Long-term Survival Following Heart Transplantation

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KALP TRANSPLANTASYONU SONRASI UZUN DÖNEM SÜRVİ

ÖZET

Amaç: *Kalp transplantasyonun (KT) kısa ve orta dönem başarısı ile ilgili veriler literatürde yeterli miktarda yer almaktadır. Ancak, uzun dönem sürvi ile ilgili veriler sınırlı sayıdadır. Bu çalışmada transplantasyon sonrasında 10 yıldan fazla yaşayan erişkin hastalarla ilgili deneyimimizi sunuyoruz.*

Materyal ve metod: *Mart 1983-Eylül 1989 arasında merkezimizde 306 erişkin hastaya transplantasyon yapıldı. Analiz ettiğimiz multipl faktörler aşağıda listelenmiştir.*

Sonuçlar: *Grup, ortalama 48±10 yaşında, 94 erkekten oluşuyor. Ortalama sürvi 12.2±1.4 yıldır ve bunların %91'i hala yaşamaktadır. %7 hastaya heterotopik KT yapıldı ve %11'i retransplantasyona gitti. Hastaların %41'inde iskemik kardiyomyopati ve %49'unda idiopatik kardiomyopati etiolojiden sorumludur. %19'u UNOS (United Nations of Organ Sharing) status I hastasıydı. Pre-transplant diabet insidansı %7.6 idi. Donör yaşı 25±8 idi. Hasta/donör eşleşmemesi (mismatch) cinsiyet için %16.7, ırk için %40, CMV için %43 idi. HLA uyumsuzluğu hasta başına 4.9±0.8 idi. İskemi süresi 127±61 dk. idi. %14 hastaya Anti-lenfosit ajan ile indüksiyon tedavisi uygulandı. Rejeksiyon insidansı 1.0±1.1 idi ve %33.9 hastada hiç rejeksiyon olmadı. Transplantasyon sonrası CMV infeksiyon insidansı %14.5 ve toplam infeksiyon insidansi %53 idi. İlk iki yıldaki Transplant koroner arter hastalığı (TKAH) insidansı %28.4 (31/109) bulundu.*

Tartışma: *KT kıymetli bir tedavi yöntemi olarak kendisini kanıtlamıştır. Perioperatif dönem hasta takibindeki ilerlemelerle ve daha özgün, daha az toksik immünosupresif ajanların geliştirilmesi ile çok tatminkar uzun dönem sürvi oranlarına ulaşılacağı aşikardır.*

Anahtar kelimeler: *Kalp transplantasyonu, uzun dönem sürvi, kalp yetersizliği.*

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Heart transplantation (HTx) is for many patients with severe or end-stage heart disease the ultimate form of therapy. The aim of HTx is to increase life expectancy of the severely ill patients beyond that of patients treated medically or with conventional surgery, and to enable an increase in his/her exercise performance and quality of life.

The exponential increase in HTx since the early 1980s indicates that this therapy has become an established procedure. According to 17th official report of the International Society for Heart and Lung Transplantation (ISHLT) [1] 55.359 HTx (pediatric and adult) were performed worldwide from 1982 through 1999. However, according to their data, the total number of HTx has been decreasing since 1996 (probably improvement in the emergency procedures and ICUs decrease the number of donor candidates).

The short and mid-term success rates of HTx are sufficiently well documented. Although a substantial number of patients survive for more than 10 years after undergoing HTx, clinical outcome analysis is based mainly on 1- or 5- year survival data. However, patients survived more than 10 years after HTx are limited.

With this retrospective study, we draw a profile of long-term (>10-year) survival patients after HTx.

MATERIAL and METHODS

We reviewed our database from March 1983 through September 1999 and 109 (36%) of the 306 adult patients (1983-1989) were identified as having over 10 years survival. We did not include pediatric (<20 y) HTx cases.

Multiple parameters related donors and recipients (pre and post Tx) were analyzed (Table-1). Because of significant number of missing parameters in our database, we did not be able to analyze all the factors. And some factors could be analyzed for less than 109 patients.

