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Cardiac transplantation beyond 55 years of age

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Abstract

Between January 1985 and December 1988, 20 patients over the age of 55 years (extremes 56-63 years; 15 men and 5 women) underwent cardiac transplantation. The cause of cardiopathy was ischemic in 70% of the cases. The immunosuppressive regimen consisted of cyclosporin A, corticoids, and azathioprine. Rejection episodes were monitored by endomyocardial biopsies and treated by pulses of corticoids or monoclonal antibodies (OKT 3). The operative mortality was 10% (n = 2). The 1-year survival rate was 70%. The 1-year incidence of infection and/or rejection episodes was 1 and 1.53 episodes/ patient, respectively. One patient was successfully retransplanted after 9 months because of intractable rejection. Age beyond 55 years is no longer a contraindication to cardiac transplantation. This change in recipient selection policy should lead to parallel changes in donor selection criteria.

Keywords: Heart transplantation, beyond 55 years of age ; Recipient age, heart transplantation ; Age, in heart transplantation

Since the first human heart transplant in 1967 [1], the 1-year survival rate has gradually risen from 20% to 65% [3,4,14]. Adherence to strict criteria in recipient selection was deemed essential in order to achieve good results. In particular, until very recently, an age limit of 50-55 years was the standard protocol [10]. The reported 1-year survival rate was less than 40% in patients older than 50 years, and age beyond 55 years was considered a major contraindication to cardiac transplantation [7].

In 1981 the introduction of cyclosporin A to the immunosuppressive regimen reduced the risk of infection and rejection. This important step led to an increase in actuarial 1-year survival to more than 80% [6].

As a consequence of improved results, recipient selection criteria have been altered so as to provide maximal benefit to the greatest number of patients. Now, clinicians confronted with "high-risk" cardiac patients may select transplantation as the best therapeutic choice. At the same time, progress in medical therapy now makes it possible for a greater number of older patients to sustain cardiac insufficiency and to become candidates for cardiac transplantation. Some centers have been encouraged to raise the age limit [5,8,11,12]. Recent studies have failed to demonstrate increased risk in patients over 50 years of age. This report details our experience with patients beyond 55 years of age.

Patients and methods

Between January 1985 and December 1988, twenty patients over the age of 55 years (extremes 56-63 years) underwent orthotopic cardiac transplantation. The general characteristics of the patients are summarized in Table 1. Six of the 20 patients (30%) had had previous cardiac surgery: 5 aortocoronary bypasses (1-10 years before) and 1 aortic valvular replacement (15 years before). Past noncardiac medical history included insulin-dependent diabetes mellitus (n = 1), emphysema due to anthracosilicosis (n = 1), and renal dysfunction related to vascular atrophy of the right kidney (creatinine clearance 40 ml/min; n = 1). One patient with end-stage renal failure due to renal polykistosis received a kidney graft simultaneously with the cardiac transplant.

All patients were screened for cytomegalovirus, hepatitis, human immunodeficiency virus, and toxoplasmosis. Donors were matched according to ABO blood group compatibility. Donor hearts were evaluated with electrocardiograms, cardiac echocardiograms, and creatine kinase isoenzymes. For donors beyond 40 years, a coronarography was obtained whenever possible. Serologic tests were routinely performed. After transplantation all patients received an immunosuppressive therapy based on corticoids, azathioprine and cyclosporin A, as

shown in Table 2. Dosages of cyclosporin were adjusted to maintain whole blood levels of 150-400 ng/ml for the first 3 months and were gradually decreased to 100-150 ng/ml. A monoclonal radioimmunoassay was used for dosages. Monitoring of rejection episodes was achieved by means of serial endomyocardial biopsies performed on a routine basis or more often if necessary. The Billingham criteria for determination of the presence and severity of rejection were used [2]. Only the stage 2 A and B or 3 rejection episodes were treated (interstitial aggregation of mononuclear cells and foci of myocyte degeneration of various importance; Table 3). In addition to the immunosuppressive treatment, prophylaxis of stress ulcus was instituted with ranitidine (800 mg/day for 6 months). Invasive herpetic infection was prevented by acyclovir intake for 6 months. Vitamin D and calcium supplementation was directed against corticoid-indiced osteoporosis.

