TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Early inhibition of the renin-angiotensin system improves the long-term graft survival of single pediatric donor kidneys transplanted in adult recipients

Rubin Zhang,[1] Heather LaGuardia,[1] Anil Paramesh,[2] Katherine Mills,[3] Mary Killackey,[2] Jennifer McGee,[2] Brent Alper,[1] Eric Simon,[1] Lotuce Lee Hamm[1] and Douglas Slakey[2]

1 Department of Medicine, School of Medicine, School of Public Health and Tropic Medicine, Tulane University, New Orleans, LA, USA
2 Department of Surgery, School of Medicine, School of Public Health and Tropic Medicine, Tulane University, New Orleans, LA, USA
3 Department of Epidemiology, School of Public Health and Tropic Medicine, Tulane University, New Orleans, LA, USA

Keywords
pediatric donor kidney, kidney transplant, hyperfiltration, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, graft survival.

Correspondence
Rubin Zhang MD, FASN, Section of Nephrology, Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave, SL-45, New Orleans, LA 70112, USA.
Tel.: +1 504 988 1457;
fax: +1 504 988 1105;
e-mail: rzhang@tulane.edu

Conflict of interest
The authors of this manuscript have no conflict of interest to disclose.

Received: 30 November 2012
Revision requested: 31 December 2012
Accepted: 13 February 2013
Published online: 19 March 2013

doi:10.1111/tri.12087

Summary

Transplanting single pediatric donor kidneys into adult recipients has an increased risk of hyperfiltration injury and graft loss. It is unknown if renin-angiotensin system (RAS) blockers are beneficial in this setting. We retrospectively analyzed 94 adults who received single kidneys from donors <10 years old during 1996–2009. The recipients were divided into group 1 with RAS blockers (n = 40) and group 2 without RAS blockers (n = 54) in the first year of transplant. There was no significant difference in any donor/recipient demographic between the two groups. Graft function, incidence of delayed graft function, acute rejection, and persistent proteinuria were not statistically different either. Kaplan–Meier estimated death-censored graft survivals were significantly better in group 1 than in group 2: 95 vs. 81.2%, 82.4 vs. 61.2%, 72.6 vs. 58.5%, and 68.5 vs. 47.2% at 1, 3, 5, and 7 years, respectively (log rank P = 0.043). Multivariable analysis found persistent proteinuria was a risk factor for graft loss (OR 2.70, 95% CI 1.33–5.49, P = 0.006), while RAS blockers reduced the risk of graft loss (OR 0.38, 95% CI 0.18–0.79, P = 0.009). Early RAS blockade therapy in the first year of transplant is associated with superior long-term graft survival among adults transplanted with single pediatric donor kidneys.

Introduction

Pediatric en bloc kidneys are routinely transplanted together into one adult recipient. The graft survival has been shown to be similar to that of adult deceased donor kidneys [1] and probably even adult live donor kidneys [2,3]. Splitting en bloc kidneys and transplanting one pediatric kidney into one recipient could double the number of kidney transplants from one donor, but this practice has not consistently produced a good graft outcome [4–11]. High incidence of surgical complications, delayed graft function (DGF), rejection, and hyperfiltration injury have been reported as an argument against such a practice [4–11]. Hemodynamic changes and functional adaptation of single pediatric kidneys in adult bodies theoretically can lead to glomerular hyperfiltration, development of proteinuria and focal segmental glomerular sclerosis (FSGS), and ultimately graft loss [7–11].

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB) are widely used antihypertensive drugs that inhibit the renin-angiotensin system (RAS). The renal protective effects of ACEi and ARB, as well as the possible mechanisms, have been well studied in animal models [12–14]. Clinical trials in humans have

also documented that ACEi/ARB therapy can protect renal function and delay the progression of kidney failure, especially in conditions associated with proteinuria [15–18]. They are believed to reduce glomerular capillary pressure by dilating the efferent arterioles of glomeruli and to alleviate or inhibit hemodynamic and molecular injuries from glomerular hyperfiltration [12–18]. However, the renal protective effect of ACEi/ARB therapy in the kidney transplant population remains inconclusive [19–24]. To our knowledge, there is no publication investigating ACEi/ARB therapy in adults transplanted with single pediatric donor kidneys.

