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The effect of cyclosporin on lower limb blood flow in renal transplant recipients

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Abstract. We investigated the effect of electively converting stable renal allograft recipients from cyclosporin A (CyA) to prednisolone and azathioprine on limb blood. We used a non-invasive method designed to measure the hyperaemic blood flow to the lower limb following a standard ischaemic insult. The hyperaemic blood flow was greater during CyA therapy – median 14 ml/100 ml tissue per minute (95% confidence limits 10.5–16.5) – than that after conversion – median 11 ml/100 ml tissue per minute (8.3–13.8; $P < 0.01$). By increasing peripheral vascular resistance and reducing limb blood flow, CyA may have caused an increase in the degree of ischaemia, so resulting in a greater hyperaemic response.

Key words: Cyclosporin A, limb blood flow – Limb blood flow, cyclosporin A – Conversion, cyclosporin A, limb blood flow

The introduction of cyclosporin A (CyA) has improved the success of renal allotransplantation. However, CyA can also be nephrotoxic [11]. Previous work has suggested that CyA nephrotoxicity may be due to a primary glomerulopathy [16] and/or to a reduction in both renal blood flow [7] and glomerular filtration rate [2]. Other investigators have reported that CyA can induce Raynaud's phenomenon, due to an increase in peripheral vascular resistance and a reduction in skin blood flow [10], and that CyA may affect hepatic drug metabolism by reducing hepatic blood flow, in addition to any effect on hepatic cytochrome P-450 activity [6].

We have previously noted an increased incidence of Raynaud's phenomenon in renal transplant recipients immunosuppressed with CyA monotherapy, starting at a dose of 17 mg/kg per day [8]. To further investigate the effect of CyA on peripheral blood flow, we studied the effect that converting stable renal transplant patients from CyA monotherapy to conventional immunosuppression with prednisolone and azathioprine had on limb blood flow, using a non-invasive technique to measure limb blood flow following a standard period of hypoxia.

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Patients and methods

Patients

Ten consecutive renal transplant patients who underwent elective conversion from CyA monotherapy to treatment with prednisolone and azathioprine were studied. The group comprised six men and four women, median age 47 years (range 30–65 years). Pretransplantation screening using electrocardiological criteria and/or two-dimensional echocardiography had revealed that four patients had evidence of left ventricular enlargement. Similarly, digital subtraction angiography showed that four patients had calcification of their internal iliac and/or femoral arteries.

Immunosuppressive therapy was changed when graft function was stable, a median of 7 months following transplantation (range 6–9 months). CyA therapy was reduced from a median daily dose of 400 mg (range 200–500 mg) in a stepwise manner for 7 days, during which time 20 mg prednisolone and 2 mg/kg azathioprine were commenced. In addition to immunosuppressive therapy, four patients were prescribed nifedipine retard, two hydralazine and two metoprolol. Apart from the immunosuppression, there was no alteration in medication during the study.

Methods

Patients were studied on the day prior to starting drug conversion and then 1 month after CyA was stopped. At each visit patients were weighed, blood pressure was checked with a Hawksley random zero spygmomanometer and the mean arterial blood pressure was taken as 1/3 the systolic + 2/3 the diastolic pressures. In addition, blood was taken, along with a 24-h urine collection for the determination of creatinine (American Parallel, Burgess Hill, Sussex, UK).

On each occasion lower limb volume was measured [5] and limb blood flow was measured during reactive hyperaemia. Pneumatic cuffs were inflated to 300 mm Hg (Fig. 1), so isolating the blood in the lower limbs from the rest of the circulation [17]. The remaining blood pool was labelled with technetium 99m-labelled human serum albumin. After 3 min of ischaemia, the cuffs were rapidly deflated

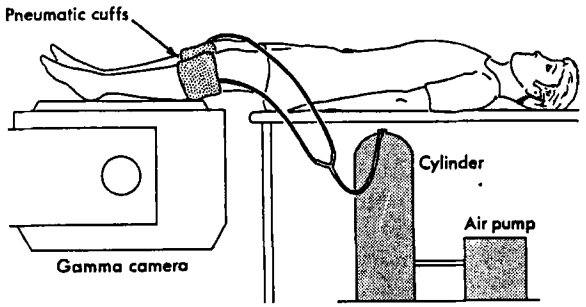

Fig. 1. Patient position for blood flow measurement

and the increase in radioactivity below the knee measured using a gamma camera [18]. The mean rate of blood flow to the limb was derived from the graph of radioactivity against time and from the radioactivity measured in a 10-ml sample of peripheral venous blood [22]. Blood flow per unit volume in ml/100 ml tissue per minute was calculated by dividing blood flow (ml/min) by limb volume (dl). Previous work has shown this method to be highly reproducible, with an intra-limb correlation of $r = 0.97$ [20].