Table 1. *Characteristics of the patients*

Stage IV functional class (New York Heart Association)
Age beyond 55 years (extremes 56-63 years)
15 men, 5 women
Origin of the cardiopathy: Ischemic: *n* = 14 (70%) Idiopathic: *n* = 5 (25%) Valvular:*n* = 1 (5%)
Previous cardiac surgery: *n* = 6 (30%)

Table 2. *Immunosuppressive protocol*

Corticoids
Methylprednisolone 500 mg IV intraoperatively 8 mg/kg per day on day 1 to 1 mg/kg per day on day 5
Oral prednisone 1 mg/kg per day on day 6 to 16 mg/day at 6 weeks (progressive reduction of doses)
Cyclosporin A
Beginning after 24 or 48 h, according to renal function
Serum levels 150-400 ng/ml for the first 3 months 100-150 ng/ml after 3 months
Azathioprine
3 mg/kg IV on days 1 and 2
2-3 mg/kg per day orally, according to hematologic and hepatic tolerances

Table 3. *Treatment of rejection episodes*

Stage 2A
Bolus of methylprednisolone (1.5 mg/kg per day for 3-4 days)
Stage 2B-3
OKT3 (5 mg/day IV for 14 days)
CyA suppressed during OKT3 therapy, same dosages of azathioprine and corticoids

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Table 4. *Results*

Operative mortality: 2 right cardiac failure	*n* = 2 (10%)
1-year survival: 4 deaths due to infection:	*n* = 14 (70%) 1 cerebral abscess 1 disseminated toxoplasmosis 2 confluent bronchopneumonia
Incidence of infection:	1 ± 1.03 episodes/patient
Incidence of rejection:	1.53 ± 0.94 episodes/patient

Results (Table 4)

The operative mortality was 10% (*n* = 2). Two patients died from right cardiac failure related to precapillar pulmonary hypertension. The mean follow-up period was 18 ± 3 months. The 1-year survival rate was 70%. All patients who survived beyond the first year post-transplantation are still alive. The longest survival to date is 4 years.

Five nonfatal bacterial infections were observed. One mediastinitis and one pyopneumothorax were successfully treated by closed drainage and continuous irrigation with iodine povidone and intravenous antibiotherapy. Two bronchopneumoniae and one catheter-related septicemia responded well to intravenous antibiotherapy. Eight reactivations of past viral infections were noted: cytomegalovirus (*n* = 2), herpes (*n* = 3), zona (*n* = 2) and Epstein-Barr (*n* = 1). Thus, the 1st year incidence of fatal and nonfatal infections was 1 ± 1.03 episodes/patient.

The 1st year incidence of rejection was 1.53 ± 0.94 episodes/patient. Three subjects received monoclonal antibodies (OKT3). One patient was successfully retransplanted after 9 months because of irreversible cardiac failure. Eleven patients were in functional class I and two in class II of the New York Heart Association. The retransplanted patient was, at the time of retransplantation, in class III and is presently in class I.

A number of side effects of the immunosuppressive therapy were related to the cyclosporin, others to either azathioprine or the corticotherapy. Systemic hypertension (systolic blood pressure higher than 160 mmHg or diastolic blood pressure higher than 95 mmHg) developed in 11 subjects (78%). Hypertension was well controlled by nifedipine. Seven patients (50%) developed hypercholesterolemia (total cholesterol > 2.5 g/l). In three patients, the parameters of renal function changed with blood levels of urea of more than 1 g/1 and of serum creatinine of more than 20 mg/l. None of these patients required hemodialysis. Diabetic mellitus, brought under control by insulin therapy, appeared in three patients receiving pulses of corticoids to treat rejection episodes. Moderate anemia (one microcytic and five macrocytic) occurred six times and, in two cases, required discontinuation of azathioprine. Miscellaneous side effects of cyclosporine therapy were also observed. A gastric lymphoma occurred 3 years after transplantation, and the patient is presently cured, 1 year after partial gastrectomy. Two patients developed hypertrichosis, and handquicers were noted in three cases.

