SUCCESSFUL TRANSPLANTATION OF ADULT-SIZED KIDNEYS INTO INFANTS REQUIRE MAINTENANCE OF HIGH AORTIC BLOOD FLOW

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Background. Nationally, results of renal transplantation in infants are inferior to those in older children and adults. Within the infant group, best results are obtained with adult-sized kidneys (ASKs) rather than size-compatible pediatric kidneys. However, transplantation of ASKs into infants has an increased risk of acute tubular necrosis and graft loss from vascular thrombosis and primary nonfunction. The aim of this study was to define and understand the hemodynamic changes induced by ASK transplantation, so that outcomes of transplantation in infants can be improved.

Methods. Nine hemodynamically stable and optimally hydrated infants were studied under a controlled sedation with cine phase-contrast magnetic resonance at three time periods: before transplantation, 8–12 days after transplantation, and 4–6 months after transplantation. Cross-sectional images of both the infant aorta and the adult transplant renal artery were obtained and blood flow was quantitated. Renal volumes were also obtained, and expected renal artery blood flow based on early posttransplant volume was calculated. In addition, renal artery blood flow was determined in 10 in situ native adult kidneys prior to donor nephrectomy. Supplemental nasogastric or gastrostomy tube feeding was carried out during the blood flow study period to optimize intravascular volume.

Results. Mean infant aortic blood flows were 331±145 ml/min before transplantation, 761±272 ml/min at 8–12 days after transplantation (P=0.0006 with pretransplant flow), and 665±138 ml/min at 4–6 months after transplantation (P=0.0001 with pretransplant flow). Mean transplanted renal artery flows were 381±158 ml/min at 8–12 days and 296±113 ml/min at 4–6 months after transplantation. Transplanted renal artery flows were less than prenephrectomy in situ donor renal artery blood flow (618±130 ml/min; P=0.02 and P=0.0003) and expected normal renal artery blood flow (665±87 ml/min; P=0.003 and P=0.001) at both 8–12 days and 4–6 months after transplantation. A 26% reduction in renal volume (P=0.003) occurred between the two postoperative time periods, and this paralleled the decrease in posttransplant renal artery flow. One-year graft and patient survival in the nine infants was 100%. The mean serum creatinine levels at 3, 6, and 12 months were 0.43±0.10, 0.48±0.15, and 0.49±0.16 mg/dl.

Conclusions. This study is the first to quantitatively document the blood flow changes occurring after ASK transplantation in infants. There was a greater than two-fold increase in aortic blood flow after ASK transplantation, and this increase was sustained for at least 4 months and appeared to be driven by the blood flow demand of the ASK. However, actual posttransplant renal artery blood flow was significantly less than normal renal artery flow. Our study suggests that aggressive intravascular volume maintenance may be necessary to achieve and maintain optimum aortic blood flow, so as not to further compromise posttransplant renal artery flow and to avoid low-flow states that could induce acute tubular necrosis, vascular thrombosis, or primary nonfunction.

Nationwide, kidney transplant graft survival in infants and small children is inferior to that in older children and adults (1–3). Within the infant group, the best results are obtained with adult-sized kidneys (ASKs*) rather than size-compatible pediatric donor kidneys. More specifically, kidneys from cadaveric donors aged ≤5 years provide the poorest graft survival in children (1), as much as 30% lower than ASKs. Although ASKs provide better graft survival in infants, there is an associated greater incidence of acute tubular necrosis (ATN), graft thrombosis, and primary graft nonfunction (1, 3–5). These problems have been generally attributed to the marked discrepancy in size between the ASK and the infant recipient.

There are no reported studies describing the hemodynamic

* Abbreviations: ASK, adult-sized kidney; ATN, acute tubular necrosis; MR, magnetic resonance; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study.
changes induced by ASK transplantation in infants. Such studies would be important in order to develop a better understanding of how the outcomes of transplantation in infants might be improved. This report describes the first study to quantitatively document recipient aorta and transplanted renal artery blood flows, as well as changes in donor kidney volume following ASK transplantation in infants. We believe our findings could have a major impact in improving transplantation outcomes in infant recipients of ASKs.

