The influence of low donor age, living related donation and pre-emptive transplantation on end-organ damage based on arterial hypertension after paediatric kidney transplantation

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Abstract

**Background.** To date, no study has described the pre-transplant and transplant risk factors for end-organ damage based on arterial hypertension in children after kidney transplantation (KTX).

**Methods.** A retrospective chart review was performed of 206 children with KTX between 1991 and 2007. Patients <120 cm were excluded as no validated percentiles for 24-h ambulant blood pressure monitoring (ABPM) exist. Complete data sets were available for 116 patients. Data were recorded at 12, 24 and 36 months post-KTX. We analysed the influence of donor age, age at transplantation, pre-emptive transplantation, living or deceased transplantation and glomerular filtration rate (GFR) on the presence of end-organ damage, ABPM, ABPM standard deviation score and the numbers of anti-hypertensives used.

**Results.** Lower donor age and the decade of transplantation were associated with less detection of end-organ damage ($P = 0.001$). A lower need for anti-hypertensive medication ($P = 0.001$) was detected in children who received organs from living donors and from deceased donors with a donor age <35 years and who were transplanted pre-emptively. Low recipient age was the only factor associated with lower ABPM ($P = 0.001$). In our study, the type of immunosuppressive regimen and the GFR had no influence on the blood pressure.

**Conclusions.** It may be speculated that the risk of arterial hypertension and associated end-organ damage in children after KTX could be reduced by using organs from young donors with an advantage for living related and pre-emptive donation.

**Keywords:** donor age; end-organ damage; hypertension; living donation; paediatric kidney transplantation

Introduction

Kidney transplantation (KTX) is the first-line treatment for children with end-stage renal disease. The effective management of patients following successful renal transplantation is essential to guarantee good long-term graft function. Post-transplant hypertension remains a significant risk factor for graft loss [1]. Additionally, end-organ damage as a result of hypertension significantly decreases life expectancy after renal transplantation [2, 3]. Articles describe between 50 and 80% of paediatric patients suffering from arterial hypertension following renal transplantation [4].

Several studies have found many factors that influence blood pressure after renal transplantation [5–7]. This evidence has changed the monitoring and treatment of arterial hypertension after renal transplantation. For example, the early discontinuation of steroids has been proved to have a positive effect on blood pressure [5], whereas chronic rejection, hypertension before transplantation, poor early graft function, oxidative stress and obesity were found to have an adverse effect on blood pressure [6–9]. Studies performed on adult populations have found concordant results, with pre-transplant hypertension, poor early graft function, chronic rejection and donor age being the main risk factors for post-transplant hypertension [10, 11].

No correlation has been demonstrated between donor age, type of donation and hypertension in paediatric patients. For instance, Nagasako et al. did not observe any effect of the age of the donor on hypertension after renal transplantation in children [12]. However, arterial hypertension was always defined by blood pressure levels in these studies, and no study has examined correlations between risk factors and the number of anti-hypertensive drugs needed to control the hypertension. After KTX, it is aimed to achieve normal height matched blood pressure values that can unfortunately not be reached in all children.

However, blood pressure values alone are no good surrogate marker of the severity of arterial hypertension, as they do not represent the need for anti-hypertensive medication. Therefore, a combination of mean blood pressure values, height and gender-matched standard deviation score (SDS) of blood pressure and the number of anti-hypertensive medications applied seems to best serve for determining the grade of hypertension.

A few investigations have aimed to assess the effect of the donor age on the outcome after renal transplantation. Paediatric en bloc renal allografts were found to be superior...
to living donor kidneys with regards to long-term graft function [13], and higher donor age led to a poorer prognosis for graft survival [14]. The objective of the present study was to assess different pre-transplantation and transplantation risk factors for arterial hypertension, graft function and end-organ damage over a 3-year period in paediatric patients undergoing renal transplantation.

