Two decades of cardiac transplantation at the Montreal Heart Institute

Frédéric Jacques MD¹, Michel Carrier MD¹, Guy B Pelletier MD², Michel White MD², Normand Racine MD², Michel Pellerin MD¹, Denis Bouchard MD¹, Philippe Demers MD¹, Louis P Perrault MD PhD¹

F Jacques, M Carrier, GB Pelletier, et al. Twenty years of cardiac transplantation at the Montreal Heart Institute. *Can J Cardiol* 2008;24(3):217-221.

BACKGROUND: The first heart transplantation in Canada was performed in 1968 at the Montreal Heart Institute (Montreal, Quebec). After nine patients transplanted in the precyclosporine era, the program was stopped. With the advent of cyclosporine, the program was reactivated in 1983.

OBJECTIVE: To review the experience of the Montreal Heart Institute with heart transplantation between 1983 and 2005.

METHODS: Three hundred patients underwent heart transplantation and were followed at the transplant clinic. Patients were divided into two groups: group 1 – first decade (1983 to 1993, n=145) and group 2 – second decade (1994 to 2005, n=155).

RESULTS: There were 125 men (86%) and 20 women (14%) with a mean age of 45±10 years in group 1 compared with 118 men (76%) and 37 women (24%) with a mean age of 48±12 years in group 2 (P=0.03 and P=0.02, respectively). Indications for transplantation included congestive heart failure and/or ischemic heart disease in the majority of patients of both groups, with 83% in group 1 and 73% in group 2, respectively. In group 1, 30 patients (21%) required preoperative pharmacological support and 13 patients (9%) were on mechanical support compared with 16 (10%) and 34 (22%) patients in group 2 (P<0.01). The mean age of donors was 27±10 years and 34±13 years in groups 1 and 2, respectively (P<0.01). Major causes of mortality for donors included a motor vehicle accident in 65 cases (45%) and brain hemorrhage in 43 cases (30%) in group 1 compared with 34 cases (22%) and 68 cases (44%) in group 2 donors (P<0.01). The one-, five- and 10-year actuarial survival rates were 86%, 77% and 71%, respectively, in group 1 compared with 84%, 80% and 68%, respectively, in group 2 (P=0.95). The one-, five- and 10-year freedom from rejection rates were 35%, 28% and 25%, respectively, in group 1 compared with 41%, 36% and 33%, respectively, in group 2 (P=0.13). The one-, five- and 10-year freedom from infection rates were 38%, 24% and 17%, respectively, in group 1 compared with 37%, 23% and 19%, respectively, in group 2 (P=0.72). The one- and five-year freedom from graft coronary artery disease rates were 93% and 67%, respectively, in group 1 compared with 88% and 81%, respectively, in group 2 (P<0.01). The one-, five- and 10-year cancer-free survival rates were 98%, 91% and 73%, respectively, in group 1 compared with 98%, 90% and 77%, respectively, in group 2 (P=0.76).

CONCLUSIONS: Patients who underwent heart transplantation in the second decade of the investigators' experience were older and in worse pre-operative clinical condition; the donors were also older. However, survival and event-free survival rates remained similar throughout both periods.

Key Words: Congestive heart failure; Follow-up study; Surgery; Survival; Transplantation

Vingt ans de transplantations cardiaques à l'Institut de cardiologie de Montréal

HISTORIQUE : La première transplantation cardiaque au Canada a eu lieu en 1968 à l'Institut de cardiologie de Montréal (Montréal, Québec). Après neuf transplantations avant l'homologation de la cyclosporine, le programme a été abandonné. Avec l'avènement de la cyclosporine, le programme a été repris en 1983.

OBJECTIF : Examiner l'expérience de l'Institut de cardiologie de Montréal en matière de transplantation cardiaque entre 1983 et 2005.

MÉTHODOLOGIE : Trois cents patients ont subi une transplantation cardiaque et ont été suivis à la clinique de transplantation. Les patients ont été divisés en deux groupes : groupe 1 – première décennie (1983 à 1993, n=145) et groupe 2 – deuxième décennie (1994 à 2005, n=155).

