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Rapid adaptation of the intrarenal resistance index after living donor kidney transplantation

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Abstract

Background. Limited data exist concerning changes of renal perfusion directly after kidney transplantation. Colour-coded duplex sonography is the accepted method to assess kidney perfusion after transplantation. A widely used, although unspecific, Doppler parameter is the intrarenal resistance index (RI). The aim of this study was to clarify the influence of different patient- and procedure-related factors on RI before and immediately after living kidney transplantation.

Methods. In a prospective study, 80 living kidney transplantation donor–recipient pairs were included. RI was measured in the donor 1 to 3 days before nephrectomy and in the recipient during the first hour after transplantation to examine the influence of age, heart rate, duration of cold and warm ischaemia time and immunosuppressive medications.

Results. Mean RI did not differ between donors and recipients. RI correlated with age, both in donors ($r = 0.58$, $P < 0.001$) and recipients ($r = 0.39$, $P < 0.001$). In recipients, 10 or more years younger than their donors ($n = 24$), an average decrease of 0.05 in RI compared to the donors' value was observed ($P = 0.01$). Heart rate, cold and warm ischaemia time and immunosuppressive medications had no influence on the recipient RI. In patients with delayed graft function, a significant increase in RI within 14 days was observed. However, the initial RI was not predictive of graft function.

Conclusions. The transplanted kidney seems to be able to adjust its RI within a short time despite several potential harmful factors that can occur during the transplantation.

Keywords: Doppler sonography; living donor kidney transplantation; vascular resistance

Introduction

Kidney transplantation has become the optimal treatment for end-stage renal disease. Colour-coded duplex sonography is the accepted first-line imaging tool after kidney transplantation which enables the detection of morphological pathologies as well as alterations in perfusion [1–3]. An important and widely used variable to assess the overall perfusion of the renal graft is the intrarenal resistance index (RI), which reflects intragraft vascular resistance [4]. However, single measurements are of limited value due to a large intrarenal variability [5]. Nevertheless, in a large cohort, Radermacher *et al.* showed that an increased RI after transplantation is associated with poor subsequent allograft performance and death [6]. Various factors are known to influence RI, such as acute or chronic rejection, ischaemic tubular necrosis, calcineurin inhibitor toxicity or renal artery stenosis and vein thrombosis [1,2,4]. Apart from transplant-related factors, vascular resistance can also be influenced by extrarenal and systemic factors (e.g. heart rate, arterial stiffness, compression of the graft). In kidney transplant recipients, examined after a mean of 7 years following transplantation, a significant correlation of the RI with age, cardiovascular risk factors as well as with atherosclerotic vessel alterations has been described [7].

Despite the importance of measurement of the RI after renal transplantation to detect acute perfusion problems, data on transplant related changes are limited. Only three small studies have investigated changes in sonographic variables before and after kidney transplantation and found no significant differences [3,8,9].

Living donor kidney transplantation opens the unique possibility of studying the influence of donor-, transplantation- and recipient-related factors on RI by studying kidneys in the donors before transplantation and in the recipients after transplantation.

The aim of this study was to clarify the influence of different factors such as age, heart rate, cold and warm ischaemia time and immunosuppressive medications on RI in the very early post-transplant period. This investigation might generate new insights into the response of the transplanted kidney to potential harmful factors during the

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transplantation procedure and facilitate the interpretation of RI in the immediate postoperative period.

