Trends and outcomes in heart transplantation: the Berlin experience

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ABSTRACT
Heart transplantation is an established procedure with acceptable, predictable long-term results and good quality of life for more than 20 years. However, it is only available for a limited number of patients. The fate of the patients is determined by the side effects of immunosuppressive drugs, increased tumor incidence and chronic vascular transplant disease. Patients living 10 to 20 years after heart transplantation show physical status equal to that of patients with various chronic illnesses. They suffer from chronic side effects of long-term medication and mainly report fears of renal insufficiency followed by osteoporosis-associated pain, cortisone-induced myopathy and risk for tumors. Only moderate psychological impairment is reported despite somatic problems. In the period 10-20 years post-heart transplantation, there is even a surprising increase in emotional well-being. The 20-year survivors are active and satisfied with daily life. They experience their own life as meaningful and have good partner, family and social relations. Heart transplantation, the most ambitious project in medicine in the 20th century has been made a reality. Its development has the strongest impact on cardiac surgery, immunology, pharmacology, medical logistics, defining life and death, ethics in medicine, acceptance of medical progress by the public and by healthcare systems. It has provided a strong solidarity among politicians, sociologists, physicians and citizens. Ethical concerns will last and will make heart transplantation an important, yet temporary episode in human medicine. It has stimulated research and development of mechanical circulatory support systems as an alternative to treat end-stage heart failure.

Keywords: heart transplantation, mechanical circulatory support devices, immunosuppression, rejection, congenital heart diseases.

INTRODUCTION
Heart transplantation has revolutionized end-stage heart failure therapy and is presently regarded as the gold standard of treatment. Looking back on its history, it is now over 45 years ago, on December 3, 1967, that the world was riveted by news of the first transplantation of a human heart, performed in Cape Town, South Africa, by the late Dr. Christiaan Barnard (1). We have progressed considerably since that time and great advances have been made even in the field of pediatric heart transplantation since the first unsuccessful effort in a 17-day-old child suffering from a severe form of Ebstein’s anomaly by Dr. Adrian Kantrowitz (2) in Brooklyn, New York, also in December 1967, which was the first human heart transplant in the USA. In Germany, heart transplantation was first
performed in Munich in 1969 and was resumed there in 1981 by its two centers, followed by Hannover in 1983 as performed by our group. After carrying out 72 heart transplants within 2 years (several of these patients survived for more than 20 years and one for more than 28 years) our group moved to Berlin where we embarked upon a very active heart transplant program at the Deutsches Herzzentrum Berlin in April 1986, performing a total of 1762 heart transplantations (181 pediatric heart transplants), including 51 re-transplantations and 101 combined heart and lung transplantations, by September 2012.

**Immunosuppression**

The immunosupression regimen has also come a long way. It was in 1980 that cyclosporin A after heart transplantation was first used in a clinical trial in Stanford group with high dose of cyclosporin A and steroids. In 1984 the group in Paris used quadruple therapy with antithymocyte globulin and steroids, delayed cyclosporin A and early cessation of azathioprine. Our group in 1984 started the quadruple therapy with antithymocyte globulin and cyclosporin A, azathioprine and steroids. Presently, our immunosuppression protocol consists of an induction therapy designed to reduce the incidence of early rejection and is started 6 hours post–heart transplantation with intravenous antithymocyte globulin 1.5 mg/kg on the first 3 days accompanied by intravenous prednisolone at 2.5-5 mg/kg/day. Thereafter, steroids are tapered to 2 mg/kg/day orally. Cyclosporin is started immediately preoperatively at 6 mg/kg orally and is continued at 2 mg/kg intravenously or 6 mg/kg orally to target a trough level of 250 ng/ml. Mycophenolate mofetil (MMF) is started preoperatively at 1000 mg orally and is continued at 1000 mg twice daily either orally or intravenously. This triple therapy with cyclosporin/MMF/steroids is alternatively applied with everolimus (2x0.75 mg orally daily, target trough levels 3-8 ng/ml) instead of MMF if there are no contraindications to everolimus.

