Long-term Survival and Function after Cardiac Transplantation

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Cardiac transplantation now permits prolonged survival for some patients with otherwise fatal heart disease. This report summarizes the hemodynamic and clinical characteristics of 25 patients who have survived five or more years after cardiac replacement. The average age of the patients at the time of operation was 40 ± 10 (SD) years; 23 were men. The average duration of survival is 6.7 years, and ranges from five to 10.5 years. Annual cardiac catheterization and clinical follow-up were performed to assess systolic cardiac function, coronary anatomy, and quality of extended rehabilitation. We found that among these long-term survivors, the left ventricular ejection fraction remained constant (0.59 ± 0.08 one year postoperatively), 0.57 ± 0.09 at most recent study, p = ns). Segmental wall motion measured by fluoroscopic examination of midwall intramyocardial markers also remained normal. Four of 21 (19%) patients with complete longitudinal studies developed significant graft coronary artery disease. Clinical evaluation revealed that the long-term survivors required fewer than one unscheduled admission to the hospital per year. Sixteen of 25 patients (64%) were gainfully employed, and 22 of 25 (88%) enjoyed substantial benefit in terms of extended rehabilitation. These 25 long-term survivors represent 27% of 92 patients transplanted between 1968 and 1975. The actuarial survival rate at five years, of patients transplanted since 1975, is 40 ± 5%. This increase in survival rate reflects improved techniques of early postoperative management. Cardiac transplantation now offers prolonged survival with good quality of life for selected patients with terminal heart disease.

THREE THERAPEUTIC ALTERNATIVES now dominate the management of irreversible, advanced organ failure: supportive care, mechanical replacement or augmentation of organ function, and transplantation. The choice of therapy in any clinical situation depends on the patient’s condition and wishes, and on the alternative technologies available for the involved organ. For irreversible myocardial disease, supportive care may prolong life for a variable period, usually with severe limitation of activity, mechanical replacement remains in the future, and mechanical augmentation is useful only for brief periods. The ideal treatment for irreversible myocardial disease would replace the function of the damaged organ, permit nearly unrestricted physical activity, and be widely available at reasonable cost. No such therapy exists, but cardiac transplantation provides the closest approximation at present.

Incomplete control of allograft rejection has inhibited the widespread use of biologic cardiac replacement to treat irreversible heart disease, but prolonged and useful survival for some patients has been achieved. The quality of cardiac function and lifestyle in these patients define our minimal expectations for the future of cardiac transplantation, and, furthermore, serve to illustrate the gap between our current ability to treat irreversible heart failure and the ideal treatment of this disorder. This study presents long-term hemodynamic and clinical evaluation of patients who have survived cardiac transplantation at Stanford University Medical Center for five or more years.

Patients and Methods

Data for this study were collected from the records of 92 patients who underwent cardiac transplant procedures at Stanford between 1968 and 1975. Twenty-five of these patients have lived five or more years with the same graft and provide the basis for this report. Two additional long-term survivors re-
required a second transplant less than five years after the first, and were excluded from this analysis. The average age of the patients at the time of transplantation was 40 ± 10 years; 23 of 25 long-term survivors were men. The indication for transplantation was irreversible myocardial failure in all patients, and all were categorized as New York Heart Association Functional Class IV. Seven patients presented with dilated cardiomyopathy and congestive heart failure. Ventricular weight at pathologic examination in this group averaged 420 g. The remaining 18 patients had severe coronary disease. All the patients had sustained at least one myocardial infarction and exhibited advanced congestive heart failure. At pathologic examination of the removed heart, all the patients had triple vessel coronary artery disease and myocardial fibrosis; five had ventricular aneurysms as well.

Complete clinical and angiographic evaluation was performed at yearly intervals following cardiac transplantation, and was focused in two areas: extent of rehabilitation, and adequacy of graft function. The data presented in this study consist of a comparison of information obtained at the most recent followup with that yielded by the first annual postoperative evaluation. The average interval between these studies was 4.4 ± 1.1 years.