RÉSULTATS : On comptait 125 hommes (86 %) et 20 femmes (14 %) d'un âge moyen de 45±10 ans dans le groupe 1 par rapport à 118 hommes (76 %) et 37 femmes (24 %) d'un âge moyen de 48±12 ans dans le groupe 2 (P=0,03 et P=0,02, respectivement). Les indications de transplantation étaient une insuffisance cardiaque congestive ou une cardiopathie ischémique chez la majorité des patients des deux groupes, chez 83 % des patients du groupe 1 et 73 % de ceux du groupe 2, respectivement. Dans le groupe 1, 30 patients (21 %) ont eu besoin d'un soutien pharmacologique préopératoire et 13 patients (9 %) étaient sur support mécanique, par rapport à 16 (10 %) et 34 (22 %) des patients du groupe 2 (P<0,01). Les donneurs avaient un âge moyen de 27±10 ans et de 34±13 ans dans les groupes 1 et 2, respectivement (P<0,01). Les principales causes de décès des donneurs étaient un accident de véhicule automobile dans 65 cas (45 %) et une hémorragie cérébrale dans 43 cas (30 %) dans le groupe 1, par rapport à 34 cas (22 %) et 68 cas (44 %) chez les donneurs du groupe 2 (P<0,01). Les taux de survie actuariels au bout d'un an, de cinq ans et de dix ans étaient de 86 %, 77 % et 71 %, respectivement, au sein du groupe 1, par rapport à 84 %, 80 % et 68 %, respectivement, au sein du groupe 2 (P=0,95). Les taux d'absence de rejet au bout d'un an, de cinq ans et de dix ans étaient de 35 %, 28 % et 25 %, respectivement, dans le groupe 1, par rapport à 41 %, 36 % et 33 %, respectivement, dans le groupe 2 (P=0,13). Les taux d'absence d'infections au bout d'un an, de cinq ans et de dix ans étaient de 38 %, 24 % et 17 %, respectivement, dans le groupe 1, par rapport à 37 %, 23 % et 19 %, respectivement, dans le groupe 2 (P=0,72). Les taux d'absence de cardiopathie du greffon au bout d'un an et de cinq ans étaient de 93 % et 67 %, respectivement, dans le groupe 1, par rapport à 88 % et 81 %, respectivement, dans le groupe 2 (P<0,01). Les taux d'absence de cancer au bout d'un an, de cinq ans et de dix ans étaient de 98 %, 91 % et 73 %, respectivement, dans le groupe 1, par rapport à 98 %, 90 % et 77 %, respectivement, dans le groupe 2 (P=0,76).

CONCLUSIONS : Les patients qui ont subi une transplantation cardiaque pendant la deuxième décennie de l'expérience des chercheurs étaient plus âgés et leur état clinique était plus préoccupant avant l'opération. Les donneurs étaient également plus âgés. Cependant, la survie et les taux de survie sans événements sont demeurés similaires pendant les deux périodes.

¹Department of Surgery; ²Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, Quebec

Correspondence: Dr Michel Carrier, Montreal Heart Institute, 5000 Bélanger Street East, Montreal, Quebec H1T 1C8. Telephone 514-376-3330,

fax 514-376-1355, e-mail michel.carrier@icm-mhi.org

Received for publication September 8, 2006. Accepted November 19, 2006

Congestive heart failure is a major and progressively greater concern for public health authorities in western countries as a result of demographic changes and improvement in the treatment of myocardial infarction (1). Today, despite advances in the medical treatment (2-5) of heart failure, development of new surgical procedures (6) and the availability of mechanical circulatory support devices, all of which improve the survival of patients suffering from heart failure, cardiac transplantation remains the most effective therapeutic method for end-stage heart failure. Despite a significant rise in the incidence of severe heart failure in the population, the volume of transplantations has remained stable due to the limited number of donors (7).

The era of cardiac transplantation began in the mid 1960s, and the Montreal Heart Institute (MHI) (Montreal, Quebec) performed the first human heart transplantation in Canada in 1968 (8-10), one year after the first successful human heart graft was implanted in South Africa (11). The program was interrupted, as were most programs worldwide, because of the lack of efficacious immunosuppressive treatments and the dismal results. A better understanding of acute rejection, combined with the development of new immunosuppressive agents (12) and the determination of pioneers, resumed the interest in the field of cardiac transplantation in the late 1970s. The MHI heart transplantation program was reactivated in 1983.

Overall, the first decade of experience with heart transplantation was characterized by a steep learning curve with use of cyclosporine immunosuppression and its systemic side effects. The second decade of our experience saw the emergence of the long-term sequelae of immunosuppression medications, accelerated coronary atherosclerosis of the transplanted heart, and a drastic change in patient and donor demographics. The objective of the present study was to review our experience with heart transplantation in the cyclosporine era from 1983 to 2005 and to analyze the changes in clinical practice and results.

