INDICATIONS AND RISK FACTORS FOR ORTHOTOPIC CARDIAC TRANSPLANTATION

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Since the first human cardiac transplant operation in 1967, cardiac transplantation has, in the last years, become an accepted therapeutic modality for end-stage cardiac disease. In properly selected recipients, survival of 75% or better at one year and 65% or better at two years can be expected with current methods of immunosuppression. Despite this, certain risk factors have been identified which portend a poor prognosis following transplantation.

Indications for Transplantation—Despite the excellent quality of life which generally results from transplantation, many uncertainties remain as to the long-term results. Because of this, cardiac transplantation should currently be reserved for patients with truly end-stage heart disease, in which the quality and duration of life cannot be expected to improve with available medical or standard surgical therapy. The one-year life expectancy should generally be less than 30%.

Recipient Selection Criteria—Cardiac transplantation should generally be reserved for patients less than about 60 years of age, and the results in infants and small children are still uncertain. Because of the lack of reserves of the normal right ventricle, pulmonary vascular resistance should be nearly normal to provide the greatest likelihood of short and long-term survival. Expect under very unusual circumstances, orthotopic cardiac transplantation is not advisable when the pulmonary vascular resistance exceeds about 5 Wood units.

It is now increasingly evident that the best results from cardiac transplantation can be expected with patients who have isolated end-stage and refractory heart failure. Because of the nephrotoxicity and occasional hepatic toxicity associated with Cyclosporine immunosuppression, patients with irreversible dysfunction of non-cardiac organ systems, and particularly irreversible hepatic or renal dysfunction should not be considered for cardiac transplantation. Other diseases which would be expected to shorten overall life expectancy or increase the susceptibility to infection act as relative contraindications to cardiac transplantation. These include: chronic obstructive pulmonary disease, symptomatic peripheral or cerebral vascular disease, poorly controlled systemic hypertension, severe obesity or cachexia, and recurrent diverticulitis. Because of the unfavorable effect of steroids on these conditions, patients with active peptic ulcer disease or insulin-dependent diabetes mellitus should currently not be considered for cardiac transplantation. Patients with documented recent pulmonary emboli are likely at increased risk for pulmonary infarction and subsequent infection, and these patients should undergo transplantation only after resolution of the embolism (about 6 weeks). Certainly, unresolved, acitve infection is a strict contraindication to transplantation. A final, very important, requirement is the psychologic and social stability of the patient. Compliance to a complex regimen of immunosuppressive therapy is critical to the success of cardiac transplantation, and patients should be carefully screened for any psychiatric, family or social abnormalities which would limit their ability to provide complete compliance.

Donor Heart Management—Improperly selected or preserved donor hearts can be an important cause of early mortality following transplantation. Once declared brain dead, a potential cardiac donor should be precisely managed for maximal cardiac preservation and assessed for underlying cardiac abnormalities or damage. In general, periods of prolonged hypotension, documented cardiac arrest, persistent high levels of inotropic support (generally greater than 10 to 15 micrograms per kilogram per minute of dopamine), persistent poor peripheral perfusion, important anterior chest trauma, and poor cardiac at the time of procurement all suggest a damaged organ with a higher than usual likelihood of poor performance upon transplantation.

Immunosuppressive Management—Maintenance immunosuppressive therapy eras of azathioprine, cyclosporine, and currently combined immunosuppressive therapy. We currently believe that optimal chronic immunosuppression is achieved with a combination of azathioprine, cyclosporine and low-dose prednisone. Prior to transplantation, patients re-

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ceive 1-5 mg/kg of cyclosporine orally, 2 mg/kg Up to 100 mg) of azathioprine orally, and intraoperative solumedrol (500 mg after cardiopulmonary bypass). Postoperatively, patients receive rabbit antithymocyte globulin (RATG) for three to five days. Solumedrol (125 mg intravenously) is administered at 8 hour intervals for three doses. Oral prednisone is administered at a dose of 1 mg/kg/day for one week, and then rapidly taper to a dose of 10 to 15 mg/day (adult patients) by 3 to 4 weeks. Cyclosporine is gradually increased to achieve levels of 600 to 800 ng/ml (whole blood RIA) for the first three weeks, 400-600 ng/ml at 3-6 weeks, and 200 to 400 ng/ml thereafter. Azathioprine is administered at a dose of 100 mg/day in adults, and the dose is lowered if the white blood count falls bellow 4,000.

Rejection episodes are generally documented by endomyocardial biopsy, and managed with three-day pulse therapy of Solumedrol (1 gm intravenously). Refractory rejection is treated with RATG or OKT3 monoclonal antibodies.

Risk Factors for Early and Late Survival—At the University of Alabama at Birmingham (UAB), 150 cardiac transplant operations in 134 patients have been performed through June 15, 1987. This includes infants and children as well as adults, and includes immunosuppression eras including azathioprine, cyclosporine, and triple drug theraphy.

An analysis of risk factors for early and late survival has been performed on a group of patients undergoing transplantation between November 1981 (beginning of cardiac transplantation at UAB) and July 1, 1985.

