CLINICAL ASPECTS OF HEART TRANSPLANTATION

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Aspecten uit "de kliniek" van harttransplantatie

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus Prof. Dr. P.W.C. Akkermans M.Lit.
en volgens het besluit van het College van Dekanen.

De openbare verdediging zal plaats vinden
op woensdag 6 oktober 1993 om 15.45 uur
door

Agnes Henrica Madeleine Maria Balk

geboren te Maastricht

PROMOTIECOMMISSIE

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Omslag: "Rotterdam boven de wolken" (Foto: Sea Sky Martin, Rotterdam)

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PREFACE

Since the first succesful procedure in man in 1967, heart transplantation has gradually evolved to an accepted treatment modality for patients with end-stage heart disease.[1] In the "field of heart transplantation" however, many questions await an answer and many problems remain to be solved.

Rotterdam's contribution to heart transplantation started in the 1970s and has continued since. In an experimental program orthotopic and heterotopic cardiac transplantations were compared in dogs and accelerated coronary artery disease in allograft recipients was studied after the development of a canine model.[2-4] However, in contrast with many other centers throughout the world, which started clinical heart transplantation soon after Barnard's successful procedure in 1967[1], we waited until June 1984 to perform the first human heart transplantation in the Netherlands. This cautious policy was dictated by the disappointingly poor survival rates in the period that maintenance immunosuppression after transplantation was based on azathioprine and steroids while no reliable methods for the detection of acute rejection had been developed. After the Stanford group reported a significant increase in survival and a decrease of complications in cardiac allograft recipients who were monitored by endomyocardial biopsies and treated by cyclosporin-A we initiated a clinical heart transplant program.[5] The program proved to be succesful which resulted in government approval for its continuation and finally in reimbursement of the costs by the insurance companies.[6,7]

The aim of this thesis is to describe the continued efforts to optimize patient care by ongoing analysis of various problems which currently predominate in heart transplantation. Chapters I-III describe our research in heart transplant candidates and in subsequent chapters specific problems of the transplant recipient are addressed. Attempts to reduce the incidence of rejection are described in Chapters IV and V. The problems of coronary vascular disease in the allograft and the angiographic findings in our patients are summarized in Chapters VI, VII and VIII. The complications of immunosuppressive therapy are subject of Chapters IX, X and XI. Finally, the results in the first 200 heart transplant recipients of the Rotterdam Heart Transplant Program are presented in Chapter XII.

For the selection and pretransplant care of the patients and for the surgical procedures a close cooperation has been developed with the departments of Cardiology, Thoracic Surgery and Social Work of the University Hospitals of Leiden and the St.Antonius Hospital, Nieuwegein. All

posttransplant care has been in the hands of the transplant-team of the University Hospital Rotterdam.

For the appreciation of the described results one has to keep in mind that the care of heart transplant recipients is complex and demanding. It requires, again and again, decision making in very complex situations through which the transplant team has not gone before. The strenght of the Rotterdam Heart Transplant Program, therefore, lies in the day to day and "hour to hour" cooperation between specialists, nursing staff and technicians of the departments of Cardiology, Thoracic Surgery, Internal Medicine I, Pathology, Microbiology, Anesthesiology, Psychiatry, Psychology and Social Work.

- Such close cooperation can only exist between friends -

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PART I

AFTER REFERRAL FOR CARDIAC TRANSPLANTATION

INTRODUCTION

Between 1984 and January 1, 1993 816 patients have been referred to the Rotterdam Heart Transplant Program. In this program transplants are performed in the Thoraxcenter Rotterdam while the care of the referrals for transplantation is shared between the University Hospitals of Rotterdam and Leiden and the St.Antonius hospital in Nieuwegein.

Patients who are referred for cardiac transplantation suffer from severe heart failure, usually of longstanding duration, caused by cardiomyopathy, by ischemic or valvular heart disease or by congenital malformations. Such patients have become severely incapacitated by the inability to perform daily tasks as dressing, showering/bathing and walking stairs. In acute heart failure dyspnea is often the most striking symptom. In contrast, fatigue is usually the main limiting symptom in chronic heart failure. Furthermore, the decline in cardiac output will be compensated for by fluid retention resulting in weight gain, hepatomegaly and edema and ascites formation. At the end, when peripheral mechanisms no longer can compensate for a decreasing cardiac output, organ hypoperfusion will occur. An easily available, early and therefore most important marker for organ hypoperfusion is peripheral vasoconstriction resulting in pallor and cyanosis of the fingers, toes, knees and earshells. At a later stage an increase of serum creatinine levels and hyponatriemia can be observed. It should be appreciated however, that the latter findings can also be complications of overaggressive diuresis leading to volume depletion and reduced glomerular filtration rate. Sleep disorders, confusion, agitation and even flourishing hallucinations can occur as results of hypoperfusion of the brain. These symptoms are often underestimated and misinterpreted. Anorexia and constipation result from a combination of congestion and hypoperfusion of the splanchnic vascular bed while a rise in serum transaminases is a clue to hypoperfusion of the liver. Persisting organ hypoperfusion asks for aggressive measures to prolong life until a definite procedure can be performed but also for measures to prevent irreversible organ damage which would make the outcome of an ultimate intervention worse.

The first step in the treatment of heart failure is elimination of the underlying or precipitating cause. Often however, such treatment will not be possible or will not be immediately available so that the physician has to rely on pharmacotherapy. In recent years, several different types of drugs have been introduced for the treatment of heart failure, including vasodilators, new positive inotropic agents and drugs which partially correct the abnormal neurohormonal profile. Angiotensin converting enzyme (ACE) inhibitors result

in hemodynamic stabilisation and improved survival of patients who are incapacitated by chronic heart disease and may prevent disease progression in patients with asymptomatic ventricular dysfunction after myocardial infarction.[1-3] Phosphodiesterase inhibitors initially improve central and peripheral hemodynamics. Unfortunately however, chronic oral administration of phosphodiesterase inhibitors has been shown to increase mortality.[4,5] The long term effects on survival of ibopamine and the newly developed quinolones, such as flosequinan are still under investigation.[6-8] Currently, the clinician is left with the challenge to select the right doses and combinations of agents for the individual patient: optimal therapy should be "tailored" instead of "ready-made".[9] Optimal pharmacotherapy is usually a combination of ACE-inhibitors, digoxine, vasodilators and diuretics guided by hemodynamic measurements. Optimized care for the patient with severely depressed left ventricular function may result in excellent survival as has been shown by the follow up results of the patients who had been referred for cardiac transplantation but for whom it was considered to be too early to put them on the waiting list for a donor heart (Chapter I). A recent extension and update of the follow up of 165 patients in whom we advised to postpone heart transplantation showed similar good results. Including the outcome of changes in policy, after the initial decision to defer transplantation, the survival rates of these patients were 91% (95% CI 87-95) and 84% (95% CI 79-89) after 1 and 2 years respectively (Fig. 1). Changes in policy had been made in 8% and 14% of the patients within 1 and 2 years.

When patients reach the end-stage of their heart disease and failure becomes refractory to maintenance oral medication the physician and his patient have three options: giving up further attemps to prolong life, temporary improvement of the hemodynamic and clinical status by (intermittent) administration of intravenous drugs or re-assessment for transplantation or other interventions. Additional intravenous drug therapy may include beta-adrenergic agonists, such as dobutamine, dopamine and dopexamine or phosphodiestase inhibitors, such as enoximone and milrinone. These agents may temporarily improve the hemodynamic status and may be used in patients with extreme heart failure as a "pharmacological bridge" when waiting for an intervention.[10-13]

Permanent solutions for the heart failure problem include conventional surgery or catheter interventions (albeit at higher risk than seemed acceptable during the time that heart failure could be managed medically), dynamic cardiomyoplasty and, as ultimum refugium, replacement of the failing heart by a donor heart.[14-22] The options for "reparative surgery" in patients with

ischemic or valvular heart disease who are referred for cardiac transplantation are described in Chapter II.

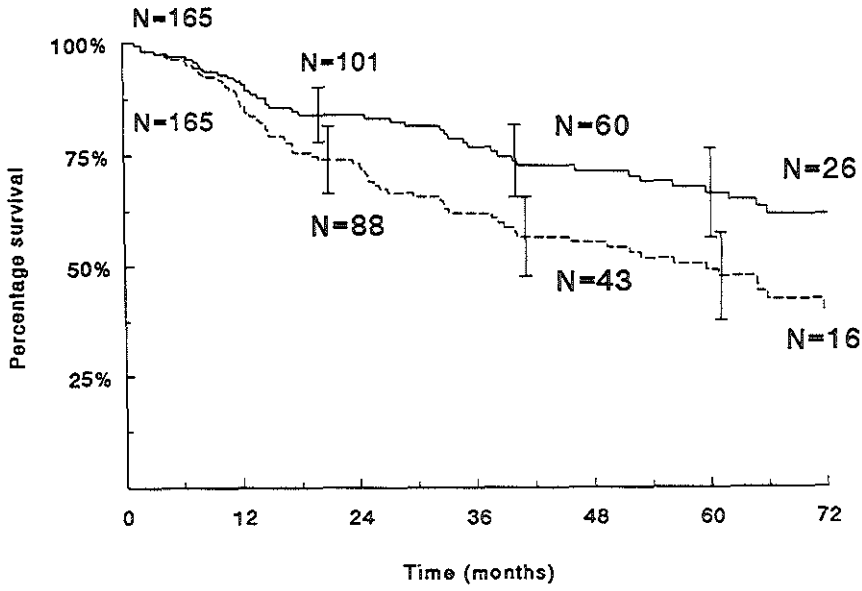

Fig. 1: Survival of 165 patients who were considered "too well" for cardiac transplantation at the time of referral to the transplant center. The solid line represents overall survival. The interrupted line represents "event-free" survival (that is without a change in policy). Vertical bars represent 95% confidence intervals. N = number of patients at risk.

In dynamic cardiomyoplasty the latissimus dorsi muscle flap is brought into the left pleural cavity and wrapped around the heart. In order to support the failing myocardium by contracting synchronically with the ventricular systole however, the fast-twitch fibers of the skeletal muscle must be transformed into fatigue-resistant slow-twitch fibers.[23-26] This requires programmed electrical stimulation of the muscle flap, during 6-8 weeks. During this preparation period the patient must sustain a thoracotomy (usually without extra corporeal circulation) and a long postoperative course without support other than used before the operation. At this moment, dynamic cardiomyoplasty is still an investigational procedure. It is uncertain which patients would benefit the most from it. Furthermore several, more technical questions remain unanswered including selection of the optimal site and mode of electrical stimulation, and the precise surgical technique: "how should the muscle be wrapped?" Finally, the physiology of cardiomyoplasty needs further

investigation because abnormalities have been found which might impair the function of the muscle during long term assistance. Some investigators have noticed diastolic impairment of the ventricles by stiffnes of the muscle flap and have observed intimal hyperplasia in the arteries of the pedicle.[27] Until now, dynamic cardiomyoplasty has not been performed by any of the surgical teams which cooperate in the Rotterdam Heart Transplant Program and the overall experience in the Netherlands is very limited.[28]

Shortage of donor hearts and limited financial resources result in extending waiting times for heart transplant candidates. As a consequence the failing circulation may need, in addition to the afore mentioned measures, mechanical support to bridge the time until a suitable donor heart becomes available.[29,30] Before pursuing such an invasive strategy one should know which support systems are available and whether the particular patient will benefit enough to make the intervention worthwhile. In Chapter III therefore, the Rotterdam experience with intra-aortic balloon counterpulsation (IABP) as "bridge to transplantation" is described. In addition an overview of other methods for mechanical circulatory support and their expected benefits is presented.

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CHAPTER I

TOO EARLY FOR CARDIAC TRANSPLANTATION. THE RIGHT DECISION?

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In: European Heart Journal 1992; 13: 1339-1344

SUMMARY

In 109 out of 479 patients who were referred for cardiac transplantation it was considered to be too early to put them on the waiting list for a donor heart. The clinical course of these 109 patients was analysed in order to verify whether this decision had been right.

The mean age of the patients was 43 years, half of them suffered from ischaemic heart disease. The systolic left ventricular function of the patients was severely depressed (mean left ventricular ejection fraction 21%) and the left ventricular cavity was markedly dilated (mean echocardiographic end diastolic dimension 73 mm). Functional capacity, measured by bicycle ergometry, was low: mean maximal workload 62% of the expected load for gender, height and age.

The median follow-up duration was 31 months. The survival rate of the patients was better than that of 175 patients who were accepted for transplantation after referral, 92%, 87%, 81%, 71% and 73%, 73%, 71%, 68% after 1, 2, 3 and 4 years respectively. Re-assessment was necessary in 29% of the patients within 1 year and in 52% within 3 years. Twenty patients died: 12 patients died before re-assessment had been initiated (eight sudden deaths), six patients because of progressive heart failure before heart transplantation could be performed and two patients died after heart transplantation.

Left ventricular ejection fraction, pulmonary capillary wedge pressure and transpulmonary gradient were not reliable predictors of the course of the patients. In retrospect, a systolic blood pressure rise of less than 20 mmHg during exercise and an echocardiographic ventricular end-diastolic dimension of more than 75 mm helped in defining a subgroup of patients, with an increased risk of clinical deterioration, who needed strict medical supervision after the decision to defer transplantation.

INTRODUCTION

Cardiac transplantation offers a normal life for a considerable number of years to patients who are severely incapacitated by end-stage heart disease. However, it remains difficult to determine the optimal moment to accept a patient onto the waiting list. The transplant team has to assess many patients ranging from very sick to moderately incapacitated. In each case three questions should be answered. First, is the current situation such that transplantation should be considered or can the decision be deferred? Second, can improvement of functional capacity and survival be expected from any therapy or procedure other than transplantation? And third, what are the expected benefits in terms of survival and quality of life from cardiac transplantation in this particular patient? Knowledge of potential reversibility of the underlying heart disease, of the effects of tailored medical therapy and of the results of the different types of conventional surgery is necessary to answer the first two questions. To answer the third question the expected

survival and quality of life after cardiac transplantation must be weighed against the expected survival and quality of life with the underlying heart disease.

In order to evaluate decision making after referral for heart transplantation during the first 5 years of our program, we reviewed the clinical course of those patients who were referred for transplantation, but in whom we expected that the clinical course would remain stable for some time, such that transplantation could be postponed. We report survival and the need for re-assessment of the initial decision in these patients. Special attention is paid to factors that can easily be determined and may help to predict a possible fatality and the need for re-assessment, despite a presumed benign clinical course.

PATIENTS AND METHODS

Between June 1984 and July 1990, 479 patients were referred to one of the three hospitals which participate in the Thoraxcentre Heart Transplant program, the University Hospitals of Rotterdam and Leiden and the St. Antonius Hospital in Nieuwegein. The patients were divided into six groups: patients still under evaluation, patients who died during assessment, patients "too early to put on the waiting list", patients in whom conventional surgery was recommended, patients with contraindications for transplantation (initially an age beyond 55 years was considered to be a contraindication) and patients accepted on the waiting list for transplantation.

The decisions were based on assessment of the patients by cardiologists of the transplant team and/or on written information from the referring physicians. Criteria used to decide that a patient was not (yet) suffering from end-stage heart disease and that it was therefore "too early to put him on the waiting list" despite severely depressed left ventricular function, included a stable clinical course without the need for hospital admissions for at least three months, absence of dyspnoea at rest, absence of fluid retention and/or hyponatremia on oral medication and the ability to tend oneself. Evaluation in the heart failure clinic included physical examination, electrocardiogram, chest X-Ray, complete blood count, serum electrolyte determinations, serum urea nitrogen and creatinine, liver function tests, glucose levels, 2-dimensional-echocardiography and exercise testing. Neuro-hormone levels were not determined on a routine base. In most cases left ventricular ejection fraction (measured by nuclear or contrast angiography) and coronary anatomy were

already known before referral to the clinic. Recent haemodynamic data from right heart catheterization were available in some of the patients only.

Functional capacity was determined by upright bicycle ergometry with workload increments of 10 $W.min^{-1}$. Pedalling speed was 60 $revolutions.min^{-1}$. Workload was expressed as a percentage of the expected maximal load for gender, age and height. Heart rate, rhythm, QRS configuration and ST-changes were monitored continuously. Blood-pressure was measured by armcuff, at rest, every 2 min during exercise, at the highest workload and every 2 min during the recovery period. Subjective symptoms such as intractable fatigue, dyspnoea, dizziness and angina pectoris, or objective signs such as increasing ventricular tachy-arrhythmias or a drop in systolic blood-pressure caused the test to be stopped. Gas exchange measurements were performed in a few patients only and have not been included in this report.

The initial data of all patients who were referred for cardiac transplantation were stored in a computer database. Follow-up data were obtained from visits to the outpatient heart failure clinic and from written information from the referring cardiologists.

Group data were expressed as means ± SD. Analysis of the 95% confidence intervals of the differences between the means was used to compare survival proportions of the patient groups (Kaplan - Meier method) and of patient characteristics.

RESULTS

Of the 479 patients who were referred for heart transplantation, 28 were still under evaluation on 1 August 1990. Of the remaining 451 patients, 51 died before assessment had been completed. In 32 patients other surgical procedures were recommended and 175 patients were accepted on the waiting list for transplantation. The median waiting time until transplantation between the end of 1986 and December 1990 increased from 52 to 147 days for patients waiting at home in a stable condition and from 8 to 30 days for patients waiting in hospital, dependent on intravenous catecholamines or intra-aortic balloon pump support. Contraindications for transplantation were present in 84 cases and in 105 cases we considered it to be too early to put the patient on the waiting list. In another four patients transplantation was recommended initially but this advice was withdrawn after clinical improvement and stabilization with oral medication. These 109 patients are described in this report.

All patients had been hospitalized at least once for treatment of severe congestive symptoms but were in New York Heart Association class II or III at the time of referral. Baseline characteristics of the patients are presented in Table 1. The age-range of 11 to 57 years is explained by our initial policy to exclude young children and patients over 55 years from cardiac transplantation. Dilated cardiomyopathy was the underlying heart disease in half of the patients. All patients, except four, had been treated with digoxine and diuretics and, in addition to these medications, angiotensin-converting enzyme inhibitors were used by 77% of the patients. Only six patients had been treated with intravenous catecholamines before referral. A marked dilatation of the left ventricle (mean echocardiographic end-diastolic dimension 73 mm) was found, as was a severely depressed systolic function (mean left ventricular ejection fraction 21%). Functional capacity was limited by dyspnoea and fatigue in all but three patients. In the latter patients angina pectoris was the main complaint.

Table 1. Baseline characteristics of 109 patients in whom it was considered to be too early for cardiac transplantation.

Age (yrs)	43	± 11
Gender		
Male	89	
Female	20	
Heart disease		
Cardiomyopathy	52	
Ischaemic heart disease	51	
Valvular heart disease	3	
Other	3	
Medication prior to referral		
Digoxine	105	
Diuretics	105	
ACE inhibitors	84	
Antiarrhythmic agents	2	
Catecholamines i.v.	6	
Phosphodiesterase inhibitors	0	
Left ventricular ejection fraction (%)	21	± 11
LV end-diastolic dimension (echo, mm)	73	± 13

ACE inhibitors = angiotensin-converting enzyme inhibitors.

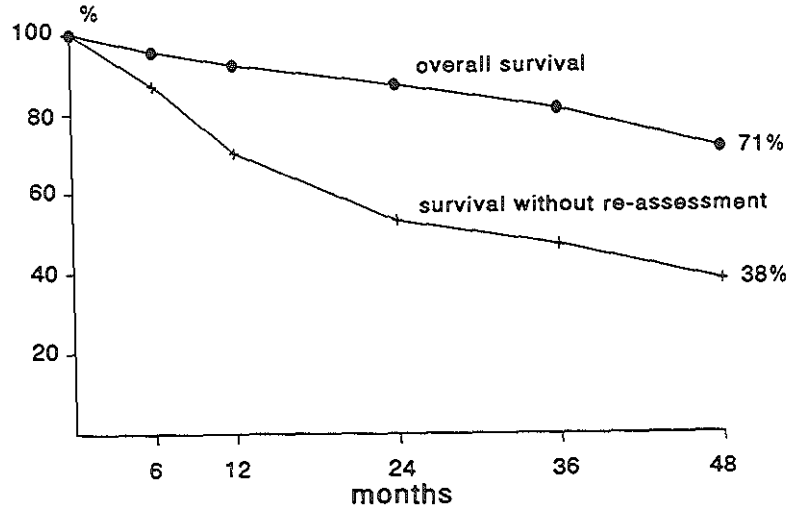

Fig 1. Survival of the 109 patients who were not, as yet, considered to be candidates for transplantation. The upper curve represents overall survival including the outcome of the change of policy. The lower curve represents "event free" or rather "re-assessment-free" survival. o = overall survival, + = survival without re-assessment.

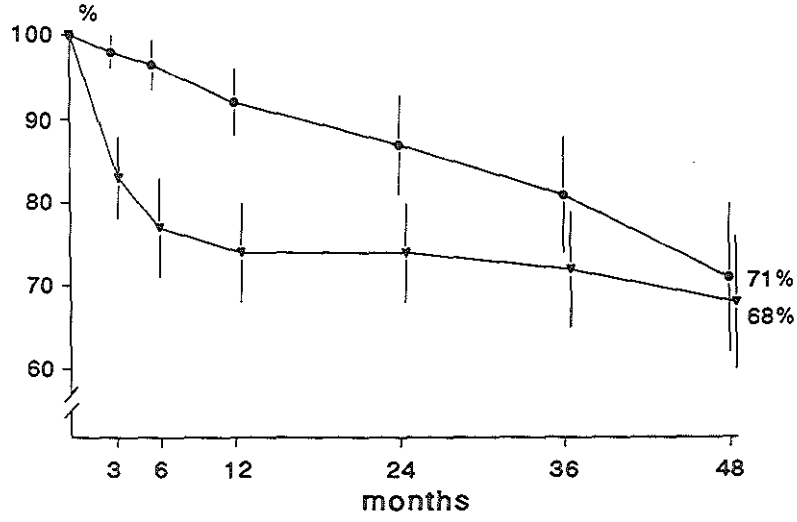

Fig 2. Survival of patients considered to be not yet candidates for cardiac transplantation compared to the survival of patients accepted for transplantation. Both curves start at the time of initial referral. o = Too well for transplantation, ▾ = accepted for heart transplantation. Vertical bars represent the 95% confidence intervals.

Exercise testing was performed in 75 patients. The maximal workload at bicycle ergometry was 62 ± 18 %. Systolic blood pressure at rest was 114 ± 15 mmHg and increased by 26 ± 19 mmHg on average during exercise. Heart rate at rest was 97 ± 17 beats.min^{-1} and increased by 50 ± 25 beats.min^{-1} during the test. In 38 patients recent invasive haemodynamic data were already available or were collected during the initial evaluation. Pulmonary capillary wedge pressure was 23 ± 7 mmHg. Mean pulmonary artery pressure was 32 ± 11 mmHg and right atrial pressure was 10 ± 7 mmHg. These data confirm the presence of heart failure in this group of patients.

The survival rates of the 109 patients were 92%, 87%, 81% and 71% at 1, 2, 3 and 4 years respectively (Fig. 1). The clinical course of 71 patients in whom no change of the initial policy, "too well for transplantation", was made is described in Table 2. Fifty-nine patients are alive, 36 of whom are in functional class I or II. During follow-up 38 patients were re-assessed 2 to 40 (median 9) months after the initial decision, while 71% of the patients survived without re-assessment for at least 12 months after the initial evaluation (Fig. 1). In 35 patients heart transplantation was reconsidered and 22 out of 24 patients who received a donor heart are alive. In three patients conventional surgery was recommended and successfully performed. Duration of follow-up for the whole group ranged from 3 to 67 (median 31) months with a larger proportion of patients with follow-up duration of more than 4 years in the group without change in policy (Table 3).

There were no differences in age (44 *vs* 42 years), distribution of gender (males 76% *vs* females 86%) and underlying heart disease (cardiomyopathy 46% *vs* 50%) between the patients who survived without re-assessment and the group of patients who died or were re-evaluated. The percentage of patients who used angiotensin-converting enzyme inhibitors at referral was lower in the group of patients who survived without re-assessment (66% *vs* 96% ; 95%CI of the difference is 14 - 45). The haemodynamic parameters and the results of exercise testing show considerable overlap (Table 4). Nevertheless left ventricular end-diastolic diameter was larger and systolic blood pressure at rest was lower in patients who needed re-assessment or those who died. Furthermore, 59% of the patients who showed a 20 mmHg blood pressure rise ore more during exercise survived without re-assessment in contrast to 35% of the patients with a less than 20 mmHg blood pressure rise (Table 4).

Table 2. Clinical course in 109 patients in whom it was considered to be too early for cardiac transplantation (1 August 1990).

No change in policy (N = 71)	Died	12		
	Alive	59	NYHA I	5
			NHYA II	31
			NYHA III	18
			NYHA IV	0
			Unknown	5
Re-assessment (N = 38)	Refused HTX (alive)	1		
	Contraindication HTX (alive)	1		
	Died during re-assessment	4		
	Died on waiting list	2		
	Alive on waiting list	3		
	Died after transplantation	2		
	Alive after transplantation	22	NYHA I	18
			NYHA II	3
			NYHA III	1
	Other surgery	3	NYHA I	2
			NYHA II	1

HTX = heart transplantation; NYHA = New York Heart Association classification.

Table 3. Comparison of follow-up duration in the patients in whom there was no change in policy and the patients who were re-assessed.

Months	No change N = 71	Re-assessed N = 38
0 - 6	9 (13%)	3 (8%)
7 - 12	12 (17%)	8 (21%)
13 - 24	10 (14%)	9 (24%)
25 - 36	16 (22%)	12 (31%)
37 - 48	14 (19%)	6 (16%)
49 - 60	9 (13%)*	0 (0%)*
> 60	1 (1%)	0 (0%)

* 95% Confidence Interval for the difference = 5-20%.

Table 4. Comparison of the distribution of parameters of functional capacity and haemodynamics at referral.

		N	+ or re-assessment	
LVEF	> 20%	31	48%	NS
	≤ 20%	53	59%	
PCW	< 20 mmHG	11	45%	NS
	≥ 20 mmHg	25	56%	
TPG	< 15 mmHg	31	52%	NS
	≥ 15 mmHg	7	14%	
RA	≤ 8 mmHg	12	33%	NS
	> 8 mmHg	12	41%	
⌂ BP	≥ 20 mmHg	14	41%	*
	< 20 mmHg	29	65%	
LVED	≤ 75 mm	33	33%	**
	> 75 mm	24	74%	

* 95% confidence interval of the difference: 0 - 47 ($p < 0.05$)
** 95% confidence interval of the difference: 14 - 67 ($p < 0.005$)
LVEF = left ventricular ejection fraction; PCW = pulmonary capillary wedge pressure; TPG = transpulmonary gradient (mean pulmonary artery pressure minus mean capillary wedge pressure); RA = right atrial pressure; ⌂ BP = change in systolic blood pressure during exercise; LVED = left ventricular end-diastolic diameter (echo). + = died, NS = not significant.

A total of 20 patients died, 12 in the group of patients in whom no change in policy was considered necessary and 8 in the group of patients in whom re-assessment took place. In the first group eight deaths were sudden and three were due to progressive pump failure while one patient died from unknown cause after an episode of congestive heart failure. In the second group four deaths were caused by rapidly progressive heart failure and in two patients death occurred suddenly. A 53-year-old man with ischaemic heart disease and a LVEF of 5% suffered sudden death at home shortly after calling attention to a mild increase of dyspnoea. A 22-year-old man with dilated cardiomyopathy died because of ventricular tachycardia deteriorating to ventricular fibrillation after admission to the hospital because of pneumonia. Survival rates at 6 months, 2 and 4 years in the groups with and without change in policy did not differ significantly: 97%, 86%, 70% and 97%, 88%,

73% respectively. Although survival after transplantation at our centre was excellent, 91% and 89% at 1 and 3 years, the survival of the patients reported here appeared to be better than the survival of the 175 patients who had been accepted on the waiting list for transplantation at the initial evaluation (Fig. 2). This is caused by the fact that, although only 13 patients died after transplantation, 34 patients died "on the waiting list", before transplantation could be performed.

DISCUSSION

The goal of this study was to verify whether the decision, "too early to put this patient on the waiting list for transplantation" had been right. It would be wrong to withhold cardiac transplantation when really needed but equally wrong to use scarce donor hearts for patients who could be expected to live acceptable lives with their own hearts for a reasonable period of time. Therefore we analysed survival and need for re-assessment in 109 patients whom we considered "not yet" candidates for cardiac transplantation at the time of referral.

Survival of these patients was better than that of the patients who were accepted on the waiting list for transplantation after referral. However, re-assessment, leading to a change of policy, appeared necessary in one third of the patients within 1 year and in half of the patients within 3 years. The excellent survival rate is, without any doubt, caused by the timely reconsideration of the policy and the ultimate advice to operate (although 11% of the patients died suddenly before re-assessment could be considered). Survival of patients who remained on medical therapy was better than in most studies of patients who were referred to other centres because of intractable heart failure, before the introduction of angiotensin-converting enzyme inhibitors.[1-3] The survival of the patients was also better than the 46% 1-year survival rate of cardiomyopathy patients with left ventricular ejection fractions below 25%, considered too well for transplantation in an earlier report.[4] This may be due in part to the fact that during the first 2 years of the program many patients were referred too early on the mere finding of severely impaired left ventricular function without allowance for adaptation mechanisms which may compensate for the failing pump. In the first two years of our program the percentage of patients accepted on the waiting list after referral was only 10%, in contrast to 45% in 1989 and 1990.

The fraction of patients who died suddenly without re-assessment is in accordance with earlier reports indicating that 30% to 60% of deaths in heart

failure patients are sudden.[5-7] Arrhythmias were the most probable cause of death in these patients but, as in the patients who were re-assessed, changes in the degree of heart failure may have contributed to the death of these patients. Although reports on the predictive value of ventricular arrhythmias on the prognosis in heart failure are contradictory,[8-10] we recommend 24-h continuous ECG-recording and to repeat this investigation after tailoring of heart failure medication in all patients referred for heart transplantation. Furthermore, we instruct the patients to pay special attention to minor signs of heart failure and to warn their physician at short notice if changes occur, such as a gain in weight, upper abdominal discomfort or the need for an extra pillow during the night.

For six of the 38 patients, in whom the initial decision to defer transplantation was reconsidered, this change of policy came too late. Symptoms of severe heart failure made hospital admission necessary. Five of the patients died either during evaluation or while waiting for a donor heart. Such deaths may be avoided by earlier recognition of progression of heart failure by the patient and the referring physician resulting in rapid referral to the transplant centre.

Several other studies have analysed predictors of mortality in patients with heart failure and reported a poor prognosis in patients with low left ventricular ejection fraction, ventricular arrhythmias, high filling pressures, high transpulmonary gradient, hyponatremia and high plasma norepinephrine levels.[4,7,11-19] In practice, however, these parameters prove to be of little help in decision making in ambulatory patients. In an attempt to predict which patients would remain stable, we compared the available data in two groups of patients: those who survived without re-assessment and those who died or in whom the initial policy was revised. This analysis was retrospective and its value is limited by missing data from some of the patients. Nevertheless, the analysis confirms that, in patients with severely impaired left ventricular function, left ventricular ejection fraction, pulmonary capillary wedge pressure, transpulmonary gradient and right atrial pressure are not reliable indicators of the future course of the disease. In earlier reports indicating the value of these measurements, more patients with only moderate ventricular impairment were included which may explain this apparent discrepancy. Although the predictive value of exercise testing in this setting was unknown until Mancini's recent report (published after the completion of this study) we used bicycle ergometry as an objective measure for functional capacity.[1,18-20]

It appeared that mortality or the need for re-assessment were lower in patients who showed a 20 mmHg or greater rise in systolic blood pressure during exercise indicating residual functional reserve of the left ventricle. In

patients with less than a 20 mmHg blood pressure rise during exercise mortality or the need for re-assessment was 50%. Furthermore, re-evaluation was needed less frequently in patients with moderately enlarged ventricles on echocardiography.

Instability of symptoms, frequent hospital admissions and the need for intravenous administration of catecholamines have been recognized as predictors of a worse outcome at short notice, especially in patients accepted for transplantation.[21] This was confirmed in the patients in whom initially transplantation seemed to be, as yet, unwarranted, since the patients condition often deteriorated rapidly after progression of heart failure.

From our initial experience it is concluded that the decision to defer transplantation was justified in most of these patients. However, revision of this decision was needed frequently. Thus, it is recommended that such patients are instructed to watch for minor signs of worsening. Patients should be kept under strict medical supervision to enable immediate referral to the transplant centre if progression of heart failure occurs. The degree of rise in systolic blood pressure during exercise and the echocardiographic dimension of the left ventricle may help to define the group of patients who need close observation.

An additional conclusion may be that reporting of the results after cardiac transplantation on the principle "intention to treat" illustrates the impact of this procedure on the survival of patients with heart failure more accurately than the methods used until now.

Future research should be directed towards the prevention of sudden death in patients with heart failure. Persistence of recurrent ventricular tachycardias or ventricular fibrillation despite optimal medical therapy may become an indication for urgent transplantation because of an increased risk for sudden death,[4] while antiarrhythmic therapy may further increase pump failure without decreasing the risk. One may speculate about the need for electrophysiological testing or implantation of an automatic internal cardioverter defibrillator, not only in patients with refractory symptomatic sustained ventricular tachycardias or ventricular fibrillation, but also in patients with non-sustained ventricular arrhythmias who are otherwise "too well" for cardiac transplantation.[22] The limited availability of donor hearts and financial resources, however, asks for the search for methods for the identification of those patients who will benefit from these procedures. Signal-average electrocardiography may provide such a method by showing late potentials. Although its usefulness appears to be limited in cases of advanced heart failure, a prospective study in stable patients being treated with tailored medical therapy may contribute to the solution of the problem.[23]

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CHAPTER II

CARDIAC TRANSPLANTATION OR HIGH RISK REPARATIVE SURGERY?

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Submitted

SUMMARY

The objective of this study was to identify among patients referred for cardiac transplantation those patients who still might benefit from reparative surgery. Retrospectively, the outcome of reparative surgery in 29 patients who had been denied such intervention in other centers was analyzed. There were 5 patients with valvular heart disease and 24 patients with ischemic heart disease. Left ventricular ejection fractions (LVEF) ranged from 12-41% (mean 26±9). In 8 patients LVEF was below 20%.

Five patients underwent valvular replacement or plasty: 4 of them are long-term survivors, one patient died after 45 months. The patients with ischemic heart disease underwent coronary artery bypass grafting alone (1 pt), bypass grafting plus mitral annuloplasty (1 pt), mitral annuloplasty alone (1 pt), left ventriculair repair alone (4 pts), and left ventriculair repair combined with bypass grafting (13 pts) or with bypass grafting and mitral annuloplasty (1 pt). There were 5 hospital deaths and 3 patients died after 5, 6 and 12 months. Another 5 patients underwent cardiac transplantation within one year after reparative surgery. Univariate analysis revealed increased risk for an unfavourable outcome (Relative risk with 95% confidence intervals) for systolic bloodpressure < 115 mmHg (9.5, 1.4 to 64.3), pulse pressure < 30 mmHg (3.6, 1.3 to 9.9), third heart sound (3.5, 1.3 to 9.9), signs of right heart failure (1.9, 1.1 to 3.1) and right atrial pressure (1.8, 1.1 to 3.1). Notwithstanding the incomplete data it may be concluded that in patients with severely impaired left ventricular function and signs of right heart failure, who are referred for transplantation, reparative surgery should not be performed. In cases of primary valvular disease the intervention of first choice should be valve-surgery.

INTRODUCTION

Cardiac transplantation offers remarkable improvement in duration and quality of life to patients with endstage heart disease. This results in increasing numbers of patients referred for transplantation. The number of donor hearts, however does not keep pace with the rising demand. This leads to a widening gap between the number of patients on the waiting-list and the number of transplants performed each year.[1] As a consequence there is a considerable prolongation of the waiting-time resulting in 7-23% of patients dying before a suitable donor heart has become available.[1-3]

In order to solve this problem efforts should be made to increase the donor pool by encouraging public opininon towards donorship and to train physicians and nurses in their difficult task to request donorship if the appropriate circumstances arise, especially in those countries which require consent. Moreover, transplantation of hearts of older donors should be considered as excellent results have been reported.[4] On the other hand, the candidacy of patients on the waiting-list should be revised when improvement

and stabilization occur after an initial episode of unstable, severe heart failure.[5] This requires methods to predict improvement or deterioration which will have to be developed more extensively.[6] A further measure to optimize the use of the donor pool is to reconsider reparative surgery in every patient with ischemic or valvular heart disease who is referred for cardiac transplantation. Without the additional morbidity and mortality of immunosuppressive therapy, corrective surgery is preferable to cardiac transplantation in a patient in whom two conditions can be fulfilled: reparative surgery should, compared to medical therapy, augment the quality of life and increase the expected survival-time. When the ultimate result of surgery appears to be not sufficient in part of the patients heart transplantation can still be performed at a later date. In fact, reparative surgery has been performed with hospital mortality rates comparable to that of cardiac transplantation and with good longterm outcome in patients with severely impaired left ventricular function and ejection fractions below 20%.[7-9]

In an attempt to identify those patients who may benefit from reparative surgery we reviewed the data of patients who underwent such procedures in stead of cardiac transplantation. These patients had been denied reparative surgery by other surgical centers and had been referred to the Rotterdam Heart Transplant Program in which cardiological and surgical teams of the University Hospitals of Rotterdam and Leiden and the Antonius Hospital in Nieuwegein cooperate closely.

PATIENTS AND METHODS

Between January 1985 and January 1992, 617 patients were referred for cardiac transplantation to the Rotterdam Transplant Program. Before referral to our center, most cases had been considered not suitable for "conventional" surgical interventions by other surgical teams in The Netherlands. Out of this group 93 patients died before clinical assesment by the transplant-team had been started or completed, 120 were considered not to be in end-stage heartfailure (yet), 127 had contraindications for transplantation (until 1990 age above 55 years was considered a contraindication for transplantation) and 237 patients were accepted on the waitinglist. Conventional surgery was performed elsewhere in 11 patients of whom the clinical data and angiogram primarily had been evaluated by our team. In 29 patients, who had been denied reparative surgery by other cardiac surgeons, reparative surgery in stead of cardiac transplantation was performed by the surgeons of the three surgical

teams participating in our heart transplant program. These patients are the subjects of this report.

Charts were reviewed for patients demographics, medical history, medication, main symptoms and findings at physical examination. In addition we reviewed the ECG, echocardiogram, chest X-ray and data from right and left heart catherization and coronary arteriography. If available, exercise or pharmacological stress tests of patients with ischemic heart disease were reviewed. Segmental left ventricular wall motion was scored by 2 observers. In case of disagreement a third observation was added and a consensus was reached. Seven segments were scored as normal, hypokinetic, akinetic, dyskinetic or hyperkinetic. Five segments in the Right Anterior Oblique projection and two in the Left Anterior Oblique projection. The degree of mitral regurgitation was graded angiographically.[10]

Statistical analysis

Data are expressed as mean ± 1SD, median or absolute numbers when appropriate. Comparisons were made by the 95% Confidence Intervals (CI) analysis for the differences between means or proportions or by the Chi-square method. Survival analysis was performed using the Kaplan Meier method.

RESULTS

Reparative surgery was recommended and performed in 29 patients who had been referred for cardiac transplantation after denial of conventional surgery by other surgeons.

Valvular heart disease was present in 5 patients, 3 women and 2 men, ages ranging from 46 to 56 years. All patients were in congestive heart failure NYHA class IV (4 patients) or III (1 patient) with dyspnea and fatigue as main complaints. All had cardiomegaly (Chest X-ray Cor/Thorax >50%) and three patients showed signs of right-sided heart failure. Two had atrial fibrillation and three were in sinus rhythm. The serum sodium concentration was normal, except in one patient (125 mmol/l). One patient received dobutamine intravenously, the others received coumarine, digoxin, diuretics and angiotensin converting enzyme (ACE) inhibitors. Only one patient had undergone cardiac surgery before (no. 2). The duration of heart failure, echocardiographic data and hemodynamic measurements are summarized in Table 1.

Table 1. Patients with valvular heart disease who underwent reparative surgery.

age	duration HF	echo LVEDD/ESD	heart catheterization RA	PA	PCW	EF	CAG	VHD	Procedure	Cross clamp	Bypass time
♀ 56	8	76 / 60	10	50	32	9	2	AoS	AVR/LIMA/SV	82	127
♀ 55	6	65 / -	3	34	25	34	0	AR/MR	AVR/MVR	105	134
♂ 46	1	65 / -	10	49	33	15	0	AS	AVR	94	120
♂ 47	1	70 / 53	5	38	22	20	0	MR	MV pl/Carp	84	135
♀ 55	12	77 / 69	5	43	26	13	0	MS	M C-tomy	23	78

AoS: aortic valve stenosis; AR: aortic valve regurgitation; AVR: aortic valve replacement; Bypass and cross clamp times in minutes; CAG: number of coronary arteries with stenoses > 50%; Carp: Carpentier ring; EF: left ventricular ejection fraction; HF: heart failure, duration in months; LIMA: left internal mammary artery; LVEDD/ESD: left ventricular end-diastolic and end-systolic dimensions in mm; MR: mitral valve regurgitation; MS: mitral valve stenosis; MV pl: mitral valve plasty; PA: mean pulmonary artery; PCW: pulmonary capillary wedge pressure; RA: right atrial pressure in mmHg; SV: saphenous vein graft; VHD: valvular heart disease.

Four patients underwent valvular replacement or plasty alone and one patient underwent coronary revascularization combined with valvular plasty (Table 1). At the time of this report, four patients are longterm survivors (18, 34, 41 and 61 months) while the patient who underwent mitral valve commissurotomy died of progressive heart failure 45 months after the operation after having refused cardiac transplantation shortly before.

Ischemic heart disease (IHD) was present in 24 patients: 22 men and 2 women, ages ranging from 41 to 56 years. All patients were in NYHA class III (12 patients) or IV (12 patients) because of heart failure (11 pts), angina pectoris (8 pts) or the combination of both (5 pts). Seventeen patients had sustained one (10 pts) or more (7 pts) myocardial infarctions. Twenty one patients had been admitted to the hospital for treatment of their cardiac condition between 1 and 4 times in the year preceding the referral for transplantation (mean 1.4 times). Fourteen patients showed signs of left-sided heart failure with pulmonay edema in 3 patients. Six patients had signs of right-sided failure as well. Cardiomegaly (C/T >50%) was observed in 15 patients. Twenty two patients were in sinus rhythm, 2 patients had atrial fibrillation. In tables 2 and 3, the characteristics of these 24 patients are presented separating 11 longterm survivors from 13 patients with unfavourable outcome. Death (in 9 patients) as well as subsequent cardiac transplantation (in 5 patients) were considered unfavourable outcomes.

Table 2. Characteristics of 24 patients with ischemic heart disease according to the outcome of reparative surgery.

