Chapter six
Renal hemodynamic adaptation six years after living kidney donation Chapter six...
Prediction of kidney function and renal adaptation six years after living kidney donation

Mieneke Rook, Hilde Tent, Charlotte Vrijman, Sijbrand Hofker, Rutger Ploeg, Jaap Homan van der Heide, Willem van Son and Gerjan Navis

Abstract

Over the last decades, mean age of the population of living kidney donors increased, reflecting the need to expand the donor pool. In our centre, mean donor age increased from 40 years in the eighties to 50 years nowadays. Previously, we found older donors to be at increased risk for post-donation renal function impairment, defined as a GFR <60 ml/min/1.73 m² (CKD stage III) early after donation. At that time, post-donation renal reserve capacity was lower in older donors as well. It is unknown whether this has consequences for long-term donor renal function in older donors.

In our centre, GFR (iothalamate), effective renal plasma flow (ERPF) and filtration fraction (FF; GFR / ERPF * 100) are measured 4 months before and 2 months after donation. 55 donors (mean age at donation 47±10) who underwent donor nephrectomy in our centre in 2000-2002 were invited for long-term GFR assessment. 37 donors consented; there was no difference in age, BMI or short-term renal function in donors available versus lost to follow-up. Mean follow-up was 6.0±0.6 yrs. Data were analysed by break-up at median age at follow-up, obtaining two groups with a mean age 46±9 (range 27-55) and 60±5 (range 55-77) years, respectively. Finally, we analysed long-term follow-up in donors with post-donation GFR ≤60 ml/min/1.73 m² (CKD stage III).

An adaptive rise in single-kidney GFR was similarly present in both older and younger donors at 6 years. In both age-groups FF was stable on follow-up, so the long-term rise in GFR reflected a rise in perfusion rather than glomerular hypertension. Donors with renal function impairment at two months after donation (n=7) displayed a rise in GFR over six years’ time of 14±5 ml/min; this exceeded the mean rise of 8±8 ml/min in donors with early post-donation GFR above 60 ml/min/1.73 m² (p≤0.05).

Not only in younger but also older kidney donors, the long-term adaptive response to nephrectomy apparently overcomes age-related renal function decline. Our data support current practice of accepting older donors, but careful screening and monitoring remains warranted.
Introduction

Kidney transplantation from a living kidney donor is the preferred treatment for end stage renal disease. So far, long-term donor outcome has been good to excellent [1-4]. Over the past decades however, criteria for living kidney donation have become less strict, reflecting the need to expand the donor pool. In our centre for instance, mean donor age increased from 40 years in the eighties to above 50 nowadays. Other centres, too, have become less reluctant in accepting elderly donors [5]. The consequences of this change in practice for long-term donor outcome are not yet clear.

In healthy subjects, renal function gradually declines with age [6], so older kidney donors have a lower pre-donation glomerular filtration rate (GFR). Accordingly, GFR is lower early and on the medium long-term after donation [7,8]. Furthermore, we found that early post-donation renal reserve capacity –tested by low-dose dopamine infusion—was lower in older donors as compared to younger donors [Rook et al.; currently under review], suggesting that the adaptive capacity of the remaining kidney is age-dependently compromised. Whether this has consequences for long-term donor renal outcome, however, has not been established. After unilateral nephrectomy, the adaptive and compensatory responses in the remaining kidney are most pronounced in the early phase [9-11] but continue over an extended period of time, that is, at least one year after nephrectomy [12]. These responses include not only a renal hemodynamic component (i.e. vasodilation), but also renal growth. The latter has been shown to be gender- and age-dependent, with less renal growth in older subjects and women [9,13].

It is important to make an adequate pre-donation predictive assessment of long-term renal function. In our centre, detailed renal hemodynamic assessment is available before and early after donor nephrectomy. For our current study, we analysed whether long-term adaptive capacity could be predicted from pre-donation donor characteristics and renal hemodynamics, as well as from the early adaptive response after donation. Since we previously found that older age was associated with a worse post-donation renal function [7] and lower renal hemodynamic reserve early after donation [Rook et al., currently under review], we hypothesized that long-term adaptation of renal hemodynamics after donor nephrectomy would similarly lag behind in older donors. Finally, in follow-up of our previous analyses, we investigated whether long-term renal hemodynamic adaptation was impaired in donors in whom early post-donation GFR was below 60 ml/min/1.73 m².