Table 1. Factors analyzed

Recipient and donor factors	
	Age, gender, race, CMV status, height, weight, body surface area
Recipient factors	
Pre transplant:	Etiology, UNOS status, diabetes mellitus, blood groups, induction therapy, ischemic time, HLA mismatches, sex mismatch, race mismatch, CMV mismatch
Pre-and post transplant:	Cholesterol level, hypertension, transpulmonary gradient, Cyclosporin A dose and level
During first 2 years of post transplant:	Rejection episodes, days to first rejection, infection (bacterial, viral, fungal, protozoal) episodes and incidence, coronary artery disease

The routine immunosuppression protocol of our center is the standard triple therapy (Prednisone+Cyclosporine+ Azathioprine). Texas Heart Institute (THI) grading system (based on 10-scale) was used for evaluation of microscopic examination of endomyocardial biopsy (EMB) material from the right ventricle. Two subsequent scores of "5" and more were considered as a rejection episode. Rejection episodes were treated on individual basis by considering severity of rejection, serologic factors, CBC results, renal and hepatic functions, cerebral symptoms, infection status and blood levels of immunosuppressive agents.

EMB schedule: The first biopsy was taken four to seven days after surgery, and the second one a week later. Then the routine biopsy frequency was decreased step by step: One biopsy a week for 3 weeks (1-3 weeks after Tx), one biopsy during 2-week period (4-5 weeks after Tx), one biopsy during 4-week period (6-9 weeks after Tx), one biopsy during 2-month period (3-4 months after Tx), one biopsy every 3 months (for the rest of the year) and one biopsy every 6 months (after the first year). If there was any suspicious about rejection episode, a high dose IV steroid was given and EMB was performed as emergency basis.

The files and databases were meticulously analyzed for the infections. The existence of an infection requiring IV antibiotic therapy for more than one week was considered as an infection episode.

Outpatient follow-up visits were once a week for several weeks. Then it was decreased in frequency as the patient move further from the date of surgery.

RESULTS

Total of 327 HTx were performed in 306 adult (>20y) patients. 36% of these patients (109/ 306) survived more than 10 years. Average survival was 12.2±1.4 years (range: 10.2-16.4 y). Actuarial 1-, 5- and 10-year survival rates of the whole series were 77% (236/306), 61% (186/306) and 36% (109/306) respectively. The patient half-life (time to 50% survival) is calculated as 8.8 years.

91% (99/109) of the patients are still alive. Four patients died from transplant-related coronary artery disease (TxCAD), two died from infection. Two of the patients had sudden death (by unknown reasons). Other two patients died on traffic accidents.

Heterotopic HTx was done in 7% (8/109) of the patients and 11% (12/109) were retransplanted. All of the retransplantations were done after 10th year of the first surgery. The recipients included 94 men and 15 women, age 48±10 years (range: 24-68 y). Average height was 175.7±9.3 cm (range: 152.4-200.7 cm) and weight was 76.5±15.5 kg (range: 42.9-114.0 kg) with 1.92±0.23 m^2 (range:1.38-2.50 m^2) body surface area (BSA). 57.8% (63/109) of the patients had positive CMV titers before Tx (Table 2). 83.5% (91/109) of the patients were Caucasian while 9.2% (12/109) Hispanic and 7.3% (8/109) Black.

Etiology was idiopathic cardiomyopathy (IDCM) for 49.5% (54/109) and ischemic cardiomyopathy for 41.3% (45/109) of the patients (Figure 1). 19% (18/96) of the patients were in Status I according to UNOS (United Nations of Organ Sharing) classification.

Donor age was 25±8 y (range: 16-51 y). Average height was 176.5±10.6 cm (range: 144.8-193.0 cm) and weight was 76.4±16.3 kg (range: 33.0-140.0 kg) with 1.93±0.23 m^2 (range:1.20-2.50 m^2) BSA. 48.8% of the donors were seropositive for CMV (Table 1).