Discussion

In the early years of clinical heart transplantation, it was said that in addition to rigorous surgical and anesthetic techniques, adequate selection of the patient was the key to success [3,7,10]. Later, improvements in both recipient and donor management and standardization of immunosuppressive protocols led to the modification of some indications. The age of the patient was one of these contraindications. Age beyond 50-55 years was a limit since, in older patients, the incidence of infection increased and the ability to sustain surgery decreased, as did survival [7].

After the introduction of cyclosporin, which allows for a reduction in corticoid requirements [6], the risk of infection was greatly reduced, with a concomitant decrease in the rejection rate. Thus, the 1-year survival rate rose to more than 75%. This led to changes in the recipient selection criteria so as to provide maximal benefit to the greatest number of patients. Subsequently, some authors reported good results in patients older than 55 or 60 years, results equal to those observed in many younger patients [5, 8, 11, 12]. Frazier et al. [8] reported a 1-year survival rate of 83% for patients over 60 years of age compared to one of 75% for other transplant patients. In the earlier study of Carrier et al. [5], actuarial survival at 1 year was 72% in patients over 50 years of age and 66% in the group under 50 years of age. In the older age group, ischemic disease was the main cause of

cardiopathy: 64% [8]-69% [5] and 70% in our series. Previous cardiac surgery was frequent (30% in our series), something which tends to increase technical difficulties. The rates of infection or rejection episodes in elderly patients were not higher than those in the younger group [5, 8, 11,12]. Thus, these authors [5, 8] concluded that a rigidly determined age criterion for cardiac transplant was illogical.

A large number of patients over 50 years of age may be considered suitable candidates for cardiac transplantation if disease of other systems is not present to limit survival [5]. But even this notion may be too rigid. In the report by Frazier et al. [8], the elderly group was at high surgical risk: all patients had preoperative renal dysfunction that complicated cyclosporin therapy and 35.7% were diabetic. That represents a major challenge in terms of steroid therapy and the prevention of infection.

A combination of factors may explain the good results observed in patients over 55 years of age. First, cyclosporin improves immunosuppression and reduces the incidence of infection [6], Thus, older patients' susceptibility to infection has become a less important factor. Second, older patients may be more tolerant of the graft because of the ill-defined "immunosenescence" [8]. Previous blood transfusions, particularly at the time of previous coronary surgery, may have contributed to a decreased incidence of rejection [11,12].

Some side effects of the immunosuppressive agents were observed in our series. After transplantation hypertension occurred in 78% of the patients. This phenomenon is common and has reached 80%-100% in some series [9, 15]. High dosages of cyclosporin were considered the etiologic factor. However, in a recent study [13], hypertension developed in almost all patients after heart transplantation, despite the lower dosage of cyclosporin with a triple drug regimen and the absence of significant renal impairment. As we observed, this hypertension generally responds to the administration of diuretic agents and vasodilatator drugs (usually calcium channel blockers) [9,13,15]. Fifty percent of our patients also developed hypercholesterolemia, which may have deleterious effects on the graft function in conjunction with hypertension. Treatment of acute rejection with pulses of corticoids led three patients to develop diabetes mellitus, which was brought under control by insulin therapy. In contrast, no severe impairment of renal function was observed.

We may conclude that the results of cardiac transplantation in patients of advanced age are equal to those obtained in a younger population, at least for the 1st year.

Thus, a rigidly defined age criterion for potential cardiac recipients is not justified. It is illogical to refuse cardiac transplantation to patients who have often been treated medically for long periods of time and who need transplantation in order to survive. Adoption of such a policy would, in turn, necessitate a broadening of donor selection criteria, for without a parallel increase in potential donors, the number of deaths among potential candidates would certainly increase. In fact, few donors over the age of 45 years are used. Older donors, who are generally considered undesirable for young recipients, should be used for transplantation in the older recipient group. Provided the heart function is good (as assessed by echocardiography and, if necessary, by coronarography) and provided the donor is free of previous cardiac disease, this option could enlarge the donor pool. Moreover, older donor hearts are generally more capable of sustaining the high pulmonary resistance that is more frequently encountered in recipients of advanced age.

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