**Technique of heart transplantation**

Almost all heart transplantation is performed by the orthotopic technique. This technique is one of the most standardized of all cardiac surgery procedures. The original biatrial anastomosis technique has been abandoned by many groups in favor of bicaval anastomoses because of seemingly less tricuspid incompetence. However, if the biatrial anastomosis technique is performed exactly as demonstrated by the Stanford group in the 1970s, there is almost no tricuspid incompetence either. The heterotrophic heart transplantation technique has been generally abandoned because of less favorable results, although quite a number of patients live long term with the additional grafts.

**Monitoring of graft rejection**

We employ mostly non-invasive techniques of rejection monitoring, in particular the intramyocardial electrogram (IMEG) and echocardiograph. The remote monitoring IMEG system which has been developed by our group since 1986 (3, 4) and has become the major diagnostic tool in our facility, has an implanted telemetric pacemaker that allows daily long-distance surveillance of the electrocardiogram and records changes consistent with both cellular and humoral rejection in a highly reliable manner. Rejection is assumed when a drop of >10% of the mean QRS amplitude paralleled by an increase of heart rate in both leads on 3 consecutive days occurs. Anti-rejection therapy is immediately initiated when tissue Doppler echocardiography in a pulsed-wave mode reveals impairment
of early diastolic left ventricular wall relaxation concomitant with QRS amplitude loss. A new Doppler imaging technology is **echocardiographic strain and strain rate imaging** which enables more reliable and comprehensive assessment of myocardial function with its ability to differentiate between active and passive movement of myocardial segments, quantify intraventricular dyssynchrony and evaluate longitudinal myocardial shortening. Its high sensitivity in the assessment of myocardial viability is helpful in detecting acute allograft rejection and early occurrence of transplant coronary artery disease after heart transplantation. **Histologic studies** from right ventricular biopsy specimens are performed for detection of leukocyte infiltrations, endocardial demarcation and myocyte damage and depiction of small vessels. Immunohistology is performed to generate and analyze leukocyte subsets in cellular rejection and is a prerequisite for the detection of humoral rejection with analysis of complement fractions and endothelial markers (5). Endomyocardial biopsy is, however, infrequently used in pediatric transplant patients, since they normally require sedation before the procedure.

**Treatment of graft rejection**

Graft rejection episodes are treated based on the severity. A schema of additional oral steroids is given for 7-10 days on an out-patient basis. For severe acute rejections, patients are admitted to the hospital and are given high-dose steroid treatment with 3-5x500 mg methylprednisolone daily combined with antibiotics and cytomegalovirus prophylaxis. In those with grade III rejection or in the presence of adverse effects on hemodynamics, anti-thymocyte globulin infusion 2.5 mg/kg/day given every 4 hours is added. Other drugs, such as OKT3, cyclophosphamide, methotrexate and rituximab, or procedures like plasmapheresis, immunoabsorption or radiation are seldom required and are performed exclusively in the transplantation centers.

**Late graft-associated diseases and sequelae of immunosuppression therapy**

Transplant vasculopathy. Development of cardiac allograft vasculopathy (CAV) has become a major concern in the long-term follow-up of transplant patients. Vasculopathy is the main cause of cardiac allograft loss and a leading cause of mortality after the first post-transplantation year. It was detected in 57 transplanted hearts in our pediatric series that freedom from CAV was 75% at 5 years, 50% at 10 years, and 25% at 15 years. Localized or focal stenosis was diagnosed in 48.9% of patients with CAV leading to interventional treatments. CAV was the main cause for re-transplantation in 10 patients after a median post-transplant time of 12.25 (0.3-17.45) years. It has been well-documented that the early onset of CAV is a predictor of rapid development of severe forms of CAV, while patients with late onset CAV have much delayed course.

