Tissue Pulsatility Index: A New Parameter to Evaluate Renal Transplant Perfusion

Thomas Scholbach,[1,3] *Elisa Girelli,*[1] *and Jakob Scholbach*[2]

Background. Chronic allograft nephropathy (CAN) is characterized by loss of parenchymal perfusion. We applied therefore the novel parameter Tissue Pulsatility Index (TPI) to quantify transplant perfusion in the long-term surveillance of renal transplants.

Methods. Color Doppler sonographic videos of renal transplants from 38 renal transplant recipients were recorded under defined conditions. TPI was calculated as ratio of the difference of mean systolic and diastolic velocities of the entire region and the average velocity.

Results. TPI was significantly different between the proximal and distal cortical layers (1.12 vs. 1.56, respectively $P=0.000$). In patients with elevated creatinine as a measure of compromised function, significantly ($P=0.016$) higher values (TPI=1.70) were found at distal cortical level compared to patients with normal creatinine (TPI=1.34). After transplantation, TPI rises significantly: 1.10 in 0–1 years vs. 1.41 in 1–2.9 years, $P=0.002$; 1.10 in 0–1 years vs. 1.37 in 3–4.9 years, $P=0.000$; 1.10 in 0–1 years vs. 1.31 in 7–8.9 years, $P=0.049$). TPI declines later on in our population to significantly lowered values in the group more than 9 years after transplantation (1.10 in 0–1 years vs. 0.94 in >9 years, $P=0.044$).

Conclusion. With the novel TPI, we could demonstrate significant differences between proximal and distal cortical perfusion, between compromised and well-functioning transplants, and could observe significant changes of transplant perfusion at various points at the posttransplantation time scale.

Keywords: Tissue perfusion, Tissue Pulsatility Index (TPI), Measurement, Color Doppler sonography, Software.

(*Transplantation* 2006;81: 751–755)

Volume and quality of renal transplant perfusion is important for sufficient transplant function. Nowadays it is common practice to evaluate transplant perfusion by measurement of resistance index (RI) in single vessels mostly interlobar arteries (*1*). This is easily accomplished as interlobar arteries are easily accessible for pulsed wave Doppler interrogation. No exact measurement of flow velocities is necessary because RI is calculated as a ratio of maximum systolic and minimum diastolic flow velocity and the procedure is completed quickly in routine practice.

There are, however, some substantial drawbacks of this technique: quality of perfusion is evaluated at single points only of single vessels, RI describes perfusion at only two extreme points of a whole heart cycle (peak systole and end of diastole) and RI in single vessels may give an impression only of perfusion quality (*2*, *3*). In certain cases, overt discrepancies between conventional Doppler indices and transplant function have been observed (*4*, *5*).

To overcome limitations of conventional Doppler indices, we have developed a quite new approach to tissue perfusion measurement and applied this to renal transplants. We calculated various perfusion parameters automatically by means of a special software (Pixelflux, Chameleon-Software, Leipzig, Germany) (*6*) during a whole heart cycle and inside of an anatomically defined region of interest (ROI).

[1] Kinderklinik am Städtischen Klinikum "St. Georg," Leipzig, Germany.
[2] Sektion Mathematik, University of Leipzig, Leipzig, Germany.
[3] Address correspondence to: Thomas Scholbach, M.D., Kinderklinik am Städtischen Klinikum "St. Georg," Delitzscher Str. 141, D-04229 Leipzig, Germany.
E-mail: thomas.scholbach@sanktgeorg.de
Received 24 August 2005. Revision requested 14 September 2005.
Accepted 30 November 2005.

ISSN 0041-1337/06/8105-751
DOI: 10.1097/01.tp.0000201928.04266.d2

As in native kidneys function of renal transplants depends on sufficient perfusion. Renal transplants (RTX) are subject to function loss over time (*7*, *8*). Chronic rejection, recurrence of transplant recipient's original disease, infections, arteriosclerosis or drug toxicity may all contribute to loss of function (*8*). All these disorders are accompanied by change of transplant perfusion. It is important to measure renal perfusion in such cases to adapt therapeutic and immunosuppressive intervention. Evaluation of perfusion in renal transplants, however, is demanding and scintigraphy is the method of choice today. This technique is not always available, is costly, and uses radiating substances. A new technique to quantify RTX parenchymal perfusion is wanted. We applied the novel Dynamic Color Doppler Sonographic Parenchymal Perfusion Measurement to renal transplants in order to evaluate changes of transplant perfusion in posttransplantation follow up.