	ALIVE N = 11	+ or HTX N = 13	DIFF - 95% CI of DIFF
age (mean)	48 ± 5	49 ± 6	
gender m/f	10 / 1	12 / 1	
AMI number 1	8	9	
> 1	3	4	
time after AMI, months	25 ± 18	13 ± 13	
angina pectoris present (nr)	8	5	
dyspnea, fatigue (nr)	5	9	
NYHA class III (nr)	6	6	
NYHA class IV (nr)	5	7	
hypertension (nr)	1	1	
diabetes mellitus (nr)	0	2	
medication			
digoxin (nr)	6	9	
ACE inhibitors	6	8	
diuretics	9	13	
calcium channel blockers	8	4	
nitrates	9	6	
beta-blocking agents	4	3	
i.v. catecholamines	1	2	
anti arrhythmic agents	3	4	
physical examination			
systolic BP (mean, mmHg)	124 ± 18	105 ± 13	18 95% CI= 5 to 32
S3 present (nr)	2	10	
right sided heart failure (nr)	0	6	

AMI: myocardial infarction; ACE: angiotensin converting enzyme inhibitors; BP: blood pressure; HTX: heart transplantation; NYHA: New York Heart association; S3: third heart sound. + : deceased

Table 3. Assessment of patients with ischemic heart disease according to outcome of reparative surgery.

	ALIVE N = 11	+ or HTX N = 13
Laboratory investigations		
HB (mean, mmol/l)	9 ± 1.5	8.6 ± 1
serum sodium (mean, mmol/l)	138 ± 6	139 ± 7
serum creatinine (mean, µmol/ml)	105 ± 28	108 ± 23
sinus rhythm (nr)	10	12
VTs on ambulatory monitoring (nr)	2	4
Chest X-ray: cor/thorax > 50% (nr)	5	10
Echocardiogram: LVEDD (mean, mm)	71 ± 7	67 ± 5
exercise test N =	9	6
max workload (mean, %)	61 ± 17	57 ± 13
change systolic BP (mean, mmHg)	22 ± 23	32 ± 24
heart rate rest (mean, b/min)	84 ± 38	82 ± 41
change heart rate (mean, b/min)	39 ± 17	49 ± 21
ischemia documented (nr)	5	3

BP: blood pressure; Hb; hemoglobulin; HTX: heart transplantation; LVEDD: left ventricular end-diastolic dimension; VT: ventricular tachycardia, runs of 4 premature ectopic beats or more; + : deceased.

Medication included digoxin, ACE inhibitors and diuretics. Three patients were on i.v. catecholamines at the time of referral and prior to the operation. Seven patients were treated with amiodarone. Exercise tests (bicycle ergometry with incremental workloads of 10 Watt/min) had been performed in 15 patients and had shown exercise capacities ranging from 27% to 85% of the expected workloads for age, gender and height (mean 60% ±15). Myocardial ischemia was documented by ECG or thallium perfusion scintigraphy in 8 of these 15 patients. Segmental left ventricular wall motion score showed a- or dyskinesia of the interventricular septum in 14/20 patients. Ten out of 20 patients had dyskinesia of at least 2 segments (involving the anterior wall and apex in all cases) and 12/20 patients showed equal than or less than 2 normal contracting segments (Table 4). There was a wide range of left ventricular ejection fractions (measured from the right oblique angiogram): 12-41%, eight patients showing ejection fractions below 20%. One-vessel coronary artery disease was present in 5 patients, 18 patients had multiple-vessel disease and

in 1 patient all major coronary branches were patent in spite of two myocardial infarctions. In 8 patients cardiac surgery had been performed before. Reparative surgery was considered suitable when, in the presence of "graftable" vessels, angina pectoris was an important limiting symptom or when myocardial ischemia had been documented by stress electrocardiography or nuclear imaging. Moreover, reconstructive surgery was recommended when dyspnea was the main limiting symptom in patients with normally or only slightly abnormally contracting left ventricular posterior walls (as all patients with large scars had sustained antero-septal infarctions) in the presence of akinesis or dyskinesis of the anterior wall, the septum and the apex of the left ventricle.

Table 4. Hemodynamic measurements in 24 patients with ischemic heart disease who underwent reparative surgery.

		ALIVE N = 11	+ or HTX N = 13	DIFF	95% CI of DIFF
right atrium (mean, mmHg)		3 ± 2	12 ± 10	9	95% CI = 2 to 16
pulmonary artery		23 ± 9	34 ± 12		
pulmoray capillary wedge		16 ± 9	21 ± 8		
LVEF (mean, %)		26 ± 11	27 ± 8		
LVEDP (mean, mmHg		14 ± 9	24 ± 7	10	95% CI = -17 to -2
Cardiac output (mean, L/min)		4.9 ± 0.7	4.4 ± 0.8		
extent CAD (mean, no. vessels)		2.5 ± 0.4	1.8 ± 1.1		
mitral regurgitation grade	0-I (nr)	7	7		
	II	3	4		
	III	1	0		
	IV	0	2		
LV wall motion score					
IVS normal/hypokinetic		7/8	7/12		
≥ 2 segments dyskinetic		4/8	6/12		
≤ 2 segments normal		6/8	6/12		
Complete revascularization					
including a-/dyskin segments		2/11	4/12		
excluding a-/dyskin segments		8/11	10/12		

CAD: coronary artery disease; IVS: interventricular septum; HTX: heart transplantation; LVEDP: left ventricular end-diastolic pressure; LVEF: left ventricular ejection fraction; + : deceased

Table 5. Surgical procedures in 24 patients with ischemic heart disease who underwent reparative surgery in stead of cardiac transplantation.

	ALIVE	Deceased Hosp	FU	HTX
Number	11	-------	13	---------
CABG alone (nr)	4	-	-	-
LV repair aneurysmectomy	1	1	-	1
EVCP	-	-	1	-
CABG + LV repair: aneurysmectomy	1	2	-	-
EVCP		2	-	1
EVCP + patch	3	2	1	1
CABG/aneurysmectomy/mitral annuloplasty	-	-	1	-
CABG/mitral annuloplasty	-	-	-	1
Mitral annuloplasty	-	-	1	-
IABP (nr)	3	4		
Aortic cross clamp time (mean, minutes)	73 ± 30	88 ± 25		
ECC perfusion time (mean, minutes)	178 ± 64	169 ± 52		
distal anastomoses (mean, nr)	3.1 ± 1.4	1.8 ± 1.9		

CABG: coronary artery bypass grafting; ECC: extra corporeal circulation; EVCP: endoventricular cardiomyoplasty, FU: during follow up; Hosp: in hospital; HTX: heart transplantation; IABP: intra-aortic balloon counterpulsation.

Table 6. Risk factors for unfavourable outcome after reparative surgery for ischemic heart disease (univariate analysis).

Risk factor present	FAV/UNFAV 11 / 13	Relative risk	95% CI
systolic BP < 115 mmHg	3 / 12	9.5	1.4 - 64.3
pulse pressure < 30 mmHg	2 / 10	3.6	1.3 - 9.9
third heard sound	2 / 10	3.5	1.3 - 9.9
signs right heart failure	0 / 6	1.9	1.1 - 3.1
RA pressure ≥ 8 mmHg	0 / 5	1.8	1.1 - 3.1

BP: bloodpressure; 95% CI: confidence intervals; FAV: favourable outcome; RA: right atrium; UNFAV: unfavourable outcome.

The patients with ischemic heart disease underwent mitral annuloplasty alone (1 pt), coronary artery bypass surgery (CABG) alone (4 pts), CABG plus mitral annuloplasty (1 pt), left ventricular repair by aneurysmectomy or endoventricular plasty alone (4 pts) and repair combined with CABG (13 pts) or with CABG and mitral annuloplasty (1 pt)(Table 5). In a patient with patent coronary arteries after two myocardial infarctions only mitral annuloplasty was performed. There were no significant differences in mean aortic cross clamp times and extra corporeal circulation perfusion times between the longterm survivors and the patients with unfavourable outcome. Mechanical assistance by intra-aortic balloon counterpulsation was applied from 3 days before the operation until 4 days postoperatively in 1 patient, and from immediately before surgery or from the end of extra-corporeal circulation to 48 hours after surgery in 4 and 2 patients respectively.

There were no intra-operative deaths. However, 5 patients died during subsequent hospital stay, from low output syndromes (3 pts), combined low output state and sepsis (1 pt) and from refractory ventricular arrhythmia (1 pt).

The median follow up of the patients who were discharged from the hospital was 41 months (range 5 to 62). Three patients, who underwent respectively aneurysmectomy, left ventricular repair by gelseal patch and mitral annuloplasty as a single procedure, died after 5, 6 and 12 months from severe heart failure while on the waitinglist for transplantation (1 pt), from heartfailure without re-referral to the transplant center (1 pt) and from acute pulmonary edema. A fourth patient underwent another (third) bypass operation, two year after the previous procedure, and subsequently died one year later during orhotopic heart transplantation when the donor heart failed because of extensive ischemia caused by obstructive coronary lesions in the donor heart (in combination with a long procedure for this fourth thoracotomy). Four patients underwent cardiac transplantation within the first year after their reparative surgery and are alive 35, 49, 42, and 62 months after transplantation. The remaining 11 patients are alive and in stable functional classes NYHA II(8 pts) and III (3 pts). The reparative procedure therefore may be considered successful in 11 patients only.

In an attempt to stratify the risks for a negative outcome of the reparative procedure (early death or cardiac transplantation within the first year) the data of the 11 surviving patients have been compared to the data of the 13 patients who died or underwent transplantation (Tables 2-5). Univariate analysis showed differences between the two groups for systolic bloodpressure, pulse pressure, the presence of a third heart sound, signs of right heart failure and right atrial pressure. The relative risks are presented in Table 6.

DISCUSSION

The short- and long-term survival of the 5 patients with valvular heart disease and severely impaired left ventricular function appears better than reported before and may result from improvements in myocardial protection and patient management.[11,12] Moreover, the excellent result is an example of the prerequisit of corrective surgery: a corrective lesion. As to the second requirement for successfull surgery, pumpfunction reserve, it seems justified to attempt reparative surgery in patients with primarily aortic or mitral valvular disease despite low left ventricular ejection fraction, at least in cases with heart failure of limited duration.

On the other hand, survival of the patients with ischemic heart disease was worse than could have been expected from cardiac transplantation and, in addition to that, several patients died before cardiac transplantation could have been performed yet. The Registry of the International Society for Heart and Lung Transplantation reported hospital mortality in cardiac allograft recipients to be 10% and survival rates of 81% and 69% after 1 and 5 years.(1) The survival rates of the first 180 patients of the Rotterdam Heart Transplant program are: 96%, 92% and 84% after 1 month, 1 year and 5 years respectively. However, the survival rates of our 237 patients who were put on the waitinglist with the intention to treat with transplantation are significantly lower (Fig. 1). A comparison of the results of reparative surgery and the results of effectuated heart transplantation therefore does not account for mortality on the transplant waitinglist. A more fair comparison between "reparative surgery" and "transplantation" would be the comparison of the survival rates of all patients who have been put on the waitinglist and of the patients who underwent corrective surgery (Fig. 2). Such analysis revealed that survival up to 5 years was not significantly different between "intention to treat with transplantation" and "intention to treat with reparative surgery" (in which group no patient died prior to surgery). Thus reparative surgery should be considered as an alternative for transplantation in a selected group of patients.

Left ventricular ejection fraction, estimated from the right oblique view of the angiogram appeared not very usefull in the assessment of the patients with large akinetic or dyskinetic areas as surgeons from other centers denied conventional surgery, based on the criterium "too bad" left ventricular function, after visual analysis of the angiogram.

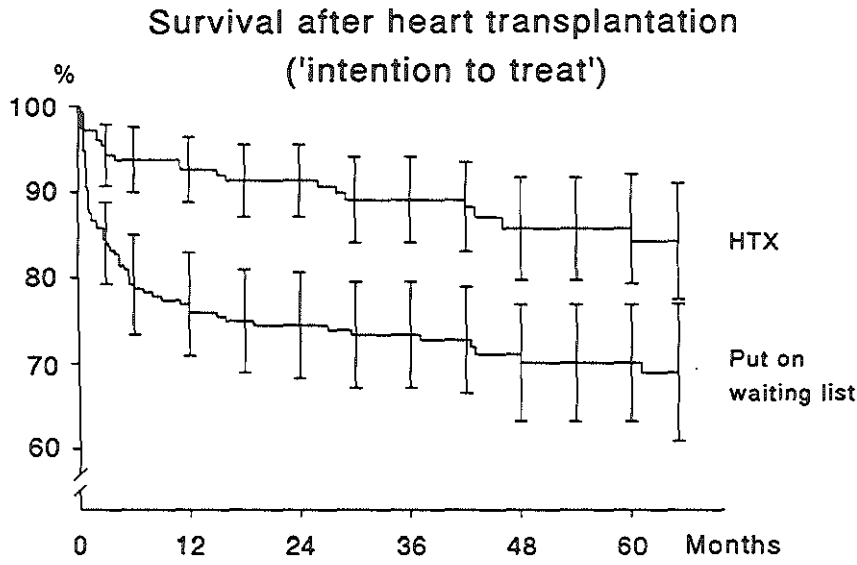

Fig. 1: Comparison of the survival rates of 180 recipients of donor hearts with a median follow up time of 43 months (HTX) with the survival rates of 237 patients who were put on the waitinglist for cardiac transplantation.

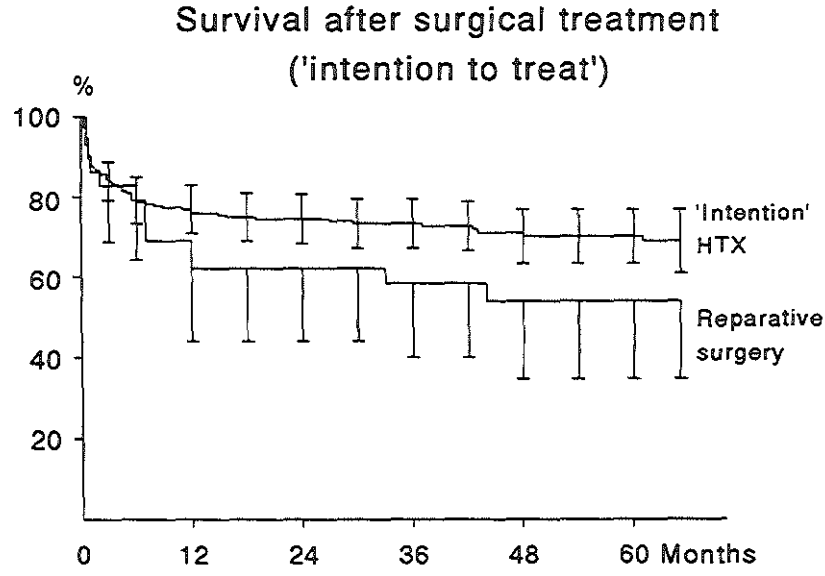

Fig. 2: Comparison of the survival rates of 237 patients who were put on the waitinglist for heart transplantation (HTX) with the survival rates of 29 patients who underwent reparative surgery instead of transplantation.

Retrospective analysis of our data demonstrated several factors which might help to identify patients with a favourable outcome after reparative surgery (Table 6). However, this analysis is limited by the relative small number of patients and incomplete data, inherent to the retrospective nature of the review. Unfortunately, the presence and extent of myocardial ischemia had not been documented in all patients prior to surgery and hemodynamic measurements had not been challenged by pharmacological interventions. Repeated hemodynamic and functional assessment after the operation could have helped to explain the results of surgery in terms of insufficient revascularization or creation of a left ventricular volume too small to deliver adequate cardiac output. In spite of these limitations the factors presented in Table 6 may help to identify, among patients with severely impaired left ventricular function after myocardial infarction, those individuals that will or will not benefit from reparative surgery. Physical examination can give clues by showing a systolic bloodpressure below 115 mmHg, a pulse pressure below < 30 mmHg and a third heart sound. Similarly, signs of right heart failure and a right atrial pressure equal to or higher than 8 mmHg indicate an unfavourable outcome. These findings are in agreement with the few earlier reports on revascularization which attempted to distinguish left ventricular impairment from the entity of congestive heart failure[13-15] and with other reports on ventricular repair.[9] In contrast with other reports, the extent to which there was left ventricular wall motion akinesis or dyskinesis or the number of normal contracting segments proved not to be discriminative in our patients.[16,17] This may be explained by the presence of severe wall motion abnormalities in all patients. Complete revascularization (in- or excluding branches with >50% diameter stenoses to a- and dyskinetic areas) failed to be identified as a factor reducing the risk for a negative outcome.[18] In patients, quite different in main presenting symptoms (angina pectoris, heart failure or arrhythmia) factors as older age, conduction abnormalities, history of hypertension, left ventricular ejection fraction, number of coronary arteries diseased, presence of left main disease or left ventricular aneurysm, need for mechanical assistance by IABP and the time period during which surgery was performed have been pointed out as risks for mortality after reparative cardiac surgery.[19-21] It was not to our surprise that we could not confirm these factors in our patients who were very sick and had been considered to have excessive risks for conventional surgery by other surgical teams.

The underlying review has several implications to the selection of patients for reparative surgery and cardiac transplantation. In an attempt to distinguish more reliably patients who may or may not benefit from reparative surgery extensive studies have to be performed in patients with ischemic heart

disease to document the presence and extent of myocardial ischemia. For the detection of viable myocardium in these patients, with considerable impairment of left ventricular function, the value of (pharmacological) stress testing in combination with echocardiography or scintigraphy and of positron emission tomography has to be assessed.[22,23] These investigations subsequently have to be repeated after the operation to study the results of revascularization. When left ventricular repair has been performed hemodynamic measurements will have to be repeated after surgery to calculate the influence of that particular type of repair on left ventricular stroke volume and right ventricular performance. On the other hand heart transplantation should be offered to patients with ischemic heart disease and signs of right heart failure on top of severely impaired left ventricular function. In cases of primary valvular heart disease the primary intervention of choice will be reparative surgery.

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CHAPTER III

MECHANICAL "BRIDGING" TO HEART TRANSPLANTATION

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The use of mechanical support in a heart transplant program is warranted when a patient, who is already on the transplant waitinglist, deteriorates and might die before a suitable donor heart has become available. In addition, the use of mechanical circulatory support systems may be considered in patients who are referred for cardiac transplantation, when such support may sustain life until assessment for transplantation can be completed or when the application of such devices will allow recovery of organ dysfunction or of other reversible problems which otherwise would be contraindications for transplantation.

Counterpulsation by intra-aortic balloon pumping (IABP) is the most widely used method of mechanical support, especially after the development of the transcutaneous femoral approach for introduction of the catheter mounted balloon.[1] Although this device is effective in many patients, the increase of cardiac output is limited (10-20%) and this may be insufficient to prevent organ damage and death. Some patients may therefore require systems which deliver their "own stroke volumes". In the Rotterdam Heart Transplant Program intra-aortic ballon counterpulsation has been applied as method for mechanical support in patients under consideration for cardiac transplantation. In this chapter our experience with IABP is summarized, as well as the experience from other groups with various other assist devices.

Intra-aortic balloon counterpulsation as a bridge to transplantation: The Rotterdam Heart Transplant Program experience

Mechanical support by intra-aortic counterpulsation has been proven usefull in cardiogenic shock, early in the course of acute myocardial infarction when part of the impaired pumping capacity is caused by ischemia, and in post-cardiotomy ventricular failure with damaged myocardium that is expected to recover.[2-5] When a definite therapeutic intervention is not immediately available, mechanical support can be used to optimize the patients' condition in preparation for future procedures. For example, patients with interventricular septal rupture or acute mitral regurgitation can be "bridged" to reparative surgery and patients with extensive myocardial ischemia can be "bridged " to revascularization procedures.[6-8] In patients with chronic heart failure, without the option of a corrective procedure, mechanical circulatory support should be used only, when the patient can be considered a candidate for heart transplantation or can be expected to become a candidate for transplantation when the use of the assist system allows recovery of organ damage.

Between 1984 and January 1, 1993 816 patients have been referred to the Rotterdam Heart Transplant Program (see Chapter XII). Mechanical support by IABP has been used in 41 patients as a "bridge to transplantation" and in 1 patient to "bridge" the time until successful conventional surgery.

At the start of the transplant program, IABP in-situ was considered a contraindication for heart transplantation, because of a presumed high risk for infection in patients under subsequent immunosuppressive therapy. Others, however demonstrated that patients who require IABP support for severe heart failure do well after transplantation.[9] Accordingly, mechanical circulatory support by IABP has been applied in the afore mentioned 42 patients who were referred for transplantation after January 1987 or who deteriorated while on the waitinglist for a donor heart: 39 men and 3 women, ages ranging from 13 to 62 years (median 49 years). Treatment by IABP was instituted in the cardiology departments of the three cooperating hospitals (Rotterdam 29 patients, Leiden 10 patients and Nieuwegein 3 patients). Ischemic heart disease, dilated cardiomyopathy and valvular heart disease were the underlying causes of heart failure in 30, 11 and 1 patients respectively. In 36 patients mechanical support was initiated because of progressive forward failure with impending organ damage superimposed on a state of chronic heart failure. The remaining 6 patients needed IABP because of cardiogenic shock early after acute anterior wall infarction. Thirty patients with chronic heart failure were treated with IABP shortly after referral for cardiac transplantation while under evaluation or while receiving treatment for temporary contraindications for transplantation, six patients deteriorated to cardiogenic shock after they had been discharged to their homes (4 patients) or to the referring hospitals (2 patients) to wait for a donor heart.

The duration of mechanical support ranged from 1 to 54 days (median 14 days). Stabilization of hemodynamics and reversal of organ damage (restoration of urine output and normalization of serum creatinine levels and aspartate/alanine aminotransferases) occurred in all but 3 patients in whom balloon counterpulsation was applied. In a 41 year old man who developed cardiogenic shock 22 days after anterior wall infarction, "reparative" surgery appeared possible. He underwent left ventricular plasty and coronary revascularization after 14 days of IABP support and is alive, 4 years after the procedure.

Twelve patients received a cardiac allograft. The transplantation procedure was successful in all and the intra-aortic balloon was removed at the end of the procedure. One patient died on postoperative day 14 from acute rejection. The remaining 11 patients are alive, 6 to 67 months after transplantation (median 39 months).

Twenty nine patients died before a suitable donor heart had become available (Table 1). Progression of pumpfailure while suffering from fever and bacteremia or severe respiratory tract infection (1 patient) was the cause of death in 10 patients who were on IABP for more than 5 days. One patient died after massive rectal bleeding during treatment of gram negative sepsis. In three patients mechanical ventilation was applied in addition to intra-aortic balloon support. One patient could be weaned from the ventilator after 14 days and stayed another 21 days on the balloon pump until transplanation, one other patient was ventilated during 6 days until transplantation and the third patient died after 24 days support by IABP and 14 days of mechanical ventilation from pump failure during severe respiratory tract infection.

Culture proven episodes of bacteremia (mainly gram positive bacteria) during counterpulsation occurred in 17 of the 42 patients who were treated with IABP. Twenty seven times suspected bacteremia was a reason for balloon replacement to another site in 14 patients (Table 1). Four of the 12 patients who received allografts had suffered from staphylococcus aureus bacteriemia before transplantation. After transplantation infection, attributable to the preoperative intra-aortic balloon, occured in one patient only. This patient developed a lymphe fistula in the groin which healed per secundam after infection with gram negative bacteria.

In conclusion, intra-aortic balloon counterpulsation is effective in restoring sufficient cardiac output to prevent organ dysfunction in most patients with acute heart failure as well as in patients with severe chronic heart failure. In many patients however, pump function will deteriorate further resulting in new organ damage and death. Moreover, patients with severe heart failure who are treated by IABP for more than a few days are threathened by bacteriemia. Therefore, patients who need cirulatory support by IABP should be candidates for *urgent transplantation* as long as there are no exclusion criteria (infection, irreversible organ dysfunction, pulmonary infarction etc.).

Table 1. Intra-aortic-balloon counterpulsation as a "bridge to transplantation". The characteristics of 42 patients who were treated by IABP, divided by outcome.

Outcome		Heart transplantation or "reparative" surgery	Dead while waiting
Number of patients		13	29
Age		45 ± 11	47 ± 9
Gender M / F		12 / 1	27 /2
Heart disease	IHD	8	22
	CMP	5	6
	VHD	-	1
Duration of IABP (days)			
< 7days (nr)		4	11
≥ 7 and < 14 days		-	7
≥ 14 days		9	11
Change of IABP insertion site			
times	0 (nr)	8	20
	1	1	4
	2	3	3
	> 2	1	2
Cause of death			
pump failure (nr)		-	18
pump failure + infection		-	10
bleeding		-	1
acute rejection		1	-
Bacteremia (nr)			
Staphyl. Aureus		4	5
Staphyl. Epidermidis		3	3
other Gram pos. bacteria		-	2
Gram neg. bacteria		-	1
Respiratory tract infection			
Pseudomonas		-	1

IHD: ischemic heart disease; CMP: cardiomyopathy; VHD: valvular heart disease; IABP: inta-aortic balloon counterpulsation; nr: number of patients.

Ventricular asist devices

In cases in which partial circulatory support by IABP is not sufficient to maintain adequate organ perfusion mechanical support systems which deliver their "own stroke volume" have been used in many centers, although not at the Thoraxcenter. Hemodynamic criteria for institution of these more complete support systems, adopted by the United States National Heart, Lung and Blood Institution are: cardiac index less than 1.8 - 2.0 l/min/m^2, systolic bloodpressure less than 90 mmHg or mean arterial pressure less than 60 mmHg, left and/or right atrial pressure greater than 20-25 mmHg, systemic vascular resistance greater than 2100 dynes.sec.cm^{-5} and urine output less than 20 ml/hr, in spite of optimal filling pressures, maximal pharmacological support and intra-aortic balloon counterpulsation.[10,11] The experience of centers which participate actively in the development of cardiac assist systems however, indicates that assist devices preferably should be inserted in an earlier stage, before the afore mentioned criteria have been reached. When the expected time which has to be "bridged" is more than a few days and the patient deteriorates while under optimal medical therapy the assist device should be inserted without the prior use of IABP.[12]

The various systems which have been developed since Spencer supported the failing circulation after cardiotomy in 1965[13] can be classified as devices for which thoracotomy is not necessary (extra corporeal membrane oxygenation and Hemopump), external centrifugal pumps, external pulsatile assist devices, implantable pneumatically driven or electrical ventricular assist systems and orthotopic biventricular replacement devices.

Extra corporeal membrane oxygenation (ECMO) using a membrane oxygenator connected to a heat exchanger and a roller or centrifugal pump can be applied after insertion of arterial and venous femoral cannulae (e.g. CPS system, Bard Inc.). This system does not require thoracotomy and can be used for resuscitative purposes.[14,15] However, its use is limited to 24-48 hours because of anticoagulation problems, immobilization, risk of sepsis and the need for continuous surveillance of a perfusionist. The Nimbus Hemopump consists of a single coaxial catheter which is inserted through the femoral artery, across the aortic valve into the left ventricle. Blood is centrifugated from the ventricle into the aorta by a fastly rotating screw.[16] Although this system looked very promising at first, it has not gained wide application because of insertion difficulties and because of its limited cardiac output of 3.5 l/min which may not be sufficient in most adult patients. *External centrifugal pumps* such as the Biomedicus pump, also require surveilance of a perfusionist.

These pumps propel blood by centrifugal force through large cannulae which are connected to the patients left atrium and aorta or right atrium and pulmonary artery. The application of these pumps is limited to periods of a few days because of the tendency for hemolysis to occur at high flows and the risk of infection through the cannulae insertion sites.[17-19] *External pulsatile devices* include the "Berlin Heart", the "Abiomed", the "Pierce-Donachy" and the "Symbion" assist devices. These systems consist of one or two extracorporeal pneumatically driven pumps and require transcutaneous cannulae which make the patient immobile and increase the risk for infection. The mechanical valves in some of these pumps (Pierce-Donachy and Symbion) require aggressive anticoagulation, thus causing bleeding complications. These systems have been used to support postcardiotomy shock patients and as bridge to cardiac transplantation.[20-23] A newly developed *pneumatically driven*, abdominally *implantable* system is the "Heartmate" which comprises a pulsatile pusher-plate bloodpump with an outer housing of rigid titanium. All blood-contacting surfaces, except the porcine xenograft valves, are textured to promote the formation of a biologic lining. The device has been successfully applied as a "bridge to transplantation" for periods up to 233 days.[24] The electrically driven version of this system is the only *electrical system* which is currently approved by the U.S.Food and Drug Administration (FDA) for use in humans. The mobility of the patient is much more improved and a protocol for discharge from the hospital of patients on this device has been submitted to the FDA. Another electrical pump is the "Novacor" assist device. This system was expected to become a prototype of future tether-free permanent systems and is currently the most frequently applied device. It is connected to an external microprocessor-based control/monitoring console with a thin power cable which allows patient mobility. The device has been used in more than 100 patients as a "bridge to transplantation" and a version of this device was the only one to "survive" the 2 year reliability test which was required to start clinical testing for permanent use. However, further support of the National Heart and Lung Blood Institute for the development in the direction of application as a permanent assist has been stopped in 1992 because of the loss of a component supplier. Both the Novacor and the Heart Mate are not suited for postcardiotomy patients because they require cannulation of the left ventricular apex thereby mutulating the left ventricle.[25,26] In patients requiring additional right-sided support, as has been reported to be necessary in 20% of patients treated with Novacor assist systems, other assist systems will have to be added because neither the "Heartmate" nor the "Novacor" system can be cannulated to the right atrium and ventricle.[26,27] Pre-device indications of the need for biventricular support therefore should be searched for allowing the

selection of the optimal device.[28] Orthotopic biventricular replacement devices or *Total Artificial Hearts* (TAH) require removal of the patients ventricles and therefore are not appropriate when recovery of the failing myocardium may be expected. Clinical experience has been gained with the pneumatically driven Jarvik-7 (Symbion, Salt Lake City), which consists of polyurethane sac-type ventricles with Medtronic disc valves through which the blood is allowed to flow as through the normal heart. The longest circulatory support provided by a Total Artificial Heart system is 438 days.[29]

Ventricular assist systems have been applied in three categories of patients: patients who develop shock due to massive acute myocardial infarction, patients with shock after cardiotomy and patients with chronic heart failure who deteriorate while on the waiting-list for heart transplantation. Before institution of the support system in patients who develop shock due to myocardial infarction or post cardiotomy, the question should be answered whether this patient will be a good candidate for transplantation. When the answer is negative the support system should not be applied. In patients who deteriorate while on the waiting-list the situation is different because they have already been assessed and accepted as candidates for transplantation. These patients can be kept alive and organ damage which would prohibit transplantation, may be prevented by timely institution of adequate circulatory support.

Mechanical bridging to transplantation is costly including the costs of the pumps and consoles and (above all) prolonged intensive care when not-implantable systems are used. Therefore such support should be restricted to patients with a reasonable probability of successful transplantation. Early results with the implantable systems look promising because patients can take care of the system themselves and can be mobilized, which enables discharge from intensive care units to general wards or even to facilities outside the hospital.

In order to assess the clinical value of various approaches to mechanical support the results of IABP applied at the Thoraxcenter and the results of more sophisticated support systems which are used as "bridge to transplantation" in other centers are compared in Tables 2 and 3. The data as reported in the Registry for the clinical use of mechanical pumps and artificial hearts do not allow comparison of the criteria for patient selection for the various devices.[29,30] Nevertheless the available data imply that IABP probably is less effective than other devices to help the patient survive until transplantation. Bacteremia caused death in 10 out of 18 patients who stayed on IABP for more than 7 days in one of the three centers which participate in

Table 2. Mechanical "bridging in patients referred for cardiac transplantation: results.

Device	IABP	LVAD	BVAD	TAH	TAH
Source	Rotterdam	Registry[30]	Registry[30]	Registry[30]	Symbion[29]
referred for HTX (Nr)	826	?	?	?	?
IABP	42	?	?	?	?
LVAD	-	122	161	?	?
TAH	-	-	?	189	171
Heart Transplantation	12 (30%)	87 (71%)	105 (65%)	135 (71%)	118 (70%)
Hospital survivors	11 (26%)	76 (62%)	73 (45%)	67 (35%)	82 (48%)
Alive 1 year after HTX	11 (26%)	-	-	?	67 (39%)

IABP: intra-aortic balloon counterpulsation; LVAD: left ventricular assist device; BVAD: biventricular assist device; TAH: total artificial heart; HTX: heart transplantation.

Table 3. Complications of mechanical support precluding heart transplantation.

	IABP[RHT]	VAD[30]	BVAD[30]	TAH[30]
Number of patients	41*	38	56	27
Bleeding	2%	31%	25%	27%
Ventricular failure	43%	45%	43%	0%
Renal failure	-	31%	27%	40%
Respiratory failure	-	17%	18%	42%
Infection	25%	21%	14%	36%
Multi organ failure	-	0%	11%	29%

VAD: ventricular assist device; BVAD: biventricular assist device; TAH: total artificial heart. RHT: Rotterdam Heart Transplant Program.

the Rotterdam Heart Transplant Program. Accordingly intra-aortic balloon counterpulsation will not be the assist system of first choice when it can be expected that the time until transplantation will be long. In contrast with the patients who were treated with other systems however, almost all IABP patients who reached transplantation survived the procedure and could be discharged from the hospital. This is probably due to the strict exclusion from transplantation of patients suffering from infection and/or organ damage while on intra-aortic balloon support in our centers. These data suggest that optimal results of prolonged mechanical support as "bridge to transplant" can be obtained by the timely application of ventricular assist devices and the subsequent strict maintenance of the inclusion criteria for transplantation. As long as tether-free permanent systems are not available, the overall results of current systems will always depend on the availability of donor hearts. The patient awaiting a donor heart will benefit the most from a support system which allows full mobilization and has the least "connections" to the outside world, while the patient, immobilized in bed and having large cannulas will be prone to further deterioration of pumpfunction, decubitus and infection.

In the Rotterdam Heart Transplant Program the following questions will have to be answered: a) should patients on IABP be granted priority on the waitinglist or b) should these patients receive donor hearts which would have been refused otherwise? (e.g. hearts from elderly donors), c) should patients who will need mechanical support for more than one week be denied IABP? and d) should a more complete assist system be selected to allow successful "bridging" for a longer time and to obtain expertise in the management of patients to prepare for future use of permanent devices?

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PART II

IMMUNOSUPPRESSIVE THERAPY AFTER CARDIAC TRANSPLANTATION

INTRODUCTION

Immunosuppressive therapy plays a key role in the management of the heart transplant recipient. This introduction therefore, will review the reason for immunosuppression, rejection. The rejection process will be described as well as measures to prevent and suppress rejection. In addition methods to detect rejection in the cardiac allograft will be presented.

Rejection

After transplantation the immune system of the recipient is in contact with donor cells. As clinical heart transplantation is an allogeneic type of grafting (genetically non-identical members of the same species) an immune respons, directed to graft injury, will be inevitable. This response is called rejection. The immune response is evoked by recognition of the graft as "non-self".

Of the foreign antigens that may be **recognized** by the immune system the human major histocompatibility complex = the Human Leucocyte Antigen (HLA)-system is the most important.[1,2] The HLA system consists of a group of closely linked genes, located on the short arm of chromosome-6, divided in three regions, which encode class I and class II cell surface glycoproteins and several components of the complement system respectively. Of the class I region the HLA-A, HLA-B and HLA-C genes are expressed on the surfaces of all nucleated cells. HLA-DR, HLA-DP and HLA-DQ, the genes of the class II region are mainly expressed on antigen presenting cells (e.g. macrophages, dendritic cells, B-cells), while expression on almost all other cells may be induced by cytokines (e.g. gamma interferon).[3] Especially important for transplantation are the HLA-A, HLA-B and HLA-DR genes.

Cells within the cardiac allograft which are able to function as antigen presenting cells include passenger leucocytes (blood derived cells that have not been washed out of the donor heart), dendritic cells and vascular endothelium. T helper cells bind with foreign class II molecules via a surface receptor. Recognition is facilitated by binding between the accessory molecule CD4 on the T helper cell and the constant part of the class II antigen resulting in activation of the T cell. Thereafter a variety of effector mechanisms is evoked in the **destruction phase** of the immune response. Macrophages are activated, produce interleukin 1 (which in return stimulates T helper cells) and may injure the graft directly (non-specific target lysis). T helper cells interact with B lymphocytes resulting in maturation of these cells and antibody production

(antibody dependent cellular cytotoxicity). Lymphokine production by the T helper cell increases the activity of natural killer cells which also may result in cell lysis. Further, the activated T cell starts producing interleukin 2 (IL-2) which is one of the primary growth factors for further expansion of the T helper cell pool.

A second event involves the recognition of HLA class I antigens by resting cytotoxic T cells bearing CD8 accessory molecules, which facilitate binding of HLA class I antigens and their T cell receptor. Resting cytotoxic T cells will develop into mature cytotoxic effector cells after stimulation by IL-2, produced by the activated T helper cell, and a second factor termed cytotoxic differentiating factor. This results in specific target cell lysis. In addition, a purely antibody-mediated response can occur when antibodies against donor antigens are already present in the recipients circulation before transplantation (e.g. after previous bloodtransfusion or pregnancy or after a previous transplant). Ultimately the immune response involves infiltration of the graft by a large number of different cells of which it is still unclear which type causes edema formation, myocyte damage and necrosis, hemorrhage, vasculitis and fibrin deposition.

The immune response can be regulated in an upward or downward direction by regulatory cells and by anti-idiotypic antibodies. The latter are formed as a secondary response to the antibody that has been produced by the B cell after recognition of the foreign antigen.

Clinically, rejection of the allograft can be divided into: hyperacute rejection, accelerated acute rejection, acute rejection and chronic rejection. **Hyperacute rejection** occurs within 24 hours of transplantation as a result of a reaction between donor antigens and preformed donor-specific antibodies. Immunologically aspecific events follow the binding of anti-donor antibodies to antigen on the endothelium: activation of clotting, fibrin deposition, fibrinolysis, capillary leakage and the influx of inflammatory cells with their own release of mediators and consequent massive tissue injury. Obstruction of the small arteries by platelet-neutrophil plugs and subsequent ischemia lead to total graft destruction. This type of rejection can be prevented by screening of the transplant candidate for anti-HLA antibodies before transplantation and by performing a leucocyte crossmatch between donor and recipient in cases where preformed antibodies have been demonstrated. Thanks to this policy such type of rejection has not occurred in the first 200 transplantations performed in the Thoraxcenter (Chapter XII). **Accelerated acute rejection** is probably also antibody mediated and occurs within the first days after transplantation. This type of rejection occurs in patients in whom no preformed antibodies have been demonstrated before transplantation. Still, the fast response on donor

antigens may be the result of previous contact with donor-like antigens. In 3 of our first 200 cardiac allograft recipients an early (10-12 days after transplantation), rapidly progressive type of rejection occurred, resulting in severe graft dysfunction and death of the patients. The absence of extensive cellular infiltrates shortly before death in two patients and the absence of infiltrates even at autopsy of the third patient suggested an antibody mediated process but immunological prove was not obtained. **Acute rejection** is the most common type of rejection in which infiltrates of mononuclear cells with or without myocyte damage, edema, vasculitis and hemorrhage can be demonstrated microscopically (Figs. 1 and 2).[5] Progressive acute rejection results in stiffening of the heart (elevation of filling pressures) and impairment of systolic function (tachycardia, lowering of blood pressure, oliguria etc.). Arrhythmias, especially of atrial origin, may occur in all stages of acute rejection. This type of rejection occurs usually after the first week and was observed in 75% of our recipients while half of the patients suffered from at least 2 episodes of acute rejection during the first year (Chapters IV, V and XII). In addition, a vascular type rejection has been reported which includes accumulation of immunoglobulin and complement in the microvasculature.[6,7] The outcome of patients who suffer from this type of rejection tends to be worse than in patients with cellular or mixed cellular/vascular rejection. Furthermore, an earlier appearance of transplant coronary artery disease has been found in recipients who show vascular rejection.[7] Because we have not performed routine immunostaining of endomyocardial biopsies we do not know whether and how frequently vascular rejection has occurred in our patients. The pathogenesis of **chronic rejection** is less clear than the other types of rejection. In the cardiac allograft this type of rejection is represented by concentric intimal thickening of the entire length of the coronary vessels. According to pathological studies, more than 90% of all grafts are affected by this process which is a major limiting factor for the long-term succes of heart transplantation.[8,9] Recent observations support the hypothesis that a localized allogeneic immune reaction, which includes T cells, is responsible for the proliferation of smooth muscle cells and extracellular matrix which results in intimal hyperplasia.[10,11] Instead of "chronic rejection" the term "allograft vascular disease" has recently been proposed for this entity.[12]

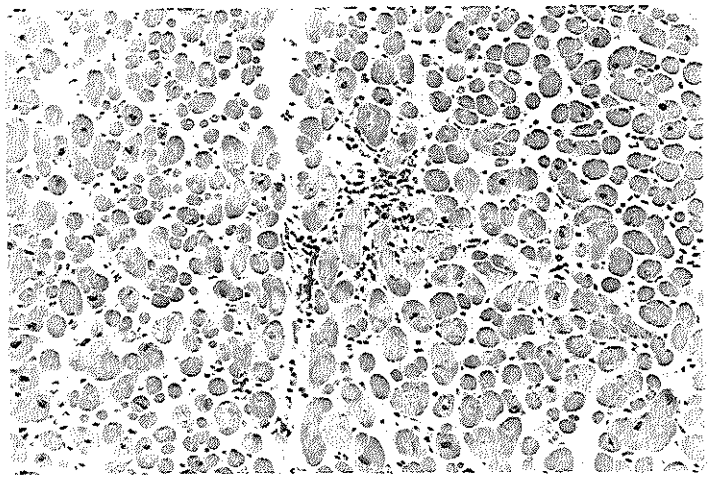

Fig. 1: Endomyocardial biopsy showing primarily transverse sections of myocytes. There is a small perivascular infiltrate of mononuclear cells without myocyte damage. Rejection was graded 1A according to the guidelines of the International Society for Heart and Lung Transplantation (ISHLT) because only three such minor infiltrates were found in a total of 4 biopsy specimens. Rejection treatment was not instituted. (HE; x 160).

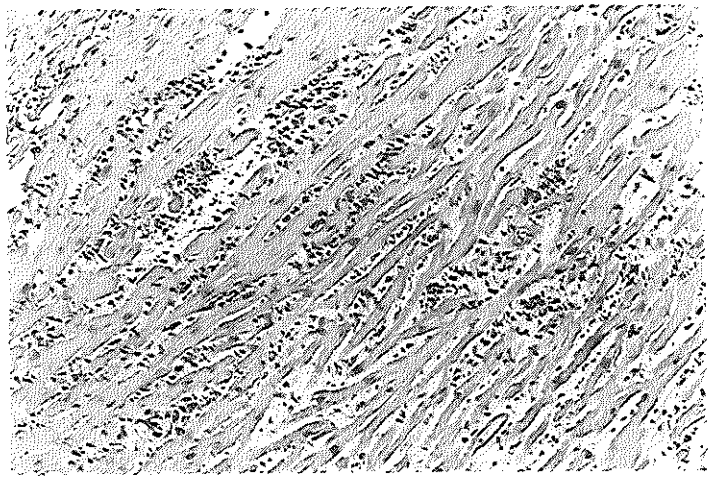

Fig. 2: Endomyocardial biopsy showing primarily longitudinal sections of myocytes. Infiltrates of mononuclear cells extend into the interstitium and surround myocytes. Myocyte damage is apparent and degeneration of myocytes is readily identified. Rejection was graded 3A according to ISHLT because such infiltrates were found at multiple sites. The patient was treated with anti-T cell antibodies because rejection persisted despite the administration of high dose corticosteroids. (HE; x 160).

Detection of rejection

Fortunately, the progression of acute rejection in patients receiving cyclosporin as the main immunosuppressive agent is more slowly than in the past. Therefore, advanced impairment of graft function resulting in symptoms of heart failure may be prevented by early detection and treatment of rejection.

