CARDIOTHORACIC TRANSPLANTATION

THIRTY YEARS OF CARDIAC TRANSPLANTATION AT STANFORD UNIVERSITY

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Background: The experience with 30 years of cardiac transplantation at Stanford University Medical Center was reviewed. A total of 954 transplants were performed in 885 patients. Patients were divided into 3 groups based on immunosuppression received: group I, no cyclosporine (INN: ciclosporin) (n = 201) (January 1968–November 1980); group II, cyclosporine (n = 248) (December 1980–June 1987); and group III, cyclosporine + OKT3 (n = 436) (July 1987–March 1998). **Results:** The 1-, 5-, and 10-year actuarial survivals were 68%, 41%, and 24% (group I); 80%, 57%, and 37% (group II); and 85%, 68%, and 46% (group III) (I vs II, $P < .01$; I vs III, $P < .005$; and II vs III, $P < .005$). The 1-, 5-, and 10-year actuarial death rates from rejection were 8%, 12%, and 14% (group I); 5%, 7%, and 7% (group II); and 2%, 5%, and 5% (group III) (I vs II, $P =$ not significant; I vs III, $P < .005$; and II vs III, $P < .005$). The 1-, 5-, and 10-year actuarial death rates from infection were 25%, 43%, and 50% (group I); 8%, 17%, and 29% (group II); and 6%, 11%, and 16% (group III) (I vs II, $P < .005$; I vs III, $P < .005$; and II vs III, $P < .05$). The 1-, 5-, and 10-year actuarial death rates from graft coronary artery disease were 0%, 5%, and 13% (group I); 0%, 12%, and 19% (group II); and 1%, 6%, and 9% (group III) (I vs II, $P < .01$; I vs III, $P < .005$; and II vs III, $P =$ not significant). There have been 69 retransplants in 67 patients with 1-, 5-, and 10-year actuarial survivals of 49%, 27%, and 15%, respectively. **Conclusions:** The evolution of 3 decades of experience with cardiac transplantation has resulted in improved overall survival. The incidence of rejection and of death from infection and graft coronary artery disease have decreased over time, primarily as a result of improvements in immunosuppression and in the prevention and treatment of infection. Continued advances in perioperative management and the development of more specific, less toxic immunosuppressive agents could further refine this initial experience and improve the survival and quality of life of patients after cardiac transplantation. (J Thorac Cardiovasc Surg 1999;117:939-51)

The first human cardiac transplant operation at Stanford University Medical Center was performed on January 6, 1968.¹ It represented the translation of more than a decade of laboratory experimentation into

the setting of clinical investigation. This report summarizes these 30 years of clinical cardiac transplantation at our institution by a team that has remained essentially unchanged during this period.

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Table I. Number of cardiac transplants in each cohort

	Group I (1968-1980): pre-CSA	Group II (1981-1987): CSA	Group III (1988-1998): CSA and OKT3	Total
Total No. of transplants	220	272	462	954
First transplants	201	248	436	885
Redo transplants	19	24	26	69

CSA, Cyclosporine.

Methods

Patients. The Stanford Transplant Database and records of all cardiac transplants performed at Stanford University Medical Center from 1968 to 1998 were reviewed. Patients were divided into groups on the basis of the date of transplantation and the core immunosuppressive protocols used: group I, no cyclosporine (INN: ciclosporin) (pre-CSA) (n = 201) (January 1968–November 1980); group II, CSA (n = 248) (December 1980–June 1987); group III, CSA + OKT3 (n = 436) (July 1987–March 1998). A total of 954 transplants have been performed in 885 patients, including 69 retransplants in 67 patients. The number of procedures performed in each group is listed in Table I. Detailed analysis was performed on 807 patients because complete data were not available for 78 patients who received primary transplants. Retransplant patients were initially included in survival data analysis from the time of their primary transplant. They were subsequently withdrawn alive from the primary database and analyzed in a separate retransplant cohort after retransplantation. Additionally, independent analysis was made for adult patients (19–70 years of age) and pediatric patients (birth–18 years of age). Selected donor and recipient characteristics for adult patients are listed in Table II.

Recipient diagnoses for each group are given in Table III.

Operative techniques. The donor cardiectomy and the technique of cardiac replacement have not changed significantly in the past 30 years.² However, bicaval anastomoses³ have been performed in 75 of the last 224 cardiac transplants. All donor hearts have been preserved with cold hyperkalemic crystalloid Stanford cardioplegic solution and cold storage (saline solution at 3°C–4°C) during transportation.