PATIENTS AND METHODS

We examined 38 RTX recipients from August 2000 to June 2002 (23 males and 15 females, age 2.5 to 27 years, mean age 15 years, standard deviation: 4.9 years), with a mean BMI of 21.6 (range 14.1 to 36.8), mean weight of 51 kg (range 13 to 102 kg), mean height of 152 cm (range 91 to 181 cm). Patients were routinely investigated according to clinical requirements. All patients from our hospital's pediatric dialysis department were included. Time after transplantation at investigation varied from 7 days to 11 years (mean 3.4 years). Mean duration of follow up was 10 months (0 [single examination] to 2 years). Every patient was investigated an average of four times (range 1 to 12, SD 2.4; only one patient was examined 11 times and another one was examined 12 times). Causes of end-stage renal failure are listed in Table 1. During the observation period, due to clinical reasons, seven biopsies were

TABLE 1. List of diagnoses responsible for end-stage renal failure in 38 renal transplant recipients

Diagnosis	N
Glomerulonephritis	7
Polycystic kidneys	5
Hemolytic-uremic syndrome	5
Megaureter	3
Vesico-ureteral reflux grade 4/5	2
Hydronephrosis	2
Juvenile nephronophthisis	2
Subvesical obstruction	1
Malformation	1
Cystinosis	1
Others	9
Total	38

taken in four patients revealing four acute and three chronic rejections.

Color Doppler Sonography

Color Doppler sonographic investigations of the renal transplants were performed with a 4–8 MHz curved array probe and a Sequoia 512 ultrasound equipment (Acuson, Mountainview, California). Longitudinal and transverse sections of the transplants were recorded. Care was taken to investigate vessels that run straight towards the transducer. This way an angle correction of the Doppler signal could be avoided. A crucial point is the presetting of the ultrasound equipment. Always the same color Doppler frequency was chosen for investigation. Otherwise, no comparison of different perfusion measurements is possible. Color Doppler frequency was 7 MHz. These presettings were used for all investigations in all patients. Color gain was fixed by the presetting and never changed. Following parameters were never changed (values applied in parentheses): spatial resolution (S1), edge (−1), color scale without variance display (V3), persistence (2), preset (low flow), color gain (50%).

To avoid aliasing, maximal color velocity (pulse repetition frequency) was adapted in a range from 4.3 to 8.6 cm/s. Focus was always at the distal edge of medullary pyramid.

Dynamic Color Doppler Tissue Perfusion Measurement

We measured intensity of perfusion automatically with a recently developed software. Color Doppler signals from digital color Doppler sonographic videos (DICOM format: **D**igital **I**maging and **C**ommunications in **M**edicine) were quantified in a novel dynamic way. Dynamic means that changes of blood flow during the heart cycle have been taken into account. This is important because blood flow velocity strongly pulsates even in tiniest arteries of a kidney. Dynamic appreciation of flow at each single point of the heart cycle is therefore fundamental for refined understanding of tissue flow phenomena. The software automatically calibrates distances and color hues as flow velocities and calculates color pixel area and flow velocity—encoded by each pixel—inside a region of interest of a video sequence. This way a quantification of blood flow inside the investigated tissue is achieved. Videos with movement artifacts were excluded from perfusion quantification.