Despite many efforts to find alternative, non-invasive, methods endomyocardial biopsy has remained the "gold standard" for the detection and monitoring of acute rejection.[5] Biopsies are harvested from the right side of the ventricular septum with a bioptome which is introduced into the right ventricle by venous access, preferably via the right jugular vein. By histologic assessment of the biopsy specimens most rejection episodes can successfully be detected and monitored after treatment. Endomyocardial biopsies are taken weekly during the first 6 weeks after transplantation, bi-monthly until 3 months and less often thereafter. A mean number of 17 biopsies are taken in the first year while approximately two or three biopsies yearly suffice after the first year (Chapter XII). From the start of our program until early 1991 we used conventional Billingham's criteria for grading acute rejection episodes and considered anti-rejection therapy necessary in cases of "moderate rejection": perivascular and interstitial mononuclear cellular infiltrates coexistent with myocyte necrosis.[5] More recently, the International Society for Heart and Lung Transplantation has proposed an universal grading system for allograft rejection allowing comparison of the results of different centers.[13] Since the introduction of the latter grading system our indication for therapy has been modified, witholding therapy in the presence of one single focus of mononuclear infiltrate with myocyte damage (grade 2) until a follow-up biopsy shows further extension of the infiltrate. In cases of multiple interstitial infiltrates with myocyte damage anti-rejection therapy will be instituted immediately.

Early in the course of the Rotterdam Heart Transplant Program we confirmed (unpublished data) the finding of other centers that the close correlation of a reduction of electrocardiographic QRS voltage with histologic evidence of rejection which existed in patients on azathioprine, no longer existed in patients on cyclosporin.[14,15] During the first 9 years of our program we investigated three other non-invasive methods to detect rejection, without apparent succes. Cyto-immunologic monitoring to determine specific subsets of T lymphocytes and the number of activated lymphocytes in the peripheral circulation,[16] appeared not usefull in our hands.[17]. This also was true for monitoring of soluble interleukin 2 receptors.[18] Echo-doppler measurements of

the cardiac allograft, although shown to be helpfull in other programs[19] did reflect differences between the groups of "rejectors" and "non-rejectors" but appeared to be unreliable for the diagnosis of rejection in individual patients.[20] Changes of the intramyocardial electrogram, nuclear imaging with indium-111 labeled leucocytes or antimyosin Fab fragments and magnetic resonance have been proposed but not used in our program.[21-23] Unfortunately these methods yielded low sensitivity and specificity rates and often promising initial results obtained by one group could not be confirmed by others.[24]

The invasive nature of the endomyocardial biopsy and the burden of the large number of procedures on the catheterization laboratory urges a continued search for non-invasive ways to detect rejection. Accordingly, measurements of the variability of the heart rate and the QRS complex were started in 1992 in our center, after reports of the possible value for detection of rejection of frequency analysis of the surface ECG by fast-Fourrier transformation.[25] Moreover, after the detection of soluble donor specific HLA-molecules in the recipients serum we are investigating the value of this finding for the monitoring of acute rejection.

Management of rejection

Management of rejection includes the induction of non-reponsiveness, early prophylaxis, maintenance immunosuppression and rejection treatment. The immune response directed towards the allograft which is very strong early after transplantation declines gradually with time resulting in less need for immunosuppressive therapy. Attempts to **induce non-responsiveness** towards the allograft, prior to transplantation have only partially been successful. Pretransplant strategies have included the establishment of a state in which donor antigens encounter an immature or suppressed immune system in the recipient through which allogens will be considered "self" and the pretreatment of the future organ recipient with cells carrying donor antigens. The former can be achieved by total lymphe node irradiation or by infusion of donor bone marrow in recipients who have been treated with anti-thymocyte globulin or monoclonal antibodies,[26-28] and the latter by blood transfusion.[29] In the clinical situation of heart transplantation however, these modalities are not feasible because irradiation of the often very sick transplant candidate is not desirable and there are only minutes or, at the utmost, hours available to perform transfusions with donor material prior to transplantation. Random bloodtransfusion before transplantation has been reported to have beneficial effects on allograft survival in the pre-cyclosporine era but its value has been

effects on allograft survival in the pre-cyclosporine era but its value has been debated since the improved survival results after the introduction of cyclosporine for immunosuppression.[29,30] Recent research suggests that the beneficial effect of the blood transfusion in patients treated with cyclosporin depends on the sharing of HLA-DR or HLA-DR and HLA-B antigens between blood donor and transplant recipient.[31,32] Pre-transplant blood transfusion has been part of the preparation for cardiac transplantation in the Rotterdam Heart Transplant Program since the start in 1984 and has been performed in all but three recipients.

Methods to suppress the immune response shortly after transplantation, when the response is the most severe and the graft is still recovering from the ischemic insult, include **early**, short-time, **interventions** directed towards all T cells (polyclonal therapy, e.g. anti-thymocyte globulins) or to specific subsets of T cells (monoclonal therapy, e.g. antibodies against the CD3 structure of the T cell receptor complex = OKT3). Such interventions in the efferent limb of the rejection cascade seemed to be successfull in the pre-cyclosporin era.[33]. The sequential use of anti-T cell therapy and cyclosporin, although advocated strongly after several trials which compared receivers with historical controls,[34-36] failed to decrease the incidence and severity of rejection compared with administration of cyclosporin, started a few hours before transplantation, without additional anti-T cell therapy.[37,38] The results of our randomized trials are presented in Chapters IV and V. Whether the failure of early anti-T cell therapy to decrease the incidence of rejection is related to the disappearance of the protective effect of DR-matched pretransplant bloodtransfusions is a subject of study at this moment.

A search for new regimens will continue: in our program a randomized trial comparing the effects of OKT3 and BT563 (a monoclonal antibody directed to the interleukin 2 receptor) on the incidence of rejection is under way.

Since its introduction into clinical heart transplantation in 1980 the fungal metabolite **cyclosporin** has become the basal constituent of todays maintenance immunosuppressive regimens.[39] Its effect is related to the inhibition of the production of interleukin-2 thereby reducing the amplification of T helper cells and the further development of mature cytotoxic T cells. All our cardiac allograft recipients have been treated with cyclosporin. Monitoring of the trough levels of this drug is necessary to achieve a targeted immunosuppressive level and to prevent unwanted side effects. Besides an increased risk for infection, which is the most detrimental side effect of all immunosuppressants, the most important side effects of cyclosporin are hypertension (in ± 90% of the patients) and nephrotoxicity (acute effects by vasoconstriction and long-term effects by the development of a chronic

progressive vasculopathy with irreversible interstitial fibrosis).[40] The extent to which cyclosporin has resulted in impairment of renal renal function of our heart transplant recipients is presented in Chapters XI and XII. Neurotoxicity has caused transient paraplegia in one of our patients and has probably contributed to the development of seizures in 3 patients who were treated with cyclosporin intravenously. Minor adverse effects may decrease quality of life but interfere less with outcome are hepatoxicity, gingival overgrowth and hirsutism.

Prednisone has been a basal constituent of immunosuppressive therapy since the early days of organ transplantation and continues to be so. It reduces foreign tissue antigeneity, reduces transiently the number of circulating monocytes and lymphocytes (thus reducing their access to allograft tissue) and reduces the formation of interleukin 1. Much of the action of prednisone during episodes of acute rejection is to reverse the secondary inflammatory response associated with acute rejection. Side effects of prednisone include Cushing's syndrome, osteoporis, myopathy, cataract, peptic ulcer, glucose intolerance and hypercholesterolemia but have not interfered with successfull medium term outcome of our transplant recipients so far (Chapter XII).

The nefrotoxic effects of cyclosporin were a reason to reintroduce **azathioprine** into immunosuppressive regimens after heart transplantation.[41] This imidazolyl derivative of 6-mercaptopurine becomes a purine analog after hepatic metabolism and inhibits nucleic acid synthesis thereby interfering with cellular proliferation in a nonspecific fashion. By adding azathioprine to the combination of cyclosporin and prednisone "triple therapy" was introduced and adopted by most heart transplant centers aiming at lower dosage of cyclosporin. More recently, steroid related side effects have spawned interest in immunosuppressive regimens without steroids. The disparity in overall results however underscore the need for randomized, prospective studies on steroid withdrawal.[42-47] Excellent overall results with the mere combination of cyclosporin and prednisone have made us continue this regimen for maintenance immunosuppression although target cyclosporin levels have been lowered recently in an attempt to reduce impairment of renal function. Azathioprine has been added only in cases of severe renal insufficiency or diabetes mellitus requiring insulin.

Acute cellular rejection will occur in 75% of the allograft recipients at least once and in half of the patients at least twice despite early prophylaxis and maintenance immunospuppression (Chapters IV and V). Treatment consists of pulsed high doses of methylprednisolon or, in case of refractory rejection, anti T cell therapy. Polyclonal antilymphocyte globulins which have been prepared by sensitization of animals (horses, rabbits) with human thymocytes,

lymphocytes or lymphoblasts have been used both as early prophylaxis and as rejection therapy. These globulins act by a dramatic reduction of the number of T lymphocytes, a process which results in release of cytokines causing high fever, pulmonary capillary hyperpermeability, chills, nausea, vomiting and muscle cramps. In addition serum sickness can occur at a later stage. In our progam a horse derived anti-lymphocyte preparation has been used as early prophylaxis (Chapter V). For treatment of refractory rejection polyclonal Rabbit-anti-T cell-globulins (R-ATG) have been used. In addition to the afore mentioned polyclonal anti-T cell preparations, we have used OKT3 as early prophylaxis as well as rejection treatment (Chapter IV). This murine antibody is the first commercially available monoclonal anti-T cell antibody. Since it is of mouse-cell origin, the patient may develop anti-mouse antibodies which may render the preparation less effectve. OKT3 binds to the CD3 antigen which is part of the receptor of the T lymphocytes. The antibody produces its effect by two mechanisms. Initially the population of antibody-coated T cells is opsonized by the reticuloendothelial system. Within a few days, new T cells are found in the circulation which lack the CD3 antigen. As long as the OKT3 antibody is present in the circulation T cells will remain ineffective. This preparation proved to be successfull in almost all steroid resistant rejections in our experience (Chapter XII). The monoclonal antibody against the interleukin-2 receptor (BT563) has been used more recently and proved successful in 3 patients. The future will tell whether investigational drugs as the macrolide antiobiotics FK506 and rapamycin or RS-61443 (the morpholinonethyl ester of mycophenolic acid) will decrease the incidence of rejection without more detrimental side effects.[48-50]

Therapy for the antibody-mediated hyper acute rejection has been disappointing and the only modality at this time is urgent retransplantation which necessitates "bridging" of the patient to the second operation. If such rejection is not immediately life-threathening an attempt may be made to remove preformed antibodies by plasmapheresis.[51] In addition, immunosuppressive therapy that is highly selective for B cells may be warranted, e.g. the substitution of cyclophosphamide for azathioprine. No specific regimens have been developed yet to treat vascular rejection. At this moment treatment is based solely on the augmentation of the overall level of immunosuppression with standard anti-rejection therapy.[52]

Since the early days of organ transplantation immunosuppressive regimens have been developed as "exquisite meal recipies". By changing the dosages of the different "spices" and by adding new "flavour" to "old recipies" every heart transplant program has established his own "cook-book". In

contrast, we have assessed regimens for early prophylaxis in sequential randomized trials and thereby proven, that up to now none of the tested regimens is superior to the other at least for the short term outcome.

The assessment of the influence of the different regimens on the long-term outcome is hampered by the small numbers of patients transplanted in each center. Therefore multicenter trials should be initiated. By doing so, the data of sufficient numbers of allograft recipients can be gathered. Review of the data by a core laboratory and central data analysis will be prerequisites for the success of such studies.

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CHAPTER IV

SEQUENTIAL OKT3 AND CYCLOSPORINE AFTER HEART TRANSPLANTATION. A RANDOMIZED STUDY WITH SINGLE AND CYCLIC OKT3.

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Study supported by a grant from the Netherlands Heart Foundation.

In: Clinical Transplantation 1991; 5: 301-305

SUMMARY

The incidence of cardiac allograft rejection and the occurrence of renal insufficiency in the early postoperative period were compared in patients randomly allocated to receive either sequential OKT3 plus azathioprine and cyclosporine or to cyclosporine alone. Both groups were in addition on low-dose steroids. Thirty-three patients received OKT3 and in 10 of them a second course of OKT3 was given after 3 weeks, regardless of the presence or absence of allograft rejection. Cyclosporine alone was given to 33 patients also. There was no significant difference in the number of acute rejections per patient in the OKT3-versus cyclosporine-treated patients (1.33 vs 1.36), nor in the freedom from rejection at 1, 3 and 6 months: 80%, 31% and 28% vs 66%, 33% and 27% respectively. No difference in freedom from rejection was found between patients who received single versus cyclic doses of OKT3. In the OKT3-treated patients there were no nephrological problems. In the cyclosporine group median serum creatinine levels increased from 115 to 208 µmol/l in the first postoperative week. There were no serious side-effects during the first course of OKT3. In the 10 patients who received a second course of OKT3 side-effects were badly tolerated, although not hemodynamically significant or life threathening. When the freedom from rejection in the OKT3 group was compared to the results in our first 32 cardiac recipients who also received cyclosporine and low-dose steroids there appeared to be a significant ($p<0.001$) delay in the occurrence of the first rejection. This delay was not significantly different in the randomized concurrent controls. This supports the need to conduct randomized trials for the comparison of immunosuppressive regimens. OKT3 facilitated patient care by preventing nephrological problems but did not reduce the incidence of cardiac allograft rejection.

INTRODUCTION

Various protocols using cyclosporine (CsA), azathioprine and steroids in combination with polyclonal and, more recently, with monoclonal antibody preparations against T lymphocytes have been developed for induction of graft acceptance after heart transplantation.

In our first 32 patients immunosuppression with cyclosporine and low-dose steroids resulted in a 85% graft survival at 1 and 3 years and a mean incidence of rejection of 1.7 episodes during the first year. Actuarial freedom from rejection was 44%, 27% and 23% after 1, 3 and 12 months. Immediate postoperative patient handling was hampered by transient impairment of renal function leading to oliguria and a marked increase of serum creatinine in the first postoperative week.

We therefore embarked on a randomized controlled study in an attempt to reduce both the incidence of rejection and of nephrological problems. The effects of cyclosporine and low-dose steroids were compared to a regimen that consisted of sequential OKT3 and cyclosporine in combination with low-dose

steroids. In addition, the effects of single and cyclic courses of OKT3 on the occurrence of rejection were compared. OKT3 was chosen because of the proven effectiveness of these monoclonal antibodies against the T-cell receptor recogition complex in the treatment of allograft rejection in renal, liver and heart transplant recipients.[1-4] Moreover, several authors have claimed reduced rates of early rejection in patients who received OKT3 as induction therapy.[5-9] This paper describes the results obtained in 66 consecutive patients.

METHODS

Between April 1987 and May 1989, 66 patients entered the trial. Eight other patients were transplanted, but were excluded because of renal insufficiency at the time of transplantation. These patients received H(orse)-ALG as induction therapy. The patients who entered the trial were randomly allocated to receive either OKT3 (Ortho Pharmaceutical, Raritan, N.J.) or intravenous cyclosporine. OKT3 was started postoperatively in a dose of 5 mg/day, 1 to 2 hours after arrival on the Intensive Care Unit, while still on the ventilator and continued for 7 days. Additionally azathioprine i.v. was administered in a dose of 50 mg/day for 6 days. Oral cyclosporine (8 mg/kg/day) was started on the evening of day 5 and adjusted to plasma trough levels. In an attempt to enhance graft acceptance by inducing a second episode of T-cell depletion, the last 10 OKT3 patients received a second course of OKT3 (5 mg/day for 5 days) after 3 weeks, regardless of the presence or absence of rejection. In patients allocated to cyclosporine this medication was started intravenously 2-4 hours before transplantation in a dose of 3 mg/kg/day. Postoperatively the dose was adjusted, guided by renal function and plasma levels of cyclosporine. Oral cyclosporine therapy was instituted 48-96 hours postoperatively.

Patients in both groups received i.v. prednisolone 20 mg prior to the operation and 60 mg/day thereafter, in two divided doses, tapered with 10 mg/3 days to 20 mg/day and thereafter with 2.5 mg/week until the maintenance dose of 10 mg was reached at approximately 8 weeks postoperatively. In the OKT3 patients half of the daily dose was given shortly before the administration of OKT3 in combination with 4 mg of clemastine to alleviate side-effects.

All CMV-seronegative transplant recipients received passive immunisation with anti-CMV immunoglobulin (Cytotect, Biotest Pharma GmbH, Frankfurt, FRG) as reported before.[10]

Cyclosporine levels were measured by specific ^{125}I-CSA radio-immunoassay (Cyclotrac, Incstar, Stillwater MN, USA) to keep plasma 12 h trough levels between 80 - 120 ng/ml in the early postoperative period and between 50 - 100 ng/ml after 9 - 12 months.

OKT3 plasma levels were measured by a specific enzyme linked immunosorbent assay (ELISA) as described by Jaffers with slight modifications.[11] Anti - OKT3 antibodies were measured by ELISA as described elsewhere.[12]

Lymphocyte phenotyping was performed with a fluorescence-activated cell sorter (FACSCAN, Becton Dickinson) using monoclonal antibodies of the Leu series (Becton Dickinson): CD3 (for pan-T cells, T-cell receptor-associated), CD4 (for helper/inducer T cells), CD5 (for pan T-cells, not associated with the T-cell receptor) and CD8 (for cytotoxic/suppressor T-cells). Additionally WT31 was used as a specific marker for the antigen-binding site of the T cell receptor complex.

The diagnosis of acute rejection was based on histological examination of endomyocardial biopsies.[13] Biopsies were taken weekly during the first 6 weeks, twice monthly until 3 months, monthly until 6 months, every 2 months for the rest of the first year and every 4 months thereafter. Rejection therapy was instituted in the case of moderate rejection (interstitial mononuclear infiltrates and myocyt necrosis). Treatment consisted of methylprednisolone 1 g i.v. on three consecutive days or R(abbit)-ATG for 14 days to keep T cells between 50 - 150/mm^3 for 14 days in case of early, persistent or recurrent rejection.

Infections were defined as symptomatic infectious episodes with concurrent demonstration of the causative agent by culture or changes in serological status. Superficial Herpes simplex type I lesions of the oral mucosa were excluded from the analysis.

Statistical analysis

Data are expressed as mean values ± SD or medians as appropriate. The significance of differences between patient groups was determined by unpaired T-tests. Chi-square analysis was used to asses the significance of differences in frequency between groups.

RESULTS

Thirty-three patients received OKT3 as induction therapy, while in 10 of them a second course was given after three weeks. Intravenous cyclosporine was used peri-and postoperatively in 33 other patients. There were no differences in age, distribution of gender, primary disease or bloodgroup between the two groups (Table 1). The number of mismatches for HLA-A, -B, -DR as well as historic and current panel-reactive activity were also comparable for both groups. Sixty-four patients received at least one blood transfusion prior to transplantation. Crossmatches of donor lymphocytes with historic and current recipient sera were negative.

Table 1. Patient characteristics

		CSA	OKT3
patients (nr)		33	33
age, years (mean)		44.8 ± 9.3	45.7 ± 10.2
gender m / f		31/2	29/4
primary disease	IHD (nr)	18	13
	CMP (nr)	14	20
	Other (nr)	1	0
bloodgroup O (nr)		15	16
A (nr)		16	10
B (nr)		2	5
AB (nr)		0	2
mismatch (mean)	HLA - A	1.27	1.24
	HLA - B	1.58	1.57
	HLA - DR	1.43	1.51
PRA median (range)	hist %	0 (0-76)%	1 (0-45) %
	current %	0 (0-45)%	0 (0-45) %

IHD: ischemic heart disease, CMP: cardiomyopathy, PRA: panel-reactive activity; nr: number

The full 7-day course of OKT3 could be completed in all 33 patients. Minor side-effects, especially fever (>38°C) were noted in almost all patients but no serious problems occurred. No hemodynamic problems or non-cardiogenic pulmonary edema were observed. Although there were no clinical significant hemodynamic changes during the second course of OKT3 after 3 weeks, side-effects were much more severe including fever up to 40.3°C, chills, arthralgia and diarrhea (Table 2).

Table 2. Side-effects of OKT3. Thirty-three patients received OKT3 as induction therapy, 10 of whom received a second course after 3 weeks.

	OKT3 first episode	OKT3 second episode
patients (N)	33	10
fever	31	6
chills	0	2
rash	10	0
diarrhea	4	2
arthralgia	0	4
hypotension	4	0
pulmonary edema	0	0

Mean plasma levels of OKT3 increased from 200 - 440 ng/ml on the first day to a median of 900 (range 400 - 2200) ng/ml between 4 and 8 days, returning to zero within 3 days after discontinuation of the drug. In the 10 patients who received a second course of OKT3, plasma levels reached comparable levels as during the first course despite the presence of anti-OKT3 antibodies, that could be detected in 28/33 OKT3-treated patients.

Pan-T lymphocytes (CD5+) decreased to approximately 200 - 300/mm^3 and returned to baseline levels within a week after starting OKT3 treatment. WT31+ cells became virtually undetectable during OKT3 and returned to the CD5+ levels 4-5 days after the last dose of OKT3. The numbers of CD4+ plus CD8+ cells were comparable to the number of CD5+ cells but higher than the level of the CD3+ cells, indicating a modulation phenomenon. Although 28/33 of the patients responded with low titers of anti-OKT3 antibodies during the first course, depletion of T cell receptor-bearing cells (WT31+) was demonstrated both during the first course as during the second course. No booster effect of the anti-OKT3 antibodies was noted during the second course.

Thirty-three patients received cyclosporine intravenously starting 2-4 hours prior to the operation in a dose of 3 mg/kg/day. This dose was reduced 12-24 hours after transplantation to 2 or 1 mg/kg/day in 17 patients and temporarily interrupted in 5 because of oliguria. Oral administration of cyclosporine was started after 48-96 hours.

Median serum creatinine levels in the cyclosporine group increased from 115 (range 78-133) µmol/l preoperatively to 208 (range 136-485) µmol/l in the first week, returning to baseline levels in the second or third week. No impairment of renal function was observed in the OKT3 treated patients. Median serum creatinine levels decreased from 116 (range 81-214) µmol/l preoperatively to 97 (range 69-228) µmol/l in the first week.

Median follow up is 19 months (range 12-36 months). A significant delay in the occurrence of the first rejection episode ($p<0.001$) was noted when the OKT3 patients were compared with our "historical" cyclosporine group (Fig. 1). However, in the randomized study there was no difference in the mean number of acute rejections per patient in the first year between the OKT3 treated group and the CsA group: 1.33 vs 1.36 (Table 3). Actuarial freedom from rejection at 1, 3 and 6 months was 80%, 31% and 28% in the OKT3 group and 66%, 33% and 27% for the CsA group. These differences were not statistically significant (Fig. 2). Also no difference in the incidence of rejection was found between patients who received single versus cyclic courses of OKT3 (Fig. 3).

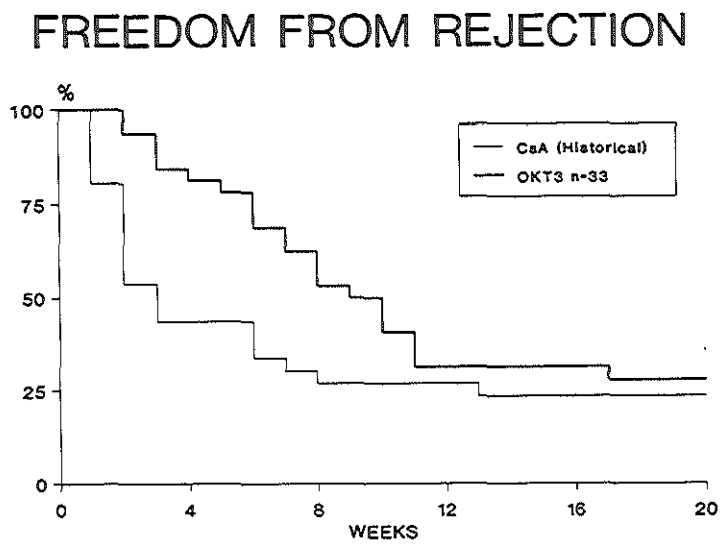

Fig. 1. Actuarial freedom from rejection. Comparison between historical controls (N=32) and all OKT3-treated patients (N=33).

Table 3. Total number of rejection episodes in the first year after heart transplantation in the CsA- and the OKT3-treated patients.

Rejection episodes (N)	CsA (33 pts)	OKT3 (33 pts)
0	9	9
1	10	11
2	10	8
> 2	4	5

The mean number of infections per patient during the first year was 1.1 in the OKT3 groups and 1.0 in the concurrent CsA group. CMV replication was demonstrated in 7 patients of each group. CMV disease developed in 5 and 2 patients of the OKT3 group and CsA group respectively (difference not statistically significant). CMV disease disappeared spontaneously in 3 patients and responded well to treatment with ganciclovir in the other 4 patients, 2 in each group. There was no difference in the occurrence of Varicella Zoster virus infections between the study groups: 2 vs 1 respectively.

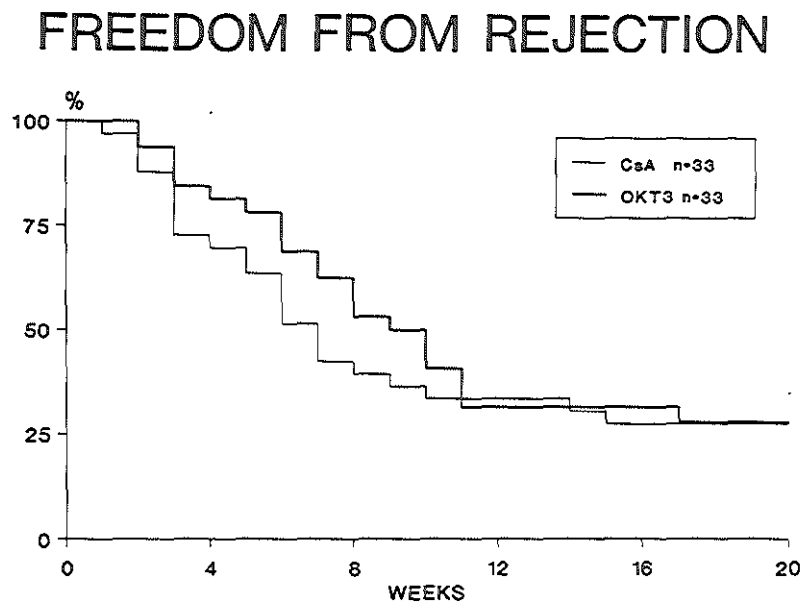

Fig. 2. Actuarial freedom from rejection. Comparison between concurrent controls and all OKT3-treated patients.

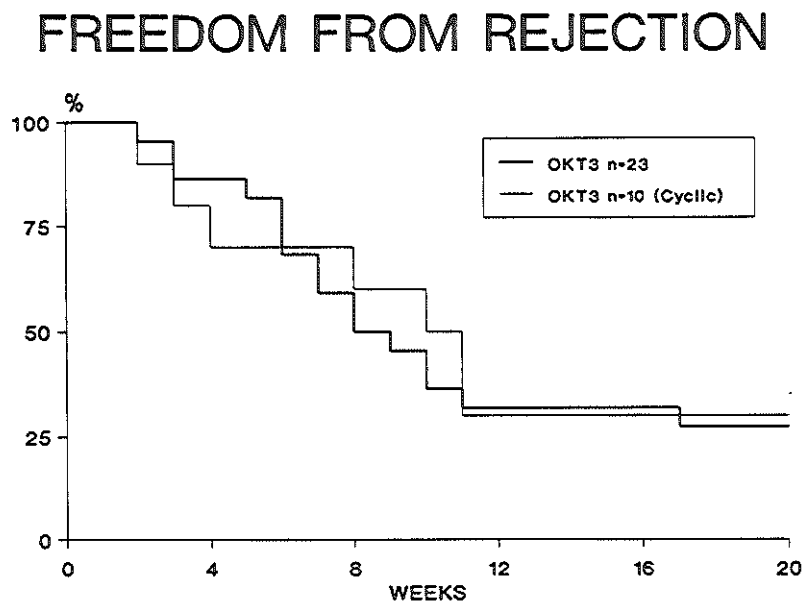

Fig. 3. Actuarial freedom from rejection. Comparison between patients who received single and cyclic OKT3 courses.

Malignancies occurred in 3 patients during the follow-up period. One patient, who remained free from rejection after OKT3 induction therapy, died from non-Hodgkin lymphoma 5 months postoperatively. A second patient, who had been allocated to CsA, experienced two rejection episodes which were treated with R(abbit)-ATG and methylprednisolone, respectively, and died from plasmocytoma, 26 months after transplantation. A third patient who received also cyclosporine i.v. initially and remained free from rejection, underwent lobectomy because of squamous cell carcinoma 22 months after transplantation and is alive 14 months after this operation.

Actuarial graft and patient survival was 91% and 94% at 2 years for the OKT3 patients and the CsA groups, respectively.

DISCUSSION

We demonstrated that controlled randomized trials are necessary to compare the effects of different immunosuppressive regimens after heart transplantation. Most other studies included only historical controls or failed to fulfill scheduled randomization.[5-9] In one study of OKT3 as induction

therapy after heart transplantation randomization could not be performed properly because of lack of availability of one of the drugs that should be compared and because of differences in the dose of the steroids and timing of the start of cyclosporine.[5] In two studies randomization was incomplete because of severe side-effects of OKT3 in the early postoperative period.[6,7] In two others the importance of the timing of initiation of cyclosporine after OKT3 induction therapy was reported but the conclusion should be questioned because historical controls were used.[8,9]

In the present randomized trial, monoclonal induction therapy did not reduce the incidence of rejection and did not delay the occurrence of the first episode of rejection. A slight delay in the occurrence of the first rejection episode proved to be not statistically significant (Fig. 2). Also, in the small number of 10 patients who received cyclic courses of OKT3, there was no reduction of the incidence of rejection in the first year.

Perioperative management of the fluid balance of patients who received intravenous cyclosporine was difficult. The impairment of renal function required extra attention during the first days but serum creatinine levels returned to baseline after 1-2 weeks. Cyclosporine levels could be kept within the targeted range. Induction with OKT3 did reduce nephrological problems in the immediate postoperative period. Management was easy both in the patients who had been waiting at home as in the patients who were hospitalized preoperatively because of the need of inotropic (N=15) and mechanical support (N=1). Because of the improved renal function it was easy to treat pre-existing fluid retention already during the first days after transplantation.

Plasma OKT3 levels ranged markedly, from 400-2200 ng/ml. Since depletion of all T-cell receptor-bearing cells was achieved in all patients, a level of 400 ng/ml seems to be sufficient to accomplish the desired response. Anti - OKT3 antibodies could be demonstrated in 28 of 33 patients. This is different from earlier reports that showed low titers of antibodies in only 20% of the patients [8,14] but confirms data obtained with competitive binding assay.[15] In the 10 patients who received a second course of OKT3, depletion of WT31+ cells was again accomplished. A booster effect on antibody formation was not seen during the second course of OKT3. This enables future re-institution of OKT3 therapy in cases of otherwise intractable rejection, as has been shown before.[14]

Contrary to earlier reports, we did not observe severe side-effects, hypotension nor pulmonary edema during the first doses of OKT3, which enabled us to continue according to the randomization schedule.[7] The tolerance of OKT3 may be related to the fact that patients were still on the ventilator during administration of OKT3.

The second course of OKT3 was badly tolerated because of severe malaise, fever, arthralgia and diarrhea. Therefore, the part of the trial that included a second course of OKT3 was discontinued.

We could not comfirm earlier reports showing an increased incidence of infection after OKT3 [16,17] and no difference in the incidence of malignancies was noted.

The results of this randomized trial indicate that OKT3 monoclonal antibody induction therapy facilitates patient care in a safe way by preventing nephrological problems. The 7 days course of OKT3, however, does not delay the occurrence of the first rejection nor the incidence of rejection in comparison with CsA. Cyclic courses of OKT3 for prophylactic reasons are not recommended because of side-effects and lack of further enhancement of graft acceptance.

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CHAPTER V

POLYCLONAL VERSUS MONOCLONAL REJECTION PROPHYLAXIS AFTER HEART TRANSPLANTATION. A RANDOMIZED STUDY.

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In: Transplant International 1992; 5 (suppl 1): S476-S479

SUMMARY

Recent studies comparing the effects of induction therapy with polyclonal antilymphocyte globulins (ALG) or with monoclonal T-cell-specific antibodies are not unanimous. Therefore, 55 heart recipients were allocated to either 7-day courses of polyclonal ALG (n=28) or of monoclonal OKT3 (n=27). Additionally, azathioprine and low dose steroids were given. There were no severe side effects after OKT3; the course of ALG, however, had to be discontinued in 20 patients because of extensive flares. No differences between the two groups were found in freedom from rejection or in the incidence of infection. The 1- and 2-year survival was 96% in both groups. Although monoclonal and polyclonal induction therapies are equally effective for rejection prophylaxis, OKT3 may be preferred because of a lack of important side effects. However, the fact that a shorter course of ALG is equally effective may be in favour of ALG.

INTRODUCTION

Polyclonal antilymphocyte or antithymocyte globulins (ALG, ATG) as well as monoclonal antibodies against T cells have proved to be effective for reversing acute cardiac allograft rejection.[1-3] Subsequently, various protocols using these antibodies, have been developed for rejection prophylaxis in heart transplant recipients.[4-7] More recently, studies comparing the effects of polyclonal and monoclonal T-cell-specific antibodies have been reported.[8-11] Their results, however, are not unanimous about the superiority of one antibody preparation with respect to another in terms of rejection prophylaxis, safety and infectious complications.

In an earlier, randomized, controlled study in heart transplant recipients, we demonstrated that OKT3 facilitates patient care by preventing renal failure in the immediate postoperative period but does not reduce the incidence of rejection when compared to cyclosporin given i.v..[4] Polyclonal anti-T-cell prophylaxis may induce broader immunosuppression resulting in fewer rejection episodes but might also give rise to more infectious complications. The present study was undertaken to compare a polyclonal horse lymphocyte-specific immunoglobulin with monoclonal OKT3 with regard to rejection prophylaxis, safety and infectious complications.

MATERIALS AND METHODS

All consecutive heart transplant recipients between 1 August 1989 and 1 August 1991 were enrolled into the trial and were subsequently allocated to

receive either OKT3 (Ortho Pharmaceutical, Raritan, N.J.) or ALG (horse lymphocyte-specific IgG2, Lymphoglobulin, Institut Merieux). OKT3 was started postoperatively in a dose of 5 mg/day, 1-2 hours after arrival at the Intensive Care Unit while still on the ventilator, and continued for 7 days. Similarly ALG was started 1-2 hours after arrival at the Intensive Care Unit, in a dose of 425 lymphocytotoxic units (0.5 ml) per kilogram of bodyweight daily and continued for 7 days. In addition, azathioprine was administered postoperatively, 50 mg/day intravenously for 6 days, and prednisolone was given prior to the operation (20 mg) and 60 mg/day thereafter, in two divided doses, tapering down by 10 mg every 3 days to 20 mg/day and subsequently by 2.5 mg/week until the maintenance dose of 10 mg/day was reached at approximately 8 weeks postoperatively. Half of the daily corticosteroid dose was given shortly before the administration of OKT3 or ALG, in combination with 4 mg clemastine i.v., to alleviate side effects. Oral cyclosporin was initiated on postoperative day 5 in a dose of 8 mg/kg daily in two divided doses and adjusted to the plasma levels.

Cyclosporin levels were measured by specific ^{125}I-CSA radio-immunoassay (Cyclotrac, Incstar, Stillwater Minn.) to keep plasma 12 h trough levels between 80 and 120 ng/ml in the early postoperative period and between 50 and 100 ng/nl after 9-12 months.

The diagnosis of acute rejection was made by histological examination of endomyocardial biopsies and graded according to Billingham's criteria of none, mild, moderate and severe rejection.[3] For the diagnosis of moderate rejection, the coexistence of mononuclear infiltrates and myocyte necrosis was required.

Treatment of acute rejection was instituted in the case of moderate rejection and consisted of R(abbit)-ATG to keep T cells between 0-150/mm^3 for 14 days for the first episode of rejection, methylprednisolone 1 g i.v. on 3 consecutive days for the second episode and OKT3 5 mg/day for 10 days in case of ongoing rejection or an early third episode of rejection.

All Cytomegalovirus (CMV) seronegative recipients received CMV seronegative blood products and passive immunization with CMV-specific immunoglobulin (Cytotect, Biotest Pharma, Frankfurt, FRG) for 10 weeks, as reported before.[13]

Infections were defined as symptomatic episodes with concurrent demonstration of the causative agent by culture or changes in serological status. CMV infection was defined by a rise of IgM antibodies, demonstration of immediate early antigen (IEA), or isolation of the virus from throat swabs or urine. CMV disease was defined as fever or signs of organ involvement in the presence of CMV infection.

Statistical analysis

Data are expressed as mean values ± SD or medians as appropriate. The significance of differences between means was assessed by the 95% confidence interval. Comparisons of proportions are based on the Chi-square test. Log rank test was used to assess the differences in freedom from rejection. For survival analysis, the Kaplan Meier method was used.

RESULTS

Twenty eight patients received ALG and 27 patients were treated with OKT3. Patient characteristics including the numbers of donor/recipient gender mismatches and numbers of mismatches for HLA-A, and -B, as well as the current panel reactive activity (PRA) were similar in both groups, although there was some difference in HLA-DR mismatches (Table 1.). All patients received at least one bloodtransfusion prior to transplantation. Crossmatches of donor lymphocytes with recipient sera, performed in case of more than 5% PRA, were negative.

The scheduled 7-day course of ALG was discontinued in 20 out of 28 patients after 5 days (range 3-6) because of extensive flares. The development of pyrexia (mean highest temperature 39.1 °C) was not different from the fever in the patients from the other treatment group.

The full 7-day course of OKT3 could be completed in all 27 patients. Fever (mean maximal temperature 39.4°C) occurred in all but 3 patients, a mild rash was noted in 4 patients and diarrhea in 1 patient.

Median follow-up was 15 months (range 3-25 months). The 1- and 2-year graft and patient survival was 96% in the OKT3 as well as in the ALG group.

No difference was found in the mean number of acute rejection episodes per patient during follow-up. Actuarial freedom from rejection at 1, 3 and 12 months was 68%, 18% and 13% in the ALG group and 74%, 33% and 20% in the OKT3 group. These differences were not significant (Fig. 1). The numbers of acute rejection episodes per patient were also equally distributed among the two treatment groups: 5, 14, 5 and 3 (ALG) versus 4, 11, 6 and 7 (OKT3) patients with respectively 0, 1, 2 or more than 2 rejection episodes.

A total of 42 patients received 1 (29 patients), 2 (12 patients) or 3 (1 patient) additional courses of polyclonal or monoclonal antibodies after the inductional therapy for the treatment of rejection.

Table 1. Characteristics of the patients who received either monoclonal or polyclonal antibodies for rejection prophylaxis.

Induction therapy			ALG	OKT3
number of patients			28	27
gender m/f			23/5	22/5
recipient age (yrs, range)			45 (18-61)	48 (15-62)
primary heart disease		CMP	16	14
		IHD	12	10
		VHD	-	3
donor age (yrs, range)			26 (14-43)	24 (12-38)
CMV serostatus negative (nr)			13	9
PRA (%, median, range)			0 (0-20)	0 (0-54)
donor/recipient gender MM (nr)			9	10
MM	HLA-A		1.3 ± 0.5	1.4 ± 0.7
	HLA-B		1.6 ± 0.6	1.4 ± 0.6
	HLA A+B		2.9 ± 0.9	2.9 ± 1
	HLA-DR		1.2 ± 0.5	1.3 ± 0.7
MM	HLA A+B	0 (nr)	1	0
		1 or 2	8	11
		> 2	19	16
MM	HLA DR	0 (nr)	1	4
		1	20*	10*
		2	7	13

ALG: Horse-anti lymphocyte IgG2; CMP: cardiomyopathy; IHD: ischemic heart disease; VHD: valvular heart disease; CMV: Cytomegalovirus; PRA: panel reactive activity; MM: mismatch;
* $p < 0.025$

The mean numbers of infections per patient were 0.9 and 0.8 in the ALG and OKT3 groups, respectively. Bacterial infections occurred more frequently than viral infections. There was no difference in the occurrence of bacterial, parasitic and fungus infections between the two treatment groups. CMV disease and herpes zoster were the main virus induced problems. Again, no difference in the occurrence of viral infections or disease between the ALG and OKT3 groups could be demonstrated (Table 2.).

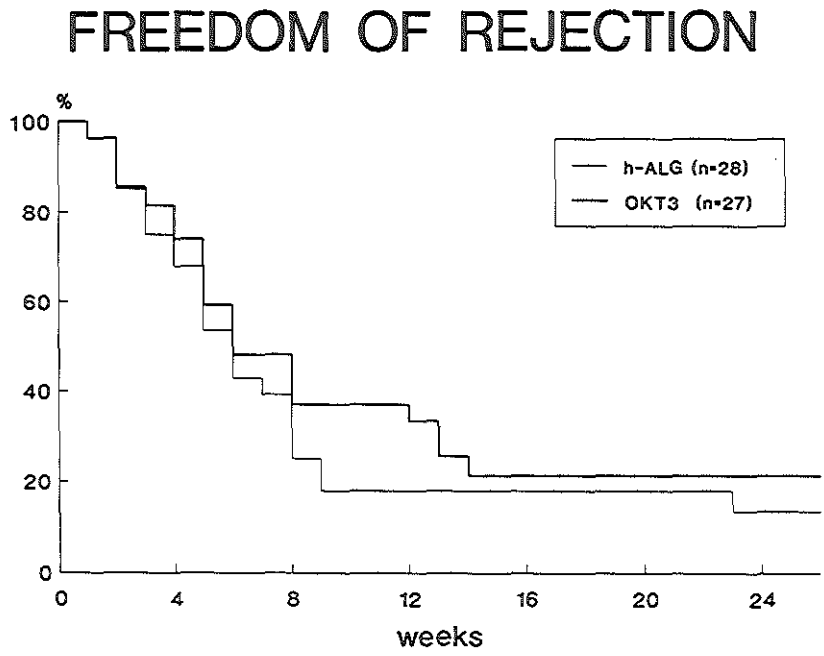

Fig. 1. Comparison of freedom from acute allograft rejection after induction therapy with ALG or OKT3 in 55 heart transplant recipients.

Table 2. Infections after polyclonal or monoclonal anti-T cell antibodies.

Induction therapy	ALG	OKT3
all infections	26	23
viral infection	9	6
CMV disease	4	2
Herpes zoster	3	1
bacterial infections	15	14
fungus infections (superficial candida)	-	1
parasitic infection	2	1
Pneumocystis Carinii	2	-
Intestinal Ascaris	-	1

In both treatment groups more, but not significantly different, bacterial infections and CMV disease or herpes zoster occurred in patients who received additional anti-T-cell therapy for rejection treatment compared with those

without it. Bacterial infections occurred in 21 out of 41 patients with additional therapy versus 8 out of 14 patients without it and CMV disease or herpes zoster in 7 out of 41 patients with versus 3 out of 14 patients without additional anti-T-cell therapy.