Statistical analysis

Student's paired t-test was used for uniformly distributed data and the Wilcoxon rank sum pair test for nonparametric data. Spearman's rank sum correlation test was also used. Statistical significance was taken at or below the 5% level.

Results

Apart from the change in immunosuppressive therapy, there had been no other alteration in medication at the time limb blood flow was studied. Body weight did not change significantly following conversion: median weight on CyA was 65.3 kg (range 42.6–88.8 kg) compared to 67.8 kg (45.5–86.8 kg) following conversion. Similarly, there was no major change in mean arterial blood pressure, from a median of 104 mm Hg (80–114 mm Hg) to 104 mm Hg (80–116 mm Hg). Serum creatinine decreased in seven patients, was static in two and increased in the remaining patient following conversion from CyA (Fig. 2). Although the median creatinine clearance increased following conversion, this was not statistically significant.

All transplanted kidneys had been inserted in the right iliac fossa, and there was no difference in limb volume between the two legs prior to conversion (Fig. 3). Similarly, there was no difference in limb blood flow following conversion.

Prior to conversion, the median hyperaemic limb blood flow was slightly, but not statistically, greater in the right leg – median 14 ml/100 ml tissue per minute (10.1–19.3) – compared to 12.8 ml/100 ml tisuse per minute (6.5–17) for the left leg. The normal range of limb flow is 10–22 ml/100 ml tissue per minute [18]. Following conversion, the hyperaemic limb blood flow after 3 min of ischaemia was reduced from a median of 13.8 ml/100 ml tissue per minute (6.5–19.3) to 11.8 ml/100 ml tissue per minute (5.6–17.8; $P < 0.01$). The reduction in limb blood flow was consistent for both the left and right legs (Fig. 3).

Discussion

In this study in renal transplant recipients, changing immunosuppressive therapy from CyA to prednisolone and azathioprine was associated with an improvement in creatinine clearance in six patients and in serum creatinine in seven. Creatinine clearance was unchanged in one subject and blood creatinine in two. Creatinine clearance and blood creatinine values deteriorated in three and one patient, respectively. No patient suffered a rejection episode requiring additional immunosuppressive therapy. This is comparable with previous studies that have reported marked reductions in serum creatinine values associated with increases in creatinine clearance [15] following elective conversion from CyA to prednisolone and azathioprine. However, in these previous studies, conversion was also associated with episodes of acute rejection [1], with an incidence of up to 28% reported in one series [15].

Following conversion there was no change in the patients' weight, limb volume or mean arterial blood pressure. As CyA has been reported to cause hypertension [13] and increased systemic vascular resistance [10], mean arterial blood pressure could have been expected to decrease following conversion. In this study mean arterial blood pressure decreased in two patients, did not alter in three and increased in five. This may reflect individual patient sensitivity to both CyA and the hypertensive effect of steroids.

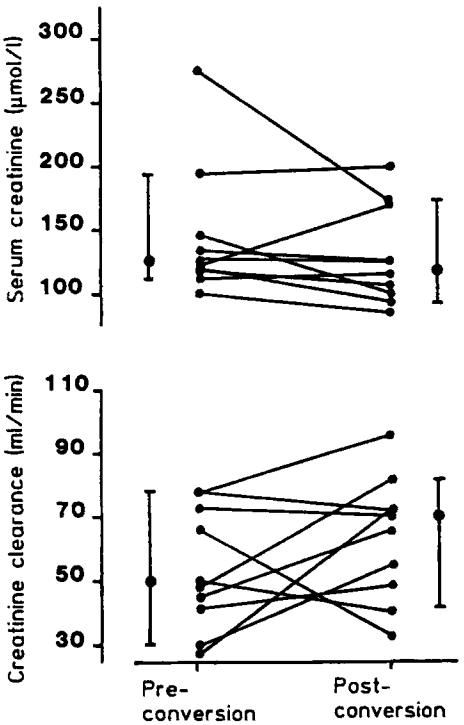

Fig. 2. Change in renal function following conversion from cyclosporin A to prednisolone and azathioprine. Median ± 95% confidence limits