Methods

For our current study, we invited all 55 donors (mean age at donation 47±12 years; mean BMI 25.7±4.4; 27% male) who completed the screening protocol with subsequent donor nephrectomy and short-term follow-up in our centre in the period 2000-2002. 37 donors consented (67%); there was no difference in age at donation, BMI at donation or short-term post-donation renal function in donors available vs. lost to follow-up. Mean follow-up was 6±0.6 years after donation. Blood pressure was measured non-invasively during the renal function measurements by Dinamap® (Critikon, Tampa, FL, USA) in a seating position, after at least ten minutes of rest. Pre-donation blood pressure was either normotensive or prehypertensive according to the JNC VII guidelines (≤140 systolic and ≤90 diastolic)
### A. Pre-donation characteristics

<table>
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<th>Total (n=37)</th>
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<th>Age &gt; median</th>
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<td>40±8</td>
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<td>Male / female ratio</td>
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<td>6-Dec</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>92±7</td>
<td>90±6</td>
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<tr>
<td>Serum creatinine (μmol/l)</td>
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<td>92±9</td>
<td>90±8</td>
</tr>
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<td>GFR (ml/min/1.73 m²)</td>
<td>105±12</td>
<td>107±13</td>
<td>102±10</td>
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<td>ERPF (ml/min/1.73 m²)</td>
<td>402±61</td>
<td>410±71</td>
<td>394±50</td>
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### B. Early after donation

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<td>Body mass index (kg/m²)</td>
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<td>25.0±3.3</td>
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<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Serum creatinine (μmol/l)</td>
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<td>115±10i</td>
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<td>GFR (ml/min/1.73 m²)</td>
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<td>70±7**</td>
<td>64±7**</td>
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<td>ERPF (ml/min/1.73 m²)</td>
<td>262±36**</td>
<td>268±40**</td>
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### C. Long-term after donation

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<td>Body mass index (kg/m²)</td>
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<td>27.6±6.0</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>96±8i</td>
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<td>99±8i</td>
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<tr>
<td>Serum creatinine (μmol/l)</td>
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<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>74±8**</td>
<td>76±8**</td>
<td>72±8**</td>
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<td>ERPF (ml/min/1.73 m²)</td>
<td>287±40**</td>
<td>291±41**</td>
<td>281±40**</td>
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**Table 1. Donor characteristics for break-up by median age.**

The population is split-up according to age below or above the median at follow-up, i.e. 55 years. Differences between both groups are tested by ANOVA for continuous variables or χ² for gender. Abbreviations: n/a, not applicable (differ by default); NS: not significant. * Paired t-test versus pre-donation p≤0.05. ** Paired t-test long-term versus short-term after donation or short-term versus pre-donation p≤0.001.
or well regulated with a maximum of one antihypertensive drug (one donor). Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. BMI was calculated (weight / length²) before and after donation. Procedures were conducted in accordance with the Helsinki declaration and all donors provided written informed consent.

Renal hemodynamic measurements

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were routinely measured 4 months before and 2 months after donation, as described below. Measurements are performed by constant infusion of low-dose radio-labelled tracers iothalamate (GFR) and hippuran (ERPF).

Subjects were in a quiet room in a seated position. After drawing a blank blood sample, the priming solution containing 0.04 ml/kg body weight of the infusion solution (0.04 MBq of ¹²⁵I-iodohippuran and 0.03 MBq of ¹³¹I-iodohippuran per ml saline) plus an extra of 0.6 MBq of ¹²⁵I-iodohippuran was given, followed by a constant infusion at 12 ml/h. To attain stable plasma concentrations of both tracers, a 2 hour stabilization period followed, after which measurements started. Clearances were measured over the next 2 hours and calculated as (U*V)/P and (I*V)/P, respectively. U*V represents the urinary excretion of the tracer, I*V represents the infusion rate of the tracer and P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of ¹²⁵I-iodohippuran with the ratio of the plasma and urinary clearance of ¹³¹I-iodohippuran. The day-to-day variability for GFR is 2.5%.