We previously reported that single kidneys from pediatric donors <5 years provided comparable 5-year graft survival to those from donors 5–10 years of age [25]. However, there was a rapid and continuous improvement in kidney function throughout the first year of transplant, which indicated underline glomerular hyperfiltration and adaptive hypertrophy during this early period. In this study, we explore the potential benefit of early ACEi/ARB therapy in adults who received single pediatric donor kidneys. We compare the complications, renal function, clinical events, graft and patient survival among those who received and those who did not receive ACEi/ARB therapy in the first year of transplant.

Methods

Retrospective analysis was performed on all adult patients (age >18 years) who received a single pediatric kidney from deceased donors aged <10 years at Tulane University Hospital and Clinic between 1996 and 2009. Our center's protocol of splitting en block pediatric kidneys, surgical technique, and medical management has been described previously [25]. Briefly, all en block pediatric kidneys offered to us were split for single kidney transplants, as long as both kidneys had no obvious damage and there was suitable arterial anatomy with single renal artery and vein with aortic cuff for carrell patch creation.

Immunosuppressive therapy

A triple immunosuppressive regimen of steroids, tacrolimus, and mycophenolic acid was used. Before 2002, patients that were six-antigen mismatch or peak panel reactive antibody (PRA) level >25% were considered high risk and given basiliximab induction. After 2002, induction with basiliximab was given to all patients. Intravenous methylprednisolone was administered before reperfusion and quickly tapered to oral maintenance prednisone. Tacrolimus doses were adjusted as per protocol to keep the 12 h trough level between 10 and 12 ng/ml for the first 3 months, then between 7 and 10 ng/ml up to the end of the first year with goal of 4–7 ng/ml after that point. Transplant patient received either mycophenolate mofetil at 1 g or enteric-coated sodium mycophenolate at 720 mg twice daily. All recipients received a 24-h infusion of low molecular weight Dextran-40 that was started intraoperatively to prevent graft thrombosis. Postoperatively, the patients were placed on aspirin 81 mg/day. Standard antifungal, antibacterial, and CMV prophylaxis were administered as per protocol.

Medical management

Hypertension was aggressively treated to minimize the "pressure" damage to small kidneys in the immediate postoperative period. Our target blood pressure was generally no more than 130/80 mmHg, and it was often as low as the patient could tolerate it during the first month after transplant. The order of choice of antihypertensive medications was calcium channel blockers, beta blockers, alpha blockers, and direct vasodilators. As per our written protocol, once graft function had stabilized and proteinuria was detected, an ACEi/ARB was started by our transplant nephrologists. The choice of ACEi or ARB was usually dependent upon the patient's previous history of RAS inhibitor usage. Proteinuria was initially detected by routine urine analysis and then confirmed by a spot urine protein/creatinine ratio >250 mg/g or a 24 h urine protein >250 mg. The dose of ACEi/ARB was slowly increased as tolerated to control proteinuria, and other antihypertensive medications were subsequently tailored individually.

Acute rejection

In cases where rejection was suspected, kidney biopsy was performed by either open technique (when graft length <10 cm) or percutaneously under the real-time guidance of ultrasound (when graft length >10 cm). Acute cellular rejection of Banff grade 1 or less was treated with pulse methylprednisone for 3 days. Any higher grade rejection or steroid resistant rejection was treated with thymoglobulin. Antibody mediated rejection and mixed rejections were treated with combination of methylprednisone, thymoglobulin, plasmapheresis, and IVIG with or without rituximab.

Outcome analysis

Outcome measures included (i) Death-censored patient and graft survivals over 7 years, (ii) Graft function as measured by serum creatinine (SCr) levels and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation, (iii) The incidence of DGF, patient underwent for-cause kidney biopsy, biopsy-confirmed and clinically treated acute rejection, and late

development of persistent proteinuria after 1 year of transplant. Graft failure was excluded from the calculation of graft function. Late persistent proteinuria was defined as no improvement in proteinuria with or without treatment after the first year of transplant. Early transient proteinuria during the first year of transplant that resolved after ACEi/ARB treatment was not counted as persistent proteinuria.

