Long term results of heart transplantation in University hospital Dubrava

Rupert, Eva

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Eva Rupert

Long term results of heart transplantation in University Hospital Dubrava

GRADUATE THESIS

Zagreb, 2019

This graduate thesis was made at the Department of Cardiac and Transplant Surgery, University Hospital Dubrava in Zagreb under the supervision of Assistant Professor Igor Rudež, MD, PhD and it was submitted for evaluation in the academic year of 2018/2019.

ABBREVIATIONS

AICD	automatic implantable cardioverter- defibrillator
AMR	antibody- mediated reaction
BiVAD	biventricular assist device
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAV	cardiac allograft vasculopathy
CMV	cytomegalovirus
CVP	central venous pressure
ECG	electrocardiogram
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSV	herpes simplex virus
HTx	heart transplantation
IABP	intra- aortic balloon pump
IJV	internal jugular vein
ISHLT	International Society of Heart and Lung Transplantation
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MMF	mycophenolate mofetil
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PRA	panel reactive antibodies
PSA	prostate- specific antigen
PVR	pulmonary vascular resistance
RVAD	right ventricular assist device
SVR	systemic vascular resistance

TAH	total artificial heart
TPG	transpulmonary gradient
VAD	ventricular assist device
VZV	varicella zoster virus

TABLE OF CONTENTS

SUMMARY

Title: Long term results of heart transplantation in University Hospital Dubrava
Author: Eva Rupert
Keywords: heart transplantation, long term results, end- stage heart failure

Heart transplantation is a life- saving and quality of life enhancing treatment option for patients with end- stage heart failure. Patients who are suitable candidates suffer from a terminal illness with prognosis of 1- year survival without transplantation less than 50%. The major limiting factor is donor organ availability, therefore it is important to choose recipients who are most likely to achieve long- term benefits and who tried other medical and surgical alternatives which did not work. Allocation of donor organs depends on recipient's priority status, which is determined by strict criteria. Both donor and recipient must be thoroughly evaluated to rule out any contraindications that might prevent them from proceeding to the surgery. Only a good match between donor organ and recipient leads to a good short- term and long- term outcome of transplantation. Decades of surgical technique improvements, effective immunosuppressive agents and development of medicine in general, which supports patients' preoperative and postoperative care, made heart transplantation a very successful treatment option with a very low perioperative mortality rate. The causes of early allograft failure are myocardial dysfunction due to donor instability, pulmonary hypertension, ischemic injury during preservation and sometimes acute rejection. Long- term complications which often tend to also become the cause of death are infections, allograft rejection, cardiac allograft vasculopathy and renal dysfunction. Chronic immunosuppression is associated with increased incidence of cancers, mostly lymphoproliferative disorders and skin cancer. Out of all complications, infection is the leading cause of morbidity and mortality. This study showed that in Clinical Hospital Dubrava, post heart transplantation survival rates at 1, 5, and 10 years were comparable to those reported by the International Society of Heart and Lung Transplantation (ISHLT).

SAŽETAK

Naslov: Dugoročni rezultati transplantacije srca u kliničkoj bolnici Dubrava
Autor: Eva Rupert
Ključne riječi: transplantacija srca, dugoročni rezultati, terminalno zatajivanje srca

