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Monitoring of renal allografts by duplex ultrasound

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Abstract. Deterioration of renal transplant function due to rejection is accompanied by changes in renal blood flow that can be measured by duplex ultrasound (DU). In the present study, 60 transplanted patients were followed up. A total of 233 duplex examinations, 68 percutaneous biopsies, 44 renal scintigraphies, and 6 transplant nephrectomies were performed on these patients. Diagnoses were made on the basis of clinical and histological data. Renal perfusion was calculated by means of DU. In addition, the arterial Doppler signals were quantified using a pulsatility index (PI). Mean perfusion of normal renal allografts was 0.47 l/min. A decrease in blood flow could be found in acute vascular and chronic rejection but not in acute cellular rejection. A lack of renal perfusion due to acute vascular rejection was observed in four patients. Mean PI, used as a parameter of DU, rose significantly in all forms of rejection, which could be diagnosed with a sensitivity of 93% and a specificity of 86%. Cyclosporin overdosage did not alter the Doppler flow shape.

Key words: Duplex ultrasound, in renal transplantation - Duplex ultrasound, in rejection of kidneys - Duplex ultrasound, in cyclosporin toxicity - Renal blood flow, with duplex ultrasound.

Real-time sonography of the transplanted kidney provides easy and rapid proof of perirenal masses and of obstruction of the collecting system [1, 14]. Transplant swelling, enlargement, and increased conspicuousness of the medullary pyramids indicate an acute rejection; a small kidney with irregular margins and poor differentiation between renal cortex and medulla point to a chronic rejection. These changes are of different intensities and allow neither an early diagnosis nor a safe differentiation from other causes of deterioration of renal function. Vascular complications in particular cannot be registered.

Up until now it was necessary to use nuclear medical or angiographic methods to prove these complications [1, 7, 14]. Improved technology has recently made it possible to visualize even deep-seated vessels by real-time sonography and to examine them simultaneously by pulsed Doppler ultrasound [2, 12, 13]. The aim of the present study was to see whether this duplex ultrasonography (DU) would be a suitable method for measuring renal blood flow and, as such, facilitate early detection of transplant rejection.

Materials and methods

Monitoring of kidney graft function

Sixty patients with cadaveric renal allografts were studied. In 18 patients, DU was performed every 2 days in the early postoperative period. Sixty-eight percutaneous biopsies, 6 transplant nephrectomies (7-15 days after transplantation), 233 DUs and real-time sonographies, and 44 nuclear scintigraphies were performed on the patients. Diagnoses were made on the basis of clinical data and response to the immunosuppressive therapy. Thirty acute rejections diagnosed during the 4-month period following transplantation, 10 chronic rejections (2-5 years after transplantation), 7 vascular rejections (7-15 days after transplantation), and 3 bacterial interstitial nephritides, 10 acute tubular necroses, and 52 periods of stable renal function (6 months to 9 years after trans-

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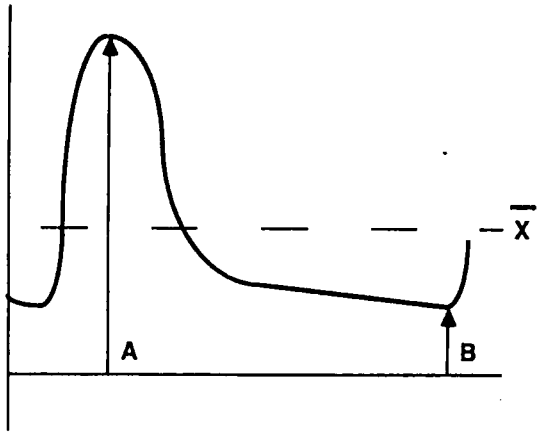

Fig. 1. Diagram shows how pulsatility index *(PI)* was calculated from the ratio of peak systolic flow *(A)* minus minimum diastolic flow *(B)* divided by the mean flow ($\bar{x}$)

plantation) were analyzed. A biopsy was done in the 50 cases of deteriorated renal function, as well as in the early postoperative phase in 18 patients with normal transplant function. The basic immunosuppression consisted of cyclosporin A (with blood levels monitored routinely every day in the early phase by radioimmunoassay; normal range 250–650 ng/ml, nonspecific) and corticosteroids.

Duplex examinations

Duplex examinations were performed with a 3.75 MHz electronic sector scanner, combined with a 3.75 MHz variable gate, pulsed-wave Doppler system (Toshiba SSA-100A).

