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Assessment of hemodynamic changes in human kidney grafts induced by cyclosporin infusion

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Abstract. Cyclosporin A (CyA) nephrotoxicity is at least partly caused by the vasoconstrictive action of the drug. In this study we set out to assess this hemodynamic effect of CyA on Doppler spectra obtained in arteries of human renal allografts. Doppler spectra of renal arteries were obtained shortly before and after the start of CyA infusion in renal transplant recipients. Doppler spectrum analysis revealed a significant change in several spectrum-derived parameters. T_{max} (acceleration time of the systolic frequency peak), in particular, showed a decrease after 4 h of CyA administration (106 ± 58 ms vs 76 ± 36 ms in segmental arteries; $P < 0.05$). On day 2 the T_{max} returned to its original value (117 ± 57 ms). Thus, Doppler spectrum analysis enables one to detect temporary hemodynamic changes in the transplanted kidney following CyA administration. These observations may be useful in differentiating causes of renal dysfunction by Doppler spectrum analysis in clinical transplantation.

Key words: Duplex, kidney – Cyclosporin, duplex, kidney

Cyclosporin A (CyA) is a potent immunosuppressive drug that has improved survival results in transplantation [9]. In kidney transplantation its major drawback is nephrotoxicity, which, particularly in the early period after transplantation, may obscure other causes of renal dysfunction. Differential diagnosis includes acute tubular necrosis (ATN), acute rejection, thrombosis of the renal artery, and CyA nephrotoxicity. Differentiation between these causes of renal dysfunction is necessary because they require different therapeutic approaches. The major problem in assessing early renal dysfunction after transplantation is the lack of reliable diagnostic procedures. Even with renal biopsy, establishing a proper diagnosis is often difficult. Moreover, a renal biopsy cannot be performed several times a week, as is sometimes necessary. Because of its noninvasive character, duplex examination can be repeated indefinitely and may be a useful tool in this diagnostic dilemma. Although the pathogenesis of CyA nephrotoxicity is not quite clear, there is evidence of increased renal vascular resistance [1, 4]. As Doppler spectrum analysis is able to demonstrate hemodynamic changes in vascular resistance [12], some effects of CyA on Doppler spectrum waveform might be expected. Several authors claim to be able to differentiate among the earlier mentioned causes of renal dysfunction by duplex examination findings only. There is, however, controversy over the effect of CyA on the Doppler spectrum waveform. Some authors claim that CyA does not alter the Doppler spectrum waveform or derived ratios [2, 14]. Others have reported changes in resistance index due to CyA nephrotoxicity [11], whereas in still other investigations these changes were only seen when CyA nephrotoxicity occurred concomitantly with ATN [7]. In a preliminary study we found some indications of CyA-induced changes of the Doppler spectrum waveform [17].

In order to investigate whether duplex examination can detect hemodynamic changes after CyA administration, we performed a prospective study to document the early changes in renal hemodynamics of continuous infusion of CyA after kidney transplantation.

Patients and methods

A total of 15 patients who had received a kidney allograft in our center between May 1989 and January 1990 were included in our study. These patients received intravenous CyA immunosuppression as described previously [8]. CyA infusion (3 mg/24 h per kg body weight) was started 6 h after opening of the vascular anastomosis.

The first duplex examination was performed half an hour prior to CyA administration and subsequent examinations were done 1 and 4 h after the start of CyA infusion. Again, on days 1 and 2 after transplantation, duplex examinations were repeated. A total of 75 examinations were performed in this study.

We used a Toshiba SSA270-A color duplex scanner. The probe (3.75 MHz) was placed next to the operation wound so that the allograft could be visualized. During each examination Doppler spectra of the large branches of the renal artery (segmental arteries) at the hilus of the allograft were obtained, as well as spectra of the interlobar arteries in the area between cortex and medulla. The angle be-

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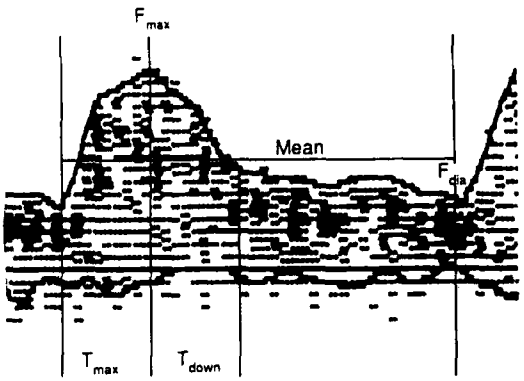

