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Evaluation of renal allograft function by Doppler spectrum analysis

A preliminary study

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Abstract. A decreased renal function is rather common after renal transplantation. The causes of this decreased function are diverse and difficult to differentiate. Yet, duplex examination, and especially quantitative Doppler spectrum analysis of the blood velocities in the renal artery, may be an effective method for differentiating between some of these causes. Forty-five renal transplant recipients were included in this preliminary study. Doppler spectra were recorded from the renal artery to the allograft. Parameters were derived from every Doppler spectrum in order to characterize each spectrum. Renal allograft function was evaluated on the basis of a number of clinical parameters. A significant correlation was found between the clinical parameters and the Doppler spectrum parameters indicative for changes in the peripheral resistance. Patients with a normal renal allograft function showed Doppler spectra with a high diastolic flow, typical of a vascular bed with a low peripheral resistance. Patients with a decreased renal allograft function caused by a stenosis in the renal artery could be distinguished by a low peak velocity and a low pulsatility index. A decreased allograft function caused by allograft rejection or cyclosporin nephrotoxicity also led to characteristic arterial flow disturbances. In these cases, the peripheral resistance was increased, and this was primarily reflected in a decrease in the diastolic blood velocity. We conclude that quantitative analysis of the blood velocities in the renal artery by Doppler spectrum analysis seems to be a useful, noninvasive diagnostic tool that discriminates between some of the causes of a decreased renal allograft function.

Key words: Renal allograft function by duplex - Doppler spectrum analysis in renal allografts - Duplex examination in renal allografts.

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A decreased renal allograft function is one of the most frequently occurring complications after renal transplantation. This unspecific, clinically based description covers several pathological entities that differ considerably in their etiology. The most common causes of a decreased renal allograft function are acute tubular necrosis, allograft rejection, impairment of renal blood flow, urological problems, and drug-induced nephrotoxicity. The diagnosis is based mainly on renal function parameters and on clinical observations. Even with supplementary evaluation of the renal allograft by echography, radionuclide renography, arteriography, or kidney biopsy, a differential diagnosis is still difficult. This is because almost all of these techniques are indirect, subjective, difficult to quantify, limited by a low spatial resolution, and/or tiring for the patient, especially in the early postoperative period [16].

Recently, several authors have reported favorably on the applicability of real-time B-mode echography combined with Doppler analysis - the so-called duplex examination - in the evaluation of renal allograft function [6, 25, 30]. It has been suggested that certain causes of a decreased renal allograft function affect the blood velocity waveforms of the renal artery in a particular way [4, 8, 14], and with this technique it is possible to detect and analyze blood velocity waveforms in the renal artery of a transplanted kidney. The emphasis in these studies has been on the value of spectral analysis of Doppler signals obtained from the renal artery to the allograft. Doppler spectrum analysis (DOSA) has the added advantages of being able to assess blood velocity characteristics quantitatively [1, 2, 7, 20] and to evaluate renal allograft function in a noninvasive way. In this preliminary study, we assessed the usefulness of DOSA in the evaluation of renal allograft function in the early stage immediately after renal transplantation.

Materials and methods

A consecutive series of 45 renal transplant recipients (26 male, 19 female), aged 16–65 years (mean 45 years), were the subjects of this study. Forty-two of them had received their allografts from cadaveric donors and 3 from living-related donors. A kidney had been transplanted into 39 patients for the first time, into 5 patients for the second time, and into 1 patient for the third time. For all transplants standard renal transplantation techniques had been applied, with both vascular anastomoses in end-to-side fashion [5].

Duplex examinations were performed between days 4 and 30 post-transplantation. Throughout the investigative period – including the early postoperative period – the examinations were tolerated well by the patients, and the quality of the Doppler signals that were obtained was, in all but two instances, sufficient for quantitative analysis.

Renal function was primarily assessed by generally accepted criteria, namely serum creatinine level and creatinine clearance. A decreased renal allograft function was defined as a serum creatinine level higher than 350 µmol/l and a creatinine clearance lower than 25 ml/min. These criteria were used as a kind of "gold standard." In addition, arbitrary threshold values of DOSA parameters were assigned in order to define a normal or decreased renal allograft function. In patients with the latter, percutaneous kidney biopsy, echography, and angiography were used for further differential diagnosis.

A real-time, pulsed Echo-Doppler apparatus (Toshiba SSA100A duplex scanner) with a 3.75 MHz linear array transducer was used for the duplex examinations.