Statistical analysis

Data are presented as mean ± standard deviation, unless stated otherwise. Correlations were analysed by univariate analysis (Pearson). Analyses were made between two age-groups of equal size, obtained by break-up at median age at follow-up. Differences were analysed by t-tests and analysis of variance (ANOVA) followed by post-hoc analysis. Statistical analyses were performed by using SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA) and data were plotted in GraphPad Prism version 4.03 for Windows (GraphPad Software, San Diego, CA, USA). A p-value equal to or less than 0.05 was considered statistically significant.

Results

Thirty-seven donors were available for follow-up hemodynamic measurements. There were no baseline differences between donors with or without 6 years post-donation renal hemodynamics assessment. Table 1 shows baseline donor
characteristics as well as characteristics short-term and long-term after donation, with a break-up according to median age. Mean age at follow-up was 53±10 years, 24% male, with a BMI at follow-up of 27±4.7 kg/m². Mean arterial pressure was significantly higher in older donors before as well as long-term after donation. Early after donation, the difference in mean arterial pressure was not statistically significant between younger and older donors.

Renal hemodynamics

Table 2 shows renal hemodynamic measurements before and after donor nephrectomy, for short-term (two months) as well as long-term (six years) follow-up for the population as a whole. Pre-donation GFR and ERPF are provided as single kidney values for easy interpretation of post-donation adaptation. It shows that early after donation, both GFR and ERPF had already increased considerably, by +29% and +31%, respectively (both p≤0.001). On long-term, a further increase in both GFR (+13%) and ERPF (+12%) was observed (compared to early post-donation values; both p≤0.001) with an unchanged filtration fraction (FF).

Data on the time course of GFR and ERPF by a break-up by median age are given in figure 1, which shows the changes in renal hemodynamics from pre-donation (given as single kidney values). It shows essentially that the changes run in parallel for older and younger donors. In older donors, mean GFR increased from a pre-donation single kidney GFR of 51±5 ml/min/1.73 m² to an early post-donation GFR of 64±7 ml/min/1.73 m², and a long-term post-donation GFR of 72±8 ml/min/1.73 m². In younger donors, these values were 54±7 ml/min/1.73 m² for pre-donation single kidney GFR, 70±7 ml/min/1.73 m² early post-donation GFR and 76±8 ml/min/1.73 m² long-term post-donation (see table 1 for statistical comparisons). In older donors, mean GFR thus increased by 8±7
ml/min/1.73 m² and in younger donors by 6±7 ml/min/1.73 m² over a period of approximately six years; these values were not significantly different.

In older donors, ERPF increased from a single kidney pre-donation ERPF of 197±25 ml/min/1.73 m² to an early post-donation ERPF of 255±31 ml/min/1.73 m² and a long-term post-donation ERPF of 281±40 ml/min/1.73 m². In younger donors, these values were 205±35 ml/min/1.73 m² for pre-donation single kidney ERPF, 268±40 ml/min/1.73 m² early post-donation ERPF and 291±41 ml/min/1.73 m² long-term post-donation (see Table 1 for statistical comparisons). So in older donors, mean post-donation ERPF further increased by 26±38 ml/min/1.73 m² and in younger donors by 23±25 ml/min/1.73 m² from early after nephrectomy until the long-term follow-up assessment. Again, these values were not significantly different.

**Prediction of long-term GFR and ERPF**

Individual values for renal hemodynamics are given in Figure 2. The line of identity is included in the figure and pre-donation values are provided as single kidney values. The figure shows, first, that both early and late post-donation GFR and ERPF are significantly correlated to their pre-donation values. Furthermore, it shows a relatively large inter-individual variability in post-donation adaptation, both on short and long-term.

