CYCLOSPORINE NEPHROPATHY AFTER HEART AND HEART-LUNG TRANSPLANTATION

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Summary

Cyclosporine nephrotoxicity after heart transplantation can lead to acute renal failure requiring haemodialysis. In four long-term heart-transplant survivors, cyclosporine nephropathy was characterised by extensive fibrosis, with uraemia, hypertension and/or anaemia. In contrast, the long-term survivor of heart-lung transplantation who had received her graft for accelerated respiratory failure, did not develop chronic renal disease. Thus, chronically reduced renal perfusion before heart transplantation may play a critical role in the development of chronic cyclosporine nephropathy.

Introduction

Cyclosporine is undoubtedly a major immunosuppressive drug for organ transplantation. Its main advantage is its corticosteroid-sparing action while nephrotoxicity constitutes an important undesirable effect [1]. As the kidneys of heart-transplant recipients treated with cyclosporine are not susceptible to develop the changes induced by graft rejection, they may represent a better model for the assessment of cyclosporine nephrotoxicity than renal transplants where it is often difficult to distinguish kidney failure due to rejection from that produced by cyclosporine itself [2]. In the present paper, cyclosporine nephrotoxicity was examined in 11 patients who received the drug for heart or heart-lung transplantation.

Patients and methods

Table I yields the main data concerning the 10 patients who, between March 1982 and December 1983, underwent orthotopic heart transplantation in our institution for New York Heart Association (NYHA) class IV cardiac failure, and one patient who received in August 1983 heart-lung transplantation for rapidly progressive pulmonary insufficiency.
TABLE I. Main clinical details of recipients

1. Heart transplants (n=10)
   Age: median 45 years (range 27–55 years)
   Sex: 9 males/1 female
   All in NYHA class IV heart failure
   Primary diagnosis: idiopathic cardiomyopathy (n=4)
   ischaemic heart disease (n=6)
   Mean duration of ischaemia of the graft: 82 ± 5 min*
   Mean duration of extracorporeal circulation: 114 ± 7 min*
   Post-operative haemodialyses: No. of patients: 6
   Mean duration of dialysis period: 13 ± 3 days*
   Present survival: 4 patients in NYHA class I

2. Heart-lung transplant (n=1)
   Age: 27 years
   Sex: female
   Primary diagnosis: pulmonary lymphangioleiomyomatosis
   Duration of ischaemia of the graft: 84 min
   Duration of extracorporeal circulation: 170 min

NYHA: New York Heart Association
* Mean ± SEM

No effort was made to obtain good HLA matches between donors and recipients but ABO blood groups were compatible and lymphocytotoxic cross-matches were negative.

For heart transplants, immunosuppression consisted of cyclosporine (Sandimmun®, kindly supplied by Sandoz, Basel, Switzerland) and corticosteroids (Salumedrol® and Deltacortril®) while azathioprine (Imuran®) and cyclosporine were used during the first 14 post-operative days in the patient with heart-lung transplantation, azathioprine being later on replaced by prednisolone, as advocated by the Stanford group [3].

The first dose of cyclosporine (11.7±1.3mg/kg) was given orally four hours before surgery. Post-operatively, the drug was given orally at a daily dosage of 8–20mg/kg during the first month. From months 2 to 14, mean daily cyclosporine doses ranged from 6.5 to 8.0mg/kg and, from months 15 to 21, they were further tapered from 6.5 to 3.9mg/kg. Trough serum cyclosporine level was monitored frequently by a radioimmunoassay using the Sandoz kit, and graft rejection diagnosed by endomyocardial biopsies. Corticosteroids were given intravenously (30±3mg/kg/day) per-operatively and were subsequently tapered to 0.2mg/kg/day at three months. Azathioprine was given orally to the heart-lung recipient at a dose of 2mg/kg/day, from days 0 to 14.