After morphological evaluation of the renal allografts, real-time sector images were used to position a cursor representing the sample volume of the pulsed Doppler system at the main renal artery near the renal hilus. Applying Doppler sonography, the angle between the ultrasound beam and the direction of blood flow was kept as small as possible, since the cosine of this angle influences the Doppler frequency shift. A mathematical correction was performed as well (Fig. 2). Doppler signals were obtained from at least four cardiac cycles.

The diameter of the artery was determined in the real-time picture. Blood flow was deduced from flow velocity, as evaluated by the Doppler equipment using the integrated computer, and from vasal diameter, assuming circular cross-section.

In addition, a quantification of the Doppler flow shape was done by calculating the pulsatility index (PI) from the ratio of peak systolic flow minus minimum diastolic flow divided by the mean flow (Fig. 1). This represented a semiquantitative degree of the peripheral vascular resistance [11].

Statistical analysis

Sensitivity and specificity were determined by applying the following equations:

$$\text{Sensitivity:} \quad \frac{\text{True-positive} \times 100}{\text{True-positive} + \text{false-negative}}$$

$$\text{Specificity:} \quad \frac{\text{True-negative} \times 100}{\text{True-negative} + \text{false-positive}}$$

Rank-sum tests (Wilcoxon, Mann-Whitney U-test) were used to evaluate significant differences. A level <0.05 was chosen to be significant.

Results

Renal blood flow in different types of transplant rejection

In stable, functioning renal allografts the mean arterial blood flow was found to be 0.47 l/min (range 0.23–0.92 l/min). There was a drop in graft perfusion to 0.23 l/min in acute vascular rejection and to 0.28 l/min in chronic rejection but not in acute cellular rejection (Table 1).

Pulsatility index (PI) due to different types of transplant rejections and correlation to histology

The arterial Doppler signals of renal allografts with a good and stable function showed a systolic peak followed by a continuous antegrade diastolic blood flow (Fig. 2). In patients with transplant rejection, a decrease in diastolic perfusion was observed (Fig. 3).

Quantifying these alterations of the Doppler waveform by the PI, the following results were obtained: mean PI rose significantly to 2.27 ± 0.51 in acute cellular rejection, to 4.30 ± 2.00 in acute vascular rejection, and to 2.12 ± 0.34 in chronic rejection, as compared to 1.26 ± 0.23 in allografts with stable function (Table 1). The increase in PI in vascular rejection was higher than in cellular rejection ($P = 0.03$).

Table 1. Pulsatility index (PI) and blood flow (Q) in allografts with stable function as compared to different types of rejection

	PI						Q					
	N	x̄	SD	Min	Max	*P*	*N*	x̄	SD	Min	Max	*P*
Stable function	52	1.26	0.23	0.88	1.77	-	52	0.47	0.21	0.23	0.92	-
Cellular rejection	28	2.27	0.51	1.49	3.36	0.001	18	0.43	0.24	0.11	0.71	NS
Vascular rejection	7	4.30	2.00	2.04	8.01	0.001	6	0.23	0.12	0.11	0.45	0.004
Chronic rejection	10	2.12	0.34	1.83	2.96	0.001	10	0.28	0.12	0.12	0.43	0.001