Statistical analysis

Statistical analyses were performed using SAS version 9.3 software (Cary, NC, USA). Chi-squared tests and *t*-tests were used to compare count and continuous data, respectively. Fisher's exact test was used for count data with small cell frequencies. Patient survival and death-censored graft survival rates were estimated with survival curves using the Kaplan–Meier and compared with log rank tests. Cox proportional hazards analysis was used for univariate and multivariate analyses. Variables identified as significant risk factors for graft loss in univariate analyses were further examined in the multivariate analysis.

Results

A total of 96 patients received primary single pediatric kidneys from donors aged 9 months (0.75 year) to 10 years from 1996 to 2009 at our center. All of them were transplanted more than 2.5 years ago (as of 30 June 2012). Two patients suffered graft thrombosis and required transplant nephrectomy; therefore they were excluded from this study. Depending upon whether patient was started with ACEi/ARB treatment in the first year of transplant, the remaining 94 patients were separated into two groups: group 1 received ACEi/ARB treatment ($n = 40$), and group 2 did not receive ACEi/ARB treatment ($n = 54$). There were 27 patients treated with an ACEi, 10 with an ARB and 3 with both ACEi and ARB. The treatment was started as early as on postoperative day 4 before patient was discharged from hospital. The majority of patients (82.5%) in group 1 initiated ACEi/ARB therapy in the first 3 months, 92.5% in the first 6 months and all in the first year after transplant surgery. There were additional 19 patients who were started ACEi/ARB therapy after 1 year of transplant for biopsy-confirmed FSGS ($n = 6$), CAN ($n = 5$), persistent proteinuria without a biopsy diagnosis ($n = 7$), and post-transplant erythrocytosis ($n = 1$), therefore they were not included in group 1. Table 1 summarizes the demographic characteristics of both donors and recipients in the two groups. There was no statistical difference in donor age, gender, body weight, kidney length, kidney surface area, or cold ischemia time (CIT) between the two groups. The recipient age, gender, race, body weight, body mass index (BMI), peak PRA, degree of human leukocyte antigen (HLA) mismatch, and the causes of ESRD were also comparable in the two groups (Table 1).

Table 1. Demographic characteristics of pediatric donors and adult recipients between group 1 (ACEi/ARB) and group 2 (no ACEi/ARB).

	Group 1 ($n = 40$)	Group 2 ($n = 54$)	*P*-value
Pediatric donors			
Age (years)			
Mean ± SD	4.4 ± 2.9	5.3 ± 2.8	0.09
Range	0.75–10.0	0.8–10.0	
Gender (%)			
Male	47.5	57.4	0.34
Female	52.5	42.6	
Body weight (kg)			
Mean ± SD	17.5 ± 8.6	19.5 ± 7.8	0.54
Range	8.2–29.3	9.1–35.7	
Kidney			
Length (cm; mean ± SD)	7.2 ± 1.0	7.5 ± 1.0	0.89
Length range	5.0–9.0	5.5–10.0	
Surface area (cm^2; mean ± SD)	27.1 ± 6.0	29.9 ± 6.5	0.40
Surface area range	16.5–40.0	19.5–48.0	0.23
CIT (h; mean ± SD)	17.5 ± 6.2	19.1 ± 6.2	
CIT range	5.0–33.5	4.0–35.0	
Adult recipients			
Age (years)			
Mean ± SD	46.3 ± 14.2	43.2 ± 17.5	0.18
Gender (%)			
Male	50.0	59.3	0.37
Female	50.0	40.7	
Race (%)			
Black	67.5	50.0	0.09
Non-black	32.5	50.0	
Causes of ESRD (%)			0.12
Hypertension	48	52	
Diabetes	25	22	
Glomerulonephritis	10	13	
Others	17	13	
Body weight (kg, mean ± SD)	79.5 ± 21.8	77.3 ± 14.8	0.60
BMI (kg/m^2, mean ± SD)	27.1 ± 5.9	26.2 ± 5.1	0.42
Peak PRA (%, mean ± SD)	11.5 ± 22.1	18.0 ± 29.6	0.10
HLA mismatch (mean ± SD)	2.9 ± 0.7	2.8 ± 0.6	0.77

