Renal failure following cardiac transplantation

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Introduction

The clinical outcome of cardiac transplantation has markedly improved over the last two decades due to the introduction of cyclosporin therapy. However, the renal side-effects of cyclosporin appear to be a major drawback to its use. The early studies by Myers et al. [1] described the renal structural and functional changes in the native kidneys of heart transplant recipients. Repeated haemodynamic investigations revealed a progressive decrease in glomerular filtration rate (GFR), a concomitant drop in renal plasma flow, and an increase in renal vascular resistance associated with systemic hypertension. Renal biopsies in a subset of patients disclosed glomerulosclerosis, striped interstitial fibrosis, and afferent arteriolopathy. In the original study a high starting dose of cyclosporin was used (17 mg/kg), which was later decreased to 10 mg/kg. However, when these two groups were compared, both of them had developed hypertension and a decreased GFR. Even with a low dose of cyclosporin the decline in GFR was approximately 45% from baseline, as compared with historical controls treated with azathioprine and prednisone without cyclosporin. Patients treated with low doses of cyclosporin had slightly lower mean serum (s-) creatinine concentrations, but similar pathological changes according to renal biopsies, than those treated with higher doses [2,3]. In addition, it was demonstrated that sequential biopsies of the native kidney in the two cyclosporin groups revealed progressive histopathological changes. Furthermore there was an approximately 10% cumulative incidence of end-stage renal disease during 10 years. The renal dysfunction could not be explained by the differences in cardiac function among the groups.

Long-term studies on renal function

In addition to the studies by Myers et al. [1–3], seven retrospective long-term analyses and one case control study regarding renal function in cardiac transplant recipients have been published during the 1990s [4–10]. These studies have shown that the renal function post-transplant, determined either by serial measurements of serum creatinine or by regular clearance measurements, revealed a biphasic response with a rapid decline up to 12 months and a slower deterioration of renal function thereafter. A similar pattern of renal response was reported in 100 consecutive heart-lung transplant recipients [11]. The early loss of renal function (within 12 months) apparently depends on the cyclosporin dose [1] and appears to be the key indicator of poor late outcome. Cyclosporin-induced nephrotoxicity is characterized by an initially reversible decline in GFR, which is most probably caused by a direct drug-induced afferent arteriolar vasoconstriction. The mechanisms underlying renal vasoconstriction and hypofiltration remain unknown, but abnormalities in endogenous vasoconstrictor and vasodilator mechanisms may be responsible [12]. In this respect, it is of interest to note that a single oral dose of cyclosporin (5 mg/kg) caused a profound impairment in renal haemodynamics. This was true for chronically treated renal transplant patients [13] as well as for healthy volunteers in whom 10 mg/kg of cyclosporin resulted in an 18% decrease of GFR [14]. The cyclosporin-induced increase in s-creatinine concentration may be associated with hypertension, a disproportionate increase in s-urea concentration, hyperkalaemia, increased uric acid concentrations.
(due to decreased fractional excretion), mild proteinuria (usually less than 1 g/24 h) and decreased fractional excretion of sodium. The blood pressure elevation could be associated with the decreased sodium excretion, stimulation of the renin–angiotensin system [15], increased local endothelin synthesis [16], and/or reduction in local nitric oxide synthesis [17]. Although withdrawal or dose reduction of cyclosporin may stabilize the renal function in some cases [18], it is by no means the rule [19]. Even if the renal function remains stable, proteinuria and morphological injury may still progress.

The deterioration of renal function in the seven studies mentioned above was conspicuous. The evolution of renal function after cardiac transplantation is shown in Table 1. The mean s-creatinine values, pooled from all seven studies, are shown in Figure 1. The most pronounced decrease in renal function was seen in the study by Greenberg et al. [4] where also the highest doses of cyclosporin were used. The lowest cyclosporin doses were used in the study by Tinawi et al. [8] and no patient developed end-stage renal failure requiring dialysis. In their study, patients with s-creatinine $\geq 200$ mmol/l during follow-up received a lower dose of cyclosporin than patients with serum creatinine $< 200$ mmol/l.

In the two large studies by Zietse et al. [7] and Lindelöw et al. [10] there was, however, no relationship between the cyclosporin concentration and the decline in renal function measured as the slope of s-creatinine vs time or by serial GFR measurements. Furthermore, in the case control study by van Gelder et al. [20] cyclosporin dose and trough levels in the 24 patients who developed renal insufficiency were not different from the patients who maintained their renal function. This may indicate that cyclosporin nephrotoxicity is determined by individual susceptibility.