Patients were examined in a supine position. The scanner head was placed laterally to the postoperative scar; in this way, a longitudinal scan of the kidney was obtained. After examination of this image, the scanner head was rotated 90 degrees to obtain a transverse image of the kidney. The renal arteries could then be found and these arteries could be followed distally towards the renal pelvis. After adjusting the angle of insonation of the ultrasound beam to get the best possible image, Doppler signals from the renal artery in the hilus of the kidney were recorded.

The main renal artery was chosen as the measuring site as blood flow in this artery is generally representative of blood flow to the whole organ. The Doppler signals were simultaneously fed into a real-time spectrum analyzer (Radionics SA 8000), and the spectra were stored on a Digital PDP 11/23 computer for off-line analysis.

From each Doppler spectrum, the maximum frequency waveform (max-curve) was determined off-line by a sophisticated algorithm [3] used in our laboratory (Fig. 1). In order to characterize the spectra, the following parameters were derived and the indices calculated from the max-curves [12]:

1. Maximum systolic frequency (F_{max})
2. Maximum frequency in the end-diastolic phase (F_{dia}) [19]
3. Duration of the deceleration phase in the spectrum (T_{dwn})
4. Slope of the deceleration flank in the spectrum (Sl_{dwn})
5. Resistance index (RI) [21]
6. Pulsatility index (PI) [13]

The serum creatinine level and the creatinine clearance were determined on the same day that the Doppler spectra were measured. The results of the duplex study had no influence on the treatment of the patients. Correlations between the DOSA parameters and the clinical parameters were determined by calculating Pearson correlation coefficients.

In order to evaluate the function of an allograft, threshold

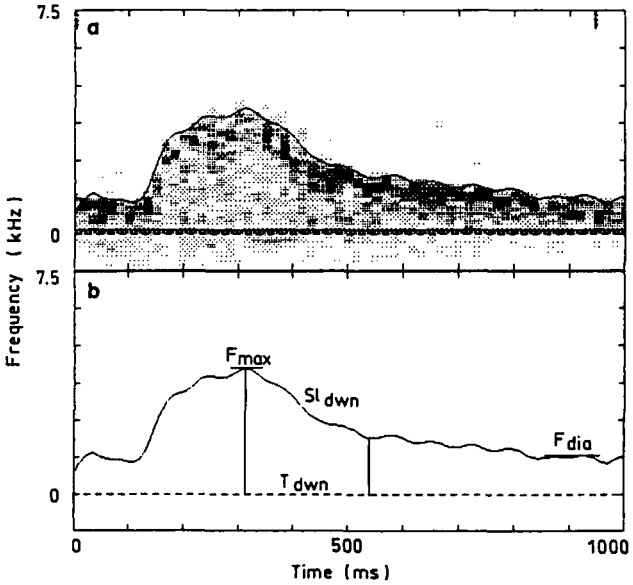

Fig. 1. a Doppler spectrum with maximum frequency wave-form (max-curve) of a patient with a normal renal allograft function; **b** the parameters derived from this analysis: F_{max}, Maximum systolic frequency; F_{dia}, maximum diastolic frequency; Sl_{dwn}, slope of the deceleration flank; T_{dwn}, duration of the deceleration phase

(separation) values for the DOSA parameters were chosen. With these values the specificity, sensitivity, and accuracy in evaluating the renal allograft function were determined [17].

The kappa-corrected diagnostic accuracy was calculated according to methods described by Cohen [9] and Fleiss [11]. This parameter allows for better comparison of the results of different examinations because it corrects the diagnostic accuracy for differences in the composition of the investigated population. The maximum value for kappa, which represents perfect agreement, is 1. A kappa value of 0 represents purely chance agreement. A kappa value of 0.75 or more is thought to represent excellent agreement, while a value between 0.4 and 0.75 represents fair to good agreement and one below 0.4, poor agreement [15].

Finally, an attempt was made to determine whether DOSA of the blood velocities in the renal artery could help to differentiate the different causes of a decreased renal allograft function.

