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Eighteen Years Of Heart Transplantation – A Single Center Experience

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A B S T R A C T

The best option for the treatment of a failing heart is heart transplantation. The transplantation program at the University Hospital Center Rebro Zagreb started in 1988. To the best of our knowledge this is the first retrospective study on cardiac transplantation in Croatia looking into survival following heart transplantation. Between 1988 and 2006, we performed 81 heart transplantations at the University Hospital Center Rebro Zagreb. Our study focused on the last ten years after establishment of the Department of cardiac surgery as a separate institution. There were thirteen different hospitals throughout Croatia, which contributed to the donor network. Average age of the heart recipient was 48±11.8 years (range 14–72), and average age of the heart donor was 34±10.7 years (range 14–56). There were more women among the heart donors (34%) then among the heart recipients (18%). During the first ten years, from 1988–1998, the average number of cardiac transplantations was 3 per year. In the period from 1998–2006, average number of cardiac transplantations increased to 6 per year. The average thirty-day mortality for the last nine years was 27%. It declined from 30% and 40% in 1998 and 1999, respectively down to 0% in the last two years. Average age of the patients who died was 50±6.5 years (range 44–62) and did not significantly differ from those who survived. The donor network has grown up to fourteen different hospitals throughout Croatia. The limiting factor in cardiac transplant surgery is the number of available donors. Therefore in attempt to form a good transplant program it is crucial to form an efficient donor network. The number of performed cardiac transplantations is expected to rise until it reaches the number of available donors. With advances in operative technique and postoperative management – immunosuppressive therapy we have observed a remarkable drop in the early operative mortality in the studied period.

Key words: *heart transplantation, living donor, immunosuppression, mortality*

Introduction

The treatment of heart failure utilizes a substantial proportion of funds in health care systems of developed countries. According to Cowie, 1999, a crude prevalence is 3 to 20 per 1000 in the general population[1] with constantly increasing incidence. Heart failure has a substantial risk of death, which is around 66% for men and 50% for women in the period of five years[2,3]. Heart failure is one of the most common reasons for hospital admissions in the elderly. Readmission is quite common even within 6 months. EuroHeart failure survey showed that suspected or confirmed heart failure caused 20% of readmissions[4].

The heart transplant surgery begun with French surgeon Alexis Carrel, who performed the first heterotopic canine heart transplant at the very beginning of the 20th century[5,6]. The era of human heart transplantation started with Christian Barnard who performed the first successful human to human heart transplantation in South Africa in 1967[7]. Shumway and his colleagues at the Stanford University revitalized cardiac transplantation in the late 1970s. Josip Sokolic performed the first successful human to human heart transplantation in Croatia in 1988 at the University Hospital Center Rebro Zagreb. Introduction of transvenous endomyocardial biopsy as effi-

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cient means of monitoring allograft rejection and recent progress in immunosuppresion and infection control has transformed cardiac transplantation and marked the beginning of the modern era of successful cardiac transplantation. Cardiac transplantation is widely accepted as a therapeutic procedure of choice for patients with end--stage heart failure. Ventricular assisting devices are now additional efficient means of treatment of heart failure used as a destination therapy or as a bridge to transplantation.

Patients with ischemic heart disease or idiopathic dilated cardiomyopathy that is not amenable to medical or surgical therapy comprise the group of candidates for heart transplantation. Those are patients with left ventricular ejection fraction lower than 20%, with high pulmonary capillary wedge pressure classified in New York Heart Association class III or IV with[8–10]. Oxygen consumption MVO2 should be equal or less than 14 L/min/kg.

Expected 1-year survival in the group of patients that are considered to meet the above mentioned criteria for heart transplantation is less than 50% without transplantation[11–17].