Results

Table I gives for the 11 patients the durations of ischaemia of the graft and of extracorporeal circulation, the number of patients requiring post-operative haemodialyses, and the present survival.
In Table II are presented, for each patient, from day 0 to day 40, the evolution of serum bilirubin and creatinine, and of systolic and diastolic blood pressures, as well as the current status and cause and time of death.

**Early post-operative course**

In all patients, serum creatinine and urea concentrations increased during the first post-operative month. Six patients required haemodialyses and four of them died while two fatalities occurred among the five patients who did not require dialysis. Three of the six fatalities were due to cerebral haemorrhage and the three other patients died in severe septic shock (Table II). In the six patients who required haemodialysis in the early post-operative course, serum bilirubin rose to a mean upper value of 10.9±3.2mg/100ml while this value reached 4.3±1.5mg/100ml in the five patients who had not been dialysed.

In all six deceased patients, postmortem examination of the kidneys disclosed variable degrees of tubular necrosis with tubulorhexis and interstitial oedema (Figure 1) without cellular infiltration.

![Figure 1](image)

**Late post-operative course**

On June 30, 1984, five patients are surviving at 10, 12, 22, 24 and 25 months, including the heart-lung recipient (10 months). In none of them have myocardial
<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum bilirubin, mg/100ml</th>
<th>Serum creatinine, mg/100ml</th>
<th>Blood pressure, mmHg</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  10  20  30  40</td>
<td>0  10  20  30  40</td>
<td>0  10  20  30  40</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIE (H)</td>
<td>2.9 10.1 8.6 6.3 3.0</td>
<td>1.8 2.3 2.3 2.1 1.5</td>
<td>90/70 130/90 130/80 130/95 140/110</td>
<td>Alive 25 mos, Scr=2.5, BP 140/100</td>
</tr>
<tr>
<td>DEN (H)</td>
<td>1.3 5.1 3.0 2.2 1.5</td>
<td>1.2 HD HD 2.4 1.5</td>
<td>110/70 150/80 160/90 150/90 150/90</td>
<td>Alive 24 mos, Scr=2.6, BP 145/95</td>
</tr>
<tr>
<td>DEM (H)</td>
<td>1.1 9.5 14.1 5.0 3.1</td>
<td>1.1 HD HD 3.5 3.2</td>
<td>110/70 150/90 160/95 150/100 150/100</td>
<td>Alive 22 mos, Scr=2.7, BP* 125/80</td>
</tr>
<tr>
<td>ARY (H)</td>
<td>0.8 1.3 1.1 1.0 –</td>
<td>1.3 1.5 1.1 1.0 –</td>
<td>110/60 140/80 150/100 140/80 –</td>
<td>Alive 12 mos, Scr=2.1, BP 160/90</td>
</tr>
<tr>
<td>TER (HL)</td>
<td>0.7 1.0 0.9 1.0 0.5</td>
<td>0.6 1.1 0.6 0.7 0.6</td>
<td>130/80 105/80 110/70 110/80 125/90</td>
<td>Alive 10 mos, Scr=0.9, BP* 110/70</td>
</tr>
</tbody>
</table>

continued
TABLE II (continued)