The outputs are:

1. Area (A) of depicted vessels inside the region of interest (ROI) (average of one whole heart cycle) (these measurements are not presented here)
2. Mean flow velocity (v) inside the ROI (average of one whole heart cycle) (results not given here)
3. Tissue Pulsatility Index (TPI) of changes of these parameters during the heart cycle (see below)
4. Measure of flow quantity inside called perfusion intensity (P) of the ROI (not further outlined here (*9*))

The ROI was chosen in the renal parenchyma in the area between the outer border of medullary pyramids and the kidney surface (Fig. 1) (*9*). The ROI was set to contain vessels running in symmetric distribution pattern to the transducer. A parallelogram was placed to enclose a complete vascular segment fed by one interlobar artery. Digital videos containing 25 to 50 images and at least one full heart cycle were recorded.

Mean values of colored area and mean flow velocity are calculated automatically by reckoning average values of all pixels inside one single image's ROI and averaging these values for all images encompassing one full heart cycle. Inside the ROI the whole area occupied by colored pixels is calculated. This calculation is automatically repeated for the same ROI for all images of a digital video. The detection of one full heart cycle is also done automatically by the software. These averaged values of flow velocity and area from a whole heart cycle inside ROI are used for calculation of TPI.

As in conventional PI (Pulsatility Index), TPI was calculated as ratio of difference of maximum systolic (v_{sys}) and minimum diastolic (v_{dia}) flow velocity of the whole ROI divided by average flow velocity ($v_{average}$) of the same region.

$$TPI = (v_{sys} - v_{dia})/v_{average}$$

The ROI was divided into two segments (p50 and d50) (Fig. 1). In p50, the whole width of the ROI but only the

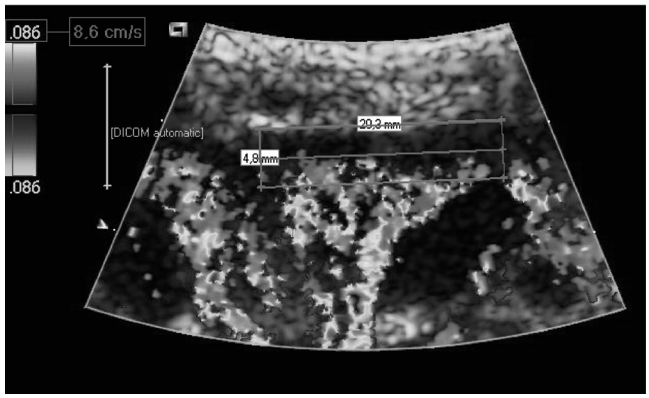

FIGURE 1. Position of region of interest for TPI measurements. Proximal cortex lower red parallelogram, distal cortex parallelogram above. ROI was set according to anatomical landmarks: encompassing a full segment distally to the outer edge of medullary pyramids (MP) fed by one interlobar artery which is directed straight toward the transducer.

proximal 50% of the height were selected. Similarly, the distal 50% (d50) were selected and separate calculations were carried out (*9*).

Altogether, 4,190 measurements from 907 videos have been performed and 104,750 single color Doppler images were analyzed automatically (2,757 images per patient).

Statistical Analysis

Means of groups were compared by Kruskall-Wallis-H-test, between two independent groups by the Mann-Whitney-*U* test. *P* values less than 0.05 were regarded statistically significant. To investigate correlation, Pearson's correlation coefficient was calculated with the same significance assumptions.

RESULTS

TPI was significantly different between the proximal and distal cortical layers (1.12 vs. 1.56, respectively; $P=0.000$; Fig. 2). In patients with elevated creatinine as a measure of compromised function, significantly ($P=0.016$) higher values (TPI=1.70) were found at distal cortical level compared to patients with normal creatinine (TPI=1.34; Fig. 3). After transplantation, TPI rises significantly: 1.10 in 0–1 years vs. 1.41 in 1–2.9 years, $P=0.002$; 1.10 in 0–1 years vs. 1.37 in 3–4.9 years, $P=0.000$; 1.10 in 0–1 years vs. 1.31 in 7–8.9 years, $P=0.049$). TPI declines later on in our population to significantly lowered values in the group more than 9 years after transplantation (1.10 in 0–1 years vs. 0.94 in >9 years, $P=0.044$; Fig. 4).