Rehabilitation after any cardiac operation is difficult to assess, because patients often change their goals and lifestyle.12,4 We included in our assessment the extent to which patients were able to perform tasks of interest to them, work status, and overall sense of well-being. For example, a patient who carried out activities normally for four of five postoperative years was considered 80% rehabilitated. Another, more objective measure of rehabilitation was made by summarizing postoperative complications, particularly intercurrent hospitalizations, late rejection episodes, and infections, as well as survival.

Graft function was evaluated in three ways. First, clinical examination including chest roentgenograms and electrocardiogram was performed. The ECG was examined because it has provided a noninvasive, though not totally accurate index of acute rejection.3 In particular, the sum of peak-to-peak QRS deflections (sum voltage) in leads I, II, III, V1 and V6 suggest acute rejection if a rapid decline of more than 20% from previous baseline values is noticed. Second, cardiac catheterization with coronary arteriography and contrast left ventriculography was performed. Significant coronary stenosis was defined as luminal narrowing by 70% or more of any coronary artery. Left ventricular ejection fraction was estimated from contrast left ventriculography in the right anterior oblique (RAO) projection.5 Third, segmental left ventricular wall motion was examined at fluoroscopic examination using computer-assisted analysis of the left ventriculogram based on midwall myocardial markers placed at operation6 (Fig. 1). The RAO silhouette of the left ventricle was divided into five segments (anterobasal, anterolateral, apical, diaphragmatic, and posterobasal), and each segment was related to a single point on the long axis of the ventricle.7 The per cent contribution of each segment to overall contraction could then be estimated. After 1973, endomyocardial biopsy procedure was added to the annual evaluation of graft status.8 A total of 337 biopsies, including those in the early postoperative course, was obtained in the 25 long-term survivors.

Survival data are presented either as actual survival or actuarial survival rates calculated by the Kaplan-Meier method9 and compared by the Gehan test.10 Other statistical data are compared, where appropriate, by the Student's t-test and are presented as mean and standard deviation.

Results

All patients received indefinite immunosuppression with the administration of azathioprine and prednisone.11 Doses of azathioprine were adjusted to maintain white blood cell counts above 5000, and ranged from 12–200 mg/day. Average prednisone dose was 0.29 ± 0.10 mg/kg/day. Details of management after operation have previously been presented.12

Extent and Quality of Survival

The 25 long-term survivors under consideration provide 167.75 years of patient follow-up; the average survival period is 6.5 years (range: 5–10.5 years). They represent 27% of 92 consecutive patients who
underwent coronary transplants between 1968 and 1975. This actual survival agrees closely with the five-year actuarial survival rate of 25 ± 5% predicted for this group. However, the actuarial estimate of five-year survival rate for the subsequent group of 106 patients undergoing transplantation is 40 ± 5% (p < 0.01) (Fig. 2). The reason for this elevation of survival rate is illustrated in Figure 2. Although the annual decrement in survival rates after the first year has remained constant, at approximately 5% per year, attrition during the first year has decreased from 51 ± 5% to 37 ± 4% (p < 0.01); this improvement reflects changes in early postoperative management. 11,12

Six patients in this analysis died between five and eight years after transplantation. Four patients developed severe graft coronary artery disease; one of these died after myocardial infarction, and three died within one year of transplantation (two of infection and one of disseminated lymphoma). 13 This distribution of fatal complications parallels the experience with all 92 patients who underwent coronary transplants more than five years ago. There were 22 late deaths among 46 patients who survived more than one year after transplantation. Of these deaths, 17 of the 22 (77%) were caused by graft atherosclerosis or infection. Late rejection caused death in only two patients surviving more than one year after transplantation.

Survival is a necessary but insufficient condition for evaluating transplantation as therapy for advanced organ failure. The quality of survival is equally important. Of 167.75 patient-years of follow-up, 143.5 (86%) were judged within the category of complete rehabilitation, as defined above. Sixteen of the 25 patients (64%) were gainfully employed throughout their postoperative course. An additional seven patients were classified as more than 50% rehabilitated.