**MATERIALS AND METHODS**

Our study was designed to quantitate changes in recipient aorta and transplanted renal artery blood flow in nine hemodynamically stable infants (mean weight: 12.1±2.6 kg; range: 9.3–16 kg) with end-stage renal failure who were scheduled to undergo ASK transplantation at Packard Children’s Hospital at Stanford University. Informed parental consent was obtained for each study patient. With controlled sedation and maintenance of maximum intravascular volume to avoid any hypotension, a noninvasive cine phase-contrast magnetic resonance (MR) technique was used to determine aortic blood flow rates at three separate time periods: before transplantation; 8–12 days after transplantation, and 4–6 months after transplantation. Transplanted renal artery flow rates were similarly determined at two separate time periods: 8–12 days after transplantation and 4–6 months after transplantation. Each patient, with their baseline pretransplant blood flow data, served as their own control, since unique patient characteristics, such as growth retardation, weight, disease etiology, degree of hypertension, and dialysis modality, prevented age matching with normal infants.

**Blood flow measurements.** Blood flow measurements were obtained at a specific standardized location in the aorta above the donor renal artery anastomosis site at the three designated time periods and in the transplanted renal artery at the two postoperative time periods. All examinations were performed utilizing a 1.5-T superconducting magnet (General Electric Medical Systems, Milwaukee, WI). Sequence parameters for the cine phase-contrast acquisition were as follows: oblique scan plane perpendicular to the vessel of interest, respiratory ordered phase encoding, first-order gradient-moment nulling, slice direction flow encoding with a velocity encoding of 120–150 cm/sec, 5-mm slice thickness, 18- to 22-cm field of view, and 256×128 matrix with two signals acquired. Data were acquired continuously throughout the cardiac cycle and retrospectively interpolated to 16 temporal phases per electrocardiogram RR interval referenced to a digital plethysmograph (Fig. 1, A, B, and C). Care was taken to prescribe a scan plane away from the origin of branch vessels as well as bifurcation points so as to eliminate the effects of turbulent flow and assure that all measured flow was well-developed laminar flow. The average volume flow rate throughout the cardiac cycle was determined from the measured phase-shift data on an off-line workstation (6). The accuracy and reproducibility of the technique has been validated in vivo (7) and has been successfully used to accurately investigate physiologic and pathologic flow patterns in a variety of vascular territories (8–11).

**Renal volume measurements.** Renal volume was also determined in these same nine patients at the same two postoperative time periods (8–12 days and 4–6 months). For determination of renal volume, a Riemann sum was calculated from the slices intersecting the kidney from a T1-weighted spin-echo sequence, T2-weighted fast spin-echo sequence, or a gradient-recalled-echo sequence. A manual trace of the renal contour was performed on each slice and multiplied by the thickness of the slice. This was repeated for each slice intersecting the kidney, with a sum of slice volumes determined for all such slices.

**Transplantation and follow-up.** Six patients received living donor kidneys from a parent or grandparent and three patients received cadaveric ASKs. In all cases, the donor renal artery was anastomosed to the infant aorta and the renal vein was anastomosed to the inferior vena cava (3). Our immunosuppressive protocol was cyclosporine-based and employed the initiation of an intravenous cyclosporine infusion in the operating room after revascularization of the kidney graft (12). In order to eliminate confounding variables in the study data, postoperative delayed graft function (failure to achieve a creatinine level ≤0.5 mg/dl by the second postoperative day), treatment for rejection during the study period, and any surgical complication or evidence of abnormal aorta or renal artery anatomy were predetermined exclusions for completion of the study. No patients were excluded from this study by these criteria.

Supplemental nasogastric or gastrostomy (if already in place) tube feeding was carried out to optimize intravascular volume and provide uniformity and consistency for the blood flow determinations. After transplantation, tube feeding was carried out for greater than 4 months and was targeted to achieve a total daily fluid intake of 2500 mL/cm2/day plus a minimum sodium intake of 8–10 mEq/kg/day. The infants were closely monitored for any evidence of renal insufficiency, during both the transplant admission and at regular intervals as outpatients. If there was a minor increase in the serum creatinine level (<0.2 mg/dl increase from baseline), the feeding prescription was augmented to correct for presumed hypovolemia. If the creatinine level did not return to baseline, or if the creatinine rise was >0.2 mg/dl, a renal biopsy was performed.