Immunosuppression. Group I patients received various combinations of azathioprine, prednisone, and polyclonal rabbit antithymocyte globulin (Stanford). Group II patients received various combinations of cyclosporine, azathioprine, prednisone, and polyclonal rabbit antithymocyte globulin or polyclonal horse antithymocyte globulin (ATGAM, Upjohn Co, Kalamazoo, Mich) for induction therapy. All group III patients were treated with cyclosporine, azathioprine, prednisone, and the monoclonal antibody OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ) for induction therapy. Additionally, since 1989 group III patients have received cytomegalovirus (CMV) prophylaxis with gancyclovir⁴ if either donor or recipient was CMV seropositive. Diltiazem has been used in most patients since 1990⁵ and lipid-lowering agents since 1993 in an attempt to reduce graft coronary

artery disease (CAD). Subsets of patients have been converted to mycophenolate (n = 54), tacrolimus (n = 10), or a combination of the 2 drugs (n = 38) as alternatives to cyclosporine and azathioprine because of persistent rejection or adverse side-effects. Total lymphoid irradiation (n = 28) and methotrexate (n = 29) have been used for recalcitrant rejection in a subset of group III patients.⁶

Rejection has been monitored by endomyocardial biopsy since 1972.⁷ Echocardiography has been used for the assessment of myocardial performance and screening for rejection since 1987.⁸ Recently, a small number of group III patients (n < 20) have undergone plasmapheresis for myocardial dysfunction in the absence of biopsy evidence of cellular rejection.

Follow-up. Patients have been closely monitored by their primary care physicians and by the posttransplant service with detailed longitudinal data entered in the Stanford Transplant Database. They have undergone extensive annual evaluations consisting of right and left heart catheterization, endomyocardial biopsy, echocardiography, coronary angiography, and more recently intravascular coronary ultrasonography. The mean follow-up time for the entire series was 4.93 ± 4.74 years. The actuarial incidence of death (all causes) and cause-specific death, rejection (diagnosed by endomyocardial biopsy or autopsy), infection, graft CAD (diagnosed by angiography and/or autopsy), lymphoid malignancy, and nonlymphoid malignancy has been recorded in most (>90%) patients.

Statistical analysis. Continuous variables are reported as the mean ± 1 SD and the range. Comparisons between continuous variables were made with an unpaired 2-tailed *t* test and discrete variables were compared with the continuity-adjusted χ^2 test. Actuarial life-table data were calculated by the Cutler-Ederer method.⁹ Time-related event-free rates are reported from actuarial estimates as the mean ± standard error. Comparisons between actuarial curves were made by the Gehan method.¹⁰

Results

Adult survival. Recipient age at the time of transplantation, donor age, waiting time on the transplant list, graft ischemic time, and the time to first rejection have all significantly increased over the 30-year period, whereas the length of postoperative hospital stay has significantly decreased over time in the adult patients

Table II. Demographics of recipients and donors for first-time adult cardiac transplant recipients

Variable	Group I (n = 115)	Group II (n = 231)	Group III (n = 349)	Comparisons
Recipient age (y)	39.5 ± 10.6 (19-56)	41.7 ± 10.6 (18-62)	49.5 ± 11.4 (18-70)	†‡
Donor age (y)	NA	23.6 ± 6.4 (12-44)	29.4 ± 10.8 (11-54)	‡
Recipient gender (M/F)	104/11	187/44	290/59	
Donor gender (M/F)	90/25	192/39	255/94	
CMV status		(27-NA)	(14-NA)	
D-;R-	NA	59 (29%)	60 (18%)	
D+; R+	NA	64 (31%)	112 (33%)	
D-;R+	NA	51 (25%)	93 (28%)	
D+; R-	NA	30 (15%)	70 (21%)	
Previous sternotomy (yes/no)	32/83	78/153	157/192	
Preop support		(124-NA)		
None	NA	70 (65%)	243 (70%)	
Inotropic drugs	NA	24 (23%)	82 (23%)	
IABP	NA	9 (8%)	3 (1%)	
LVAS	NA	4 (4%)	21 (6%)	
Waiting time (d)	41.9 ± 34.3 (2-121)	45.7 ± 54.2 (1-291)	183.7 ± 204.7 (1-999)	†‡
Ischemic time (min)	92.2 ± 54.4 (15-192)	131.4 ± 51.4 (38-260)	170.0 ± 47.8 (40-309)	*†‡
CPB time (min)	94.6 ± 23.1 (57-143)	111.7 ± 32.4 (61-222)	115.0 ± 34.6 (32-319)	*†
LOS (d)	69.0 ± 35.1 (2-236)	36.7 ± 21.0 (1-175)	20.1 ± 30.8 (1-379)	*†‡
Time to first rejection (d)	33.9 ± 51.9 (6-428)	46.9 ± 127.6 (2-1073)	85.0 ± 259.7 (5-3330)	†‡

Data are mean ± SD (range). M, Male; F, female; CMV, cytomegalovirus; D, donor; R, recipient; +, positive; -, negative; NA, not available; IABP, intra-aortic balloon pump; LVAS, left ventricular assist system; CPB, cardiopulmonary bypass; LOS, length of stay.