Transplantacija srca je terapijska mogućnost liječenja i poboljšanje kvalitete života za bolesnike u završnoj fazi zatajenja srca. Bolesnici koji su prikladni kandidati boluju od terminalnog kroničnog srčanog zatajenja s prognozom od 1 godine preživljavanja bez transplantacije manjom od 50%. Glavni ograničavajući čimbenik je dostupnost organa davaoca, stoga je važno odabrati primatelje koji će najvjerojatnije postići dugoročnu korist i kod kojih su ostale medicinske i kirurške metode liječenja iscrpljene. Dodjela organa ovisi o prioritetnom statusu primatelja, što je određeno strogim kriterijima. I donor i primatelj moraju biti temeljito procijenjeni kako bi se isključile kontraindikacije. Samo dobra podudarnost između organa primatelja i donora dovodi do dobrog kratkoročnog i dugoročnog ishoda transplantacije. Desetljeća poboljšanja kirurške tehnike, učinkoviti imunosupresivni lijekovi i razvoj medicine općenito, učinili su transplantaciju srca vrlo uspješnom opcijom liječenja s vrlo niskim perioperativnim mortalitetom. Uzroci ranog otkazivanja alografta su disfunkcija miokarda uslijed nestabilnosti donora, plućne hipertenzije, ishemijske ozljede tijekom transporta srca i ponekad akutnog odbacivanja. Dugotrajne komplikacije koje često postaju uzrok smrti su različite infekcije, odbacivanje alografta, vaskulopatija srčanog alografta i disfunkcija bubrega. Kronična imunosupresija povezana je s povećanom učestalošću karcinoma, uglavnom limfoproliferativnih poremećaja i raka kože. Od svih komplikacija, infekcija je vodeći uzrok morbiditeta i mortaliteta. Ovo je istraživanje pokazalo da su u Kliničkoj bolnici Dubrava, stope preživljavanja nakon transplantacije srca na 1, 5 i 10 godina bile usporedive s onima koje je prijavilo Međunarodno društvo za transplantaciju srca i pluća (ISHLT).

1. INTRODUCTION

1.1 HISTORY OF HEART TRANSPLANTATION

Heart transplantation has become an effective therapy available worldwide for patients with end- stage heart failure. Today, this is a routine treatment for those who cannot be treated with other appropriate medications and surgical therapies alone, however, it was not always like that. In the early experimental period, heart transplantations were performed on animal models and the neck was a preferred location of implantation. The first heterotropic canine heart transplantation was performed by a French surgeon Alexis Carrel in 1905 but it was unsuccessful due to a cardiac allograft rejection. Later, in 1946, a Russian surgeon Vladimir Demikhov successfully implanted the first intrathoracic heterotropic heart allograft but again, because of donor and recipient incompatibility the heart was eventually rejected. Many years have passed and in that time medicine developed enough that in 1964 an American surgeon James Hardy successfully implanted a chimpanzee xenograft into a human body. The use of moderate hypothermia, cardiopulmonary bypass and atrial cuff anastomotic technique all helped to make it a successful surgery, however, the primate's heart was unable to maintain the recipient's circulatory load and the patient died few hours after surgery. So the next step was to try and implant a human heart into a human patient, which successfully happened three years later in Cape Town, South Africa, where surgeon Christiaan Barnard performed the first human- to human heart transplantation. The surgery went well, the patient lived for another 18 days but then due to a severe pulmonary infection, that occurred because of an aggressive immunosuppressive therapy, he died. First successful orthotopic heart transplantation in the United States was done in 1968 at Stanford by doctor Norman Edward Shumway, who developed the Shumway technique, which became a standard technique for heart transplantation. It was not until 1981 when the modern era of successful cardiac transplantations started due to a discovery of immunosuppressive agent cyclosporine, which dramatically increased patient's survival.[1] Nowadays, the limiting factor is not anymore

allograft rejection but the donor organ availability. The first transplantation in Croatia was performed exactly 20 years after the first successful transplantation in the world in 1988 in Zagreb by a surgeon Josip Sokolić and since then it has become a standard treatment for all end- stage heart failure patients who fit the recipient selection criteria. [2]

