ELSEVIER

Heart Transplantation in a Low-Organ-Donation Environment: A Single Center Experience

A. Gkouziouta, S. Adamopoulos, A. Manginas, G.K. Karavolias, E. Leontiadis, L. Tsourelis, D. Zarkalis, L. Loukas, G. Stavridis, T. Antoniou, D. Degiannis, E. Melissari, L. Kaklamanis, G. Saroglou, P. Sfirakis, and P. Alivizatos

ABSTRACT

Objective. Heart transplantation is the "gold standard" for treating patients in end-stage heart failure who satisfy strict selection criteria. However, infrequent transplant performance, eg, less than nine per year, may be associated with suboptimal results.

Methods. We reviewed our 13-year clinical experience (1996–2008) with 73 orthotopic heart transplants performed under strict selection criteria and followed closely thereafter at the only accredited center in Greece, a country with an annual rate of only seven donors per million population.

Results. Low perioperative (5.47%) and long-term (7.5%) mortality rates were responsible for a 94% survival rate in the first year, 92% at five years, and 70% at ten years—similar to those reported worldwide—along with excellent functional recovery.

Conclusion. Strict recipient and donor selection criteria, combined with a rigorous multidisciplinary follow-up, yield excellent results despite the existing shortage of available grafts.

HEART transplantation is the most effective treatment for patients in end-stage heart failure offering the potential for a full functional recovery.[1] At the same time, a minimum of nine heart transplants annually seems to be a prerequisite for satisfactory results.[2] Having said that, the registry of the International Society for Heart and Lung Transplantation (ISHLT) does not provide separate survival curves for low-volume (less than ten per year) vis-à-vis high-volume centers.[3] It makes sense, therefore, to investigate whether strict adherence to the existing international guidelines for recipient and donor acceptance along with meticulous long-term care compensate for possible deficiencies resulting from the infrequent performance of transplantations.

METHODS

Patient Selection

Absolute requirements for placement on the transplant waiting list were the exhaustion of all conventional medical and surgical therapies[4] and the documentation of a low functional class[5] (American College of Cardiology/American Heart Association [ACC/AHA] stages C and D previously New York Heart Association classes III and IV), along with poor life expectancy according to internationally accepted criteria.[6] In recent years, the use of ventricular assist devices (VAD) has altered the transplant horizon considerably,[7] with temporary clinical stabilization serving as a "bridge" in selected patients until discovery of a suitable donor.[8,9] Herein, we present our experience with 73 patients who underwent transplantation for end-stage heart failure during a 13 year period (1996–2008) in the only accredited transplant center in Greece. Our hospital's heart transplantation team follows the guidelines of the American Cardiology Societies (ACC/AHA)[10] and of the International Society for Heart and Lung Transplantation (ISHLT).[11] Briefly, suitable candidates for transplantation should be under 65 years of age, in end-stage heart failure, and without systemic disease or recent infection. Exhaustion of all conventional methods of treatment is an absolute requirement, as is a compliant patient free of drug, alcohol, or nicotine dependence and with a supportive social environment.[12] Among the selection criteria, special attention is paid to evaluation of the pulmonary circulation. Proof of

From the Heart and Lung Transplantation Unit, Onassis Cardiac Surgery Center, Athens, Greece

The transplant team thanks the "Alexander S. Onassis" Charitable Foundation for supplying the program's infrastructure and for the staff training abroad.

Address reprint requests to Peter Alivizatos, Onassis Cardiac Surgery Center, 356 Syngrou Ave, Athens, Attiki 17674, Greece. Email: serlokali@yahoo.gr

0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.09.079

Heart Transplantation in a Low-Organ-Donation Environment: A Single Center Experience

A. Gkouziouta, S. Adamopoulos, A. Manginas, G.K. Karavolias, E. Leontiadis, L. Tsourelis, D. Zarkalis, L. Loukas, G. Stavridis, T. Antoniou, D. Degiannis, E. Melissari, L. Kaklamanis, G. Saroglou, P. Sfirakis, and P. Alivizatos

TRANSPLANTATION PROCEEDINGS 41 (2009) 4289–4293

ELSEVIER

Heart Transplantation in a Low-Organ-Donation Environment: A Single Center Experience

A. Gkouziouta, S. Adamopoulos, A. Manginas, G.K. Karavolias, E. Leontiadis, L. Tsourelis, D. Zarkalis, L. Loukas, G. Stavridis, T. Antoniou, D. Degiannis, E. Melissari, L. Kaklamanis, G. Saroglou, P. Sfirakis, and P. Alivizatos

ABSTRACT

Objective. Heart transplantation is the "gold standard" for treating patients in end-stage heart failure who satisfy strict selection criteria. However, infrequent transplant performance, eg, less than nine per year, may be associated with suboptimal results.