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<tr>
<th>Table 1. Rehabilitation</th>
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<tr>
<td>Total patient-years of follow-up</td>
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<td>Total patient-years rehabilitated</td>
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<td>Patients employed</td>
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<td>Routine hospitalizations/patient-year</td>
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<td>Nonroutine hospitalizations/patient-year</td>
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<td>Total hospital days/patient-year</td>
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Patients remained chronically disabled from infection (two patients) and corticosteroid-induced orthopedic complications (one patient).

A summary of the periods of hospitalization and major complications is presented in Table 1. There were 132 routine admissions to the hospital (0.79 hosp/pt-yr) for annual evaluation (three-day admission). There were 122 nonroutine admissions to the hospital (0.73 hosp/patient-year). The average period of hospitalization was 13.7 ± 12.4 days. Infection accounted for more than half of these (66 of 122), and for an even larger proportion of hospital days. There were only 16 admissions to the hospital for late graft rejection episodes, thereby accounting for fewer than 0.1 hospitalizations per patient-year.

**Cardiac Function**

The results of clinical evaluation of cardiac function including physical, chest roentgenographic, and electrocardiographic examinations were generally unchanged in the absence of acute intercurrent complications. Average electrocardiographic sum voltage declined 14% throughout the entire period. Significant decreases (greater than 20% of first-year baseline values), however, occurred in 12 of the 25 patients. In no patient was there associated evidence of graft rejection at examination of a biopsy specimen. Biopsy specimen data are difficult to quantitate. However, in the absence of acute rejection, endomyocardial biopsy specimens were remarkably constant, showing only a slight increase in interstitial fibrosis in some patients.

Complete hemodynamic data were available in 21 of 25 (84%) long-term survivors. In three of these, the original baseline data were not available, and one patient has subsequently refused invasive follow-up investigation. Figure 3 compares left ventricular ejection fraction at the first annual cardiac catheterization with that obtained at the most recent study (5.4 ± 1.1 years after operation). The values 0.59 ± 0.08 and 0.57 ± 0.09, respectively, were not significantly different. Figure 4 illustrates similar results for segmental left ventricular function. Per cent change in segment area from diastole to systole is shown on the ordinate along with the normal range for each seg-
ment. The small declines calculated for anterolateral, apical, and diaphragmatic segments were not statistically significant. However, eight of 25 patients did experience declines in the function of one or more segments below the accepted norm for that segment. Five patients had declines in the function of two segments and three patients had declines in the function of one segment. The most commonly involved segment was the anterobasal, followed by anterolateral and apical segments. Coronary arteriography showed that four of 21 patients (19%) developed graft coronary artery disease. Segmental function in the areas served by the stenotic artery in these patients, however, did not consistently decline. In two of the patients who developed coronary artery disease, no decline in segmental function was noticed in the area served by the affected artery. It should be noticed, however, that all studies were performed at rest only.\textsuperscript{14,15}

**Discussion**

This study illustrates four points. First, extended survival after cardiac transplantation is possible for some patients with otherwise fatal heart disease. Second, the quality of survival is acceptable. Third, cardiac graft function may remain intact for prolonged periods. Fourth, the outstanding residual problems of cardiac transplantation are graft coronary atherosclerosis and complications associated with current immunosuppression.

The five-year survival rate in this early period of our experience with cardiac transplantation (1968–1975) was 27%. This is comparable with results reported for a similar period of renal transplantation. The Advisory Committee to the Renal Transplant Registry reported five-year survival rates with a functioning graft of 28.6–34.6%, between 1968 and 1970.\textsuperscript{16} Since then, overall patient survival after renal transplantation has improved with early aggressive retransplantation or return to dialysis.\textsuperscript{17,18} Similarly, overall survival among cardiac transplant recipients has improved with refinements in early postoperative management. We expect that long-term survival after renal transplantation will generally exceed that of cardiac transplantation because of the additional option of prolonged mechanical support of renal function available to patients with end-stage renal disease, a facility that, as yet, has no analog for cardiac patients. This option has reduced the complexities of retransplantation and permitted control of infection in the absence of immunosuppression.