The renal graft function as measured by SCr and eGFR at 1, 3, 5, and 7 years are shown in Table 2. There was no statistical difference in the eGFR between the two groups. The incidence of DGF, which was determined by the need for dialysis support during the first week after transplant, was not different in the two groups. Other captured events including the biopsy-confirmed and clinically treated acute rejections, patients underwent for-cause renal biopsy, as well as late persistent proteinuria was also similar in the two groups (Table 3). Among the 26 patients who had biopsy-confirmed and clinically treated acute rejections, 24 patients had acute cellular rejections, one patient had

Table 2. Summary of renal graft function, Kaplan–Meier estimated patient and death-censored graft survival rates between group 1 and 2.

	Year 1		Year 3		Year 5		Year 7	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Renal function								
SCr (mg/dl)	1.42 ± 0.46	1.76 ± 2.59	1.33 ± 0.50	1.39 ± 0.75	1.44 ± 0.95	1.60 ± 1.13	1.48 ± 0.51	1.84 ± 1.75
eGFR (ml/min)								
Mean ± SD	61.4 ± 24.2	58.3 ± 21.2	68.9 ± 28.7	59.1 ± 25.7	62.0 ± 31.5	54.9 ± 29.9	58.6 ± 29.0	46.4 ± 31.7
P	0.59		0.25		0.49		0.37	
Survival rates								
No. at risk	40	50	38	44	34	39	28	33
Patient (%)	100.0	92.6	94.9	83.3	92.1	79.4	86.6	75.4
Graft (%)	95.0	81.2	82.4	61.2	72.6	58.5	68.5	47.2

Table 3. Post-transplant events and causes of graft loss and patient death.

	Group 1 (n = 40)	Group 2 (n = 54)	*P*-value
Events, *n* (%)			
DGF	10 (25)	12 (22.2)	0.75
Biopsied patient	21 (52.5)	32 (59.3)	0.51
Acute rejection	8 (20)	18 (33.3)	0.15
Persistent proteinuria	12 (30)	24 (44.4)	0.15
Total graft loss, *n* (%)	14 (35)	35 (64.8)	0.004
Causes of graft loss			0.89
CAN	5	11	
DWFG	4	8	
FSGS	2	10	
Rejection	1	3	
Infection	1	2	
TMA	1	1	
Total patient death, *n* (%)	5 (12.5)	13 (24.1)	0.16
Causes of patient death			0.91
Cardiac disease	2	7	
Stroke	1	2	
Infection	1	2	
Cancer	1	1	
Suicide	0	1	

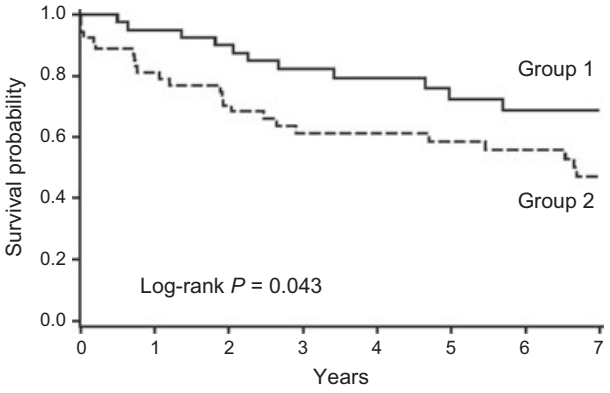

Figure 1 Seven-year death-censored graft survival by Kaplan–Meier analysis.