METHODS

The MHI transplant database and records of 300 transplanted patients from April 1983 to May 2005 were reviewed. Patients were divided into two groups based on the date of transplantation. Patients were usually discharged two weeks after transplantation or according to clinical evaluation. After hospital discharge, patients were followed at the transplantation clinic at regular intervals. Endomyocardial biopsies (13) were performed every week for the first month, every two weeks for the following three months, then at six months and one year. Overall, each patient underwent 10 biopsy procedures during the first year. Coronary angiography was performed one or two years after transplantation. Noninvasive imaging procedures, such as echocardiography, Doppler studies of carotid arteries or abdominal ultrasonography, were performed as clinically indicated. Chest x-rays were obtained every six months.

At each visit, nurses recorded vital signs, including weight, and drew blood samples to assess renal function and immunosuppression levels. Physical examinations were performed by transplant cardiologists, who also adjusted medications for the patients as required. Acute rejection was diagnosed according to the International Society for Heart and Lung Transplantation classification (14). Significant rejection episodes (grades 3 and 4) were treated. This post-transplant surveillance protocol provided the opportunity to identify rejection episodes and detect cancers, renal failure and other complications, permitting a complete and regular update of the MHI transplant database.

The operative technique has remained essentially the same during the two decades of study, consisting of a biatrial anastomosis with retrograde or antegrade sanguineous cardioplegia during graft implantation since 1996 (15). In some cases, especially with congenital end-stage cardiomyopathy, a bicaval approach was used. De Vega tricuspid annuloplasty was also performed in the most recent part of our experience.

Immunosuppressive regimen

The immunosuppression protocol of the MHI transplantation program has been based on triple therapy. Induction therapy consisted of

intravenous methylprednisolone administered intraoperatively in all patients. In 1987, the use of polyclonal antibodies was introduced. All subsequent patients received thymoglobulin intravenously during the first three postoperative days (rabbit anti-thymocyte immunoglobulin, Pasteur Mérieux, France). Every dose of thymoglobulin (125 mg/day) was preceded by acetaminophen, diphenhydramine and methylprednisolone. Patients received intravenous methylprednisolone (500 mg) during surgery and 125 mg every 24 h for the subsequent three days, followed by 1 mg/kg oral prednisone tapered progressively to 0.1 mg/kg/day. Selected patients were weaned off prednisone, according to rejection profile, six to 12 months following transplantation. Since 1987, azathioprine (3 mg/kg) has also been started after extubation. Azathioprine was titrated to maintain the white blood cell count of more than 5000 cells/mm³. Mycophenolate mofetil (1 g twice daily) replaced azathioprine from 1997 to 2005 in most patients and was administered at a steady dose of 1 g twice daily. Oral cyclosporine (2 mg/kg to 6 mg/kg) was initiated on postoperative day 2 to 5, and adjusted according to renal function. Whole blood trough levels of cyclosporine were maintained between 200 mmol/L and 300 mmol/L for the first three months, between 200 mmol/L and 250 mmol/L from months three to six, and between 100 mmol/L and 200 mmol/L after six months post-transplantation. Episodes of acute rejection were treated with methylprednisolone 1 g for three days, or intravenous thymoglobulin for three days in a case of refractory rejection.

Statistics

Data are expressed as mean $\pm$ SD when appropriate. Patient age in each group was compared using Student's *t* test. Diagnoses of heart failure, sex, recipient clinical status in both groups, as well as the causes of donor death, were compared by the χ^2 method. The actuarial survival was calculated using NCSS software (NCSS, USA). Actuarial survival curves were then compared by the log-rank method. $P < 0.05$ was considered to be statistically significant. Cox model multivariate analyses were performed to determine risk factors of rejection, infection, cancer and decreased long-term survival. The factors included in the model are shown in Tables 1 and 2.

RESULTS

Recipients and donors

One hundred forty-five patients – 125 men (86%) and 20 women (14%) averaging 45 ± 10 years of age – underwent heart transplantation during the first decade of the present study (group 1). One hundred fifty-five patients – 118 men (76%) and 37 women (24%) averaging 48 ± 12 years of age – underwent transplantation during the second decade (group 2). Recipients of the second decade were significantly older ($P = 0.02$), and there was a greater proportion of women in that group ($P = 0.03$) than in group 1 (Table 1).