x̄, mean value; SD, standard deviation

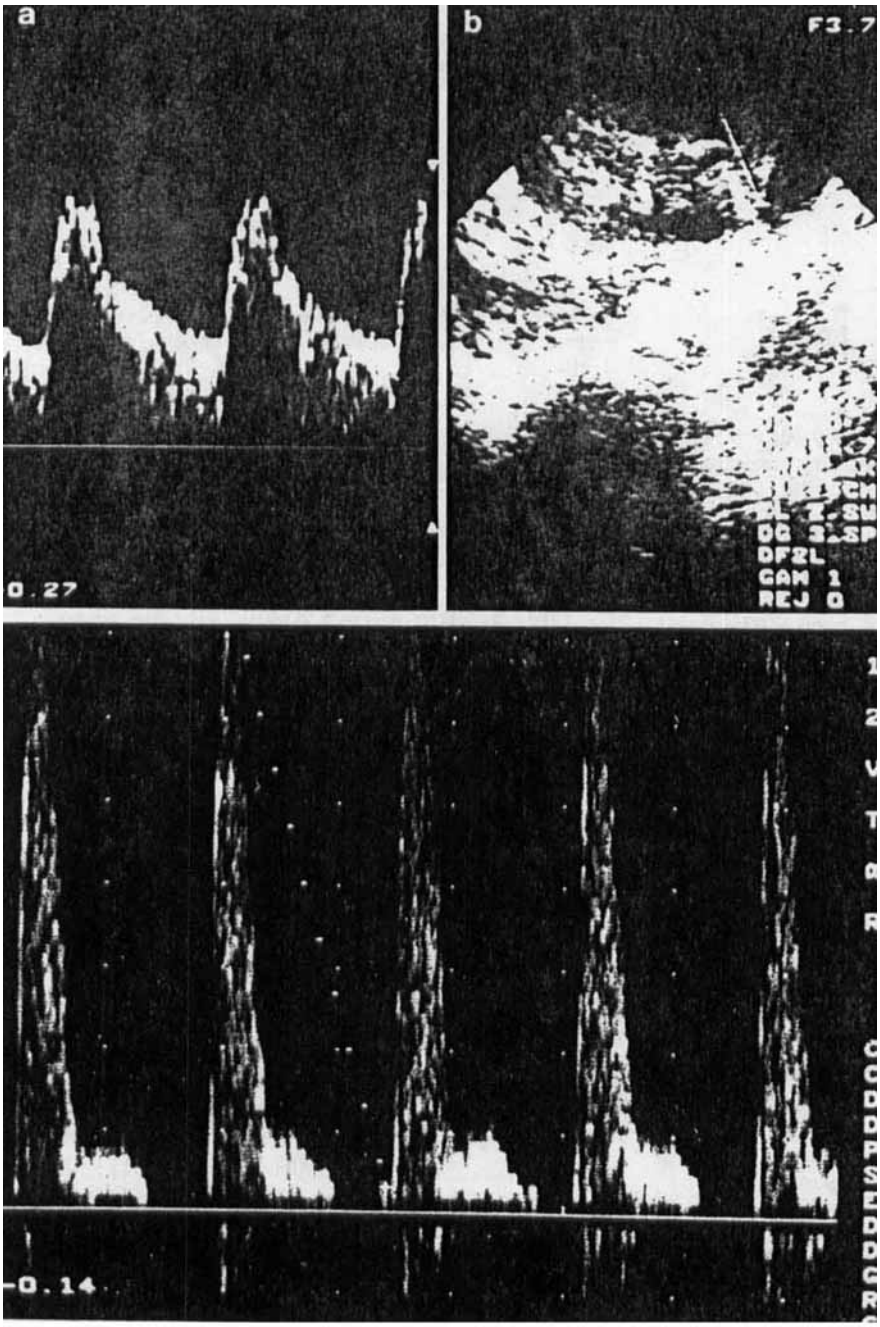

Fig. 2. a Renal arterial Doppler signals of a normally functioning allograft. A systolic peak is followed by a continuous antegrade diastolic blood flow. **b** Real-time scan of a renal allograft. The *cursor* representing the sample volume of the pulsed Doppler system is positioned at the main renal artery near the renal hilus. The *dotted line* represents the ultrasound beam, the *continuous line* the direction of blood flow

Fig. 3. Doppler signals of a renal allograft in mild acute rejection with decreased but still demonstrable diastolic flow

The diagnoses of 68 biopsies were compared with the PI. At a threshold value of 1.7, corresponding to two standard deviations, 28 true-positive, 32 true-negative, 5 false-positive, and 2 false-negative cases were diagnosed. The sensitivity was calculated as being 93% and the specificity as 86%. In three patients suffering from bacterial interstitial nephritis (diagnosed clinically and confirmed histologically), the PI was also high (1.9, 2.2, and 1.8).

Correlations with cyclosporin A (CyA) blood levels

In the early postoperative phase after transplantation, 21 patients were monitored routinely: 11 with initially well-functioning grafts and 10 with initially nonfunctioning grafts (3 due to rejection and 7 due to acute tubular necrosis).

In 5 of the 7 patients with acute tubular necrosis (ATN), blood levels of more than 650 ng/ml were found (Table 2). These levels were said to be toxic.