Malignancies occurred in 1 patient from the ALG group and in 3 patients in the OKT3 group. The first patient, who received ALG for induction therapy, developed a squamous cell carcinoma of the external acoustic meatus 9 months after transplantation. The second patient died 18 weeks after transplantation from malignant lymphoma. After OKT3 induction therapy he had been treated with R(abbit)-ATG and a second course of OKT3 for intractable rejection. The third patient who received OKT3 initially, was operated upon because of adenocarcinoma of the antrum, 7 months after transplantation. In the fourth patient a mucodermoid carcinoma of the palatum was noted, 12 days after transplantation.

DISCUSSION

Although excellent short and medium term survival after heart transplantation can be achieved without the use of polyclonal or monoclonal anti-T-cell induction therapy,[14] no efforts have been spared to develop an immunosuppressive regimen that would reduce the incidence of rejection as well as the complications of immunosuppression. In our centre the 2-year actuarial survival rates of 91% and 94% were achieved in heart transplant recipients, prior to this study, with and without OKT3 induction therapy, respectively.[4] The fact that OKT3 facilitated the immediate postoperative care by avoiding the administration of cyclosporin in the immediate postoperative period, but could not reduce the incidence of rejection made us embark in the present study, comparing the effects of polyclonal and monoclonal antibodies on cardiac allograft rejection. The graft and patient survival in both treatment groups was excellent. No superiority of one regimen to the other could be demonstrated with respect to freedom from rejection or time to detection of the first rejection.

The administration of ALG was hampered by fever and rapidly evolving, giant flares in 20 patients, necessitating premature discontinuation of the medication. No other complications were noted.

As in a previous study, almost all patients developed fever, but none experienced severe side-effects during or after the initial doses of OKT3.[4] In contrast with the results of others, no haemodynamic deterioration or pulmonary oedema occurred. This may be explained by the fact that the first

dose of OKT3 was given immediately postoperative at the time the patiens were still on the ventilator, while isoprenaline and dopamine were administered continuously.[15-19] Moreover, special care was taken to administer fluids in order to correct the drop of arterial blood pressure and right sided filling-pressures resulting from the decrease in systemic arterial and venous vascular resistance.

Bacterial and viral infections occurred frequently and were associated with significant morbidity. No difference in the incidence of bacterial and viral infections was observed between the ALG and OKT3 groups despite the more selective action of OKT3. In earlier reports there is no agreement about a difference in the incidence and nature of infections after monoclonal and polyclonal antibodies.[8,9,11] However, comparison of the numbers of infections in patients who received additional anti-T-cell therapy with those in patients in whom the induction course was the only antibody therapy revealed that more bacterial as well as viral infections occurred in the patients who received additional antibodies. The difference was not significant.

Malignancy was the cause of death in one patient and appeared to have been treated effectively in two patients. The duration of follow-up is too short to appreciate the final effect of therapy. Although more malignancies occurred in the prophylactic OKT3 group, this difference was not significant. A longer follow-up will be necessary to confirm our earlier findings, in a larger group of patients, that malignancy is not associated with one specific antibody but with the total immunosuppressive load.[20]

The data from this randomized trial indicate that polyclonal and monoclonal antibodies are equally effective for rejection prophylaxis after cardiac transplantation. OKT3 induction therapy may be preferred because of a lack of important side-effects. However, the fact that a shorter course of ALG (the scheduled course was discontinued early because of side-effects in the majority of patients) induces a similar freedom from rejection with subsequently similar incidences of the major complications of immuno-suppressive therapy may be in favour of ALG.

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PART III

VASCULAR DISEASE IN THE CARDIAC ALLOGRAFT

INTRODUCTION

Dempsters call "to continue experimental work in heart transplantation in a relentless way" was as applicable to the problem of coronary artery disease of the cardiac allograft in 1968 as it is in 1993.[1] This accelerated type of coronary vascular disease is dominated by concentric intimal hyperplasia (Fig. 1) and affects not only the entire lenght of the major epicardial branches but also the intramyocardial branches. The early call for research was responded by Bos and Penn, who studied the development of coronary artery disease in the transplanted canine heart at the Thoraxcenter in the 1970s, and by many other investigators.[2-6] They demonstrated that graft vascular disease occurred in all cardiac allografts irrespective of the administration of immunosuppressive therapy. Initially these findings seemed contradicted by reports on vascular disease in human heart recipients.[7-10] However, subsequent postmortem studies of allografts, quantitative analysis of angiograms and intravascular ultrasound imaging revealed that the initial reports underestimated the occurrence of coronary artery disease in human heart transplant recipients (Chapter VI).[11-13] Graft vascular disease is now reported to be a major cause of medium-term morbidity and mortality after cardiac transplantation[14-17] although it is still unclear to which extent this disease limits the long-term prognosis as data of recipients surviving for more than 7 years are limited.[15]

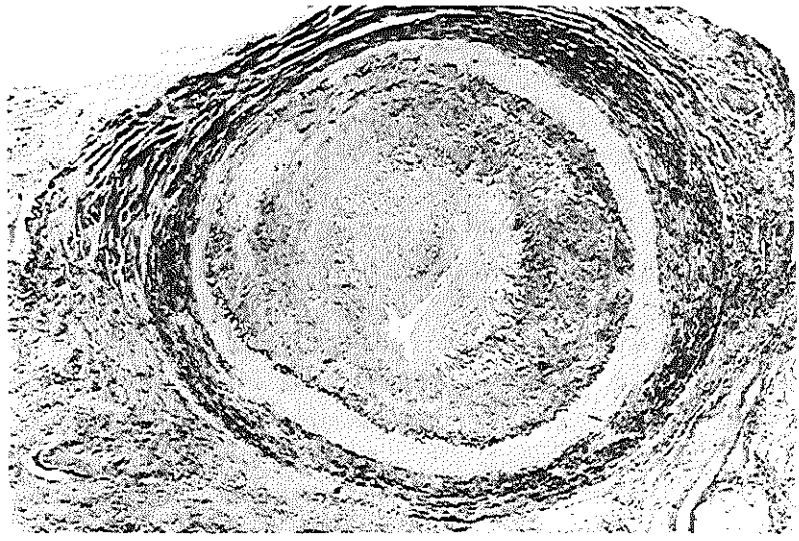

Fig. 1: Transverse section of an epicardial artery of a heart transplant recipient who died from coronary artery disease, 43 months after transplantation. Note the extensive hyperplasia of the intimal layer resulting in near total occlusion of the lumen.(Elastica von Gieson; x 160).

After the early experimental work, clinical research on cardiac graft vascular disease has been continued in the Rotterdam Heart Transplant Program. Initially the development of coronary artery disease was studied by visual assessment of annual coronary arteriography (Chapter VII - Figs. 2 and 3) while a systematic follow-up study was initiated using quantitative analysis of coronary angiography and coronary flow reserve (Chapter VIII - Fig. 3). In our series morbidity and mortality caused by coronary artery disease were limited. Particularly mortality from coronary artery disease in our recipients seems lower than reported by other centers: 28% of deaths after the first year compared with 33% to 68% in other series.[15,16,18]
A comparison of the incidence of graft vascular disease between our recipients and patients transplanted in other centers is hampered by the different criteria used for the diagnosis of cardiac allograft vascular disease.[11-13,19,20]

Careful review of the angiograms of 119 patients revealed that patients at high risk for the development of clinically significant coronary artery disease within the first 4 years after transplantation can be identified from the first year angiogram (Chapter VII). Thus annual angiography appeared not necessary in 85% of the patients. Quantitative analysis of serial coronary arteriograms of our heart transplant recipients confirmed that the changes in coronary artery luminal diameter are insignificant in the 2nd, 4th and 5th years while larger changes occur in the 1st and 3rd years after transplantation (Chapter VIII, study supported by the Netherlands Heart Foundation).[21] For the investigation of the etiology of graft vascular disease future research will be directed to the events occurring in the first months after implantation of the graft. Accordingly a specific line of experiments (supported by the Netherlands Heart Foundation) has been initiated by the Laboratory of Internal Medicine I in an attempt to unravel the etiology of graft vascular disease. We have demonstrated lysis of donor heart endothelial cells by graft infiltrating cells, cultured and propagated from endomyocardial biopsies taken in our patients.[22] Libby recently developed the hypothesis that a localized chronic cell-mediated immune response may stimulate cytokine driven smooth muscle cell proliferation. Thus we will investigate the relation of lysis of endothelial cells with the development of coronary artery disease as lysis of cells may be the trigger for the response which results in smooth muscle cell proliferation.[23]

In order to learn how we may intervene in graft vascular disease continuation of coronary angiography in our transplant recipients seems justified. Visual and quantitative analysis of the angiograms, application of intravascular ultrasound and measurements of coronary flow reserve may help to assess the value of experimental approaches to treatment of the disease such as the administration of vasodilating drugs or drugs that block smooth muscle

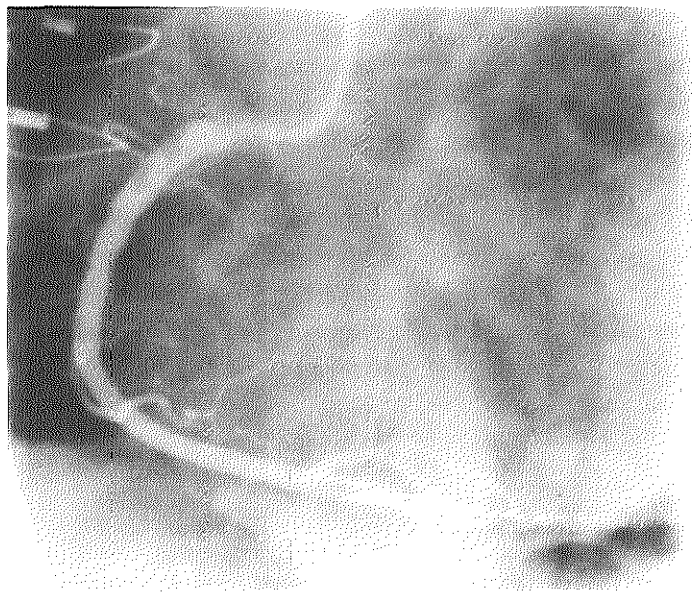

Fig. 2: Angiogram of the right coronary artery of a male cardiac allograft recipients, 12 months after transplantation. Note the slight wall irregularities.

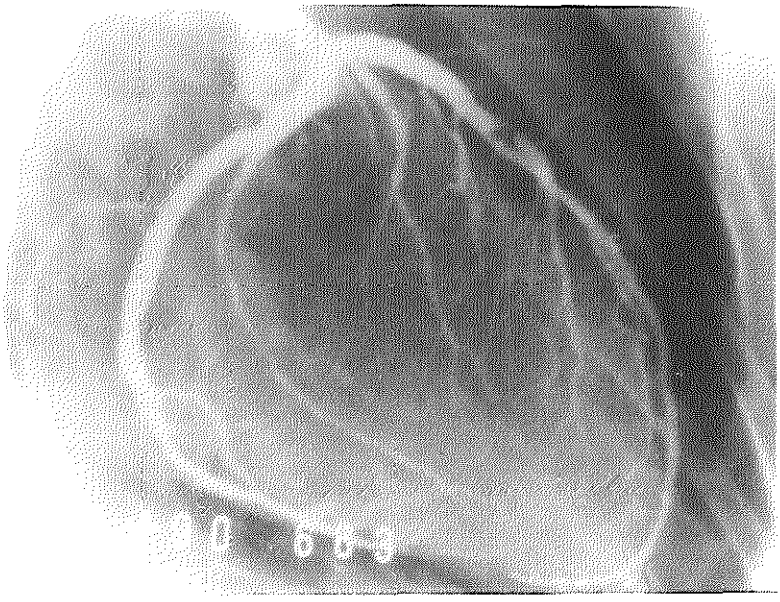

Fig. 3: Angiogram of the left coronary artery of a 37 year old female cardiac allograft recipient, 48 months after transplantation (donor age was 22 years at the time of transplantation). The coronary artery is diffusely affected and there is severe narrowing of the left anterior descending artery. The latter stenosis was successfully treated by balloon angioplasty.

cell proliferation (e.g heparin) or the somatostatin analog angiopeptin.[24-26] In addition, the value of interventions which are "established" in non-transplant coronary artery disease, such as percutaneous transluminal coronary angioplasty (PTCA) or atherectomy have to be assessed. We found that segmental myocardial ischemia disappeared after PTCA of localized lesions in two of our patients (MIBI perfusion scintigraphy) and others have shown that PTCA is feasible with complication rates comparable to angioplasty in non-transplant patients.[27,28] However, whether percutaneous interventions prolong patient survival remains to be determined. Because the number of suitable candidates for such procedures per center will be limited multicenter trials have to be initiated.

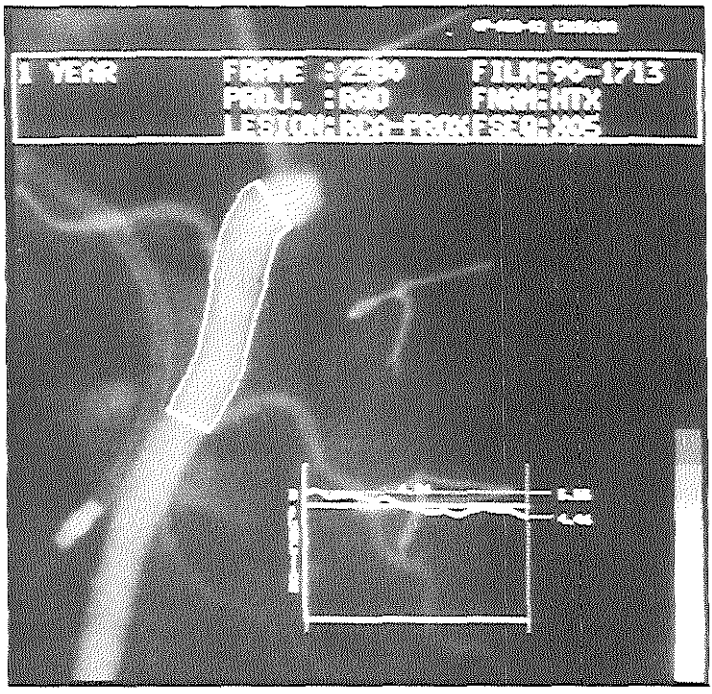

Fig. 4: Quantitative analysis of the angiogram of a cardiac allograft recipient, 12 months after transplantation. A single frame angiogram of a proximal portion of the right coronary artery with superimposition of the contours, detected automatically (CAAS system) is shown. Beneath this the diameter function of the detected contours is presented.

Detailed studies will have to be performed using atherectomy, instead of balloon dilatation because this technique offers the opportunity to analyze specific cell types involved in the disease process and allows the propagation of cell cultures by which the hyperplastic vascular response may be studied. The latter could also be a target of future research in the Thoraxcenter as experience has been gained already in the field of the "response to injury" in coronary arteries of non-transplanted patients who underwent balloon dilatation or stent implantation and in one transplanted patient.[29-32]

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CHAPTER VI

CHRONIC HEART GRAFT REJECTION IN THE CLINICAL SETTING

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In: Organ Transplantation, Paul LC, Solez K eds. Marcel Dekker, Inc. New York 1992, pages 187-195

INTRODUCTION

The long-term survival of heart transplant recipients is mainly limited by the development of a diffuse occlusive form of coronary artery disease, commonly referred to as "chronic rejection". Contrary to the progress made in the detection, prevention, and treatment of acute rejection episodes and of infectious complications after heart transplantation, the knowledge about etiology, pathogenesis, and thus prevention of transplant coronary artery disease is preciously little. Until recently it extended no further than weak associations between the occurrence of this disease and traditional risk factors for coronary atherosclerosis,[1-4] incidence of acute rejection,[3-5] presence of anti-HLA antibodies,[1,6] and CMV disease.[7,8] Even the prevalence of chronic rejection after heart transplantation is largely unknown as there are no uniform criteria in judging coronary arteriographic data. Moreover, underestimation of the process occurs when arteriographic data are compared to histologic findings.[9] Finally, no consensus exists on the clinical relevance of chronic rejection as we are still not aware of the proportion of patients with impaired cardiac function or of the number of cardiac deaths, including the need for retransplantation, due to chronic rejection.

This chapter summarizes the clinical data on the extent of the problem and its clinical relevance as well as on the etiology and pathology as far as these data were available at the time of the writing of this chapter (March 1990).

Clinical presentation and diagnosis

Angina pectoris, a very sensitive marker for hemodynamically significant coronary obstruction is absent in patients with denervated hearts. Therefore, the clinical picture is determined by other sequelae of coronary artery obstruction or occlusion. Myocardial ischemia and infarction may evoke arrhythmias that are noticed by the patient and demonstrated on the electrocardiogram (ECG) or during continuous ECG monitoring. ST-segment changes or the development of new Q waves may be observed on the ECG during routine follow up. Mitral regurgitation caused by ischemia or rupture of the papillary muscles or by dilatation of the ventricular cavity can be detected by physical examination and by echo-Doppler techniques. Enlargement of the heart may be noticed on the chest x-ray when ventricular function decreases after one large or multiple smaller myocardial infarctions. Echocardiography or radionuclide angiography will demonstrate more specifically dilatation of

the ventricles and wall motion abnormalities even before classical symptoms and signs of heart failure arise. Myocardial perfusion scintigraphy may be helpfull to detect ischemia, but can give false positive as well as false negative results. A false positive diagnosis may be the result of ischemia due to transient vasculitis during acute rejection episodes, while persisting perfusion defects also can be caused by scar tissue after graft rejection. On the other hand, perfusion scintigraphy may not be sensitive enough to detect the sequelae of lesions that are diffusely distributed along large epicardial, medium and small-sized arteries.[10,11]

Qualitative evaluation of serial angiography can demonstrate anatomical changes in the branches of the coronary artery system, but compared to pathological anatomical examination, this method is quite insensitive.[9] In contrast, quantitative assessment of coronary arteriographic findings can show gradual decrease in luminal diameters over time while "eyeball" judgment of the coronary arteriogram may reveal no abnormalities.[12-14] In 1988 the Stanford group reported a comprehensive description of coronary arteriographic findings in heart recipients.[15] Gao et al. distinguished three categories of angiographic lesions: type A: discrete or tubular stenoses in the proximal, middle, or distal segment branches; type B: diffuse concentric narrowing with onset in mid to distal arteries (type B1: proximal vessel maintaining normal diameter with abrupt onset of distal concentric narrowing and obliteration; type B2: gradual transition from normal proximal vessel with gradually increasing concentric narrowing distally); type C: narrowed irregular vessels with occluded side branches. Types B1, B2 and C appeared mainly in the secondary (major branches of primary epicardial coronary vessels) and tertiary graft vessels (small side branches of both primary and secondary vessels). Type A lesions were sporadically seen in the primary vessels, which is in contrast to the findings in nontransplanted patients, who showed type A lesions only.

Pathological findings

Between Lower's description of coronary artery changes in long-surviving canine heart transplant recipients in 1968 and the elaborate report on coronary artery morphological features by Johnson et al. in 1989, the histological pattern of transplant coronary artery disease has been the subject of many publications.[9,16-26] There are two ways to classify allografts in which coronary artery changes have developed: in a localization-dependent and in a time-dependent way. Johnson et al. distinguished two patterns of localization of the vascular changes confined to either the proximal regions of the

epicardial arteries, or the entire coronary system. The former lesions are confined to the proximal and mid-regions of the epicardial arteries and consist of intimal thickening secondary to smooth muscle cell proliferation and accumulation of collagen and ground substance. This pattern can be observed as early as 2 weeks after transplantation and develops via an intermediate form of fatty lesion with lipid-laden mononuclear cells to the ultimate lesion that closely resembles the naturally occurring, often eccentric, coronary atherosclerotic lesion. The final atherosclerotic lesions were observed after the first posttransplant year only, while the intermediate forms were always diagnosed within a follow-up of 5 years.[9]

In the allografts in which the entire coronary system was affected, Johnson et al. distinguished an early form consisting of necrotizing vasculitis and a late form of diffuse fibrous intima thickening with or without atheromatous plaques. Necrotizing vasculitis was associated with acute rejection and showed histologically media necrosis, endothelial denudation, and transmural infiltration by lymphocytes and plasma cells. Others, using immunofluorescence, identified "vascular rejection", characterized by deposition of immunoglobulins and complement factors, in which lymphoid cellular infiltrates were absent, and "mixed rejection", with components of both cellular and vascular rejection.[9,16,17,21,26,27] Three reports mention decreased survival rates in patients showing vascular rejection in endomyocardial biopsies.[16,26,27] Johnson's late form of diffuse coronary artery disease, occurring a mean of 56 months after transplantation, in large and small epicardial and intramyocardial arteries consisted of diffuse fibrous intimal thickening in combination in most cases with atheromatous plaques. Based on the combination of their pathologic observations and causes of death, Johnson et al. concluded that patients with diffuse disease are at higher risk for myocardial infarction, death, or retransplantation than patients with localized disease.

Etiology

Gao et al. reported in 1987 a 33% prevalence of transplant coronary artery disease in a group of 132 cardiac transplant recipients surviving at least 1 year.[2] The only two variables that were statistically different between the 44 recipients with coronary changes and the 88 without these changes were donor age (23 vs 21 years, $p < 0.05$) and plasma triglycerides levels (223 vs 170 mg/dl, $p = 0.07$). Whether these differences in age and triglyceride levels, (large standard deviations) are clinically relevant is very doubtful since these findings have not been confirmed in larger studies.

Narrod et al. observed a significantly higher incidence of diabetes mellitus in patients who survived for more than 1 year and had coronary vascular changes compared with patients without coronary artery disease.[3] However, data on larger groups and longer follow-up periods of diabetic cardiac transplant recipients are needed for more conclusive statements.
As early as 1983, Hess et al. described 11 patients with hyperlipidemia and posttransplant coronary sclerosis, who were longitudinally followed for the presence of B cell antibodies. In the 6 patients who developed these antibodies, coronary artery disease appeared to be severe, as all six died within 8-30 months after transplantation, five due to myocardial infarction and one from rejection and infection. The remaining five patients without B-cell antibodies developed coronary disease at a later stage and one of those died from myocardial infarction.[1]

The Columbia University group in New York drew attention to a correlation between humoral immune response in the first 6 postoperative months and long-term patient survival.[6,28] The 76 of 118 patients who showed anti-lymphocyte antibodies against a panel of 70 cells had a 81%, 70%, and 53% actuarial survival rate at 1, 3 and 5 years, respectively. This was significantly lower than the survival rates in the 42 patients without antibodies, who showed actuarial survival rates of 93%, 90% and 90%, respectively. However, evidence for graft atherosclerosis was found only in 12 of 76 patients with and in 1 of 42 patients without anti-lymphocyte antibodies. Moreover, graft atherosclerosis was the cause of death in 4 of 37 nonsurviving antibody-producing patients. These data suggest that there is no correlation between this humoral immune response and clinically relevant coronary artery sclerosis.

Correlations between the total number of acute rejection episodes or the number of rejection episodes after the first year in particular and the prevalence of coronary artery changes have been noted by some investigators, but these observations are not confirmed by others.[3,5] The assumption that patients who needed transplantation because of end-stage ischemic heart disease are at higher risk for transplant coronary artery disease than patients with cardiomyopathy or valvular heart disease also seemed to be incorrect. On the contrary, Olivary et al. reported a trend to higher incidence of coronary changes in patients in whom the underlying heart disease was cardiomyopathy.[29] Again, this could not be confirmed by others. Until now, no association has been found between smoking habits, hypertension, ischemic time of the donor heart, or immunosuppressive regimen and the development of transplant coronary artery disease. Recently, several groups demonstrated

frequent and severe graft atherosclerosis and high mortality rates in patients with Cytomegalo virus infection.[7,8,30]

Grattan et al. showed that 9 of 91 patients with Cytomegalo virus (CMV) infection died and another two needed retransplantation because of transplant coronary artery disease, whereas coronary artery disease was the cause of death in four and the reason for retransplantation in anonther four patients in the group of 210 patients without CMV infection.[8] Cameron et al. found a relative risk 4.6 of developing coronary vascular changes for CMV infection in a study of 83 1-year survivors, of whom 16 developed coronary artery disease.[30] McDonald et al. reported the occurrence of CMV infection in 10 of 16 patients with and in 22 of 86 patients without coronary disease.[7] As CMV disease may result from anti-rejection therapy and coronary artery disease may be associated with the incidence of acute rejection, a causal relationship between this events is difficult to establish.

In the first 80 consecutive patients who underwent heart transplantation in our center since the introduction of prophylactic CMV hyperimmunoglobulin administration in CMV seronegative recipients, we did not observe a relation between CMV disease, IgM antibody titer rise or CMV virus replication and the development of transplant coronary artery disease.

Treatment

The diffuse nature of transplant coronary artery disease makes retransplantation the only therapeutic option in most patients with ischemia or heart failure due to coronary obstruction. Only in cases with localized lesions in the proximal segments of the large epicardial arteries can dilatation of these lesions be attempted by percutaneous techniques, which may result in a temporary solution of the problem.[35] It has to be determined whether other interventional techniques, such as atherectomy, will be of any use.

Extent of the problem and its clinical relevance

While the number of cardiac transplants performed worldwide is approaching 15.000, the total number of patients included in the reports on coronary artery changes after transplantation in 12 centers is less than 1400.[1-3,5,6,12,14,20,22,23,29,31-33] As far as can be deduced from the reports, there seems to be no difference in the incidence of transplant coronary artery disease

between different immunosuppressive regimens consisting of azathioprine and prednisone, cyclosporine and prednisone, or triple therapy. However, criteria used for detection of transplant coronary artery disease by qualitative angiography (i.e., eyeball judgment by experienced angiographers), differ widely and it is often not clear whether changes of the small intramyocardial branches are included in the assessments. Emerging data about quantitative assessment of coronary arteriographic findings are promising both for early detection of the disease as for follow-up purposes.[12,14] Using this technique, the absolute decrease in luminal diameter can be measured and changes that cannot be observed by qualitative grading can be detected. Nevertheless, histopathological examination of the coronary arteries of cardiac transplants from recipients who died from various causes has revealed a considerably greater percentage of patients with vascular changes than expected from coronary arteriography.[6,11,20] Taking these limitations into account, we may expect to find 2-14%, 15-33%, 26-40%, and 42-60% of grafts with coronary artery changes after 1, 2, 3 and 5 years, respectively, using qualitative angiography. Using quantitative angiography, Gao et al. found in 10 of 25 patients a significant decrease in luminal diameters between 1 and 12 months postoperatively and O'Neill and collaborators observed a decrease in diameters in 16 of 20 patients between 12 and 24 months.[12,14] Annual coronary arteriography or autopsy in the 1-year survivors of the first 89 patients who underwent orthotopic heart transplantation in the Thoraxcenter in Rotterdam showed an actuarial incidence of coronary vascular changes in 25%, 28%, 47% and 50% of the patients after, respectively, 1, 2, 3 and 4 years. These percentages were observed using qualitative grading of the coronary vascular changes, which included any irregularity of vessel wall lining.

Trying to deduct the relevance of transplant coronary artery disease from available data is difficult. Assessment of the problem based on mortality and need for retransplantation provided only limited insights. Data on numbers of patients with decreased myocardial function as a result of ischemia or infarction, or with impaired exercise capacity, are lacking. From the annual reports of The International Society for Heart Transplantation, which show actuarial survival rates of 78%, 74%, and 73% after 1, 5 and 10 years respectively, it is hard to deduce which fraction of patients is dying from the sequelae of transplant coronary artery disease because no differentiation has been made between the causes of cardiac death occurring after 1 month.[34] Table 1 shows that the reported incidence of death or retransplantation because of transplant coronary artery disease is approximately 3-5%. We have to take into account, however, that this applies to only the first few years after transplantation, as only limited data on survivors beyond the first few years are

available. To establish the true clinical relevance of chronic rejection, we need more detailed follow-up with the emphasis on coronary angiography findings and left ventricular function parameters.

Table 1. Number of patients with failure of the cardiac graft due to chronic rejection

Author	Ref.	*n*	Medication	Follow-up (years)	+ / re Tx
English	33	129	-	0-7	3 / 2
Gallino	31	56	-	1-2	1 / 1
O'Neill	12	156	CsA/pred Csa/pred/AZA	0-7	4
Narrod	3	173	CsA/pred/AZA	-	4
Gao	4	202	-	-	/ 19
Petrossian	28	123	CsA/pred CsA/pred/AZA	0-7	4
Olivari	29	74	CsA/pred/AZA	0-5	2 / 1

Ref: reference number; n: number of patients; +: deaths; re-Tx: re-transplantation

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CHAPTER VII

CORONARY ARTERY DISEASE AFTER HEART TRANSPLANTATION: TIMING OF CORONARY ARTERIOGRAPHY.

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In: Journal of Heart and Lung Transplantation 1993; 12: 89-99

SUMMARY

The increasing numbers of long-term survivors after heart transplantation make yearly coronary arteriography, used by most centers to study the development of transplant coronary artery disease, less practical. Therefore the prevalence and clinical relevance of coronary artery disease in 119 one-year survivors of heart transplantation were studied. Visual analysis revealed two main patterns of vascular changes: abnormalities of the epicardial vessels and their major branches and abnormalities of the tertiary branches. The prevalence of all abnormalities in the coronary vascular tree increased from 34% after one year to 79% after 5 years. The prevalence of anatomical significant lesions (more than 50% stenosis in the epicardial branches or abrupt ending/proximal occlusion of tertiary branches) was only 11% after 5 years. During follow-up of 25 to 87 (median, 43) months, no significant coronary artery disease developed in the 101 patients who showed normal epicardial vessels or abnormal tertiary branches only at their first year angiography and none of the patients died from ischemic heart disease. Of the 18 patients with abnormal epicardial vessels, three patients died of ischemic heart disease; one of these patients was treated with atherectomy and is alive at the moment of this report, and two patients showed progression of discrete lesions without evidence of ischemia until now. Based on these findings, a schedule for timing of angiography was developed depending on the first-year coronary findings.

INTRODUCTION

Short term survival after heart transplantation is excellent, because of current reliable methods for prevention, detection and treatment of acute rejection and infection. Long-term survival, however, is less satisfactory, in the order of 40% to 60% at 10 years.[1] Accellerated coronary artery disease is reported to be the major limiting factor for medium and long-term survival after heart transplantation. Centers with a long-standing experience in heart transplantation have reported 33% and 68% of all deaths after the first year to be caused by coronary artery disease.[2,3] The prevalence of coronary artery disease, as observed by coronary arteriography at 1 year, ranges from 2% to 18% and after 5 years from 50% to 73%.[4-7] Most centers perform annual coronary arteriography after transplantation to study the development of coronary artery disease and to detect abnormalities that are amenable to interventions, such as balloon angioplasty.[8-11] In patients with extensive coronary artery disease, retransplantation may be the only option to prevent early death.[12]

Ongoing research is highly desirable for the elucidation of the process of transplant coronary artery disease. In view of the increasing numbers of long-term survivors after heart transplantation, however, yearly coronary

arteriography becomes less practical for patient care purposes. Being able to identify patients with a low likelihood of the development of significant coronary artery disease would justify a reduction of the number of arteriograms in such patients.

The current study was undertaken to assess the prevalence and the clinical relevance of coronary artery disease over a 5-year period after heart transplantation. Progression of the different patterns of transplant coronary artery disease was analyzed and related to clinical outcome. Finally, a schedule for timing of angiography was developed based on the findings in individual patients, 1 year after transplantation.

METHODS

Patients

All patients who received a heart transplant between the beginning of the Thoraxcenter Transplant program in June 1984 and May 1, 1990, were entered into this study. Physicians of two other hospitals, the University Hospital Leiden and the Antonius Hospital, Nieuwegein, The Netherlands, participated in patient selection and transplant surgery. Follow-up of all patients occurred at the Thoraxcenter.

Immunosuppression

Maintenance immunosuppression consisted of cyclosporine and low-dose steroids throughout the whole period. Prednisolone was started before the operation (20 mg) and continued after the operation starting with a dose of 60 mg/day decreasing to 10 mg/day within 8 weeks. In the first 32 patients cyclosporine was initiated intravenously before the operation in a dose of 3 mg/kg/day and adjusted to plasma trough levels and renal function thereafter. Early immunosuppressive prophylaxis with anti-T-cell therapy was used in two successive randomized, controlled trials. Seventy-four patients consented to participate in a study comparing the effects on early renal function and incidence of acute rejection of initial therapy with cyclosporine alone with OKT3-prophylaxis (Ortho Pharmaceutical, Raritan, N.J.) followed by cyclosporine.[13] Eight patients were excluded from this study because of preoperative renal insufficiency, and they received horse antithymocyte globulin (H-ATG) (horse antilymphocyte immunoglobulin G2, lymphoglobulin; Institut Merieux, Lyon, France) prophylaxis. In a subsequent study 23 patients

were randomized to 7 day courses of either polyclonal induction therapy with antilymphocyte globulin (H-ATG) or monocolonal therapy with OKT3.[14] Maintenance cyclosporine was started on postoperative day 5 in patients who received induction therapy with OKT3 or H-ATG.

Treatment of acute rejection episodes consisted of pulsed doses of methylprednisolone, 1 gm on 3 consecutive days, rabbit-ATG or OKT3.

Azathioprine was added to the maintenance immunosuppressive regimen only in case of ongoing rejection despite several courses of anti-T-cell therapy. In patients with steroid-induced diabetes mellitus requiring administration of insulin, prednisone was replaced by azathioprine.

Other prophylactic measures

Patients without preformed antilymphocytic antibodies received at least one blood transfusion before transplantation.[15] All patients were treated with antiplatelet agents, dipyridamole 75 mg three times daily, or aspirin 80 mg/day. Cytomegalovirus (CMV)-seronegative recipients received seronegative blood products and were, after the first nine patients, treated for 10 weeks with anti-CMV immunoglobulins (Cytotect; Biotest Pharma GMBH, Frankfurt, Germany) for passive immunization.[16]

CMV infection was defined as any appearance of immunoglobulin M, any isolation of CMV from urine, throat, or blood, and any demonstration of immediate early antigen. CMV disease was diagnosed when an infection was co-existent with two of the following symptoms: fever of more than 38^{0}C for at least 2 consecutive days; gastrointestinal, lung, retina or central nervous system involvement; leukocytopenia (less than 2.5 x 10^9/L); thrombocytopenia (less than 100 x 10^9/L); elevation of serum alanine or aspartate aminotransferases (more than 2x normal).

Detection and grading of acute rejection

Detection and monitoring of acute rejection was performed by endomyocardial biopsy. Biopsy specimens were taken weekly for 6 weeks, bimonthly until 3 months, monthly until 6 months, and every two months until the end of the first year. After the first year, biopsy specimens were taken three times a year on a routine base. Grading of the biopsy specimens was according to Billingham's criteria of none, mild, moderate and severe rejection initially.[17] From December 1990 grading was according to the guidelines of the

International Society for Heart and Lung Transplantation.[18] Treatment was instituted in case of moderate rejection with myocyte necrosis or severe rejection initially and later from grade 3A, respectively.

Anatomical evaluation of coronary artery disease

The occurrence of coronary vascular changes was evaluated by annual coronary arteriography and by histopathological examination in patients who died. Coronary arteriography (CAG) was performed by the femoral approach, using 7F or larger catheters. Standard projections were noted and replicated at subsequent arteriography. Vasodilatation was standardized by the administration of 5 to 10 mg isosorbide-dinitrate sublingually, 5 minutes before angiography. The CAG were analyzed visually and were compared side-by-side (consensus of two observers) with special attention to the presence of minimal coronary vascular changes in all branches of the coronary vascular tree. Two main patterns of changes were distinguished: changes of the large epicardial vessels and their major branches and changes of the tertiary branches (small epicardial side branches and intramyocardial branches). The latter were subdivided in wall irregularities and abrupt ending or proximal occlusion of branches.

Variability of the arteriogram readings

To test the interobserver variability kappa measure of reliability was determined for 20 CAG read by two observers who were experienced in the reading of CAG of heart transplant recipients. In addition kappa was determined for the consensus about these 20 CAG, reached by the two observers at different times.

Evaluation of the consequences of coronary artery disease

Physical examination, electrocardiography, left ventricular ejection fraction (LVEF), and exercise capacity were used to detect the sequelae of coronary artery disease. Electrocardiograms, routinely performed at each visit to the outpatient clinic or at admission to the hospital, were reviewed for the development of new Q waves and conduction disturbances. LVEF, determined from the right anterior oblique view of the ventricular angiogram at the time

of annual angiography, was determined as a parameter of global systolic left ventricular function. Exercise capacity was tested every year, by symptom-limited bicycle ergometry, using load increments of 20 watt/min. Exercise levels are expressed as percentages of the expected normal values for age, gender, and height.

Statistical analysis

Data are expressed as mean ± 1 SD or absolute numbers when appropriate. Comparisons between groups were made by the 95% confidence intervals analysis for the differences between means or proportions or by the chi-square method. Survival analysis was performed with the Kaplan-Meier method.

RESULTS

One hundred thirty-one patients, 115 male and 16 female, underwent heart transplantation at the Thoraxcenter between June 1984 and May 1990. Recipient ages ranged from 12 to 56 years (mean age, 43 years). Cardiomyopathy and ischemic and valvular heart disease were the underlying heart diseases in 64, 64, and 3 patients, respectively. Orthotopic heart transplantation was performed with a median ischemic time of 154 minutes (range, 87 to 280 minutes). Donor ages ranged from 11 to 36 years (mean, 24 years). A gender mismatch occurred between recipient and donor in 50 patients. Early immunosuppressive therapy (first week) consisted of OKT3 in 44 patients and of H-ATG in 22 patients. Sixty-five patients received intravenous cyclosporine initially without early anti-T- cell prophylaxis. Maintenance immunosuppression consisted of cyclosporine and low-dose steroids in 128 patients. Two patients received triple-drug therapy; one patient was treated with the combination cyclosporine and azathioprine without steroids after 6 months. The preoperative CMV- serostatus was negative in 53 recipients and positive in 78 recipients.

Survival

In May 1992, the duration of follow-up ranged from 25 to 87 months (median, 43 months). Graft survival rates were 90% and 84% at 1 and 5 years, with 95% confidence intervals 85% to 95% and 77% to 91%, respectively. Twenty-one patients died. The most frequent cause of death was malignancy (6 patients). Death or graft failure was directly attributable to coronary artery disease, which developed after transplantation, in four patients. One patient died because of coronary artery disease in the donor heart and technical surgical problems (Table 1).

Coronary arteriography

We were able to distinguish three groups of patients: patients with normal CAG, patients with only abnormal tertiary branches, and patients with abnormal epicardial and tertiary branches. The prevalence of abnormalities in all coronary branches increased from 34% after 1 year to 79% after 5 years (Table 2). Nevertheless, the number of presumed anatomical significant abnormalities (more than 50% lesions in the epicardial branches or abrupt ending/proximal occlusion of tertiary branches) was low. At 1 year after transplantation there were no anatomical significant lesions in the primary and secondary epicardial branches. The arteriogram of one patient showed an abrupt ending of a distal tertiary side branch of the obtuse marginal branch. The findings at 1 year appeared a reliable predictor of death caused by accelerated coronary artery disease and of development of what we arbitrarily defined as *significant disease*. Because of a limited follow-up however, this holds only for the subsequent 4 years as presented.

Seventy-eight patients had normal coronary angiograms at 1 year. Six of these died during follow-up. None of these deaths, however, were attributable to coronary artery disease. Moreover, development of anatomical significant lesions was not seen in any of these patients within the study period. In fact one half of the patients remained completely free from arteriographically visible epicardial disease during the subsequent years (Table 3). CAG of the other half of the patients showed only wall irregularities of the epicardial branches.

Table 1. Cause of death/graft failure in 21 heart transplant recipients.

Time after transplantation.	Cause of death / graft failure.
during the procedure	* Extensive myocardial ischemia due to prolonged procedure (4th thoracotomy), two vessel CAD in donor heart (1 patient)
< 1 month after HTX.	* Right heart failure (1 patient) * Anoxic encephalopathy (1 patient) * Acute, mainly vascular, rejection (3 patients) * Acute tamponnade by aortic suture dehiscence (1 patient)
> 1 and < 12 months.	* Rapidly progressive heartfailure due to diffuse CAD, fibrocellularintimal proliferation of epicardial branches, multiple infarctions (retransplantation in 1 patient) * Acute rejection with vasculitis, sudden death (1 patient) * Malignant lymphoma in combination with ongoing rejection and CMV disease (1 patient) * Non-Hogkin lymphoma (1 patient) * Panencephalitis (cause Toxoplasmosis or CMV?) (1 patient)
> 1 year	* Sudden death with known CAD, thrombus on fibrocelluar intimal proliferation (1 patient, 43 months) * Sudden death; combination of acute rejection with myocyte necrosis and extensisve vasculitis with occlusion of small intramyocardial branches, multiple infarctions (1 patient, 43 months) * Progressive heart failure due to myocardial infarctions (known coronary artery disease) (1 patient, 65 months) * Malignant lymphoma (2 patients, 31 and 60 months) * Plasmacytoma (1 patient, 26 months) * Squamous cell lung carcinoma (1 patient, 46 months) * Unexplained graft failure and renal failure (1 patient, 17 months) * Cerebral hematoma after bicycle accident, clotting disturbances due to hepatic failure caused by alcohol abuse (1 patient, 26 months)

CAD: coronary artery disease. CMV: Cytomegalo virus.

Table 2. Coronary arteriographic findings in 1-year survivors after heart transplantation.

Time (years)	N	Normal (%)	EPIC (%)	TERT (%)	AS (%)
1	119	78 (66)	1 (15)	23 (19)	1 (1)
2	114	57 (50)	2 (25)	29 (25)	1 (1)
3	80	29 (36)	3 (43)	17 (21)	1 (1)
4	51	16 (31)	2 (39)	15 (30)	2 (4)
5	28	6 (21)	1 (57)	6 (21)	3 (11)

EPIC: abnormal primary and secondary epicardial branches; *TERT*: abnormal tertiary branches; *AS*: anatomical significant lesion (> 50% stenosis in epicardial branches or abrupt ending/proximal occlusion of tertiary branches).

The development of clinically relevant lesions was more frequent in those 41 patients with an abnormal first-year arteriogram. In patients with abnormal epicardial branches, three deaths appeared directly attributable to coronary artery disease. In one patient from the same group atherectomy of a discrete stenosis in the proximal circumflex artery has been performed after 49 months, because of ischemia, which was documented on perfusion scintigraphy. Furthermore, three patients had progression from minor wall irregularities to less than 50% diameter stenosis in the circumflex and anterior desending arteries in the first 5 years after transplantation. Myocardial ischemia could not be shown. In the group with abnormal tertiary branches at 1 year no patient died, although in seven patients minor wall irregularities of the epicardial branches developed in the subsequent years. No significant difference was noted in the survival rates at 3 and 5 years between the patients with abnormal epicardial branches and the other patients, 93% and 74% vs 94% and 88%, respectively.

Table 3. Evolution of arteriographic abnormalities in patients with normal CAG at 1-year (group A), abnormal tertiary branches only (group B) or abnormal epicardial branches (group C) (N = 78)

	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
Group A					
Normal	78	54	28	15	5
Tert.	0	13	11	11	4
Epic.	0	7	16	12	10
Total	78	74	55	38	19
Group B					
Epic.	0	5	7	7	3
Total	23	23	23	13	7
Group C					
Signif.	0	0	1	1*	2 (1*)
Total	18	17	12	6	5

Tert: development of abnormalities in tertiary branches; *Epic*: development of abnormalities in epicardial branches; *Signif.* development of anatomical significant lesions. * New case.