Subjects and methods

In a prospective study performed at a tertiary hospital, all kidney living donor–recipient pairs were considered for inclusion from May 2004 to May 2007. The study was approved by the local ethics committee. Donors and recipients gave written informed consent. Donors were examined 1–3 days before nephrectomy and recipients postoperatively within the first hour after transfer to the intensive care unit. Colour-coded duplex sonography was performed by two experienced investigators (CT, MA) using a HDI 5000 duplex device (Philips, Best, the Netherlands) with a curved 7–4 MHz transducer following a standardized protocol [3]. Implicating the variability of Doppler measurements, RI was calculated as the mean of two Doppler waveform tracings obtained from the superior, middle and inferior regions of the kidney, resulting in one RI value per kidney [5]. The RI was calculated as follows: [peak systolic velocity – end-diastolic velocity]/peak systolic velocity [2,5]. Ischaemia time was extracted from the operation protocol. For immunological low-risk patients, initial immunosuppression consisted of a combination of calcineurin-inhibitor (in most cases tacrolimus), mycophenolate mofetil or mycophenolic acid sodium (in rare cases azathioprine) and steroids and basiliximab (Day 0 and Day 4). For immunological high-risk patients, the immunosuppression consisted of an induction therapy with antilymphocyte antibodies (ATG-Fresenius®), intravenous immunoglobulin and a maintenance immunosuppression of tacrolimus, mycophenolate mofetil and steroids. Immunosuppressive therapy was started about 12 h before transplantation.

In patients with delayed graft function (DGF) or other clinical events (e.g. decrease in diuresis, arterial hypertension) duplex sonography with RI measurements was repeated at the discretion of the clinician. RI values within the first 14 postoperative days were collected and compared with those immediately after transplant.

Statistical analysis was performed with SPSS, version 15 (SPSS Inc., Chicago, IL, USA). Correlations of RI with donors, recipients, age, heart rate, time of cold and warm ischaemia and groups of immunosuppressive medication were tested using a multivariate linear regression model. Group comparisons were performed by Wilcoxon signed-rank tests. Descriptive values are given as mean \pm standard deviation; range values are given if appropriate.

Results

Eighty of 83 living-donor/recipient pairs were included in the study. Three pairs did not give informed consent. Baseline characteristics are presented in Table 1. The mean age in donors was 5 years higher than in recipients ($P = 0.07$). Sixty-eight percent of all donors were female, whereas 73% of all recipients were male. The mean heart rate was normal,

Table 1. Study population clinical data, $n = 80$

	Donors	Recipients
Age (years)	52.2 \pm 10.6 (28–71)	47.5 \pm 13.3 (18–70)
Sex (M/W)	25/55	59/21
Heart rate (bpm)	66.3 \pm 11.7 (44–106)	84.7 \pm 14.5 (54–137) ^a
Resistance index	0.63 \pm 0.1 (0.52–0.75)	0.62 \pm 0.1 (0.39–0.86) ^a
Creatinine (μ mol/L)	65.3 \pm 13.0 (40–98)	168.4 \pm 103.1 (58–586) ^b
Creatinine clearance (mL/min) ^c	104.8 \pm 30.0 (58–105)	57.1 \pm 22.3 (9–121) ^b
Proteine/creatinine ratio (mg/mmol)	<11	116.0 \pm 276.1 (13–1259) ^b

Values expressed as mean \pm SD (range).

^aDirectly postoperative.

^b14 days post-transplant.

^cCockcroft–Gault formula.

but 18 beats per minute higher in recipients than in donors ($P < 0.001$). In all but two recipients, the 1-h postoperative period was uneventful. In the remaining two patients, severe transplant ischaemia was detected by duplex sonography, followed by an immediate and successful reoperation.

Overall, the difference in mean RI between donors and recipients did not reach statistical significance (mean difference -0.013 ; $P = 0.06$). RI significantly correlated with age both in donors ($r = 0.58$, $P < 0.001$) and recipients ($r = 0.39$, $P < 0.001$) (Figure 1), whereas the direct correlation between donor RI and recipient RI showed a much weaker correlation ($r = 0.22$; $P = 0.047$). Perioperative differences in RI were dependent on the age difference between donors and recipients ($P = 0.019$). In recipients more than 10 years younger than their donors ($n = 24$), a significant decrease in RI compared to the donors' value was observed (Figure 2; mean difference -0.05 , $P = 0.01$). RI between donors and recipients was not different when recipients were within ± 10 years ($n = 43$, $P = 0.88$) or more than 10 years older ($n = 13$, $P = 0.55$) than their respective donors. There was no correlation between heart rate and RI in donors ($P = 0.31$); in recipients only a tendency for a weak correlation was found ($r = 0.22$; $P = 0.05$). In the multivariate regression model age of the recipient, the age difference and heart rate difference between recipient and donor were better determinants of the RI after transplantation than age, heart rate and RI of the donor. Cold and warm ischaemia times, as well as different immunosuppressive regimes revealed no correlation with RI.

