.995–1.020	0.247
Induction treatment	2.761	1.268	0.955–1.677	0.097
DGF	12.523	1.615	1.238–2.106	**<0.0001**
AR	7.632	1.532	1.132–2.073	**0.006**
HCV	16.202	2.649	1.648–4.257	**<0.0001**

AT, anastomosis time; DGF, delayed graft function; ECD, expanded criteria donor; PRA, panel of reactive antibodies. Bold values mark significant parameters.

nowadays, understood incompletely, although a local activation of the complement system and its critical influence on the development of IRI could be shown convincingly via experimental animal studies [30,31]. Despite the important approaches that have been made in understanding the mechanisms underlying IRI in research models [32], little progress has been made in therapeutic options during the last years. If DGF occurs after DDRT, hemodialysis is still the supportive therapy of choice and no effective treatment is available in the daily transplant routine.

Transplanting older patients using marginal organs leads to high sophisticated anastomotic procedures, due to the arteriosclerotic plaques that may lead to a significant longer AT. Beside a recipient BMI >25 kg/m^2, our investigations pointed donor hypertension out as the second significant factor resulting in an AT longer than 30 min. These results have to be considered especially under the aspect that the number of marginal organs is increasing and the transplanted population is aging. During the last two decades, in which renal transplantation became the therapy to strive for end-stage renal disease, the demand has overtaken the supply of deceased organ donors and led to the consideration of alternative strategies to provide more transplantable kidneys. An increasing number of donors with comorbidities, for example, hypertension and diabetes mellitus or deceased due to stroke, have been used since the beginning of the 1990s [33]. The challenge is now to improve the outcome, implying appropriate transplantation strategies during all transplant phases, including reduction of cold and warm ischemia time, recipient selection, and adaptation of immunosuppressive drug regimens.

If there is no option to combat the damage through IRI with new immunosuppressive protocols, the challenging question is how to shorten the AT? We are aware that the presence of multiple vessel, the quality of the Carrel aortic patch, whether it was used or cutoff, may influence AT and optimization of arterial anastomosis, especially in kidneys from older, obese, hypertensive, or diabetic donors. Another aggravating factor, concerning the recipient, could be the fact that a retransplantation has to be performed in the same side as the first kidney. The means to achieve shorter AT involve better vessel exposure, an experienced surgeon and suturing training devices to improve techniques as well as the awareness that AT is important.

Finally, to provide a clinical tool for predicting the outcome after DDRT, risk quantification scores have been developed and published already. Watson *et al.* [34] evolved an index including donor age, history of donor hypertension, increased donor body weight, longer hospital stay before death, and use of adrenaline as the most important significant factors associated with poorer outcomes up to 3 years post-transplant. Another index, developed by Rao *et al.* [35], provides an useful decision-making tool at the time of deceased donor kidney offer. Based on our results, we suggest to include AT into these scores.

In summary, prevention of renal allograft damage starts with interventions that occur surrounding the organ procurement of deceased organ donors. Long AT is correlated with an inferior long-term survival. We suggest that AT, as one of the most important modifiable transplant factors, should be considered as a major risk factor for long-term outcome after DDRT and thus kept short.

Authorship

AW: research design, data collection, and writing of the paper. RO: data collection. BC: data collection. SW: data collection; HU: data analysis, and revision of the paper. CB: data collection. SS: advisory activity. JP and RÖ: research design, advisory activity, revised, and approved the article.

Funding

No funding sources were given to the authors.

Acknowledgements

We kindly thank Wolfgang Bichler, Hermann Fetz, and Paul Schobel for their assistance in data acquisition.

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