Donors of the first decade were significantly younger, with a mean age of 27 ± 10 years compared with 34 ± 13 years of age in donors of the second decade ($P < 0.01$). Donors were predominantly male in both groups: 99 men (68%) in group 1 and 94 men (62%) in group 2 ($P = 0.25$) (Table 1). The causes of donor death in the first decade included a motor vehicle accident in 65 donors (45%), head injury in 24 donors (17%) and brain hemorrhage in 43 donors (30%) compared with 34 donors (22%), 30 donors (19%) and 65 donors (42%), respectively, in group 2 ($P = 0.01$) (Table 1).

Indications for transplantation in group 1 included ischemic cardiomyopathy in 87 patients (60%) and dilated cardiomyopathy in 33 patients (23%) compared with 80 patients (52%) and 32 patients (21%), respectively, in group 2 ($P = 0.03$) (Table 2). In the first decade, 30 patients (21%) required inotropic support and 13 patients (9%) required mechanical support before transplantation in group 1 compared with 16 patients (11%) and 33 patients (22%), respectively, in group 2 ($P = 0.01$). In group 1, mechanical circulatory support consisted of intra-aortic balloon pump. In group 2, left ventricular assistance with the Thoratec (Thoratec Corporation, USA) and Novacor (WorldHeart, USA) devices, as well as the CardioWest total artificial

TABLE 1
Patient characteristics

	1983–1993	1994–2005	P
Recipients			
Men, n (%)	125 (86)	118 (76)	
Women, n (%)	20 (14)	37 (24)	0.03
Age, years (mean $\pm$ SD)	45 $\pm$ 10	48 $\pm$ 12	0.02
Indication for transplantation, n (%)			0.03
Ischemic cardiomyopathy	87 (60)	80 (52)	
Dilated cardiomyopathy	33 (23)	32 (21)	
Viral cardiomyopathy	7 (5)	16 (10)	
Other	18 (12)	27 (18)	
Donors			
Men, n (%)	99 (68)	94 (62)	0.25
Women, n (%)	46 (32)	61 (38)	
Age, years (mean $\pm$ SD)	27 $\pm$ 10	34 $\pm$ 13	<0.01
Cause of death, n (%)			0.01
Motor vehicle accident	65 (45)	34 (22)	
Head trauma	24 (17)	30 (19)	
Brain hemorrhage	43 (30)	65 (42)	
Gunshot/stabbing injury	9 (6)	4 (3)	

TABLE 2
Pretransplantation clinical status

	1983–1993	1994–2005	P
Outpatient (with follow-up)*, n (%)	84 (58)	86 (55)	
Hospitalized, n (%)			
Pharmacological support	48 (33)	35 (23)	
Mechanical support	13 (9)	33 (22)	P=0.01

*Comprised patients unable to work, not requiring hospitalization but unable to perform their own activities of daily living and requiring the support of local health services on a regular basis

heart (SynCardia Systems Inc, USA) were also used ($P=0.01$) (Table 2).

Survival and complication rates

Eight patients (6%) in group 1 and nine patients (6%) in group 2 died within the first week after transplantation. The one-, five- and 10-year actuarial survival rates averaged 86%, 77% and 71%, respectively, in group 1 compared with 84%, 80% and 66%, respectively, in group 2 ($P=0.75$) (Figure 1). The only predictive factor for increased mortality at follow-up was recipient age at the time of transplantation; older patients were at greater risk (hazard ratio [HR] 1.041 [95% CI 1.017 to 1.065; $P<0.001$]). The one-, five- and 10-year freedom from rejection rates were 35%, 28% and 25%, respectively, in group 1 compared with 38%, 33% and 29%, respectively, in group 2 ($P=0.33$) (Figure 2). The year of intervention was the only predictive factor for rejection; patients operated on during the most recent years had a lower rate of acute rejection (HR 0.961 [95% CI 0.934 to 0.989]; $P=0.006$). The one-, five- and 10-year survival free from infection rates were 38%, 24% and 17%, respectively, in group 1 compared with 33%, 19% and 16%, respectively, in group 2 ($P=0.34$) (Figure 3). Patients supported with mechanical circulatory assist devices before transplantation were at greater risk of infection than patients who were not mechanically supported (HR 2.010 [95% CI 1.305 to 3.094]; $P=0.002$). The one- and five-year survival free from graft coronary artery disease rates were 93% and 67%, respectively, in group 1 compared with 87% and 78%, respectively, in group 2 ($P=0.02$) (Figure 4). Coronary angiography was used liberally according to clinical signs and symptoms, and routinely in a part of the cohort. The one-, five- and 10-year cancer-free survival rates were