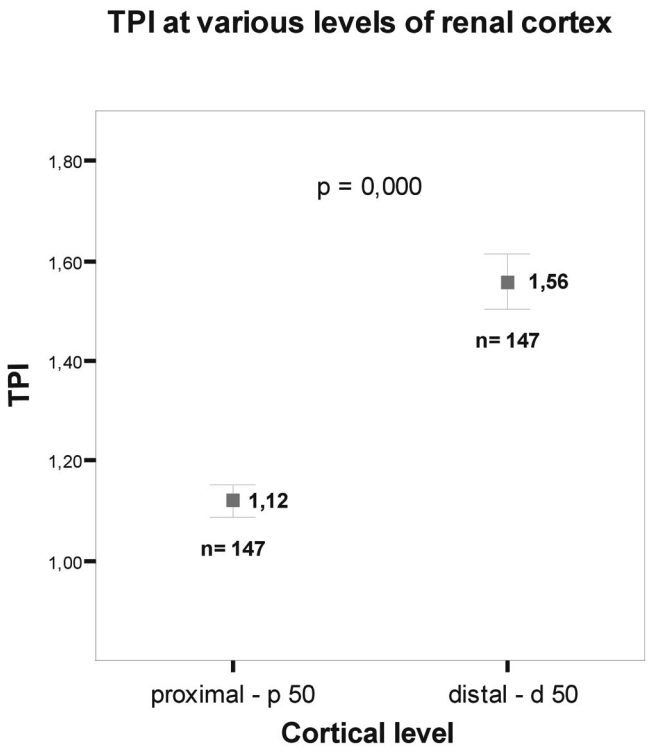

FIGURE 2. TPI mean values and standard error of the mean in proximal and distal cortex. Significantly lower TPI in proximal cortex.

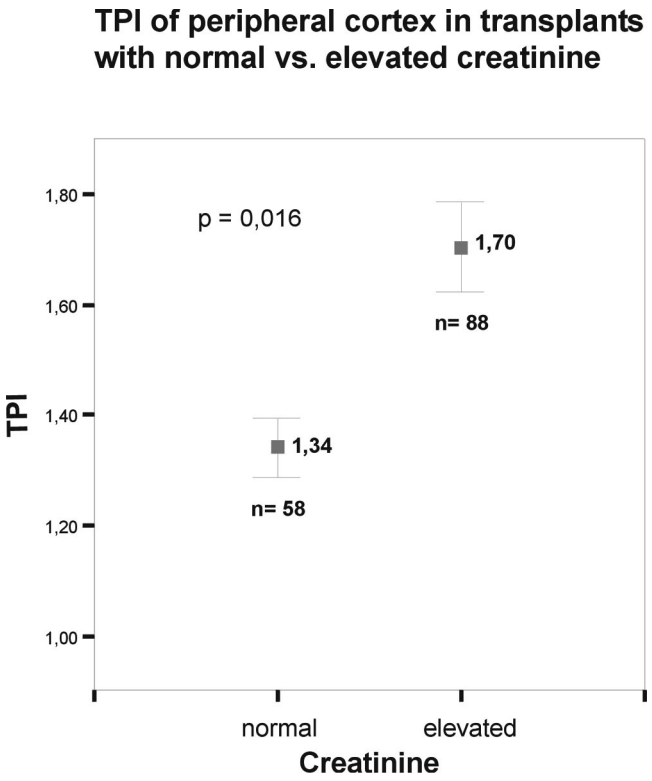

FIGURE 3. Significantly higher TPI in distal cortex of transplant recipients with elevated serum creatinine (means and standard error of the mean).