Patient/donor was mismatched for sex in 16.7% (14/84), race 40% (25/63), and CMV 43% (21/49) of

Table 2. Baseline characteristics of recipient and donor gropus

	Recipient group	Donor group
Age (year)	48±10	25±8
Height (cm)	175.7±9.3	176.5±10.6
Weight (kg)	76.5±15.5	76.4±16.3
BSA (m^2)	1.92±0.23	1.93±0.23
CMV infection (%)	57.8	48.8

BSA: Body surface area, CMV: Cytomegalovirus

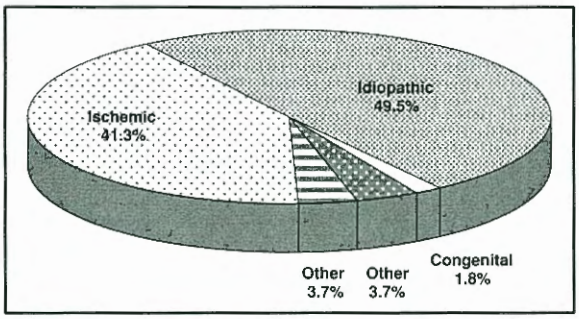

Figure 1. Reason for transplantation

cases. Total HLA mismatch was 4.9±0.8 (range:3-6) per patient (1.44±0.55 for HLA A, 1.71±0.46 for HLA B and 1.73±0.50 for HLA DR).

The ratio of blood groups were 45.5% (35/77) for A, 16.9% (13/77) for B, 3-9% (3/77) for AB, 33.8% (26/77) for O and 89.6% (69/77) for Rh positive.

Ischemic time was 127±61 minutes (range: 50-303 min).

Average transpulmonary gradient was 9.1±5.1 mmHg (range: 2.0-21.0 mmHg) before Tx and 7.7±3.6 mmHg (range:2-20 mmHg) after one year of Tx. Before Tx, 27.0% of them and one year after Tx, only 23.8% of them had more than 12 mmHg transpulmonary gradient.

Pre Tx incidence of diabetes mellitus (DM) was 7.6% (7/92). Pre Tx Cholesterol level was 183.3±65.6 mg/dl (range: 59.0-434.0 mg/dl), while 1 year post Tx level was 245.4±52.0 mg/dl (range: 102.0-386.0 mg/dl) (Figure 2). Also, 18.4 % (16/87) patients were hypertensive, before Tx, while 77.2 % (71/92) of them were hypertensive after (1 year) Tx.

Thirteen of 92 patients (14%) underwent induction therapy with anti-lymphocyte Globulin preparation.

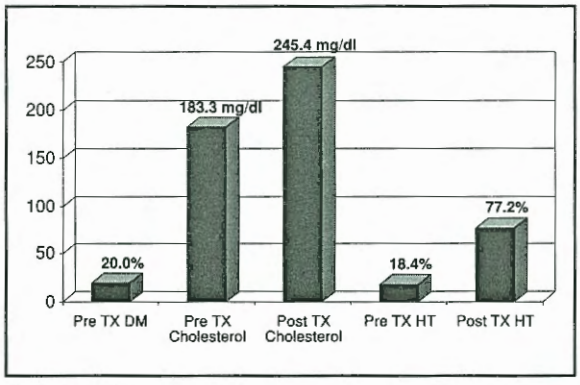

Figure 2. Other risk factors

Cyclosporin A dose at time of HTx (admission) was 11.2±3.3 mg/kg (range: 1.2-19.0 mg/kg), while the level is 450.2±280.6 ng/ml (range: 31-1723 ng/ml). After 1 year of Tx the dose was 4.6±2.3 mg/kg (range: 1.4-13.2 mg/kg) while the level was 263.7±205.8 ng/ml (range: 35-1479 ng/ml).

Rejection was diagnosed by using microscopic examination of endomyocardial biopsy (EMB) material (according to the Texas Heart Institute grading scale, more than 5 score is considered as rejection episode). Incidence of rejection was 1.0±1.1 (range: 0-5) with 33.9% (37/109) rejection-free for the first two years of transplantation. Days to first rejection episode were changed between 3 to 1647 days (191±472 days; median: 14 days). In the 15% (13/87) of the patients, baseline immunosuppressive therapy was increased following EMB.