Overall, creatinine level decreased significantly to 164 \pm 95 μ mol/L, mean creatinine clearance was 57.1 \pm 22.3 mL/min and proteine/creatinine ratio was 116.0 \pm 276.1 mg/mmol after 14 days (Table 1).

DGF occurred in eight patients (10%). However, RI immediately after transplantation was not different comparing patients with DGF and those with normal renal function ($n = 72$; RI 0.61 and $P = 0.053$). During the first 14 days, RI of patients with DGF significantly rose by 0.10 (from 0.66 to 0.76; $P = 0.025$). In 37 patients with uneventful clinical course, RI slightly rose by 0.05 (from 0.61 to 0.66, $P < 0.001$) but remained significantly lower than in patients with DGF (0.66 versus 0.76, $P < 0.001$).

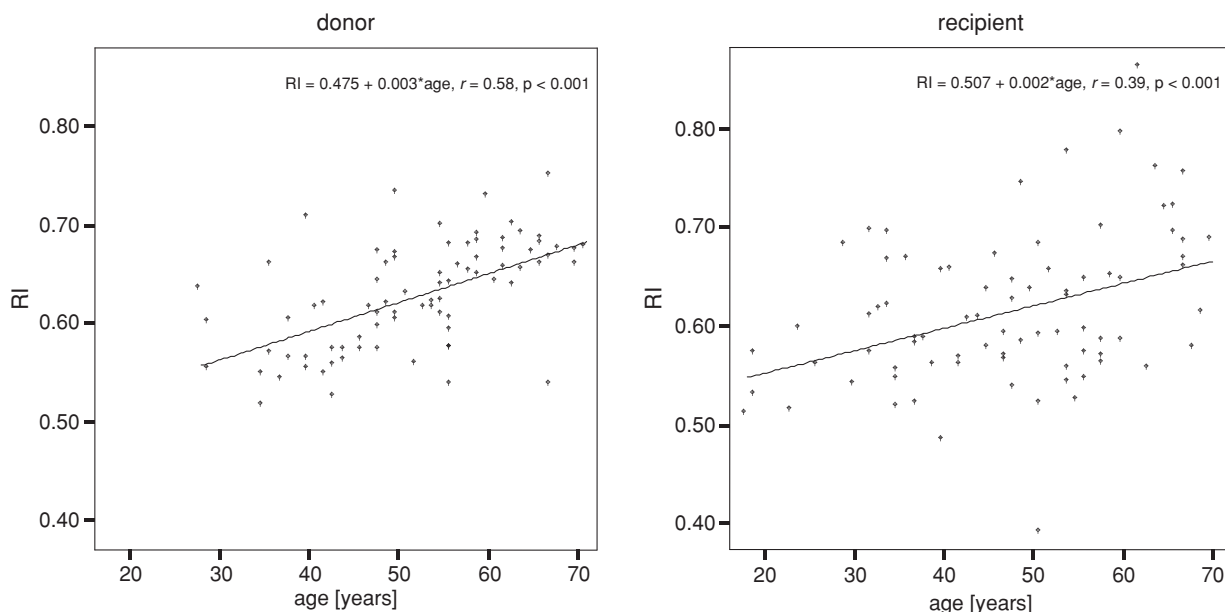


Fig. 1. Correlation of the intrarenal resistance index (RI) in donors and recipients with age (years).