The conventional risk factors were not related to the presence or absence of coronary artery disease at 1 year after transplantation (Table 4). In patients with abnormal coronary vessels the donor age was higher than in patients with normal CAG at 1 year (difference = 3 years; 95% confidence intervals of the difference = 2 to 6 years). This was caused by older donors in the patients with abnormal epicardial branches (difference = 5 years; 95%

confidence intervals of the difference = 1 to 9 years). Recipients with abnormal tertiary branches had a higher number of mismatches for the HLA-A locus than those with abnormal epicardial branches (difference = 0.6; 95% confidence intervals of the difference = 0.3 to 1 mismatches, respectively). Other factors appeared not to be associated with coronary artery disease at 1 year, including the number of rejection episodes and CMV infection. Also, no relationship was found between posttransplantion coronary artery disease and ischemic heart disease as pretransplantion diagnosis.

Interobserver kappas for the epicardial branches and the tertiary branches were 0.72 and 0.52, respectively, indicating good and fair agreement. Kappa for the consensus, reached at different times (median time between readings, 11 months) was 0.79 both for the epicardial and the tertiary branches, indicating strong agreement.

Consequences of coronary artery disease

Physical examination

The development of transplant coronary artery disease resulted in clinical symptoms in two patients only. A 31-year-old male recipient experienced rapidly progressive heart failure 6 months after transplantation. LVEF was 23%, and coronary arteriography showed diffuse disease of the large epicardial branches (with occlusion of diagonal and posterolateral branches) and of the small side branches. A retrospective donor-recipient lymphocytic crossmatch proved to be positive. After determination of the HLA-locus to which donor-specific antibodies were directed, retransplantation was performed successfully. The patient is alive and well 5 years after undergoing retransplantation, and his 5-year arteriogram, showed only irregularities of the tertiary branches. Right heart failure developed in a 29-year-old female recipient 60 months after transplantation. Atherectomy of a 75% stenosis in the left anterior descending artery (LAD) had been performed successfully, 1 year before. Her 5-year arteriogram showed, besides a patent proximal LAD, considerable progression of disease with occlusion of the right coronary artery and of several tertiary branches of the left coronary artery. She died of progressive heartfailure 65 months after transplantation.

Table 4. Patient characteristics, 1 year after heart transplantation.

CAG		NORM	ABN	EPIC	TERT
number of patients		78	41	18	23
follow-up (median, months)		47 ± 15	42 ± 16	43 ± 17	41 ± 14
gender (male/female)		71 / 7	33 / 8	15 / 3	18 / 5
recipient age (yrs)		43 ± 11	43 ± 11	42 ± 12	44 ± 10
donor age (yrs)		23 ± 7@/*	26 ± 8@	28 ± 7*	24 ± 8
heart disease					
	CMP (nr)	39	18	6	12
	IHD (nr)	37	22	12	10
	VHD (nr)	2	1	0	1
hypertension (> 150/90)(nr)		57	26	12	16
diabetes mellitus (nr)		4	2	0	2
serum cholesterol (mmol/L)		7.1 ± 1.6	7.3 ± 1.8	7.0 ± 1.5	7.5 ± 2.1
serum triglycerides (mmol/L)		2.4 ± 1.0	2.4 ± 1.1	2.4 ± 1.2	2.5 ± 0.9
cold ischemia time (min)		160 ± 40	158 ± 32	157 ± 42	160 ± 22
rethoracotomy (nr)		13	6	4	2
gender MM donor/recipient		29	16	6	10
race MM donor/recipient		3	0	0	0
MM	HLA - A (mean, nr)	1.3 ± 0.6	1.3 ± 0.6	1.0 ± 0.7#	1.6 ± 0.5#
	HLA - B	1.6 ± 0.6	1.6 ± 0.5	1.5 ± 0.6	1.6 ± 0.5
	HLA - DR	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.7	1.3 ± 0.5
	HLA - A+B	2.8 ± 0.9	2.9 ± 1	2.6 ± 1	3.1 ± 0.9
	HLA - B+DR	3.0 ± 0.9	2.9 ± 0.9	2.9 ± 1	2.7 ± 1
MM	HLA - B+DR >2 (nr)	60	27	13	14
Induction imm.therapy					
	none	40	17	8	9
	OKT3	29	12	5	7
	H-ATG	9	12	5	7
AR episodes < 1 yr (mean, nr)		1.4 ± 1.3	1.5 ± 1.3	1.5 ± 1.3	1.5 ± 1.3
AR episodes total (mean, nr)		1.3 ± 1.3	1.8 ± 1.5	1.9 ± 1.5	1.8 ± 1.6
nr of patients with					
	0 AR	22	10	4	6
	1 AR	23	14	7	7
	2 AR	21	8	3	5
	>2 AR	12	9	4	5
EMB in first year (mean nr)		17 ± 2	17 ± 3	17 ± 2	17 ± 3
EMB + infiltrates (mean indiv. %)		50 ± 17	53 ± 22	50 ± 24	56 ± 18
PRA, current (mean, %)		4 ± 10	5 ± 12	2 ± 3	8 ± 16
PRA, current > 0% (nr)		17	13	4	9
CMV preop serostatus neg. (nr)		36	12	5	7
CMV infection postop (nr)		36	20	9	11
CMV disease postop (nr)		13	6	3	3
use of calcium antagonist (nr)		47	24	8	16

CAG: coronary arteriography; *NORM*: normal CAG; *ABN*: abnormal CAG; *EPIC*: abnormal epicardial branches; *TERT*: abnormal tertiary branches; *CMP*: cardiomyopathy; *IHD*: ischemic heart disease; *VHD*: valvular heart disease; *MM*: mismatch; *AR*: acute rejection episode; *EMB*: endomyocardial biopsy; *CMV*: Cytomegalo virus; *PRA*: panel reactive activity; Induction therapy: early anti-T cell prophylaxis. @, *, # Significant difference, see text for 95% confidence intervals of the differences.

Electrocardiogram

New Q waves on the electrocardiogram were observed in four patients outside the immediate postoperative period. Anteroseptal infarction developed in one patient after dissection of the LAD during coronary arteriography, 4 weeks after transplantation. Furthermore new Q waves were observed in the patient who underwent retransplantation and in the two patients with localized stenoses in the epicardial vessels. Both patients had a perfusion defect by scintigraphy and were treated by atherectomy.

Left ventricular ejection fraction

LVEF was normal (more than 55%) in most patients at every annual check-up (Fig.1). Subnormal values were found in 9, 6, 3, 1 and 1 patients after 1, 2, 3, 4 and 5 years, respectively. No relation could be found between the presence of coronary artery disease and ejection fraction except in the patient who underwent retransplantation after 7 months and in the patient in whom occlusion of the right coronary artery occurred after 60 months. Analysis of other possible risk factors for left ventricular dysfunction revealed that the abnormal LVEF at 1 year was associated with more frequent abnormal findings (mild or moderate rejection) on myocardial biopsies: in patients with LVEF of less than 55% a higher percentage of biopsy specimens taken in the first year had shown infiltrates (Table 5.). Recovery of left ventricular function was observed in eight of nine patients.

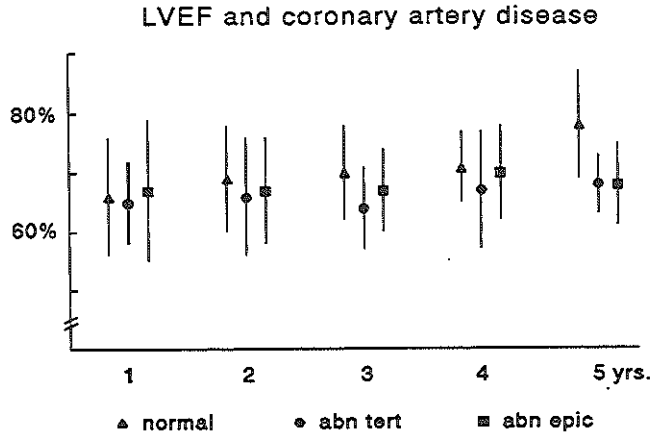

Fig. 1. Left ventricular ejection fraction, determined at annual angiography. Stratification of the patients according to the findings at coronary arteriography. *Abn tert*: abnormal tertiary branches only; *Abn epic*: abnormal epicardial branches as main abnormality.

Table 5. Left ventricular ejection fraction (LVEF) at 1 year: patient characteristics.

LVEF		≥ 55%	< 55%
number of patients		105	9
cold ischemia time (min)		160 ± 38	151 ± 34
MM	HLA - A	1.3 ± 0.6	1.3 ± 0.4
	HLA - B	1.6 ± 0.6	1.4 ± 0.5
	HLA - D	1.4 ± 0.6	1.5 ± 0.5
	HLA - A+B	2.9 ± 1	2.7 ± 0.5
	HLA - B+DR	3 ± 1	2.9 ± 0.8
immunosuppressive induction			
	none	51	5
	OKT3	38	2
	H-ATG	16	2
AR episodes < 1 yr (mean, nr)		1.4 ± 1.3	1.4 ± 1.1
AR episodes total (mean, nr)		1.5 ± 1.4	1.7 ± 1.6
EMB + infiltrates (mean, indiv %)		49 ± 20	## 68 ± 20
hypertension (nr)		76	7
use of calcium antagonist (nr)		63	7

MM: mismatch; *AR*: acute rejection episode; *EMB*: endomyocardial biopsy; *EMB+infiltrates*: mean percentage of biopsies of individual patients showing infiltrates during the first year; *nr*: number; ## Difference = 19%, 95% confidence interval for the difference: 6 to 32.

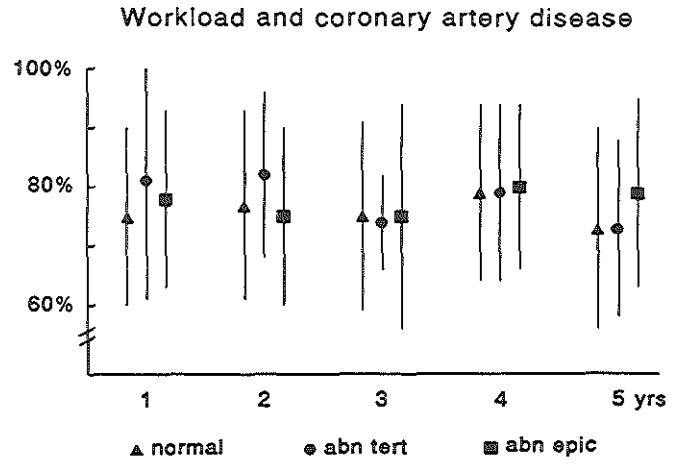

Fig. 2. Maximal workload at bicycle ergometry, assessed at annual checkup visits. Stratification of the patients as in Fig. 1.

Exercise testing

In general, exercise capacity was subnormal in most of the patients. No difference was noted in maximal workload between the patients who showed normal CAG and the patients with the two types of abnormal arteriograms (Fig. 2).

DISCUSSION

The wide variation in the incidence of transplant coronary artery disease (TCAD) according to the reports of individual centers may be caused by different prophylactic and treatment regimens but also may be a mere reflection of different detection methods (arteriography versus autopsy versus intravascular ultrasonography), of different methods for analysis of the arteriograms (qualitative versus quantitative and visual versus automated) or of different criteria when visual analysis of CAG is performed. [4-7,19-29] Because abnormal coronary arteries are found in most patients who die after cardiac transplantation, we applied a very low threshold for establishing the angiographic diagnosis of TCAD. Minimal wall irregularities of the epicardial and of the intramyocardial branches were included as abnormal. Using these criteria the percentage of abnormal CAG increased from 34% to 79% at 1 and 5 years. Still, the percentage of patients with anatomical significant lesions increased only from 1% to 11% in the same time period.

Please note that this "eye-ball" method is subjective and is used in one center only. Moreover the method has been used in a transplantation program with survival rates higher than those reported by most other centers.[1-3] In our hands, however, interobserver variability and variability between the consensus reached at different times indicated good and strong agreement, especially for the epicardial branches. Visual reading, although poor for research purposes, may therefore be accurate enough for clinical management of the heart transplant recipient, at least for the first 5 years. To study factors that influence the early development of TCAD, more accurate quantitative methods will be necessary.[4,27,28]

Neither the cause of TCAD nor the risk factors predisposing for its accelerated course are elucidated although the recent demonstration of a chronic immune reaction to activated graft endothelial cells in donor coronary arteries supports the "response to injury mechanism", which is widely believed to be the basic etiologic factor for the development of TCAD.[30,31] In organ transplantation, endothelial damage is likely to occur during harvesting of the

graft and during graft rejection.[32] In earlier reports a number of risk factors have been associated with TCAD: plasma triglycerides [21], diabetes mellitus [22], donor age [22,29], presence of B-cell antibodies [20] or anti-HLA antibodies [29], the number of acute rejection episodes [22,23] and Cytomegalovirus infection.[33-38] The association of a factor with TCAD found by one group has often not been confirmed by others, however. This discrepancy may be due to the relatively small patient numbers, to different criteria for TCAD, or to differences in patient management.

Anti-HLA antibodies specific for the first donor heart appeared the cause of TCAD in our patient in whom progressive disease rapidly developed, leading to graft failure within 7 months after transplantation. A second donor heart now is free from arteriographically visible coronary artery disease, 5 years after retransplantation, which was performed with avoidance of the specific HLA-locus in the donor heart. This observation raises the question whether low titers of donor specific anti-HLA antibodies in the recipient, not detected by the usual panel, could initiate the humoral response necessary for the primary vascular injury.[29] Furthermore, the development of TCAD appeared to be associated with donor age and HLA mismatch. No relation between TCAD and the presence of ischemic heart disease before transplantation could be demonstrated. Also, no relation was found between TCAD and gender, age, donor/recipient gender mismatch, number of acute rejection episodes, percentage of endomyocardial biopsies with infiltrates, hypertension, use of calcium antagonists, or preoperative reactivity against a panel of lymphocytes. Similarly, we could not confirm the recently reported association of TCAD and Cytomegalovirus (CMV) infection. This may be explained by prophylactic treatment of CMV-seronegative recipients with anti-CMV immunoglobulin, which regimen has shown to protect the CMV seronegative recipient of the heart of a seropositive donor to the same extent as the seropositive recipients with naturally acquired immunity.[16]

Because worldwide 33% to 68% of the deaths in patients surviving heart transplantation for more than 1 year are caused by TCAD, this disease entity is qualified as the major limiting factor for long-term survival. Such figures are derived from individual transplantation programs with the longest experience, with more than 500 (Stanford) or 300 (Papworth) cardiac allograft recipients, and with follow-up periods of 10 years.[2,3] Similarly, the Registry of the International Society for Heart and Lung Transplantation, summarizing the data of more than 16000 cardiac allograft recipients all over the world, reports that more than 40% of deaths after the first year are related to chronic rejection. Uncertain, however, is whether the term *chronic rejection* is always used synonymously with TCAD by the reporting centers.[1]

The finding that TCAD was the cause of death/graft failure in only four of 21 (17%) of our patients has to be judged in the setting of excellent survival rates after cardiac transplantation. One could only hypothesize about the better outcome of our patients because most reports do not contain detailed information about donor/recipient gender or race mismatches, about immunosuppressive regimens (such as cyclosporin levels, targeted leukocyte counts, total dose of anti-T cell therapy), or about which grade of rejection has been treated and which definitions of infection have been used. Differences that might have contributed to our results are the preoperative blood transfusions, the remarkable population homogeneity (only 3 donor/recipient race mismatches) and the use of anti-CMV hyperimmunoglobulin.

In our series both TCAD and malignancy appeared equally important limiting factors for survival after heart transplantation: six deaths were from malignancy. TCAD sequelae of clinical importance were noted in three patients only: myocardial infarction after dissection of the LAD and two lesions amenable for atherectomy. No relation was found between the presence of TCAD and left ventricular function. Impaired left ventricular function at 1 year appeared to be related to persistence of mononuclear infiltrates throughout the first year and recovered in almost all patients in the subsequent years. Exercise capacity did not change significantly during the first years after transplantation and showed no relation to the presence of coronary abnormalities.

Three groups of patients could be distinguished, based on the findings at coronary arteriography after 1 year: patients with completely smooth epicardial and intramyocardial branches, patients with irregular linings of the primary and secondary epicardial branches (in combination with abnormal tertiary branches) and patients with abnormal tertiary branches only. The first-year arteriogram appeared to be predictive of subsequent death and morbidity from TCAD because no death from TCAD was reported in patients with either normal coronary arteries or abnormal tertiary branches. Furthermore, the first year arteriogram was predictive of future events: death from TCAD and development of significant epicardial disease or abrupt ending or proximal occlusion of tertiary branches, which occurred only in patients with abnormal epicardial branches at 1 year. Because the overall mortality after heart transplantation is lower than in most other centers the predictive value of the first-year arteriogram may not apply to other programs.

Because coronary angiography is not without risk (myocardial infarction developed in one of our patients) and the increasing numbers of arteriographies for patient care reasons are a heavy task for the catheterization laboratory, we now schedule, at least during the first 5 years after transplantation, routine CAG according to the findings at the first-year

investigation (Table 6). In the patients without abnormalities and in those with only irregularities of the tertiary branches, without abrupt ending or proximal occlusion, the next arteriogram is delayed until 4 years after transplantation. Arteriography is delayed for 2 years when the first-year CAG shows minor wall irregularities of the epicardial branches only. Yearly arteriography will be recommended when the first-year angiogram shows localized lesions in the epicardial branches. Depending on the findings at subsequent CAG follow up investigations can be planned in a similar fashion. Coronary arteriography for research purposes is performed independently on the mentioned findings.

A proposal that shows some similarity with the current schedule has been developed in Papworth where first-year angiography was omitted and, depending on the findings at a 2-year angiographic study, CAG was repeated at 3 (when abnormal) or at 4 years (when normal) after transplantation.[19]

Because the development of TCAD in the first year after transplantation appears crucial for the course of this disease in the subsequent 4 years, all effort should be put in the elucidation of the factors responsible for the origin of coronary artery disease within the first year after transplantation. In addition to visual analysis of CAG, quantitative analysis of the arteriograms or intravascular ultrasonography may be required for this purpose.[27,28]

Table 6. Thoraxcenter schedule for coronary arteriography (CAG) after heart transplantation.

CAG	Normal EPI or abn TERT only	Abnormal EPI	
		Wall irreg	Local lesion
at 2 years	No	No	YES
at 3 years	No	Yes	YES
at 4 years	YES	Depending on 2nd-year CAG	YES

EPIC: epicardial branches; *abn*: abnormal; *TERT*: tertiary branches.

Coronary artery disease is an important limiting factor for the long-term survival after heart transplantation; but, in our experience, reduction of the risk of malignancy would improve survival at least to the same extent. Comparison of the results in various centers is hampered by the use of different definitions of transplant coronary artery disease. Development of a consensus of criteria for this disease should be encouraged.

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CHAPTER VIII

SHORT AND LONG-TERM QUANTITATIVE ANGIOGRAPHIC FOLLOW-UP AFTER CARDIAC TRANSPLANTATION

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Study supported by a grant from the Netherlands Heart Foundation

In: Quantitative Coronary Angiography in Clinical Practice.
Serruys PW, Foley DP and Feyter de PJ (eds).
Kluwer Academic Publishers, Dordrecht, The Netherlands 1993.

SUMMARY

Survival after cardiac transplantation has improved over the last years with a 1-year survival rate of greater than 80% in most transplant centers.[1] At present, one of the most limiting factors for medium and long-term survival is the process of graft vasculopathy, an accelerated and diffuse form of coronary atherosclerosis.[2] It accounts for approximately 60 % of all retransplantation procedures.[3]

The exact cause of this disease is thought to be immunologic, however direct proof is lacking. A major problem comparing the incidences at individual centers are the different definitions and methods to assess this diffuse vasculopathy. Therefore quantitative coronary angiography is thought to be a more sensitive and objective method for assessment, which offers potential for better understanding the pathophysiology and for investigating the influence of different treatment strategies on this process.

INTRODUCTION

In the beginning of this century the first experimental work on cardiac transplantation was performed by Carrel and Guthrie. They transplanted the heart of one dog into the neck of another dog: the first heterotopic transplantation. The first successful clinical cardiac transplantation was performed by Barnard in 1967. Following this promising experience a large number of transplants were performed throughout the world. However, the immediate results after transplantation did not meet with the expectations, because of acute allograft rejection and infection and consequently only a few centers continued with the development of this technique. During the 1970's indications and contraindications for cardiac transplantation were defined. Treatment of rejection was greatly enhanced by the use of rabbit anti-thymocyte-globulin. The detection and surveillance of rejection were facilitated by the introduction of transvenous right ventricular biopsy and the development of a grading system for the histologic findings.[4-6]

One year survival increased from 22% in 1968 to 65% in 1978.[7] The greatest step forward however, has been made in the early 1980's by the introduction of cyclosporin A for immunosuppression.[8]

As a result of the use of cyclosporin, cardiac transplantation has been developed to a generally accepted treatment for end-stage heart disease. According to the ninth report of the Registry of the International Society for Heart and Lung Transplantation, up to december 1991 over 19,000 heart transplantations have been performed and the one-year survival rate has increased to approximately 80%.[1]

Accelerated Coronary Artery Disease

With the improvement of short term survival, it became clear that the process of accelerated coronary artery disease is one of the important factors limiting the long term survival of cardiac transplant recipients.[2] Due to the lack of innervation of the cardiac allograft, angina pectoris is usually absent, and electrocardiographic signs of myocardial infarction, congestive heart failure or sudden death may be the first signs of graft coronary arteriosclerosis.[9]

The histologic findings of graft coronary arteries after human transplantation were first described by Bieber et al.[10] and confirmed by others.[11-14] The earliest change consists of concentric fibrosis and smooth muscle cell proliferation with collagen accumulation creating diffuse intimal thickening. This is seen as early as one week after transplantation. Subsequently, these lesions may progress to diffuse obliterative lesions creating longitudinal narrowing and distal pruning. The lesions are generally present in the large epicardial vessels as well as in the small intramyocardial branches. Therefore, because of the diffuse nature of the process, standard revascularization techniques such as bypass grafting and percutaneous transluminal coronary angioplasty are of limited value.

To detect the onset and progression of coronary disease in an early phase, coronary angiography is performed annually in most transplant centers. Gao et al.[15] first described the specific angiographic morphology of the lesions found after transplantation by dividing them into 3 categories: type A, discrete or short tubular stenosis in the proximal, middle or distal segments of major coronary arteries or their branches, type B; diffuse concentric luminal narrowing in the middle to distal segment branches; and type C, diffusely narrowed irregular distal branches that are squared of and end abruptly, the latter two groups both unique to the post-transplant patients. Despite this clear categorization, the reported incidences of visually detectable coronary artery disease vary considerably, ranging from 2 to 34% at 1 year, and ranging from 50 to 73% at 6 years after transplantation.[15-23] Thus, visual interpretation of coronary angiography has limitations for both clinical and research purposes: The results of different transplant centers are not comparable, and the influence of different treatment strategies cannot be assessed.

Quantitative coronary angiography

Quantitative coronary angiography has the advantage of being more accurate and reproducible in the assessment of coronary artery disease. De

Feyter et al.[24] discussed the value of quantitative coronary angiography in clinical trials concerning progression or regression of coronary artery disease. A specific tool to assess the progression of **diffuse** coronary artery disease is the mean segment width measured in millimeters. It is also the single measurement to detect both **diffuse** and **focal** atherosclerosis. Therefore mean segment width should be the appropriate measurement to be used in cardiac transplant recipients. The description of progression and regression of allograft coronary artery disease should include 2 parameters: Firstly, a description based on coronary status of an individual patient: **the patient global score**, which is defined as the average of the mean width of all analyzable segments of the coronary tree (including those with lesions) per patient. The patient global score change is defined as the average change in the mean width of the segments (Table 1). Secondly, a description based on all the segments measured in a study: **the segment global score**, which is defined as the mean of the coronary segment widths of all these measured segments. Segment global score change is defined as the average change of all segments (Table 1).

O'Neill et al.[23] were the first to report a significant reduction of coronary luminal diameter, using quantitative coronary angiography in cardiac transplant recipients. Mean coronary diameter of the left main coronary artery decreased from 5.4 ± 0.9 mm at 1 year to 4.7 ± 0.8 mm at 3 years after transplantation in 20 patients having serial coronary angiography. The coronary luminal diameters of the proximal and mid left epicardial artery segments also showed a significant decrease. However, distal epicardial segments did not change significantly. Quantitative analysis was performed by two observers. In this study vessel borders were manually traced in end diastolic frames and measured using digital calipers. The patient global score was not presented. Furthermore no relation was found between these changes and potential risk factors for development of accelerated coronary artery disease.

Stanford University reported the use of quantitative coronary angiography by automated computerized edge detection in a study describing the changes in coronary luminal diameter in the first year after transplantation.[26] In a group of 25 patients mean coronary diameter decreased from 2.44 ± 0.26 mm at an average of 5.1 weeks after transplantation to 2.21 ± 0.34 mm at 1 year follow-up ($p<0.001$). Although absolute changes were less in smaller arteries, there was no significant difference between large (>2.9 mm), medium (2.0-2.9 mm) and small (<2.0 mm) vessels with regard to percentage change (-9.4, -10.9 and -6.4 %, respectively). In this study also no relation with potential risk factors for transplant coronary artery disease could be found. Mills et al.[27] recently reported coronary artery segment

Table 1. Example of the calculation of patient global score and patient global score change in a cardiac transplant recipient.

SEGMENT NUMBER *	BASELINE (mm) †	FOLLOW-UP (mm) ‡	CHANGE (mm)
1	3.75	3.64	-0.11
2	3.65	3.28	-0.37
3	3.29	3.23	-0.06
5	4.00	3.47	-0.53
6	4.44	3.99	-0.45
7	3.19	3.23	0.04
8	2.40	2.28	-0.12
11	2.70	2.57	-0.13
13	2.24	2.13	-0.11
patient global score	3.30 ± 0.74	3.09 ± 0.63	-0.20 ± 0.20

* Segment number according to the American Heart Association Classification [25]
† Mean segment width at baseline coronary angiography
‡ Mean segment width at follow-up coronary angiography

measurements in 18 patients from 1 to 3 years after cardiac transplantation, using cine-videodensitometry. All angiograms were visually interpreted as "normal" by an experienced investigator, using side-by-side projectors. No loss of distal branches was seen. Using quantitative analysis all segments except the proximal left anterior descending segment showed a significant decrease from the first to the third postoperative year (range -0.19 to -0.48 mm). They concluded that graft arteriopathy is ubiquitous in heart transplant recipients, however no new insights on the pathogenesis of graft arteriopathy were given.

The Thoraxcenter Experience

Visual analysis of the coronary angiograms of all patients who underwent a cardiac transplantation between June 1984 and May 1990 at the Thoraxcenter, made as part of their annual follow-up protocol, revealed a prevalence of abnormalities of the epicardial vessels in this patient group

increasing from 34% at one year to 79% after 5 years. A very low threshold for assessment of visual coronary artery disease was used by two observers experienced in the reading of post transplant coronary angiograms. However, the prevalence of anatomical significant lesions (>50% stenosis in the epicardial branches or abrupt ending/proximal occlusion of tertiary branches) was only 1% at one year and 11% after 5 years.[20]

In order to provide a more accurate and objective evaluation of the development of coronary artery disease, a study was initiated at the Thoraxcenter to describe the changes in coronary luminal diameter of the epicardial branches using serial quantitative coronary angiography. Furthermore, these changes were correlated with potential risk factors, as described in the literature.

PATIENTS

All cardiac transplant recipients who underwent coronary angiography, as part of their annual follow-up protocol, between September 1989 and September 1990 were included in this study. Five subgroups could be identified: The first group consisted of 30 patients undergoing early angiography within one month after transplantation. The second, third, fourth and fifth groups consisted of 28, 21, 23 and 9 patients having angiography 1, 2, 3, and 4 years after cardiac transplantation respectively (Table 2). In the subsequent year all patients underwent follow-up coronary angiography, thus achieving serial one year follow-up coronary angiography.

Six patients were excluded from this study: 1 patient died before follow-up angiography, in 2 patients follow-up angiography was not performed because of severe kidney failure, and in 3 patients follow-up angiography was postponed because of either infective disease or rejection.

Early prophylactic immunosuppressive therapy consisted of either polyclonal anti-T cell antibodies (Horse anti-thymocyte globulin, anti-thymocyte IgG2, Lymphoglobulin, Institute Merieux) or monoclonal anti-T cell therapy (OKT3, Ortho Pharmaceutical, Raritan, N.J.).[28] Maintenance immunosuppression consisted of low dose steroids and cyclosporin. Azathioprine was added to this regimen in 16 patients because of recurrent rejection, detected and monitored by endomyocardial biopsies. The histologic findings of these biopsies were graded according to Billinghams criteria[5] until December 1990, and by the guidelines of the International Society for Heart and Lung Transplantation[6] from January 1991. In cases of moderate rejection with definite myocyte necrosis (moderate rejection according to Billingham)

or grade 3A according to latter criteria, additional treatment was instituted, consisting of pulsed high dose steroids and poly- or monoclonal anti-T cell therapy.

In Cytomegalo virus (CMV) seronegative recipients, anti-CMV hyperimmunoglobulin (Cytotect, Pharma GmbH, Dreiech, Germany) was administered during the first 10 weeks after transplantation.[29] CMV infection was defined as any rise in serum IgM, isolation of CMV from urine throat or blood, or evidence of CMV immediate early antigen. CMV disease was defined as infection accompanied with fever >38°C for at least 2 days, and either leukocytopenia (<2.5 x 10^9/l) and thrombocytopenia (<100 x 10^9/l), or symptoms of organ involvement.[29]

In patients, who never received a blood transfusion before transplantation, a transfusion was administered pre-operatively.[30] All patients were treated with antiplatelet agents, consisting of either dipyridamole 75 mg tid or aspirin 80 mg daily. Hypertension was preferably treated with nifedipine.

Quantitative Coronary Angiography

All patients underwent left heart catheterization and selective coronary angiography by the femoral approach. Right heart catheterization with pressure measurements was performed and five endocardial biopsies were obtained, using the percutaneous transjugular approach.

To reduce the influence of dynamic vessel tone, isosorbide-dinitrate (5 mg) was given sublingually before contrast injection. At baseline coronary angiography, standard projections were used and replicated at follow-up.

Off-line quantitative analysis was performed using the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail previously (Fig.).[31,32]

Nine epicardial coronary segments, identified by anatomic landmarks,[25] were selected and analyzed in two orthogonal views avoiding foreshortening. Of the right coronary artery the proximal, mid and distal segment were analyzed, of the left coronary artery the main branch and segments 6, 7, 8, 11 and 13 were chosen for analysis.

The results were expressed in a patient global score and a segment score as described before.

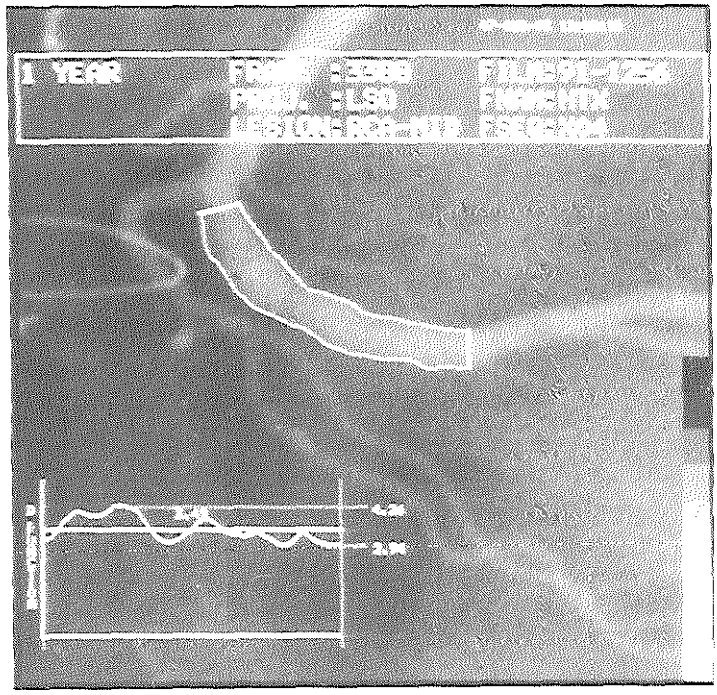

Fig.: Quantitative analysis of the angiogram of a cardiac allograft recipient, 12 months after transplantation. The single frame shows the contours of the mid portion of the right coronary artery (CAAS-automated edge detection system). The diameter function of the detected contours in the left lower corner presents minimal and maximal lumen diameters. In addition the mean segment width of 3.49 mm is shown.

Statistical Analysis

All data are presented as mean ± SD. Statistical analysis was performed using the Wilcoxon Matched-pairs Signed-ranks test. Unpaired *t* tests, one-way analysis of variance and logistic regression were used to compare differences in potential risk factors for accelerated coronary artery disease. Statistical significance was defined as a p value of 0.05 or less.

RESULTS

Clinical Data

The clinical data of the cardiac transplant recipients in the different subgroups are described in Table 2. The number of rejections and Cytomegalo

virus infections was, as expected, higher in the first year after transplantation in comparison with the other periods. There was no significant difference between groups for mean recipient- and donor age, gender mismatch, HLA-A+B or -DR mismatch, total serum cholesterol, triglyceride, high-density lipoprotein cholesterol levels, and the other described risk factors for graft atherosclerosis. The only risk factor we could identify was the presence of coronary artery disease prior to transplantation. In the first subgroup of patients, a significantly larger patient global score change was found in patients with this disease (N=14), than in patients with other indications for transplantation (-0.13 ± 0.17 mm versus 0.03 ± 0.20 mm, $p<0.05$). The changes in minimal luminal diameter were -0.15 ± 0.16 mm and 0.04 ± 0.23 mm ($p=0.01$), respectively.

Quantitative Angiography

In the 5 different subgroups of patients 249, 227, 173, 186 and 75 segments were analyzed respectively. Only one patient in the last subgroup showed a significant narrowing (>50%) of the left anterior descending artery.

Patient global score

The results are outlined in Table 3. The largest decrease in patient global score occurred in the first and third postoperative year. These changes did not prove to be significant.

Segment global score

In Table 4 the results of segment global score calculations are described. It can be appreciated that, according to these calculations, the largest changes also occurred in the first and third year after transplantation. This decrease was 0.05 and 0.07 mm respectively, and proved to be statistically significant.

Table 2. Clinical data

	group 0-1yr	*group 1-2yr*	*group 2-3yr*	*group 3-4yr*	*group 4-5yr*
Number of patients	30	28	21	23	9
Number of segments	249	227	173	186	75
Immunosuppressive regimen *					
- Cyclosporine plus prednisone (N)	25	25	17	20	8
- Triple therapy (N)	5	3	4	3	1
Recipient age (yr) †	45 ± 12	45 ± 11	47 ± 7	44 ± 10	36 ± 13
Donor age (yr)	26 ± 8	25 ± 8	23 ± 7	24 ± 8	21 ± 8
Gender (F/M)	2 / 28	4 / 24	2 / 19	2 / 12	1 / 8
Gender mismatch (pts)	9	9	7	10	5
HLA-mismatch (nrs)					
A	1.4 ± 0.6	1.3 ± 0.7	1.3 ± 0.6	1.3 ± 0.6	1.2 ± 0.7
B	1.6 ± 0.5	1.6 ± 0.6	1.5 ± 0.5	1.5 ± 0.7	1.7 ± 0.5
DR	1.5 ± 0.7	1.4 ± 0.7	1.5 ± 0.6	1.2 ± 0.5	1.3 ± 0.9
Rejection episodes between angiography median (range)	1 (0-5)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Cholesterol (mmol/l) ‡	7.4 ± 1.7	7.0 ± 1.6	7.9 ± 1.5	7.3 ± 1.5	7.6 ± 1.2
Triglyceride (mmol/l) ‡	2.3 ± 0.8	2.2 ± 0.8	2.4 ± 0.9	2.4 ± 1.3	2.5 ± 1.0
HDL-cholesterol (mmol/l)	1.5 ± 0.5	1.3 ± 0.4	1.5 ± 0.5	1.3 ± 0.4	1.5 ± 0.3
Donor heart ischemia time (minutes)	154 ± 31	169 ± 38	151 ± 38	159 ± 45	190 ± 44
Smoking (Yes/No) *	7 / 23	6 / 22	1 / 20	5 / 18	2 / 6
Diabetes (pts) *	2	1	1	1	2
CMV infection (pts) *	12	3	3	3	1
CMV disease (pts) *	7	0	0	0	0
Use of nifedipine (pts) §	20	18	14	16	5

F=female; M=male; CMV=Cytomegalo virus; HDL=High Density Lipoprotein; * = during the follow-up period; † = at the time of the transplantation; ‡ = mean during the follow-up period; § = at follow-up catheterization;

Table 3. Patient global score

	number of patients	patient global score (mm)		patient global score change		
		baseline	follow-up	mm	%	
group 0-1yr	30	3.39 ± 0.34	3.35 ± 0.34	-0.05	-1.5	NS
group 1-2yr	28	3.18 ± 0.37	3.19 ± 0.39	0.01	0.3	NS
group 2-3yr	21	3.34 ± 0.40	3.26 ± 0.38	-0.08	-2.3	NS
group 3-4yr	23	3.17 ± 0.27	3.16 ± 0.41	-0.01	-0.3	NS
group 4-5yr	9	3.23 ± 0.51	3.23 ± 0.46	0.00	0.0	NS

Table 4. Segment global score

	number of segments	segment global score (mm)		segment global score change	
		baseline	follow-up	mm	
group 0-1yr	249	3.40 ± 0.82	3.36 ± 0.83	-0.05	p=0.007
group 1-2yr	227	3.17 ± 0.85	3.17 ± 0.82	0.00	NS
group 2-3yr	173	3.35 ± 0.87	3.28 ± 0.81	-0.07	p=0.005
group 3-4yr	186	3.18 ± 0.78	3.19 ± 0.83	0.00	NS
group 4-5yr	75	3.23 ± 0.90	3.24 ± 0.86	0.00	NS

DISCUSSION

In view of the described studies, the changes in this group of patients were small, both for patient global score and segment global score, ranging from -0.08 - -0.01 mm in the different yearly postoperative periods.

The exact cause of accelerated coronary artery disease is not yet eludicated. However, it is widely believed that immune mediated phenomena play an important role in the pathogenesis of this disease, because of it's diffuse nature, involving the entire length of the coronary artery tree with sparing of the native vessels, and it's development in patients of all ages. The "response to injury mechanism", due to damage to the endothelium during graft rejection, is widely believed to be the most basic etiologic factor, although both in this study as in others this hypothesis could not be confirmed.[19,20,26,33,34] A number of potential additional risk factors such as the presence of Cytomegalo virus infection[35-37], the presence of B-cell antibodies[38]

or anti-HLA antibodies,[39] the immunosuppressive regimen,[40] plasma triglycerides,[41] diabetes mellitus,[42] donor age[37,39,42] could also not be confirmed by other studies. Please note that most of these studies are based on visual, and thus subjective, interpretation of coronary angiography. Our study shows that quantitative coronary angiography offers potential for a better and more objective description of the changes in the coronary artery tree and for investigating the factors that influence the development of the disease.

One of the first studies comparing the effect of different treatment strategies using an objective edge detection system was described recently in a report of Stanford.[43] In a placebo controlled study in 106 patients, the beneficial effect of the calcium-antagonist diltiazem to inhibit early post-transplant coronary luminal narrowing was described. In the 57 patients, who received placebo, segment global score decreased significantly from 2.41 ± 0.27 mm at baseline (median, 19 days after transplantation) to 2.22 ± 0.26 mm at 2 year follow-up. In the same period, segment global score of the patients who received the calcium-antagonist, changed from 2.32 ± 0.22 mm to 2.36 ± 0.22 mm, a not statistically significant change. In our study most transplant recipients also received a calcium-antagonist (nifedipine), but no relation was found observed between the use of nifedipine and the development of post transplant coronary artery disease.

An increase in coronary artery dimension was first reported by Von Scheidt et al.[44] in 5 out of a group of 68 patients after transplantation (7.3%). No causal relation with clinical data could be determined. However, this process was assessed by visual interpretation of coronary angiography and has not been confirmed by quantitative methods.

Conclusion

The coronary luminal diameter, expressed in a patient global score and a segmental score, decreased in the first and third year after cardiac transplantation. However, we observed only minimal changes in comparison with other post transplant studies.[23,26,27] Furthermore, these changes seemed to be clinically insignificant. Pre-transplant coronary artery disease of the recipient was identified as a risk factor for the development of transplant coronary atherosclerosis in the first postoperative year. No relation was found with other described potential risk factors.

To overcome the differences in definition of accelerated coronary artery disease, serial quantitative coronary angiography, if used in larger studies, can be an objective method to assess the incidence of this disease. Therefore, it

offers potential for better understanding the pathophysiology of accelerated coronary artery disease, and for investigating the influence of different treatment protocols on this process.

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PART IV

COMPLICATIONS OF IMMUNOSUPPRESSIVE THERAPY

INTRODUCTION

Rejection of the cardiac allograft, allocated to the recipient without matching for HLA antigens, is almost inevitable. Survival of transplant recipients therefore will depend on effective immunosuppression. However, todays immuosuppressive regimens are not without major draw backs. Complications of aspecific immunosuppression cause considerable morbidity and mortality after heart transplantation. Of particular concern is the increased occurrence of infection and malignancy. In addition, cyclosporin causes impairment of renal function and hypertension.

Despite impressive advances in the last decades, infection continues to be a problem because immunosuppressive drugs produce defects in host defense mechanisms. Cell-mediated immunity is decreased thereby predisposing the patient to opportunistic infections. Pathogens, including intracellular bacteria (Listeria, Salmonella), the Herpes viruses (Herpes simplex virus, Epstein Barr virus, Varicella zoster virus and Cytomegalo virus) and protozoa (Pneumocystis Carinii and Toxoplasma gondii) which are normally suppressed by T-cell-mediated defense mechanisms and hence of low virulence may cause severe disease now.[1-4] In addition, immunosuppressive agents may interfere with other components of the host defense system. Corticosteroids impair delayed hypersensitivity reactions and adversely affect the bactericidal action of neutrophils and the reticuloendothelial system. Cytotoxic agents, such as azathioprine impair antibody formation by its effect on B cell function and decrease neutrophil number and function resulting in infections with gram negative bacilli and Aspergillus. The introduction of cyclosporin as the basic immunosuppressive agent has been shown to result in a significant reduction of the total number of infections and the number of deaths ascribed to infection. This is probably the result of a decreased number of rejection episodes due to the use of cyclosporin. A lower net state of immunosuppression, resulting from less rejection therapy, will decrease the risk of infection. The most striking differences have been noted for bacterial infections of the lungs and Cytomegalo virus (CMV) disease.[5]

Notwithstanding the decrease in fatal infections since the introduction of cyclosporin, infection still accounts for 20% of the deaths reported by The Registry of the International Society for Heart and Lung Transplantation.[6] In the first postoperative month infections are usually caused by bacterial pathogens encountered in surgical patients. Opportunistic infections, especially Cytomegalo virus, dominate in months 1 to 4 after transplantation. After this period a mixture of conventional and opportunistic infections occur (Chapter XII).[7,8]

Cytomegalo virus infection, recognized as the most frequent and important viral infection in allograft recipients, with incidences ranging from 64-92%,[9-11] has been studied from the early days of our program.[12-14] The finding of an decreased incidence of CMV disease after passive immunization with anti-CMV hyperimmunoglobulin encouraged us to continue such policy in CMV seronegative recipients who receive the heart of a seropositive donor. An update of the results of passive immunization is presented in Chapter IX.[15]

Heart transplant recipients suffering from infection may pose unique problems. It may be difficult to make the diagnosis of infection since steroids can mask fever and may suppress other signs of inflammation such as peritoneal irritation after perforation of the gut (Chapter XII). Patients on steroids may consider their symptoms to be unimportant or may appear less ill than actually is the case. Multiple infections may coexist. White blood counts may be falsely low by the use of azathioprine and rise of antibodies may be delayed or lacking as has been the case in one of our patients who developed Hepatitis-C infection (Chapter XII). For these reasons transplant recipients have to be instructed how to detect and monitor signs and symptoms of infection. Moreover, they require serious consideration by medical and nursing staff members and need aggressive diagnostic testing and early treatment. The latter approach results in frequent hospitalization for infection.