Figure 1) Actuarial survival of patients ($P=0.75$) Figure 2) Actuarial freedom from rejection ($P=0.33$) Figure 3) Actuarial freedom from infection ($P=0.34$)

98%, 91% and 73%, respectively, in group 1 compared with 98%, 90% and 75%, respectively, in group 2 ($P=0.98$) (Figure 5). Recipient age at transplantation was significantly related to the development of cancer after heart transplantation; older patients were at greater risk (HR 1.038 [95% CI 1.005 to 1.071]; $P=0.02$). Serum creatinine levels between the two groups were comparable at long-term follow-up ($P=0.47$), with a mean level of 143 ± 38 $\mu\text{mol/L}$ and 143 ± 34 $\mu\text{mol/L}$ in groups 1 and 2, respectively (Figure 6).

DISCUSSION

The present study showed that the proportion of women undergoing heart transplantation increased during the two decades of observation, as did donor and recipient age. In addition, patients were in worse clinical condition before surgery in the second decade of our

Figure 4) Actuarial freedom from graft coronary artery disease ($P=0.02$)

Figure 5) Actuarial freedom from cancer ($P=0.98$)

experience. Overall, clinical results represented by patient survival and rate of freedom from acute rejection were similar in the two decades of experience.

There was a significant increase in the number of female recipients over the past two decades. On the other hand, men were still the most frequent donors in both the first and the second decade. There are still controversies in the literature about the impact of the donor sex: some authors suggest that recipients of female hearts have worse outcomes (16,17). The age of both recipients and donors increased significantly in the second decade. As with sex, the importance of age of both recipients and donors is also still a matter of controversy in the literature (18): many authors have reported excellent results with older donors and recipients (19,20). In the present analysis, recipient age at transplantation was the only independent risk factor for mortality at follow-up. Older donor age did not affect early and mid-term survival following transplantation. The majority of donors died from motor vehicle accidents in the first decade, whereas brain hemorrhage was the leading cause of death in the second decade. The change in the causes of donor death explains, in part, the current shortage of organ donors.

The indications for heart transplantation have changed over the past two decades, with a greater heterogeneity of preoperative diagnosis compared with the first decade. However, ischemic cardiomyopathy and dilated cardiomyopathy remained the two most frequent causes of end-stage heart failure. Most recently, we also encountered a greater number of patients with corrected and uncorrected end-stage congenital heart disease. Patients in the second decade of study were more frequently on mechanical circulatory support at the time of transplantation. The poor general condition of patients in the most recent experience is reflected by the greater need for mechanical circulatory support before transplantation, whereas patient survival was similar in the two decades. Mechanical circulatory support systems are now widely available to

Figure 6) Serum creatinine post-transplantation ($P=0.47$)

most transplantation centres, and mechanical support is being offered to patients who may not otherwise survive until transplantation. Although patient survival was greatly improved by the use of mechanical circulatory support, our analysis showed that these patients remained at greater risk of infection after transplantation.

The objective of the present study was to compare the outcomes of patients who underwent heart transplantation at the beginning of our program with that of our most recent experience. We showed that our more current recipients and donors were older and in worse general condition. However, perioperative mortality and long-term patient survival remained unchanged throughout the experience. Although the overall rates of acute rejection were similar in the two groups despite improvement in drugs and protocols, multivariate analysis showed that patients operated on during the more recent years were at lower risk of rejection. We suggest that newer pharmacological approaches are especially effective at decreasing side effects, whereas acute rejection remains a significant issue. Clinical infection immediately after transplantation and cancer in long-term survival remain significant complications related to immunosuppressive drugs (21). The fact that cancer occurred more frequently in older patients at the time of transplantation correlates with the increased incidence of cancer with age in the general population. Even with the improvements of immunosuppressive drugs, the stress on renal function is still a common complication of heart transplantation. Furthermore, we noted a significant decrease in the number of patients with graft coronary disease at follow-up. This may be related to the more aggressive use of prophylaxis with statins to curtail the development of graft coronary artery disease (22), although only prospective studies with coronary intravascular ultrasound monitoring can firmly establish a decreasing incidence of graft coronary artery disease.