Methods. We reviewed our 13-year clinical experience (1996–2008) with 73 orthotopic heart transplants performed under strict selection criteria and followed closely thereafter at the only accredited center in Greece, a country with an annual rate of only seven donors per million population.

Results. Low perioperative (5.47%) and long-term (7.5%) mortality rates were responsible for a 94% survival rate in the first year, 92% at five years, and 70% at ten years—similar to those reported worldwide—along with excellent functional recovery.

Conclusion. Strict recipient and donor selection criteria, combined with a rigorous multidisciplinary follow-up, yield excellent results despite the existing shortage of available grafts.

HEART transplantation is the most effective treatment for patients in end-stage heart failure offering the potential for a full functional recovery.[1] At the same time, a minimum of nine heart transplants annually seems to be a prerequisite for satisfactory results.[2] Having said that, the registry of the International Society for Heart and Lung Transplantation (ISHLT) does not provide separate survival curves for low-volume (less than ten per year) vis-à-vis high-volume centers.[3] It makes sense, therefore, to investigate whether strict adherence to the existing international guidelines for recipient and donor acceptance along with meticulous long-term care compensate for possible deficiencies resulting from the infrequent performance of transplantations.

METHODS

Patient Selection

Absolute requirements for placement on the transplant waiting list were the exhaustion of all conventional medical and surgical therapies[4] and the documentation of a low functional class[5] (American College of Cardiology/American Heart Association [ACC/AHA] stages C and D previously New York Heart Association classes III and IV), along with poor life expectancy according to internationally accepted criteria.[6] In recent years, the use of ventricular assist devices (VAD) has altered the transplant horizon considerably,[7] with temporary clinical stabilization serving as a "bridge" in selected patients until discovery of a suitable donor.[8,9] Herein, we present our experience with 73 patients who underwent transplantation for end-stage heart failure during a 13 year period (1996–2008) in the only accredited transplant center in Greece. Our hospital's heart transplantation team follows the guidelines of the American Cardiology Societies (ACC/AHA)[10] and of the International Society for Heart and Lung Transplantation (ISHLT).[11] Briefly, suitable candidates for transplantation should be under 65 years of age, in end-stage heart failure, and without systemic disease or recent infection. Exhaustion of all conventional methods of treatment is an absolute requirement, as is a compliant patient free of drug, alcohol, or nicotine dependence and with a supportive social environment.[12] Among the selection criteria, special attention is paid to evaluation of the pulmonary circulation. Proof of

From the Heart and Lung Transplantation Unit, Onassis Cardiac Surgery Center, Athens, Greece

The transplant team thanks the "Alexander S. Onassis" Charitable Foundation for supplying the program's infrastructure and for the staff training abroad.

Address reprint requests to Peter Alivizatos, Onassis Cardiac Surgery Center, 356 Syngrou Ave, Athens, Attiki 17674, Greece. Email: serlokali@yahoo.gr

0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.09.079

Table 1. Recipient and Donor Ages

Age, y	Recipients	Donors
10–19	13	16
20–29	10	35
30–39	12	16
40–49	17	4
50–59	18	2
60–69	3	0
Mean	41.2 ± 12.1	25.1 ± 7.6

nonreversible hypertension namely >4 Wood units or of a transpulmonary gradient >15 mm Hg, was an absolute contraindication to orthotopic heart transplantation.[13,14]

Preoperative Support

In 22 patients (30.1%), there was a need for preoperative intravenous inotropic vasodilator support by continuous low-dose dobutamine or milrinone administration via a Hickman catheter connected to a portable infusion pump.[15] This inotropic support had the additional benefit of reducing resistance in cases of persistent pulmonary hypertension, as we have previously reported.[16]

A further six patients (8.1%) received combined inotropic and mechanical circulatory support, using an intra-aortic balloon pump before surgery. Twenty-six patients were transplanted after VAD implantation. Finally, 40 patients (54.7%) underwent preoperative defibrillator implantation for treatment of malignant tachyarrhythmias.