Materials and methods

Between 1991 and 2007, 206 children received a renal transplant in our centre. We aimed to define factors that influenced end-organ damage, based on arterial hypertension using a retrospective chart review. The inclusion criteria were: age between 1 and 17 years, an observation time of 3 years and a minimum height of 120 cm, which was necessary due to the lack of valid ambulant blood pressure monitoring (ABPM) percentiles for children <120 cm. As a consequence, 86 children were excluded according to height, 10 according to graft loss within the first 3 years and 2 children who died within observation time. In total, 116 children were included. The mean age at transplantation was 11.2 ± 2.2 years (range, 7–17 years). Forty-seven per cent of the patients received a cadaveric transplant, and 53% of patients an organ from a living donor. Pre-emptive transplantation was possible in 37% and 62% of the patients underwent dialysis before transplantation. Underlying renal diseases are listed in Table 1. It was not possible to find information about pre-transplantation blood pressure in every patient due to failure in the documentation in some patients who underwent transplantation >10 years ago. Information was available for 65/116 patients, with 36 being hypertensive before transplantation and 29 being normotensive. The treatment standard with anti-hypertensives was as follows: angiotensin-converting enzyme (ACE) inhibitors as first-line therapy (if no contraindication exists) and if needed, an escalation with diuretics, β-blockers, calcium channel antagonists and AT1 antagonists was performed. Of our patients, 85% were treated with ACE inhibitors. Fourteen per cent patients did not receive any anti-hypertensive drugs and 21% only needed one drug to control their blood pressure. In total, 57% patients needed a combination therapy of anti-hypertensives.

To evaluate end-organ damage, patients underwent electrocardiography and echocardiography performed by paediatric cardiologists once yearly. Left ventricular hypertrophy (LVH) was measured in M-mode in two-dimensional echocardiography. LVH was defined as a left ventricular mass index >38 g/m². Furthermore, fundoscopy was performed at the same time accomplished by ophthalmologists using the standard procedure on dilated pupils detecting the presence of fundus hypertonicus. Twenty-four-hour ABPM was performed in all patients by SpaceLabs 90207 or 90217 device (SpaceLabs Healthcare, Issaquah, WA). The measurements were taken every 15 min at day time and 30 min at night. The patients were instructed to behave normally during measurement and to keep records of their activities. According to Hadstein et al. [13], blood pressure was classified into percentiles depending on the height of the patient and height-associated SDS of mean arterial pressure (MAP) and blood pressure percentiles were similar at all time points in patients receiving organs from living and deceased donors and did also not differ according to donor age (Table 4). However, ANOVA demonstrated a significant difference between a lower need for anti-hypertensive treatment when organs from living donors or pre-emptive transplantation were used (Table 5). Lower donor age also led to a significantly lower number of anti-hypertensives used at 6, 12, 24 and 36 months after transplantation. The data for our study was drawn retrospectively 6, 12, 24 and 36 months after transplantation. We investigated the following potential risk factors: donor age, age at transplantation, the duration since the transplantation, pre-emptive transplantation, body mass index, underlying disease, pre-transplant hypertension, glomerular filtration rate (GFR), the type of immunosuppressive regimen and whether the transplant was from a living relative or a deceased donor. Each factor was correlated with end-organ damage, ABPM, ABPM SDS as well as the number of anti-hypertensive drugs GFR was calculated using the Schwartz formula taking into account that all creatinine values were determined by enzymatic method [16]. Furthermore, the outcome of hypertensive patients was investigated testing the risk factors named above for loss of transplant.

All statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). The influence of different factors was defined by multivarince or covariance analysis. Mean was compared using analysis of variance (ANOVA). Bonferoni correction was applied.

Results

The mean donor age was 30.5 years (range 1–58 years). Three donors were >50 years. The nature of the immunosuppressive regimens used is shown in Table 2. Despite treatment, approximately one-third of the patients remained hypertensive (>95th percentile) during regular 24-h ABPM at our post-transplantation outpatients clinic. Twelve months after KTX, 30% of patients were found to be hypertensive, and this rose to 35% after 36 months. Hypertension in ABPM was always followed by an increase in anti-hypertensive medication.