**Pretransplant donor renal artery blood flow.** Pretransplant renal artery blood flows were obtained separately in 10 in situ native adult kidneys prior to donor nephrectomy, in renal donors mean weight-matched to the actual cadaver and living donors who provided kidneys for our recipients. Similar MR imaging techniques and methodology were utilized as in the infant studies. These prenephrectomy renal artery blood flow measurements were compared with the posttransplant infant renal artery flows. In addition, both prenephrectomy and posttransplant renal artery flows were compared with expected normal renal artery blood flow based on kidney volume. Normal renal artery flows based on kidney volume had been recently determined at our center to be 3.47 ml/min/cm3 of renal volume (13).

**Statistical methods.** Standard statistical methods were used to analyze the data. Results are reported as means ± SD. Student’s paired t test was used to evaluate statistical significance.

**RESULTS**

Mean infant aortic and transplanted renal artery blood flows for the three study time periods are given in Table 1. Aortic blood flow increased more than twofold by 8–12 days after transplantation, and this highly significant increase was sustained for at least 4–6 months. The same degree of aortic blood flow change was observed in all patients at all study time periods, regardless of whether the patient had pretransplant bilateral native nephrectomy (n=4) or not (n=5).

Transplant renal artery flow was slightly greater than pretransplant infant aortic flow early after transplantation, despite the small infant blood volume. At 4–6 months after transplantation, renal artery flow was reduced, although aortic flow remained elevated. Simultaneous anatomic images of the renal artery and its aortic anastomosis revealed widely patent renal blood vessels and aorta during every study time period in every patient.

Mean in situ donor renal artery blood flow prior to donor nephrectomy was 618±130 ml/min. This blood flow was significantly greater than the posttransplant renal artery flows shown in Table 1 at 8–12 days after transplantation (P=0.02) and at 4–6 months after transplantation (P=0.0003).

Mean renal graft volume measured 192±25 cm3 at 8–12 days and 143±23 cm3 at 4–6 months (P=0.003) after trans-
TABLE 1. Infant aortic and renal artery blood flow (ml/min)

<table>
<thead>
<tr>
<th>Time</th>
<th>Aortic blood flow (ml/min)</th>
<th>Renal artery blood flow (ml/min)</th>
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<tbody>
<tr>
<td>Before transplantation</td>
<td>331±148</td>
<td>NA</td>
</tr>
<tr>
<td>8–12 days after transplantation</td>
<td>761±272&lt;sup&gt;a&lt;/sup&gt;</td>
<td>385±158</td>
</tr>
<tr>
<td>4–6 months after transplantation</td>
<td>665±138&lt;sup&gt;b&lt;/sup&gt;</td>
<td>296±113</td>
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<sup>a</sup> P=0.0006 with pretransplant aortic flow.
<sup>b</sup> P=0.0001 with pretransplant aortic flow.

plantation. A 26% reduction in renal size was thus clearly evident despite the continued maintenance of optimum intravascular volume and the absence of both ATN and rejection during the 6 months of MR blood flow studies in our patients.

Expected early renal artery blood flow based on renal volume (13) was calculated to be 666±87 ml/min. This was essentially identical to actual prenephrectomy renal artery flow and was also much greater than actual renal artery flows at 8–12 days after transplantation (P=0.003) and 4–6 months after transplantation (P=0.001).

One-year graft and patient survival was 100% without the occurrence of ATN during the first 6 months after transplantation. The mean serum creatinine levels at 3, 6, and 12 months were 0.43±0.10, 0.48±0.15, and 0.49±0.16 mg/dl.