Malignancy is another unfortunate consequence of chronic immunosuppression. In general, transplant recipients have a threefold increase in the incidence of various cancers when compared with age-matched controls.[16] The most common tumors are skin/lip carcinomas (more often squamous cell than basal cell carcinoma), lymphoproliferative disorders, Kaposi sarcoma, and uterine, cervical and vulval carcinomas. The use of cyclosporin has affected the incidence and pattern of malignancy when compared with conventional immunosuppression (prednison/azathioprine). Tumors occur earlier and lymphoproliferative disorders have assumed greater importance in some series.[16] Factors that contribute to the propensity of transplant patients towards neoplasms include impairment of immunosurveillance (impaired ability of the immune system to recognize and remove mutant neoplastic cells), direct action of immunosuppressive agents, chronic antigenic stimulation by the allograft and activation of oncogenic viruses.[17,18] Specific monoclonal anti-T cell antibodies have been incriminated for increasing the incidence of malignant lymphoproliferative disorders after transplantation.[18] In our patients however no relation was found between the use of specific mono- or polyclonal anti-T cell antibodies and the occurrence of lymphoproliferative disease. The net state of immunosuppression seemed associated with an increased risk of this disease

(Chapter X)[19,20] although this association could not be confirmed in a larger number of patients (Chapter XII).

The third major draw back of todays immunosuppressive regimens, impairment of renal function, is a consequence of the use of cyclosporin. Its unique renal toxicity was recognized, while the superior immunosuppressive action resulted in significant better survival rates after transplantation.[21,22] When started perioperatively, the nefrotoxic effect hampered patient management to such extent that we and others have selected methods to omit cyclosporin during the first days after transplantation.[23-25] The long-term deleterious effects on renal function resulted in the reintroduction of azathioprine in cyclosporin based immunosuppressive regimens to allow lowering of the cyclosporin dose.[26,27] We however, have used the mere combination of cyclosporin and prednisone in most patients. Our experience with such a regimen, described in Chapter XI, however has recently made us decide to lower target cyclosporin blood levels in the hope not to increase the incidence of rejection.

In an ideal regimen suppression of allograft rejection should be achieved without toxicity of the immunosuppressive agents. Apparently such ideal regimen has not yet been found. As a consequence basic research has to be directed to the development of unresponsiveness to the allograft and selective immunosuppression. Clinical research has to compare the effects of different regimens. Studies on the early effects (incidence of rejection and infection) as well as on the long-term effects (malignancy, renal dysfuntion and allograft coronary disease) have to be initiated and/or continued. Considering the many different methods used for the detection and grading of infection, renal dysfunction and coronary artery disease comparison of the results between different centers is almost impossible. An international grading system for endomyocardial biopsies has been the first step to allow comparisons and further standardization of follow up should be encouraged.[28]

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CHAPTER IX

PASSIVE IMMUNIZATION AGAINST CYTOMEGALO VIRUS IN ALLOGRAFT RECIPIENTS

The Rotterdam Heart Transplant Program Experience

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In: Infection 1993; 21: 1-6

SUMMARY

We analyzed the results of passive immunization against CMV in 146 heart transplant recipients. The 65 seronegative recipients were prophylactically treated with anti-CMV immunoglobulins during and after the operation. Twenty nine of these 65 patients received a seropositive donor heart. CMV infection occurred in 21/65 seronegative and in 40/81 seropositive recipients (difference not significant). The incidence of CMV infection in seronegative recipients of a CMV-matched donor heart (3/34) was significantly lower than in seronegative recipients of a positive donor heart and lower than in seropositive recipients, but no significant difference in infection was found between the two latter groups (18/29 vs 40/81). Although primary infection more frequently resulted in CMV disease than secondary infection (11/21 vs 10/40) no difference in incidence of disease was noted between seronegative and seropositive patients (11/65 vs 10/81), nor was there a difference in the severity of symptoms following primary or secondary infection. There was a higher incidence of CMV disease in all patients who received a heart from a seropositive donor versus a seronegative donor. However, after transplantation of a heart from a seropositive donor the same incidence (27%) of CMV disease was observed in our passively immunized seronegative patients as in the patients with naturally acquired seropositivity. There was no difference in the prevalence of coronary artery disease between patients with and without CMV infection or disease. We conclude that using the current passive immunization scheme the occurrence of CMV infection and disease is largely dependent on the serostatus of the donor.

INTRODUCTION

Cardiac allograft recipients often receive courses of high dose corticosteroids and poly- or monoclonal anti-T cell antibodies, for treatment of rejection, in addition to a maintenance immunosuppressive regimen. This makes them highly susceptible for infection, especially by the Cytomegalovirus (CMV). Such infection may be caused by reactivation of latent virus in seropositive recipients or from transmission of virus through the graft or blood products resulting in primary infection in CMV seronegative recipients. There are several reasons to prevent CMV infection in cardiac allograft recipients. Infection in general is one of the main causes of death early after transplantation, in adults accounting for more than 25%,[1] and CMV appeared to be the single most frequent causal agent of infection in a recent survey.[2] Furthermore, CMV infection may run a more severe course in the highly immunosuppressed patient which frequently results in organ damage, especially in primary infections. [3-6] Another reason for the prevention of CMV infection

and disease is the putative association between CMV and accelerated coronary artery disease in the donor heart.[7-13]

Methods for prevention of CMV infection include avoidance of transmission of the virus by selection of CMV seronegative heart donors,[14] the use of antiviral agents,[15-22] and active [23,24] or passive immunization.[25-30] Our early experience with anti-CMV immunoglobulins in cardiac allograft recipients suggested that passive immunization reduces the incidence and severity of CMV disease in seronegative recipients.[31] The present report describes the experience with the use of anti-CMV immunoglobulins during the first 6 years of the Rotterdam Heart Transplant Program.

PATIENTS AND METHODS

Between June 1984 and March 1991, 156 patients underwent heart transplantation in the Thoraxcenter of the University Hospital Rotterdam. The use of prophylactic anti-CMV immunoglobulins in seronegative recipients was started after patient number 9 in January 1986 and one CMV seropositive patient died during surgery. The other 146 patients survived at least 7 days (the time of the first CMV specimen sampling) and are the subjects of the study: 128 men and 18 women. Recipient ages ranged from 12 to 62 years (median 47) and donor ages from 11 to 41 years (median 24). The original heart disease was cardiomyopathy in 71, ischemic heart disease in 69 and valvular heart disease in 6 patients.

Immunosuppression

Maintenance immunosuppression consisted of cyclosporin A and prednisone. Azathioprine was added to this regimen in 11 patients because of recurrent rejection within the first year and in 4 patients, in order to reduce the cyclosporin dose for reasons of severe renal failure, after the first year. Early rejection prophylaxis, during the first postoperative week, consisted of cyclosporin i.v. and corticosteroids in 55 patients. Polyclonal anti-T cell antibodies (Horse-ALG, antilymphocyte IgG2, Lymphoglobulin, Institut Merieux) were used in 34 patients and monoclonal anti-T cell therapy (OKT3, Ortho Pharmaceutical, Raritan, N.J.) in 57 patients. Acute rejection was treated either by pulsed doses of methylprednisolon (1 gram i.v. on 3 consecutive days) or by polyclonal (Rabbit-ATG, National Institute for Public Health, Bilthoven, The Netherlands) or monoclonal anti-T cell antibodies (OKT3) for very early, recurrent or ongoing rejection.

Prophylactic measures against CMV

CMV seronegative recipients received blood products from seronegative donors. When no blood from seronegative donors was available buffycoat depleted blood products were used. CMV seronegative recipients received anti-CMV immunoglobulins (Cytotect, Biotest Pharma GmbH, Dreiech, FRG) irrespective of the donor serologic status. The preparation contained 100 mg protein per ml and had a specific IgG antibody level of 40.000 ELISA units/ml (50 U/ml ELISA against the Paul Ehrlich Standard). The CMV neutralizing antibody titer was 1:3000. A first dose of 150 mg/kg body weight was administered during the operation, shortly before the end of extracorporeal circulation. Thereafter, doses of 100 mg/kg were given at days 2, 7, 14, 28, 42, 56 and 72 after transplantation. This regimen resulted in preinfusion IgG titers of 1700 to 2100 ELISA units during the first two weeks after transplantation. Mean levels during the next 10 weeks were 1050 ELISA units.[32]

Virologic definitions / studies

Initially the CMV serologic status of the transplant recipients was screened for anti-CMV IgG by an ELISA developed in our own laboratory.[33] From March 1989 a commercial kit was used (ETI-Cytok G, Sorin Biomedics Saluggia, Italy). Recipients with pretransplant IgG titers of respectively <1:100 U or <1:500 U were considered to be seronegative. Until March 1989, IgM antibodies were determined by an indirect immunofluorescence assay[34] and subsequently by an ELISA (ETI-Cytok M reverse, Sorin). Similarly serum of the allograft donor was screened for CMV antibodies. Monitoring for CMV infection after transplantation involved testing urine, throathwash and blood for isolation of the virus and antibody determinations on days 7, 14, 28, 56, 72 and every 3 months thereafter. Additional specimens were obtained when CMV disease was suspected. Isolation of CMV was performed by a low speed centrifugation assay in combination with immunofluorescence using monoclonal antibodies against early antigen (EA) of CMV.[35] Buffycoat samples were cultured on human embryonic lung fibroblasts and screened for cytopathic changes. From 1991 monoclonal antibodies against CMV PP65 antigen were used for the detection of virus antigen in peripheral blood leucocytes.[36]

CMV infection was defined as any appearance of IgM, any isolation of CMV from urine, throathwash or blood or any demonstration of the antigen. CMV disease was presumed to be present when there was infection coexistent

with two of the following sypmptoms: otherwise unexplained fever > 38°C for at least 2 consecutive days; gastrointestinal, lung, retina or central nervous system involvement; leukocytopenia (< 2.5 x 10^9/l); thrombocytopenia (< 100 x 10^9/l); elevation of serum alanine or aspartate aminotransferases (>2 x normal). Lung, central nervous system or gastrointestinal tract involvement had to be confirmed by biopsy or culture.

Depending on the severity of the symptoms, either no specific measures were taken, or patients were treated by either decrease / interruption of immunosuppressive medication in the early phase of the program or by administration of ganciclovir in the later phase.

Detection and monitoring of acute rejection

Frequent endomyocardial biopsies (EMB) were performed, resulting in a mean of 17 biopsies within the first year and 3,5 EMB per year thereafter. Grading of the biopsies was according to Billingham until December 1990[37] and according to the guidelines of the International Society for Heart and Lung Transplantation thereafter.[38] Anti rejection therapy was instituted in case of moderate acute rejection with myocyte necrosis until the end of 1990 and subsequently in cases with biopsies graded 3A or higher.[38]

Detection and monitoring of coronary artery disease

The occurrence of coronary vascular changes was evaluated by annual coronary arteriography. Standard projections were replicated at subsequent angiograms and vasodilatation was standardized by the administration of isosorbide-dinitrate before angiography. We distinguished two main patterns of vascular changes: changes of the large epicardial vessels and their major side branches and changes of the small, mainly intramyocardial, branches.[39]

Statistical analysis

Data are expressed as mean ± 1 standard deviation, median or absolute numbers when appropriate. Comparisons between groups were made by the 95% Confidence Intervals (CI) analysis for the differences between means or proportions.[40] Survival analysis was performed using the Kaplan Meier method.

RESULTS

The preoperative CMV serologic status of the 146 cardiac allograft recipients was positive in 81 and negative in 65. Anti-CMV immunoglobulins were administered to these 65 CMV seronegative patients according to the above mentioned protocol. Side effects were minimal: there were no notable hemodynamic changes and a transient rash appeared in 3 patients only. No transmission of Hepatitis B virus or Human Immunodefiency virus became apparent. Monitoring of Hepatitis C virus was not routinely done during the study period.

Follow up ranged from 13 to 73 months (median 43). Survival rates were 95% (95% CI: 91 to 98), 91% (95% CI: 87 to 96) and 83% (95%CI: 76 to 91) after 1 month, 1 year and 5 years respectively.

The mean number of rejection episodes was 1.4 ± 1.2 in the first year and 1.5 ± 1.3 including episodes after the first year. There was no difference in the total number of rejection episodes between CMV seronegative and seropositive recipients.

Out of the group of 65 CMV seronegative recipients, 34 received a CMV negative donor heart, 29 received the heart of a seropositive donor and in 2 patients the serologic status of the donor was not available. CMV infection occurred in 3 seronegative recipients of a CMV matched donor heart. This incidence was significantly lower than in seronegative recipients of the heart of a CMV seropositive donor and lower than observed in seropositive recipients (Table 1). CMV disease was diagnosed in 21 patients. Eleven of these had been seronegative preoperatively, 8 of whom received the heart of a seropositive donor (Table 1). There was no difference in the incidence of CMV disease between CMV seronegative and positive recipients (11/65 vs 10/81). However, the percentage of patients who developed CMV disease after primary infection proved to be higher than the percentage of patients in whom reactivation occurred: 11/21 vs 10/40 respectively (Difference = -27%, 95% confidence intervals for the difference: -53% to -2%). In addition to this finding there appeared a statistically significant higher incidence of CMV disease in all patients who received the heart from a known seropositive donor (11/40 vs 4/47, difference = 19%, 95% CI: 3% - 35%).

The addition of anti-T cell therapy to the immunosuppressive regimen, either prophylactically or for treatment of rejection did not increase the risk for CMV disease (Table II). Likewise, when the administration of OKT3 was analysed separately from polyclonal anti-T cell antibodies, there was no difference in the occurrence of CMV disease in patients with and without

courses of OKT3. This proved to be true both in the CMV seronegative and in the seropositive recipients (Table 2).

Table 1. Number of patients who developed CMV infection or disease related to the matching of donor and recipient (rec.) for serological status.

CMV infection/disease and CMV serological status				
donor / rec. serostatus	infection		disease	
	N	%	N	%
neg / neg (N = 34)	3	9 *○♠♥	3	9 ♪
pos / neg (N = 29)	18	62 *	8	27 ♪
? / neg (N = 2)	0	0	0	0
neg / pos (N = 13)	6	46 ○	1	8
pos / pos (N = 11)	8	73 ♠	3	27
? / pos (N = 57)	26	46 ♥	6	11

* Difference is -53%, 95% CI of Diff = -73% to -33%.
○ Difference is -37%, 95% CI of Diff = -66% to -35%
♠ Difference is -64%, 95% CI of Diff = -91% to -35%
♥ Difference is -37%, 95% CI of Diff = -53% to -21%
♪ Difference not significant.

Table 2. Number of patients who developed CMV disease related to the adminstration of anti-T cell therapy in general or OKT 3 in particular.

CMV disease and anti-T cell therapy				
CMV disease	anti-T cell therapy (in general)		OKT 3	
	YES (N)	NO (N)	YES (N)	NO (N)
YES	17 *	4 *	10 ■	11 ■
NO	94	31	54	71
	111	35	64	82

* and ■ : Differences not significant.

The time of manifestation of CMV disease was 8.9 ± 5.7 weeks and 9.7 ± 5.8 weeks in the seronegative and seropositive recipients respectively (difference not significant). There was no difference in the severity of the symptoms and organ involvement between CMV seropositive and negative recipients (Table 3). In no patient CMV disease was the cause of death. The only patient with signs of encephalitis during CMV disease recovered after treatment with ganciclovir. There were 7 patients with pulmonary involvement but none with overwhelming, bilateral disease and no patient needed artificial ventilation. The symptoms resolved without specific treatment in 6 patients with CMV disease. Decrease of immunosuppression by lowering the dose of cyclosporin was successful in 4 patients and 10 patients were treated with ganciclovir. One 10-14 day course of ganciclovir therapy was sufficient in 9 patients. In 1 patient symptoms recurred 2 months later during treatment of rejection. This patient recovered after a second course of antiviral medication.

Table 3. Symptoms of CMV disease after primary (NEG REC) and secondary (POS REC) infection.

MAIN PRESENTING SYMPTOMS OF CMV DISEASE		
	NEG REC. N	POS REC. N
fever + mild ALAT / ASAT ↑	7	4
gastrointestinal symptoms	2	2
lung involvement	2	4
encephalitis	0	1

ALAT/ASAT represent serum aminotransferases. Patients may have presented with more than one symptom.

One hundred thirty four patients survived at least one year. Coronary arteriography in 133 revealed abnormal epicardial branches in 26 patients. All vascular changes were minor irregularities. There were no differences in the prevalence of abnormalities of the epicardial branches at 1 year after transplantation between CMV seropositive and seronegative recipients. In addition, no difference in the prevalence of coronary artery disease could be found between patients with and without CMV infection or CMV disease

(Table 4). Moreover, there was no difference in the prevalence of coronary vascular changes between recipients of donor hearts from known seronegative (9/41) and seropositive (6/36) donors.

Table 4. Number of patients who developed angiographically abnormal epicardial branches related to the occurrence of CMV infection or disease.

ACCELERATED CORONARY ARTERY DISEASE ONE YEAR AFTER TRANSPLANTATION (N = 133)				
		Epicardial branches abnormal		
		YES N	NO N	
CMV infection	YES	11	46	NS
	NO	15	61	
CMV disease	YES	4	15	NS
	NO	22	92	
Primary CMV infection		3	16	NS
Secondary CMV infection		8	30	

NS = difference not significant.

DISCUSSION

CMV infection in heart transplant recipients may be prevented by avoidance of CMV transmission, by the use of antiviral agents and by active or passive immunization. However none of these approaches is completely satisfactory. Matching of donor and recipient according to the CMV serologic status will prolong the time on the already long heart transplant waitinglist. Reports on the prophylactic use of acyclovir in kidney transplant recipients are controversial.[15-17] Neither interferon-α nor interferon-ß have been able to reduce the incidence of CMV disease while the administration of interferon-α was associated with severe acute rejection episodes.[18-21] Ganciclovir is effective in the treatment of CMV disease [12,41] although the addition of specific immunoglobulins has been advocated for more effective treatment of CMV pneumonia in bone marrow transplant recipients.[42] More recently, prophylactic use of ganciclovir has been reported to reduce the incidence of CMV illness

in seropositive heart transplant recipients[22] but such prolonged use could result in the development of resistant CMV strains.[43] Active immunization with an attenuated CMV strain in seronegative kidney transplant recipients did not prevent CMV infection or disease although the disease did run a milder course.[23,24] Passive immunization with anti-CMV immunoglobulins has been used in recipients of bone marrow and solid organ transplants.[25-30] These studies suggested that passive immunization may reduce the severity of CMV disease in seronegative recipients. The experience in the early phase of our program appeared to confirm these findings which encouraged us to continue this policy.[31]

The present study showed that with passive immunization against CMV there was no difference in incidence of CMV infection between CMV seronegative recipients of seropositive donor hearts and seropositive recipients who had naturally acquired resistance. Also, no difference in the incidence of CMV disease was noted between these two groups, although CMV disease occurred more frequently after primary infections than after reactivation of latent virus. The occurrence of CMV disease in 27% of our seronegative recipients of the heart of a seropositive donor contrasts sharply with the 83% incidence in untreated patients, cumulated from earlier reports.[3-6] Nevertheless our findings also indicated that the temporarily specific humoral immunity is not sufficient for the prevention of CMV disease in all patients. The 27% incidence (8/29) of disease in CMV seronegative recipients of a seropositive heart was not different from the reported 35% incidence (7/20) in patients receiving ganciclovir.[22] Also, the incidence was not different from the incidence of CMV disease in seronegative recipients in whom no prophylactic measures were taken.[22] However, the finding in the ganciclovir prophylaxis study that there was no difference in incidence of CMV disease between the two placebo groups (seropositive recipients and seronegative recipients of a positive donor) is clearly divergent from earlier studies and can not be explained from the report because of a lack of detailed information.[22]

The lack of correlation between the incidence of CMV disease and the administration of anti-T cell antibodies in our patients contrasts with other reports.[2,44] We did not find, neither in the CMV seronegative nor in the CMV seropositive group, a difference in the incidence of CMV disease between patients who received anti-T cell therapy in addition to their maintenance immunosuppressive regimen and patients who received no rejection treatment or corticosteroids only. After separation of the different kinds of anti-T cell antibodies we could also not demonstrate an increased risk for the development of CMV disease in patients who received OKT3, prophylactically or as rescue therapy for rejection. An explanation for the discrepancy with other reports [2,44]

may be that the proportion of patients who received at least one course of poly- or monoclonal anti-T cell antibodies was large (76%) which makes the number of patients without anti-T cell therapy small. Comparisons between the levels of immunosuppression in the different CMV studies however, are hampered by lack of detailed information.

Contrary to earlier reports there was no correlation between CMV infection or disease and coronary artery disease in our patients.[7-13] This might be caused by differences in regimens used by the centers or by differences in the definitions for CMV disease. Also, methods to investigate coronary artery disease as well as thresholds for the diagnosis of transplant vascular disease, when angiography is used, have differed widely until now. The establishment of strict definitions for CMV infection and disease and of objective parameters for transplant coronary artery disease by quantitative angiography [45-47] or intravascular ultrasound[48] may help to solve the problem of the differences between centers.

Despite prophylactic measures, the incidence of CMV disease in our patients is still substantial. A more effective way to prevent CMV disease and thereby lower the costs of cardiac transplantation would be the use of hearts of CMV seronegative donors for not only seronegative recipients but, according to our findings, also for seropositive recipients. This approach however would result in prolongation of the time on the waiting-list with a subsequent higher chance of mortality before a suitable donor heart has become available. Such increased mortality on the waitinglist would not be acceptable since CMV disease can be treated effectively.[12,41,42]

The current study demonstrated that the administration of anti-CMV immunoglobulins to cardiac allograft recipients is safe and results in a comparable incidence of CMV infection in CMV seronegative and seropositive recipients. However, primary infections still resulted more frequently in overt CMV disease than secondary infections (reactivation or reinfection) although there was no difference in symptoms between CMV disease following primary or secondary infections. Moreover the incidence of CMV disease was higher in all patients who received the heart of a seropositive donor than in patients who received a seronegative donor which asks for quantitative measures of virus load and a search for different CMV strains as causal agents of reinfection.

In view of our findings and the demonstration that ganciclovir is effective in reducing the risk of CMV illness in recipients with naturally acquired seropositivity[22] the prophylactic administration of ganciclovir in passively immunized CMV seronegative recipients of a seropositive heart might lower the incidence even more. Such regimen should be the subject of

future investigations. It should be appreciated that passive immunization as used in our program is rather expensive, accounting for $ 6000 per patient. To assess the cost/benefit ratio of measures against CMV infection and disease, the costs of prophylactic drugs and hospitalizations for administration of these drugs and for treatment of CMV disease have to be weighed against the decrease in mortality and morbidity including a possible limitation of the occurrence and progression of transplant coronary artery disease.

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CHAPTER X

OCCURRENCE OF LYMPHOPROLIFERATIVE DISORDER AFTER HEART TRANSPLANTATION IS RELATED TO THE TOTAL IMMUNOSUPPRESSIVE LOAD

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In: Transplant International 1992; 5 (suppl 1): S259-261
Letter to the Editor, N Engl J Med 1991; 324: 1437

SUMMARY

Heart transplant recipients are at a high risk for the development of post-transplant lymphoproliferative disorders (PTLD). We explored the relationship between the incidence of PTLD and the immunosuppressive therapy in 150 consecutive patients who received a cardiac transplant at our centre. None of our patients treated with cyclosporin A and prednisone only (n=41) developed PTLD. In contrast, 6 of 101 patients who were previously treated with anti-T-cell preparations suffered from PTLD. No relationship was found between the type of anti-T-cell therapy and the incidence of PTLD. We conclude that the high incidence of PTLD in heart transplant recipients is related to the total immunosuppressive load and not related to a single agent like OKT3.

INTRODUCTION

The long-term use of immunosuppressive drugs after organ transplantation is associated with an increased incidence of neoplasia. Of great concern is the striking number of lymphoproliferative disorders in heart and heart-lung recipients.[1,2] These tumours, commonly of B-cell origin, frequently occur at extranodal sites, are associated with Epstein-Barr virus infections, are often fatal, but may undergo regression if immunosuppressive therapy is reduced.[3-6] A major factor influencing the development of post-transplant lymphoma appears to be the intensity and type of immunosuppression. Several authors reported an additional increased risk after the administration of OKT3.[7,8] The objective of our study was to explore the relationship between the use of anti-T-cell therapy and the incidence of PTLD in heart transplant recipients.

METHODS

Patients

Between June 1984, the beginning of the cardiac transplantation program, and 20 December 1990, 150 orthotopic heart transplantations were performed at the University Hospital, Rotterdam. One patient received a second transplant, for whom the data are combined. Six patients who died within 15 days of transplantation and two patients with a follow-up less than 1 month were excluded from the present analysis. We therefore were able to include data on 142 patients in our variables associated with the risk of having post-transplantation lymphoproliferative disorder after cardiac transplantation (PTLD), The mean age of our patients was 44 ± 11 years. The indications for

transplantation were dilated cardiomyopathy (69 patients), ischaemic cardiomyopathy (70 patients) and valvular heart disease (3 patients).

Immunosuppressive regimens

Maintenance immunosuppression consisted of the prednisone-cyclosporin A combination in all patients. For immunoprophylaxis in the first week after transplantation several protocols were used. All patients received high-dose steroids in the perioperative phase which was gradually decreased to a maintenance dose of 10 mg prednisone after 2 months. In 62 patients cyclosporin A was given intravenously during the first 5 days after transplantation and oral administration of CsA was started at day 4, in the remaining patients equine antithymocyte globulin (hATG) (Institute Merieux, Lyon, France), 425 lymphocytotoxic units (0.5 ml) per kilogram for 3-7 days (n=28) or anti-T-cell monoclonal antibody OKT3 (Orthoclone OKT3, Ortho Pharmaceutical, Raritan, N.J.,USA), 5 mg/day for 7 days (n=51) was given. These 79 patients also received short-term (5 days) azathioprine (50 mg/day) and CsA was started at day 5 (8 mg/kg) orally per day).

In all patients, CsA dosage was adjusted to the plasma levels of the drug. Until November 1988, a non-specific assay for CsA (RIA, Sandoz, Basel, Switzerland) was used (target range 100-200 ng/ml). After November 1988, a specific monoclonal antibody (Cyclo-Trac SP, Incstar, Stillwater, Minnesota, USA) was used to measure the plasma concentration of the parent drug (target range 50-125 ng/ml).

Rejection episodes were treated in a uniform manner throughout the study period. Endomyocardial biopsies were graded using the criteria as proposed by Billingham. In the case of moderate or severe rejection in the first 4 weeks after transplantation, patients were treated with rabbit ATG (rATG, National Institute for Public Health, Bilthoven, The Netherlands) in a dosage to keep the T-cell count < 150 mm^3 for 3 weeks). First-line treatment for moderate rejection occurring more than 4 weeks after transplantation was 1 g methylprednisolone per day intravenously for 3 days. Refractory rejection episodes were treated with either rATG (see above) or OKT3 (5mg/day) for 10 days.

Pathological studies

The diagnosis of post-transplantation lymphoproliferative disorder was based on histological examination of excision biopsy or autopsy material.

Table 2. Characteristics of the patients with post-transplantation lymphoproliferative disorder

Patient No.	Cumulative OKT3 dose (mg)	Cumulative rATG dose (mg)	Cumulative hATG (days)	Time to PTLD (months)	Pathological findings		Clinical status (time from diagnosis)
					Hist	IP	
4	none	4200	5	6	IBL	M	Dead (5 months)
28	none	none	3	30	IBL	P	Dead (1 month)
52	none	920	none	25	PC	M	Dead (1 month)
59	50	960	none	7	IBL	M	Alive in CR (29 months)
79	35	none	none	11			Alive with recurrence (16 months)
84	35	none	none	4	DM	P	Dead (1 month)

rATG: rabbit antithymocyte globulin; *hATG*: equine antithymocyte globulin; *IP*: immunophenotype; *Hist*: histology; *IBL*: immunoblastic lymphoma; *PC*: plasma cell tumor; *DM*: diffuse mixed lymphoma; *M*: monoclonal; *P*: polyclonal; *CR*: complete remission.

RESULTS

One and three year survival in our patients was 91% and 89%, respectively. Detailed information on the indication for anti-T-cell therapy is given in Table 1. In six patients, treated with anti-T-cell therapy, a diagnosis of post-transplantation lymphoproliferative disorder was made. Three of these patients were treated with OKT3 (two patients with OKT3 alone), three patients with polyclonal anti-T-cell therapy and one patient both with OKT3 and RATG. Detailed information on the characteristics of these patients is given in Table 2.

Table 1. Indication for anti T-cell therapy.

	Patients (N)
Prophylaxis only	
hATG	10
OKT3	28
For treatment of rejection	
rATG	17
OKT3 and rATG	5
Both for prophylaxis and treatment of rejection	
hATG and rATG	16
OKT3 and rATG	23
hATG, rATG and OKT3	2
TOTAL	101

rATG: rabbit antithymocyte globuline; *hATG*: equine antithymocyte globulin; *OKT3*; monoclonal antibody to T-cell receptor. Cumulative dose: OKT3 43 mg (25-100 mg): rATG 1090 mg (299-4200 mg)

In contrast, none of the 41 patients treated with CsA and prednisone alone developed PTLD (incidence 0%. 95% Confidence Internal 0-9%). The difference in incidence between the two groups was 6%, 95% confidence interval of the difference 1-13% ($p<0.05$).

A number of factors that might be associated with the development of PTLD were examined. No statistically significant differences were found in age, time after transplantation, cumulative CsA dose, plasma levels or cumulative steroid dose.

Four patients died, despite reduction or withdrawal of immunosuppression and treatment with acyclovir i.v.

DISCUSSION

The most striking observation in our study was that none of the patients who was treated with CsA and prednisone alone developed a post-transplantation lymphoproliferative disorder. Of the six patients who developed PTLD, all were treated with anti-T-cell therapy, either as immunoprophylaxis or for treatment or rejection. Of these six patients only three were treated with OKT3 whereas the remaining three received a polyclonal anti-T-cell preparation. Our findings are in contrast with the observations made by Swinnen et al.[8] They concluded that a substantial increase in the incidence of post-transplantation lymphoproliferative disorder occurred after the addition of OKT3 to their immunosuppressive regimen. They also found a relationship between the incidence of PTLD and the cumulative dosage of OKT3. How can this discrepancy be explained? One possibility is the type of maintenance immunosuppression. Swinnen et al. used triple drug treatment (CsA, prednisone and azathioprine) whereas at our centre patients are treated with CsA-prednisone only. Furthermore, the cumulative dose of OKT3 given to their patients who susbsequently developed PTLD was high (between 70 and 135 mg per patient) and our patients received a median total dose of 35 mg. In view of this difference and our observation that none of our patients treated with CsA and prednisone alone suffered form PTLD, it is more likely that the high incidence of PTLD in their patients was due to a greater total immunosuppressive load, than that a single agent, like OKT3, was responsible.

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CHAPTER XI

TIME-COURSE OF THE DECLINE IN RENAL FUNCTION IN CYCLOSPORINE TREATED HEART TRANSPLANT RECIPIENTS

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In: Am J Kidney Dis (in press)

SUMMARY

Renal side-effects are a major limitation of the use of cyclosporine-A (CsA) following heart transplantation. In an effort to define the time-course of the decline in renal function and to identify a group of patients especially prone to the nephrotoxic effects of CsA, we studied 187 orthotopic heart transplant recipients who had a follow-up of at least one month. All patients received oral CsA in a starting dose of 8 mg/kg and low-dose steroids. Renal function decreased steadily after transplantation. Serum creatinine was > 150 µmol/L in 52 % of the patients after two years. After four years serum creatinine was > 250 µmol/L in 13 % of the patients. No relation could be found between the decline in renal function (as defined by the slope of serum creatinine^{-1} versus time) and age, sex, creatinine levels before transplantation, bloodpressure, CsA blood levels, the number of rejections or the use calcium channel blocking drugs.
We conclude that, despite reduction of CsA dosage, progressive renal insufficiency can be observed in an increasing percentage of heart transplant recipients. We were not able to identify patients with a poor renal prognosis in an early phase after transplantation.

INTRODUCTION

The clinical outcome of cardiac transplantation has markedly improved after the introduction of Cyclosporine A (CsA).[1] The renal side effects of CsA however, appear to be a major drawback of its use. The occurrence of end stage renal failure necessitating renal replacement therapy can be as high as 10% on an actuarial basis after a median followup of ten years.[2] It has been suggested that high dosages of CsA, as initially employed by most centres, are associated with more severe impairment of renal function than most current treatment schedules.[3] This is largely due to the co-employment of azathioprine (AZA) which enables lower CsA dosing; i.e. triple therapy. In kidney transplant recipients, this strategy has been shown to improve renal function.[4] However, a direct comparison of heart- with renal transplant recipients is difficult because in in the latter chronic rejection, infection, reflux and recurrence of the original disease can also cause a decline in renal function. Few studies have been reported in which the sensitivity for the nephrotoxic effects of CsA were assessed on an individual basis. We therefore reviewed the time-course of the decline in renal function in 187 consecutive heart transplant recipients. We also studied the relation between poor outcome of renal function as defined by serum creatinine levels increasing to values above 250 µmol/L and various donor and recipient characteristics. Furthermore, we attempted to correlate the decline in renal function, assessed by the slope of serum creatinine^{-1} to various clinical and laboratory patient characteristics.

PATIENTS AND METHODS

Since june 1984, 202 heart transplantations have been performed at our center. One hundred eighty-seven of these patients were had a follow up of at least one month at the time of analysis. There were 158 men and 29 women, mean age 45 ± 11 years at the time of transplantation. The mean numbers of mismatches for HLA-A, -B and -DR were 1.3, 1.6 and 1.4 respectively. The mean donor age was 24 ± 7 years. Before transplantation the average serum creatinine level was 124 ± 14 µmol/L. All patients were treated with oral cyclosporine from day 2-5 onwards at a starting dose of 8 mg/kg/day. Prednisone was started at 50 mg/day and tapered to 10 mg/day within 8 weeks. Of the patients reported, 138 received early prophylaxis with either polyclonal or monoclonal antibodies directed against T-cells. Rejection surveillance was performed by endomyocardial biopsies. The grading of biopsies was initially done according to the criteria of Billingham and later using the guidelines of the International Society of Heart Transplantation.[5,6] The follow-up of all patients was performed at our outpatient clinic. At these visits clinical (weight, dose of cyclosporine, bloodpressure) and laboratory data (serum creatinine, cyclosporine level) were collected. We analyzed the course of these parameters throughout the follow-up period. We identified a subgroup of 24 patients with a poor prognosis of renal function as defined by a serum creatinine rising above 250 µmol/l. These patients were compared with the 163 patients with a more favourable prognosis of renal function. Also, we calculated the slope of creatinine^{-1} versus time in a subgroup of patients with a follow-up of at least 3 months in which more than 10 measurements were available (n=167). Data on the decline in renal function were correlated with clinical patient characteristics.

Laboratory measurements

Plasma cyclosporine trough levels were determined using a monoclonal antibody directed against the native compound. Dosage of cyclosporine was adjusted in order to obtain plasma levels between 100 and 120 ng/ml for the first 3 months and between 50 and 80 ng/ml thereafter. Serum creatinine was measured using a modified Jaffé reaction.[7]

Table 1. Cyclosporine dosage and renal function in heart transplant recipients.

	n=	Cyclosporine dose mg/kg	Serum Creatinine median (range)	≤150 µmol/L %	151-200 µmol/L %	201-250 µmol/L %	>250 µmol/L %
1 month	187	7.2 (2.7-33)	107 (46-250)	87	13	3	0
3 months	179	7.1 (2.9-23)	120 (54-262)	77	23	4	1
6 months	169	6.6 (2.3-24)	131 (53-324)	69	31	5	1
1 year	153	6.4 (2.7-17)	143 (79-326)	57	43	12	3
2 years	130	5.5 (2.4-17)	152 (80-407)	48	52	13	2
3 years	103	5.1 (2.6-15)	164 (86-788)	43	57	22	8
4 years	69	4.7 (2.3-15)	174 (92-802)	26	74	28	13
5 years	39	4.6 (2.5-9.4)	190 (89-733)	33	67	36	13

Statistics

All data are presented as median (range) unless stated otherwise, because most of the data did not follow a normal distribution. For this reason correlations were assessed non-parametrically using Spearmans rank correlation. Differences between groups were tested using the Wilcoxon rank-sum test. Differences in qualitative data were assessed using the chi-square test. All calculations were performed using the SPSS-PC+ statistical package. A p-value below 0.05 was considered significant.

RESULTS

Following transplantation, the prescribed dose of cyclosporine (mg/kg) decreased over time, as shown in table I. Renal function steadily worsened over time. Two years after transplantation more than half of the patients had moderate renal insufficiency; i.e. serum creatinine levels above 150 µmol/l. The number of patients with severe renal impairment (creatinine > 250 µmol/l) reached 10% after 3 to 4 years. Overall, six patients have reached end stage renal failure necessitating renal replacement therapy. The course of creatinine levels in all individual patients over time is shown in Fig. 1. Patients who progressed to end stage renal failure showed a steep terminal slope of creatinine versus time; renal failure seemed to progress rapidly after a long period of apparent stability. Renal function was not directly related to dosage of CsA (Fig. 2) or to cyclosporine trough levels. Patients with poor renal function had lower doses of CsA, most likely due to dose reduction in the face of rising creatinine levels. We could also find no correlation between either systolic or diastolic bloodpressure and serum creatinine levels (Fig. 3). In the total group of patients no correlation existed between CsA dose and plasma levels, although such a correlation did exist in the individual patients. CsA levels during episodes of rejection were not significantly different from those associated with unobtrusive histological findings.

No correlation could be found between the rate of decline of renal function (slope of serum creatinine^{-1} versus time) and age, creatinine levels before transplantation, peak serum creatinine within the first month of transplantation or the number or rejection episodes (Table 2). When comparing the patients with an unfavourable outcome of renal function with those in which renal function was preserved, mortality was significantly higher in the latter group. All other characteristics were not significantly different (Table 3).

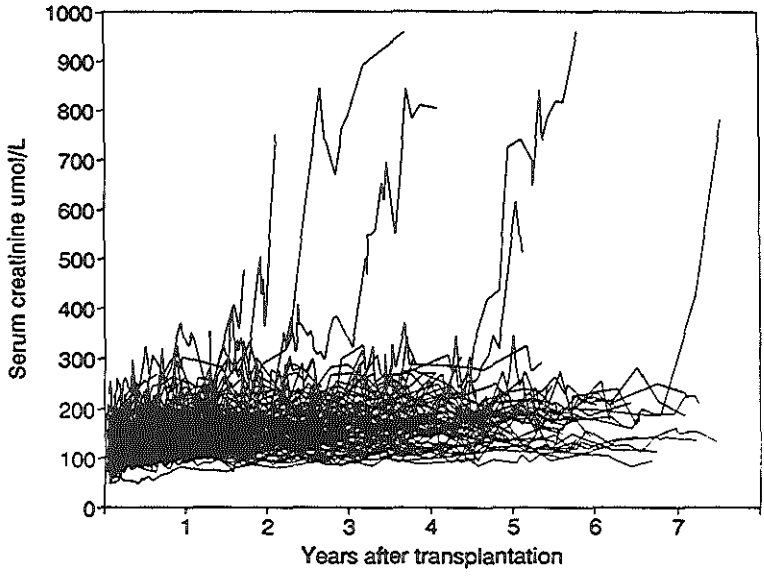

Fig. 1: Individual time-course of serum creatinine in 187 heart transplant recipients.

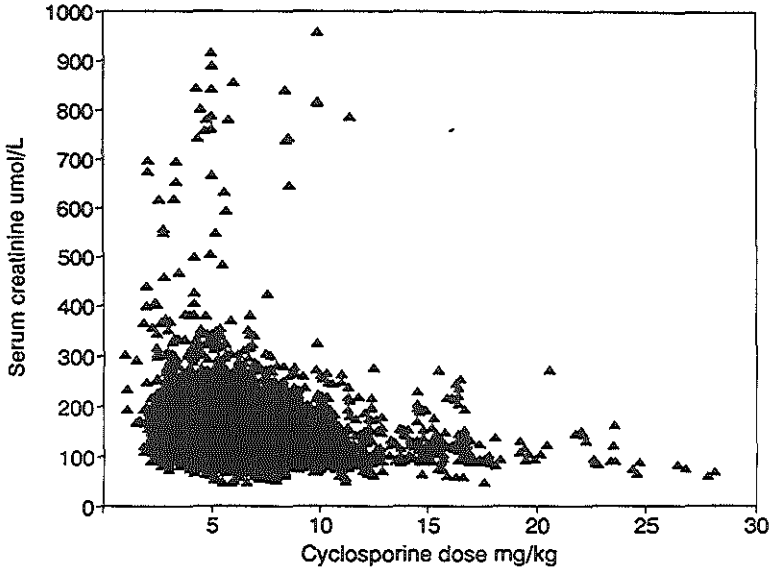

Fig. 2: Individual serum creatinine levels plotted against the corresponding dose of cyclosporine. Note that patients with very high creatinine levels received relatively low doses of cyclosporine.

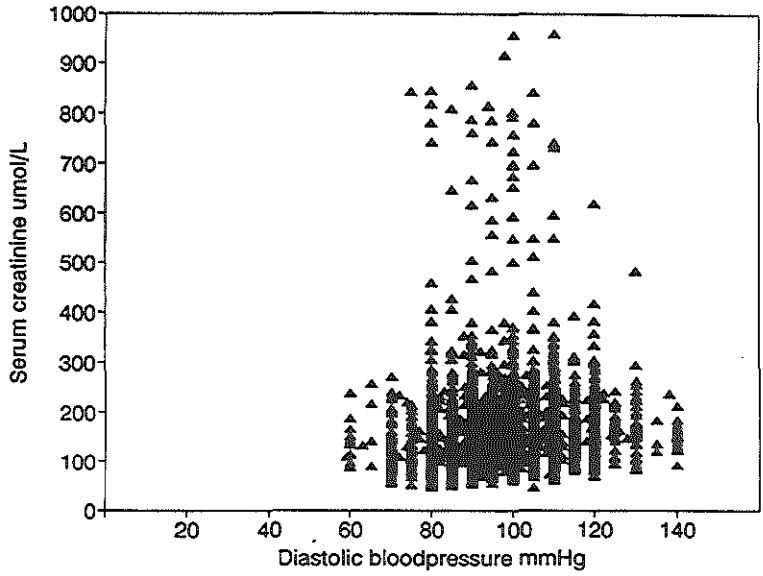

Fig. 3: Lack of relation between individual serum creatinine levels and diastolic blood pressure.