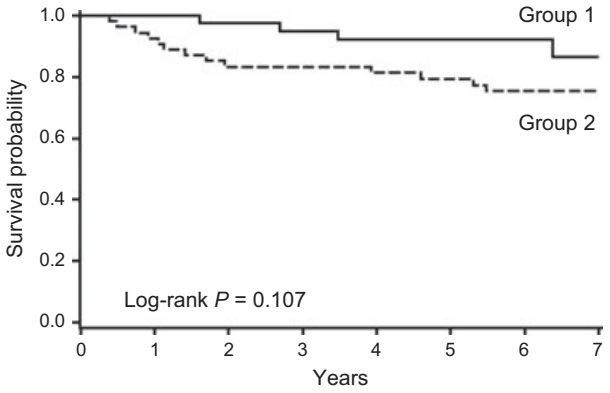

Figure 2 Seven-year patient survival by Kaplan–Meier analysis.

antibody-mediated rejection (in group 2), and one patient had mixed rejections (in group 1).

Compared with the group 2, group 1 has a superior death-censored graft survival as estimated by Kaplan–Meier curves over 7 years (Fig. 1, log rank $P = 0.043$). Patient survival trended higher, but not statistically different, in group 1 compared with the group 2 (Fig. 2, log rank $P = 0.107$). The death-censored graft survival rates as well as the patient survival rates at 1, 3, 5, and 7 years, are summarized in Table 2. The causes of graft loss and patient death are summarized in Table 3. The overall causes of graft loss and patient death were not statistically significant between the two groups. CAN, DWFG, and FSGS were the predominant causes of graft loss, and cardiovascular diseases were the main cause of patient death in both groups. Acute cellular rejection caused one graft loss in group 1 and two graft losses in group 2, while antibody mediated rejection caused another graft loss in group 2 (Table 3). Donor and recipient factors were analyzed by univariable analysis for risk of graft loss. Late persistent

proteinuria after 1 year of transplant was identified as the sole risk factor for graft loss, while treatment with early ACEi/ARB therapy before 1 year lowered the risk of graft loss (Table 4). These two significant factors were further analyzed by multivariable analysis, which indicated that late persistent proteinuria was an independent risk factor of graft loss (OR 2.70, 95% CI 1.33–5.49, $P = 0.006$), while early ACEi/ARB therapy effectively reduced the risk of graft loss (OR 0.38, 95% CI 0.18–0.79, $P = 0.009$).

Discussion

In our transplant center, en block pediatric donor kidneys were routinely split for adult patients. Previously, we reported that single kidney transplants from pediatric donors <5 years provided comparable 5-year graft survival to those from donors 5–10 years of age [25]. The youngest donor was only 9 months old, weighed 8 kg and had kidney length of 5 cm. There are variable numbers of glomeruli or nephron units in human kidneys, ranging from 0.5 to 2 million per kidney [26]. The variation in nephron number is largely determined by genetic factors and intrauterine nutrition that affect organogenesis and fetal growth before birth [26, 27]. The donor age and body weight after birth can affect the size of nephron, but not the number of nephron units in each kidney. Theoretically, even a small kidney from a very young baby may provide a similar number of nephron units as an adult donor kidney.

Table 4. Univariable and multivariable analysis of risk factors for renal graft loss.

	Univariable analysis		Multivariable analysis	
Parameter	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Pediatric donors				
Age (years)	1.02 (0.91, 1.14)	0.71		
Body weight	1.00 (0.96, 1.04)	0.82		
Kidney length	1.09 (0.79, 1.50)	0.60		
Adult recipients				
Age (years)	1.00 (0.98, 1.02)	0.85		
Race (black versus non-black)	1.16 (0.59, 2.26)	0.67		
Body weight	1.01 (0.99, 1.03)	0.33		
BMI	1.01 (0.96, 1.07)	0.63		
Causes of ESRD				
Diabetes	0.81 (0.24, 2.63)	0.72		
Hypertension	1.37 (0.48, 3.90)	0.56		
Glomerulonephritis	1.79 (0.63, 5.08)	0.28		
Others	reference			
Peak PRA level	1.00 (0.99, 1.02)	0.51		
Acute rejection (yes versus no)	1.78 (0.89, 3.56)	0.10		
Persistent proteinuria (yes versus no)	2.19 (1.15, 4.17)	0.03	2.70 (1.33, 5.49)	0.006
ACEi/ARB (yes versus no)	0.46 (0.21, 0.98)	0.04	0.38 (0.18, 0.79)	0.009
HLA mismatch	1.19 (0.96, 1.47)	0.11		
CIT	1.00 (0.95, 1.06)	0.97		