Heart transplantation has its contraindications. Major concern in the early postoperative period is the function of the right ventricle. There are several reasons for such concern. First, depending on the method of delivery, cardioplegia reaches right heart chambers less efficiently than the left ones. This is often times a cause of myocardial stunning and reperfusion injury. On top of that, given usual long duration of heart failure before patients meet criteria for transplantation, recipients often times have some degree of pulmonary vascular hypertension and increased pulmonary vascular resistance, which both put the right heart under a higher strain and can both precipitate right heart failure. Fixed pulmonary vascular resistance greater than six Wood units is an absolute contraindication for heart transplantation and those patients should undergo heart-lung transplantation if possible[18–25]. General contraindications for cardiac transplantation are active infection, renal or hepatic dysfunction, chronic lung disease, severe peripheral atherosclerotic vascular disease, severe systemic connective tissue disorder (SLE), sarcoidosis and malignancy to mention some of the most common ones. End-organ damage such as nephropathy or retinopathy in diabetes is contraindication for heart transplantation[26,27]. The upper age limit, as a cut off for heart transplant, is currently defined as age>70 years. Older patients tend to have more advanced systemic diseases and somewhat higher rate of complications after surgery. However the quality of life after transplantation and survival is comparable to the younger ones.

Patients and Methods

We performed first retrospective study on cardiac transplantation in Croatia since it first begun in 1988. There were total of 81 human-to-human cardiac transplantations performed at the University Hospital Center Rebro Zagreb, but our database covered only the period of last 9 years. During that period of time we performed fifty-one heart transplantations. Technique that we used was orthotopic heart transplantation with no heterotopic transplantations. Average age of the heart recipient was 48±11.8 years (range 14–72), and average age of the heart donor was 34±10.7 years (range 14–56). There were more women among the heart donors (34%) compared to the heart recipients group (18%). There were no heart re-transplantations and none of heart recipients has undergone major cardiac surgery such as valve replacement or aortocoronary bypass after successful cardiac transplantation.

Immunosuppressive protocol at our institution included combination of corticosteroids, cyclosporine, and azathioprine. Azathioprine was later on excluded from the protocol and replaced with mycophenolate mofetil due to its potential toxicity. We titrated cyclosporine to achieve a serum level between 100 and 300 ng/mL. Corticosteroids were first line therapy for acute rejection. Recently we included polyclonal anti-T-cell preparations (ATG) in the early postoperative period. In our current immunosuppressive protocol ATG is replaced with cyclosporine after 3 days. Corticosteroid regimen started with solumedrol at 1.5 mg/kg four times per day. By the postoperative day seven solumedrol was replaced with prednisone starting at 50mg twice a day and further titrated depending on the level of rejection. The bicaval heart transplantation technique as we perform it is shown in Figure 1a–d.

Results

We observed an average number of 3 heart transplantations per year till 1998. After the Department of the cardiac surgery was formed as a separate institution in 1998 average number of cardiac operations increased to 6 per year (Figure 2).

There were 51 cardiac transplantations in the last nine years compared to 30 during the first ten years.

First nineteen explantations were all performed at the University Hospital Center Rebro Zagreb. Ever since the first donor heart came from Rijeka in the year 1994, donor network has expanded to a total of fourteen Hospitals throughout Croatia (Table 1).

Average thirty-day mortality for the last nine years was 27%. It dropped from 30 and 40% in 1998 and 1999, respectively down to 10% in the last four years (table 2). Average age of the patients who died was 50±6.5 years (44–62) and did not significantly differ from patients who survived (p=0.066 according to student T test).