Results

Twenty-eight patients with a normal renal allograft function and 17 patients with a decreased renal allograft function were distinguished on the basis of the creatinine values. Additional tests identified a rejection in 8 patients, a renal arterial stenosis in 2 patients, and a ureter obstruction in 2 more patients. Cyclosporin nephrotoxicity was diagnosed in 3 patients, based on the immediate drop in the serum creatinine level after conversion from cyclosporin to azathioprine. One patient suffered from a nephrotic syndrome and another developed an acute respiratory disease (ARD) syndrome. Both syndromes were considered causative factors for the decrease in

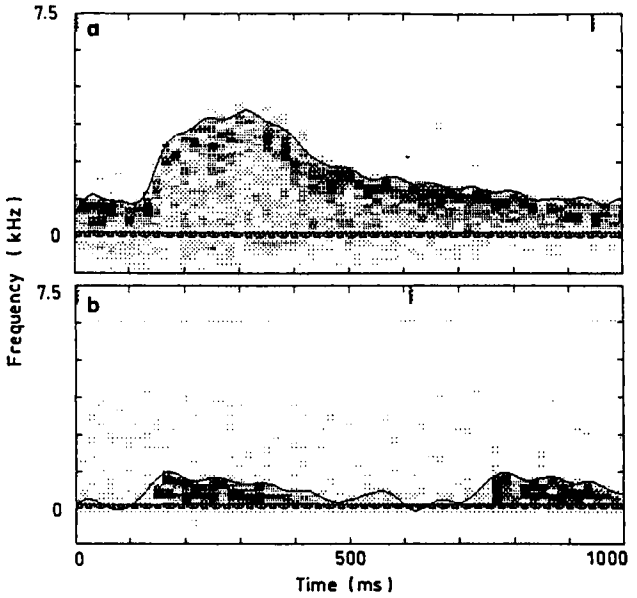

Fig. 2 a, b. Doppler spectrum with max-curve: **a** of a patient with a normal renal allograft function; **b** of a patient with a decreased renal allograft function caused by allograft rejection

allograft function. In 5 of the 17 patients with a decreased renal allograft function, supportive treatment with hemodialysis was provided.

In all, 93 duplex examinations were performed on patients with a normal renal allograft function and 27 were performed on patients with a decreased renal allograft function. In 2 of these examinations the quality of the Doppler signals was poor, and for one patient clinical data were incomplete. The results of the remaining 117 examinations, however, were found to be suitable for further analysis.

Figure 2a shows a Doppler spectrum of the blood velocity in the renal artery of a patient with a normal renal allograft function. A pulsatile waveform is superimposed on a continuous advanced flow. The presence of advanced flow during the diastole indicates a low peripheral resistance [29]. Similar spectra were consistently obtained in all examinations in patients with a normal renal allograft function.

Figure 2b shows the Doppler spectrum typical of a patient with a renal allograft rejection. Not only are the blood velocities low during systole, but there is virtually no flow during diastole. This can be explained by an increase in the vascular resistance of the renal allograft. In order to characterize the Doppler spectra, primary DOSA parameters and indices were calculated. Of the different primary DOSA parameters evaluated in this study, only the parameter F_{dia} could be obtained in a reproducible way between subsequent examinations on the same subject. The indices derived from the Doppler spectra were less variable than the primary parameters. These indices are dimensionless figures and are not dependent on the angle of insonation, which may vary in subsequent examinations. They showed only minimal variation between subsequent measurements on the same subject. A comparison of DOSA parameters with the clinical parameters reveals a significant correlation for the parameters that can be duplicated (correlation coefficient about 0.5 for F_{dia}, PI, and RI; Table 1).

Table 1. Correlation between the clinical parameters and some Doppler spectrum analysis (DOSA) parameters. F_{max}, maximum systolic frequency; F_{dia}, maximum diastolic frequency; T_{dwn}, duration of the deceleration phase; Sl_{dwn}, slope of the deceleration flank; RI, resistance index; PI, pulsatility index

Clinical parameter	DOSA parameter	Correlation coefficient	*P*-value
Creatinine clearance	F_{max}	0.278	<0.05
Creatinine level	F_{max}	-0.304	<0.05
Creatinine clearance	F_{dia}	0.504	<0.05
Creatinine level	F_{dia}	-0.524	<0.05
Creatinine clearance	T_{dwn}	0.197	<0.05
Creatinine level	T_{dwn}	-0.132	NS
Creatinine clearance	Sl_{dwn}	0.098	NS
Creatinine level	Sl_{dwn}	0.150	NS
Creatinine clearance	RI	-0.481	<0.05
Creatinine level	RI	0.549	<0.05
Creatinine clearance	PI	-0.453	<0.05
Creatinine level	PI	0.535	<0.05