Donor Choice

Donors who were mostly younger than 45 years of age were accepted in the face of the routine absence of a coronary angiogram. In this respect, scrutiny of donor history to rule out risk factors for coronary artery disease was of vital importance.[17] Graft preservation was effected, in situ with cold (4°C) HTK cardioplegia (histidine/tryptophane/ketoglutarate; "Custodiol").[18,19] The mean donor age was 25.1 ± 7.6 years (Table 1) and the mean graft ischemia 238 ± 50.4 minutes.

Surgical Technique

Despite the introduction and subsequent widespread application of the bicaval anastomoses in the 1990s,[20,21] the brilliantly simple biatrial technique of Lower and Shumway[22] was used in almost all (n = 71) cases.

Table 2. Demographics of 73 Heart Transplant Patients

Age (years)	35.1 ± 10.3
Gender (M/F)	59/14
Heart failure pathology	
Dilated cardiomyopathy	52 (71.23%)
Ischaemic cardiomyopathy	17 (23.28%)
Valvular cardiomyopathy	4 (5.48%)
Functional class (ACC/AHA)	
Stage C	43 (58.9%)
Stage D	30 (41.09%)
Peak oxygen consumption (mL/kg/min)	12.3 ± 3.4
Left ventricular ejection fraction (%)	19.8 ± 5.8

Table 3. Preoperative Hemodynamic Parameters

Mean pulmonary artery pressure (mm Hg)	31.1 ± 9.9
Pulmonary capillary wedge pressure (mm Hg)	24.0 ± 9.8
Transpulmonary gradient (mm Hg)	7.2 ± 3.2
Pulmonary resistance (Wood units)	1.85 ± 0.92

Postoperative Medications

Postoperative immunosuppression consisted of induction with antithymocyte globulin (ATG)[23] and maintenance with cyclosporine, low-dose steroids,[24] and mycophenolate mofetil.[25] The rest of the medical treatment consisted of an antihypertensive regimen, statins,[26,27] aspirin, and agents for the prevention of opportunistic infections and of osteoporosis from long-term steroid use.[28,29] All patients followed a strict protocol of myocardial biopsies.[30,31]

RESULTS

As expected, a number of candidates (n = 36) died before a suitable graft could be obtained (on-list mortality 33.6%), after waiting for 123.3 ± 252.8 days (range 3–1,387 days). However, the mortality on the waiting list was not the same at the beginning of the program (1996–2003) compared with that in recent years (2004–2008), the reason being the introduction of VADs as a "bridge" to transplantation in 2003. The waiting time to transplantation or death in 55 patients who entered the list before VAD introduction was 143.2 ± 216.1 days, 26 patients died without receiving a transplant (on-list mortality 47.2%). In contrast although the waiting times (133.4 ± 151.3 days) of the 65 transplant candidates enrolled after VAD introduction did not differ significantly, only ten died without transplantation (on-list ymortality 15.3%) and only three of them were on mechanical support.

Overall in these 13 years 73 patients received grafts after a mean wait of 138 ± 152.2 days (range 0–744 days). The etiologies were dilated cardiomyopathy (n = 52), ischemic (n = 17) and valvular (n = 4); (Table 2). Periodic clinical and hemodynamic examinations were performed on all candidates, including those on mechanical support. None of the latter showed cardiac recovery while on VAD support, based on hemodynamic, echocardiographic, and functional criteria. The clinical data of the 73 transplants are shown in Tables 2–6.