Discussion

Long-term survival of the transplanted heart recipient is limited firstly by allograft rejection and side effects of immunosuppression. It was the advent of cyclosporine that significantly changed survival, marking the beginning of modern era of cardiac transplantation. Imu-

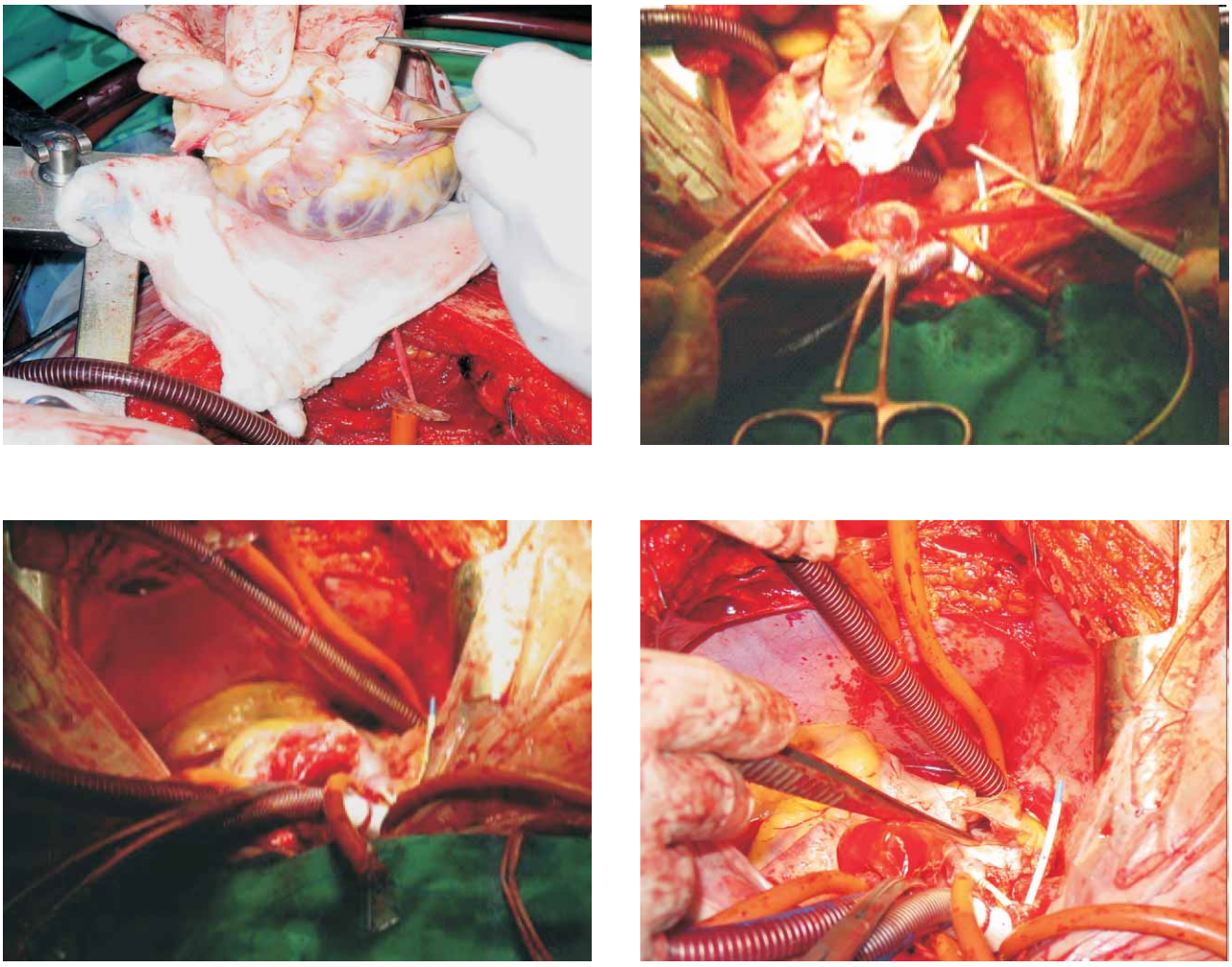

Fig. 1. Bicaval heart transplantation technique: a) first, left atrial anastomosis is created, b) followed by inferior vena cava and aorta (as shown on the figure). c) Transplantation is completed once pulmonary artery and finally d) superior vena cava have been created.

