Treatment of end-stage renal failure after heart transplantation

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Abstract

Background. Five to 10% of heart-transplant recipients develop end-stage renal failure (ESRF). Little is known about the outcome of these patients under renal replacement therapy.

Methods. We conducted a retrospective study in 16 men (mean age 52.8 ± 7.4 years at heart transplantation) who developed ESRF 5.3 ± 2.1 years later.

Results. Haemodialysis (HD) was the first-line treatment (mean Kt/V 1.35 ± 0.4). Vascular access was unsuccessful in six patients (37.5%) due to peripheral arteriopathy and they were treated with tunneled catheters for an average 15 months without bacterial infection. Mean weight was 68.4 ± 10 kg at onset of HD and 61.7 ± 9 kg one month later. Despite this reduction in extracellular overload, one antihypertensive drug was required in 75% of patients and two drugs in 12.5%. One patient tolerated automated peritoneal dialysis (PD) for 16 months (weekly Kt/V 2.1) despite persistent anuria. Renal transplantation (RT) was contraindicated in eight patients because of aortoiliac arteriopathy (n=5), poor general status (n=2), or ischaemic heart disease (n=1). RT was performed in eight patients with no acute episode of heart or renal graft rejection. There were no serious infectious complications. Three months after RT, mean serum creatinine was 115 μmol/l. One patient developed post-transplant lymphoproliferative disorder 3.5 months after RT and was successfully treated with transplant nephrectomy. Sudden death occurred in two patients 18 and 33 months after RT. Overall patient survival was 100, 78, and 59%, 1, 2 and 3 years after HD onset respectively. Using a time-dependent variable, the Cox model analysis demonstrated that heart-transplant recipients with ESRF have a relative risk of death 3.2 times higher than those without ESRF (95% CI=1.3–7.8).

Conclusions. HD, PD, and RT can be useful for the treatment of ESRF after heart transplantation. After initiating HD, patient survival is nearly the same as that reported in patients in Europe undergoing HD for other causes. But ESRF seems to reduce life expectancy in heart-transplant recipients.

Key words: end-stage renal failure; heart transplantation; haemodialysis; peritoneal dialysis; renal transplantation

Introduction

Early results after heart transplantation have been greatly improved with cyclosporin. However, moderate chronic renal failure often develops shortly after heart transplantation and exceptionally may progress to end-stage renal failure (ESRF) [1]. There is little data in the literature which would help guide therapeutics in heart transplant recipients with ESRF [2–4]. We report our results in a series of patients who were treated with haemodialysis (HD), peritoneal dialysis (PD), or renal transplantation (RT).

Subjects and methods

Between 1984 and 1992, 241 heart transplantations were performed at the Nancy University Hospital. The standard immunosuppression protocol included cyclosporin. Among these heart-transplant recipients, ESRF developed in 16 men (6.6%) with a mean age of 52.8 years (range 39–63.4) at heart transplantation. Indications for heart transplantation were ischaemic heart disease (50%), idiopathic cardiomyopathy (43.75%), and valvulopathy (6.25%). One of the patients was diabetic. Six of the 16 patients (37.5%) had been treated for chronic renal failure prior to onset of dialysis therapy for ESRF, but the other 10 patients refused treatment for renal insufficiency prior to the development of ESRF. Dialysis began a mean 5.3 years (range 2.6–9) after heart transplantation. None of the patients had heart failure at the onset of dialysis.

First-line treatment for ESRF was chronic intermittent HD in all patients with three sessions (81.25% of patients), or two sessions (18.75% of patients) per week. We recorded the type of vascular access, type of dialysis membrane, and duration of dialysis sessions. In order to evaluate the quality of HD, urea Kt/V was estimated from pre- and post-dialysis
serum levels according to the standard recommendations [5]. Variations in weight and blood pressure were also recorded as well as any antihypertensive treatment. Cyclosporin and corticosteroids were used for immunosuppression.

PD was used in two patients. One developed acute poorly tolerated colestasis after insertion of a Tenckhoff catheter which had to be ablated, and the other benefited from long-term PD.

RT was performed in eight patients; indications and outcome are reported.

The survival curve in the heart transplantation recipients with ESRF was established with a Kaplan–Meier plot. Survival rate was compared with that in heart-transplantation recipients without ESRF who had survived more than 2 years after transplantation. A Cox model with one time-dependent variable was used to account for the different delays to development of ESRF [6].

Results

Chronic haemodialysis

Mean duration of dialysis sessions was 4.5 ± 0.5 h. Cuprophane, polycarbonate, or cellulose triacetate membranes were used in 43.75%, 43.75% and 12.5% of patients respectively. No manifestations of an allergic reaction to the HD membrane were observed. An arteriovenous fistula could not be created in six patients (37.5%) because of the poor status of the peripheral vessels. A tunnelled central venous catheter was used for dialysis in these patients for a mean 15 months (range 6–24). No septic complications were observed. For these six patients, the indication for heart transplantation was ischaemic heart disease in 66%; this rate was only 30% in patients for whom a fistula could be created.