DISCUSSION

Description of transplant perfusion is an important task to evaluate transplant well-being. Without a certain degree of perfusion, a normal function cannot be maintained. Usually perfusion is assessed sonographically by a measurement of flow velocity indices in intrarenal arteries. Resistance Index (RI) and Pulsatility Index (PI) are still in use and trace back to a period before introduction of color Doppler (*10*, *11*). In these times, the course of vessels could not be displayed and hence calculation of an index of flow velocities circumvented the lack of correct absolute measurements. Simple RI and PI are reported to be of limited value for transplant function surveillance and prognosis (*10*, *12*). Nowadays color gives not only information on the course of vessels but offers detailed flow information at each single point of streaming blood. We developed a novel method to extract this information by calculation of flow velocities at any location in tissues simultaneously at any time point of a video sequence. This way evaluation of tissue perfusion becomes feasible beyond the point to point interrogation of only a few larger vessels. Quality of tissue perfusion is thus perceivable in a much more detailed manner. Our results demonstrate that tiny slices of only a few millimeters thickness inside renal cortex have a significantly different perfusion judged by our novel parameter TPI (Fig. 2). TPI has capacity to describe the state of the renal vascular tree in a formerly unmatched subtlety.

In accordance with our prior results (*9*) in healthy kidneys with perfusion intensity, we could clearly distinguish

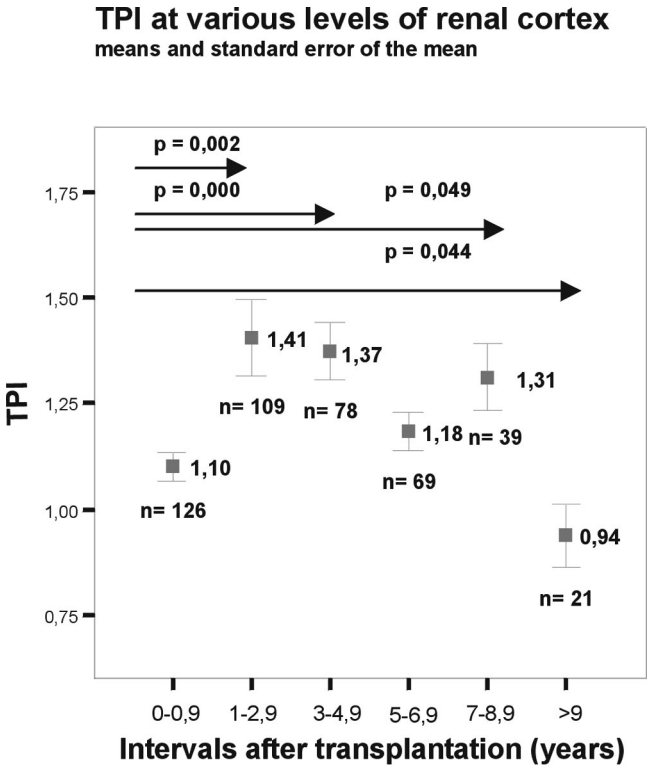

FIGURE 4. Significant differences of mean cortical TPI in various intervals to transplantation in 38 recipients. Significant differences indicated by arrows and *P* values (means and standard error of the mean).

pulsatility of perfusion in standardized cortical tissue layers.

Comparison of pulsatility of perfusion in layers lying above each other could award insights in mechanical properties of flow itself and of tissue surrounding the vascular treetop. With loss of function TPI rises significantly (Fig. 3) in the outer cortex. This points to a loss of small vessels which is reducing capacity of vascular bed and thereby elevating impedance of flow, as expressed by TPI. Nevertheless, more investigations are necessary to confirm these interesting first results. Noninvasive description of vascular changes in renal transplants is a pivotal point in longtime surveillance. This is stressed by results from serial protocol biopsies reported by Laftavi et al. (*13*), who demonstrated increased allograft fibrosis, which was significant at 1 year after transplantation. Nankivell et al. (*7*) describe histologically a distinct triphasic course of in following stages: 1) "an intense but limited peak of damage in the first month;" 2) "glomerulosclerosis then occurred as a late consequence of earlier immune-mediated tubular damage;" and 3) "subsequent progressive GS occurred beyond 4 years". This description fits to our own perfusion data where a steep rise of TPI occurred in the second year. Schwarz et al. (*14*) found chronic tubulointerstitial changes as early as 26 weeks after transplantation and a significant increase of chronic tubulointerstitial changes from 6 to 26 weeks after renal transplantation. Interstitial fibrosis leading to stiff structures around small cortical vessels could be reflected by rise in TPI in our series. Clearly larger series have to be investigated to decide on this assumption. In contrast to Nankivell et al. (*7*), we investigated transplants without selection of biopsied ones and our study population consisted of children, adolescents and young adults (i.e., in our population, the percentage of well-functioning transplants might be higher). This might explain diverging results in the later years. We observed in surviving transplants a slight decrease of TPI in the interval > 5 years. Others used color Doppler images that have been fixed in systole (*15*, *16*) or single power Doppler images (*16–18*). With these techniques reduction of tissue perfusion was found in chronic allograft nephropathy as well as with other causes of transplant damage like acute rejection, acute tubular necrosis and cytomegalovirus infection. Due to a lack of objective means to assess vascularity and/or tissue perfusion, subjective scores have been proposed by some investigators (*19*, *20*).