Univariate prediction of post-donation GFR from pre-donation GFR was better for short-term (R²=0.41) than for long-term GFR (R²=0.33, both p≤0.001), as can be derived from Figure 2. We attempted to predict long-term GFR from pre-donation characteristics by multivariate modelling. The model including pre-donation GFR (β=0.47), BMI (β=0.23) and age (β=0.32) best predicted long-term GFR, accounting for 53% (p≤0.001) of the variation in long-term GFR.

![Figure 2. Prediction of renal hemodynamics at 2 months and 6 years after donor nephrectomy from pre-donation renal hemodynamics.](image)

Open circles and discontinuous lines represent the relation between pre-donation and early post-donation renal hemodynamics. Closed circles and continuous lines represent the relation between long-term post-donation renal hemodynamics. Regression coefficients are for univariate predictive capacity from pre-donation values (all p<0.001). Dashed lines represent lines of identity. Two-month and six-year post-donation values are connected for each individual donor to indicate long-term post-donation adaptation.
term GFR, although BMI did not quite reach statistical significance (p=0.11).
For ERPF, a similar model, including pre-donation ERPF (β=0.58), BMI (β=0.19) and age (β=-0.22) could account for 47% (p≤0.001) of the variation of long-term ERPF, however, neither age (p=0.14) nor BMI (p=0.19) contributed significantly to the model.

To assess, furthermore, whether a smaller adaptive response early after donation persisted on the long-term, we analysed the data by break-up at the median of absolute early response in GFR and ERPF, respectively, as shown in figure 3. Remarkably, the smaller adaptive response early after donation did not persist in the long term. In donors in whom the early rise in GFR had been below the median of 15 ml/min/1.73 m², the subsequent long-term rise was 10±7 ml/min/1.73 m², which was significantly more than the long-term rise of 5±7 ml/min/1.73 m² in donors in whom early rise had been above the median (p≤0.05). For ERPF, the late response was 30±40 ml/min/1.73 m² for donors with an early response below the median of 63 ml/min/1.73 m², as compared to 19±19 ml/min/1.73 m² for donors with early response above the median (p=0.18).

### Donors with renal function impairment short-term after donation
A post-donation GFR ≤60 ml/min/1.73 m² was classified as moderate renal function impairment, according to K/DOQI guidelines. In our current population, seven donors (19%) had a GFR ≤60 ml/min/1.73 m² short-term after donation. Characteristics are shown in table 3. In line with our previous report [7], these donors were significantly older and had a higher BMI at donation. However, when we analysed their adaptive response on the long-term, this was not impaired after donation. On the contrary, the post-donation rise in GFR over six years’ time was higher in donors with a short-term post-donation GFR ≤60 ml/min/1.73 m² (p≤0.05).

### Donors with a decline in GFR long-term after donation
A change in GFR that exceeded the variation of measurement (i.e. 2.5%) was considered a significant increase or decrease. Compared to short-term post-donation, GFR increased in thirty donors, was stable in four, and declined in three donors. We could not identify anthropomorphic risk factors for this decline in GFR, as there were no significant differences with respect to age, BMI, pre-donation nor post-donation GFR between

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GFR≤60 (n=7)</th>
<th>GFR&gt;60 (n=30)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Male/female ratio</td>
<td>1/6</td>
<td>8/22</td>
<td>NS</td>
</tr>
<tr>
<td>Age at donation (years)</td>
<td>55±9</td>
<td>45±9</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Body mass index at donation (kg/m²)</td>
<td>29±7</td>
<td>25±3</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Late GFR adaptation (ml/min)*</td>
<td>14±5</td>
<td>8±8</td>
<td>≤0.05</td>
</tr>
</tbody>
</table>

Table 3. Donors with post-donation GFR ≤ or > 60 ml/min/1.73 m².
* The late GFR adaptation is calculated as the change in GFR from 2 months after donation to 6 years after donation.
donors whose GFR declined and donors whose GFR increased.