In the case control study it was also demonstrated that renal failure after heart transplantation was not limited to elderly patients with ischaemic heart disease, but also occurred in young patients having dilated cardiomyopathy. This finding supported the observation by Zietse et al. [7] that no relationship could be found between the decline in renal function post-transplant and the age at transplantation. On the other hand, Greenberg et al. [4] and Lindelöw et al. [10]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Early serum creatinine (µmol/l)</th>
<th>Follow up serum creatinine (µmol/l)</th>
<th>Follow up time (years)</th>
<th>Follow up renal disease (%)</th>
<th>Serum CsA conc 1 year (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg et al. [4]</td>
<td>228</td>
<td>106</td>
<td>290</td>
<td>7</td>
<td>2.2</td>
<td>267</td>
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<tr>
<td>Lewis et al. [5]</td>
<td>100</td>
<td>114</td>
<td>176</td>
<td>4</td>
<td>1</td>
<td>153</td>
</tr>
<tr>
<td>Gonwa et al. [6]</td>
<td>69</td>
<td>114</td>
<td>141</td>
<td>4</td>
<td>1.3</td>
<td>3.5 mg/kg</td>
</tr>
<tr>
<td>Zietse et al. [7]</td>
<td>187</td>
<td>107</td>
<td>190</td>
<td>5</td>
<td>3.2</td>
<td>6.4 mg/kg</td>
</tr>
<tr>
<td>Tinawi et al. [8]</td>
<td>133</td>
<td>111</td>
<td>146</td>
<td>3</td>
<td>0</td>
<td>149</td>
</tr>
<tr>
<td>Goral et al. [9]</td>
<td>39</td>
<td>113</td>
<td>133</td>
<td>6</td>
<td>4</td>
<td>3.9 mg/kg</td>
</tr>
<tr>
<td>Lindelöw et al. [10]</td>
<td>151</td>
<td>108</td>
<td>157</td>
<td>9</td>
<td>4</td>
<td>253</td>
</tr>
</tbody>
</table>

Table 1. Seven retrospective studies describing evolution of renal function in cardiac transplant recipients on cyclosporin treatment.

Fig. 1. A pooling of the results from the studies described in Table 1. Only the mean values from the different studies have been used. The mean values are represented in relation to the number of patients who actually had a serum creatinine determined. The numbers of patients are shown above the time points in the diagram.
reported that high recipient age was an independent predictor of post-operative renal dysfunction. In the latter study it was also shown that the recipient age combined with GFR at 1 year post-transplantation predicted the development of severe dysfunction (<20 ml/min/1.73 m²). This occurred in 20% of the patients during 9 years follow-up.

In three of the above-mentioned studies GFR was determined by means of iothalamate or Cr-EDTA clearance measurements. Gonwa et al. [6] showed a 17% decrease in GFR during the first year post-transplant but no significant change occurred during 3 years. In the study by Goral et al. [9] no pre-operative GFR was recorded, but between year 1 and year 7 there was no change in renal function. Lindelöw et al. [10] found 21, 33 and 44% decrease in GFR 1, 5 and 9 years after transplantation respectively.

In none of the seven studies did any other parameter such as renal function before transplantation, blood pressure, or treatment with specific antihypertensive drugs show a correlation to the decline in renal function after transplantation. Patients with renal insufficiency before transplantation and those with a more pronounced depression of renal function at 6 months post-transplantation had a high risk for progressive kidney failure after heart transplantation, according to the study by Sehgal et al. [21]. The patients who developed renal insufficiency were older than those who did not. Contrary to this report, Goral et al. [9] demonstrated that patients with an initial post-transplantation GFR < 60 ml/min/1.73 m² had a stable renal function during the follow-up period. Lindelöw et al. (unpublished observation) found that patients with a baseline GFR ≤ 66 ml/min/1.73 m² had a reduced decrease in renal function as compared to those with GFR > 66 ml/min/1.73 m².

As shown in Table 1, the development of end-stage renal failure requiring renal replacement therapy was 2–4% during a 4–7-year follow-up in six out of seven studies. The corresponding figures for the large Stanford [22] and Rotterdam [20] studies were 3.3 and 8% respectively.