1.2 RECIPIENT SELECTION

Since the major limiting factor is donor organ availability, it is important to choose recipients who are most likely to achieve long- term benefit. Every potential candidate is evaluated by a committee. Firstly, patient's end- stage heart failure must really be irreversible. There are many other medical and surgical procedures, such as ventricular assist devices, that must be explored first before considering heart transplantation. Secondly, the etiology of patient's end-stage heart failure must be determined because it can influence the outcome. Mostly, the reasons are ischemic heart failure and dilated cardiomyopathy. Other reasons are valvular, adult congenital and miscellaneous. If the etiology cannot be determined, endomyocardial biopsy must be done to exclude diseases, such as amyloidosis, which are contraindications for heart transplantation because they can repeat in the transplanted heart as well. The initial evaluation consists of patient history and physical examination. With this basic information one can find out if the patient has any contraindications, which put him immediately off the transplant list. After this, laboratory workup must be done. Blood must be taken to evaluate CBC, blood type, IgG and IgM antibodies against CMV, HS, HIV, VZV, HBV, HCV and toxoplasmosis. Then, tuberculin skin test, 24-hour urine for creatinine clearance and total protein, urinalysis and urine culture must be done. For male patients over 50 years of age, PSA must be measured and for female patients over 40 years of age, mammogram and PAP smear must be done. Lastly, screening against a panel of donor antigens and HLA phenotype must be performed. After this general assessment, the patient's heart itself must be very thoroughly assessed. Routine 12- lead electrocardiogram, Holter monitor, echocardiography, cardiopulmonary exercise tests and right- sided heart catheterization must be performed. Once the functional capacity is known and

contraindications like severe pulmonary hypertension are excluded, patient can be put on transplant waiting list. It is important to notice that every potential candidate must also be examined by neurologist to evaluate brain function and psychiatrist to see if any psychiatric illnesses are present. [1]

Patients with elevated levels of preformed PRAs to HLAs have higher rates of organ rejection and decreased survival. Therefore, some medical transplant centers do cross- matching. Either by flow cytometry or enzyme- linked immunosorbent assay but this is time- consuming and costly. Patients with previous VAD placement have higher levels of preformed reactive antibodies. All donor antigens are known at the time of allocation and assessment can be made without an actual tissue/sera assay. To lower PRA levels, plasmapheresis, intravenous immunoglobulins, cyclophosphamide, MMF and rituximab are effective. While waiting on the heart transplant list, patients receive medical therapy or surgery where a device is implanted into the body. The first one is called pharmacologic bridge to transplantation. If the patient's condition is very bad, admission to ICU might be necessary so he can get intravenous inotropic therapy with either dobutamine (eosinophilic myocarditis can develop), milrinone, dopamine (can result in systemic vasoconstriction) or combination of these drugs for higher efficacy. Other option is mechanical bridge to transplantation which must be considered, if patients with heart failure are refractory to initial medical therapy. Placement of IABP, BiVAD, LVAD, TAH is possible, depending on patient's condition. If patients with heart failure have a history of symptomatic ventricular tachycardia, AICD should be implanted, radiofrequency catheter ablation or long- term antiarrhythmic therapy with amiodarone should be applied. Patients on the waiting list should be examined at least every three months for reevaluation of the recipient status. Yearly everyone on the waiting list should get right- sided heart catheterization and also those who were primarily rejected because of severe pulmonary hypertension. [1,6,16]

1.3 RECIPIENT PRIORITIZATION

Patient prioritization is based on survival and quality of life expected to be gained in comparison with maximal medical and surgical alternatives. In Croatia, allocation of donor organs depends on recipient's priority status. Organ match characteristics which determine the priority status are ABO blood group, donor age, virology (CMV, IgG), sepsis, meningitis, malignant tumor, IV drug abuse and many other. Duration of time at a particular status level and geographic distance between donor organ and recipient also play an important role. Geographic priority leads to reduced preservation time, improved organ quality and survival outcomes. The better the match, the lower the risk of a rejection and a loss of an organ. Therefore, the larger the pool of donors and recipients, the easier it is to achieve a good match, which leads to better short- term and long- term outcomes of transplantation. That is why Croatia joined Eurotransplant.

