Determinants of Intrarenal Doppler Indices in Stable Renal Allografts

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Abstract. Color Doppler sonography has been introduced for graft monitoring after renal transplantation. Little is known, however, about independent factors that have an impact on intrarenal Doppler indices as indicators for transplant dysfunction. Therefore, in this study, potential determinants of the resistive index (RI) and of the pulsatility index (PI) in 110 patients with stable renal allografts were studied. The mean RI and PI were 0.70 ± 0.07 (range, 0.53 to 0.88) and 1.36 ± 0.21 (range, 0.91 to 1.98), respectively. In multivariate regression analysis, RI and PI correlated significantly with age and arterial pulse pressure of the recipient. There was no correlation with donor age, heart rate, mean arterial blood pressure, and cyclosporine trough levels. Furthermore, parameters of kidney function, such as serum creatinine concentration, creatinine clearance rate, $^{51}$Cr-ethylenediaminetetraacetate clearance rate, and proteinuria, showed no significant correlation with the Doppler indices. The data indicate that intrarenal Doppler indices of the grafts are hemodynamic indices, primarily depending on the recipient-related vascular compliance rather than on the function of the graft. Therefore, only intraindividual comparison of the Doppler indices may be useful to detect potential changes of graft resistance during long-term follow-up. (J Am Soc Nephrol 8: 813–816, 1997)

Doppler sonography of intrarenal arteries was initially introduced to screen for renovascular disease of native kidneys (1–3). Recently, however, Doppler indices have been used also to evaluate renal allograft dysfunction, with contrasting results (4–9). Most investigators used either a resistive index (RI) or pulsatility index (PI) obtained from the intrarenal arteries to gain information about graft integrity (7,10–15).

It is likely that Doppler indices of intrarenal graft arteries are influenced by several factors, such as arterial blood pressure, heart rate, and vascular compliance of the recipient. On the other hand, the vascular compliance of the graft itself, graft function, and drugs, e.g., cyclosporine, inducing vasoconstriction may alter intrarenal Doppler indices. The relative importance of each of these various factors has not been thoroughly investigated (16–19).

We therefore analyzed potential determinants of Doppler resistance parameters in 110 stable renal allografts to determine whether Doppler indices may be useful in gaining information about graft integrity.

Materials and Methods

Patients

Patients with stable renal function over a 3-month period were enrolled. Patients with transplant renal artery stenosis or with evidence of urinary tract obstruction were excluded.

One hundred ten patients (47 women) aged 45 ± 13 yr (range, 16 to 74 yr) were studied for 4 to 200 months (mean, 38 ± 38 months) after transplantation. Patients were advised to take their medication in the morning. Color Doppler examinations were performed between 2 and 4 h later with a phased-array 2.5 to 3.5 MHz transducer (Acuson 128× P10; Mountain View, CA) in supine position. In interlobar and segmental renal arteries, RI and PI were calculated from the Doppler spectra by using the following ratios:

RI = peak systolic velocity − end diastolic velocity/peak systolic velocity

PI = peak systolic velocity − end diastolic velocity/mean velocity

The values of six different spectral samples were averaged to the mean RI or PI of the graft. Angle-corrected (<60°) peak systolic velocity (mean, 123 ± 33 cm/s; range, 60 to 199 cm/s) in the transplant renal artery was obtained to rule out stenosis (2).

Heart rate and blood pressure were measured manually during Doppler examination while the patient was in a supine position. Mean arterial blood pressure and pulse pressure (systolic minus diastolic arterial blood pressure) were correlated with the Doppler indices. Cyclosporine trough levels, measured by a fluorescence-polarization-immunoassay (TDx) on the day of Doppler examination, were correlated with both RI and PI. Additional clinical data (Table 1) were obtained from the patients’ records for correlation with Doppler indices.

Serum and urine creatinine levels (24-h urine collection) were determined in all patients to calculate the endogenous creatinine clearance. Additionally, in 34 randomly assigned patients, the GFR was assessed by the plasma clearance of $^{51}$Cr-ethylenediaminetetraacetate ($^{51}$Cr-EDTA) (20). The creatinine clearance rate of these patients did not differ from that of the other patients ($N = 34$, mean, 69.3 ± 23.6 mL/min versus $N = 76$, mean, 65.2 ± 20.7 mL/min; $P = 0.507$, $t$ test). All parameters of renal function were correlated with the Doppler indices.
Association between Doppler indices and each of the individual parameters that are listed in Table 1 on the age (P = 0.0238), pulse pressure (P = 0.05). Pulse pressure of the recipient in the univariate and multivariate analysis. In contrast, no such significant correlation was found for donor age. RI and PI obtained from intrarenal arteries of native kidneys rise with age in normotensive and hypertensive subjects (22,23). This rise in the elderly is probably a result of a reduction of prerenal aortic compression chamber function by atherosclerosis. This interpretation is supported by in vitro experiments, which demonstrated a relationship between vascular compliance and the variability of Doppler waveform (24).