Transplanting single pediatric donor kidneys into adults does have several unique technical challenges and medical complications [1–11,25]. After transplant surgery, the small kidney is exposed to an adult blood pressure that is much higher than pediatric blood pressure, which causes intraglomerular hypertension. The large body mass and high metabolic demands of adult recipients stretch small nephron units to go through adaptive hypertrophy under functional and hemodynamic stresses. This type of hyperfiltration can cause glomerular injury, development of proteinuria and FSGS, and eventually graft failure [7–11,25].

We previously noted that there was a rapid and continuous rise in graft function from glomerular hyperfiltration and adaptive hypertrophy throughout the first year of transplant [25]. In our patients, blood pressure was aggressively controlled after transplant surgery to as low as the patient could tolerate. ACEi/ARB therapy was started when graft function had stabilized and proteinuria was detected as per our protocol, as new onset of proteinuria during the first year of transplant likely indicated development of hyperfiltration injury. We found that early ACEi/ARB treatment in this setting is associated with superior long-term graft survival compared to no ACEi/ARB treatment. The graft survival benefit of ACEi/ARB therapy may come from their ability to dilate the efferent arterioles of glomeruli, subsequently, to reduce intra-glomerular blood pressure and alleviate hyperfiltration injury.

Historically, physicians feel reluctant to use ACEi/ARB in patients with solitary kidneys, as it might compromise the renal function [19]. This concern may be particularly true in transplant patients, as some published papers suggest a harmful rather than a beneficial effect on renal function or graft survival [19–22]. Any rise in SCr could trigger an extensive work-up for graft dysfunction, including kidney biopsy. There are few reports investigating ACEi/ARB therapy in kidney transplant population, and the benefit seems to be limited to proteinuria only [19, 28, 29]. Development of proteinuria is very common and it has been shown to be associated with reduced graft survival [28,29]. However, ACEi/ARB therapy has not been persistently shown to improve graft survival in kidney transplant patients.

A multicenter study from Spain found that usage of RAS inhibitors at 12 months was an independent risk of graft loss at 4 years and was associated with 64% higher risk for graft loss [20]. A similar negative result was also reported by the University of Wisconsin transplant center [21]. A large collaborative study reported no patient or graft

survival benefit with ACEi/ARB therapy [22]. In another retrospective study from Austria, ACEi/ARB therapy was shown to improve long-term patient survival, but not death-censored graft survival ($P = 0.57$) [23]. A recent single center study also has noted that ACEi/ARB therapy was associated with lower risk of patient mortality, but not graft loss [24]. These studies were about the usual practice of transplanting adult donor kidneys to adult recipients and about treating the late development of proteinuria and CAN. Failure to detect graft survival benefit from ACEi/ARB therapy in these studies may be explained by our recent knowledge that the immunological factors (such as chronic rejection) play more important roles than the non-immunological factors (such as hyperfiltration injury) in determining long-term graft survival [30].

When adult patients are transplanted with single pediatric kidneys, hyperfiltration and other hemodynamic stresses are accelerated and much more severe than the usual transplants with adult donor kidneys. This may explain why graft survival benefit from early ACEi/ARB therapy for hyperfiltration injury in the first year of transplant can be detected in our current study. Both univariable and multivariable analyses found that persistent proteinuria after 1 year was a risk factor for graft loss, which is consistent with previous studies [28,29]. Late development of proteinuria is very common, and it usually indicates the development of CAN [28–31]. We want to emphasize that our current study is different from the previous ones in that we are not investigating ACEi/ARB therapy for late proteinuria or CAN. A subanalysis of our data in initiating ACEi/ARB therapy after 1 year of transplant ($n = 19$) for various causes (FSGS, CAN, late proteinuria, and post-transplant erythrocytosis) did not show any graft or patient survival benefit.