Fig. 1. Doppler spectrum obtained from a segmental artery as analyzed by Quindops. F_{max} Maximum frequency; F_{dia} diastolic frequency; T_{max} acceleration time; T_{down} deceleration time; *Mean* mean frequency during one heart cycle

tween artery and insonating ultrasound beam was kept between 40 and 60 degrees when acquiring Doppler spectra and was kept as constant as possible in order to be able to compare angle-dependent parameters. Special attention was given to the location of the Doppler sample in relation to the anatomy of the allograft so that in subsequent examinations in the same patient spectra would be comparable. Doppler signals were recorded on magnetic tape. Afterwards, these signals were analyzed with a spectrum analyzer (Mediasonics SA 8000). The spectra were digitally stored on a personal computer for off-line analysis. A program called Quindops (*Quantitative Interpretation of Doppler Spectra*), developed in our laboratory, enables us to analyze Doppler spectra in a standardized way [18]. From the spectrum a maximum frequency curve (MAX-curve) is calculated for the positive and negative frequency shifts separately. The algorithm by which the MAX-curves are calculated comprises local convolution of the spectra with a window five spectral lines wide and three frequency bits high, followed by fast Fourier transform 20 Hz low-pass filtering of the MAX-curves. From these curves Quindops then derives several parameters that characterize the Doppler spectrum waveform.

Figure 1 shows a Doppler spectrum obtained from a segmental artery, the MAX-curves as calculated by Quindops, and some of the calculated parameters. We took special interest in parameters that can indicate changes in vascular impedance according to hemodynamic models, as proposed, for example, by Skidmore et al. [16]. These include F_{max}, F_{dia}, T_{max}, T_{down}, and mean frequency as described by Fronek et al. [5]. They are shown in Fig. 1. Resistance index (RI) and pulsatility index (PI) were also calculated. Definitions of RI, as proposed by Planiol and Pourcelot [13], and of PI, according to Gosling et al., [6] are respectively:

$$RI = \frac{F_{max}-F_{dia}}{F_{max}}$$

$$PI = \frac{F_{max}-F_{dia}}{Mean}$$

Clinical data such as blood pressure, pulse rate, and diuresis of patients were registered without knowledge of duplex examination findings.

Clinical data and differences in spectrum-derived parameters between measurements were analyzed with the Wilcoxon matched pairs test or the paired *t*-test when appropriate. Probability values below 0.05 were considered significant.

Results

Clinical data on the 15 transplant recipients are shown in Table 1. There were significantly higher blood pressures on days 1 and 2 after transplantation than on the day of transplantation. Other clinical parameters remained unchanged. Clinically, no CyA nephrotoxicity was suspected during the first days after transplantation.

Figure 2 shows the MAX-curve-derived parameters of spectra obtained in the segmental arteries and in the interlobar arteries, respectively. Mean values ± SEM in consecutive measurements are displayed for each parameter.

When comparing third duplex examinations (4 h after the start of CyA infusion) with first examinations (before the start of CyA infusion), a significant decrease in F_{max}, F_{dia}, and T_{max} was seen. T_{max} increased again between the third and fifth examinations (day 2 after transplantation). Parameters tended to return to their original values on day 2 after transplantation. These trends were found in

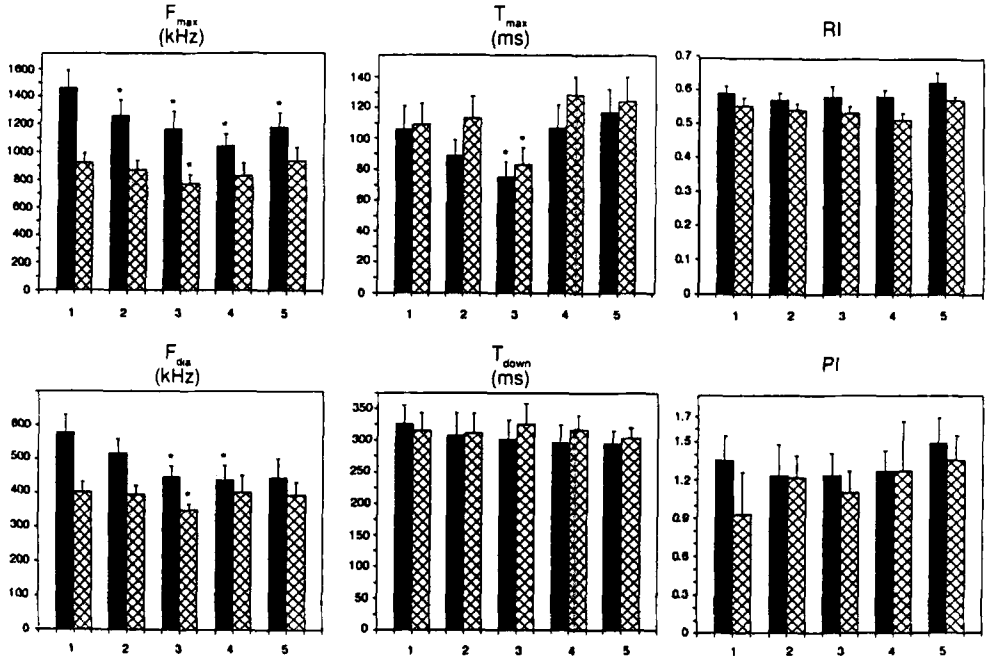

Fig. 2. Doppler spectrum-derived parameters in five consecutive duplex examinations on patients receiving intravenous cyclosporin A. Values are displayed as mean ± SEM. ■ Parameters of segmental arteries; ▨ parameters of interlobar arteries. * $P < 0.05$ when compared to measurement 1