**Cyclosporin-induced renal injury**

No significant correlation has been described between the cyclosporin dose or blood concentration and the initial remarkable decline in renal function post-transplant revealed in any of the studies. There is consensus that the drug is responsible for the renal injury, since irreversible loss of renal function has been reported even with low doses of cyclosporin after liver, pancreas, and bone marrow transplantation, and also in patients with uveitis, insulin-dependent diabetes, rheumatoid arthritis, and psoriasis.

Bertani et al. [23] performed an important study where renal biopsies were obtained at the same time as the renal haemodynamics were measured in 10 heart transplant recipients who had been on low-dose cyclosporin therapy for more than 2 years. GFR and renal plasma flow were significantly depressed in these recipients. Light microscopy of autopsy specimens showed no structural renal abnormalities, either in patients without a history of renal disease or in patients who had died from dilated cardiomyopathy without a heart transplantation. However, arteriolopathy and glomerulosclerosis were seen in the cyclosporin-treated patients. Thus, cyclosporin given for more than 2 years induced moderate to severe renal failure associated with obliterator arteriolopathy and glomerular ischaemia in all patients. During the development of cyclosporin nephropathy two sub-populations with glomeruli of abnormal size emerged; these comprised patients with (i) small glomeruli and global or segmental sclerosis, and (ii) large glomeruli. In a follow-up study of these patients 2 years later a stabilization of GFR and renal plasma flow was noted but at that time no histopathology was recorded [24].

Many short-term studies have shown surprisingly good renal function 1 year after heart transplantation, yet renal dysfunction may appear later with proteinuria and progressive, mostly irreversible, histological lesions.

There is a dissociation between progressive tubulointerstitial and arteriolar disease on the one hand and renal function on the other. Experimental studies of cyclosporin nephropathy have found that GFR returned to normal 1 month after the discontinuation of cyclosporin therapy, whereas tubulointerstitial pathology persisted [25]. Such dissociation may reflect differences in pathogenesis, since Kon et al. [26] showed that haemodynamic changes after cyclosporin therapy can be inhibited by endothelin antagonists, whereas ACE inhibitors reduce fibrosis. In animal models of cyclosporin nephrotoxicity, both angiotensin II and endothelin seemed to play roles in the renal injury. Blockade of the renin–angiotensin system protected the kidneys from morphological vascular and tubulointerstitial injury, but without any effect on the decline in GFR [27]. On the other hand, endothelin blockade prevented the decline in GFR without protecting against the morphological injury [26]. These data suggest that angiotensin II, but not endothelin, may participate in the cyclosporin-induced fibrosis.

Calcium antagonists are potent vasodilators of the afferent arteriole and have been demonstrated to reduce the acute cyclosporin nephrotoxicity [28,29]. In human studies, no convincing favourable effect of blockade of the renin–angiotensin system on post-transplant renal failure has been described. However, at least three studies have disclosed a positive effect of calcium antagonists in heart transplant recipients in this respect [30–32]. The effect of endothelin antagonists on the evolution of renal function in transplant recipients remains to be studied.

**Preventive measures**

Except for a possible favourable effect from calcium-channel blockers on preventing or reversing the
nephrotoxic effects of cyclosporin after cardiac transplantation, there are no known treatments that are uniformly effective in heart and renal transplant recipients. Although most studies have been unable to show a correlation between the cyclosporin level and renal function following heart transplantation, it is generally agreed that close monitoring of cyclosporin blood levels is critically important in preventing or limiting progressive decline in renal function. Renal dysfunction has occasionally been described as reversible upon temporary cyclosporin withdrawal. There are several drugs that alter the cyclosporin levels or cause additive nephrotoxic effects in combination with cyclosporin. Consequently, the initiation or withdrawal of any drug should be done with caution and close follow-up of cyclosporin levels to maintain a therapeutic effect should be advocated.

Possible preventive measures to delay the development of renal dysfunction should be instituted at an early stage. This could include treatment of hypertension with calcium-channel blockers, prevention of rejection episodes, and of atherosclerosis by treatment with statins, reduction in the number of coronary angiographies, and screening for renal artery stenosis if there is a clinical suspicion. Risk factors for development of renal dysfunction in non-transplanted patients should also be considered, including intensive treatment of diabetes mellitus and prevention of smoking.

References