The graft function in group 2 were numerically worse than group 1 throughout this study period, as indicated by higher SCr and lower eGFR levels. But the difference did not reach statistical significance. This was likely because of small sample size, as we excluded those who had graft failure from calculation of graft function. Also, it is possible that RAS blockers might increase SCr in group 2, which could narrow the difference of graft function between the two groups. ACEi/ARB therapy was not associated with a higher percentage of patients who required for-cause kidney biopsy or higher incidence of biopsy-confirmed acute rejection. Our study suggests that ACEi/ARB therapy may also provide better long-term patient survival. However, our data did not reach statistical significance owing to small sample size. The possibility of patient survival benefit is not surprising. ACEi/ARB therapy is well known for their cardiovascular protection in addition to renal protection in the general population, and cardiovascular protection has been reported in transplant patients treated with ACE/ARB previously [23,24].

This study is limited by its single center data and retrospective observational design. Despite the similar baseline demographic characteristics in the two groups, our patients in group 1 were "selected' for ACEi/ARB therapy based on early development of proteinuria during the first year of transplant. Without intervention of ACEi/ARB therapy, these patients (in group 1) would theoretically have a higher risk of graft injury and graft loss than those in group 2. Therefore, it should be considered remarkable that ACEi/ARB therapy can provide a better graft survival in patients with higher risk. We speculate that even the patients in group 2 could have benefited from ACEi/ARB therapy. Actually, we have changed our protocol to start ACEi/ARB on all patients transplanted with single pediatric donor kidneys, as soon as the graft function becomes stable and before proteinuria is detected. Because of small sample size and incomplete quantity data of proteinuria over times, we were unable to provide detailed analyses, such as various brand or dose of ACEi or ARB drugs, other antihypertensive medications, degree of proteinuria reduction in graft survival, specific causes of graft loss, association of donor specific antibody with rejection, or graft loss, etc.

In summary, our study indicates that early ACEi/ARB therapy during the first year of transplant may protect single pediatric kidneys from hyperfiltration injury and could provide a graft survival benefit.

References

1. Pelletier SJ, Guidinger MK, Merion RM, *et al.* Recovery and utilization of deceased donor kidneys from small pediatric donors. *Am J Transplant* 2006; **6**: 1646.
2. Sureshkumar KK, Reddy CS, Nghiem DD, *et al.* Superiority of pediatric en bloc renal allografts over living donor kidneys: A long-term functional study. *Transplantation* 2006; **82**: 348.
3. Sharma A, Fisher RA, Cotterell AH, *et al.* En block kidney transplantation from pediatric donors: comparable outcomes with living donor kidney transplantation. *Transplantation* 2011; **92**: 564.
4. Balachandran VP, Anull MJ, Goris M, *et al.* Successful transplantation of single kidneys from pediatric donors weighting less than or equal to 10 kg into standard weight adult recipients. *Transplantation* 2010; **90**: 518.
5. Dharnidharka VR, Stevens G, Howard RJ. En-bloc kidney transplantation in the United States: An analysis of United Network of Organ Sharing (UNOS) data from 1987 to 2003. *Am J Transplant* 2005; **5**: 1513.
6. Harmon WE, Stablein D, Alexander SR, *et al.* Graft thrombosis in pediatric transplant recipients: A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 1991; **51**: 406.
7. Hayes JM, Novick AC, Streem SB, *et al.* The use of single pediatric cadaver kidneys for transplantation. *Transplantation* 1988; **45**: 106.