Thus, the correlation between age and intrarenal Doppler indices of native kidneys reflects the age-dependency of vascular compliance. Our data indicate that the vascular compliance determined by the patient's (recipient's) age is also the most important influencing factor for RI and PI of renal allografts. This view is supported by the significant correlation between intrarenal Doppler indices of the grafts and the pulse pressure of the recipient in the univariate and multivariate analysis. Similar data have been reported previously for native kidneys in patients with aortic insufficiency. In these patients, RI was shown to be elevated because of a large blood pressure amplitude (25,26). Graft vascular compliance per se, possibly determined by donor age, seems to play no role for intrarenal Doppler indices.

Impact of Renal Function and Number of Rejections
Renal function was determined by three different methods, including the “gold standard” ($^{51}$Cr-EDTA clearance) (20) in a subgroup of patients. In contrast to Quarto di Palo et al. (27), we found no correlation between Doppler indices and renal function in the multivariate regression analysis. However, in our study, renal function had been stable at least over a period of 3 months, with a smaller range of serum creatinine levels than that in the study by Quarto di Palo et al.. It can be speculated that very poor graft function is associated with elevated intrarenal Doppler values. In our group of 110 patients, a substantial number (seventy-seven) of histologically proven acute rejections had occurred. One would expect that these rejections would lead to an increase in vascular resistance of the grafts because of interstitial fibrosis. This relationship may indeed be reflected by the significant correlation of RI with the number of histologically proven rejections. It needs to

Statistical Analyses
All values are expressed as means ± SD. Statistical analysis was done by t test or by Mann-Whitney rank sum test for data that was not normally distributed to detect differences between two groups. Univariate linear regression analysis was performed to determine the association between Doppler indices and each of the individual parameters mentioned above. Multiple linear regression analysis was performed to avoid overinterpretation of potentially linked variables. Probability values less than 0.05 were considered to be significant.

Results
The clinical characteristics of all patients are shown in Table 1. Intrarenal Doppler indices were successfully measured in all patients. The mean RI was 0.70 ± 0.07 (range, 0.53 to 0.88), and mean PI was 1.36 ± 0.21 (range, 0.91 to 1.98).

Univariate and multiple linear regression analysis included the dependent variables RI or PI and all of the clinical parameters that are listed in Table 1. The relationship of PI with donor age, recipient age, and pulse pressure are shown in Figure 1.

The multivariate analysis (Table 2) revealed that intrarenal RI depends only on recipient age ($P < 0.05$), pulse pressure ($P = 0.0003$), and number of rejections ($P < 0.0055$) ($r = 0.527$; RI = 0.545 + (0.00113 · age) + (0.00156 · pulse pressure) + (0.0238 · number of rejections). PI depended only on the age ($P < 0.0001$) and the pulse pressure of the recipient ($P < 0.05$) ($r = 0.632$; PI = 0.826 (0.00867 · age) + (0.00258 · pulse pressure). Creatinine clearance rate correlated significantly with RI and PI only in the univariate (not shown) but not in the multivariate regression analysis.

Discussion
Intrarenal Doppler indices have been used to distinguish acute rejection from other causes responsible for renal allograft dysfunction. So-called “normal” values of RI and PI were established (6,7,9,21) without critical consideration of factors that influence these indices. The crucial question is whether intrarenal Doppler indices are determined by the graft recipient or by the graft itself. One could argue that only in the latter case is Doppler follow-up of renal transplant function is useful. To answer this question, several clinical characteristics of recipients and donors were analyzed for their impact on RI and PI.

Impact of Age and Vascular Compliance
There was a strong correlation between intrarenal RI or PI and the age of the recipient in the univariate and multivariate analysis. In contrast, no such significant correlation was found for donor age. RI and PI obtained from intrarenal arteries of native kidneys rise with age in normotensive and hypertensive subjects (22,23). This rise in the elderly is probably a result of a reduction of prerenal aortic compression chamber function by atherosclerosis. This interpretation is supported by in vitro experiments, which demonstrated a relationship between vascular compliance and the variability of Doppler waveform (24).
be emphasized that no other parameters (see Table 1) correlated with both RI and PI of renal function.

Drugs, which modulate vascular tone, may have an impact on intrarenal Doppler indices. A recent study reported elevations of RI and PI after the administration of cyclosporine (17); however, other studies have not confirmed this relationship (18,19). In our study, cyclosporine trough levels were measured on the day of Doppler examination and did not correlate with intrarenal Doppler indices. It is possible that cyclosporine peak levels may influence RI and PI; however, we did not perform Doppler follow-up of the patients after the administration of cyclosporine.

**Conclusion and Outlook**

We propose that intrarenal Doppler indices of transplanted kidneys are hemodynamic indices that primarily depend on the recipient’s vascular compliance. Previous acute rejections seem to have an additional impact on these indices. Renal function and

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**Figure 1.** Correlation between pulsatility index (PI) with either recipient age (A), donor age (B), or pulse pressure (C). The univariate regression analysis demonstrates a significant correlation between recipient age and PI and also between pulse pressure and PI obtained from the intrarenal arteries of the graft. No correlation was found between donor age and PI.
integrity of the graft, however, cannot be predicted from RI or PI. In stable renal allografts, RI and PI should be determined as baseline values in each patient for long-term follow-up. Only then may changes of renal resistance detected by intraindividual comparison of these indices be of clinical use.

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References