Post transplant CMV infection incidence was 14.5% (12/83). Average total infection episodes (number of infection requiring IV antibiotic therapy for more than one week) was 0.89 per patient in the first two years (0.55 for bacterial, 0.18 for viral, 0.06 for fungal and 0.09 for protozoal). Total infection incidence was 53% (47/89) for the same period (33.7% for bacterial, 14.8% for viral, 3.4% for fungal and 6.8% for protozoal) (Figure 3).

Incidence of TxCAD (based on coronary angiography findings) was 28.4% (31/109) in the first two years. Only three (9.7%) of these patients were re-transplanted.

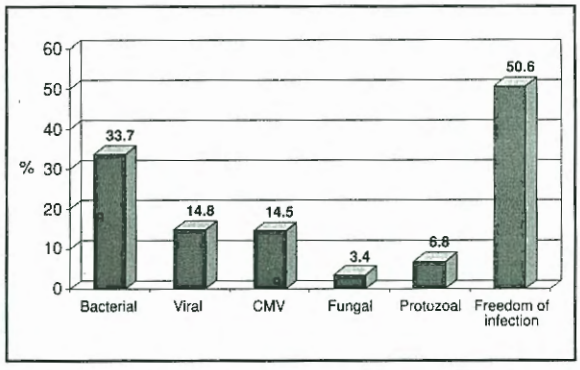

Figure 3. Post transplant infection rates

DISCUSSION

In this study, we drew the profile of long-term survivors of heart transplant recipients and their donors. We believe, it was not a complete profile because of

two main reasons: 1- We did not include the patients operated after September 1989 and being still alive. It is obvious that an important number of them will survive more than ten years. 2- We had some missing parameters in our database for some of the factors we investigated.

Based on the 5-year survival results, it is possible to estimate survival half- life times for the period from the first to the fifth post-transplant year, and to extrapolate from these to project 10-year survival rates. According to Collaborative Heart Transplant Study (CHTS) [2], these hypothetical assumptions revealed 48% for first HTx (12.3 y half-life) and 19% (5.8 y half-life) for second HTx. According to 17th Registry of ISHLT, the patient half-life is 9.8 years and in those surviving the first years, the patient half-life is 12.1 years [1]. 10-year survival (adults and pediatric cases) is about 48%. The reason for HTx is CAD (44.3%), cardiomyopathy (43.7%), valvular heart disease (4.9%), congenital heart disease (1.5%) and ReTx (2.0%). Hartford Hospital database [3] showed the five-year survival rate was 69% and was 43% at 10 years. Sarris et al. [4] had experience with 496 patients (1980-1983) who underwent primary cardiac transplantation since the introduction of cyclosporine immunosuppression. In their series, actuarial survival estimates for all patients at 1, 5, and 10 years are 82% (83% adult, 77% pediatric), 61% (65% adult, 64% pediatric), and 41% (40% adult, 54% pediatric), respectively.

Various factors that can effect long-term survival. Besides demographic factors related with recipient and donor, hormonal and peripheral vascular responses of the denervated heart, exercise tolerance, pulmonary function, and parenting may also be important.

Donor factors: It is generally believed that the older donor organs may be more susceptible to ischemic injury. However, the careful selection of older donors, with close monitoring of the coronary situation after HTx and expanded indications for revascularization of older hearts, could make HTx with older hearts, even in older recipients, a safe option [5]. In our series, the oldest donor was 51 years-old.

Donor -recipient BSA mismatch can potentially lead to complications due to restrictive cardiac physiology in the recipient. Hearts taken from donors whose body mass is within 20% of that of the potential recipient are generally adequate to support the circulation. The height and the muscle mass of the two subjects should also be compatible.