Pre-transplant diagnosis—Greater than 95% of patients undergoing cardiac transplantation carry a diagnosis of cardiomyopathy or ischemic heart disease[1]. In the UAB experience (through April, 1987), a diagnosis of congenital heart disease has been important risk factor for early and late death following cardiac transplantation. The precise reasons for this are unclear, but such patients have frequently had multipe previous operations, and only moderate elevation of pulmonary vascular resistance may be less reversible in this patient group.

Age—Cardiac transplantation at UAB has been performed in patients up to 65 years of age, and older age has not been a risk factor for early or late mortality. It is particularly in these patients, however, that non-cardiac organ function be well preserved. A similar favorable experience with older patients has been reported by Carrier, Copeland and colleagues[2].

Pulmonary Vascular Resistance—A UAB risk factor analysis has identified elevated pulmonary vascular resistance as a major risk factor for death both early and late following cardiac transplantation. Among patients undergoing transplantation through April, 1987, the one and three year survival rate was 78% and 53% respectively for patients with a pulmonary vascular resistance (PVR) index ($U \cdot m^2$) less than 5, but only 55%. and 23%. respectively, when the pulmonary vascular resistance index was 5 or greater. With the PVR as low as 2.5, however, survival was 57%, at 5 years.

Acute cardiac descompensation—The UAB analysis, as well as reports by Hardesty and colleagues from Pittsburgh[3] indicates that patients undergoing car diac transplantation with inotropic or intra-aortic balloon support at the time of transplantation have a survival equal to that of stable patients with end-stage heart failure. However, if acute cardiac decompensation is accompained by multiple organ failure, the results are poor.

Local vs. Distance Procurement—It remains controversial whether the results of transplantation are importantly improved by local vs. distant procurement. A detailed analysis by Emory and colleagues from Arizona[4] revealed a significant improvement in survival at one to two years among patients receiving locally procured hearts as compared to distant procurement. They reported a two year survival in excess of 80% with local procurement, compared to 40% with regional or distant procurement. In the UAB analysis, we have not demonstrated a relationship between ischemic time and survival, but very few of our hearts are procured locally. This dilemma underscores the lack of available information regarding the potential late damaging effects of extended ischemic periods on late cardiac function.

Immunosuppressive Regimen—The registry of the International Society for Heart Transplantation has reported a significant improvement ($P<0.01$) among patients undergoing orthotopic cardiac transplantation with cyclosporine vs. azathioprine[1]. At UAB, the analysis through July, 1985, examined the effect to continued maintenance therapy of cyclosporine and prednisone vs. maintenance therapy of azathioprine. Patients who were maintained on cyclosporine and prednisone had an actuarial survival of 68% at 2 years, which was nearly twice that of patients maintained on azathioprine and prednisone, although this difference may have been due to chance ($P = 0.15$). The 1 year actuarial survival among patients at UAB undergoing orthotopic cardiac transplantation with cyclosporine is 73% at 1 year.

It is likely that triple-drug therapy with cyclosporine, azathioprine and low-dose prednisone will superior adults. At the University of Minnesota, a three drug protocol has yielded an 87% 2 year survival, compared to only 40% 2 year survival using cyclosporine and prednisone[5]. At UAB, a triple-drug protocol has been employed since February, 1986, in which cyclosporine, azathioprine and prednisone have been administered pert-operatively and continued as maintenance immunosuppression. Among 46 patients undergoing cardiac transplantation with this protocol (through June 15, 1987), 37 (greater than 80%) are currently alive, and all 13 patients undergoing cardiac transplantation since January 1,1987, are currently alive.

It is clear that the results of cardiac transplantation are improving, but are not yet optimal. With continued refinements in the selection process of recipients coupled with ongoing improvements in immunosuppressive management, the best possible results can be achieved with this very limited resource.

REFERENCES

1. Solis, E.; Kaye, M.P.—The registry of the International Society for Heart Transplantation: Third official report—June 1986. J Heart Transplant, 5: 2, (1986).
2. Carrier, M; Emery, R. W.; Riley, J. E.: Levinson, M. M.: Copeland. J. G —Cardiac transplantation in patients over the age of 50 years J Am Coll Cardiol. 8: 285. (1986)
3. Hardesty, R. L.: Griffith. B. P.: Trento. A.: Thompson. M. E.: Ferson, P. F.: Bahnson. H. T.—Mortally ill patients and excellent survival following cardiac transplantation. Ann Thorac Surg. 41: 126, (1986).
4. Emery, R. W.: Cork, R. C.: Levinson, M. M.: Riley, J. E.: Copeland. J.: McAleer, M. J: Copeland. J. G.—The cardiac donor: A six year experience Ann Thorac Surg, 41: 356, (1986).
5. Andreone, P. A.: Olivari, M. T.: Elick, B.: Arentzen, C E.: Sibley. R. K.: Bolman, R. M.: Simmons, R. L.: Ring, W. S.—Reduction of infectious complications following heart transplantation with triple drug immunotherapy. J Heart Transplant, 5: 13, (1986)