DISCUSSION

Within the first 2 years after heart transplantation, moderately impaired renal function was observed in 52 % of our patients. Over time, this incidence increased, while CsA dosage declined. Median serum creatinine levels were comparable to those reported in heart transplant recipients at Stanford[3] and Pittsburg.[8] The incidence of renal failure in liver and lung transplantation also appears to be similar.[9,10] Within the group of patients with poor renal function the number of patients with severe renal function increased steadily (Table 1). This shift was not readily apparent from the median creatinine levels.

So far, six of a total of 202 patients transplanted at our center have progressed to end-stage renal failure. Similar numbers have been observed by various other cardiac transplant centres,[2,5] although some centres have reported lower rates of renal failure.[11,12] In the patients progressing to end-stage renal failure, the terminal decline in renal function occurred rapidly. This may be explained by the discrepancy that has been observed between renal function and the structural changes seen microscopically, which suggests a compensatory response of a population of glomeruli that appears to escape the CsA effect.[3,13] Presumably, once a critical mass of glomeruli are affected, the compensatory response of surviving glomeruli fails and renal failure ensues.

Table 2. Correlations between clinical patient characteristics and the slope of serum creatinine^{-1} versus time.

	correlation coefficient r_s	p-value
Age	0.12	n.s.
Mean number of AR		
first year	0.12	n.s.
total	0.08	n.s.
Serum creatinine before transplantation	0.04	n.s.
Peak creatinine first month after transplantation	0.15	n.s.

AR: acute rejection episode.

The use of calcium entry blocking drugs has been reported to ameliorate the detrimental effects of cyclosporine on the kidney.[14] In the present study, the administration of calcium entry blockers did not prevent cyclosporine induced renal failure.

We set out to see if a group of patients with a high risk of renal failure could be identified retrospectively. Unfortunately no correlation was found between the decline of renal function and the parameters studied. Also the group of patients that did progress to overt renal failure was not significantly different in characteristics from those with relatively stable renal function. Mortality was significantly higher in the patient-group with depressed renal function, illustrating the severity of the problem. Inversely, patients with an excellent renal function after four years did not differ from other patients. Therefore at present we are unable to predict the course of renal function at an early stage.

Table 3. Patient characteristics in heart transplant recipients with relative stable renal function and patients with marked cyclosporine nephrotoxicity.

	Serum creatinine <250 umol/L (n=163)	Serum creatinine >250 umol/L (n=24)	
Age	45 (14-61)	41 (16-59)	n.s.
Gender (m/f)	137/26	22/2	n.s.
Mean number of AR			
first year	1.7 ± 1.5	1.6 ± 1.0	n.s.
total	1.8 ± 1.6	2.0 ± 1.2	n.s.
Mortality	16/163 (9.8 %)	8/24 (33.3 %)	p<0.05
Serum creatinine before transplantation	123 (65-675)	138 (95-293)	n.s.
Peak creatinine first month after transplantation	154 (48-628)	202 (60-633)	n.s.
Malignancies	9/163 (5.5 %)	4/24 (16.7 %)	n.s.
Use of calcium channel blocking drugs	116/163 (71.2 %)	15/24 (62.5 %)	n.s.
Mean LVEF one year after transplantation	66 ± 8.8	67 ± 6.5	n.s.

AR: acute rejection episode, LVEF: left ventricular ejection fraction.

Several strategies can be followed in order to reduce the incidence of renal failure. Many centres have added azathioprine to the immunosuppressive treatment regimen in order to allow a reduction of CsA doses. The doses of CsA administered in our patient group were lower than those reported by most groups using CsA and prednisone maintenance therapy,[3] but higher than doses reported in triple drug treatment regimens.[3,8] Low dosage of cyclosporine does not prevent the occurrence of renal failure,[3,10] and even after lowering of CsA doses renal histological lesions have been reported to progress.[2] Therefore total discontinuation of CsA may be necessary to alter the progression of renal failure in some patients. Such a strategy could only be effective if started relatively early and only in those patients prone to develop renal problems. CsA could be continued in the group of patients tolerating the drug, with the benefit of a superior rejection prevention. As we are presently unable to

predict which patient will be seriously affected by cyclosporine nephrotoxicity, conversion from CsA to Aza can only be performed in patients with already moderate renal dysfunction. It is questionable whether the decline in renal function is reversible at that stage. Conversion of all patients to AZA poses the risk of increased rejection rates.[15] As patient survival in the current patient group is excellent, caution should be taken to alter the treatment schedule in such a drastic way. This is especially significant since recent data indicate that long term graft survival in renal transplant recipients may be better in patients with relatively high cyclosporine levels.

We conclude that two years after heart transplantation, renal function is moderately impaired (serum creatinine > 150 µmol/L) in one half of the patients, treated with cyclosporine at moderate doses, and that severe renal impairment (serum creatinine > 250 µmol/L) occurs in more than 10% of these patients after four years. Retrospectively, we were unable to identify those patients with a poor prognosis of renal function in an early phase.

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PART V

HEART TRANSPLANTATION AT THE THORAXCENTER

CHAPTER XII

THE ROTTERDAM HEART TRANSPLANT PROGRAM 1984 - 1993

200 Cardiac allograft recipients

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In: Neth J Cardiol (in press)

SUMMARY

Two hundred patients with end-stage heart disease have received a cardiac allograft in Rotterdam between June 1984 and January 1993. This resulted in one and five year patient survival rates of 92% (95% confidence interval 88-96%) and 84% (78-90%) respectively.

An in depth overview of the results of these heart transplantations is presented to inform referring cardiologists, nurses of the Departments of Cardiology and others who take care of patients with end-stage heart disease about this treatment modality. Being familiar with these data will allow adequate selection for referral and preparation of future transplant candidates.

INTRODUCTION

Heart transplantation has been performed in Rotterdam as early as the 1970s. In an experimental program orthotopic and heterotopic transplantations were compared in dogs and accelerated coronary artery disease was studied after the development of a canine model.[1-3] Although many other centers throughout the world started clinical heart transplantation soon after the first successful procedure by Barnard in 1967[4], we waited until June 1984 to perform the first human heart transplantation in the Netherlands. This wait-and-see policy was dictated by disappointingly poor survival rates in the period that maintenance immunosuppression after transplantation was based on azathioprine and steroids while no reliable methods for detection of acute rejection had been developed. After the Stanford Group reported a significant increase in survival and decrease in complications in cardiac allograft recipients who were monitored by endomyocardial biopsy and treated with cyclosporin A a clinical heart transplant program was initiated.[5]

The first clinical heart transplantation in Rotterdam was performed by a team from the Thoraxcenter, Erasmus University Rotterdam and the University Hospital Leiden on June 23, 1984. After considerable political discussion, two centers were allowed to continue heart transplant programs in 1985: the University Hospital of Rotterdam and the University Hospital of Utrecht. These centers cooperated with the University Hospital of Leiden and the St.Antonius Hospital in Nieuwegein and with the University Hospital of Groningen respectively. Initially, the costs of a limited number of transplantations per year were reimbursed by the "Law for Special Health Costs" (Algemene Wet Bijzondere Ziektekosten). Based on an independent cost-effectiveness analysis by a team of the Institute of Social Health Care and the Department of Economics of the Faculty of Law, both of the Erasmus University Rotterdam, the Health Council recommended in 1989 that both

transplant programs should be continued.[6,7] It took until 1992 however, before reimbursement by the Public Health Funds (Ziekenfondsen) and the private insurance companies was accomplished.

The cardiologist who plans to refer a patient for heart transplantation should be familiar with the indication and contraindications for this treatment modality. To allow adequate preparation of the patient for referral he should be aware of the current results of transplantation including perspectives in terms of survival, quality of life and complications. Therefore we report our experience regarding the first nine years of our Transplant Program in which 200 patients received a cardiac allograft.[8,9]

PROCEDURES

Referral

Patients are referred to one of the three hospitals cooperating in the Rotterdam Transplant Program. Preferably, assessment for transplantation is started on an outpatient basis and is completed during a short hospital stay, if the patient seems to be a suitable candidate. Patients requiring hospitalization because of intravenous inotropic support or mechanical assistance are transferred from the referring hospital to the departments of cardiology of the participating centers. The in-hospital assessment period is used to confirm the decision that no benefit can be expected from therapy other than transplantation, to rule out contraindications for transplantation and to gather information about potential problems which might require special attention after the transplant procedure. Equally important, these days are used to inform the patient and his relatives about heart transplantation. The waiting time, the operation procedure, the perspectives with respect to survival and quality of life as well as the potential complications are discussed by different members of the transplant team. After completion of the assessment procedure each case is discussed in a (weekly) meeting of the transplant team where the treatment of preference (medical therapy, conventional surgery or cardiac transplantation) is decided upon agreement.

Follow up data of all patients who have been referred are collected and stored in a computer database. This system enables us to follow not only patients who have been transplanted but also those patients to whom an advise other than transplantation has been given. After transplantation, additional demographic data, HLA-tissue typing, details of the immunosuppressive

protocol and the occurrence of rejection, infection and other complications are stored in a separate database.

Indication

The two Dutch heart transplant programs have agreed upon a common protocol which specifies that heart transplantation may be offered to patients suffering from end-stage heart disease, thus having a very limited life expectancy, in whom no benefit can be expected from any other medical or surgical intervention. The patients should be willing and able to comply with intensive medical treatment and close follow up. Compliance with a strict medical regimen and willingness to report changes in their condition are prerequisites for successful transplantation. Moreover, patients should be able to cope with many uncertainties in particular during the waiting time, during the first months after transplantation (chance of rejection and infection) and in later years when complications of chronic immunosuppression arise.

Contraindications

In an attempt to achieve optimal use of donor organs several contraindications are applied strictly. Patients who will profit only to a limited extent will be denied cardiac transplantation. In the starting phase of both Dutch transplant programs an upper age limit of 55 years for cardiac transplant candidates had been agreed upon. This age limit was abandoned in the spring of 1990. Contraindications for transplantation, as currently applied by the Dutch heart transplant centers as well as by most other transplant centers throughout the world, are summarized in Table 1.

Preoperative measures

Anti-HLA antibodies are determined preoperatively in all heart transplant candidates. In patients who show antibodies against more than 5% of the leucocyte panel a preoperative crossmatch is performed between serum or spleen cells of the donor and serum of the recipient to prevent hyperacute rejection. In an attempt to improve graft survival a bloodtransfusion is given to transplant candidates who never had transfusions before, provided they do not show anti-HLA antibodies.[10,11] Patients who have been put on the waiting-

list but who appear able to wait at home receive close follow up by the referring cardiologist and, with longer intervals, by the cardiologists of the transplant team. They are advised to contact their physician immediately in case of worsening heart failure symptoms, including dyspnea and gain in body weight, as well as for fever and other unexpected problems to enable timely intervention. Without further delay medication will then be adapted and treatment of infection, which would preclude transplantation at that time, will be initiated. When heart failure symptoms can not be managed sufficiently by oral medication and failure progresses to impending organ damage, transplant candidates are admitted to the (preferably local) hospital, for intravenous inotropic support, and are given priority on the waiting-list.

Table 1.

Contraindications for Heart Transplantation in The Netherlands

*	pulmonary vascular resistance > 6 Wood Units (the effect of administration of 100% O_2, and vasodilators should be assessed). Increased risk for right sided failure of donor heart when the pulmonary vascular resistance is > 4 Wood Units or when the trans pulmonary gradient is > 15 mmHg.
*	infection or focus for infection.
*	irreversible renal failure (creatinine clearance < 30 ml/min)
*	irreversible liver dysfunction.
*	diabetes mellitus with secondary organ damage and/or the need of insulin.
*	peripheral vascular disease to such an extent that surgery may be expected.
*	other disease processes which may have a negative impact on the prognosis and/or future treatment (for example systemic disease, malignancy, mental disorders, drug or alcohol addiction).

Trans pulmonary gradient = mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure.

The operation

The transplantation procedure consists of orthotopic cardiac replacement, by a minor modification of the technique, described by Lower.[9,12] Via a median sternotomy the recipients heart is excised leaving the back walls of both atria in place. Four suture lines are necessary to connect the donor heart with the recipients circulation: the aorta, the pulmonary artery and both

atria are connected. In patients with congenital cardiac abnormalities the technique of transplantation is adapted to the actual anatomic situation. Before weaning the patient from extracorporeal circulation, isoprotenerol, dobutamine and nitroglycerin are administered to support the denervated donor heart which has become ischemic between harvesting, transport and reinstitution of perfusion. If necessary, atrial or AV-sequential pacing is applied to accomplish heart rates of at least 110 beats/min.

Rejection surveillance

Histological examination of repeated endomyocardial biopsies from the right ventricle (interventricular septum), taken via the right jugular vein, is used for the detection and monitoring of acute rejection. In the first year approximately 17 biopsies are taken and subsequently 2-3 biopsies/year. Grading of rejection has initially been by Billingham's criteria and since 1991 according to the guidelines of the International Society for Heart and Lung Transplantation.[13,14]

An extensive search for noninvasive methods to replace the biopsies has been initiated and is still ongoing. Echocardiographic and echo-doppler measurements (studies granted by the Netherlands Heart Foundation), cytoimmunological monitoring and serological markers have been studied extensively but failed to be of clinical use.[15-18] The invasive nature of the biopsy and the impact of the frequent procedures on the catheterization laboratory has stimulated us to continue a search for new, non-invasive methods including an ongoing study of changes of heart rate, QRS and T wave configurations during rejection episodes.

Immunosuppression

Rejection of the cardiac allograft is almost inevitable because of the random allocation of donor hearts to patients. Matching for HLA-tissue antigens of the donor and the recipient is not feasible within the limited time available. Moreover, methods to render the transplant recipient unresponsive to the allograft have failed until now or are insufficient. Therefore lifelong immunosuppressive medication is necessary to prolong graft survival.

Maintenance immunosuppression consists of cyclosporin (CsA) and prednisone. Cyclosporin levels are monitored closely by plasma (currently whole blood) trough levels to assure adequate immunosuppression and to

minimize adverse effects. Different regimens of initial immunosuppression have been compared in order to facilitate patient management during the first days after transplantation (CsA reduces renal blood flow resulting in oliguria) and in an attempt to decrease the incidence of rejection. In three randomized trials the effects on renal function and on rejection incidence of the sequential use of monoclonal or polyclonal anti-T cell antibodies (first seven days) and oral CsA were compared with the effects of intravenous CsA followed by oral cyclosporin. Two trials have been completed while the third is ongoing.[19,20]

Azathioprine is added to the maintenance immunosuppressive regimen in patients suffering from recurrent rejection episodes, in patients who develop diabetes mellitus (thereby allowing discontinuation of prednisone) and in patients who develop cyclosporin related severe renal failure (thereby allowing reduction of the dose of CsA).

Rejection episodes are treated by pulsed high doses of methylprednisolon (1 gram iv on three consecutive days) on an outpatient basis, or by polyclonal or monoclonal anti-T cell antibodies (rabbit-antithymocyte globulin or OKT3-monoclonal antibodies against the T cell receptor) in cases of ongoing or frequently recurring rejection episodes, after admission to the hospital.

Infection, preventive measures

Preoperatively all infections should be eradicated. Special attention should be given to potential sources of infection including dental status, history of diverticulitis, symptomatic gallstones, recurrent urinary tract infections or bronchitis. Care is taken to exclude recent pulmonary infarction because the infarcted area is susceptible for secondary infection.

Cytomegalo virus (CMV) infection is particularly frequent after transplantation and may be dangerous. Therefore all heart transplant recipients who were seronegative for CMV initially were treated prophylactically with anti-CMV hyperimmunoglobulin after transplantation. Currently this prophylaxis is used only in CMV seronegative recipients who receive the heart of a seropositive donor because the risk for developing CMV infection or disease is extemely low in CMV seronegative patients who receive a heart from a seronegative donor.[21,22] Recipients who are seronegative for the parasite Toxoplasma gondii and receive the heart of a seropositive donor are treated prophylactically with pyrimethamine to prevent primary infection via the transplanted heart. Spiramycin was used for this purpose in the early phase of the program.[23]

Detection of coronary artery disease

Coronary artery disease of the allograft has been reported to be the most important limiting factor for long-term survival after cardiac transplantation.[24] Angina pectoris however, does usually not occur when the denervated heart becomes ischemic and non-invasive tests for ischemia are not reliable because of scar formation from rejection episodes in many patients. Therefore annual coronary arteriography has been performed in all heart transplant recipients.

The progression of coronary artery disease in the allograft has been studied in detail by quantitative analysis of serial coronary angiography (study supported by the Netherlands Heart Foundation).[25] In addition to this clinical study, in vitro models have been developed. Graft infiltrating lymphocytes have been successfully cultured and subsequently propagated from endomyocardial biopsies.[26] After the demonstration that such proliferated cells can lyse donor derived endothelial cells a study of the relation of T-cells and the development of transplant coronary vascular disease has been initiated (study supported by the Netherlands Heart Foundation).[27]

Routine follow up

Patients are kept under close surveillance by members of the transplant team to ensure early detection of infection and rejection and to facilitate recognition of complications of immunosuppression. They are advised to contact the transplant nurse immediately in case of fever (> 37.5°C) or other changes in physical or mental condition. The transplant cardiologist will then decide whether the problem can be handled by the local physician or whether the patient has to be seen in the transplant center. When hospital admission is necessary the patient will usually be admitted to the Transplant Unit of the Thoraxcenter or to a specific department of the University Hospital Rotterdam.

Frequent follow up visits are necessary for monitoring of rejection, for surveillance of the adverse effects of CsA, such as hypertension and renal insufficiency, and for surveillance of other complications of immunosuppression, such as malignancy. Moreover, less impressive side effects such as hirsutism and gingival hyperplasia need attention and the development of diabetes mellitus, cataract and avascular osteonecrosis, caused by corticosteroids, must be watched.

In addition to the information routinely gathered at follow up visits, quality of life assessment has been performed by investigators of the Institute

of Medical Technology Assessment of the Erasmus University.[28] Specific psycho-social aspects of heart transplantation have been studied by members of our psycho-social team.[29-31]

Statistics

Group data are presented as means ± SD or as absolute numbers or medians when appropriate. Differences are analyzed by the 95% confidence intervals (CI). The Kaplan Meier method is used for analysis of the survival rates. One patient received a second allograft 7 months after transplantation and has been included as one single case in the survival analysis.

RESULTS

Referrals

Between 1984 and December 31, 1992 816 patients were referred for cardiac transplantation. Initially a gradual increase of the number of patients referred per year was observed. In the last five years however, stabilization occurred at approximately 100 (86-118) patients per year. The abolishment of an upper age limit of 55 years for transplant candidates resulted in the referral of 105 patients older than 55 years between January 1, 1990 and December 31, 1992 which represent 31% of referrals during that period.

The outcome of the referrals is outlined in Table 2. Thirty six patients died between the initial contact by the referring cardiologist and assessment by the transplant center and 68 patients died during the actual assessment period. As a result of the increasing experience of the referring cardiologists the percentage of patients who were considered "too well" for transplantation has decreased from 21% in 1986 to 17% in 1989 and 15% in 1991.[32] Transplantation was denied in 152 patients as summarized in Table 3. Conventional surgical procedures such as coronary artery bypass grafting, left ventricular plasty or valvular replacement were advised to 55 patients.[33] In 39 other patients heart-lung transplantation appeared more suitable than heart transplantation because of high pulmonary vascular resistance or primary pulmonary problems. Referral to other transplant centers occurred in the very early phase of the program, when awaiting approval to perform heart transplantation in the Netherlands (2 patients referred to centers in Belgium and England). Because of lack of intensive care facilities in Rotterdam, 14

very ill patients who needed urgent assessment were referred to the Utrecht Transplant Center.

Table 2.

Referred to the Rotterdam Heart Transplant Program
1984 - January 1, 1993
816 patients
Results of assessment by the Transplant Team

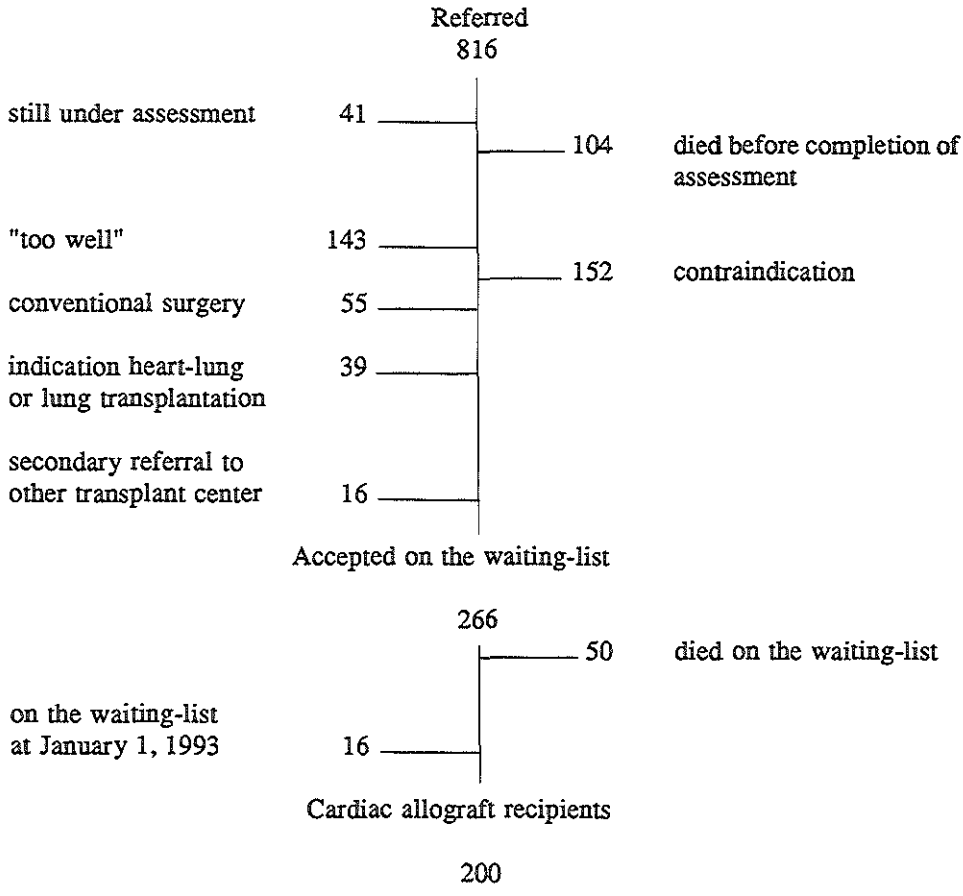

Table 3.

Reasons for denial of heart transplantation in 152 patients

contraindication	number
age > 55 years (before 1990)	34
peripheral vascular disease	20
diabetes mellitus	15
impaired renal function	15
systemic disease	6
psychiatric disorders	6
pulmonary infarction / bronchiectasies	6
pulmonary vascular resistance too high	4
persistent infection	3
patient refusal	3
alcohol / drug addiction	3
earlier malignancy	2
heparin induced thrombocytopenia	2
inability to communicate	2
living outside the Netherlands	2
sequelae of cerebrovascular accident	1
combinations of the above	28

Waiting-time

Two hundred sixty six patients were accepted for transplantation. Their ages ranged from 13 to 65 years. The mean age increased from 44 ± 10 before 1990 to 49 ± 11 years thereafter (Fig.1). The median waiting time gradually increased from 19 days (range 1-83) to 62 days (range 5-549). One hundred and twenty four patients were granted priority on the waiting list because of their dependence of inotropic or mechanical support (by intra-aortic balloon counter pulsation). Fifty patients died, mainly because of intractable heart failure, before a suitable donor heart had become available. Thirty six of the latter patients had been granted priority on the waiting list.

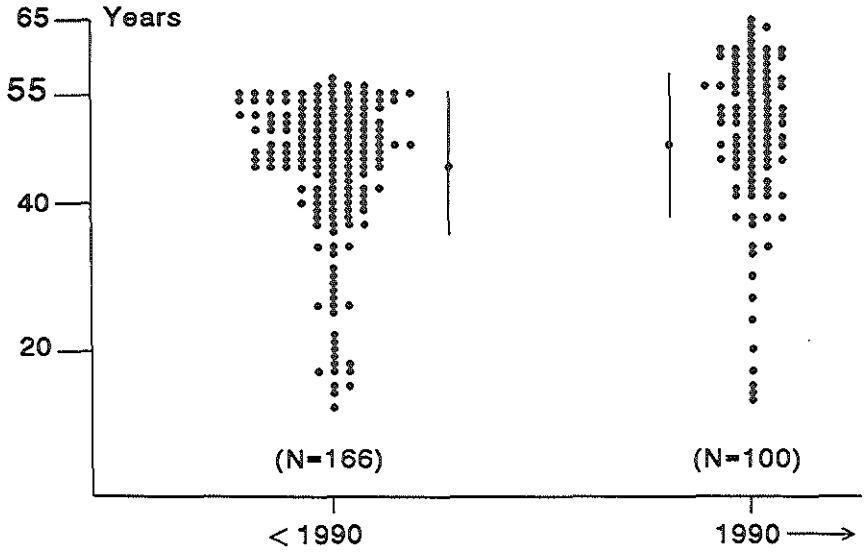

Fig. 1: Distribution of the ages of the 266 patients who were accepted on the waitinglist for a donor heart before and after early 1990. In the first period an upper age limit of 55 years was used. Means and standard deviations have been indicated.

Heart transplantation

Two hundred and one orthotopic cardiac transplantations were performed in 200 patients. One hundred and twenty four patients were in hospital, requiring intravenous inotropic support (in 110 patients) or additional mechanical assistance by intra-aortic balloon pumping (14 patients) at the time that a donor heart became available. The characteristics of the recipients are outlined in Table 4. The cold-ischemic time of the donor heart ranged from 74 to 280 minutes (median 154). Two patients died during the operation because of primary donor heart failure. Rethoracotomy in the immediate postoperative period was necessary in 33 patients, including 13 patients with prolonged bleeding, 6 patients with tamponade and 3 patients with cardiac arrest. In 3 other patients rethoracotomy was performed to rule out tamponade as the reason for low output. Right ventricular failure proved to be the main problem

in 2 of these patients and poor left ventricular function was the cause in one. In one patient with originally dextrocardia, rethoracotomy was necessary to relieve spatial problems of the implanted heart. Rethoracotomy was necessary in two patients because of dehiscence of the sternum after respectively 14 and 15 days. Reopening of the wound and closure over suction-irrigation tubes was performed in 5 patients with mediastinitis 1, 12, 21, 30 and 32 days respectively.

Table 4.

Characteristics of 200 Cardiac Allograft Recipients

gender m / f (nr)		168 / 32
recipient age (median, range)		47 (12-65)
underlying heart disease	CMP	92
	IHD	100
	other	8
donor age (median, range)		23 (9-43)
mismatch	HLA - A+B	2.9 ± 0.9
	HLA - DR	1.4 ± 0.6
mismatch gender donor / recipient		76
CMV recipient seroneg / donor positive		39

CMP: cardiomyopathy; IHD: ischemic heart disease; Other: valvular or congenital heart disease; HLA: Human Leucocyte Antigens; CMV: Cytomegalo virus serologic status.

Survival

The median follow up of the 200 allograft recipients is 46 months (range 3 to 94). The patient survival rates after 1 month, 1 year, 5 years and 7 years are 96% (95% confidence interval 93-99%), 92% (88-96%), 84% (78-90%) and 77% (69-85%) respectively (Fig.2). Malignancy, graft coronary artery disease and rejection were the main causes of death (Table 5).

The 30-day mortality in our transplant recipients has been remarkably low, 4% compared to the 9-10% reported by the International Society for Heart and Lung Transplantation.[34] This is especially worth mentioning when one takes into account that half of the patients were in the hospital requiring inotropic or mechanical support. In such patients a 30-day mortality of 14% has been reported.[35] In our series however, the 30-day mortality of patients on inotropics was comparable to the patients who were stable, at home: 4/110

versus 4/86. Only one patient who had been supported by intra-aortic balloon counterpulsation in addition to inotropic support died within thirty days after transplantation.

Table 5.

Causes of death (N = 29)

time	cause of death
during the operation	- right ventricular failure (1 pt) - failure both ventricles (1 pt)
< 1 month	- hypoxic encephalopathy (1 pt) - right ventricular failure (1 pt) - tamponnade by aortic suture dehiscence (1pt) - acute rejection (3 pts)
> 1 month and < 1 year	- malignant lymphoma (3 pts) - acute rejection and pericardial constriction (1 pt) - acute rejection (1 pt) - cerebral Toxoplasmosis (1 pt) - panencephalitis (Toxoplasmosis or viral infection)(1 pt)
> 1 year	- adenocarcinoma of stomach (14 months) - intracerebral hemorrhage after bicycle accident, clotting disturbances after alcohol abuse (15 months) - chronic donor heart failure (unknown cause) and renal failure (16 months) - Kaposi sarcoma (23 months) - plasmacytoma (26 months) - malignant lymphoma (31 and 60 months) - coronary artery disease (after 42, 43, 65 and 91 months respectively) - squamous cell carcinoma of lung (46 months) - sepsis after laparotomy for bleeding ulcer, end-stage renal disease (57 months) - Hepatitis-C virus hepatitis, encephalopathy (64 months)

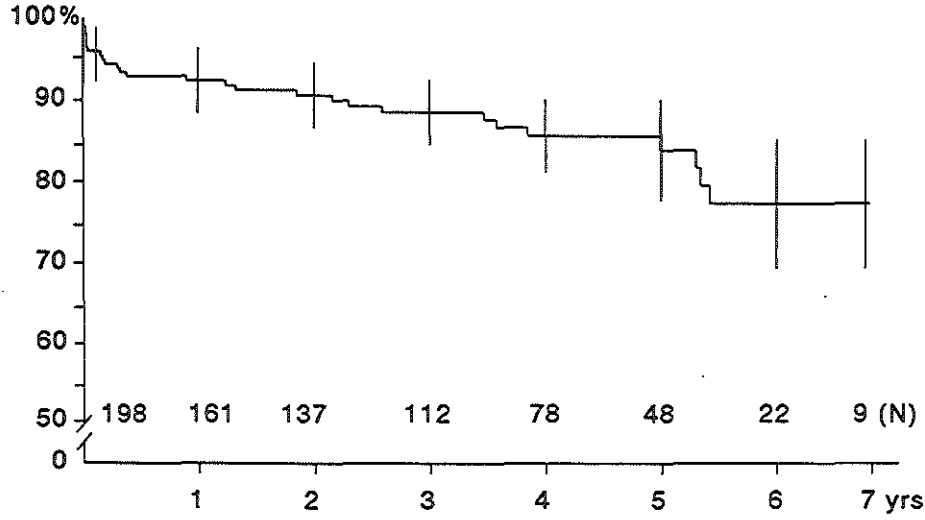

Fig. 2: Survival of the first 200 patients who received a cardiac allograft in Rotterdam. For each year the 95% confidence intervals are shown. The patient who received a second transplant is included once, leaving the second operation out of account.

Cardiac graft function - exercise tolerance

Systolic graft function, measured as the angiographically determined left ventricular ejection fraction, remained good over the years, with 90% (139/155), 96% (88/92) and 99% (36/37) of the patients showing ejection fractions higher than 55% after 1, 3 and 5 years. In contrast, exercise tolerance, measured by symptom limited bicycle ergometry, reached normal levels in a few patients only (Fig.3). This is caused by the combination of the delayed chronotropic response of the denervated heart, the myopathic effect of prednisone and lack of training.[36,37]

Quality of life

All patients have resumed their daily activities and most of them feel not impaired. All 8 youngsters have restarted school. Work resumption however is low. Evaluation of the activities of 106 transplant patients who

were unable to work prior to transplantation and who survived at least one year revealed that 23 (24%) resumed their former work full time and 13 (13%) part time. Sixteen patients (15%) have changed jobs but 54 (52%) remained out of work. This was mainly caused by the fact that they had been incapacitated for a long time prior to transplantation and thereby lost their jobs. Some patients are not eager to resume work. This may be the result of the endurement of a long-waiting time, which was characterized by physical exhaustion, of the uncertainty of surviving long enough to receive a donor heart and of the struggle through the problems of the first months after transplantation. Of the 14 women who had worked as housekeepers, 7 had resumed work for 100%, 6 for 50-75%, while 1 did not.

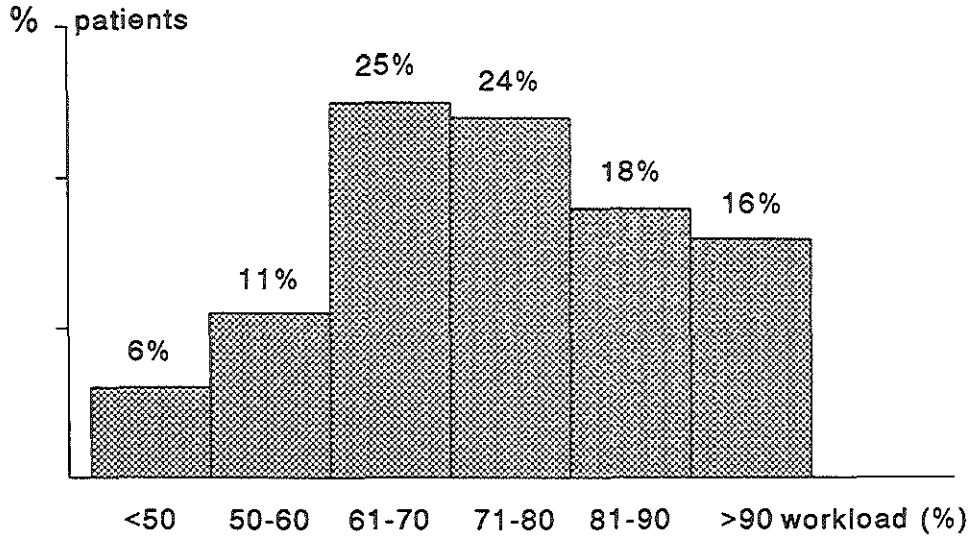

Fig. 3: Exercise tolerance, measured by bicycle ergometry, 1 year after heart transplantation in 156 patients. The percentages of patients who achieved distinct workloads, expressed as percentage of the normal value for gender, age and height, are presented.

Quality of life measurements using psychological questionaires, performed in 48 patients by investigators of the Institute of Medical Technology Assessment of the Erasmus University Rotterdam, showed that social and free time activities were not or hardly impaired after transplantation.

Subjective feelings of well-being were higher than in patients who were seen at the outpatient clinic for general cardiac problems. Scores for mental depression remarkably improved after transplantation, but remained worse than usual for a healthy (american) population.[28]

The main problems after transplantation

A summary of the major complications per year after transplantation is presented in Table 6.

The immediate postoperative period

Most patients experienced some degree of right ventricular failure. In 5 patients right heart failure resulted in low output and necessitated prolonged vasodilator and inotropic support. A sixth patient died because of right heart failure after seven days. One patient required intra-aortic balloon support for left ventricular failure, twelve hours after transplantation. The cause for this failure was not obvious as rejection was ruled out. After a year without rejection episodes, the left ventricular angiogram showed hypokinesis of the anterior wall without coronary lesions. The most probable explanation for the early failure, therefore, was damage of the myocardium during harvesting, transport or during transplantation. The median stay on the postoperative Intensive Care unit was 3 days (range 1 to 14 days). More than 90% of the patients could be transferred to the medium care area within 5 days after transplantation.

Patients in whom cyclosporin was started intravenously prior to the transplant procedure suffered from oliguria and hypertension. Oliguria hampered management of the fluid balance especially in patients who were volume overloaded preoperatively. Fever, chills and rashes resulting from cytokine release dominated the first two days of patients who were treated with anti-T cell therapy (OKT3 or anti-thymocyte globulin) for early immuno-suppressive prophylaxis.

Three patients suffered from seizures from cyclosporin neurotoxicity 4, 5 and 6 days after surgery. These patients recovered within days without sequelae. In a fourth patient, who also was treated by cyclosporin intravenously, asymmetrical paraplegia was noted 24 hours after transplantation. He recovered gradually, although it took 3 weeks until he was able to walk without help and 8 months until he was able to empty his bladder spontaneously.

Table 6.

Complications after transplantation								
Time after HTX	0	1	2	3	4	5	6	7 YEARS
Number at risk	200>198	161	137	112	78	48	22	9
Patients (%) with								
acute rejection	75	4	4	5	5	-	-	
infection								
bacterial	33	17	9	13	10	4	14	
viral	31	11	5	4	3	2	5	
other	9	-	-	-	-	-	-	
hypertension	90							
end-stage renal disease	-	-	1	1	1	2	5	
malignancy	3	1	2	1	1	2	-	
new cardiac event								
coronary	1	-	-	2	1	6	-	
other	4	1	-	-	-	2	5	
other major complications	5	4	4	3	1	4	18	
Patients (%) without major problems (other than hypertension)	8	65	76	70	73	75	55	

Major complications after heart transplantation (HTX). Data are presented as percentage of patients with each complication within each year following transplantation. End-stage renal disease: patients requiring renal function replacement therapy. After the first year, all rejection episodes and all infections (except one) could easily be managed medically. Other major complications included for example abdominal surgery for cholecystitis, surgery for peripheral vascular disease and hip replacement.

Most patients needed atrial stimulation to maintain the rate of the denervated heart above 100 beats/minute during the first postoperative days. Nevertheless, all patients could be discharged from the hospital with adequate rates of sinus rythm. The longest dependency on atrial stimulation was 21 days. Contrary to what has been reported by others, permanent electrical stimulation of the donor heart became necessary in 3 patients only (1.5% versus 12%)[38] A permanent pacemaker was inserted for sinus-node dysfunction (2 patients) and 3rd degree AV block (1 patient) after 13, 14 and 84 months respectively.[38]

We observed a high incidence of organic psychosyndromes in the immediate postoperative period. Visual and auditive hallucinations, manic behaviour and depressive mood changes occurred in 26 patients (13%) probably as results of extra corporeal circulation in combination with high dose corticosteroids. With growing experience and help of the psychiatrists, the nursing staff and other members of the transplant team have learned to recognize these symptoms early, which allows timely treatment with haloperidol often in combination with lorazepam. Recognition of mood changes and mental disturbances appeared easier in patients who were well known by members of the transplant team prior to transplantation.

Endomyocardial biopsy

More than 18000 biopsy samples (a mean of 17 procedures in the first year and 2-3 procedures therafter with 4-5 biopsies per procedure) have been taken without major problems. Perforation of the right ventricle occurred three times without hemodynamic sequelae. Tiny fistulas between coronary arteries and the right ventricle have developed in a number of patients as a result of repeated biopsies. In two patients such fistulas have grown to large left to right shunts after 3 and 72 months respectively. This gave cause for transcatheter embolization of the shunt in the latter patient.[39]

Rejection

As could be expected after random assignment, most donor hearts were poorly matched for HLA-A, HLA-B and HLA-DR loci (Table 4). Despite heavy immunosuppression acute rejection occurred often, especially during the first months after transplantation (Table 6). One patient suffered sudden death, probably from arrhythmogenic origin, 2 months after transplantation. Extensive

mononuclear infiltrates and myocyt necrosis were found at autopsy. Hemodynamically compromizing rejection episodes occurred in 4 patients. Fever accompanied rapidly progressive heart failure in three patients, 10-12 days after transplantation, resulting in death within 12 hours. Biopsies in 2 of these patients had been without rejection infiltrates 48 hours earlier while extensive infiltrates and myocyt necrosis were found in the myocardium at the time of hemodynamic deterioration and at autopsy. In the third patient myocardial ischemia and necrosis were found without infiltrates. Immunostaining was not performed, although this might have revealed antibodies and interferon as signs of humoral rejection. A fourth patient presented with fever, hypotension and hepatomegaly 2 months after transplantation. Her biopsy showed signs of acute rejection, which was treated with methylprednisolon and OKT3. Inotropic support was necessary for 10 days. She recovered fully and is alive, 3 years after transplantation. In all other patients, rejection episodes occured without noticeable symptoms. Twenty five percent of the recipients remained free from rejection but another 22% suffered from more than 2 episodes in the first year (Table 7). Ongoing rejection, not reacting to repeated courses of high doses of steroids and anti-T cell antibodies was a problem in 4 patients. Over time, however the rejection infiltrates gradually subsided while graft function remained good.

After the first year only 31 rejection episodes were noted in 25 patients. This can be explained by the fact that the rejection process subsides over time it has also to be appreciated that biopsies were taken only 2-3 times per year in this period after transplantation. None of these late rejection episodes caused hemodynamic deterioration.

Table 7.

Incidence of acute rejection in the first year after transplantation

rejection episodes	N	(%)
0	49	(25)
1	65	(32)
2	42	(21)
3-4	35	(17)
> 4	10	(5)

N: number of patients. The patient who received a second transplant is included twice.

Immunosuppressive therapy

Early immunosuppressive prophylaxis consisted of intravenous cyclosporin, polyclonal anti-T cell antibodies (Horse-ATG), monoclonal antibodies against the CD3 structure of the T cell receptor complex (OKT3) or monoclonal antibodies against the interleukin-2 receptor (BT563) in 64, 41, 78 and 16 patients respectively. Cyclosporin was started prior to the operation and anti-T cell antibodies shortly after surgery. The two patients who did not survive the operation had been treated perioperatively by corticosteroids only. The patient who underwent a second cardiac transplantation received cyclosporin intravenously at the time of the first operation and was treated with Horse-ATG after the second procedure.

The first randomized trial revealed that the sequential use of OKT3 and oral cyclosporin (initiated after 5 days) facilitated patient management by the prevention of renal failure which occurred when CsA was started intravenously at the time of the operation. In the second trial, initial therapy with Horse-ATG caused more allergic reactions (skin flares) compared with OKT3. No differences in the incidences of rejection episodes were found.[19,20]

Maintenance immunosuppression consisted of cyclosporin and low dose prednisone. In 25 patients azathioprine was added because of recurrent rejection episodes (16 patients, after a median of 4 months, range 2 to 10) or because of renal insufficiency (9 patients, after a median of 11 months, range 1 to 54). The combination cyclosporin/prednisone was replaced by cyclosporin/azathioprine in 4 patients because of diabetes mellitus (3 patients) or avascular osteonecrosis (1 patient). In another patient with progressive heart failure and renal insufficiency, 14 months after transplantation, cyclosporin was replaced by azathioprine. He died from heart failure, without signs of rejection tree months later. The replacement of prednisone by azathioprine because of diabetes mellitus failed in another patient, as rejection occurred soon after prednisone was stopped. Thereafter the patient was kept on triple therapy.

We demonstrated that controlled, randomized trials are necessary to compare the effects of different immunosuoppressive regimens. Comparison with historical controls appeared not reliable, since fewer rejection episodes were found in patients treated with OKT3 when compared to our first 33 patients who received cyclosporin while such difference was not shown in the randomized trial.[19] As an ideal regimen for the prevention of rejection has not been found yet, research will continue to prevent the alloreactive response by rendering the future recipient unresponsive towards the graft e.g. by selective

bloodtransfusion.[10,11] For this purpose multicenter randomized trials should be pursued because the numbers of allograft recipients per center are limited.

Complications of immunosuppressive therapy: infection

In this report infection is defined as infectious disease requiring treatment unless stated otherwise. Superficial lesions of the oral mucosa from Herpes simplex I virus occurred in almost all patients between the end of the first week and the fourth week. Also superficial dermal fungus infections (Pityriasis versicolor) were frequent (15% of the patients) but systemic fungus infections did not occur. Other, more severe infections occurred in 75% of the patients in the first year (Table 6).

In the early postoperative period, sternal wound infections ocurred in 8 patients. Reopening of the wound was necessary in 5 patients for this reason and drainage of superficial abcesses in 3 others. All 8 patient recovered. Two of 15 patients who had been treated by intra-aortic balloon pumping developed infected lymphe fistula in the groin. Both patients fully recovered although hospitalization was prolonged and the rehabilitation was delayed.