Clinical features and laboratory results during the first 6 months of HD are given in Table 1. No antihypertensive treatment was needed in 12.5% of patients, one drug was used in 75%, and two drugs in 12.5%. Converting enzyme inhibitor was prescribed in one patient. Human recombinant erythropoietin was used in 12 patients. During HD, mean dosage of cyclosporin was 3.4 mg/kg/day.

Peritoneal dialysis

Bronchogenic carcinoma was diagnosed in one patient 18 months after heart transplantation. Left pneumectomy was required and the patient developed ESRF 8 years after heart transplantation. Chronic HD was complicated by poor vascular access from the onset. As a long-term central catheter could not be inserted, we opted for automated PD. Despite persistent anuria, clearance was satisfactory: weekly peritoneal creatinine clearance = 54 l; weekly Kt/V = 2.1; nPCR = 2.2. No medical peritonitis developed despite immunosuppression. After 7 months of PD, this patient developed a strangled inguinal hernia which was cured by surgery. After 16 months the patient developed progressively worsening extracellular hyperhydration as the peritoneum became inadapted to dialysis.

Before attempting chronic HD again, a cervical angiography identified the left subclavian vein as the only accessible vessel. Because of the anatomic remodelling, the catheter was inserted under brilliancy control by a radiologist. The procedure took more than 2 h to insert a two-way tunnelled catheter, and at the cost of a compressive cervical haematoma. Fourteen months later the catheter remains functional and the patient is in good general health.

Renal transplantation

An RT work-up was obtained in all patients. RT was contraindicated in eight cases due to severe aortoiliac arteriopathy (n=5), poor general status (n=2) or coronary artery disease (n=1). In six of these eight patients (75%), heart transplantation had been performed for ischaemic heart disease.

A cadaver kidney was transplanted in eight patients. Of these, only 25% had had ischaemic heart disease prior to heart transplantation. Their mean age was 56.2 years (range 43.5–68.3) at renal transplantation which was performed 1.2 years (range 0.66–2.5) after onset of dialysis. For the first six renal transplantations, prophylaxis included antilymphocyte serum or OKT3 monoclonal antibodies. All grafts functioned satisfactorily after implantation and no severe infections were observed. Three months after renal transplantation, mean serum creatinine was 115 ± 11 µmol/l, mean creatinine clearance was 54 ± 14 ml/min/1.73 m². Cyclosporin was given at the dose of 3.6 mg/kg/day and mean trough cyclosporin level was 155 ng/ml.

One patient complained of pain in the kidney graft 3.5 months after transplantation. Renal function also declined. Ultrasonography revealed a round hilar mass, which was removed. Pathology reported post-transplant lymphoproliferative disorder (PTLD) local-

Table 1. Clinical and biological characteristics of heart-transplant recipients during the first 6 months of haemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Beginning of haemodialysis</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>68.4 ± 10</td>
<td>61.7 ± 9</td>
<td>62.5 ± 9</td>
<td>64.5 ± 9</td>
</tr>
<tr>
<td>Interdialytic A weight (kg)</td>
<td>X</td>
<td>+2.2 ± 1</td>
<td>+2.4 ± 1.3</td>
<td>+2 ± 1</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>159.9 ± 25</td>
<td>156.5 ± 15</td>
<td>146.5 ± 9</td>
<td>145.6 ± 15</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>93.2 ± 18</td>
<td>91.7 ± 13</td>
<td>92.8 ± 12</td>
<td>85.6 ± 8</td>
</tr>
<tr>
<td>Kt/V</td>
<td>X</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.5</td>
<td>1.35 ± 0.4</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>8.8 ± 1.7</td>
<td>8.7 ± 1.2</td>
<td>10 ± 0.9</td>
<td>9.5 ± 1.7</td>
</tr>
</tbody>
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ized in the graft. Surgical ablation of the graft was performed without modifying the immunosuppressive therapy. Immunohistochemistry showed B cells carrying lambda light chains on their surface associated with Epstein–Barr virus. The patient was given prednimustine (50 mg/day) for 2 years. More than 3 years after kidney graft ablation, the patient continues HD and shows no sign of progressive PTLD. This patient is now on the waiting list for another graft.

Following this case of PTLD, we decided to reduce the dose of the immunosuppression induction protocol prior to renal transplantation. Thus, for the seventh and the eighth renal transplant patients, maintenance levels of cyclosporin were not changed and corticosteroids were increased. These patients have not developed any signs of acute rejection.

**Follow-up**

Overall patient survival at 1, 2 and 3 years after onset of dialysis was 100, 78 and 59% respectively. In patients whose heart transplantation had been performed for ischaemic heart disease, these survival rates were 100, 62 and 62% respectively. For those with another type of heart disease they were 100, 100 and 40%.