Discussion

This study supports the presence of long-term adaptive capacity in the remaining kidney after living kidney donation. Both glomerular filtration rate and renal plasma flow, measured 6 years after living kidney donation, increased compared to values measured at 2 months after donation. Remarkably, the long-term adaptive response of GFR and ERPF were independent of age.

Whereas normally renal function slowly declines with age, this effect could not—or perhaps not yet—be detected in our study. Actually, the long-term adaptive response to donor nephrectomy seemed to overcome age-related renal function decline, at least as estimated from the two post-donation time points available. It would be of great interest to reassess renal hemodynamics in the same subjects five and ten years from now to see whether or when an age-related decline will occur and at what rate.

In donors in whom the early adaption was below average, this smaller adaptive response did not persist on the long-term, neither for GFR nor for ERPF. In other words: when the short-term rise in a remnant kidney’s GFR and ERPF was pronounced, it was less prominent over the longer-term, and conversely, if the early response lagged behind, the long-term response tended to catch up. Whether this is an effect of regression to the mean cannot be excluded. However, it could also indicate that different subjects adapt to donor nephrectomy over a different time-frame. Unfortunately, our short-term follow-up data do not allow drawing conclusions over differences in the time-frame of renal adaptation in

![Figure 3. Effect of the initial adaptation in single kidney renal hemodynamics on long-term adaptation.](image)

The early rise in GFR was calculated as the difference between GFR at two month post-donation and GFR before donation, in which pre-donation GFR was divided by 2 to obtain single kidney values. The median value was used as cut-off and to compare differences in short-term and long-term adaptation. At six years, there was no longer a significant difference between both groups, suggesting that there are individual differences in the rate of adaptation to unilateral nephrectomy. * significant difference by default.
reaction to contra-lateral nephrectomy. Previous studies showed that the vast amount of renal adaptation after contra-lateral nephrectomy occurs in the first few weeks after surgery. [9,11,14] So at two months after nephrectomy, adaptive changes in renal hemodynamics are already prominent, but not complete, which is in line with our current analyses. Thus, when a donor is seen for short-term follow-up and renal function appears below par, there might still be a slower, longer adaptive response lying ahead. This was also the case for donors with an early post-donation GFR below 60 ml/min/1.73 m². Whereas according to K/DOQI guidelines, these donors would have been classified as having moderate renal function impairment, or CKD stage III, fortunately, the remaining kidney seemed to have sufficient capacity to adapt to the new single kidney situation on the long term. It should be mentioned here, however, that the K/DOQI classification has been developed for subjects with renal disease. The clinical significance of a GFR below 60 ml/min/1.73 m² in a single healthy kidney is likely to be different from a similar GFR in two diseased kidneys. However, for the moment no such classification is present.

Our current analyses are, moreover, limited by our small population of 37 donors. However, aim of this study was not to provide a large cohort with follow-up of donor renal function. Rather, the aim was to investigate the renal hemodynamic adaptive response to donor nephrectomy on the medium to long-term and to analyse a potential role of age, as we previously found the short-term adaptive capacity to be reduced in older donors. As to the small population, our sample size is actually similar to previous studies [9,10,15]. Still, we cannot exclude that we would indeed find age-related differences in hemodynamic adaptation when the population would be larger. Therefore, additional analyses are currently ongoing and five-year follow-up of donors is being implemented in our centre.

Another limitation of our study, is that the age range was not very large, which may also hamper the power to detect age-related differences. Baseline GFR and ERPF prior to donation were slightly lower in older donors, but this was not statistically significant. This may indicate that our older donors represent a population selected for renal function, which is likely, considering donor acceptance policy. This may limit generalizability of our results, as selection for renal function could also affect long-term renal adaptive capacity.

In conclusion, renal hemodynamic adaptation after donor nephrectomy is profound and in this population occurred irrespective of initial renal function and donor age. Donors with short-term renal function in the lower ranges displayed adequate long-term renal function. Our data thus support current practice of accepting older donors, but careful screening and monitoring remains warranted.
References