nosuppression is crucial to the success of cardiac transplantation, especially in the early induction phase. Most centers use tipple immunosuppressive regimen with var-

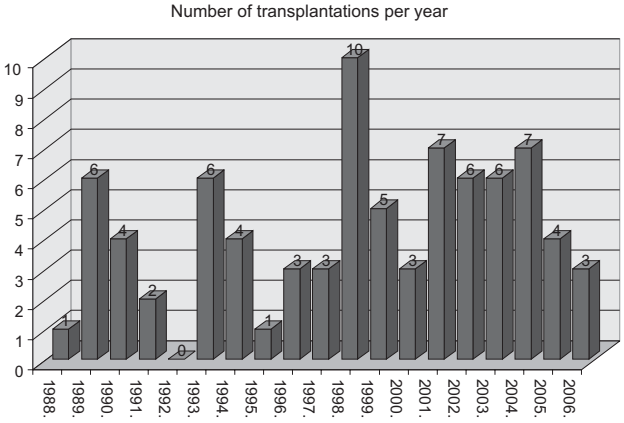

Fig. 2. Number of cardiac transplantations per year.

TABLE 1
THE DONOR NETWORK – CONTRIBUTION OF DIFFERENT HOSPITALS TO THE HEART TRANSPLANT PROGRAM

City	Number of donors	%
Zagreb	42	52.5
Split	6	7.5
Varazdin	6	7.5
Rijeka	5	6.3
Osijek	4	4.4
Dubrovnik	3	3.7
Pula	3	3.7
SI. Brod	2	2.5
Zadar	1	1.3
Sibenik	1	1.3
Karlovac	1	1.3
Cakovec	1	1.3
Koprivnica	1	1.3

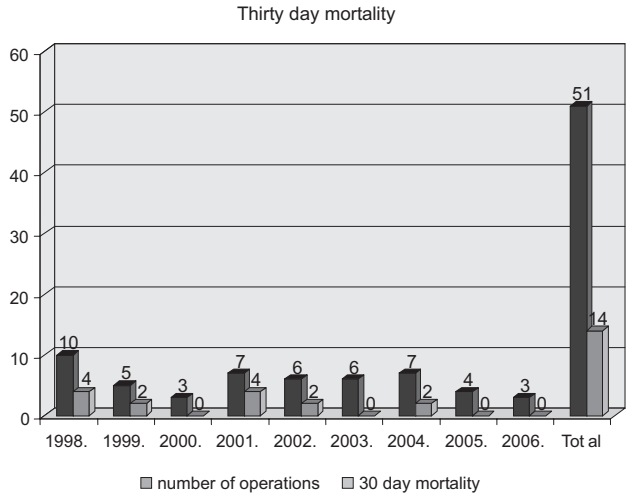

Fig 3. Thirty-day mortality following the heart transplantation.

ious dosages. In patients that develop complications associated with immunosuppressive agents some nonpharmacological immunosuppression may play a significant role. Radiation to lymphatic tissues provides several weeks of nonspecific immunosuppression. Peripheral mononuclear antibodies obtained via leukophoresis have a suppressor effect on T lymphocytes and they may reverse acute rejection. Plasma exchange may permit removal of circulating antibodies.

Operative (i.e., 30-day) mortality for cardiac transplantation ranges from 5 to 10%[28]. We reported a higher 30-day mortality (average 27%), but it has been significantly reduced in the last four years to 10% and it is expected to further decline with larger series of patients. Average age of the heart recipient (48 years) in our group is still well bellow 65 years of age which is generally considered upper limit for cardiac transplantation eligibility. We expect that the average age of our patients rises. Some of our patients will need retransplantation and some will undergo valve replacement or aortocoronary bypass procedures given the natural course of coronary artery disease and valve degeneration.