According to CHTS [2], the survival rate of male-to-male Tx is 3% higher at 5 years than that of female-to-male grafts, or that of male or female donor grafts into female recipients. While the lower success rate of female donor hearts in male recipients might be explainable by a comparatively lower physiological muscle capacity of female-donor hearts, which on average are smaller than male hearts, this does not explain the lower survival of male-to-female or female-to-female grafts.

Opelz [2] showed that HTx from white donors into white recipients had a 15% higher survival rate at 5 years than transplants from black donors into black recipients. Tx from black donors into white recipients or white donors into black recipients had intermediate survival rates.

HLA Antigens: HTx are carried out without consideration of the prospecting HLA matching.

Kerman et al. [6] expressed the relationship between donor-recipient HLA mismatching, rejection and death as a result of coronary artery disease (CAD) in 448 cardiac Tx recipients. In that study, matching of donor-recipient HLA did not improve outcome in that 1-, 3- and 5- year survival rates for well-matched versus poorly matched recipients were comparable and not significantly different.

There is a straight correlation of graft outcome with matching for the HLA DR antigens [2]. The influence of matching for the HLA A and HLA B antigens is smaller. However, considering the three loci together (A+B+DR) further improves the HLA matching effect.

A significant association between improved graft survival and HLA-DR mismatching was found over 1, 5, and 10 years after transplantation (no mismatch 1 year 92%, 5 years 83%, 10 years 76%; one mismatch 1 year 81%, 5 years 73%, 10 years 59%, and two mismatches 1 year 78%, 5 years 70%, and 10 years 52%, $p = 0.02$) [7]. HLA matching reduces the frequency and severity of acute cardiac allograft rejection and improves graft survival for up to 10 years. Their preliminary results suggest that it is pos-

sible to use HLA matching prospectively for the selection of recipients.

Ischemia time: The hearts can optimally be preserved with current preservation methods for up to 4 hours. The rate of function declines noticeably, but not dramatically, with longer preservation times (maximum ischemia time was 303 minutes in our group).

Recipient factors: Women compose a much smaller proportion of patients who undergo HTx, but their mortality risk is much higher than that of men [8]. Since women are more susceptible to autoimmune diseases than men, they may be immunologically more reactive and thus more likely to experience life-threatening rejection episodes.

Borkon et al. [9] pointed out that the late survival is adversely influenced by advanced age. Older patients (>55 years) with pre-transplant diagnosis of ischemic cardiomyopathy were particularly at high risk for death.

The mortality risk of age is particularly marked in patients over the age of 65. The presence of concomitant complicating problems such as vascular disease or a predisposition to DM, in addition to greater susceptibility to infection, probably contribute to the enhanced mortality risk associated with older age.

Heart transplantation in selected patients 65 years of age and older can be performed successfully, with a morbidity and mortality comparable with those seen in younger patients. Advanced age should not be an exclusion criterion for heart transplantation, but selective criteria should be applied that identify risks and benefits individually (the oldest recipient was 68 years old in our group).

DM has been considered a contraindication to HTx for a long time, because corticosteroid immunosuppressive therapy exacerbates hyperglycemia and can increase the already high potential for infection in diabetic patients. In addition, diabetic patients have been considered poor risks for HTx because of suggestions that they are prone to accelerated peripheral vascular disease and coronary artery disease.

Patients with a high PVR and high pulmonary pressures should receive donors who match or exceed the recipients' weight [10].

TxCAD: Graft CAD leading to ischemia with consequent loss of ventricular function, myocardial infarction, or death remains the major factor limiting the longer term results of cardiac transplantation and represents the major indication for retransplantation. It has been documented to occur as early as 6 weeks following Tx [8].

Collateral formation is quite unusual in TxCAD. Koegh et al. [11] pointed out that once TxCAD has developed, expected survival falls significantly.

We found that 28% of our patients showed evidence of CAD in the first two years of HTx and they survived for more than ten years.