Eurotransplant is a non- profit international service organization that acts as a mediator between donor hospitals (donors) and transplant centers (recipients). Its main goal is to enable the best possible match between available donor organs and patients with end- stage organ failure who are on the transplant waiting list. This can be achieved with a good allocation and distribution system which is based on medical and ethical criteria. The allocation system is objective, transparent, reproducible and valid. The match is based upon two general principles; expected outcome and urgency. Eurotransplant was founded in 1967 by Prof. Dr. Jon J. Van Rod and it started with allocating only kidneys. It was not until late seventies when Eurotransplant expanded its services with the allocation of hearts, livers and pancreas. Later, lungs and intestines were also added to the list of donor organs so today there are six different organs in the allocation system. There are eight countries currently participating in this program; Austria, Belgium, Croatia, Hungary, Luxembourg, Germany, the Netherlands and Slovenia, serving a total population of around 136 million people. Since these countries are all in European Union, the Eurotransplant organization needs to act in accordance with EU regulations and ethical principles as well as with national member states legislation for cross- border exchange of deceased donor organs. There are three current systems of organ donation; presumed consent, informed

consent and required consent. Most of Eurotransplant members including Croatia have presumed consent, meaning that organ donation is automatically considered in patients diagnosed brain dead, unless they have specifically registered their wish that they do not want to donate. Some other members like Germany have informed consent, which means that relatives need to give permission at the time of death. The third type of system of organ donation is required consent, where physicians in charge of potential donors need to speak to the family of a deceased about possible organ donation. None of Eurotransplant member countries have this type, but most known outside of Eurotransplant is USA. [3]

Eurotransplant is constantly improving itself by monitoring and evaluating allocation outcomes, patient and graft survival rates. The major limiting factor in international organ exchange is the cold ischemia time. After removal, a donor organ needs to be transplanted within a few hours because there is a limited time in which organs stay healthy outside the body (the cold ischemic period). Nevertheless, cross border exchange is still an important way of increasing the number of organs available to a wider population and is especially significant in a certain groups of patients such as highly- urgent or highly- immunized patients. If there is a risk that a patient will die in a short period of time, he becomes categorized as highly urgent and gets on the top of the waiting list. The highly-immunized patients are those who have a high risk of having antibodies that will react to blood of tissue from another person. Therefore, Eurotransplant has signed agreements with seventeen other organ exchange organizations. If there is no suitable recipient found within Eurotransplant, the donor organ is offered to or received from other organizations. [3]

There are two heart transplantation centers in Croatia, one in University Hospital Center Zagreb, and the other in University Hospital Dubrava. Croatia joined the Eurotransplant organization in May 2007 and since then, the system of organ donation and transplantation has improved a lot. The average number of donors per million inhabitants of Croatia is now more than 35 donors per million inhabitants.[3]

1.4 INDICATIONS

Prognosis of 1-year survival without transplantation should be less than 50%. There are many predictors of poor prognosis but one of the strongest independent predictors of survival are low LVEF (less than 35%) and low VO_{2max} (less than 10 ml/kg/min).[1] The causes of systolic heart failure are mostly dilated and ischemic cardiomyopathies. Other diagnoses, which are very uncommon, are intractable angina, intractable arrhythmia, hypertrophic cardiomyopathy, congenital heart disease, cardiac tumor and restrictive cardiomyopathy. [16,19]

Table 1: Indications for heart transplantation[1]

Indications for heart transplanation
1. Systolic heart failure (as defined by ejection fraction <35%) A. Accepted etiology 1. Ischemic 2. Idiopathic 3. Valvular 4. Hypertensive 5. Other B. Controversial etiology 1. HIV infection 2. Cardiac sarcoma
2. Intractable angina A. Ineffective maximal tolerated medical therapy B. Not a candidate for direct myocardial revascularization, percutaneous revascularization, or transmyocardial revascularization procedure C. Unsuccessful myocardial revascularization
3. Intractable arrhythmia A. Uncontrolled with pacing cardioverter defibrillator 1. Not amenable to electrophysiology- guided single or combination medical therapy 2. Not a candidate for ablation therapy
4. Hypertrophic cardiomyopathy A. Class IV symptoms persist despite interventional therapies 1. Alcohol injection of septal artery 2. Myotomy and myomectomy 3. Mitral valve replacement 4. Maximal medical therapy 5. Pacemaker therapy
5. Congenital heart disease in which severe fixed pulmonary hypertension in not a complication
6. Cardiac tumor A. Confined to the myocardium B. No evidence of distant disease revealed by extensive metastatic workup
7. Restrictive cardiomyopathy A. Class IV symptoms persist despite interventional therapies B. Amyloid (if concomitant therapy such as chemotherapy/autologous stem cell transplant feasible)