* $P < .05$, group I versus group II.

† $P < .05$, group I versus group III.

‡ $P < .05$, group II versus group III.

(Table II). A significant increase in the number of female recipients was observed from group I to group II; however, there was no difference in actuarial survivals for male recipients compared with female recipients in any group. The actuarial survival was significantly better in group II recipients who received hearts from donors less than 30 years of age than from donors over 30 years of age ($P < .05$). Such a difference, however, was not observed in group III recipients. Additionally, there was no statistically significant difference in the actuarial rate of death from graft CAD for older (>30 years of age) donor hearts in either group.

There were 106 total deaths in 115 group I patients (18 early [within 90 days of operation], 88 late), 168 in 231 group II patients (32 early, 136 late), and 122 in 349 group III patients (24 early, 98 late) (Tables IV and V). The early operative mortality rates (within 90 days of operation) were 16% (group I), 14% (group II), and 7% (group III) (I vs II, $P = \text{NS}^*$; I vs III, $P < .05$; II vs III, $P < .05$). The 1-, 5-, and 10-year actuarial survivals were 68%, 41%, and 24% (group I); 80%, 57%, and 37% (group II); and 85%, 68%, and 46% (group III)

*NS = Not significant.

Table III. Diagnoses in adult first-time cardiac transplant recipients

Diagnosis	Group I	Group II	Group III
Coronary artery disease	51 (44%)	100 (43%)	153 (44%)
Idiopathic cardiomyopathy	59 (51%)	96 (41%)	139 (40%)
Viral cardiomyopathy	1 (0.8%)	13 (5.5%)	12 (3%)
Postpartum cardiomyopathy	0	7 (3%)	5 (1.4%)
Familial cardiomyopathy	2 (1.7%)	5 (2%)	6 (1.7%)
Congenital defect	1 (0.8%)	3 (1.3%)	6 (1.7%)
Valvular disease	0	0	18 (5.2%)
Other	1 (0.8%)	7 (3%)	10 (2.9%)
Total	115	231	349

(Fig 1). A statistically significant increase in survival was observed in the group III patients as compared with the other groups. The actuarial survival of group II patients was better than that of group I patients, but the statistical significance of the difference was not as dramatic as the difference from group III survival (I vs II, $P < .01$; I vs III, $P < .005$; and II vs III, $P < .005$). A total of 150 patients have survived 10 years, 38 patients have survived 15 years, and 8 patients have survived 20 years after transplantation, with the longest survival

Table IV. Causes of death (early < 90 days) for first-time adult recipients

Diagnosis	Group I (n = 115)	Group II (n = 231)	Group III (n = 349)
Infection	13 (72%)	14 (44%)	12 (50%)
Rejection	2 (11%)	6 (19%)	3 (12.5%)
Pulmonary embolus	0	1 (3%)	0
Pulmonary hypertension	2 (11%)	2 (6%)	1 (4%)
Cerebrovascular accident	1 (5.5%)	4 (12.5%)	1 (4%)
Graft failure	0	5 (15.5%)	3 (12.5%)
Bleeding	0	0	1 (4%)
Multisystem organ failure	0	0	3 (12.5%)
Total	18	32	24

time being 23.5 years. Previous cardiac surgery had been performed in 267 of 695 (38%) adult recipients, but there was no significant difference in early (<90 day) operative or late actuarial survival as compared with recipients who had not undergone previous cardiac operations.

Rejection. The 1-, 5-, and 10-year actuarial death rates from rejection were 8%, 12%, and 14% (group I); 5%, 7%, and 7% (group II); and 2%, 5%, and 5% (group III) (Fig 2). The only significant improvement in death from rejection was observed in the comparison between group I and group III patients (I vs II, $P = \text{NS}$; I vs III, $P < .05$; and II vs III, $P = \text{NS}$). The rates for freedom from rejection at 1, 5, and 10 years were 11%, 10%, and 10% (group I); 10%, 6%, and 6% (group II); and 23%, 19%, and 15% (group III) (Fig 3). Although the majority of the patients had at least one episode of rejection, the incidence of rejection was significantly reduced in the group III patients compared with the other groups (I vs II, $P = \text{NS}$; I vs III, $P < .005$; II vs III, $P < .005$).