<table>
<thead>
<tr>
<th>Patient POD</th>
<th>Serum bilirubin, mg/100ml</th>
<th>Serum creatinine, mg/100ml</th>
<th>Blood pressure, mmHg</th>
<th>Main cause and time of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 10 20 30 40</td>
<td>0 10 20 30 40</td>
<td>0 10 20 30 40</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAC (H)</td>
<td>1.7 2.9 + − − −</td>
<td>1.0 1.3 + − −</td>
<td>110/90 210/140 + − −</td>
<td>Cerebral haemorrhage 14 POD</td>
</tr>
<tr>
<td>HAQ (H)</td>
<td>1.6 20.8 + − − −</td>
<td>1.0 HD + − −</td>
<td>100/70 110/80 + − −</td>
<td>Cerebral haemorrhage 17 POD</td>
</tr>
<tr>
<td>GA1 (H)</td>
<td>1.0 + − − − − − −</td>
<td>1.1 HD+ − − − −</td>
<td>110/70 230/140+ − −</td>
<td>Cerebral haemorrhage 6 POD</td>
</tr>
<tr>
<td>SYM (H)</td>
<td>1.6 9.1 13.4 10.4 19.6</td>
<td>1.3 HD HD 1.6 0.4</td>
<td>85/60 125/90 130/80 130/70 140/90</td>
<td>Sepsis 40 POD</td>
</tr>
<tr>
<td>HAM (H)</td>
<td>− 6.7 + − − − − −</td>
<td>1.7 HD + − − − −</td>
<td>115/85 120/60 + − −</td>
<td>Sepsis 18 POD</td>
</tr>
<tr>
<td>JOO (H)</td>
<td>1.9 1.6 − + − − − −</td>
<td>1.4 1.3 − + − −</td>
<td>130/80 120/80 120/70 + −</td>
<td>Sepsis 23 POD</td>
</tr>
</tbody>
</table>

POD=post-operative day; (H)=heart transplant; (HL)=heart-lung transplant; BP=blood pressure under anti-hypertensive therapy, in mmHg; BP*=blood pressure without anti-hypertensive therapy, in mmHg; + =death occurred during the 10-day period preceding this day; HD=on haemodialysis; Scr=serum creatinine, in mg/100ml
biopsies demonstrated any sign of rejection so that corticosteroid therapy was constantly maintained at a low level. The heart-lung recipient did not show any increase in serum creatinine and urea levels or in blood pressure. The other four patients showed increased serum creatinine and urea concentrations from 10 to 25 months later, without proteinuria or abnormal urine sediment, but three of them are hypertensive and one is anaemic (Table II). In three of these patients currently surviving over 22 months percutaneous renal biopsies (Figure 2) uniformly showed extensive interstitial fibrosis with glomerular, tubular and arterial changes indistinguishable from those of nephroangiosclerosis.

![Figure 2](image)

In the three heart recipients surviving over 22 months, mean serum creatinine concentration decreased from 3.5 at month 14 to 2.5mg/100ml at month 21 as the mean daily cyclosporine dosage was tapered from 6.5 to 3.9mg/kg but urea concentration was not affected and no further decrease in creatinine was observed thereafter. The heart-transplant recipient (ARY) presently surviving at 12 months received smaller doses of cyclosporine (from 10 to 3.1mg/kg/day). Nevertheless, he developed chronic renal failure and hypertension (Table II).

**Discussion**

Our observations confirm that cyclosporine nephropathy may present a clinical and morphological picture of *acute renal failure*, often associated with cholestatic
jaundice and/or malignant hypertension with early lethal cerebral haemorrhage. This latter event is similar to the picture produced in acute cyclosporine toxicity in animals [4].

Jaundice may aggravate cyclosporine nephrotoxicity through interfering with biliary excretion of the drug [5]. Poor pre-operative hepatic and renal perfusion in our 10 heart transplant recipients, who were all in class IV heart failure at the time of surgery, could explain the high incidence of acute cyclosporine hepat- and nephrotoxicity in this series. The heart-lung recipient, who was not in heart failure before surgery, developed only transient increments in serum creatinine (3.5mg/100ml on day 2) and in serum bilirubin (2.6mg/100ml on day 1).

Of great concern is the development of renal fibrosis in the long-term survivors of heart transplantation. Excessive doses of cyclosporine may play an important role in the occurrence of this complication but, one patient presently surviving at 10 months with a daily cyclosporine dosage maintained between 10.0 and 3.1mg/kg is currently uraemic. Hypertension was observed in three of our four long-term heart transplant survivors, as reported in a larger series [6].