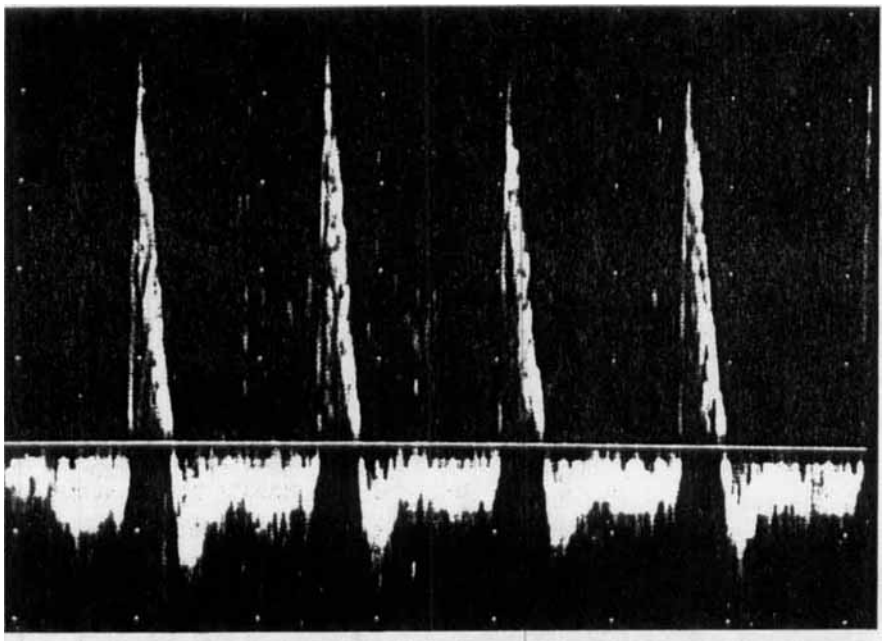

Fig. 4. Doppler signals of a renal allograft in severe acute vascular rejection with reversal flow in diastole. Calculating the mean flow, a stop in the blood flow was diagnosed and confirmed scintigraphically and intraoperatively

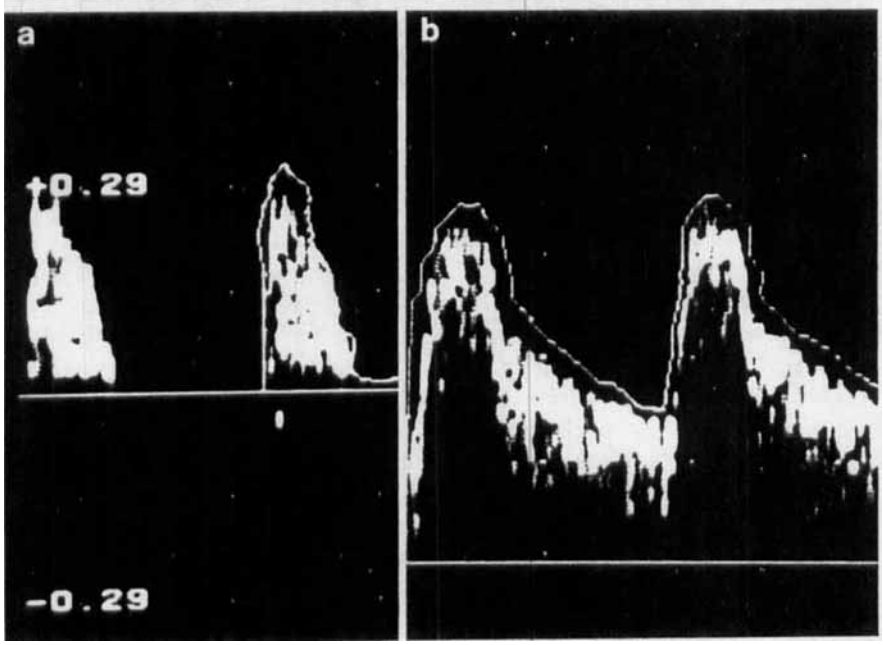

Fig. 5. Doppler signals in a patient with acute severe cellular rejection 48 h after transplantation: **a** before treatment: obliterated flow throughout diastole; **b** 24 h later, after corticoid pulse therapy: normal Doppler flow shape with continuous diastolic flow

The PI in these patients ranged from 1.6 to 2.3. In the 2 patients with normal blood levels, the PI was 1.4 and 1.0. In the 11 patients with initially functioning grafts, there was no obvious influence of the CyA blood levels. The number of patients studied was too small for a statistical analysis.

The PI and renal blood flow of 25 patients with grafts functioning well (serum creatinine 1.4 ± 0.3 mg/dl) for more than 6 month were compared with the CyA blood levels (Table 3). No correlation was found between these parameters and CyA blood levels (range 86–871 ng/ml).

Monitoring of nonfunctioning grafts

In six patients a lack of renal perfusion could be detected by DU. As can be seen in Fig. 4, in these cases systolic antegrade flow in the main renal artery was followed by reversal flow in the diastole. Histological examination of these nephrectomized grafts revealed severe vascular rejection.