Renal graft survival at 1 year was 83.3%, not taking into account the one case of sudden death the day of renal transplantation. This patient had refused routine coronarography. Coronarography was performed in the seven other renal-transplantation candidates to assess the heart graft. Two patients with no evidence of lesions on the coronarograms died of cardiogenic shock and sudden death 18 and 33 months respectively after renal transplantation, possibly due to accelerated heart rejection. No autopsies were performed.

Survival in heart transplant recipients with ESRF was 53% 10 years after heart transplantation (Figure 1). Seven patients had died at the study endpoint. After beginning HD, four patients have survived for more than 4 years. The Cox model shows that the risk of death in heart transplant recipients with ESRF was three times greater than that in those without ESRF (relative risk = 3.2, 95% confidence interval = 1.3–7.8).

**Discussion**

To our knowledge, no study has addressed the question of renal substitution therapy in heart-transplantation patients with ESRF. The main problem is to create a vascular access acceptable for long-term HD in patients who often have peripheral arteriopathy involving the upper limbs. Iterative venepuncture for haemodynamic catheterization or heart-graft biopsy may provoke vessel narrowing or thrombus formation in the cervical trunks. PD is a possible alternative. A recent study has shown that central catheters were the leading risk of septicemia in haemodialysis patients [7]. In our series, despite immunosuppression and a high rate of catheter use, we did not encounter any infectious complications.

When dialysis is initiated, patients are in a state of major extracellular hyperhydration as revealed by high blood pressure and weight loss greater than 9% compared with the initial weight. Progressive depletion appears to be well tolerated by the heart graft. In one recently reported series, it was shown that mean cardiac index was unchanged before onset of HD and one year later [3]. In 1996, among the 120 patients undergoing haemodialysis in our unit, 66% had no antihypertensive regimen, 28% were taking one antihypertensive drug, and 6% were taking two. In our heart-transplantation recipients with ESRF, these figures were 12.5, 75 and 12.5% respectively. No data were available concerning the prevalence of hypertension in heart-transplant patients without ESRF. The high rate of hypertension is probably a consequence of the lack of heart graft innervation and maintained cyclosporin therapy [8].

Weight gain between dialysis sessions is considerable, over 2 kg. This is possibly due to stimulation of thirst by the renin–angiotensin system [1,8] or to poor patient compliance to fluid intake restriction.

The quantity of dialysis delivered to our patients was estimated by Kt/V. The figures obtained during the first 6 months of dialysis were comparable with those obtained in our population of 120 HD patients without heart transplantation: 1.36 ± 0.3. Problems with the vascular access do not apparently compromise correct dialysis. This was confirmed by a gain in lean body mass 6 months after dialysis onset and by improved general health.

The Stanford team did not give any details as to why a kidney graft was not used in five of their 14 heart-transplantation patients [4]. In our experience, renal transplantation was mainly contraindicated by severe aortoiliac atheroma found in those patients with ischaemic heart disease prior to heart transplantation. The long-term survival of heart transplant recipients

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**Fig. 1.** Kaplan–Meier estimates of survival for heart-transplant recipients with ESRF (n = 16). (Number of patients at risk indicated by parentheses.)
is difficult to assess. Angiographic abnormalities in the epicardial coronary arteries are present in 50% of patients 5 years of heart transplantation [9,10]. But angiography is a relatively insensitive technique that correlates poorly with the degree of allograft vasculopathy documented by pathological examination [10]. In our study, two patients with normal coronarography at renal transplantation developed fatal heart failure 18 and 33 months later. Compared with coronary angiography, intracoronary ultrasound improves detection of diffuse intimal thickening, particularly in small arteries [11]. But we have not used this technique in our patients.

Does secondary renal grafting aggravate the risk of allogenic reaction to the heart graft [2,4]? What preventive treatment should be administered after renal transplantation to prevent the risk of heart rejection? The team at Stanford [4] used OKT3 monoclonal antibodies in three patients who underwent concomitant second heart transplantation and renal transplantation. Their six other heart-transplant recipients who had only renal transplantation were given 0.5–1 g methylprednisolone during the surgical procedure followed by oral prednisolone rapidly tapered off to 15 mg. The dose of cyclosporin was adjusted to obtain a residual cyclosporin level between 100 and 150 ng/ml. Patients were also given azathioprine (2 mg/kg). They observed several cases of heart graft failure and renal graft rejection. In their series, the immunosuppression induction protocol included antilymphocyte serum and OKT3 monoconal antibodies and we observed no episodes of acute rejection of the heart or renal grafts. Nevertheless, as was the case in one of our patients, this immunosuppressive protocol can favour post-transplant lymphoproliferative disorders [12,13].

In the United States it has been demonstrated that 1-year survival after onset of HD is 75%, a figure identical to that in patients dialysed for other causes [3]. In our experience, survival appears to be better, 100 and 78% respectively 1 and 2 years after HD, a result which is comparable with that in other haemodialysis patients in the same age range in Europe [14]. However, as in the United States and the United Kingdom [3,15], risk of death in our series of heart transplant recipients with ESRF was three times higher than that in heart-transplant recipients without ESRF.

References


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