Infection. The 1-, 5-, and 10-year actuarial death rates from infection were 25%, 43%, and 50% (group I); 8%, 17%, and 29% (group II); and 6%, 11%, and 16% (group III) (Fig 4). These data demonstrate a progressive and significant decrease in the risk of death from infection (I vs II, $P < .005$; I vs III, $P < .005$; and II vs III, $P < .05$). The rates for freedom from any infection at 1, 5, and 10 years were 16%, 10%, and 10% (group I); 21%, 10%, and 7% (group II); and 35%, 20%, and 19% (group III) (Fig 5). The incidence of infection was significantly reduced in the group III patients compared with the other groups (I vs II, $P = \text{NS}$; I vs III, $P < .005$; and II vs III, $P < .005$).

The status of recipient and donor CMV serology was compared only between groups II and III, because this information was not available for group I patients. There was no significant difference in actuarial survival

Table V. Causes of death (late > 90 days) for first-time recipients

Diagnosis	Group I (n = 115)	Group II (n = 231)	Group III (n = 349)
Infection	40 (45%)	39 (28.5%)	26 (27%)
Rejection	10 (11%)	8 (6%)	11 (11%)
Coronary artery disease	14 (16%)	39 (28.5%)	21 (21%)
Lymphoid malignant disease	6 (7%)	10 (7%)	3 (3%)
Nonlymphoid malignant disease	6 (7%)	14 (10%)	11 (11%)
Pulmonary failure	0	0	1 (1%)
Pulmonary embolus	1 (1.1%)	1 (0.7%)	0
Cerebrovascular accident	0	4 (3%)	1 (1%)
Bleeding	0	1 (0.7%)	1 (1%)
Renal failure	0	1 (0.7%)	1 (1%)
Other	11 (12.5%)	19 (14%)	22 (22%)
Total	88	136	98

or death rates from rejection, infection, or graft CAD for the combination of a CMV-negative recipient receiving a heart from a CMV-negative donor. A significant decrease in actuarial survival was observed between the groups for any combination that included either a seropositive recipient or donor compared with the use of a seronegative graft in a seronegative recipient: R+/D+ ($P < .05$); R+/D- ($P < .05$); R-/D+ ($P < .005$). The death rate due to infection was significantly lower in the group III patients for CMV-positive recipients receiving CMV-negative hearts ($P < .05$). A significantly lower death rate from graft CAD was observed in the group III CMV-positive recipients who received a CMV-negative heart ($P < .005$). No significant difference in the death rates from rejection between the groups was observed for any recipient/donor combination.

Graft CAD. The 1-, 5-, and 10-year actuarial death rates from graft CAD were 0%, 5%, and 13% (group I); 0%, 12%, and 19% (group II); and 1%, 6%, and 9% (group III) (Fig 6). The probability of death from graft CAD was significantly higher for the group II patients than for the other groups (I vs II, $P < .05$; I vs III, $P = \text{NS}$; II vs III, $P < .05$). The rates for freedom from graft CAD at 1, 5, and 10 years were 88%, 52%, and 43% (group I); 94%, 71%, and 57% (group II); and 93%, 75%, and 67% (group III) (Fig 7). The incidence of graft CAD was significantly reduced in the latter 2 groups compared with group I patients. No significant difference, however, was observed between the group II and III patients (I vs II, $P < .01$; I vs III, $P < .005$; and II vs III, $P = \text{NS}$).

Lymphoproliferative and nonlymphoid malignant disease. The 1-, 5-, and 10-year actuarial death rates

Fig 1. Comparison of actuarial survival between groups. CSA, Cyclosporine.

Fig 2. Comparison of actuarial death rates from rejection between groups. CSA, Cyclosporine. NS, not significant.

from lymphoproliferative disease were 0%, 3%, and 11% (group I); 1%, 3%, and 6% (group II); 1%, 1%, and 2% (group III). No statistically significant difference in the actuarial death rates from lymphoproliferative disease were observed among the groups (I vs II, $P = NS$; I vs III, $P < .10$; II vs III, $P < .10$), nor was there a difference in the incidence of death from nonlymphoid malignant disease among the groups.

Lymphoproliferative disease was the cause of death

in 19 patients (I, $n = 6$; II, $n = 10$; III, $n = 3$) and non-lymphoid malignant disease in 31 patients (I, $n = 6$; II, $n = 14$; III, $n = 11$) (Table V).

