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Haemodynamic changes in human kidney allografts following administration of nifedipine: assessment with doppler spectrum analysis

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Abstract. Cyclosporin (CyA) has been demonstrated to increase the vascular resistance of renal allografts (RVR), whereas calcium channel blocking agents like nifedipine may counteract this effect. In this study RVR was calculated from renal blood flow (RBF), measured by the clearance of para-aminohippurate (PAH), and mean arterial pressure (MAP). Analysis of Doppler spectra obtained under ultrasonographic guidance was used as a non-invasive method of assessing renal haemodynamics. A comparison was made between these two methods to detect changes in renal haemodynamics which were caused by the administration of 10 mg nifedipine orally to 11 renal transplant recipients treated with CyA. RBF increased significantly (444 ± 176 vs 559 ± 192 ml/min per 1.73 m^2; $P < 0.05$) despite a decrease in MAP (116 ± 10 vs 101 ± 11 mm Hg; $P < 0.05$) after administration of nifedipine. Calculated RVR decreased from 0.31 ± 0.17 to 0.20 ± 0.07 mm Hg × min/ml ($P < 0.05$). Results of Doppler spectrum analysis were in concordance with these observations. Resistance index (RI) in interlobar arteries decreased from 0.60 ± 0.04 to 0.56 ± 0.06 ($P < 0.05$) and acceleration time (T_{max}) of the Doppler spectrum decreased from 133 ± 32 to 98 ± 32 ms ($P < 0.05$). Theoretically, a lower RI and decreased T_{max} indicate a reduced vascular resistance and changes in vascular wall compliance, respectively. Analysis of Doppler spectra may thus become a useful device for non-invasive assessment of acute changes in RVR.

Key words: Doppler spectrum analysis – Nifedipine – Renal vascular resistance

Analysis of Doppler spectra can be used to assess haemodynamic properties of vascular beds. In human kidney transplantation the analysis of Doppler spectra has been used to estimate haemodynamic changes in kidney allografts. Several reports have been published on the merits of Doppler spectrum analysis in the differential diagnosis of renal dysfunction after transplantation [3, 15]. Parameters derived from Doppler spectra were used to discriminate between different causes of renal dysfunction. The accuracy of this technique, however, is still a matter of debate [13]. More specifically its value in the detection of the nephrotoxic effects of the immunosuppressive drug cyclosporine (CyA) is a matter of controversy [7]. CyA has been shown to increase renal vascular resistance [5], and we have previously shown that intravenous administration of CyA has an impact on renal haemodynamics that can be detected with analysis of Doppler spectra [11]. Calcium channel blockers have been used to ameliorate CyA-mediated renal side-effects, vasodilation most probably being responsible for their beneficial effect [6, 12].

In this study we investigated whether analysis of Doppler spectra enables detection of acute changes in allograft haemodynamics following administration of a calcium channel blocker to patients on CyA treatment. We compared the results of Doppler spectrum analysis before and after administration of nifedipine to CyA-treated kidney allograft recipients undergoing conventional measurements of renal haemodynamics. These observations may contribute to a better understanding of the physiological interpretation of Doppler spectrum-derived information.

Patients and methods

Eleven recipients of a cadaveric renal allograft (9 males, 2 females; mean age 39 ± 12 years) with stable graft function approximately 12 weeks after transplantation were included in the study. The transplantation procedure and post-transplantation care were as described previously [10]. All patients received CyA immunosuppression and low-dose prednisone. None of them were treated with a calcium channel blocker. All patients gave informed consent. Measurements were performed in the out-patient clinic and were started between 8 and 9 a.m. Measurements of renal haemodynamics and echo-Doppler examinations were performed before and after the oral administration of 10 mg nifedipine.