Chronic renal failure was also recently reported by Moran et al [7] in 13 cyclosporine-treated heart transplant recipients over one year while this complication was absent in eight patients who had received azathioprine instead of cyclosporine. On the other hand, Tauxe et al [8] noted that effective renal plasma flow was very low before surgery, and rose only to half-normal values five to 10 days after cardiac transplantation. They concluded that not all post-transplant renal dysfunction in cyclosporine-treated heart recipients should be attributed to the drug.

In our own series, the only patient without chronic renal failure was the heart-lung recipient who received her graft for respiratory and not for circulatory failure. The doses of cyclosporine used in this patient were of the same magnitude as those used here in the more recent heart recipients. More data should be gathered in heart-lung transplant recipients without circulatory failure before drawing definite conclusions concerning the precise role of poor renal perfusion in the setting of chronic cyclosporine nephropathy as observed in heart transplant recipients. It is obvious that similar ischaemic factors may also play an important role in cyclosporine nephrotoxicity after kidney transplantation.

Acknowledgments

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References


Open Discussion

BONOMINI (Chairman) Thank you very much Dr Toussaint for this very important paper.

ROTTEMBOURG (Paris) I am speaking as a participant of a team of Cabrol in La Pitié, and not as a nephrologist. For the last three years in Paris the Cabrol group have transplanted about 46 patients with heart transplants using cyclosporine. We have never seen acute renal failure requiring haemodialysis but we have seen some renal failure in our patients. At what time to you begin cyclosporine therapy after heart transplantation? Secondly, have you seen any difference in your young group of patients treated with cyclosporine compared with your older patients, because I see that your patients are rather older than ours in Paris?

TOUSSAINT Cyclosporine is started orally a few hours before surgery.

For the second question, of course this series is very small and the age range of the patients is quite wide. It may be that because these patients were waiting for a transplant for many weeks, many of them were in a very bad condition. Nevertheless, the Stanford group reported a few weeks ago in the New England Journal of Medicine exactly the same thing, and they have presented this in abstract form previously. We did not start cyclosporine immediately before, but on day one or day two when the patient had a good urinary flow. We think that this plays a major role in preventing renal failure after heart transplantation. The second thing is that we think that many of the patients, particularly patients with cardiomyopathy, could have renal damage before transplantation and this damage could be enhanced by the cyclosporine therapy.

PICHLMAYR (Hannover) I think we are very much in agreement. I do not want to take too much from the discussion of this afternoon, but I have been very interested in your heart-lung recipient patient that you did not observe these complications and this suggests that the combination of say pre-operative injury to the kidney and the nephrotoxicity may be a problem for you. You also argued that your doses of cyclosporine are high. The levels you observe are indeed high. Would you reduce the cyclosporine dose in the future considering the fact that you have, in a group of patients, also confirming a high dosage of cyclosporine? Do you agree?
TOUSSAINT Completely. Another point, if I may add, is that this heart transplant recipient is presently going back into pulmonary failure with chronic obstructive bronchiolitis on lung biopsy, as has been described by the Stanford group in Minneapolis a few months ago. This also may be an effect of cyclosporine in one-third of the heart-lung patient. It may be post-ischaemia because of course there is no suture of the bronchial arteries.

RATTAZZI (Seattle) Is there any correlation between cyclosporine blood levels and renal toxicity? I think the Stanford group has demonstrated that not to be the case, so what are you using to guide your dosage of cyclosporine therapy in heart transplantation?

TOUSSAINT I completely agree that there is absolutely no correlation with the blood levels and nephrotoxicity so there is so far in this transplant patient no guide, except that the patient was still alive, except those who died of course.

PINCHLMAYR I have one comment to this question. I think one cannot exclude a correlation between nephrotoxicity and blood or serum levels if one is over the toxic range in all patients. Some patients will tolerate this without nephrotoxicity but I think we have to go much further below the toxic levels to say whether there is a correlation or not. I would like to deal with this this afternoon.

TOUSSAINT Well, we have no autopsy material from many of our patients because all deaths occurred before day 40. There were no arterial lesions in any organs in these patients.