Recipient pretransplantation hemodynamic status. The Novacor left ventricular assist system (LVAS; Baxter Healthcare Corp, Novacor Div, Oakland, Calif) has been implanted in 34 patients as a bridge to cardiac replacement since 1984.¹¹ Nine LVAS-supported patients died before transplantation (multisystem organ

Fig 3. Comparison of actuarial freedom from rejection between groups. CSA, Cyclosporine; NS, Not significant.

Fig 4. Comparison of actuarial death rates from infection between groups. CSA, Cyclosporine.

failure, $n = 6$; hemorrhage, $n = 2$; thromboembolic event, $n = 1$). Cardiac transplantation was performed in the other 25 LVAS-supported patients with 1 early death from infection (postoperative day 2) and 3 late deaths from nonlymphoid malignant disease. The 1-, 5-, and 10-year actuarial survivals for this cohort of patients were 92%, 78%, and 78%, respectively.

A significantly higher actuarial survival was observed in patients requiring hemodynamic support

(either mechanical or pharmacologic) (UNOS status 1 [United Network for Organ Sharing]) compared with patients not requiring such support (UNOS status 2) in group III ($P < .05$) without a significant increase in the incidence of infection. However, there was no difference in actuarial survivals in group III patients who received no preoperative inotropic support compared with patients who received inotropic support alone, an analysis which excludes the outstanding survival of the

Fig 5. Comparison of actuarial freedom from infection between groups. CSA, Cyclosporine; NS, not significant.

Fig 6. Comparison of actuarial death rates from graft coronary artery disease (CAD) between groups. CSA, Cyclosporine; NS, not significant.

LVAS-supported patients from the UNOS status 1 cohort. No significant difference in actuarial survival was observed between group II UNOS status 1 patients and UNOS status 2 patients. Actuarial survival was significantly better for UNOS status 1 patients in group III versus UNOS status 1 patients in group II ($P < .005$),

but no difference was noted for UNOS status 2 patients between the groups.

Late reoperation. Eight patients have undergone tricuspid valve replacement with a porcine bioprosthesis for iatrogenic (biopsy-related) tricuspid regurgitation and decompensated right heart failure. No deaths have

Fig 7. Comparison of actuarial freedom from graft coronary artery disease (CAD) between groups. CSA, Cyclosporine; NS, not significant.

Fig 8. Actuarial survival of retransplant recipients.

occurred in this cohort of patients and all have had symptomatic improvement with resolution of ascites and peripheral edema. Two patients required pericardiectomy for constrictive disease and 1 patient required donor mitral valve replacement 10 years after transplantation for mitral regurgitation from leaflet prolapse.

Retransplants. Detailed data were available for 66 of the 69 patients undergoing retransplantation. Twenty-three procedures were performed early, within 30 days of the primary transplant operation (acute rejection, $n = 16$; acute graft failure, $n = 7$), and 43 were performed late after primary cardiac transplanta-

Fig 9. Comparison of actuarial survivals of pediatric patients in groups II and III. CSA, Cyclosporine; NS, not significant.

tion (graft CAD, $n = 39$; constrictive disease, $n = 3$; late graft failure, $n = 1$). The overall 1-, 5-, and 10-year actuarial survivals for this cohort were 49%, 27%, and 15% (Fig 8). Stratification of the results of retransplantation based on the timing of retransplantation demonstrates that survival is better for patients undergoing retransplantation for late graft failure than for early graft failure; however, the 5- and 10-year survivals are poor for both cohorts (3-month and 1-, 5-, and 10-year survivals: 79%, 57%, 27%, and 18% [late] versus 48%, 35%, 26%, and 10% [early]).

Pediatric patients. Data were analyzed from the latter 2 groups because only 6 pediatric patients underwent transplantation before 1980. The 1-, 5-, and 10-year actuarial survivals of all patients less than 19 years of age were 82%, 68%, and 52% (group II) and 73%, 63%, and 60% (group III) (Fig 9). No statistically significant difference in actuarial survival was detected between these groups.

Discussion

The purpose of this review was to examine the changes that have occurred in the cardiac transplant program at Stanford over the past 30 years in an attempt to identify features that have contributed to our current results. The fact that so many variables have entered into this equation, combined with the limitations of retrospective assessment, ensure that the final analysis will be observational at best. The mentality of the program has combined radical persistence, even when

early success was limited, with a conservative methodical progression by a team whose core members have remained constant and have worked together with hundreds of contributors over the past 3 decades. The following comments will emphasize some of the highlights of this work in progress.