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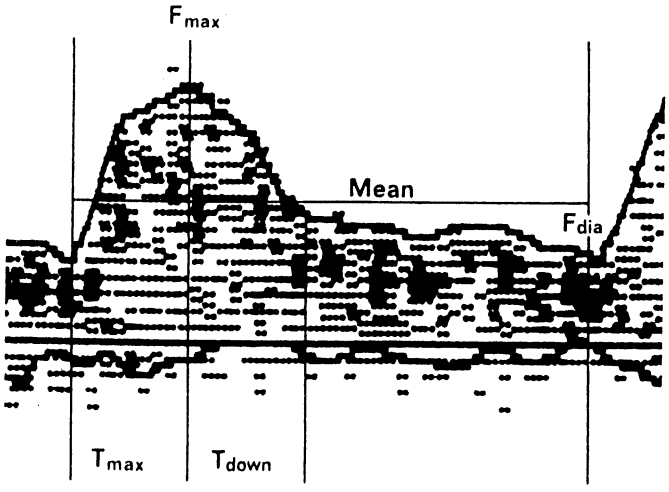

Fig. 1. Doppler spectrum from an interlobar artery with maximum frequency curve and descriptive parameters. F_{max}, maximum systolic frequency shift; F_{dia}, diastolic frequency shift; T_{max}, acceleration timeof the systolic deflection; T_{down}, deceleration time of the systolic deflection; Mean, mean frequency shift during one heart cycle

Measurements of renal haemodynamics

During the study patients were in a supine position except during voiding. Blood pressure and heart rate were measured every 3 min with an automatic device (Dinamap, Critikon). Renal clearance of para-aminohippurate (PAH) was used as a marker of effective renal plasma flow (ERPF). After a priming dose, PAH was given by continuous intravenous infusion in a dose adjusted to renal function. After an equilibration period of at least 75 min, urine was collected during three consecutive 30 min intervals. Blood samples were drawn at the midpoint of each interval. A sufficient diuresis was established by an oral water load of 10 ml/kg upon arrival in the ward, followed by IV infusion of a solution of NaCl 0.25% and glucose 3.3% at a rate of 400 ml/h, and replacement of excess urinary loss by giving water orally. PAH was measured in serum and urine samples and haematocrit (Ht) in blood samples using standard semi-automated techniques. PAH clearance (ERPF) was calculated using the standard formula UV/P. Renal blood flow (RBF) was calculated as ERPF/1-Ht) and corrected for a standard body surface area of 1.73 m^2. The mean values of five consecutive 3-min interval readings of blood pressure and heart rate around the midpoint of each clearance period were used for analysis. Renovascular resistance (RVR) was defined as mean arterial pressure (MAP) divided by RBF.

Echo-Doppler examinations

Non-invasive examinations were performed with an echo-Doppler scanner (Toshiba SSA-270A), using the B-mode image for guidance of the pulsed wave Doppler sample volume. Doppler spectra were obtained from segmental arteries in the medulla of the allograft and from interlobar arteries near the cortico-medullary junction with a 3.75 MHz sector probe. The angle between the Doppler beam and the artery under investigation was kept below 50° and in the same range in consecutive examinations. With each examination a Doppler spectrum from the common femoral artery on the side of the allograft was also obtained using the 5.0 MHz linear array probe. Doppler spectra were stored on a personal computer for off-line analysis by a user-written program. The program determined a Doppler waveform from the Doppler spectrum representing the instantaneous maximum frequency for every time moment. Subsequently several parameters describing the Doppler waveform were calculated. Figure 1 shows a Doppler spectrum from a segmental artery and the derived parameters as produced by the computer program. Restistance index (RI) and Pulsatility index (PI) were calculated according the methods of Planiol and Pourcelot [14] and Gosling et al. [9].

The means of blood pressure, heart rate, RBF and RVR of the first three consecutive 30-min periods were used as base-line values. The accompanying first ech-Doppler examination was performed during the third period. Immediately after the end of this period the patient received 10 mg nifedipine orally. Repeated measurements of renal haemodynamics took place from 30 to 60 min after administration of nifedipine. During this period the second echo-Doppler examination was performed.

