# UV TRANSPLANTATION

Doppler Ultrasonographic Indexes in Kidney Transplant Recipients Its Relationship With Kidney Function

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**Introduction.** Doppler ultrasonography (DU) is mostly used for assessment of both graft and native kidneys' vascular status. In this study, correlation between the DU indexes and kidney allograft function was evaluated.

**Materials and Methods.** Hospital records of 273 kidney transplant patients (154 men and 119 women) were reviewed. In all cases, DU had been performed 1 month after kidney transplantation. We evaluated the data on the resistive index (RI) and pulsatility index (PI) in the interlobar arteries and renal artery stenosis (RAS), and renal vessels thrombosis were determined. Concurrent serum creatinine and cyclosporine values were assessed in relation to the DU findings.

**Results.** The RI and PI had significant linear correlations with serum creatinine (P = .03 and P = .002, respectively). Also, there were direct linear correlations between the age of the patients and the RI and PI values. The frequency of RAS was 10.3%. In patients with RAS, the mean creatinine level ( $2.08 \pm 1.70 \text{ mg/dL}$ ) was significantly higher than that in patients without RAS ( $1.48 \pm 0.97 \text{ mg/dL}$ ; P = .004). Despite this finding, RI and PI were significantly lower in patients with RAS than in the patients with patent renovascular tributary ( $0.59 \pm 0.15 \text{ versus } 0.65 \pm 0.11$ ; P = .03 and  $1.02 \pm 0.40 \text{ versus } 1.18 \pm 0.46$ ; P = .049, respectively). There were no associations between serum cyclosporine level or panel reactive antibodies and the RI or PI.

**Conclusions.** The RI and PI are valuable DU markers for determining the kidney allograft function and the related vascular complications.

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## INTRODUCTION

Although Doppler ultrasonography (DU) of the intrarenal arteries was initially introduced for screening of renovascular diseases of native kidneys,<sup>1</sup> recently Doppler indexes have been used also to evaluate kidney allograft dysfunction, as well.<sup>2-4</sup> Most of investigators use both resistive index (RI) and pulsatility index (PI) of the intrarenal arteries to gain information about the allograft integrity.<sup>4,5-7</sup> Despite this utilization, some controversies are encountered on the accuracy of DU in kidney transplant recipients.<sup>8</sup> This study was designed to determine the relationship between the DU indexes, including the RI and the PI, and kidney allograft function. We evaluated the frequency of vascular complications in the kidney allograft arteries and veins as well.

#### MATERIALS AND METHODS

In this retrospective study, we reviewed 273 living

unrelated kidney transplants that were performed between November 2002 and February 2007 in Imam Khomeini Hospital of Tabriz University of Medical Sciences in Tabriz, Iran. Immunosuppressive regimen was composed of prednisolone, cyclosporine, and mycophenolate mofetil or azathioprine. Acute rejection, hypotension, cyclosporine toxicity (serum cyclosporine levels greater than 400 ng/mL), hydronephrosis, perinephric fluid collection, and any cause that might strongly affect the DU indexes were the exclusion criteria.

All of the patients had undergone assessment of the allograft by the DU, 1 month after transplantation. All of the DUs had been performed by a single radiologist using a Hitachi model EUB 525 (Hitachi Medical Corp, Tokyo, Japan) with the help of 3.5- and 7.5-MHz convex probes. The DU Indexes including the RI, the PI, percentage of lumen stenosis, and renal artery or vein thrombosis were collected. For the interlobar renal arteries, the RI and PI had been calculated from the Doppler spectra using the following formulae:

RI = (peak systolic velocity - end diastolic velocity)/peak systolic velocity

PI = (peak systolic velocity - end diastolic velocity)/mean velocity

Pretransplant level of panel reactive antibodies (PRA) was recorded for each patient. Laboratory studies including serum level of creatinine (Jaffe method; mg/dL), serum through level of cyclosporine (monoclonal radioimmunoassay; ng/dL) determined just prior to the DU were also collected.

