Transplant Int (1992) 5 [Suppl 1]: S21–S22

TRANSPLANT
International


# Cyclosporine renal cortical vasoconstriction measured by colour doppler imaging in kidney transplantation

**F. Quarto Di Palo[1], D. Castagnone[3], R. Rivolta[3], F. Ceccherelli[2], A. Elli[1], M. Parenti[1], P. Palazzi[1], and C. Zanussi[1]**

[1] Clinica Medica 1°, and [2] Laboratory Analisi Cattedra 4 Igiene, Università di Milano, Milano, Italy,
[3] Servizio di Radiologia Medica Ospedale Maggiore Milano, Milano, Italy

Important side-effects limit the use of cyclosporine A (CSA), the most insidious of which is nephrotoxicity, which manifests as a preglomerular arteriolar vasoconstriction causing a reduction in glomerular filtration rate (GFR) and renal plasma flow (RPF). This condition is initially purely functional, but with time can become anatomic and irreversible [4].

In clinical practice we lack suitable methods for evaluating CSA vasoconstriction. Our present knowledge is based on indirect information obtained from repeated measurements of plasma creatinine levels and from blood concentrations of the drug. Sometimes more complex and non-routine tests, such as the evaluation of GFR and RPF, or invasive methods, such as renal biopsy, are also employed.

In this study we used the colour-Doppler technique to measure directly the vascular effects of CSA in patients with transplanted kidneys, evaluating changes in blood flow at the hilus and on the cortex of the kidney when the drug was at trough or peak levels.

**Key words:** Renal transplantation – Cyclosporine – Vasoconstriction – Doppler imaging

## Materials and methods

We studied 14 patients with cadaveric renal transplants (seven men and seven women) with a mean age of 34.5 ± 8.5 years. The transplants were well established (34.6 ± 27 months), with good renal function (plasma creatinine < 140 m*M*/l). None of the patients was taking antihypertensive drugs. All were under triple immunosuppressive therapy, with identical doses of steroids and azathioprine. CSA was taken in two equal daily doses at a mean dose of 4.5 ± 0.5 mg/kg per day. Whole-blood levels of the drug, measured by FPIA (Abbott polyclonal antibody), ranged between 350 and 700 ng/ml. Before the trial, patients took no medications for 12 h.

At 9 a.m. blood samples for the measurement of CSA trough levels and plasma creatinine were taken, mean arterial blood pressure (MAP) was determined and colour-Doppler spectra obtained. At the end of the procedure, patients took their doses of CSA and 3 h later (peak time) the same determinations were repeated.

To evaluate the effect of the drug on the chronically damaged kidney, the same parameters were repeated on a group of 13 cadaveric renal transplant patients with reduced, but stable, renal function (plasma creatinine 140–350 m*M*/l).

The ATL Ultramark-9 apparatus with a 3.5 or 5 MHz probe was used to obtain the hilar and cortical colour-Doppler spectra. We used the indices RI (resistive index = peak systolic velocity minus the lowest diastolic velocity divided by peak systolic velocity) and PI (pulsatility index = peak systolic velocity minus the lowest diastolic velocity divided by mean velocity) to eliminate the bias associated with the angle of determination of the velocity in the vessel. With this system it is possible to compare the data obtained at different times with a large margin of specificity, sensitivity and accuracy [1, 3, 6, 7]. All the colour-Doppler values presented are the mean of five successive measurements.

The values are presented as means ± SE. The significance of the differences between the values obtained at trough and peak levels was determined by the *t*-test for paired data. Linear regression analysis was used to look for relationship between blood cyclosporine and colour-Doppler parameters.

## Results

In our patients, the mean CSA blood levels increased from 338 ± 36 ng/ml (trough) to 801 ± 106 ng/ml (peak) ($P < 0.002$). Mean blood pressure (MAP) did not change significantly, being 107.5 ± 5 mm Hg at the trough time and 114 ± 3 mm Hg at the peak time.

The PI and RI measured at the hilus of the kidney did not vary significantly (PI, trough 1.01 ± 0.05 vs peak 1.17 ± 0.10; RI, trough 0.62 ± 0.02 vs peak 0.64 ± 0.03.

The changes in the Doppler spectra of the renal cortex after CSA were more striking. The PI increased from a trough value of 0.82 ± 0.02 to a peak value of 1.11 ± 0.03 ($P < 0.0001$). The change in the RI was analogous, going from a trough value of 0.54 ± 0.009 to a peak value of 0.64 ± 0.007 ($P < 0.0001$).