Statistics

All values are expressed as means ± SD. For comparison of measurements before and after administration of nifedipine, the *t*-test for matched pairs was used. Spearman correlation coefficients *(r)* were calculated to quantify the correlation between the results of renal function measurements and Doppler parameters. Probability values below 0.05 were considered significant.

Results

The effects of the administration of nifedipine on blood pressure and renal haemodynamics are given in Table 1. Systolic and diastolic blood pressures decreased significantly after nifedipine administration. Mean arterial pressure fell from 116.3 ± 10.0 to 101.1 ± 11.1 ($P < 0.01$). The increase in RBF, despite this fall in MAP, is reflected in a significant reduction in calculated RVR.

Significant changes were also observed in Doppler parameters derived from spectra obtained from the segmental and interlobar arteries of the renal allograft. The acceleration time of the systolic peak of the Doppler waveform (T_{max}) became shorter in both arteries. In the interlobar arteries a significant decrease was found in RI and PI. When renal vascular resistance was correlated with RI obtained from segmental and interlobar arteries, only weak, non-significant, correlations were found (r = 0.45 (P = 0.16) and r = 0.57 (P = 0.07), respectively) before administration of nifedipine. After administration of nifedipine, however, RI showed a significant correlation with RVR (r = 0.66 (P = 0.03) and r = 0.76 (P = 0.007) in segmental and interlobar arteries, respectively). Figure 2 shows this relationship between RVR and RI from interlobar arteries before and after the administration of nifedipine.

Table 1. Effects of administration of nifedipine on blood pressure and renal haemodynamics

	Nifedipine administration		
	Before	After	*P* value
Systolic BP (mm Hg)	163.0 ± 16.2	142.5 ± 16.6	< 0.01
Diastolic BP (mm Hg)	90.6 ± 10.8	77.0 ± 9.6	< 0.01
MAP (mm Hg)	116.3 ± 10.5	101.1 ± 11.7	< 0.01
Heart rate (bpm)	63.5 ± 8.6	75.0 ± 14.5	< 0.01
RBF (ml/min per 1.73 m^2)	445 ± 168	559 ± 184	< 0.01
RVR (mm Hg × min/ml)	0.32 ± 0.17	0.20 ± 0.07	< 0.01

BP, blood pressure; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance

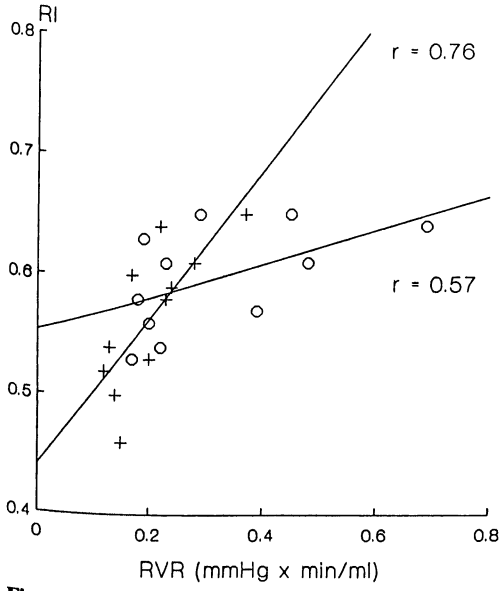

Fig. 2. Correlation of renal vascular resistance (RVR) and resistance index (RI) from interlobar arteries before and after administration of nifedipine. ○, Before administration of nifedipine ($r = 0.57$; $P = 0.07$); +, after administration of nifedipine ($r = 0.76$; $P = 0.007$)

In Doppler spectra obtained from the common femoral artery, just distal to the end-to-side anastomosis of the renal artery with the iliac artery, no significant changes were noted after administration of nifedipine.

Discussion

The primary goal of this study was to assess whether Doppler spectrum analysis can detect haemodynamic changes in human kidney allografts after drug-induced haemodynamic interference. We compared changes in Doppler parameters to nifedipine-induced changes in RVR, which was calculated from PAH clearance, haematocrit and MAP. Although the latter calculation only provides a rough estimate, it is commonly used to gain information on global renal vascular resistance [5].