The increased success of the cardiac transplantation resulted in more operations per year with the same number of available organs. Number of cardiac transplantations in Croatia is still below number of available donors. In most western countries number of donors is the limiting factor for cardiac transplantations. Xenograft transplantation may become an additional source of donor organs once xenograft rejection is resolved.

Critically ill patients are admitted to intensive care unit prior to the transplantation. Some may require aggressive pharmacologic support or even placement of an intra-aortic balloon pump is necessary[29–35] to maintain adequate cardiac output and tissue perfusion prior to transplantation. Mechanical devices such as Ventricular assist devices (VAD) or total artificial hearts (TAH) may provide a bridge to transplantation[36]. Patients with mechanical devices have improved survival and quality of life (REMATCH trial). Approximately 70% of patients are successfully bridged to transplantation[37].

Clinical outcome of heart transplantation has dramatically improved with potent immunosuppressive regimen resulting in lesser degree of rejection and improved survival. The success of cardiac transplantation should not be measured only by the survival of the patients, but also by their quality of life.

Conclusion

The number of cardiac transplantations per year is expected to rise until it reaches the number of available donors. With advancement in cardioplegic solutions, operative technique and immunosuppressive protocol we have observed a dramatic drop in the early operative mortality in the studied period. We have reached the point of learning curve where we cannot expect further dramatic decrease in mortality. Additional survival benefit may be seen after introduction of ventricular assisting devices as a mean of therapy at our institution. Development of a ventricular assisting device program will not eradicate the need for heart transplantations but has a well-established potential to postpone heart transplantation. The cut off time for heart ischemia for a transplanted heart is 4–6 hours; therefore we are emphasizing the importance of logistic support (hospital network, staff education, efficient transportation) to assure adequate graft preservation. Heart transplantation can be safely performed at our institution with acceptable mortality.

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OSAMNAEST GODINA ISKUSTVA U TRANSPLANTACIJI SRCA – ISKUSTVA JEDNOG CENTRA

S A Ž E T A K

Najbolji rezultati u liječenju srčanog zatajenja postižu se transplantacijom srca. Transplantacijski program na Kliničkom Bolničkom Centru Rebro Zagreb započeo je 1988. Prema našim spoznajama ovo je prva retrospektivna studija o transplantaciji srca u Hrvatskoj koja analizira preživljenje nakon transplantacije srca. Između 1988. i 2006. izvedena je 81 transplantacija srca na KBC Zagreb. Naša studija se fokusirala na posljednjih 10 godina nakon formiranja Klinike za kardijalnu kirurgiju kao zasebnog odjela. Trinaest različitih bolnica u Hrvatskoj sačinjava mrežu za donaciju organa. Prosječna dob primaoca bila je 48±11.8 godina (raspon 14–72), a prosječna dob donora bila je 34±10.7 godina (raspon 14–56). Žene su češće bile donori srca (34%), nego primaoci (18%).Tijekom prvih deset godina od 1988–1998 prosječno je bilo tri transplantacije srca godišnje. U razdoblju od 1998–2006 prosječan broj transplantacija srca porastao je na šest transplantacija godišnje. Prosječan 30 dnevni mortalitet za posljednjih devet godina iznosi 27%. Mortalitet je pao s 30% i 40% u 1998 i 1999 godini na 0% u posljednje dvije godine. Prosječna dob umrlih bolesnika iznosila je 50±6.5 godina (raspon 44–62) i nije se statistički razlikovala od dobi preživjelih bolesnika. Mreža bolnica donatora povećala se na četrnaest bolnica diljem zemlje. Transplantacijski programi su limitirani brojem dostupnih donora. Stoga je za formiranje dobrog transplantacijskog programa ključno oformiti učinkovitu donorsku mrežu. Broj transplantacija očekivano raste dok ne dosegne broj dostupnih donora. Napredak u operacijskoj tehnici i poslijeoperacijskom tretmanu – imunosupresivnoj terapiji rezultirao je zamjetnim padom mortaliteta u ranom poslijeoperacijskom razdoblju.