Statistical analyses were performed by the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). The values of continuous variables were presented as mean  $\pm$  standard deviation. The *t* test, the Pearson correlation test, and multiple linear regression analysis were utilized for data analyses. A *P* value less than .05 was considered significant.

#### RESULTS

In our study, hospital records of 273 kidney transplant recipients were reviewed. The mean age of the patients was  $36.7 \pm 13.2$  years (range, 6 to 75 years). The patients were 154 men (56.4%) and 119 women (43.6%). The mean duration of posttransplant hospital stay was  $26.8 \pm 13.2$  days. The mean PRA value was  $2.4 \pm 6.8\%$ . The mean

serum levels of creatinine and cyclosporine were  $1.55 \pm 1.09 \text{ mg/dL}$  and  $278.51 \pm 141.11 \text{ ng/dL}$ , respectively.

The mean RI and PI in all of the patients were 0.64  $\pm$  0.12 (range, 0.33 to 1.00) and 1.16  $\pm$  0.46 (range, 0.2 to 3.9). The 17 retransplanted patients (6.3%) had higher RIs than the recipients of their first kidney allograft (0.72  $\pm$  0.16 versus 0.64  $\pm$  0.12; P = .01). The Pearson correlation test revealed a strong linear correlation between the RI and the PI (P < .001; r = 0.72). Interestingly, the RI and the PI had also significant direct linear correlations with serum creatinine level (P = .03; r = 0.13 and P = .002; r = 0.19, respectively). Figures 1 and 2 show the linear regression analysis plots of serum creatinine in relation to the RI and the PI, respectively. Also,



**Figure 1.** Linear regression between the resistive index and serum creatinine level in kidney allograft recipients (P = .03; r = 0.13).



Figure 2. Linear regression between pulsatility index and serum creatinine level in kidney allograft recipients (P = .002; r = 0.19).

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	Kidney Transplant Patients			
Variables	With RAS	Without RAS	All	Р
Age, y	41.6 ± 13.1	36.0 ± 13.0	36.7 ± 13.1	.03
Doppler Ultrasonography				
RI	0.59 ± 0.15	0.65 ± 0.11	0.64 ± 0.12	.03
PI	$1.02 \pm 0.40$	1.18 ± 0.46	1.16 ± 0.46	.049
PRA, %	$3.8 \pm 8.4$	$2.3 \pm 6.6$	$2.4 \pm 6.8$	.33
Hospital stay, d	24.61 ± 8.79	27.12 ± 13.70	26.83 ± 13.24	.32
Serum creatinine, mg/dL	2.08 ± 1.70	$1.48 \pm 0.97$	1.55 ± 1.09	.004
Serum cyclosporine, ng/mL	274.55 ± 156.24	279.02 ± 139.40	278.51 ± 141.11	.87

Means ± Standard Deviations of Variables in Kidney Recipients With and Without Renal Artery Stenosis\*

\*RAS indicates renal artery stenosis; RI, resistive index; PI, pulsatility index; and PRA, panel reactive antibodies.

there was a direct linear correlation between age of the patients and the RI and PI values (P = .004; r = 0.17 and P = .003; r = 0.18, respectively). There was no association of cyclosporine level and PRA with the RI and PI.

Of 273 patients, 36 (13.2%) had vascular complications of the kidney allografts, of which 5 (1.8%) had renal vein thrombosis, 3 (1.1%) had renal artery thrombosis, and 28 (10.3%) had renal artery stenosis (RAS). In the patients with RAS, 23 (8.4%) had a moderate stenosis (50% to 70% of the lumen) and 5 (1.8%) had a severe one (greater than 70% of the lumen). The mean values of age, RI, PI, PRA, hospital stay, and serum creatinine and cyclosporine levels for the patients with and without RAS are listed in the Table. Age and serum creatinine level were greater and the DU indexes were lower significantly in the patients with RAS than those without it.