According to 11-year Texas Children Hospital experience on pediatric HTx (64 patients) [12], on 22 patients (34%) TxCAD was developed. Overall survival was 80%, 60%, and 57% at 1, 5, and 10 years, respectively. Of outcome variables analyzed, rejection frequency was significantly increased in patients who subsequently developed CAD, but the presence of CAD was not significantly correlated with mortality. Five- and 10-year survival are significantly reduced in smokers vs. non-smokers [13]. Smokers had a higher prevalence of transplant vasculopathy as revealed by coronary angiography and/or autopsy.

Overall actuarial survival rates with the current triple drug protocol at Stanford University [11] are 82% at 1 year, 61% at 5 years and 41% at 10 years after Tx. These survival rates represent substantial improvement over the results achieved before the clinical availability of Cyclosporine (approximately 20 percentage points at each time interval). The development of CMV infection has been shown to limit long-term survival and to be associated with higher rates of death from TxCAD.

Infections: A multi institutional study [14] dictates bacterial and viral infections are the most common agents of infection post Tx, accounting for 47% and 41%, respectively, of all events. Fungi and protozoa make up the remainder of infectious agents, but these agents carry a much higher risk of mortality at 36% versus approximately 13% for the aggregate group of infections.

Approximately 27% of CMV-negative recipients who received a CMV-positive heart developed ac-

tive CMV infections versus 15% of all other post HTx patients. They also found that the rate of infection with any organism was higher in patients who received OKT3 or antithymocyte globulin induction therapy (41% with induction therapy versus 35% without induction therapy), and that induction therapy enhanced the risk of CMV infection during the first year post Tx (19% with induction versus 12% without induction). They noted that the risk of mortality from CMV is greatest among the patients who had frequent infections with any other organism, suggesting that these patients were particularly susceptible to infection.

ISHLT database [8] identifies the CMV-negative recipient/CMV-positive donor to be a risk factor for post Tx mortality. On the other hand, CHTS [2] database indicates there is no any effect of recipient preTx CMV status on graft survival.

Panel Reactive Antibody (PRA): Recently, left ventricular assist device usage has become increasingly common, and it has been associated with strikingly increased pretransplantation PRA levels. When they occur together, the data indicates that these patients are at a very high risk for graft failure.

CHTS [2] showed that patients with high PRA or a positive lymphocytotoxic crossmatch is a 5% lower graft survival rate at 1 year than patients with a negative crossmatch.

Other factors: The occurrence of systemic HT has been the rule rather than the exception since the introduction of Cyclosporine.

Lipid-lowering therapy appears to confer a survival benefit in cardiac transplant recipients who survive beyond the first year [15].

Wenke and his co-workers [16] showed the combination of a low-cholesterol diet and simvastatin after heart transplantation led to a significant reduction in cholesterol levels, a significantly higher long-term survival rate, and a lower incidence of TxCAD.

Carrier et al. [17] showed that the cholesterol-lowering intervention was not effective in decreasing the prevalence of allograft coronary artery disease.

In their another work [18], they showed higher pretransplant triglyceride levels were independently related to the development of CAD after cardiac Tx. Thus, TxCAD remains an important cause of late death after heart transplantation.

Conclusion: Although, most of the studies we discussed emphasize existence of TxCAD as a risk factor, we found one-third of the long-term survival patients had early development of TxCAD.

In the second step of our study [19], we compared long-term survival group with mid-term (2-6 years) survival by using uni- and multi variate analysis. And the study had showed that subgroup of factors that can potentially be altered during the first two years after transplant (bacterial infections, rejection episodes and pre-transplant diabetes mellitus) plays an important role in determining long-term survival.

The obvious success of HTx can be attributed to substantial improvements in different areas, including the preoperative management and organ preservation, prevention and treatment of rejection, and the early aggressive management of medical and infectious complications. We believe, with all improvements in these areas, long-term survival will no longer be a challenge.