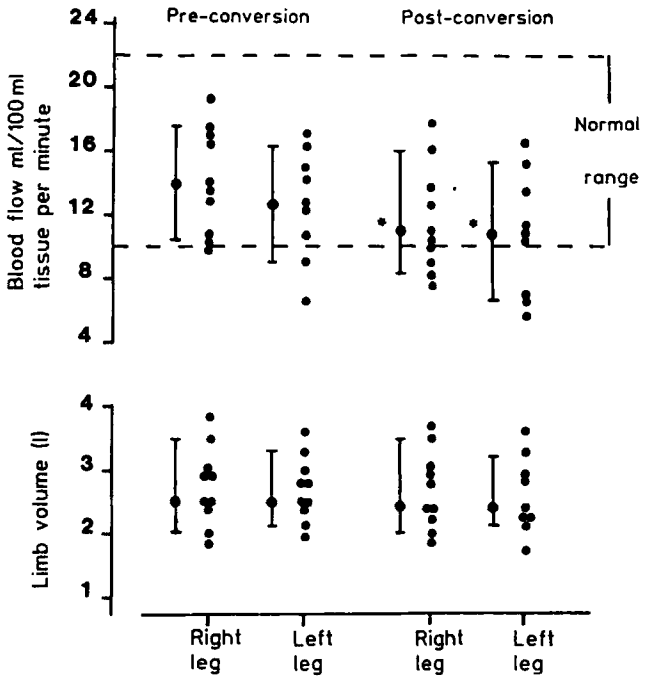

Fig. 3. Effect on both the hyperaemic blood flow response to a standard period of limb ischaemia and limb volume following conversion from cyclosporin A to prednisolone and azathioprine. * $P < 0.05$ vs pre-conversion. Median ± 95% confidence limits

Prior to conversion, limb blood flow following a standard 3-min ischaemic period was normal in all but two of the limbs studied. Both of these subjects were known to have vascular calcification and atheroma of the pelvic vessels on pretransplant digital subtraction angiography. Following conversion the hyperaemic limb blood flow decreased and was abnormally low in seven limbs, all from patients known to have abnormal pelvic vessels. No patient with normal pelvic vessels prior to transplantation had an abnormally low hyperaemic limb blood flow. This is in agreement with previous work using this technique to determine the aetiology of lower limb pain precipitated by exercise [17], as only patients with atheroma-induced claudication were found to have an abnormally reduced hyperaemic limb blood flow [12].

The limb blood flow was slightly greater in the right leg, both prior to and following conversion. As all grafts had been placed in the right iliac fossa, this may have been related to the alteration in vascular supply to the leg because of vascular steal by the transplanted kidney.

The hyperaemic limb blood flow was greater when patients were taking CyA. The differences in limb blood flow could be explained by major changes in renal function, leg volume or mean arterial blood pressure and cardiac output. In this study there were no significant changes in these parameters and, therefore, the changes observed must have been due to the change in immunosuppressive therapy. CyA would have been expected to cause a reduction in blood flow to the leg due to its effect on peripheral vascular resistance [7].

In this study we measured the hyperaemic limb blood flow following a standard period of ischaemia, and blood flow under these conditions was greater during CyA therapy than during treatment with prednisolone and azathioprine. If CyA reduced total limb blood flow, perhaps mediated by an increase in endothelin [4] and a reduction in vasodilator prostaglandin synthesis [3] or other local vasoactive mediators, then oxygen delivery to the leg would be reduced and the tissue may have a reduced anaerobic threshold [19, 23]. Under these circumstances, the standard hypoxic insult in our model of limb blood flow may result in a greater degree of limb ischaemia and an increased release of the products of anaerobic metabolism, resulting in greater vasodilatation at the arteriolar level [14] and an increased hyperaemic blood flow. This hypothesis would be supported by the data obtained in this study comparing the two legs. Limb blood flow would be expected to be reduced in the right leg, due to vascular steal; yet, the hyperaemic limb blood flow was greater in this leg both prior to and following conversion. The difference in hyperaemic blood flow between the two legs was reduced following conversion from CyA, suggesting that the reduction in resting limb blood flow with CyA increased the difference between the legs by further sensitising the right leg to a reduced blood flow.

Conversely, data from another study that investigated the effects of the vasodilator prostacyclin on patients with claudication showed a reduction in the hyperaemic blood flow following prolonged treatment with iloprost [21]. In this situation, prostacyclin could have increased resting limb blood flow, as judged by the improvement in claudicant symptoms. Hence, this may have then reduced the response to hypoxia.

This study suggests that the changes in vascular resistance and reduction in renal blood flow [7] observed with CyA therapy are not limited to the transplanted kidney but are also found in limb blood flow and may account for the increased incidence of Raynaud's phenomenon observed in patients treated with CyA.

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