#### **DISCUSSION**

Following kidney transplantation, some complications such as RAS and thrombosis of the renal vessels may occur. For decades, research has been focused on noninvasive diagnostic techniques that would reliably predict the outcome of transplantation and kidney allograft function after revascularization of the transplanted kidney. Doppler ultrasonography has been steadily improved over the past 5 years and is now frequently used as the first-line screening test for kidney transplant recipients.<sup>5-7,9,10</sup> It is not only a useful tool for early evaluation of the kidney allograft vasculature and function,<sup>11</sup> but also is a reliable noninvasive tool readily available for identifying patients who may benefit from kidney allograft revascularization and for assessing the effectiveness of the procedure.12 Its usefulness was seen also

in early diagnosis of kidney allograft vascular thrombosis and RAS in the present study. Hence, patients with renal vessels thrombosis and RAS could be diagnosed noninvasively and timely.

In 2 studies done in Iran, the mean values of the RI for kidney transplant patients were 0.61± 0.08 and  $0.57 \pm 0.55$ , which were lower than the values determined in our assessment.<sup>13,14</sup>In a recent study by Nouri-Majelan and Nafici, the mean RI and PI were reported to be  $0.69 \pm 0.06$  and 1.30 $\pm$  0.30, respectively,<sup>14</sup> finding close to the range of our finding. At least, we can conclude that the mean and the range of the RI and PI are similar in various studies on kidney allograft recipients.<sup>13-15</sup> It should also be mentioned that our study showed a significant correlation between the RI and the PI. Ardalan and colleagues' results also showed the same significant correlation.<sup>15</sup> Although these indexes come from different formula, it seems they have close linear correlation with each other.

Chudek and colleagues found significant reverse correlations between the donor's glomerular filtration rate and the PI and RI.<sup>16</sup> If we consider serum creatinine level as an index of kidney function that has a reverse relation with glomerular filtration rate and creatinine clearance, serum creatinine level must have a direct linear correlation with the RI and PI. It means that in patients with higher levels of creatinine, the RI and PI levels is also high. Although changes in these DU indexes can show altered perfusion in the renal parenchyma,<sup>17</sup> they might be affected by other factors such as arterial blood pressure, heart rate, and vascular compliance of the recipient. On the other hand, the vascular compliance of graft itself, graft function, and vasoconstriction-inducing drugs-eg, cyclosporine-may alter the intrarenal Doppler indexes.<sup>18-21</sup>

Ardalan and coworkers showed a significant correlation between the RI or PI indexes and serum creatinine level during the 2nd, 9th, 16th, and 23rd days posttransplantation,<sup>15</sup> and congruous with our findings, they suggested a positive linear relationship between serum creatinine and the PI and RI. In Kahraman and colleagues' study,<sup>11</sup> there was a negative correlation between the RI and PI and the 1-month and 1-year creatinine clearance values, respectively. However, surprisingly Wang and associates failed to find any correlation between serum creatinine and either the RI or PI values.<sup>22</sup> The current study demonstrated that the RI and PI indexes of the DU determined early after transplantation might be a valuable method to predict allograft function in stable cases during the early period of transplantation.<sup>11</sup> Supporting our findings, Radermacher and colleagues from Germany recently reported that the RI was the strongest predictor of declining in creatinine clearance as compared to other parameters.<sup>23</sup> Gaschen and Schuurman studied on a nonhuman primate kidney transplant model. They showed that application of DU imaging provided valuable data on the kidney allograft functional state and its scores had a better predictive value of histology than serum creatinine values alone.24 This study and the one by Tarzamni and colleagues<sup>25</sup> demonstrated a linear correlation between the DU scores and serum creatinine as well.