REFERENCES

1. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ: The registry of the International Society for Heart and Lung Transplantation: Seventeenth official report-2000. J Heart Lung Transplant 2000; 19:909-31

2. Opelz G: Results of cardiac transplantation and factors influencing survival based on the Colloborative Heart Transplant Study. In: Cooper DKC, Miller LW, Pattensos CA (eds). The Transplantation and Replacement of Thoracic Organs. The Present Status of Biological and Mechanical Replacement of the Heart and Lungs. 2nd ed. Boston (MA), Kluwer Academic Publ., 1996. p. 417-27

3. Schweizer RT, Dougherty JE, Rossi MA, Low HB: Long-term survivors of heart transplantation: the Hartford Hospital experience. Conn Med 2000; 64:131-4

4. Sarris GE, Moore KA, Schroeder JS, et al: Cardiac transplantation: the Stanford experience in the cyclosporine era. J Thorac Cardiovasc Surg. 1994; 108:240-51

5. Potapov EV, Loebe M, Hubler M, et al: Medium-term results of heart transplantation using donors over 63 years of age. Transplantation 1999; 68:1834-8

6. Kerman RH, Kimball P, Scheinen S, et al: The relationship among donor-recipient HLA mismatches, rejection, and death from coronary artery disease in cardiac transplant recipients. Transplantation 1994; 57:884

7. Smith JD, Rose ML, Pomerance A, Burke M, Yacoub MH: Reduction of cellular rejection and increase in

longer-term survival after heart transplantation after HLA-DR matching. Lancet 1995; 346:1318-22

8. Cinequegrani MP, Hosenpud JD: Results of cardiac transplantation and factors influencing survival based on the registry of the International Society for Heart and Lung Transplantation and the cardiac transplant research database. In: Cooper DKC, Miller LW, Pattensos CA (eds).The Transplantation and Replacement of Thoracic Organs. The Present Status of Biological and Mechanical Replacement of the Heart and Lungs. 2nd ed. Boston (MA), Klower Academic Publ., 1996. p. 409-16

9. Borkon AM, Muehlebach GF, Jones PG, et al: An analysis of the effect of age on survival after heart transplant. J Heart Lung Transplant 1999; 18:668-74

10. Macris MP: Donor selection and management. In: Frazier OH (ed). Support and Replacement of the Failing Heart. Philadelphia (PA), Lippincott-Raven Publ., 1996.p. 87-98

11. Keogh AM, Smith SA, Sarris GE, Hunt SA, Miller J: Follow-up, late problems, and results of cardiac transplantation. In: Smith JA, Mc Carthy AM, Sarris GE, Stinson EB, Reitz BA (eds). The Stanford Manual of Cardiopulmonary Transplantation. Armonk, (NY), Futura Publ., 1996. p. 151-68

12. Gajarski RJ, Smith EO, Denfield SW, et al: Long-term results of triple-drug-based immunosuppression in nonneonatal pediatric heart transplant recipients. Transplantation 1998; 65:1470-6

13. Nagele H, Kalmar P, Rodiger W, Stubbe HM: Smoking after heart transplantation: an underestimated hazard? Eur J Cardio-thorac Surg 1997; 12:70-4

14. Miller LW, Naftel DC, Bourge RC, et al: Infection after heart transplantation: A multiinstitutional study. Cardiac Transplant Research Database Group. J Heart Lung Transplant 1994; 13:353-64

15. Stapleton DD, Mehra MR, Dumas D, et al: Lipid-lowering therapy and long-term survival in heart transplantation. Am J Cardiol 1997; 80:802-5

16. Wenke K, Meiser B, Thiery J, et al: Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. Circulation 1997; 96:1398-402

17. Carrier M, Pelletier GB, Genest J Jr, Cartier R, Leclerc Y, Pelletier LC: Cholesterol-lowering intervention and coronary artery disease after cardiac transplantation. Ann Thorac Surg 1994;57: 353-6

18. Carrier M, Pelletier G, Leclerc Y, et al: Accelerated coronary atherosclerosis after cardiac transplantation: major threat to long-term survival. Can J Surg 1991; 34:133-6

19. Radovancevic B, Konuralp C, Radovancevic R, et al: Factors predicting survival beyond 10 years following heart transplantation. J Heart Lung Transplant. 2000; 19:78