The quality of survival among long-term survivors of cardiac transplantation is acceptable. The patients presented in this report required fewer than two hospitalizations per year with a total average length of stay of 16.7 days. Eighty-six per cent of cumulative postoperative course of the total group could be designated within the category of full rehabilitation. With respect to work status, 64% of the long-term cardiac transplant recipients remained employed. This is similar to the work status of patients following coronary artery bypass operation.\textsuperscript{1,2,20} Similar data for rehabilitation after renal transplantation are limited, but Gutman and co-workers have recently summarized the physical activity and employment status of patients on maintenance dialysis.\textsuperscript{19} They found that only 60% of nondiabetic patients on dialysis were capable of a level of physical activity beyond

![Fig. 3. Comparison of global left ventricular ejection fraction at first annual postoperative study with that obtained at most recent study.](image)

![Fig. 4. Comparison of segmental ejection fraction at first annual postoperative study with that obtained at most recent study.](image)
that of caring for themselves. No mention of duration of dialysis was included, and it was presumably less than five years. Furthermore, these patients were not subjected to immunosuppression.

Finally, we are encouraged by the stability of cardiac graft function in this group. This does not, however, lessen our awareness that current methods for immunosuppression fail to uniformly prevent graft atherosclerosis, and furthermore, account for the majority of complications and deaths that occur after heart transplantation. Recent developments, specifically, the availability of cyclosporin A,1 in immunosuppressive therapy after transplantation may ameliorate these problems and extend the benefits of prolonged survival to a larger number of patients with irreversible myocardial failure.

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References


Discussion

Dr. Lloyd M. Nyhus (Chicago, Illinois): I am truly perplexed at the lack of discussion of this presentation.

Most of you know that a member of my department, Dr. C. Thomas Bombeck, on August 1, 1978 had a heart transplantation by the Shumway-Stinson team.

We often see numbers but tend to forget all the aspects of living by those persons who have been saved by this technique.

My colleague is a true miracle of medical science. I received a letter just two days ago from Denmark, wanting to know how Tom was. The correspondent thought he had departed this world several years ago. It was a pleasure to write to Denmark indicating how well he was and what he was doing.

Tom Bombeck, now 2½ years after the transplant, is the chief of the section of surgical gastroenterology at the University of Illinois Hospital. He is actively supervising the care of that unit, a unit which has some 20 patients, many of them with complex esophageal problems.

He has always had an active mind, and has been interested in surgical education, particularly the development of questions for examinations. Because of this expertise, for the last two years he has been the Chairman of the Committee on Appraisal of the Abraham Lincoln School of Medicine. This is a hard job.

Most exciting to me, as the departmental chairman, is that in the past year he has written and had approved and funded as of 1 April 1981, a major National Institutes of Health research grant.

Well, it may seem superficial to tell you these things, but we do not hear about these personal facets enough.

He was so ill when he was flown out to Stanford that, rather than wait the usual month of induction, he had to have an emergency heart transplant and received the first heart that was available. He received the heart of a woman, some 17 or 18 years old. When Tom was interviewed within the first six months of returning to Chicago, the moderator of the program said to Tom: "Dr. Bombeck, is there anything that's bothering you, after having had this very important thing happen to your life?"

He remembered about the 18-year-old woman, and Tom, without a moment's hesitation said: "Well, yes, there is something that bothers me." He said, "Every time an 18-year-old boy walks by, my heart goes flip-flop." We at Illinois will always be indebted to the Stanford Group for their excellence in patient care, the care of the living.

Chairman Pruett: Dr. Stinson, do the observations made on the myocardial biopsy specimens help you in determining the need for modification of the immunosuppressive regimens, and does the fibrosis correlate with decreased myocardial function?

Dr. Edward B. Stinson (Closing discussion): It is difficult to quantify myocardial fibrosis on the basis of endo/myocardial biopsy specimens alone. To the degree to which that can be done, there has been no correlation with functional class, but the lack of the correlation derives principally from the consideration that 97% of the patients have returned to functional Class I status.