Table 2. Results of Doppler spectrum analysis compared to results of clinical data (abbreviations as in Table 1)

	Decreased renal allograft function ($n=25$)	Normal renal allograft function ($n=89$)
$F_{dia} < 500$ Hz	11	3
$F_{dia} \geq 500$ Hz	14	86
RI ≥ 0.8	12	0
RI < 0.8	13	89
PI ≥ 2.0	7	1
PI < 2.0	18	88
RI ≥ 0.7	22	19
RI < 0.7	3	70

Table 3. Sensitivity, specificity, accuracy, and kappa factor for the different criteria ($n=114$; abbreviations as in Table 1)

Criterion	Sensitivity	Specificity	Accuracy	Kappa
$F_{dia} < 500$	44%	97%	85%	0.48
RI ≥ 0.8	48%	100%	89%	0.59
PI > 2.0	28%	99%	83%	0.34
RI ≥ 0.7	88%	79%	81%	0.55

In order to use DOSA for the evaluation of the renal allograft function, arbitrary threshold (separation) values for the DOSA parameters were chosen. These values were selected on the basis of the best separation of the positive and negative clinical diagnoses. The patients with a stenosis in the renal artery, which was confirmed angiographically, were excluded from this analysis. The spectra of patients with a renal artery stenosis could easily be identified because of their characteristic shape, which resembles spectra obtained from peripheral arteries with a proximal, hemodynamically significant obstruction.

Of all the DOSA parameters, the RI appeared to have the best separating capacity. An RI value greater than 0.8 was found only in patients with a decreased renal allograft function. All patients with a normal renal allograft function had RI values less than 0.8. Twelve of the 25 allografts with a decreased function could be identified on the basis of this criterion (Table 2). When the threshold value for the RI was lowered to 0.7, almost all of the allografts with a decreased function (88%) could be identified. However, this brought the specificity down from 100% to 79% (Table 3).

When the parameter F_{dia} was used for evaluation, a value lower than 500 Hz was considered indicative of a decreased renal allograft function (Table 2). This parameter appeared to be less sensitive than the RI value in evaluating a renal allograft function. For the PI, the best threshold value was 2.0; a higher value was taken to be indicative of a decreased allograft function. This criterion was less accurate in distinguishing a normal from a decreased renal allograft function than either RI or F_{dia}. Furthermore, it appeared that almost all examinations with a PI greater than 2.0 also had an RI value greater than 0.8. In Table 3 the sensitivity, specificity, accuracy, and kappa factor of the different criteria related to the gold standard are presented.

The different subgroups of causes of decreased renal allograft function were observed in numbers that were too small to allow for a reliable analysis of the ability of DOSA to differentiate between them. However, observations in individual patients strongly suggest that Doppler spectra are affected in different ways by these different subgroups of causes. These observations can be illustrated by the following case reports.

Case 1

The patient was a 42-year-old female. It was her first transplant and the spectrum presented in Fig. 2b was obtained 16 days after transplantation. On the basis of clinical criteria an acute rejection was diagnosed. The Doppler spectrum shows a low overall velocity (low values for F_{max} and F_{dia}) and high values for the indices RI and PI.

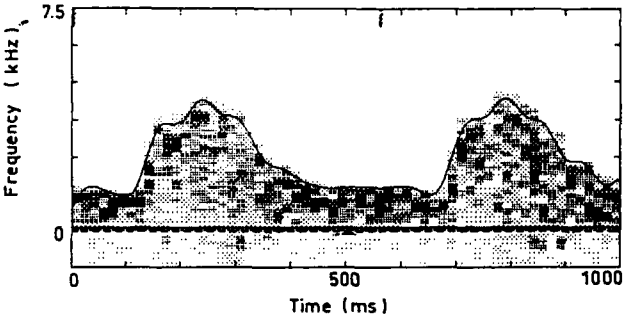

Fig. 3. Doppler spectrum with max curve of a patient with acute tubular necrosis

Case 2

The patient was a 34-year-old female. It was her first transplant and the duplex examination was performed 10 days after transplantation. Clinical data suggested a decreased renal allograft function. DOSA revealed a quite normal pattern (Fig. 3). Renal biopsy showed an acute tubular necrosis. The clinical parameters of renal function improved in subsequent days.