Most infections outside the immediate postoperative period were of bacterial or viral origin (Tables 8 and 9). The respiratory and urinary tracts were the most common localizations for bacterial infections. Cytomegalo virus was the most common viral agent. All bacterial and all viral infections except one could be managed medically. Of major concern were the occurrence of Hepatitis-B virus infection in one patient and Hepatitis-C virus infection in another. Whether these infections had been transmitted by bloodproducts or by the donor organs could not be traced. Hepatitis-B virus infection resulted in a mild form of chronic hepatitis. Hepatitis-C virus infection resulted in chronic aggressive hepatitis, ultimately leading to hepatic encephalopathy, coma and death. The significance of infection with the Hepatitis-C virus for the immunosuppressed transplant recipient has only recently be identified and discussion has been started among transplant centers whether Hepatitis-C positive donors should be used.[40] Serological signs of Herpes simplex I infection were found in one patient who developed severe confusion and hallucinations, 12 days after transplantation. Considering the diagnosis of Herpes simplex I encephalitis treatment with acyclovir was initiated. Symptoms however, subsided within 12 hours after the first dose of acyclovir which made the diagnosis of encephalitis unlikely.

Table 8.

Viral and protozoal infections after heart transplantation

agent	time of occurrence < 1 year	> 1 year
Cytomegalo virus	31	-
Herpes simplex virus type I		
keratitis	4	-
encephalitis	1	-
Herpes simplex type II	4	-
Human papilloma virus	2	1
Varicella zoster virus	11	13
Epstein Barr virus	3	2
Hepatitis-B virus	1	-
Hepatitis-C virus	1	-
Pneumocystis Carinii	4	-
Toxoplasma gondii	5	-

Influenza virus infections and "viral syndromes" without determination of the agent are not presented.

Infection with Toxoplasma gondii has caused major problems. One patient with strong serological evidence of toxoplasmosis died from encephalitis 4 months after transplantation. However, no Toxoplasma parasites or antigens were found at autopsy. A second patient, with minor changes in Toxoplasma serology, also died from encephalitis and showed cysts in cerebro as well as in the heart. Both patients had been seronegative prior to transplantation and had received hearts of seropositive donors. The first patient had been treated prophylacticall with spiramycin which more recently has been shown not to protect against seroconversion.[41] In the second case primary infection could develop when pyrimethamine prophylaxis was withheld because of leukocytopenia in the early postoperative phase. Pneumocystis Carinii infection caused pneumonitis in 4 patients and could be successfully treated by cotrimoxazol.

Table 9.

Bacterial infections after heart transplantation

localization	time of occurrence < 1 year	> 1 year
ear, nose, throat and bronchi	33	58
urinary tract	22	8
lungs	4	8
skin / nails	3	13
intestinal tract	2	-
bacteremia (Listeriosis/Salomonellosis)	3	-
gallbladder / bile ducts	-	3
Nocardiosis of lungs[70]	1	-

Early sternal wound infections have not been included.

It should be noted that the CMV infections and all parasitic infections occurred within the first year. The early occurrence of these infections, which are rare in patients who are not immunocompromised, may be explained by the heavy immunosuppression during that time which is characterized by many rejection episodes and by the fact that primary infections can be the result of transplantation of the heart of a CMV seropositive donor or a heart containing Toxoplasmose cysts into recipients who not had been infected before.

Complications of immunosuppressive therapy: hypertension and renal insufficiency

Ninety percent of the patients have developed hypertension (bloodpressure > 150/95) as a result of cyclosporin. This hypertension is characterized by lack of circadian variation as we have described before.[42] The incidence of hypertension in our population equals incidences reported by others.[43] Several factors contribute to this hypertension: cyclosporin increases the vascular smooth muscle tone and the smooth muscle tone response to vasoconstrictors and increases the production of endotheline.[44,45] In addition, the production of prostacycline by vascular endothelium is blunted.[46] In our

experience calcium channel blockers have been most successfull in lowering bloodpressure although normal blood pressure was rarely achieved.

Hemodialysis was necessary in the immediate postoperative period in two patients, both suffering from low cardiac output. One of these patients died from intractable right heart failure and the other recovered. During longer follow-up, impaired renal function due to cyclosporin appeared to be a major problem. The initial effect of cyclosporin on renal function is acute, reversible, dose dependent, reduction in renal blood flow by vasoconstriction of the afferent glomerular arterioles. Prolonged use may result in chronic, progressive renal obliterative vasculopathy with irreversible interstitial fibrosis resulting in severe impairment of renal function.[47] Moderate to severe renal failure, with serum creatinine levels between 150 and 250 µmol/l, developed in 38%, 56% and 67% of the patients after 1, 2 and 5 years respectively (Fig.4). Up to March 1993, 6 patients had progressed to end-stage kidney disease and required hemodialysis or peritoneal dialysis (Table 6). One of the latter patients received a kidney allograft. Unfortunately, this graft failed primarily and has been removed subsequently.

Based on these results and on the fact that the patients until now have been on relatively high doses of cyclosporin (6-7 mg/kg/day in the first year) we have recently decided to lower the targeted cyclosporin blood levels to prevent further deterioration of renal function, hopefully without excessive increase of rejection episodes.

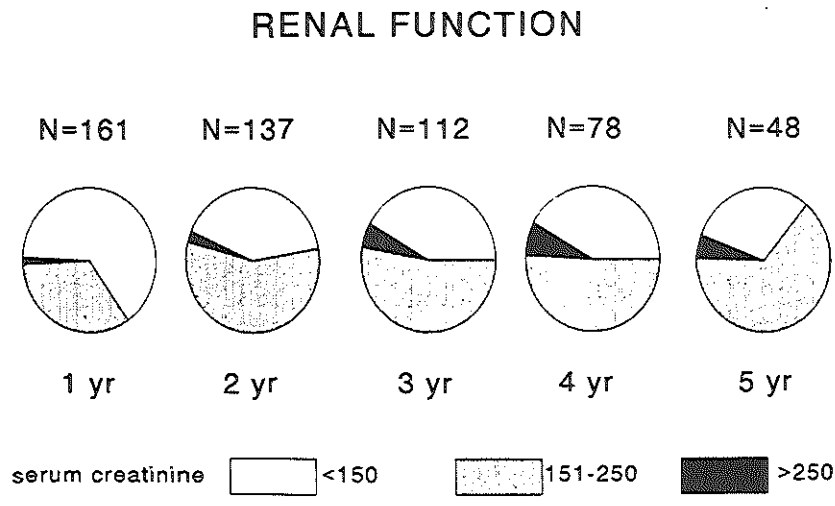

Fig. 4: Percentages of patients with impaired renal function, per year after transplantation.

Complications of immunosuppressive therapy: malignancy

Clinically overt malignant disease occurred in 15 patients with an average rate of 2% per year (Table 6). Five patients developed rapidly progressive malignant lymphoproliferative disease (MLPD) after 4, 4, 11, 31 and 60 months respectively and died within weeks. In one of the patients in whom MLPD was diagnosed 4 months after transplantation, squamous cell carcinoma of the lung had been found one month earlier. A sixth patient currently is treated for malignant lymphoma by chemotherapy. In a patient from mediterranean origin, epidermoid carcinoma of the palatum was diagnosed one week after transplantation and successfully treated by laser excision. The patient died 23 months after transplantation from Kaposi sarcoma. In another patient adenocarcinoma of the stomach was diagnosed after 7 months; he died eight months later. Two further patients died from plasmocytoma and squamous cell carcinoma of the lung after respectively 22 and 24 months. One patient underwent nephrectomy for renal cell carcinoma, 57 months after transplantation and is well 11 months later. Superficial neoplasias from the skin have been treated surgically in 4 patients: carcinoma in situ (1 patient), squamous cell carcinoma (2 patients) and basal cell carcinoma (1 patient).

Malignancy in transplant recipients can originate from pre-existing malignancy in the recipient, from unsuspected neoplasms in the donor or can be de novo cancer. The incidence of malignancy varies in different centers and has been reported to be higher in heart transplant recipients than in renal transplant recipients as a result of higher net state of immunosuppression. In our series of patients who survived at least one month, malignancy occurred in 3/39 patients (8%; 1 pt MLPD) in whom whom no other immunosuppressive agents than cyclosporin and prednisone were administered and in 12/153 patients (8%; 5 patients MLPD) who received at least one course of monoclonal or polyclonal anti-T cell therapy. Although we initially reported a higher rate of malignancy in patients who had received more intense immunosuppression,[48,49] analysis of the current data shows no statistically significant difference, neither for malignancy in general nor for MLPD, between these two groups of patients.

An overall 10% risk of malignancy has been found in cardiac allograft recipients, malignant lymphoproliferative disease and carcinoma of the skin and lips being the most common forms of cancer.[50,51] Although impressive, the incidence of neoplasia in our patients therefore is not allarmingly high (Table 6).

Cancer was probably already present prior to transplantation in two patients. Thus a higher suspicion towards pre-existent malignancy may be warranted. An epidermoid carcinoma of the palatum became evident within one week after transplantation in one patient in whom also gastrointestinal localisations of Kaposi's sarcoma were demonstrated after 11 months. In retrospect, Kaposi skin lesions already had been noticed by the patient and his relatives prior to transplantation. The language barrier between the patient or his relatives and the transplant team may have contributed to the fact that such information did not reach us. The vast extension of an adenocarcinoma of the stomach in a second patient, 7 months after transplantation, made curative resection impossible. In this patient also pre-existent malignancy may have been overlooked because he had been complaining of anorexia prior to transplantation. This anorexia however had been ascribed to end-stage heart disease with liver and gastrointestinal congestion.

An association between Epstein Barr virus (EBV) infection and lymphoproliferative disease, as has been reported since 1988, could be demonstrated in two of our patients.[52] In one patient, with reactivation of latent EBV infection, malignant lymphoma was preced by mononucleosis-like symptoms 5 months earlier, which initally responded well to treatment with acyclovir. The second patient, with primary EBV infection, progressed within two months from minor febrile illness to generalized malignant lymphoma and death. Further research directed to the precise relation of the development of lymphoproliferative disease and EBV virus infection will be necessary.

Other complications of immunosuppressive therapy

Perforation of the intestines and subsequent peritonitis occurred in three patients (diverticula of the sigmoid in 2 patients and appendicitis in 1 patient) and caused diagnostic problems. Symptoms characteristic for peritoneal irritation (pain and reflex spasm of the abdominal musculature) were absent as a result of the blunted inflammatory reaction caused by immunosuppressive therapy. All three patients survived this complication.

Gingival overgrowth, as a result of the use of cyclosporin, was observed in 67% of all patients who are without complete dental prosthesises.[53] Gingivectomy has been performed in 7 patients. The concomittant use of nifedipine may have contributed to the development of gingival overgrowth.[54] Meticulous daily dental hygiene and regular removal of plaque are the currently prescribed preventive measures, because plaque formation results in

chronic inflammation of the gingiva which is enhanced by the use of cyclosporin and nifedipine.

Twenty patients developed hyperglycemia after the institution of steroids although none of the patients reported here suffered from diabetes mellitus before transplantation. Insulin therapy has become necessary in three patients only.

Avascular osteonecrosis occurred in two patients. A 50 year old man underwent total hip replacement and a 16 year old girl underwent osteotomy of the femurhead 4 and 2 years after transplantation respectively. The latter patient had been treated with massive amounts of steroids before transplantation in an attempt to treat active myocarditis.

Hypercholesterolemia is a frequent finding in all heart transplant recipients because of the effects of steroids and cyclosporin.[55] Despite dietary recommendations, the mean total cholesterol levels in our series were 7.3 ± 2.0 mmol/l and 7.4 ± 1.5 mmol/l after 1 and 2 years respectively with 31% of the patients having levels above 8 mmol/l. HDL-cholesterol levels however, were within normal limits : 1.32 ± 0.27 and 1.52 ± 0.33 mmol/l respectively in patients with and without coronary artery disease as the underlying problem before transplantation. Until now we have refrained from aggressive medical treatment because of lack of evidence that such hypercholesterolemia has a significant negative impact on the progression of transplant coronary artery disease.[25,56] Moreover, the combination of HMG CoA reductase inhibitors and cyclosporin may result in severe rhabdomyolysis[57] while the administration of resins and fibrates may interfere with cyclosporin absorption resulting in subtherapeutic blood levels.

Psychiatric disorders were observed in 8 patients outside the immediate postoperative period. Five patients suffered from depression 6, 8, 11, 16 and 26 months after transplantation respectively. Psychosis occurred in two patients 7 and 26 months after transplantation. One of the latter patients had been denied heart transplantation, because of former psychiatric disease, by an other transplant team while he lived in Belgium. Five patients needed psychiatric help and medication only temporarily. Two patients still take medication and one patient has withdrawn from psychiatric support.

Allograft coronary artery disease

Rapidly progressive graft failure 6 months after transplantation was the result of severe, diffuse coronary artery disease in a 31 year old man. A retrospectively performed crosmatch with historic sera appeared positive

contrary to the prospective negative test with current serum, prior to the transplantation. He received a second donor heart, not expressing the HLA-A locus against which he had preformed antibodies, and is alive 5 years after this procedure (without significant coronary artery disease).

Four patients died because of coronary artery disease, 42, 43, 66 and 91 months after transplantation. In the latter two patients balloon dilatation and atherectomy of proximal lesions of the left anterior descending and circumflex arteries had been performed 17 and 22 months earlier. One other patient sustained acute right ventricular infarction 68 months after transplantation, 11 months after demonstration of a less than 50% stenosis of a small right coronary artery. He presented with pain located in his left shoulder accompanied by ECG changes compatible with myocardial infarction. His complaints were not typical and were probably caused by pericardial irritation although angina pectoris and other signs of reinnervation in patients with devervated hearts have been reported before.[58-60]

Completely smooth epicardial branches were found in 80% and 39% of the patients after 1 year and at 5 years respectively (Table 10) while slight wall irregularities were observed in most other patients. Localized lesions with >50% reduction of the luminal diameter were rare. Pruning and complete obliteration of small branches, earlier described as typical for graft arteriosclerosis, were noted only twice. Similarly, serial quantitative measurements of the coronary luminal diameters showed no significant changes in mean luminal diameter.[25] Other centers did report a gradual development of coronary artery narrowing.[61] Until now, we have not been able to identify risk factors for the development of graft vascular disease using visual analysis of the angiograms.[56] Applying quantitative analysis of angiograms however, a relation of coronary artery disease prior to transplantation with the decrease of mean coronary luminal diameter was found.[25]

By visual analysis of angiograms of 119 patients, who have survived at least one year after transplantation, we have been able to distinguish two groups. After one year there were 101 patients with completely smooth epicardial branches and 18 patients who showed irregular epicardial wall linings. Neither ischemic events, myocardial infarctions, nor death by coronary artery disease occurred in patients with smooth epicardial branches and no significant coronary artery disease became visible on the angiograms in the subsequent 4 years. In contrast, 5 of the 18 patients with irregular wall linings, developed severe coronary artery disease within four years. This implies that the development of coronary artery disease is related to events occurring in the first year after transplantation, although the precise nature of these events is

still uncertain. Based on these findings we now postpone angiography until after the 4th year in patients with normal epicardial branches after one year. In the other patients angiography is repeated after one or two years.[56]

Table 10.

Coronary arteriography (visual analysis)

CAG	Number	Normal	> 50 stenosis	minor abnormalities
1 year	161	127 (79%)	1 (1%)	33 (20%)
3 years	94	54 (57%)	3 (3%)	37 (40%)
5 years	38	15 (39%)	5 (13%)	18 (48%)

The incidence of coronary artery disease in our patients is limited. However, it is hard to compare these results with results of other centers because different definitions have been used for the diagnosis of vascular disease of the allograft and different methods were used to analyze the occurrence of the disease (e.g. pathological examination, qualitative angiography, quantitative angiography, intravacular ultrasound).[25,61-64] Nevertheless the number of patients who died from coronary artery disease, 4 deaths during 663 patient years follow-up (median 3.8 years) seems lower than reported by other centers.[65] This difference may be a chance finding but it may also represent a delay in the occurrence of vascular disease in the graft related to the use of calcium blocking agents.[66] or to the relatively high cyclosporin doses. Longer follow up will be necessary to allow an answer to this question. The identification of a subgroup of patients, based on coronary angiography after one year, who are at high risk for developing early coronary artery disease, opens perspectives for future research directed to the association between changes in vascular walls and immunological processes directed to vascular endothelium.

DISCUSSION

The postponed start of the program in 1984 allowed us to build on the experience of the few heart transplant centers which had continued research despite early disappointing results and on the vast experience of the internists in our hospital who, at that time, had managed more than 400 renal transplants. Accordingly the survival rates have been excellent from the start. In fact, the survival rates of our transplant recipients equal the best results reported by a single center,[67] compare favourable with those reported by most other European and North American transplant centers with longstanding experience[24,65,68] and are far better than the overall survival rates rates reported in the Registry of the International Society for Heart and Lung Transplantation: 92% one year survival in our series versus overall 80% survival at one year.[34] In our opinion these results can be partially explained by strict adherence to the protocol and by continued follow up by a limited number of specialists. To prevent the three most threathening problems of the early post transplant phase (donor heart failure, rejection and infection) meticulous attention was paid to recipient and donor selection, to exclusion of those patients with persistent infection and to inotropic and vasodilatory support of the implanted heart. The daily care of the allograft recipients has been in the hands of the transplant cardiologists who cooperated closely with the nursing staff and with colleagues from the departments of thoracic surgery, internal medicine/transplantation, anesthesiology, pathology, microbiology and psychosocial care. The nurses of the transplant outpatient-clinic appeared invaluable by their ability to detect, report and monitor problems of the patients after discharge from the hospital.

In spite of the excellent results one has to appreciate that the costs of a transplant program which "takes care of" a limited number of patients, are high. The costs per life year gained have been calculated at Dfl 57.650. This compares favourably with for example hemodialysis (Dfl 65.000 - 88.000) and treatment of hypertension (DFL 44.000).[28] Without closing the eyes for the needs of other patients who might be cured by less expensive treatment modalities, one should appreciate the impact of the experience, gained in heart transplant programs, on the care of other patients. For example: by "bridging" patients with end-stage heart failure to transplantation we have learned how treatment of other patients with severe heart failure, a group of patients which is rapidly increasing, can be improved.

The indication for heart transplantation has gradually become clear to the referring physicians and the percentage of patients who were considered "too well" has declined over the years. During the early years of the transplant program patients were referred on the mere finding of a low left ventricular

ejection fraction without allowance for the mechanisms which may compensate for the failing pump. The excellent survival rates of those patients who were considered "too well for transplantation" support the policy which has been practised.[33] More attention is required at the other side of the referral spectrum: one third of the patients who died before assessment had been completed were never seen by the transplant team. They died after the initial contact between their cardiologist and the transplant team, before actual assessment had been possible. It should be appreciated that transplantation can not be considered an emergency procedure and will not be able to save patients with rapidly progressive heart failure since donor hearts are not immediately available. Accordingly, patients with chronic heart failure who might benefit from transplantation should be referred timely to allow assessment by the transplant team.

Still, when offering heart transplantation to a patient, one should remember the limitations of Heart Transplant programs as presented in this paper. In addition to the medical limitations, the capacity of the two Dutch transplant centers is limited. In 1991 and 1992 respectively 92 and 69 hearts have been reported available but only 43 and 44 have been used in The Netherlands while 20% of potential recipients died on the waiting list.[69] One reason for this discrepancy is the fact that the Dutch centers apply more strict donor criteria than some other centers abroad. Moreover, optimal use of donor organs in the Netherlands is hampered by lack of capacity of the transplant programs. Both in 1991 and in 1992 we could not accept 10 hearts which were offered mainly because of shortage of intensive care nurses.

The near future

The referral for heart transplantation has remained below an estimated minimum number of 150 transplantations per year (advise Health Council 1989).[7] One may expect however, that the referrals will increase steadily over the next years because of the growing awareness of the benefits of transplantation and because of the abolishment of the upper age limit for recipients. With the current number of donor hearts this will result in a growing deficit between need and supply. Therefore two problems have to be solved: shortage of donor hearts and lack of facilities in the transplant centers.

The number of donor organs can be increased. Besides measures taken by the government including a new law and programs to increase awareness of the general population towards donation, cardiologists can play an active role by drawing their neurological and neurosurgical colleagues' attention to

organ donation. In addition cardiologists may encourage the institution of protocols for donation in their hospitals and may, during medical audits, comment on patients who died without the consideration of organ/tissue donation.

In order to accomodate the heart transplant program, the facilities of the Thoraxcenter have been extended. However, during recent years the program requirements exceeded these additional facilities, while also other developments required additional space and personal such as the program for interventional cardiology and extension of the program for cardio-thoracic surgery. Continuation of the heart transplant programs in Rotterdam and Utrecht at the current volumes requires more personal and more space. Alternatively a third center for cardiac transplantation in The Netherlands might be developed.

As a result of the excellent survival rates of the transplant recipients the continuation of care of these patients requires additional facilities. In Rotterdam, in-hospital and outpatient-clinic facilities have reached their limits, which necessitates either additional investments in the Thoraxcenter or the search for other models for patient care. Enlarging the capacity of the transplant center will result in concentration of diagnostic and therapeutic expertise. Such concentration of expertise will facilitate further research and will probably be the most cost-effective approach. Another approach might be to split the long-term care of the cardiac transplant recipients up between the three centers which participate in the Rotterdam Heart Transplant Program or between other centers with expertise in organ transplantation, for example centers for kidney transplantation. The main draw back of the latter choice would be the loss of research specifically directed to the cardiac allograft. A third possibility might be continuation of the direction of care by the transplant center leaving the technical execution of diagnostic and therapeutic procedures to the referring cardiologists. The referring cardiologist however, lacks experience in the detection, monitoring and treatment of problems of patients under immunosuppressive therapy and when the transplant center is asked to advise there will always be a delay. In making the decision on which way to go one has to keep in mind that an immense amount of work has been done by many people to achieve the results presented here.

In conclusion, heart transplantation offers good quality of life for a considerable number of years to patients who otherwise are deemed to death. Transplantation however, can be offered to a limited number of patients only and almost 20% of the candidates die on the waiting list. The cardiac allograft recipient will experience many problems most of which can be solved by

meticulous care and attention. These efforts however, appeared very rewarding and the current results encourage the transplant team to proceed.

ACKNOWLEDGEMENTS

The care of heart transplant recipients requires, again and again, deliberations about complex situations through which the transplant team has not gone before. The strenght of the Rotterdam program lies in the day to day and "hour to hour" cooperation between many specialists. For the achieved results we are indebted to our colleagues "at a distance" of the departments of Cardiology and Thoracic Surgery of the University Hospital, Leiden and the St.Antonius Hospital, Nieuwegein. "At home" we thank our colleagues of the departments of Cardiology, Thoracic Surgery, Internal Medicine I, Pathology, Microbiology, Pulmonary Medicine, Anesthesiology, Psychiatry, Psychology and Social work for their dedication. Special thanks go to the nursing staff who has added a "new horizon" to the care of the cardiac patient. The Transplant Coordinators have enabled us to harvest the grafts and the investigators of the (transplant) laboratory of Internal Medicine I have opened our eyes for what is happening inside the transplanted heart.

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SUMMARY

This thesis describes part of the efforts of the Rotterdam Heart Transplant Team to optimize the care of the patients referred for heart transplantation. These efforts include analysis of the problems which currently predominate in heart transplantation and subsequent clinical research directed to the solution of these problems.

Part I addresses the patient who is referred for heart transplantation. It is shown that, with current medical regimens, many patients with severely depressed pumpfunction may have an acceptable survival rate, allowing postponement of transplantation to a later date. Part of the deaths of patients who initially appeared "too well" for transplantation can be prevented by offering heart transplantation yet when heart failure symptoms worsen. Nevertheless shortage of donor organs still will result in death of some of these patients (Chapter I).

A review of the results of conventional surgery in patients who had been referred for transplantation identified patients at high risk for unfavourable outcome of such procedures. Systolic bloodpressure below 115 mmHg, pulse pressure below 30 mmHg, a third heart sound and signs of right heart failure proved to be factors associated with poor prognosis (univariate analysis). This finding has refined our choice between conventional surgery and heart transplantation and has resulted in further exploration of the limits of reparative surgery in the Thoraxcenter (Chapter II).

Methods for mechanical circulatory support in patients with extreme heart failure are reviewed in Chapter III. Our experience with one of such methods, intra-aortic balloon counterpulsation, shows that this method is effective in restoring cardiac output sufficiently to prevent organ damage, even in patients with chronic heart failure. However, after that pumpfailure will increase in many patients beyond the ability of the balloon pump resulting in death. Moreover, within a few days patients are threathened by infection which consequently makes them no longer suitable candidates for tranplantation. The question how to proceed with mechanical circulatory support is left open.

Part II reviews the necessity for immunosuppression and presents the results of two randomized trials comparing immunosuppressive regimens. In an attempt to reduce the incidence of rejection and the extent of nephrological problems early after transplantation the effects of cyclosporin (started

intravenously prior to the operation) were compared with a regimen consisting of sequential OKT3 and cyclosporin. In both groups low dose steroids were used. No difference in freedom from rejection was found. Nephrological problems however were prevented by omission of cyclosporin during the first days after transplantation (Chapter IV). In a second trial the effects of early rejection prophylaxis with monoclonal anti-T cell antibodies (OKT3) were compared with the effects of polyclonal anti-T cell antibodies (horse-ATG). Both regimens were equally effective but horse-ATG caused extensive flares, in 20/28 patients (Chapter V).

We demonstrated that only controlled randomized trials can truly compare the effects of different immunosuppressive regimens. Comparison of the OKT3 regimen of the first trial with historical controls showed a significantly lower incidence of rejection in the former patients while no such difference was apparent within the randomized trial. With limited numbers of allograft recipients per center, transplant centers therefore should cooperate in multicenter trials for the assessment of long-term effects of immunosuppression, e.g. the incidence of infection and malignancy or the occurrence of graft vascular disease.

Part III puts "accelerated coronary artery disease" of the cardiac allograft in a clinical perspective. Data from the literature do not allow comparison of the incidences of graft vascular disease in the different heart transplant centers because different methods are applied for the detection of graft vascular disease such as histology, angiography and intravascular ultrasound. Moreover, when angiography is used, definitions of graft vascular disease differ widely (Chapter VI). Visual analysis of the annual coronary angiograms of the Rottterdam heart transplant recipients revealed two main patterns of vascular changes: abnormalities of the large epicardial vessels and abnormalities of the tertiary, mainly intramyocardial branches. A median follow up period of 43 months showed that significant coronary obstructive lesions or death by coronary artery disease occurred only in those patients who had abnormal epicardial branches at their first year angiogram. Based on these findings we reduced the number of annual coronary angiograms in our patients (Chapter VII). In addition to visual analysis we applied quantitative analysis of coronary angiograms after automated edge detection and concluded that this method can overcome the differences in definition of graft vascular disease thereby allowing objective comparisons between different centers or various treatment regimens. Decreases in luminal coronary artery diameter appeared small. The finding of a significant decrease in the first year however, was in agreement

with the results of the visual analysis and has incited us to initiate further studies on early development of graft vascular disease (Chapter VIII).

Part IV reports the main draw backs of aspecific immunosuppression in general: infection and malignancy and of cyclosporin in particular: impairment of renal function. Especially Cytomegalo virus infection and disease have been studied because in the transplant literature this pathogen appeared to be responsible for a high incidence of morbidity and even mortality in allograft recipients. We have applied passive immunization against this virus in CMV seronegative transplant recipients. Such regimen resulted in comparable infection rates in seronegative recipients of the heart of a positive donor and in seropositive recipients. A striking finding was a higher incidence of CMV disease in all patients who received the heart of a seropositive donor versus a seronegative donor, thus irrespective of recipient serology. In contrast with the findings in other transplant programs no relation was found between the ocurrence of CMV infection or disease and cardiac graft vascular disease (Chapter IX).

Malignancy accounts for one third of the deaths in our program and half of these malignancies were of lymphoproliferative origin. Therefore, we explored the relation between the occurrence of lymphoproliferative disorder and immunosuppressive therapy. Initially it appeared that the incidence of this disease is related to the total immunosuppressive load as 6 of 101 patients who were treated with additional anti-T cell therapy suffered from transplant lymphoproliferative disorder as contrasted with none of 41 patients treated with cyclosporin and prednisone alone (Chapter X). However, extension of the patient population and longer follow up demonstrated no statistically significant difference in survival free from malignancy in general or lyphoproliferative disorder in particular between these two groups of patients (Chapter XII).

We have been confronted with an increasing number of heart transplant recipients suffering from impaired renal function which has resulted in end-stage renal failure necessitating renal function replacement therapy in 6 patients up to the spring of 1993. Therefore, we studied the consequences of the nephrotoxic effects of cyclosporin in an attempt to define a group of patients especially prone to impairment of renal function after heart transplantation. Unfortunately such identification in an early phase after transplantation appeared not possible. Also we found no relation between cyclosporin dosage or serum levels and impairment of renal function (Chapter XI). Nevertheless we recently decided to lower target cyclosporin blood levels hopingthereby not to increase the incidence of rejection.

Part V summarizes the results of the first 9 years of the Rotterdam Heart Transplant Program. Survival of the allograft recipients has been excellent with one and five year patient survival rates of 92% (95% CI 88-96%) and 84% (95% CI 78-90%) respectively. An overview is presented of the main problems after heart transplantation allowing adequate preparation of future transplant candidates for referral to the transplant center. Finally the limited capacity of the Heart Transplant Programs in the Netherlands is discussed. This limitation necessitates either additional investments in the existing two centers or the development of other models of care for the cardiac allograft recipient (Chapter XII).

Conclusion: Meticulous care and attention for the individual patient, analysis of the occurring problems again and again and clinical research directed to the solution of these problems explain the excellent results of the Rotterdam Heart Transplant Program. Because heart transplantation reaches far beyond the conventional boundaries of cardiology and thoracic surgery, these results could only been achieved by the day to day and "hour to hour" cooperation between many specialists and nurses dedicated to the care of the cardiac allograft recipient.

SAMENVATTING

Dit proefschrift beschrijft een deel van het onderzoek dat het Rotterdamse Harttransplantatie Team heeft verricht met als doel optimale zorg voor patiënten die verwezen worden voor harttransplantatie. De belangrijkste problemen die voor en na harttransplantatie kunnen optreden zijn geanalyseerd waarna het onderzoek gericht is geweest op het oplossen van deze problemen.

Deel I gaat in op de problematiek van de patient die wordt verwezen voor harttransplantatie. Met het huidige medicamenteuze arsenaal hebben veel patiënten met een ernstig verminderde pompfunktie toch een acceptabele levensverwachting. Hierdoor is het in veel gevallen mogelijk om harttransplantatie uit te stellen. Een deel van deze patiënten die in eerste instantie "te goed" voor transplantatie worden geacht gaat achteruit waardoor alsnog tot harttransplantatie moet worden over gegaan. Niettemin zal, door een tekort aan donor organen, een aantal van de laatst genoemde patiënten overlijden ondanks het feit dat achteruitgang van hun toestand tijdig opgemerkt wordt (Hoofdstuk I).

Sommige patiënten, die verwezen worden voor harttransplantatie, kunnen baat vinden bij conventionele chirurgie, zij het met verhoogd risico. Faktoren die samen gingen met een slecht resultaat van een dergelijke ingreep bleken te zijn: systolische bloeddruk lager dan 115 mmHg, polsdruk van minder dan 30 mmHg, de aanwezigheid van een derde harttoon en symptomen van rechts decompensatie (Hoofdstuk II). Deze bevindingen hebben het mogelijk gemaakt om een beter gefundeerde keuze te maken tussen conventionele chirurgie en harttransplantatie en hebben geleid tot verder onderzoek naar de grenzen van conventionele chirurgie.

In Hoofdstuk III wordt een overzicht gegeven van alle mogelijkheden tot mechanische ondersteuning van het falende hart. Onze ervaring met een van deze methoden, de intra-aortale ballon pomp, laat zien dat het hartminuut volume door toepassing van de ballonpomp voldoende wordt vergroot om beschadiging van belangrijke organen te voorkomen, zelfs bij patiënten met chronisch hartfalen. Bij veel patiënten zal de ballonpomp echter niet in staat blijken om het hemodynamische evenwicht langdurig te handhaven waardoor ze alsnog zullen overlijden. Na enkele dagen wordt de patient bovendien bedreigd door infektie, een probleem dat transplantatie niet wenselijk maakt. De vraag, welke plaats mechanische ondersteuning in de toekomst zal gaan innemen in het harttransplanatatie programma, wordt open gelaten.

Deel II legt de noodzaak van immunosuppressie voor de hartontvanger uit en beschrijft de resultaten van twee gerandomizeerde trials waarin verschillende immunosuppresieve behandelings strategieen worden vergeleken. Wij stelden ons ten doel het aantal afstotingsreakties te verminderen en nierfunktie problemen kort na transplantatie te voorlomen. Daartoe werd het effekt vergeleken van cyclosporine (intraveneuze toediening gestart voor de operatie) met sequentiele toediening van OKT3 en, oraal toegediende, cyclosporine. Lage doses corticosteroiden werden gebruikt door de patiënten in beide onderzoeksgroepen. Er bleek geen verschil te zijn in vrijheid van afstotings reakties. Het achterwege laten van cyclosporine in de eerste dagen na transplantatie bleek echter nierfunktiestoornissen te voorkomen (Hoofdstuk IV). In een tweede onderzoek werden de effekten vergeleken van vroege immunosuppressieve profylaxe met monoclonale anti-T cel antilichamen (OKT3) versus polyclonale antilichamen (paarden-ATG). Deze antilichamen bleken even effektief in het voorkomen van afstoting maar paarden-ATG veroorzaakte uitgebreide huidreakties bij 20/28 patiënten (Hoofdstuk V).

Uit onze gegevens blijkt dat de effekten van verschillende behandelingsmethoden alleen vergeleken mogen worden in gecontrolleerd, gerandomizeerd onderzoek. Bij vergelijken van de resultaten van OKT3 toediening in het eerst genoemde onderzoek met een "historische" controle cyclosporine groep werd een significant lagere incidentie van afstoting gevonden. Vergelijking van het effekt van OKT3 en cyclosporine in het gerandomizeerde onderzoek liet echter geen verschil zien. Gezien het relatief kleine aantal hart ontvangers per centrum zijn multi-center trials aangewezen, vooral voor het bestuderen van lange-termijns effekten van immunosuppressiva zoals infektie, kwaadaardige nieuwvormingen en versneld opredende coronaire vaatziekte.

Deel III beschrijft coronaire vaatafwijkingen die versneld optreden in het donor hart. Het blijkt onmogelijk om, op grond van gegevens uit de literatuur, de incidentie van deze vaatafwijkingen in de diverse hart transplantatie programma's met elkaar te vergelijken. Er worden namelijk verschillende methoden gebruikt om deze afwijkingen op te sporen (histologie, angiografie en intravasculaire echografie) en binnen een methode, bijvoorbeeld de angiografie, worden bovendien geen eensluidende definities gebruikt (Hoofdstuk VI). Visuele analyse van de jaarlijkse coronair angiogrammen van de "Rotterdamse" hartontvangers bracht twee soorten coronaire vaatafwijkingen aan het licht: afwijkingen van de grote, epicardiale takken en afwijkingen van de kleine, grotendeels intramyocardiaal verlopende takken. Bij een mediane vervolgduur van 43 maanden werd waargenomen dat belangrijke coronaire

vernauwingen en mortaliteit ten gevolge van coronaire vaatafwijkingen alleen voorkwamen bij de patiënten van wie het eerste-jaars coronair angiogram reeds abnormale epicardiale takken had laten zien. Op grond van deze bevinden hebben wij het aantal jaarlijkse coronair angiografieen gereduceerd (Hoofdstuk VII). Naast de visuele beoordeling van de coronair angiogrammen is er ook kwantitatieve analyse verricht met behulp van het CAAS (automatische contour detectie) systeem. Deze methode maakt objectieve meting mogelijk van veranderingen in de coronaire diameter. Verschillen tussen centra of behandelingsstrategieen binnen een centrum kunnen dan op een objectieve manier gedetecteerd worden. Wij vonden slechts kleine veranderingen in de diameter van de coronaire vaten waarbij de significante afname van de diameter in het eerste jaar in overeenstemming was met de bevindingen bij de visuele analyse. Bij verder onderzoek naar de ontwikkeling van coronaire vaatafwijkingen in het donor hart zullen wij ons vooral richten op het eerste jaar (Hoofdstuk VIII).

Deel IV bespreekt de belangrijkste nadelen van immunosuppressie in het algemeen: infektie en maligiteit, en van cyclosporine in het bijzonder: nierfunktie verlies. Vooral Cytomegalo virus infektie en Cytomegalo virus ziekte zijn onderwerp van studie geweest omdat uit de literatuur was gebleken dat dit agens verantwoordelijk was voor hoge morbiditeit en zelf mortaliteit na transplantatie. Wij hebben CMV seronegatieve hartontvangers passief geimmunizeerd tegen dit virus. Met deze handelwijze was de infektie incidentie bij seronegatieve ontvangers van het hart van een seropositieve donor gelijk aan de incidentie bij seropositieve ontvangers. Opvallend was dat de incidentie van CMV ziekte hoger was in alle ontvangers van het hart van een positieve donor, onafhankelijk van de serologie van de ontvanger. Een relatie tussen CMV infektie en ziekte en het optreden van coronaire vaatafwijkingen hebben wij, in tegenstelling tot de bevindingen in andere transplantatie centra, niet gevonden (Hoofdstuk IX).

Een derde deel van de mortaliteit in ons programma wordt veroorzaakt door kwaadaardige nieuwvormingen en de helft hiervan is van lymfoproliferatieve oorsprong. Daarom hebben wij onderzocht of er een verband bestaat tussen het optreden van lymfoproliferatieve processen and immunosuppressieve therapie. In eerste instantie leek de incidentie van deze ziekte gerelateerd aan de totale immunosuppressieve belasting omdat 6 van de 101 patiënten die naast hun onderhoudsbehandeling van cyclosporine en corticosteroiden ook anti-T cel therapie hadden ontvangen een lymfoproliferatief ziektebeeld ontwikkelden terwijl dit niet voorkwam bij de 41 patiënten die geen anti-T cel therapie kregen (Hoofdstuk X). Bij een grotere

populatie en een langere vervolgduur bleek er tussen patiënten met/zonder anti-T cel therapie geen significant verschil te bestaan in overleving vrij van maligniteit en in incidentie van kwaadaardige lymfoproliferatieve aandoeningen (Hoofdstuk XII).

Wij werden geconfronteerd met een groeidend aantal hart ontvangers bij wie de nierfunktie aanzienlijk gestoord raakte. Tot begin 1993 heeft dit bij 6 patiënten geleid tot terminale nierinsufficientie waarvoor nierfunktie vervangende therapie nodig is. Een poging om (retrospectief) in een vroeg stadium de patiënten te identificeren die een verhoogd risico hebben op het ontstaan van vroegtijdige nierinsufficientie mislukte (Hoofdstuk XI). Ook werd er geen verband gevonden tussen de gebruikte cyclosporine doseringen en daarmee bereikte serum spiegels en het nierfunktie verlies. Desalnietemin hebben we recent besloten tot verlaging van de na te streven cyclosporine bloedspiegels waarbij gehoopt moet worden dat hierdoor het aantal afstotingsreakties niet zal toenemen.

Deel V geeft een samenvatting van de resultaten van de eerste 9 jaren van het Rotterdamse Harttransplantatie Programma. De overleving van de hart ontvangers is uitstekend met respektievelijke een en vijf jaars overlevingspercentages van 92% (95% betrouwbaarheids interval 88-96) en 84% (79-90). Er wordt een overzicht gegeven van de belangrijkste problemen na harttransplantatie. Met deze kennis is het mogelijk om toekomstige harttransplantatie kandidaten adekwaat voor te bereiden op verwijzing naar het transplantatie centrum. Tenslotte wordt er ingegaan op de beperkte capaciteit van de Nederlandse harttransplantie programma's. Om deze beperkte capaciteit op te heffen zullen aanvullende investeringen in de bestaande centra nodig zijn danwel andere modellen van zorg voor de hart ontvangers gezocht moeten worden (Hoofdstuk XII).

Conclusie: gerichte aandacht voor details, steeds opnieuw analyseren van alle problemen en onderzoek gericht op het oplossen van de problemen hebben bijgedragen tot de goede resultaten van het Rotterdamse Harttransplantatie Programma. Omdat harttransplantatie zich uitstrekt tot ver buiten de conventionele grenzen van de cardiologie en thoraxchirurgie konden deze resutaten slechts geboekt worden door middel van intensieve samenwerking tussen vele specialisten en verpleegkundigen die zich op de zorg voor de hart ontvanger hebben toegelegd.

NAWOORD

Harttransplantatie in Rotterdam is een kind van drie vaders: Bos, Simoons en Weimar. Voor het grootbrengen van dit kind was de hulp van vele anderen nodig. Zo ontstond het unieke samenwerkingsverband waarvan ik sinds 1986 deel uit maak. Nauwe samenwerking, gebaseerd op wederzijds respekt en waardering, heeft geleid tot de resultaten die in dit proefschrift beschreven zijn. Vriendschap is daarbij steeds een steun in de rug geweest.

- Harttransplantatie Team bedankt -

Slechts enkelen zijn nauw betrokken geweest bij het tot stand komen van het proefschrift. Maarten Simoons en Willem Weimar, mijn promotores, adviseerden bij de analyse van de transplantatie problemen en initieerden onderzoek. Bij de rapportage stuurden zij ieder op hun eigen wijze en met een eigen doel voor ogen. Daardoor was het vinden van de juiste richting niet altijd gemakkelijk, maar daar leerde ik van.
Bedankt, vooral omdat ik steeds weer bij jullie terecht kon.

Dat ik de hoofdstukken VIII, X en XI, met als eerste auteurs Marc van der Linden, René Brouwer en Bob Zietse, heb opgenomen in dit proefschrift weerspiegelt een gevoel van jarenlange saamhorigheid en mijn waardering voor hun bijdragen aan het onderzoek betreffende de Rotterdamse hartontvanger.

Tenslotte, de basis van mijn loopbaan werd gelegd door het opbouwen van "basic trust" tijdens de opleiding cardiologie in het St.Antonius Ziekenhuis. Overstappen van de perifere cardiologische praktijk naar mijn huidige superspecialisme zou echter nooit mogelijk geweest zijn zonder de zeven, in meer dan een opzicht rijke, jaren in Enschede.

CURRICULUM VITAE

1947	August 25, born in Maastricht, The Netherlands.
1961 - 1967	Undergraduate education at the Jeanne d' Arc Lyceum, Maastricht (Gymnasium ß division).
1967 - 1973	Medical School, University of Utrecht
1973 - 1975	Training in Internal Medicine. Ziekenhuis De Stadsmaten, Enschede. (Supervisor: R.Th.J.M. Ypma).
1975 - 1978	Training in Cardiology. St. Antonius Ziekenhuis, at that time in Utrecht. (Supervisor: Dr. A.V.G. Bruschke).
1979 - 1986	Cardiologist, staffmember Ziekenhuis Ziekenzorg, Enschede.
1986 -	Cardiologist, staffmember of the Department of Cardiology, Thoraxcenter, University Hospital Rotterdam-Dijkzigt. (Head of the Department: Prof. Dr. J.R.T.C. Roelandt). Main activities: the care of patients referred for heart transplantation.