The RI and PI obtained from the intrarenal arteries of a native kidney rise with age in normotensive and hypertensive individuals.<sup>26</sup> We found a statistically significant correlation between these indexes and recipients' age as already demonstrated by Nouri-Majelan and Nafici in 2007, too.<sup>14</sup> This rise in the elderly individuals probably occurs as a result of reduction in prerenal aortic compression chamber function by atherosclerosis. This interpretation is supported by in vitro experiments that demonstrated a relationship between vascular compliance and the variability of Doppler waveform.27 Thus, the correlation between age and intrarenal Doppler indexes of the native kidneys reflects the age dependency of vascular compliance. Our data indicated that the vascular compliance determined by the patient's age is also among the most important influencing factors for the RI and PI of a transplant kidney. Like our results, other researchers have reported

a good correlation between the RI and the age of kidney transplant patients.<sup>22,28,29</sup> On the other hand, the same correlation of age with RI and PI is seen in diabetic patients in whom atherosclerosis is a prominent vascular change by aging.<sup>30</sup> This emphasizes that RAS may occur in relation to agerelated factors including atherosclerosis.

Cyclosporine, due to its vasospastic characteristics, may increase the intrarenal vascular resistance as reported before.<sup>19</sup> Although some authors demonstrated a negative association between cyclosporine level and the RI,<sup>23,28</sup> others did not confirm this relationship.<sup>9,20,21,31</sup> Results of our study, like these studies and another done recently,<sup>15</sup> neither showed any correlation between the RI and PI and cyclosporine level, nor demonstrated any differences in serum cyclosporine level between the patients with and without RAS. In contrast to some previous studies,<sup>23,28</sup> it seems that we could not consider cyclosporine level as a culprit agent for the RAS pathophysiology.

Renal artery stenosis is the most common vascular complication of transplanted kidneys due to arterial atherosclerosis in the donor, suture technique, and trauma to the renal or iliac artery in the donor or recipient. Its early diagnosis is critical, because early intervention could save graft function. Doppler ultrasonography is an excellent method for screening patients suspected to have RAS and can help also to select the scheduled patients for arteriography.<sup>32</sup> It has been shown that stenosis of the transplanted renal artery is found in 1% to 23% of recipients.33-35 In a study in Iran, this prevalence was 10%,<sup>13</sup> and in our study it was 10.3%. Compared to some others,<sup>8</sup> the rate we reported was low, but in 2 studies from Turkey, its prevalence was 0.9% in adults and 2.3% in children, respectively.<sup>33,36</sup> These differences may be because of technical problems in the first study and the children's best wound-healing process in the second study. In contrast to other studies in which renal artery thrombosis included less than 0.1% to 1% of the kidney allograft recipients, 33, 37-39 in our study, thrombosis was revealed in more cases. It may be due to technical problems, such as intimal manipulation, kinking of the artery, prolonged warm ischemia, or patients' related risk factors such as severe dehydration, hypotension, multiple renal arteries, unidentified intimal graft, and hypercoagulable state.<sup>37,40,41</sup> Contrary to the higher rate of renal artery thrombosis, the frequency of venous thrombosis in our series was similar to the other reports, ranging between 0.3% and 4.2%.<sup>42-44</sup> In addition to venous compression by hematomas or lymphoceles, anastomotic stenosis and extension of underlying deep venous thrombosis should be noted in this disease as underlying etiologies.<sup>37</sup>

In a study which was done in Slovenia,<sup>8</sup> there was no significant difference in serum creatinine between kidney transplant patients with and without RAS. This finding is against ours. However, in agreement with our results, a significant difference between the RI values measured in kidney transplant patients with and without RAS has been reported.<sup>45</sup> In a normal condition, the diastolic velocity approaches 50% of the peak systolic velocity. Hence, with increased resistance, this value decreases and the RI increases. Renal artery stenosis reduces renal perfusion, causing elevation of the serum creatinine level. But, because of the decreased peak systolic velocity, the RI is less than 0.5 (parvus-tardus pattern).<sup>46</sup>

## **CONCLUSIONS**

There is a strong correlation between the PI and PI which shows we can use each of them instead of the other in patients with a kidney allograft undergoing DU. Because of the significant correlation between these DU indexes and serum creatinine level, we can use the DU as a tool to predict kidney function in association with serum creatinine, but its applicability depends heavily on the operator's skill. The frequency of vascular complications and RAS in out patients was analogous to the previous reports, and accordingly, RAS was a common vascular complication.

#### **CONFLICT OF INTEREST**

None declared.

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