The conceptualization and development of the technique of orthotopic cardiac transplantation evolved serendipitously from early investigations of myocardial preservation. Several groups were experimenting with various techniques of cardiac transplantation, which included total cardiac replacement with separate pulmonary venous and bicaval anastomoses,¹² en bloc heart and right lung transplantation,¹³ and en bloc heart-lung replacement¹⁴ in the 1950s. Success was limited primarily by technical difficulties with the pulmonary venous and caval anastomoses. The preservation of biatrial cuffs at the time of recipient cardiectomy first described by Lower and Shumway² in 1959 led to reliably reproducible canine cardiac replacement and established the foundation for over a decade of subsequent experimental investigations of cardiac transplantation.

The consistent long-term survival of canine cardiac transplant recipients immunosuppressed with prednisone and azathioprine eventually justified the translation of laboratory experience into the experimental phase of human cardiac transplantation at Stanford in 1968.¹⁵ Results during the first 5 years of clinical cardiac transplantation was established that the operation was a technically simple, safe, and reproducible proce-

dures and that the denervated human allograft could support normal physical activity.^{16,17} Additional information was documented concerning the hemodynamic performance of the allograft.¹⁸ Consequently, the operative technique has remained essentially unchanged since this initial period. Evolution of the program has continued with gradual refinements in immunosuppression combined with improvements in the treatment and prophylaxis of infection which, in turn, are obviously dependent on the degree of immunosuppression. During the early phase of the program, meticulous attention to detail was required for any patient to survive through the initial period of cellular rejection. Despite use of frequent electrocardiographic assessment in conjunction with physical examination for the diagnosis of rejection, a relatively high incidence of death from infection and rejection persisted because of an inability to fine-tune immunosuppression according to the severity of rejection and level of success in treating rejection. The introduction of endomyocardial biopsy in 1972⁷ established an objective method for diagnosing rejection, thereby providing evidence-based guidance for the intensity of recipient immunosuppression. The introduction of lympholytic rabbit antithymocyte globulin (ATG) in 1973 provided a potent, somewhat more targeted immunosuppressive strategy.¹⁹ The almost simultaneous adoption of these 2 new modalities constituted a major improvement in the immunosuppressive strategy. The enactment of laws codifying brain death and the introduction of distant donor procurement²⁰ in 1973 were also incremental advances contributing to the expansion of clinical experience.

The next major period of the program's evolution began in 1980 with the introduction of cyclosporine.^{21,22} The ability to provide potent and probably more selective long-term oral maintenance immunosuppression resulted in significantly improved survival, primarily through a reduction in infection-related deaths. Improved treatment and prophylaxis of infection (eg, *Pneumocystis carinii* infection) additionally contributed to improved results during this period.²³

On October 17, 1986, the US government decreed an end to the experimental phase of human cardiac transplantation by approving Medicare reimbursement for the procedure at this institution.

The introduction of more specific and standardized lympholytic induction therapy with the monoclonal anti-CD3 antibody preparation OKT3 was initiated in 1987 and represented the next major change in the immunosuppressive strategy of the program.^{24,25} Prolongation of the interval to the first episode of rejection has been the most obvious benefit of this approach to immunosuppression. Contemporaneously, the pro-

phylaxis and treatment of CMV infection improved with the liberal use of gancyclovir⁴ and later of hyperimmune globulin preparation.

The statistical analysis of results in the present study is limited by the arbitrary division of patients into 3 cohorts based on the major alterations in the immunosuppressive protocol used. Several modalities have been introduced and modified within each group, and new modalities for the care of patients have been incorporated independent of the immunosuppressive protocol. Also, general progress has occurred over these years in many areas that affect patient survival, such as the diagnosis and treatment of infectious and malignant complications. Despite these limitations of this analysis, several important observations can be made.

Group III patients were significantly older at the time of transplantation, received organs from older donors with longer graft ischemic times, and waited longer after selection for transplantation. However, they had significantly higher early and long-term actuarial survivals than the other 2 groups. These results can be attributed to a progressive decrease in the incidence of rejection and death due to infection, but not death due to rejection, which has always remained low. Additionally, the incidence of graft CAD has progressively decreased. Death related to graft CAD was higher for group II patients than for group III patients. However, no significant change in the incidence of graft CAD was observed between the group II and III patients, suggesting that this disease process may have been stabilized or retarded by the use of diltiazem and lipid-lowering agents. A significant increase in actuarial survival was observed after the introduction of cyclosporine in group II patients, as compared with group I patients, but this significance was less dramatic than the results observed for group III patients. The improved survival in group II patients compared with group I patients was predominately due to a dramatic reduction in the death rate from infection, since there was no significant decrease in operative or rejection-related deaths.