1.5 CONTRAINDICATIONS

There are absolute and relative heart transplantation contraindications. Absolute contraindications are; age >65-75. The upper age limit for recipients is center specific. It is important to notice that patient's physiologic rather than chronologic age should be evaluated. Then, fixed pulmonary hypertension, usually manifested as elevated PVR. Fixed PH increases the risk of acute right ventricular failure when the right ventricle of the allograft is unable to adapt to significant PH in the immediate postoperative period. A fixed PVR greater than 5-6 Wood units and a TPG greater than 15mmHg are accepted as absolute criteria for rejection of a candidate. Next absolute contraindication is systemic illness that will limit survival despite transplantation. If systemic disease has a poor prognosis, if it has a potential to recur or if it has potential to undergo exacerbation with immunosuppressive therapy; active malignant disease and active systemic infection are such contraindications. Transplantation in cases like that needs to be delayed until the disease or infection is resolved. However, nowadays, many patients have LVADs which can get infected. In such cases, urgent transplantation is indicated despite active infection. HIV infection is a contraindication if CD4 is less than 200 cells per mm^3. Irreversible renal function is also a contraindication, if creatinine clearance of less than 50mL/min and a serum creatinine concentration is greater than 2mg/dL, because it leads to decreased survival and increased risk of dialysis. Such patients may be considered for combined heart and kidney transplantation. Another absolute contraindication is irreversible hepatic dysfunction. If transaminase levels are more than twice their normal level or if coagulation abnormalities are present. Percutaneous liver biopsy needs to be done to exclude primary liver disease.

Relative contraindications are; recent malignancy because there is a high chance that it will recur due to immunosuppressive therapy. Chronic obstructive pulmonary disease or severe chronic bronchitis. It may predispose a person to a pulmonary infection or may result in prolonged ventilatory support after surgery. Poor candidates are patients with ratio of FEV1/FVC less than 40-50%. Diabetes mellitus but only if there is an end- stage damage present (neuropathy,

nephropathy, retinopathy). Recent and unresolved pulmonary infarction and pulmonary embolism; peripheral vascular or cerebrovascular disease (severe non- cardiac atherosclerotic disease); active peptic ulcer disease; current or recent diverticulitis; severe obesity or cachexia (BMI less than 20 or more than 35); severe osteoporosis; active alcohol, nicotine or drug abuse; history of noncompliance or psychiatric illness- psychosocial stability and compliance are very important for successful recovery because of multidrug therapy, frequent clinic visits and routine endomyocardial biopsies; absence of psychosocial support; effect of metabolic risk factors- hypertension, diabetes, obesity- there is an increasing mortality with addition of each risk factor. Patients with all 3 have the highest mortality rate. [1,12,15,16,19,20]

Table 2: Absolute and relative contraindications of heart transplantation[1]