Four patients (5.47%) died in hospital, the first one from catastrophic hemorrhage after a fourth-time redo; another from pneumonia due to panresistant *Pseudomonas*, a third from hyperacute rejection, and the fourth due to superior

Table 4. Preoperative Medications

Diuretics	73 (100%)
Angiotensin-converting enzyme inhibitors	43 (58.9%)
Angiotensin II receptor blockers	30 (41.09%)
Digoxin	34 (46.5%)
Beta-blockers	65 (89%)
Amiodarone	37 (50.68%)
Antiplatelet–Vitamin K antagonist	24 (32.8%)

vena cava damage during BiVAD explantation at the time of transplantation.

Complications were common after transplantation, but with few exceptions they were treated successfully (Table 6). All transplants required inotropic support for a variable time. An IABP was used in 20 cases for significant but transient graft dysfunction. Inhaled prostaglandins and nitric oxide were liberally used in cases of elevated pulmonary arterial pressures.

During scheduled myocardial biopsies, 30 patients (41%) showed acute cellular rejection, which was treated successfully with optimization of immunosuppression (additional steroids or ATG). In six patients it was deemed necessary to replace cyclosporine with tacrolimus for persistent cellular rejection.[32] The five patients (9.4%) who developed acute renal failure after transplantation were placed temporarily on hemodialysis. Another 15 (11 men and 4 women) showed renal dysfunction with serum creatinine values elevated above the upper normal limit of 1.6 mg/dL in men and 1.4 mg/dL in women.

Post-transplant diabetes mellitus was observed in 14 patients; however, their blood glucose levels returned to normal after discontinuation of steroid use (Table 6).

Postoperative infections occurred in 52 patients (71.2%), with 80% of the episodes observed in the first 6 months. We documented 23 cases of pneumonia (31.5%), 20 urinary tract infections, 5 gastroenteritis, 10 herpes zoster, and 2 thrombophlebitis of the internal jugular vein. Primary bacteremia was found in 17 patients and treated successfully. In addition, laboratory tests in 30 patients showed cytomegalovirus infections, which were treated with gancyclovir. Five patients suffered transient strokes, including one due to an *Aspergillus* brain abscess (diagnosed by needle aspiration) that responded to intensive antifungal treatment. Six patients underwent permanent pacemaker implantation later in the follow up, while another four demonstrated early (within 30 days) tricuspid regurgitation, necessitating tricuspid replacement in one of them.

All patients underwent coronary angiography, at one month after transplantation and annually thereafter. In recent years it was supplemented by intravascular ultrasound (IVUS). Despite the administration of statins and aspirin, the study showed the presence of cardiac allograft vasculopathy in 20 patients (27.3%), usually begining several years after the transplantation (Table 6). In four patients, coronary artery disease already present on the first angiogram was attributed to preexistent disease in donors over 45 years of age. In another 3 patients we successfully performed angioplasty with stenting. Out of 69 patients discharged four died during follow-up; two from lymphoma (8 and 15 months after transplantation); one from alcoholism (after 6.5 years), and one from chronic graft rejection (after 8 years). Thus, the overall mortality, including the immediate postoperative deaths, was 10.9% (n = 8) over a mean follow-up of 55.1 ± 34.6 months (range 1–156 months).

Table 5. Preoperative Support

Implantable defibrillator	40 (54.7%)
Preoperative use of intra-aortic balloon pump	6 (8.2%)
Ventricular assist device	24 (32.8%)
Home administration of inodilators	22 (30.13%)

Table 6. Clinical Events in 73 Transplant Patients in Relation to the Time from Operation

	0–30 days	1–6 months	6–12 months	>1 year
Deaths	4	—	—	4
Rejection	22	4	4	—
Infections	27	21	10	19
Tricuspid regurgitation	4	—	—	—
Allograft vasculopathy	0	0	6	14
Acute renal failure (temporary dialysis)	5	0	0	0
Renal dysfunction	4	3	4	4
Bradyarrhythmia	1	0	3	2
Diabetes mellitus (de novo)	14	0	0	0
Neoplasm	0	0	0	2

DISCUSSION

This paper has described our experience with 73 patients receiving a heart transplant for end-stage cardiac failure over a 13 year period, ie with an average output of 5.6 transplants per year, which is well below the recommended activity.[2] However, the survival rates of 94% in the first year, 92% at 5 years, and 70% at 10 years were similar to those provided by the ISHLT[3] (Fig 1). The 65 transplant survivors are free of symptoms and enjoy a good quality of life. These results compared favorably to those reported from established busier programs in other countries.[33] Despite the paucity of donors in Greece,[34] which indirectly also discourages candidate referral, even further limiting the number of transplants, we believe that thorough patient selection with particular attention to the reversibility of pul-