The significantly prolonged time to first rejection in group III patients can be directly attributed to the use of OKT3. The virtual elimination of early perioperative rejection combined with the current mentality of early hospital discharge has been associated with shorter hospital stays and a reduced incidence of infection without any change in actuarial death rates from lymphoproliferative disease or nonlymphoid malignant disease. Additionally, OKT3 induction therapy permits the luxury of a gradual institution of cyclosporine in the immediate postoperative period when renal insufficiency may be problematic, especially in this increas-

ingly older group of patients. The aggressive prophylaxis and management of CMV disease in group III patients also has contributed to improved survival by virtue of a decreased incidence of infections and possibly even rejection. Such derivative effects are difficult to fully define but have almost certainly contributed to enhancement of survival.

The major continuing limitation to the volume of cardiac transplantation has been that of donor availability. Despite intense public education in this regard, the donor pool has remained static during this decade. This fact emphasizes the need for strategies to assure optimum use of donor grafts and may preclude, except in rare circumstances, the use of hearts for retransplantation because of the relatively poor results obtained. In a real sense, the issue of human organ donation is not a medical one, but rather a societal one.

Many refinements in the care of cardiac transplant patients have been incorporated at our institution over the past 30 years. The sum of the components has been more important than any single factor, as is the usual case. Although results have progressively improved, many limitations remain. The results of cardiac transplantation will not approach the results of other cardiac surgical procedures until nonspecific, poorly targeted immunosuppression is replaced by highly specific immunomodulation or the achievement of tolerance induction.

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Discussion

Dr Bartley P. Griffith (Pittsburgh, Pa). Rarely does one have an opportunity to comment on a 30-year experience. It is special for me because the topic is heart transplantation and the report is from its originators. Dr Robbins, while you have

just described remarkable progress, it is important for me to acknowledge how well Dr Shumway, you, and his other trainees, many of whom helped to lead this Society, have carried the responsibility. During the early years poor results brought criticism. Persistence led to incremental improvement and the development of enabling endomyocardial biopsy and antithymocyte globulin.

An expanded experience that accrued during the 1970s, combined with cyclosporine in 1980, permitted a striking upgrade in prospects, chiefly due to reduced deaths by infection and fewer episodes of rejection. When the rest of the world joined you at this milepost, it did so often without proper understanding of your prior sweat equity.

The Stanford program, however, remained humble and dissatisfied. As an inevitable consequence, results continued to inch upward. In the 1990s, antiviral and alternative targeted immunosuppression have improved the outlook further. It is notable that 159 of 436 group III recipients, your most recent cohort, received adjunctive therapy to the stated maintenance immunosuppressive regimens. We and others join you with recent improved survivals that are now associated with half-life estimates of 9 years, certainly acceptable and far better than the 5 years possible as recently as the early 1980s. I would agree that multiple interrelating factors not obvious by multivariate analysis are responsible.

Dr Robbins, I do have some questions about statistical methods used to infer the data in the manuscript. The reason for the exclusion of 78 patients with incomplete follow-up is unclear. Did they live? What groups were they from? When combined with the 69 retransplantation patients who were withdrawn from analysis alive, we have almost 17% of the total experience "not" or perhaps incorrectly accounted for. The large number of associations investigated between 5 outcomes made it likely that false associations could be and probably were found by chance.

Why was the Gehan method used instead of the log rank method to distinguish among the groups? This would have had the effect of excessive weighting of early results over later ones.

Finally, your overall and group III incidence of transplantation of status 1 patients is only 30%, far lower than the national average of nearly 68% in 1996. How do you explain the wellness of your recipients and the fact that the waiting time, averaging only 183 days for group III patients, is less than half the 559 days for UNOS status 2 recipients?

Dr Robbins. Thank you, Dr Griffith, for those comments. Let me take the last question first. Our waiting times are shorter than the national average, and only 30% of our patients undergo transplantation from the status 1 category. I think that our transplant cardiologists, particularly led by Michael Fowler, John Schroeder, and Randy Vagelos, have frequently published data looking at aggressive angiotensin-converting enzyme inhibition and β -blockade. Our philosophy is to try to keep patients out of the hospital in the status 2 category. We do not list patients as status 1 until the maximum oxygen consumption is less than 14, and we make every effort to keep them out of the hospital. We have been very

lucky in our OPO that we are able to perform transplants in many of our patients who are in UNOS status 2.