Table 1. Clinical data (mean ± SD) in 15 transplantation recipients in relation to duplex examination

Measurement	Time relation with cyclosporin A administration				
	$-\frac{1}{2}$ h	+1 h	+4 h	Day 1	Day 2
	1	2	3	4	5
Blood pressure (mm Hg)					
Systolic	138 ± 19	138 ± 17	136 ± 20	153 ± 22*	158 ± 21*
Diastolic	80 ± 13	83 ± 14	81 ± 10	94 ± 12*	94 ± 12*
Diuresis (ml/h)	30 ± 48	37 ± 46	38 ± 50	37 ± 53	42 ± 44
Heart rate (bpm)	84 ± 10	85 ± 9	85 ± 9	79 ± 10	83 ± 10

* $P < 0.05$ when compared to measurement 1

both segmental and interlobar arteries. Changes were, however, more pronounced in segmental arteries.

Discussion

Vasoconstriction of the afferent glomerular arteriole after CyA administration has been documented in rats [1, 4]. In human kidney transplantation, increased vascular resistance of the kidney allograft, due to CyA, has been found within 2 weeks after transplantation [3]. With Doppler spectrum analysis we found a change in renal hemodynamics 4 h after the intravenous infusion of CyA. The parameter in which change was most evident 4 h after CyA infusion was T_{max}. We also consider this to be the most reliable parameter because it is not dependent on the insonation angle of the Doppler beam. F_{max} and F_{dia} showed the same trend as T_{max} in consecutive measurements. Changes were most evident in the segmental arteries. Using the analysis of hemodynamic models as, for example, presented by Skidmore and Woodcock [16], it can be understood that a decrease in F_{max} and F_{dia}, and even more a decrease in the angle-independent. T_{max}, indicates a change in vascular impedance. The decrease in T_{max} implies increased vascular wall tonus, as postulated in the Laplace model that Skidmore and Woodcock used in their hemodynamic approach. This increased tonus apparently did not have enough impact on parameters that are indicative for peripheral resistance, RI, and PI. The measured decrease in F_{max} and F_{dia} implies a decrease in overall blood flow through the kidney, which is in accordance with the registered change in vascular impedance. It seems that CyA, in a therapeutical dose, changes renal impedance by increasing vascular wall tonus. In overt nephrotoxicity this increased tonus may well lead to vasoconstriction. The decrease in F_{max} and F_{dia} was more obvious in segmental arteries than in interlobar arteries. A possible explanation for this observation is that the hemodynamic changes that were measured in a segmental artery monitored the combined effects of CyA infusion in the larger peripheral vascular bed of the interlobar arteries.

The return of the Doppler spectrum waveform to its original shape may have been caused by the increase in blood pressure on days 1 and 2. In vitro models have shown that Doppler spectrum-derived parameters are influenced by systemic pressure [10]. Moreover, using the earlier mentioned hemodynamic model, it can be understood that T_{max}, as an indicator of vascular impedance, is related to arterial blood pressure. Thus, it may be important to consider blood pressure in detecting CyA nephrotoxicity with the aid of Doppler spectrum analysis. The return of the Doppler spectrum waveform may also have been caused by an autoregulation mechanism of the vascular bed that decreases smooth muscle tonus. It is possible that this autoregulation is insufficient at high CyA levels and may then lead to renal dysfunction and/or hypertension.

In animal models, increased vascular resistance due to CyA has been more easily demonstrated than tubular toxicity [15]. Our results also suggest a vascular mediated effect of CyA. If, indeed, a changing vascular impedance is the primary mechanism of CyA nephrotoxicity [4, 15], Doppler spectrum analysis could be helpful in the future in determining CyA nephrotoxicity or in evaluating the effect of pharmacological manipulations to reverse these hemodynamic effects. Studies evaluating the effect of CyA on Doppler spectrum waveform in the post-transplantation period are needed to establish the value of spectrum analysis in this regard. It can be speculated that when CyA alters Doppler spectrum waveform in therapeutical dosages, a detectable effect on Doppler spectrum waveform can be expected in overt CyA nephrotoxicity.

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