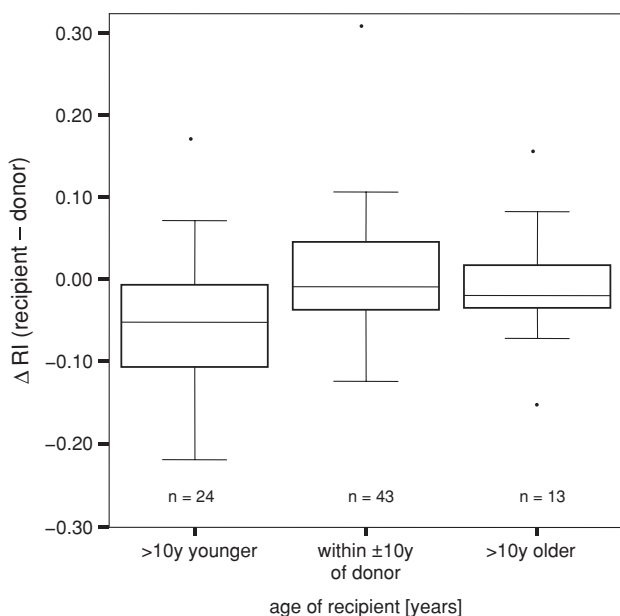


Fig. 2. Box plot showing difference of the intrarenal resistance index (Δ RI) from recipient to donor against age difference between recipients and donors.

Discussion

We report here the largest study investigating RI between living kidney donors and their cohort of transplant recipients.

Intrarenal RI reflecting vascular resistance is known to be very susceptible to changing conditions. In native kidneys, a significant response to vasodilatory agents was shown within a few minutes after application [10]. Immediate changes in RI have also been reported in transplanted

kidneys following operative revision of a renal artery or vein stenosis [11]. Hence, it was expected that an intervention involving nephrectomy, warm and cold ischaemia, reimplantation with hyperaemia and confrontation with potentially vasoconstrictive immunosuppressive drugs would induce major changes in RI.

Previous data on this topic were inconclusive and limited by small numbers of patients [3,8,9]. Isiklar *et al.* reported on 12 donor–recipient pairs and described a non-significant increase in RI on the first postoperative day [8]. Recently, 22 kidney donors and their recipients were examined; in this study, a non-significant initial decrease in RI from 0.65 to 0.60 was observed [3].

Despite the severe stress on the transplanted organ, mean RI did not differ between the donors and recipients even in our substantially larger population. Keeping in mind the theoretically anticipated change in RI, these findings suggest that the transplanted kidney has the capacity to recover from multiple potentially noxious factors within a short time. We additionally observed a significant decrease in RI in recipients, who were >10 years younger than their donors; this was likely due to a rapid adaptation of vascular resistance in the recipient environment. Surprisingly, the RI of the transplanted kidney significantly correlates with the recipients’ age after implantation into the recipients’ body, a further indication for the exquisite ability of the organ to recover from the peritransplant stress and equilibrate to the physiological conditions in the recipient’s body.

In donors, a remarkable correlation of increasing RI with age was observed. This supports the findings by Keogan [5], who also reported a significant correlation of RI with age in 58 healthy subjects, who were on average a decade younger than in our study.

In a standardized setting of living donor kidney transplantation, the immediate postoperative mean RI was within normal limits. As demonstrated by the absence of a

significant RI difference between patients with DGF and the rest of the study population, it seems that early transplant function cannot be predicted by measuring RI. Moreover, a moderate increase of RI (within normal limits) was observed in a subpopulation of 37 patients with normal graft function. This further documents the inability of RI measurements to accurately predict renal function post-transplantation. However, mean RI in patients with DGF increased significantly to pathological values (mean RI 0.76) compared to baseline. RI also increased in a subpopulation of 37 patients with normal graft function, but remained within normal levels (mean RI 0.66).

Our data support the idea that following kidney transplantation from a living donor, graft perfusion as reflected by RI remains stable and within normal limits. While an immediate postoperative determination of RI is not predictive of early transplant function, the intrarenal resistance rises within a few days from normal to pathological levels when DGF is present.

Our observations may eventually allow a better understanding of intrarenal resistance during the very early post-transplantation period; however, the long-term significance of RI remains an open question. Whether this knowledge will translate into a reduction of early postoperative vascular failure has to be evaluated in further studies.

In conclusion, we were able to document that RI is stable following kidney transplantation from living donors, suggesting an unexpected ability of the transplanted organ to re-establish its vascular resistance within 1 h following transplantation despite the presence of multiple, potentially influential factors. Furthermore, older healthy kidneys have the potential to adapt to the recipients' circulation when transplanted to considerably younger patients.

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Conflict of interest statement. None declared.

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