In the ten cases with initially nonfunctioning grafts, arterial and venous blood flow could be demonstrated, and identification of the vessels was possibly due to the Doppler flow profile. The re-

Table 2. Correlation of the pulsatility index (PI), cyclosporin A (CyA) blood levels, and function of the kidneys in the early post-transplantation period (2 weeks). Patients were monitored every 2nd day

Cyclosporin A blood levels	*n*	Acute tubular necrosis PI	*n*	Initially functioning graft PI
CyA >650 ng/ml	5	2.0 (1.6-2.3)	3	1.0 (0.5-1.1)
CyA <650 ng/ml	2	1.4/1.0	8	1.2 (1.0-1.5)

Table 3. Correlation of blood flow (Q) and pulsatility index (PI) with cyclosporin A (CyA) blood levels in 25 patients with stable functioning renal allografts

	$\bar{x}$	SD	r^a
CyA	418.0	157 ng/ml	-
Q	0.45	0.11 l/min	0.11
PI	1.27	0.24	0.06

[a] Linear correlation

sults corresponded to those of the nuclear scintigraphy.

In three of these cases of initially nonfunctioning grafts, one cellular and two vascular rejections were diagnosed by DU 24-48 h after transplantation. They were confirmed histologically and treated successfully by rescue immunosuppressive therapy. The Doppler flow shapes documented in the patient with cellular rejection before and after therapy are shown in Fig. 5. Twenty-four hours after steroid pulse therapy, the previously obliterated diastolic blood flow was clearly visible.

In the two cases of ATN with regular CyA blood levels PI was normal, whereas in five patients with ATN and CyA levels above 650 ng/ml an elevation of the PI was found (Table 2).

Discussion

Duplex ultrasound is a suitable method for evaluating renal perfusion in addition to morphological examination of the transplanted kidney by real-time sonography. In contrast to nuclear medical or angiographic methods, the patient does not run the risk of being exposed to ionizing radiation or contrast media. Examinations can, therefore, be repeated at any time.

The most important limitation to quantitative blood measurement is the determination of vasal diameter, which influences the calculation by its square. In renal allografts with normal function, the mean arterial blood flow was found to be 0.47 l/min. This corresponds to intraoperative measurements by Lewis et al. [6], who determined values of 0.47 l/min (range 0.13-1.0 l/min).

A decrease in graft perfusion was found in acute vascular and chronic rejection, but not in acute cellular rejection. The normal blood flow in grafts with cellular rejection - in spite of the rise in arterial resistance - can be explained by the increase in systolic blood flow.

The arterial Doppler signals of normal renal allografts show continuous antegrade diastolic flow, reflecting a low peripheral vascular resistance. In patients with transplant rejection, a decrease in diastolic perfusion, leading to a rise in the PI, was observed. A vasospasm and a decrease in blood flow were described by Hollenberg et al. [5] in an experimental study. Several reasons can be suggested for this increase in vascular resistance documented by the Doppler flow shape. First, there is a direct vessel alteration due to an endovasculitis [9] and, at least as important, there is an interstitial edema [15]. It has also been suggested that metabolites of arachidonic acid, induced by vascular lesions, act as mediators of vasospasm [4].

Our study shows, in accordance with the findings of Rigsby et al. [10, 11], that the evaluation of PI by DU is a very sensitive method for detecting renal transplant rejection. Indeed, sensitivity of more than 90% could be achieved in the present study. It was found that vascular rejections in particular, which are very difficult to diagnose by histological examination, could be diagnosed immediately with a high specificity.

In stable functioning renal allografts, CyA blood levels did not influence renal blood flow or PI, nor was any elevation of PI found in ATN. However, there is reason to believe that in the case of ATN, high CyA blood levels are associated with an increase in PI. Indeed, experiments have shown that the first toxic effect of CyA overdosage is the induction of a vasospasm of the small arterial vessels [8]. It has also been observed in clinical studies [3] that the toxic effect of CyA is enhanced in ischemia-damaged kidneys. One must therefore conclude that CyA toxicity is detectable by DU only in grafts with ATN and not in initially functioning grafts.

DU was most helpful in monitoring nonfunctioning grafts. A stop in renal arterial blood flow could easily be diagnosed. Rejection episodes were detectable by alterations of the PI. However, because CyA toxicity may also alter the PI in ischemia-damaged kidneys, a biopsy should be done to make an exact diagnosis.

In conclusion, duplex Doppler sonography is a highly sensitive, noninvasive, radiation-independent, repeatable, low-cost method for diagnosing renal al-

lograft rejection. The main indication is the monitoring of the immediate post-transplantation phase, when serum creatinine concentrations are still high and thus difficult to interpret. Regular monitoring of the PI during this period makes it possible to obtain an early diagnosis of rejection and a timely renal biopsy for verification. Moreover, the effectiveness of immunosuppressive treatment can easily be monitored.

In this study, a decrease in allograft perfusion could be found in acute vascular and chronic rejection, but these data are not at all as indicative of rejection episodes as the Doppler signal quantification using the PI.

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