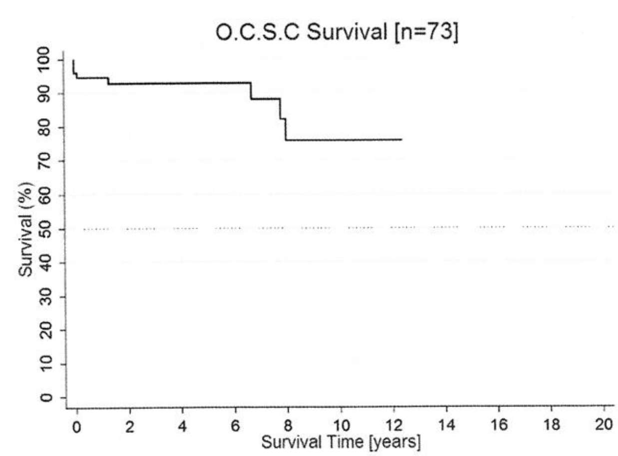

Fig 1. Heart transplantation on survival at the Onassis Cardiac Surgery Center (OCSC), 1996–2008.

monary hypertension,[35,36] careful donor-recipient matching, aggressive treatment of complications, and compulsive follow-up were responsible for our salutary results. Candidate care before transplantation was intensive, as evidenced by the high rate of intravenous inotropic dilators, biventricular pacing/defibrillation and VADs use. Mechanical support as a bridge to transplantation, including reduction of pulmonary hypertension, has been proven to decrease the waiting list mortality.[37,38]

Concerning donor selection, body dimensions, age, predicted ischemia time, and the presence of recipient pulmonary hypertension are crucial, not only for the immediate outcomes but also for the long-term survival. These matching decisions result from hard-won experience after the performance of a large number of transplants. It is our belief, based on previous unfavorable experiences,[39] that grafts from donors aged over 50 years especially with long ischemic times,[40] or those from smokers or hypertensive or diabetic individuals, or from those with marked left ventricular hypertrophy[41] or in subjected to excessive noradrenaline administration,[42] are at a high risk for early failure.[43] Even when the recipient survives the surgery, the probability of future allograft vasculopathy is high, thus influencing long-term results.[44,45] Acute rejection was not a cause of death in this series of transplants, probably because of the aggressive immunosuppression used even for low grades of the disorder (ISHLT 1B or 2). We share the conviction that long-lasting low-grade cellular rejection left untreated gradually leads to allograft vasculopathy.[46,47,48] Furthermore, rejection rates decreased with time; thus, 30 out of the 73 instances (41.09%) were observed in the first 6 months after surgery. The development of graft vasculopathy, the main reason for compromised life expectancy in the heart transplant population,[49] occurred in only 27.4% of our subjects, a rate that is lower than that reported internationally, where 50% of the recipients show varying degrees of coronary lesions within the first 5 years. Currently, all of our vasculopathic patients are being treated with the proliferation signal inhibitor everolimus.[50] Our annual IVUS results, which are promising so far, will appear in a future report.

The small number of patients reported in this paper do not allow predictions as to the maintenance of the satisfactory results obtained so far. As the number of transplants increases, the survival rates may be affected. However, we believe that continuing adherence to the aforementioned guidelines and to the close follow-up will allow the program to enjoy the same success rates in the future.

In conclusion, review of our experience after 73 heart transplants justifies the continuation of a low-volume program in a country known for one of the lowest organ donation rates in Europe. The results prove beyond a doubt that strict adherence to international guidelines and to compulsive care can compensate for the infrequent performance of transplants potentially associated with suboptimal results.