In transplants surviving more than 9 years, we found in our population a drop of TPI below initial values. Whether this is a sign of good adaptation or a hint to genetic differences of therapeutic side effects allowing preservation of function over longer periods awaits further investigation in larger population. We did not perform routine biopsies and therefore cannot correlate TPI with histological criteria. Compared to conventional parameters, our technique is unique and advantageous in several ways. Conventional RI and PI are single vessel parameters (*21*, *22*) and suffer from the fact that, in decreased perfusion, only those vessels that are visible can be interrogated. Dynamic tissue perfusion measurement and TPI overcomes such limitations. Regional tissue evaluation displaces single vessel evaluation. This technique has proven its feasibility and clinical impact in healthy kidneys, renal transplants, in healthy bowel, chronic inflammatory bowel disease, and tumors (*9*, *23–26*). It allows the first time to calculate tissue perfusion from conventional color Doppler investigations with respect to perfusion changes during heart action (thus "dynamic" perfusion measurement). No additional equipment is needed. A software calculates perfusion in a reproducible ROI and long-term comparisons can be made in the time course of one patient and between different patients. We recently demonstrated the use of this technique in renal transplants by calculating flow signal intensity in transplant cortex. Here too we found a significant difference in kidneys with compromised function compared to normal ones and a loss of perfusion after the first posttransplantation year (*23*). Both parameters are therefore useful in transplant follow up. In contrast to perfusion intensity, TPI does not refer to perfused area. So it is easier to calculate and has fewer claims to sonographic equipment.

RI or PI and creatinine are reported to be inversely correlated (*11*) and may even better correlated to histologic changes than to serum creatinine (*27*) Others found no correlation of simple RI and PI values to transplant function (*2*). Drudi et al. (*10*) tried to improve the conventional RI by introducing a RI ratio of renal artery to cortical vessels. They demonstrated a higher positive predictive value of this new parameter compared to simple RI. TPI goes beyond these techniques in measuring many cortical vessels simultaneously. Further studies on larger groups are necessary to confirm the use of TPI in the follow up of renal transplants.