By the study protocol, only one infant required a renal biopsy during the first posttransplant year. This infant received an ASK transplant at age 8 months. At 7 months after transplantation, after reduction of his salt and water intake, his serum creatinine level increased from a baseline value of 0.5 mg/dl to 0.9 mg/dl. A renal biopsy revealed chronic ATN without evidence of acute rejection or cyclosporine nephrotoxicity (Fig. 2). By augmenting the salt and water component of the tube feeding prescription, especially through the night, the serum creatinine level returned to 0.4 mg/dl and has remained at this level for the current 12 months of follow-up from this event.

**DISCUSSION**

Our study suggests a possible physiologic explanation for some of the failure observed with ASK transplantation in infants and provides fundamental principles which could lead to a dramatic improvement in future results. The blood flow data obtained from our nine infants were unencumbered by the confounding variables usually found in transplantation studies, as it was obtained under optimal circumstances: all patients had immediate excellent graft function; none had any evidence of ATN during the 6-month posttransplant period of blood flow determinations; none ever experienced an acute rejection episode; none had any surgical complication; and all had documented, widely patent normal aortic and renal artery anatomy during all phases of the study.

wherever there is flow in that direction. (B) Velocity-reconstructed images from the same pretransplant study display caudal flow as white and cephalad flow as black. Note the variation of signal in the aorta throughout the cardiac cycle with a transient flow reversal (black signal in aorta) during late diastole. (C) Velocity-reconstructed images were taken in the posttransplantation period. Note the continuous forward (caudal) flow throughout the cardiac cycle due to the low resistance vascular bed of the large kidney graft.
The importance and pertinence of our study to improving the outcomes of kidney transplantation in infants can be appreciated from the following. Available data clearly show that infants do not do well with size-compatible pediatric grafts (donors aged ≤5 years), since their 1-year graft survival rate is only 52% for recipients aged <2 years old and 77% for recipients aged 2–5 years (Ken Sullivan for the North American Pediatric Renal Transplant Cooperative Study [NAPRTCS], personal communication, 1998). In contrast, the best 1-year graft survival rate in infants is obtained with living donor ASK transplantation: 84% for recipients aged <2 years old and 88% for recipients aged 2–5 years (Ken Sullivan for NAPRTCS, personal communication, 1998). However, in comparison to older pediatric and adult recipients, these latter results are still suboptimal and in large part result from the higher incidence of ATN, vascular thrombosis, and primary graft nonfunction associated with ASK transplantation in infants (1, 4).

When ATN requiring dialysis occurs, graft survival decreases by >20% in pediatric recipients of cadaver donor grafts and by >30% in recipients of living donor grafts at 1–3 years after transplantation, compared with patients without ATN (1). The rates of graft loss due to vascular thrombosis are 9% and 5.5% for cadaver graft recipients aged <2 years and 2–5 years, respectively, and 3.5% and 3.4% for living donor recipients aged <2 years and 2–5 years, respectively (4). This makes vascular thrombosis the third leading cause of graft failure for both cadaver and living donor recipients, after acute and chronic rejection (1, 4). In addition, ATN in a small pediatric recipient is an established principal risk factor for the development of vascular thrombosis (4). Thus, transplantation of an ASK into an infant can be problematic, most likely because of the major physiologic discrepancies that result from the placement of a large ASK with a large blood flow demand into a small child with a small heart, a small blood volume, and small blood vessels.

The importance of optimal renal blood flow in the maintenance of renal function is universally recognized. On the basis of the aortic and renal artery blood flow results described in this study, it appears that the inherent blood flow demand of the prenephrectomy ASK persists in good part after transplantation into infants. However, since infants receiving living donor ASKs have a 10% incidence of dialysis-dependent ATN (14), compared with a near 0% incidence for adult recipients of living donor kidneys, this strongly suggests significant posttransplant renal hypoperfusion of ASKs in these infants. Living donor kidneys are removed under the most ideal circumstances and therefore, with adequate perfusion, should function immediately after transplantation.