REFERENCES

1. Robbins RC, Hunt SA, Stinson EB, Shumway NE, et al: Thirty years of cardiac transplantation at Stanford University. J Thorac Cardiovasc Surg 117:939, 1999
2. Hosenpud JD, Breen TJ, Edwards EB, et al: The effect of transplant center volume on cardiac transplant outcome. A report of the United Network for Organ Sharing Scientific Registry. JAMA 271:1844, 1994
3. Taylor DO, Edwards LB, Aurora P, et al: Registry of the International Society for Heart and Lung Transplant Report—2008. J Heart Lung Transplant 27:943, 2008
4. Copeland JG, Emery RW, Levinson MM, et al: Selection of patients for cardiac transplantation. Circulation 75:2, 1987
5. Hunt SA: 24th Bethesda Conference: Cardiac transplantation, Nov. 5–6, 1992. J Am Coll Cardiol 22:1, 1993
6. Kirklin JK, Young JB, McGiffin DC, editors: Recipient evaluation and selection. Heart Transplantation. 1st ed. New York: Churchill Livingstone; p. 198–231, 2002
7. Rose EA, Gelijns AC, Moskowitz AJ, et al: Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 345:1435, 2001
8. Stevenson LW, Kormos RL, Bourge RC, et al: Mechanical cardiac support 2000: current applications and future trial designs. J Am Coll Cardiol 37:340, 2001
9. Drakos SG, Kfoury AG, Long JW, et al: Effect of mechanical circulatory support on outcomes after heart transplantation. J Heart Lung Transplant 25:22, 2006
10. A report of the ACC/AHA task force on practical guidelines for the evaluation and management of heart failure. In collaboration with the American College of Chest Physicians and the ISHLT. J Am Coll Cardiol 46:1116, 2005
11. Mehra MR, Kobashigawa J, Starling R, et al: Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 25:1024, 2006
12. Boyle A, Colvin-Adams M: Recipient selection and management. Semin Thorac Cardiovasc Surg 16:358, 2004
13. Stobierska-Dzierzek B, Awad H, Michler RE: The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 38:923, 2001
14. Klotz S, Wenzelburger F, Stypmann J, et al: Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. Ann Thorac Surg 82:1770, 2006
15. Canver CC, Chanda J: Milrinone is for long-term pharmacologic support of the status 1 heart transplant candidates. Ann Thorac Surg 69:1823, 2000
16. Karavolias GK, Adamopoulos SN, Manginas AN, Alivizatos PA: Prolonged continuous outpatient parenteral inotropic support in heart transplant candidates with reversible pulmonary hypertension. J Heart Lung Transplant 21:1 (Abstract 69–70), 2000
17. Cooper DKC, Paradis IL: Selection and management of the donor. In Cooper DKC, Muller LW, Patterson AG, editors: The transplantation and replacement of thoracic organs. 1st ed. London: Kluwer Academic Publishers; 1996, p 19
18. Hendry PJ, Labow RS, Keon WJ: A comparison of intracellular solutions for donor heart preservation. J Thorac Cardiovasc Surg 105:667, 1993
19. Gu K, Kin S, Saitoh Y, et al: HTK solution is more effective than UW solution for cardiac preservation. Transplant Proc 28: 1906, 1996
20. Sievers HH, Weyand M, Kraatz EG, Bernhard A: An alternative technique for orthotopic cardiac transplantation, with preservation of the normal anatomy of the right atrium. Thorac Cardiovasc Surg 39:70, 1991
21. El Gamel A, Yonan NA, Rahman AN, et al: Alternative heart transplantation technique. Ann Thorac Surg 59:258, 1995
22. Lower RR, Shumway NE: Studies on orthotopic homotransplantations of the canine heart. Surg Forum 11:18, 1960

23. Gonwa TA, Mai ML, Alivizatos PA: Stability of long-term renal function in cardiac transplant patients treated with induction therapy and low dose cyclosporine. J Heart Lung Transplant 11:926, 1992

24. Yacoub M, Alivizatos P, Khaghani A, Mitchell A: The use of cyclosporine, azathioprine and antithymocyte globulin with or without low-dose steroids for immunosuppression of cardiac transplant patients. Transplant Proc 17:221, 1985

25. Ensley RD, Bristow MR, Olsen SL, et al: The use of mycophenolate mofetil (RS-61443) in human heart transplant recipients. Transplantation 56:75, 1993