LVH, a surrogate marker of end-organ damage, was detected significantly less in children who received organs from younger donors (Table 3). An influence of other pre-transplant or transplant factors, underlying disease or body mass index on this end point could not been shown. A significant improvement was observed over the years with less end-organ damage in the last decade of monitoring. The number of blood pressure medications administered was significantly higher in those patients with LVH than in those without LVH 2 and 3 years after KTX (2.1 ± 1.5 versus 3.5 ± 0.7, P = 0.04; 2.1 ± 1.5 versus 3.2 ± 1.6, P = 0.05). However, there was no statistically significant difference in ABPM SDS according to LVH. For the other surrogate marker of end-organ damage, fundus hypertonicus, no association with any of the factors could be shown.

MAP and blood pressure percentiles were similar at all time points in patients receiving organs from living and deceased donors and did also not differ according to donor age (Table 4). However, ANOVA demonstrated a significant difference between a lower need for anti-hypertensive treatment when organs from living donors or pre-emptive transplantation were used (Table 5). Lower donor age also led to a significantly lower number of anti-hypertensives used at 6,

### Table 1. Underlying causes of renal disease leading to the need for transplantation

<table>
<thead>
<tr>
<th>Underlying renal diseases</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Uropathies</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Focal sclerosing glomerul n</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Rapid progressive glomerulonephritis</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Henoch–Schoenlein purpura</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Congenital nephrosclerosis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

### Table 2. Nature of immunosuppressive regimen

<table>
<thead>
<tr>
<th>Immunosuppressive regimen</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A + prednisolone</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Tacrolimus + prednisolone</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Basiliximab + cyclosporine A + prednisolone</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Basiliximab + cyclosporine A + everolimus + prednisolone</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Basiliximab + cyclosporine A + MMF + prednisolone</td>
<td>33</td>
<td>29</td>
</tr>
</tbody>
</table>
12, 24 and 36 months after KTX (P = 0.001, P = 0.008, P = 0.013 and P = 0.003, respectively) and to a lower risk of transplant loss (P = 0.009). As expected, a lower recipient age was the only factor associated with lower MAP but not MAP SDS in multivariate analysis (Table 6).

Multivariate analysis of the risk factors showed significant results for an association between a lower number of anti-hypertensives and living donation and pre-emptive transplantation. The strongest correlation was found for living donation. Donor age, kidney function, immunosuppressive regimen, recipient age and the presence of hypertension before KTX had no significant effect on the number of anti-hypertensives administered in the multivariate analysis (Table 6).
Discussion

Arterial hypertension following renal transplantation in children is a common and severe problem. Close monitoring and effective treatment is necessary to avoid long-term end-organ damage [2, 3]. Little is known about the risk factors prior to transplantation that influence blood pressure after successful transplantation in children.

Mean arterial blood pressure in ABPM or ABPM SDS alone are not adequate as a surrogate parameter for arterial hypertension after KTX in a study like this, as treatment usually aims for normal values. The number of anti-hypertensive drugs might help additionally to assess the grade of hypertension. Hypertension is more severe in patients with the same MAP if they require more anti-hypertensives. Several other studies have investigated the number of anti-hypertensive drugs used after KTX as a surrogate marker of arterial hypertension rather than blood pressure values themselves. Bohlke et al. [17] defined hypertension by the use of anti-hypertensive drugs to assess risk factors for post-transplantation hypertension, as did Cosio et al. [18], who monitored hypertension after KTX with the doses of anti-hypertensive drugs taken. A further study found poorer graft and patient survival rates correlated with the increasing usage of anti-hypertensive drugs [19].

Most study designs suggest the use of combining the blood pressure percentiles or SDS and whether or not anti-hypertensive drugs were necessary [20]. Therefore, we have analysed both parameters.

Our study showed an overall need to improve the treatment of hypertension after KTX with 35% of the patients having hypertension blood pressure values 2 years after transplantation despite treatment. Moreover, we found end-organ damage in 24% of the patients and 10 patients lost their transplant. Even as LVH might not only be caused by arterial hypertension but also by other factors, it can be assumed that arterial hypertension is the leading cause. A complete evaluation of the relevance of LVH according to left ventricular function and ejection fraction was unfortunately not possible, as not complete data sets exist. Additionally, the analysis of the decade of age that the transplantation was performed in proved that there was significantly less end-organ damage over the time, probably because of a higher awareness for the need of adequate treatment. However, other studies have described similar results with 31% of the patients being hypertensive after 3 years [21] or even 46% after 1 year [22].