The 78 patients who were excluded were from group I. I went back to our database primarily. Because we did not have complete data on some of the first 78 patients, I chose to leave them out of the analysis, but they are all from group I. When patients undergo retransplantation, they go into a separate database and are analyzed separately. Your point is well taken that they are basically conferred immortality when they are taken out alive.

This is a retrospective review and it includes all of the problems associated with that type of analysis, which is complicated by the fact that many things have changed over the years. The arbitrary division of the patients into the 3 groups certainly leaves us open for criticism, but that was the best method I could devise.

Dr Adnan Cobanoglu (Portland, Ore). I would like to congratulate Dr Robbins and the pioneers at Stanford University for their outstanding efforts over the past 3 decades. This data presented certainly represent a lot of sweat, late nights, early mornings, and hard work over the past 30 years.

I wanted to comment on the grouping of the patients. We started our heart transplant program in Portland, Oregon, in 1985 with a group of patients analogous to your group II, based on triple immunosuppression. Our regimen has remained pretty much the same over the past 13 years. We have used OKT3 only as necessary in those patients with pre-existing renal dysfunction. Our 1-year, 5-year, and 10-year survivals are 87%, 76%, and 59%, respectively. The reason I mention this is that it is possible to achieve good late results with the group II type immunosuppression regimen based on triple immunosuppression that includes cyclosporine.

I have a couple of questions. One is related to increased early mortality in the group of patients who received donor hearts from bigger, heavier donors. That, to me, seems somewhat contrary to the experience of others, in which smaller donor size has caused problems with early mortality and morbidity.

Second, based on your experience with retransplantation, should we really consider retransplantation seriously in this era of ever-increasing donor paucity? If we do, who would be the best candidates for retransplantation? Do you still do retransplantations at Stanford?

Any such discussion of cardiac transplantation has to include some donor-related data and the concern about limited availability of donor organs. This continues to be the main issue limiting our ability to perform transplantations. What should we do to increase the available donor pool?

Dr Robbins. I agree that many programs have good experience and good results without induction therapy. We at Stanford have been very conservative and slow to change, but we do acknowledge that excellent results can be obtained without induction therapy.

In terms of the heavier donor hearts, we redid the multivariable analysis and that did not fall out as one of the positive significant variables. I thought it was a bit strange also, and we therefore reworked the multivariable analysis.

We have been disappointed with retransplantation even in what appeared to be good-risk patients for graft CAD. For acute graft failure I think the risks are prohibitive. Patients undergoing retransplantation for early indications were early in the experience, before LVASs were available. Today it is possible that with LVAS support we can make these patients better candidates. However, results were marginal even in the candidates with graft CAD. For these reasons we have backed off from retransplantation and would consider only a young patient who has no other comorbidities. The most important comorbidity is renal dysfunction. Thus for a young person who was a good candidate in every other way, we would still consider retransplantation.

Donor availability, obviously, is still the limitation to increasing the numbers of transplants. I think the only way to improve that situation is through public education and then possibly exploring xenotransplantation.

Dr Roland Hetzer (*Berlin, Germany*). I rise to pay homage to the unique achievement of the Stanford group. Not only did they establish heart transplantation almost single-handedly, but they also provided decisive stimuli in many fields of medicine and beyond. By closely following the Stanford protocols over the years, we have performed 1047 heart transplants, with a survival of approximately 50% at 10 years and 84 patients living longer than 10 years. Studying those long-term survivors generated many questions that need to be answered. I would like to ask Dr Robbins just 3 of

those questions, well knowing that they may be difficult to deal with.

First, are there any data that might define those patients who are likely to become long-term survivors?

Second, are there any concepts offering permanent social aid, in particular to the young transplant patients, which might enhance longevity and quality of life?

Third, what is the estimated life expectancy of a patient who is undergoing heart transplantation today?

Dr Robbins. Thank you, Dr Hetzer, for those comments. More than 150 of our patients have survived more than 10 years, 38 more than 15 years, and 8 patients more than 20 years. The longest survival was 23.5 years. I know of no data that will identify which of the survivors will live longer. We did not have enough numbers to look at, for instance, HLA matching. That did not emerge as a significant reason for long-term survival. We have evaluated these 150 patients who have survived more than 10 years, and it is difficult to come up with an answer.

I do not have a good answer regarding social aid, either. It is very important for the patient to have a good, strong family support system, because the patient is trading one disease for another.

Regarding life expectancy, I have actuarial data suggesting that about half of our patients will be alive at 10 years, just as in your series. It is very difficult to project a life span for a patient after transplantation. As Craig Miller always says, it is binary logic, either 100% or 0%.

Targeted

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