8. Terasaki PI, Koyama H, Cecka J, *et al.* The hyperfiltration hypothesis in human renal transplantation. *Transplantation* 1994; **57**: 1450.
9. Hayes JM, Steinmuller DR, Streem SB, *et al.* The development of proteinuria and focal segmental glomerulosclerosis-in recipients of pediatric donor kidneys. *Transplantation* 1991; **52**: 813.
10. Satterwaithe R, Aswad S, Sunga V, *et al.* Outcome of en bloc and single kidney transplantation from very young cadaveric donors. *Transplantation* 1997; **63**: 1405.
11. Modlin C, Novick AC, Goormastic M, *et al.* Long term results with single pediatric donor kidney transplants in adult recipients. *J Urol* 1996; **156**: 890.
12. Remuzzi A, Puntorieri S, Battaglia C, *et al.* Angiotensin converting enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. *J Clin Invest* 1990; **85**: 541.
13. Zoja C, Corna D, Bruzzi I, *et al.* Passive Heymann nephritis: evidence that angiotensin-converting enzyme inhibition reduces proteinuria and retards renal structural injury. *Exp Nephrol* 1996; **4**: 213.
14. Sofue T, Kiyomoto H, Kobori H, *et al.* Early treatment with olmesartan prevents juxtamedullary glomerular podocyte injury and the onset of microalbuminuria in type 2 diabetic rats. *Am J Hypertens* 2012; **25**: 604.
15. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349**:1857.
16. Kunz R, Friedrich C, Wolbers M, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148**: 30.
17. Hou FF, Xie D, Zhang X, *et al.* Renoprotection of Optimal Antiproteinuric Doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol* 2007; **18**: 1889.
18. Hellemons ME, Persson F, Bakker SJ, *et al.* Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria: a post hoc analysis of the IRMA-2 trial. *Diabetes Care* 2011; **34**: 2078.
19. Hiremath S, Fergusson D, Doucette S, *et al.* Renin angiotensin system blockade in kidney transplant: a systematic review of the evidence. *Am J Transplant* 2007; **7**: 2350.
20. Morales JM, Marcén R, Andrés A, *et al.* Renal transplantation in modern immunosuppressive era in Spain: four-year results from a multicenter database focus on post-transplant cardiovascular disease. *Kidney Int* 2008; **111**: S94.
21. Dalburg R, Muth B, Samaniego M, *et al.* One year serum albumin is an independent predictor of outcomes in kidney transplant recipients. *J Ren Nutr* 2010; **20**: 392.
22. Opelz G, Zeier M, Laux G, *et al.* No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. *J Am Soc Nephrol* 2006; **17**: 3257.
23. Heinze G, Mitterbauer C, Regele H, *et al.* Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* 2006; **17**: 889.
24. Hernández D, Muriel A, Abraira V, *et al.* Renin-angiotensin system blockade and kidney transplantation: a longitudinal cohort study. *Nephrol Dial Transplant* 2012; **27**: 417.
25. Zhang R, Paramesh A, Florman S, *et al.* Long-term outcome of adults who undergo transplantation with single pediatric kidneys: how young is too young? *Clin J Am Soc Nephrol* 2009; **4**: 1500.
26. Keller G, Zimmer G, Mall G, *et al.* Nephron number in patients with primary hypertension. *N Engl J Med* 2003; **348**: 101.
27. Grob ML, Amann K, Ritz E. Nephron number and renal risk in hypertension and diabetes. *J Am Soc Nephrol* 2005; **16**: S27.
28. Amer H, Cosio F. Significance of proteinuria in kidney transplant recipients. *J Am Soc Nephrol* 2009; **20**: 2490.
29. Amer H, Fidler ME, Myslak M, *et al.* Proteinuria after kidney transplantation, relationship to allograft histology and survival. *Am J Transplant* 2007; **7**: 2748.
30. Khan IE, Zhang R, Simon E, *et al.* The alloimmune injury in chronic allograft nephropathy, Chronic Kidney Disease. Prof. Monika Göőz (Ed.), ISBN: 978-953-51-0171-0, InTech, March 2012, Pages 401.
31. Birnbaum LM, Lipman M, Paraskevas S, *et al.* Management of chronic allograft nephropathy: A systematic review. *Clin J Am Soc Nephrol* 2009; **4**: 860.