REFERENCES

1. Jakobsen JA, Brabrand K, Egge TS, Hartmann A. Doppler examination of the allografted kidney. *Acta Radiol* 2003; 44: 3–12.
2. Krumme B, Grotz W, Kirste G, et al. Determinants of intrarenal Doppler indices in stable renal allografts. *J Am Soc Nephrol* 1997; 8: 813–816.
3. Hollenbeck M, Hetzel GR, Hilbert N, et al. Doppler sonographic evaluation of the effectiveness of an antirejection treatment after kidney transplantation. *Dtsch Med Wochenschr* 1995; 120: 277–282.
4. Heine GH. No rise in renal Doppler resistance indices at peak serum levels of cyclosporin A in stable kidney transplant patients. *Nephrol Dial Transplant* 2003; 18: 1639–1643.
5. Restrepo-Schafer IK, Schwerk WB, Muller TF, et al. Intrarenal doppler flow analysis in patients with kidney transplantation and stable transplant function. *Ultraschall Med* 1999; 20: 87–92.
6. PixelFlux, Chameleon-Software, Leipzig, Germany. Available at: www.chameleon-software.de.
7. Nankivell BJ, Borrows RJ, Fung CL, et al. Evolution and pathophysiology of renal-transplant glomerulosclerosis. *Transplantation* 2004; 78: 461–468.
8. Radermacher J, Mengel M, Ellis S, et al. The renal arterial resistance index and renal allograft survival. *N Engl J Med* 2003; 349: 115–124.
9. Scholbach T, Dimos I, Scholbach J. A new method of color Doppler perfusion measurement via dynamic sonographic signal quantification in renal parenchyma. *Nephron Physiol* 2004; 96: 99–104.
10. Drudi FM, Cascone F, Pretagostini R, et al. Role of color Doppler US in the evaluation of renal transplant. *Radiol Med (Torino)* 2001; 101: 243–250.
11. Kahraman S, Genctoy G, Cill B, et al. Prediction of renal allograft function with early Doppler ultrasonography. *Transplant Proc* 2004; 36: 1348–1351.
12. Sharma AK, Rustom R, Evans A, et al. Utility of serial Doppler ultrasound scans for the diagnosis of acute rejection in renal allografts. *Transpl Int* 2004; 17: 138–144.
13. Laftavi MR, Stephan R, Stefanick B, et al. Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. *Surgery* 2005; 137: 364–371.
14. Schwarz A, Mengel M, Gwinner W, et al. Risk factors for chronic allograft nephropathy after renal transplantation: a protocol biopsy study. *Kidney Int* 2005; 67: 341–348.
15. Nankivell BJ, Chapman JR, Gruenewald SM. Detection of chronic allograft nephropathy by quantitative doppler imaging. *Transplantation* 2002; 74: 90–96.
16. Lu MD, Yin XY, Wan GS, et al. Quantitative assessment of power Doppler mapping in the detection of renal allograft complications. *J Clin Ultrasound* 1999; 27: 319–323.
17. Venz S, Kahl A, Hierholzer J, et al. Contribution of color and power Doppler sonography to the differential diagnosis of acute and chronic rejection, and tacrolimus nephrotoxicity in renal allografts. *Transpl Int* 1999; 12: 127–134.
18. Gaschen L, Schuurman HJ. Renal allograft vasculopathy: ultrasound findings in a non-human primate model of chronic rejection. *Br J Radiol* 2001; 74: 411–419.
19. Turetschek K, Nasel C, Wunderbaldinger P, et al. Power Doppler versus color Doppler imaging in renal allograft evaluation. *J Ultrasound Med* 1996; 15: 517–522.
20. Hilborn MD, Bude RO, Murphy KJ, et al. Renal transplant evaluation with power Doppler sonography. *Br J Radiol* 1997; 70: 39–42.
21. Ikegami M. Estimation of renal transplant dysfunction by color Doppler sonography. *Nippon Hinyokika Gakkai Zasshi* 1997; 88: 541–549.
22. Drudi FM, Pretagostini R, Padula S, et al. Color Doppler ultrasound in renal transplant: role of resistive index versus renal cortical ratio in the evaluation of renal transplant diseases. *Nephron Clin Pract* 2004; 98: c67–c72.
23. Scholbach T, Girelli E, Scholbach J. Dynamic tissue perfusion measurement: a novel tool in follow-up of renal transplants. *Transplantation* 2005; 79: 1711–1716.
24. Scholbach T, Scholbach J, Krombach GA, et al. New method of dynamic color doppler signal quantification in metastatic lymph nodes compared to direct polarographic measurements of tissue oxygenation. *Int J Cancer* 2005; 114: 957–962.
25. Scholbach T, Herrero I, Scholbach J. Dynamic color Doppler sonography of intestinal wall in patients with Crohn disease compared with healthy subjects. *J Pediatr Gastroenterol Nutr* 2004; 39: 524–528.
26. Rouviere O, Curiel L, Chapelon JY, et al. Can color doppler predict the uniformity of HIFU-induced prostate tissue destruction? *Prostate* 2004; 60: 289–297.
27. Gaschen L, Schuurman HJ. Ultrasound score is more predictive than serum creatinine in assessment of cellular rejection in cynomolgus monkey renal allografts. *Invest Radiol* 2002; 37: 376–380.