**Post-transplant lymphoproliferative disease**

Post-transplant neoplasia, primarily lymphoma and other forms of (PTLD), remains a challenging long-term problem for patients undergoing cardiac transplantation. PTLD appears to be largely the result of the effectiveness of current agents used for long-term immunosuppression, and the neoplasms typically harbor the Epstein Barr virus (EBV) genome, which is presumed to play a major role in neoplastic transformation. Children are potentially at greater risk for developing PTLD than adults because of the frequency which with they are seronegative for EBV at the time.
of transplant (6). There has been some concern that induction therapy might increase the risk of cytomegalovirus (CMV) disease or the development of PTLD, driven by the EBV (7). However, no relationship has been found between the reported rate of CMV disease according to donor/recipient status combinations and the use of induction therapy. Others. Post-transplantation, new diseases may occur or there may be worsening of preexisting diseases. In the first post-transplant year, 75% of patients develop hypertension and this increases to up to 95% by 5 years after transplantation. Renal insufficiency develops among 35% of patients until 5 years after transplantation, and 10% have a creatinine value of >2.5 mg/dl. At this time, 2-3% require chronic dialysis and some eventually undergo renal transplantation. The renal insufficiency occurring after heart transplantation is dependent on cyclosporin A, arterial hypertension, atherosclerosis and humoral consequences of denervation of the graft. Hyperlipidemia, mostly hypercholesterolemia occurs in 85% of patients. Thirty-five percent of patients develop diabetes mellitus 2-5 years post-transplantation. This occurs in approximately 4-5% of patients on cyclosporin therapy and in 10-15% of patients on tacrolimus. Eight years post-transplantation, 25% have developed malignant skin tumors and epithelial carcinoma. Osteoporosis, hip necrosis and other musculoskeletal diseases as well as neurological tremors, epilepsy and focal neurological seizures may develop. Use of mechanical circulatory assist device as a bridge to transplantation Mechanical circulatory support as a bridge to transplantation was successfully introduced by our group in 1987 (8, 9). The ensuing routine use of assist devices to keep patients alive until transplantation paved the way to their clinical use as an established treatment for end-stage heart failure by itself. This has become essential in the face of the increasing donor organ shortage, with many patients receiving permanent assist devices and fewer receiving heart transplants. Overall survival After the epochal achievement of the Stanford group in the early 1980s, the survival rate of transplant patients reached a level almost as good as that of today based on the 2011 ISHLT Report (10). During the 25-year period, mean duration of follow-up was 16.08±0.8 (range 8 months-26 years). Our overall survival rates are 68.3%, 52.8%, and 22.4% at 5, 10 and 20 years, respectively. In those transplant patients who lived longer than 10 years, 68.1±2.6% lived more than 16 years and 45.5±4.7% survived for more than 20 years. In recent years, the results have rather become worse because many patients are transplanted because of complications of assist device support such as device infections or stroke, which by themselves are high risk factors for the transplantation. In addition, patients have to go through a long waiting time under intensive care treatment where they gradually deteriorate. Furthermore, donor age has significantly increased because of organ shortage, and grafts of less than optimal status are being accepted. Psychosocial development in the heart transplant patient Based on psychological analyses in a larger series of 182 patients of the impact of receiving heart transplantation, the side effects of chronic immunosuppression play a great role, such that its burden results in
depression in conjunction with an uncertain perspective towards certain social interactions. Overall, the transplant patients do well in all socio-psychological aspects and the results are comparable to those of the general population. However, a certain percentage of patients have a difficult time adjusting to work and tend to have significant impairment in their functional activity compared to that of their healthy peers (11).

**Ethical dilemma**

With time, patients tend to develop graft vasculopathy and would require re-transplantation to remain alive. The results of re-transplantation are definitely inferior than those of the primary transplantation and, in the face of organ scarcity, serious ethical considerations become an issue.

A potential solution for this problem for the time being is the use of mechanical circulatory support devices, which in cases of pump failure can be easily exchanged. Rapid progress in the technology of these devices may ultimately lead to them being used more extensively for long-term support, as we are already doing presently in the elderly.

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