At 8–12 days after transplantation, mean renal artery blood flow was 385 ml/min, which probably reflected the maximal achievable flow in these infants. It is doubtful that posttransplant renal artery flow in the infant could have been greater, considering that this blood flow was already greater than the infant pretransplant aortic flow. On the other hand, the 8- to 12-day renal artery flow was actually less than the generally accepted average blood flow of a single in situ ASK (greater than 600 ml/min for men and 500 ml/min for women), where total renal blood flow to two in situ adult kidneys typically exceeds 20% of the cardiac output (15). Our in situ renal artery blood flow determinations prior to donor nephrectomy are consistent with these expected normal renal blood flows and are significantly greater than both the early (P = 0.02) and late (P = 0.0003) posttransplant renal artery flows. In addition, a recent study at our center, which determined normal renal artery blood flow to be 3.47 ml/min/cm³ of renal volume (13), further validates our data and our cine phase-contrast MR techniques.

In order to achieve the reported transplanted renal artery blood flow, blood flow in the infant aorta above the renal artery anastomosis markedly increased, more than doubling from the pretransplant level. Our results at 4–6 months demonstrated that this increased blood flow in the aorta was sustained and, interestingly, that the blood flow in the ASK renal artery decreased from the early postoperative period. In addition, measurement of renal volume showed a parallel decrease in renal mass at 4–6 months from the early postoperative determination. It is possible that the diminished renal arterial flow at 4–6 months is due in part to the fact that the ASK, which initially represents a much greater amount of functioning renal mass than the infant needs, subsequently shrinks with time as part of a functional adaptation and reverse "work hypertrophy" (16). It could also be that relative suboptimal renal perfusion, compared with that experienced in the renal donor prior to nephrectomy, leads to some ischemic atrophy secondary to hypoperfusion, even with the supplemental fluid therapy employed in our infant recipients. This relative hypoperfusion could also be a major factor in the oftentimes difficult-to-treat hypertension found in small pediatric recipients of kidney grafts.

It is not unreasonable to assume that an ASK in an infant should respond in the same manner as the pretransplant adult in situ kidney when hypoperfused. Because of this assumption, prior to this study we made a concerted effort to assure optimal intravascular volume perioroperatively after transplantation of ASKs into infants. In previous reports (12, 17), we demonstrated that intraoperative, intravenously administered fluid to children weighing <15 kg was twice as great as that administered to children weighing >15 kg (P < 0.001). We also reported that we continued aggressive early postoperative fluid resuscitation in infants and maintained most small children on postoperative mechanical ventilation for 1 to 2 days to obviate the need for fluid restriction.
at this critical time because of the potential for pulmonary edema (12, 17).

Obviously, our blood flow studies suggest that the need to assure optimum intravascular volume does not cease after the immediate perioperative period. The results of our aggressive nasogastric or gastrostomy fluid supplementation suggest that this supplementation is probably desirable until the infant achieves enough somatic growth to maintain good aortic flow and thereby sustain adequate blood flow to the ASK. On such a regimen, serum creatinine levels remained low and stable and none of our patients experienced ATN during the first 6 months after transplantation.

We acknowledge that the avoidance of vascular thrombosis is also dependent upon a careful vascular anastomoses of the discrepant adult-to-infant blood vessels and the avoidance of redundancy in the donor artery and vein (3, 12). But from our studies, it appears that maintenance of optimal intravascular volume may be a prerequisite to the success of ASK transplantation in infants, as important as surgical technique. If supraphysiologic infant aortic blood flow can be maintained, this should sustain adequate (although not normal) posttransplant renal artery flow and ASK perfusion. It is doubtful that the marked physiologic discrepencies between the infant recipient and the ASK would ever permit the same renal perfusion level that occurs in the in situ environment of the adult renal donor. Considering that an infant can at times be prone to poor oral fluid intake and various illness states that would predispose hypovolemia, it would not be unreasonable to assume that the consequences of hypovolemia to an ASK in an infant with a small blood volume could be much more drastic than the well-known consequences to a native in situ ASK. This should not be unexpected when the baseline ASK artery flow in the infant, under conditions of optimal intravascular volume, is already significantly less than the normal renal artery blood flow. Therefore, we suspect that anything less than our reported infant blood flows, obtained with good intravascular volumes, could predispose the ASK infant recipient to problems and inferior graft survival.

REFERENCES


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