Case 3

The patient was a 27-year-old male. It was his first transplant. During treatment with cyclosporin, the registered Doppler spectra showed a waveform similar to those observed in the case of an allograft rejection (low velocities in the diastolic phase with a rather high RI value). After conversion the renal function improved clinically and the Doppler spectra showed an improved pattern characteristic of normalization (Figs. 4a, 4b).

Case 4

The patient was a 38-year-old male. It was his first transplant and the duplex examination was performed 18 days after transplantation. In this case, the decrease in function of the renal allograft was suspected to have been caused by a stenosis in the renal artery. Arteriography confirmed this diagnosis. The registered Doppler spectrum revealed a waveform characteristic of blood velocities in an artery with a proximal obstruction (Fig. 5). The proximal obstruction caused a decrease in the acceleration slope. The spectra were already decreased in the systolic phase.

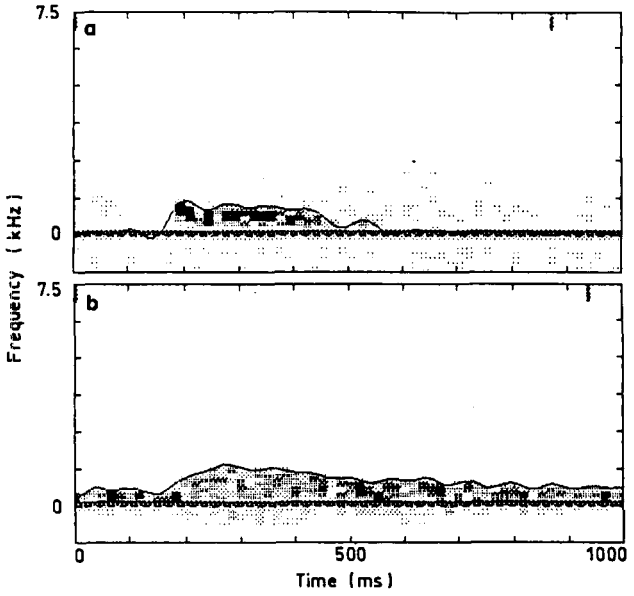

Fig. 4 a, b. Doppler spectrum with max-curve of a patient with a decreased renal allograft function caused by the nephrotoxic effect of cyclosporin: **a** before conversion; **b** after conversion

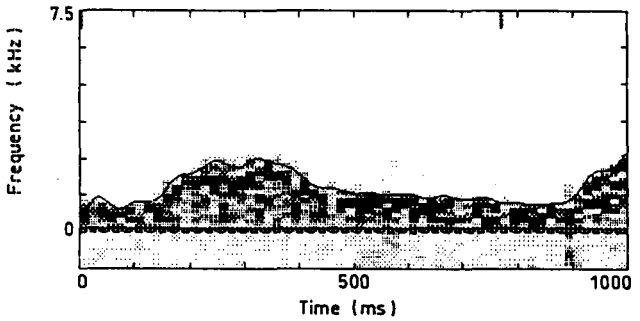

Fig. 5. Doppler spectrum with max-curve of a patient with a stenosis in the renal artery

Discussion

Several studies [1, 7, 14, 18, 20] have suggested that changes in the blood velocity in the renal artery of a transplanted kidney may be used to evaluate renal function. New technological developments in ultrasonographic equipment, which combine echographic imaging with high quality Doppler spectrum analysis (duplex), have made it possible to accurately study the blood velocities to a renal allograft [6, 25, 30]. In this preliminary study, we based our observations exclusively on the analysis of the Doppler spectra. The echo-mode of the duplex scanner was only used to localize the sampling. From more than 97% of the insonated arteries, Doppler signals were obtained which could be used for further analysis. The quality and reproducibility of the registered signals were satisfactory. Of the various DOSA parameters, only F_{dia} appeared to be reliable in evaluating the blood velocity characteristics in relation to the renal allograft function [29]. F_{max} was less useful. A mild rejection caused a decrease in F_{dia}, whereas F_{max} remained unchanged. F_{max} decreased only in the event of a severe rejection. Rifkin et al. [23] and Murphy et al. [18] also observed a decrease in F_{dia} in patients with allograft rejection. They found that only in patients with a severe increase in the arterial resistance did F_{max} diminish together with a disappearance of F_{dia}.