Lower donor age was associated with a lower number of anti-hypertensive drugs administered and a reduced presence of end-organ damage and transplant loss. The percentage of end-organ damage is similar at the three time points, however, 24 and 36 months after transplantation (Tx), the mean donor age is much higher in the patients with end-organ damage than 12 months after Tx. One can speculate that pre-existing LVH from the time of dialysis is responsible for the detection of LVH 12 months after KTX. LVH could be detected less in children who received organs from donors of low age and who needed less treatment with antihypertensives. Interestingly, MAP in ABPM itself does not play a key role, probably because it reflects only a snapshot. It can be speculated that lowering blood pressure alone to standard values in ABPM does only partly help to reduce end-organ damage. Those patients with high blood pressure that is very difficult to steer, requiring more medications, might have more intermittent hypertensive episodes making end-organ damage more likely. Several studies found a significant influence of the donor age on graft function independent of the age of the recipients [23, 24]. Assessing risk factors for delayed graft function, Humar et al. [25] found that a donor age >50 years was an independent risk factor. Additionally, donor age was found to be a risk factor for graft loss, like in our study, and increased patient mortality [26]. De La Vega et al. [27] found a significantly lower GFR at 1, 12 and 24 months post-transplantation in children who received transplants from donors >50 years.

This could be confirmed by the large registry study from Opelz et al. [28], calculating a cut-off age of 49 years that is followed by worse outcome. In 2002, Dubourg et al. [29] found a better long-term functional adaptation of kidneys from paediatric donors compared to adult donors.

In our study, living donation and pre-emptive transplantation were found to be a major factors associated with a lower need of anti-hypertensive drugs in order to achieve the same MAD values. As the rate of acute rejections was higher in the patients who received kidneys from deceased donors, it can be speculated that the higher amount of immunosuppression administered to this group might have substantially influenced ABPM. Other positive consequences of living donation have been identified previously. Living donor kidneys showed a significantly better primary graft function than transplants from deceased donors [30], and a further study showed that well-matched donors and recipient age also improved graft survival [31]. Rees et al. [32] examined the long-term outcome of paediatric patients undergoing renal transplantation and they found a significant difference in graft survival when deceased and living-related donors were compared (66 and 87% for 5 years after KTX). Hardy et al. [33] found a significantly lower unadjusted graft survival in children who received deceased donor kidney transplants along with inferior graft survival rates.

Pre-emptive KTX was also found to improve graft survival [34, 35]. Kessler et al. [36] described a higher risk for delayed graft function in patients undergoing dialysis before KTX. The results of the Eurotransplant study found a significant difference in graft survival between patients who were not on dialysis and those on dialysis at 6 years (82 and 69%, respectively) [37]. Impacts on the risk of post-transplant hypertension have not been investigated.

We have not found an influence on the different immunosuppressive regimens used in our study on ABPM or LVH. There was no difference between patients treated with tacrolimus or cyclosporine. As >90% of patients were on daily steroid therapy, the influence of steroids on LVH or ABPM could not be evaluated.

The prevention and treatment of post-transplant hypertension and associated end-organ damage is one of the main goals after renal transplantation, with hypertension having an important influence on graft and patient survival. Our study showed novel pre-transplantation risk factors in the paediatric population, which demonstrate that the selection of donors is critical. Lowering blood pressure alone in children with severe arterial hypertension does not prevent end-organ damage. It might be an advantage to select organs...
from younger donors, if possible associated with living-related and pre-emptive donation, for this population to minimize the risk of hypertension and thereby end-organ damage and final graft loss. Dialysis before transplantation is an independent risk factor for hypertension after KTX in our study. Additionally, our results prove that there is a general need for improvement in the treatment of post-transplant hypertension to prevent long-term end-organ damage.

Conflict of interest statement. None declared.

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27. De La Vega LS, Torres A, Bohorquez HE et al. Patient and graft outcomes from older living kidney donors are similar to those from younger donors despite lower GFR. Kidney Int 2004; 66: 1654–1661

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