CONCLUSIONS

The current organ shortage leads us to emphasize improvement in the medical treatment of congestive heart failure, and the development of permanent mechanical circulatory support systems and surgical alternatives. Although heart transplantation remains the most effective treatment of end-stage heart failure, chronic donor shortage is a significant barrier to the use of this treatment modality. Although pioneers of transplantation dreamed of a definitive treatment of end-stage heart disease, transplant physicians and their patients must face the current reality of the highly limited primary resource – the cardiac donor.

ACKNOWLEDGEMENTS: The authors thank the dedicated nurses of the transplantation program at the Montreal Heart Institute: Carole Rompré, Danielle Dumesnil, Johanne Vézina, Denise Normandin, Denise Pagé, Marie-Claude Gaudreault, Caroline Dupré, Mélanie Cloutier, Virginie Harris and Nancy Chénard for their accurate follow-up of our patients.

REFERENCES

1. Tsuyuki RT, Shibata MC, Nilsson C, Hervás-Malo M. Contemporary burden of illness of congestive heart failure in Canada. *Can J Cardiol* 2003;19:436-8.
2. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;94:2807-16.
3. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
4. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
5. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;327:685-91. (Erratum in 1992;327:1768).
6. Dor V, Kreitmann P, Jourdan J, et al. Interest of physiological closure (circumferential plasty on contractile areas) of left ventricle after resection and endocardectomy for aneurysm of akinetic zone: Comparison with classical technique about a series of 209 left ventricular resections. *J Cardiovasc Surg* 1985;26:73. (Abst)
7. Hosenpud JD, Bennett LE, Keck BM, Fiore B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: Fifteenth official report – 1998. *J Heart Lung Transplant* 1998;17:656-68.
8. Grondin CM. The Montreal Heart Institute: The idea and the man behind it. *Can J Cardiol* 2005;21:1007-10.
9. Grondin CM. In Memoriam: Pierre Grondin M.D. 1925–2006. *J Card Surg* 2006;21:527-8.
10. Canadian Broadcasting Channel. May 31, 1968: Canada's first heart transplant. <archives.cbc.ca/IDC-1-75-2252-13408-10/on_this_day/science_technology/twt> (Version current at November 7, 2007).
11. Barnard CN. The operation. A human cardiac transplant: An interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *S Afr Med J* 1967;41:1271-4.
12. Oyer PE, Stinson EB, Jamieson SA, et al. Cyclosporin A in cardiac allografting: A preliminary experience. *Transplant Proc* 1983;15:1247-52.
13. Caves PK, Stinson EB, Billingham M, Shumway NE. Percutaneous transvenous endomyocardial biopsy in human heart recipients. Experience with a new technique. *Ann Thorac Surg* 1973;16:325-36.
14. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005;24:1710-20.
15. Carrier M, Leung TK, Solymoss BC, Cartier R, Leclerc Y, Pelletier LC. Clinical trial of retrograde warm blood reperfusion versus standard cold topical irrigation of transplanted hearts. *Ann Thorac Surg* 1996;61:1310-4.
16. Prendergast TW, Furukawa S, Beyer AJ III, Browne BJ, Eisen HJ, Jeevanandam V. The role of gender in heart transplantation. *Ann Thorac Surg* 1998;65:88-94.
17. Reed E, Cohen DJ, Barr ML, et al. Effect of recipient gender and race on heart and kidney allograft survival. *Transplant Proc* 1992;24:2670-1.
18. Borkon AM, Muehlebach GE, Jones PG, et al. An analysis of the effect of age on survival after heart transplant. *J Heart Lung Transplant* 1999;18:668-74.
19. Demers P, Moffatt S, Oyer PE, Hunt SA, Reitz BA, Robbins RC. Long-term results of heart transplantation in patients older than 60 years. *J Thorac Cardiovasc Surg* 2003;126:224-31.
20. Carrier M, Emery RW, Riley JE, Levinson MM, Copeland JG. Cardiac transplantation in patients over 50 years of age. *J Am Coll Cardiol* 1986;8:285-8.
21. Robbins RC, Barlow CW, Oyer PE, et al. Thirty years of cardiac transplantation at Stanford university. *J Thorac Cardiovasc Surg* 1999;117:939-51.
22. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995;333:621-7.