The indices derived from Doppler spectra were more useful in the evaluation of the changes in the blood velocity. PI and especially RI were indicative not only of changes in the blood velocity in the insonated artery but also of the renal allograft function. An accuracy of 89% could be obtained using a threshold value of 0.8 for RI. When corrected for the distribution of patients, accuracies (kappa values) could be obtained which were significantly higher than could be expected from chance agreement alone. For the parameters RI and F_{dia}, these values represented a fair to good agreement.

What is worth noting is the high specificity that can be obtained by DOSA (Table 3). It indicates that almost all normally functioning renal allografts are evaluated as normal by DOSA. However, in these cases, the sensitivity is rather low. The same finding has been reported elsewhere in the literature [26], and there are two plausible explanations for it. Firstly, the number of patients with a decreased renal allograft function is rather small in comparison with the number of patients with a normal allograft function. Secondly, it is possible that the clinical evaluation of the renal function does not always resemble the actual status of the allograft. Clinical diagnoses based on the serum creatinine level are measurements with a delay time with respect to the renal function [10]. Blood velocity waveforms of the renal artery, however, reveal the actual status of the allograft during examination. Thus, the timing of the Doppler measurements in relation to the clinical measurements may have affected the results of our study.

Several authors [18, 25, 26] have reported that, in the case of acute rejection, blood velocity waveforms in the renal allograft change earlier and normalize earlier in response to immunosuppressive therapy than other clinical parameters. These observations may explain the divergence between interpretations based on results of Doppler studies and those based on clinical data.

An RI threshold value of 0.7 seems to be a more suitable value for clinical practice because it gives a rather high sensitivity (88%). For clinical use, the diagnosis of a decreased renal allograft function may,

in fact, be of more value than confirmation of a normal allograft function. However, it must be noted that a higher sensitivity means the number of false-positive observations increases and the specificity decreases (from 100% to 79%; Table 3).

In addition to the correlation of DOSA parameters with the global function of the renal allograft based on clinical data, the results of our study suggest that the analysis of blood velocity waveforms can also distinguish some of the different causes of a decreased renal allograft function. Stenosis of a renal artery affects the blood velocity waveform in the same way as the waveform in peripheral arteries is changed when a hemodynamically significant stenosis is present. In peripheral arteries a minor stenosis can be distinguished by specific changes in the blood velocity waveforms in response to a decrease in the peripheral resistance. In a normally functioning renal allograft, the peripheral resistance is already low. Therefore, less significant stenoses in the renal artery will also considerably influence the blood velocity waveform distal to the stenosis [27].

Our results suggest that acute tubular necrosis does not affect a Doppler spectrum registered from the renal artery. In this particular situation, the blood velocity waveform in the renal artery does not appear to be considerably depressed, even though the renal function has been impaired [6, 8, 10]. This observation is in agreement with that of Rifkin et al. [24], who observed that the RI value in patients with acute tubular necrosis is almost the same as that in patients with a normal renal function and that it is not increased as in patients with an acute rejection. However, it is known that in some cases of acute tubular necrosis, the renal blood flow can be compromised by severe oedema [6].

In this preliminary study, which is based on a limited number of observations, we did not find any differences between Doppler spectra obtained from patients with an allograft rejection and those from patients with a decreased allograft function caused by the nephrotoxic effect of cyclosporin. However, the spectra of both groups of patients did differ from those of patients with a normal renal allograft function. The observations of others, often based on single cases as well, are divergent. Rifkin et al. [24] did not notice any significant differences between spectra recorded from patients with nephrotoxicity caused by cyclosporin and those of patients with normal function, while Murphy et al. [18] observed Doppler spectra similar to those recorded from patients with rejection. Moreover, earlier studies [24] have suggested that only in acute rejection (the vascular type) is the peripheral resistance increased considerably; in the case of an interstitial rejection (the cellular type), the peripheral resistance is not affected. Thus, it is possible to record normal Doppler spectra in these cases. Doppler spectra similar to those measured in patients with a normal renal allograft function were reported by Sampson et al. [28] in patients with a decreased allograft function in cases of pyelonephritis and cortical necrosis.

On the basis of previous studies and our own experience, we conclude that DOSA is a promising method for evaluating renal allograft function. Its noninvasive nature and good reproducibility can make it a method of choice for the follow-up of patients with a renal allograft [22]. Future prospective studies based on more data are necessary to confirm the validity of our observations. They may also be able to distinguish between a decreased renal function caused by rejection and that caused by cyclosporin nephrotoxicity.

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