In the cortex, a positive linear correlation between CSA level and PI value ($r$, 0.60; $P < 0.02$; $n = 28$) was found. The higher the level of the drug, the more the pe-

*Offprint requests to:* F. Quarto Di Palo

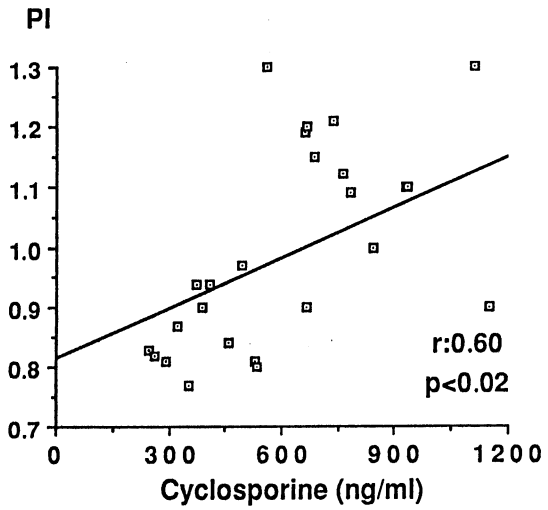


**Fig. 1.** Relationship between CSA levels in whole blood and pulsatility index (PI) measured on the renal cortex at the same time ($n$ = 28)

ripheral resistance increased and the diastolic flow decreased (Fig. 1).

The effect of CSA on colour-Doppler spectra of the kidney in the group of patients with chronically impaired renal function was identical to that observed in well-functioning grafts, except for higher trough values. At the hilus of the kidney PI was $1.32 \pm 0.12$ at trough vs $1.41 \pm 0.15$ at peak (NS) and RI was $0.68 \pm 0.03$ at trough vs $0.70 \pm 0.03$ at peak (NS). On the renal cortex PI was $1.07 \pm 0.09$ at trough vs $1.43 \pm 0.016$ at peak ($P < 0.02$) and RI was $0.62 \pm 0.03$ at trough vs $0.71 \pm 0.03$ at peak ($P < 0.03$).

## Discussion

Cyclosporine dose-dependently decreased cortical blood flow in the transplanted kidney. The effect was specific and agreed with other reports that show a vasoconstrictive action of the drug on afferent arterioles [5].

Orally administered CSA causes continuous cyclic changes in renal cortical blood flow and in renal vascular resistance related to the varying blood levels of the drug during the daytime. In the patients with good graft function, these variations did not appear to have produced any clinically relevant renal damage. However, the greater nephrotoxicity related to the higher peaks obtained when CSA was given once a day [2] indicates that these vascular changes are not entirely risk free.

The vasoconstrictive effect of CSA is not modified by the presence of impaired renal function. In these cases, an identical level of the drug will produce a greater reduction in blood flow than in the well-functioning kidneys.

It is therefore reasonable to believe that at higher doses of CSA, or in the presence of other concomitant disease states that reduce renal function, these variations in cortical blood flow might play a part in the production of the complex physiopathological phenomenon that leads to nephrotoxicity. If this hypothesis is true, then colour-Doppler imaging which is sensitive, repeatable and non-invasive, may be a new tool for monitoring renal blood flow over time and for evaluating the risk of nephrotoxicity associated with CSA therapy.

## References

1. Allen KS, Jorkasky DK, Arger PH, Velchik MG, Grumbach K, Coleman BG, Mintz MC, Betsch SE, Perloff LJ (1988) Renal allografts: prospective analysis of doppler sonography. Radiology 169: 371–376
2. Dieperink H, Leyssac PP, Starklint H, Kemp E (1988) Cyclosporine A administration: once a day or in fractional doses? Transplant Proc 20 [supp 2]: 703–706
3. Leichtman AB, Sorrell KS, Wombolt DG, Hurwitz RL, Glickman MH (1989) Duplex imaging of the renal transplant. Transplant Proc 21: 3607–3610
4. Mason J (1990) Renal side-effects of cyclosporine. Transplant Proc 22: 1280–1283
5. Myers BD (1989) What is cyclosporine nephrotoxicity? Transplant Proc 21: 1430–1432
6. Rifkin MD, Needleman L, Pasto ME, Kurtz AB, Foy PM, McGlynn E, Canino C, Baltarowich OH, Pennel RG, Goldberg BB (1987) Evaluation of renal transplant rejection by duplex doppler examination: value of the Resistive Index. AJR 148: 759–762
7. Skotnicki SH, van Asten WNJC, Beijneveld WJ, van Roosmalen R, Hoitsma AJ, Wijn PFF (1989) Evaluation of renal allografts function by doppler spectrum analysis. Transplant Int 2: 16–22