Doppler parameters indicated changes in the haemodynamic properties of the renal allograft. The RI and PI decreased significantly in the interlobar arteries. Also T_{max} decreased in segmental and in interlobar arteries. There were no changes in the Doppler spectra obtained from the femoral artery distal to the renal allograft. Thus it is most likely that the changes observed in the arteries of the allograft are indicative of changes located in the allograft itself, and are not merely the result of a decrease in systemic mean arterial pressure. Moreover, when systemic pressure decreases, no change in RI is expected when renal resistance remains unchanged [2]. The decrease in RI and PI indicates a decrease in vascular resistance. The changed impedance of the renal allograft was confirmed with the measurements of renal haemodynamics, which showed a decrease in RVR.

Correlation of RI and RVR improved markedly after administration of nifedipine. This suggests that one of the two methods of estimation of vascular resistance is more influenced than the other by a variable that has less impact after administration of nifedipine. A possible explanation for this observation is that, after administration of nifedipine, RVR becomes more dependent on the resistance of arteries from which RI was obtained.

RI and PI are generally considered reliable parameters for the estimation of resistance of the distal part of a vascular bed. We found a significant decrease in these parameters in interlobar arteries, which are closest to the probable site of the vasoconstrictive action of CyA [1, 8]. Nifedipine may be expected to have the largest influence on haemodynamics at that site. T_{max} is a parameter which is more difficult to interpret. In clinical renal transplantation, T_{max} has been indicated by Arima et al. [4] as a parameter that is correlated with renal function. In their study a shorter T_{max} was found in renal allografts with stable function, whereas T_{max} was longer in allografts with poor function. In the mathematical model for Doppler waveform analysis introduced by Skidmore and Woodcock [16], T_{max} was regarded as indicative of the elastic properties of the vascular wall: changes in T_{max} reflect changes in vascular wall compliance. Apparently, the vasodilatory effect of nifedipine on the vascular wall of renal arteries that are preconstricted by CyA is reflected in shortening of T_{max} in the Doppler spectrum waveform.

In summary, the changes in renal vascular resistance due to vasodilatory effects of nifedipine are reflected in the Doppler spectrum waveform, in changes in RI, indicating decreased distal resistance to flow, and in changes in T_{max}, reflecting changes in vascular wall compliance. From these observations we conclude that haemodynamic changes in human kidney grafts due to drug interventions can be detected with Doppler spectrum analysis. This may make this non-invasive technique suitable for monitoring acute haemodynamic changes due to drug interventions in human kidney allografts.

Table 2. Results of analysis of Doppler spectra before and after administration of nifedipine

	Nifedipine administration		
	Before	After	*P* value
Segmental artery:			
F_{max} (Hz)	1612 ± 663	1842 ± 411	0.241
F_{dia} (Hz)	635 ± 328	712 ± 203	0.441
T_{max} (ms)	130 ± 41	79 ± 34	0.014*
RI	0.61 ± 0.05	0.62 ± 0.07	0.874
PI	1.07 ± 0.15	1.08 ± 0.21	0.899
Interlobar artery:			
F_{max} (Hz)	932 ± 209	1037 ± 285	0.261
F_{dia} (Hz)	374 ± 92	448 ± 122	0.070
T_{max} (ms)	133 ± 32	98 ± 32	0.008*
RI	0.60 ± 0.04	0.56 ± 0.06	0.025*
PI	1.07 ± 0.15	0.93 ± 0.17	0.048*
Femoral artery:			
F_{max} (Hz)	2655 ± 783	2927 ± 778	0.056
F_{dia} (Hz)	− 833 ± 233	− 773 ± 222	0.468
T_{max} (ms)	105 ± 14	104 ± 17	0.932
PI	6.1 ± 0.9	5.6 ± 1.5	0.395

* $P < 0.05$; for explanation of parameters see legend to Fig. 1

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