26. Lubitz SA, Baran DA, Alwarshetty MM, et al: Improved survival with statins, angiotensin receptor blockers, and steroid weaning after heart transplantation. Transplant Proc 38:1501, 2006

27. Kobashigawa J, Katznelson S, Laks H, et al: Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 333:621, 1995

28. Cremer J, Struber M, Wagenbreth I, et al: Progression of steroid-associated osteoporosis after heart transplantation. Ann Thorac Surg 67:130, 1999

29. Kapetanakis EI, Antonopoulos AS, Antoniou TA, et al: Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J Heart Lung Transplant 24:526, 2005

30. Caves PK, Stinson EB, Billingham ME, et al: Diagnosis of human cardiac allograft rejection by serial cardiac biopsy. J Thorac Cardiovasc Surg 66:461, 1973

31. Griepp RB, Stinson EB, Dong E Jr, et al. Acute rejection of allografted human heart. Ann Thorac Surg 12:113, 1971

32. Onsager DR, Canver CC, Jahania MS, et al: Efficacy of tacrolimus in the treatment of refractory rejection in heart and lung transplant recipients. J Heart Lung Transplant 18:448, 1999

33. Kirklin JK, Pambukian SV, McGiffin DC, et al: Current outcomes following heart transplantation. Semin Thorac Cardiovasc Surg 16:395, 2004

34. National Transplant Organisation. [Year 2004 outcomes]. p. 49. Greek

35. Chang PP, Longenecker JC, Wang NY, et al: Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. J Heart Lung Transplant 24:998, 2005

36. Goland S, Czer LS, Kass RM, et al: Pre-existing pulmonary hypertension in patients with end- stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. J Heart Lung Transplant 26:312, 2007

37. Salzberg SP, Lachat ML, von Harbou K, et al: Normalization of high pulmonary vascular resistance with LVAD support in heart transplantation candidates. Eur J Cardiothorac Surg 27:222, 2005

38. Zimpfer D, Zrunek P, Roethy W, et al: Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. J Thorac Cardiovasc Surg 133:689, 2007

39. Mercau de Gandolfo A, Adam M, Bret JR, et al: Heart transplantation at Baylor University Medical Center: an 8-year experience. BUMC Proc 7:7, 1994

40. Russo MJ, Chen JM, Sorabella RA, et al: The effect of ischemic time on survival after heart transplantation varies by donor age: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg 133:554, 2007

41. Grauhan O: Criteria for the assessment of the donor heart. Transplant Proc 35:2111, 2003

42. Khasati N, Barnard J, Bittar MN, et al: Donor heart selection: Wythenshawe experience. Transplant Proc 37:1331, 2005

43. Gupta D, Pacentino V, Macha M, et al: Effect of older donor age on risk for mortality after heart transplantation. Ann Thorac Surg 78:890, 2004

44. Ott GY, Herschberger RE, Ratkovec RR, et al: Cardiac allografts from high-risk donors: excellent clinical results. Ann Thorac Surg 57:76, 1994

45. Walker AH, Fildes JE, Leonard CT, et al: The influence of donor age on transplant coronary artery disease and survival post heart transplantation: is it safe to extend donor age? Transplant Proc 36:3139, 2004

46. Stoica SC, Cafferty F, Pauriah M, et al: The cumulative effect of acute rejection on development of cardiac allograft vasculopathy. J Heart Lung Transplant 25:420, 2006

47. Kobashigawa JA, Miller L, Yeung A, et al: Does acute rejection correlate with the development of transplant coronary artery disease? A multicenter study using intravascular ultrasound: Sandoz/CVIS investigators. J Heart Lung Transplant 14:S221, 1995

48. Raichlin E, Edwards BS, Kremers WK, et al: Acute cellular rejection and the subsequent development of allograft vasculopathy after cardiac transplantation. J Heart Lung Transplant 28:320, 2009

49. Pinney SP, Mancini D: Cardiac allograft vasculopathy: advances in understanding its pathophysiology, prevention, and treatment. Curr Opin Cardiol 19:170, 2004

50. Eisen H, Kobashigawa J, Starling RC, et al: Improving outcomes in heart transplantation: the potential of proliferation signal inhibitors. Transplant Proc 37(Suppl 4S):4S, 2005