Absolute contraindications
1. Age >65-75 (may vary at different centers)
2. Fixed pulmonary hypertension (unresponsive to pharmacologic intervention) A. Pulmonary vascular resistance >4-6 Wood units B. Transpulmonary gradient >12-18 mm Hg
3. Systemic illness that will limit survival despite transplant A. Neoplasm other than skin cancer (<2-5 years disease- free survival) B. HIV/AIDS (CDC definition of CD4 count of <200 cells/mm^3) C. Systemic lupus erythematosus (SLE) or sarcoid that has multisystem involvement and is currently active D. Any systemic process with a high probability of recurrence in the transplanted heart E. Irreversible organ (e.g. renal, hepatic, pulmonary) dysfunction
Relative contraindications
1. Recent malignancy
2. Chronic obstructive pulmonary disease
3. Recent and unresolved pulmonary infarction and pulmonary embolism
4. Diabetes mellitus with end- organ damage (neuropathy, nephropathy and retinopathy)
5. Peripheral vascular or cerebrovascular disease
6. Active peptic ulcer disease
7. Current or recent diverticulitis
8. Other systemic illness likely to limit survival or rehabilitation
9. Severe obesity or cachexia
10. Severe osteoporosis
11. Active alcohol, nicotine or drug abuse
12. History of noncompliance or psychiatric illness likely to interfere with long-term compliance
13. Absence of psychosocial support

1.6 DONOR SELECTION AND MANAGEMENT

Every brain- dead individual who is a potential cardiac donor goes through many phases of screening. Past medical history is important to search for potential contraindications and physical examination is performed. Patient's age, height, weight and BMI are determined. Donor' s weight should be within 30% of recipient's weight, larger donor is preferred only in case of elevated PVR in the recipient when Wood units are 5-6, because then there is reduced risk of right ventricular failure in the early postoperative period. Furthermore, ABO blood type, cause of death, routine lab data including CMV, HIV, HBV, HCV serologies must be known. ABO barriers should not be crossed because incompatibility can result in fatal hyperacute graft rejection. Arterial blood gas, ECG, chest x- rays, and echocardiogram should be performed to search for any anatomical abnormalities. Coronary angiography is indicated if donor's age is above 45 in males and above 50 in females, if there is a history of cocaine abuse or presence of three and more risk factors for CAD (hypertension, diabetes, smoking history, dyslipidemia or family history of premature CAD). Final assessment of the donor's heart is intraoperative, right before organ procurement. Direct visualization allows surgeons to evaluate if right ventricular or valvular dysfunction, previous infarction, myocardial contusion secondary to closed chest compressions or blunt chest trauma is present. Palpation is also important to feel any gross calcifications that might not be visible to the eye and would indicate atheromatous disease. After all these examinations, if everything fits the criteria, the recipient's hospital is notified and donor cardiectomy is performed.

Cardiac donor criteria consist of age below 50-60 and absence of any of the following: prolonged cardiac arrest, prolonged severe hypotension, preexisting cardiac disease, intracardiac drug injection, severe chest trauma indicating cardiac injury, septicemia, extracerebral malignancy and glioblastoma, positive serologies for HIV, HBV and HCV and hemodynamic stability without high- dose inotropic support. Once cardiac donor is evaluated and is ready to be explanted, everything must be done to preserve the organ in as good condition as possible. Inotropic support is provided to maintain mean arterial blood pressure at least 60 mmHg in the presence of CVP of 6-10 mmHg. Low dose vasopressin is effective

because it improves arterial blood pressure and reduces exogenous inotrope requirement. Correction of anemia (target hematocrit 30%, hemoglobin 10g/dL), acidosis (target pH is 7.40- 7.45), hypoxemia (target is PO2>80 mmHg, O2 saturation >95%) and hypercarbia (target is PCO2 30-35 mmHg) if necessary. Maintenance of normal body temperature, thermoregulation goal is between 34-36°C. There is some evidence that thyroid hormones and steroids have beneficial effects on cardiac performance in brain dead patients, therefore methylprednisolone, triiodothyronine and arginine vasopressin are applied. Donors also receive insulin and in certain cases broad spectrum antibiotic therapy with a cephalosporin after blood and urine collection is also given. [1,14,16,18,19]

Use of marginal donors for marginal recipients is an option when there is a match between hearts that would otherwise go unused and recipients who did not make it on the transplant waiting list. Expanded donor criteria includes: donors substantially smaller than recipients, donors with coronary artery disease that may require CABG, left ventricular dysfunction, donors who are older, HBV or HCV positive and if they are alcohol and cocaine abusers. [1]

1.7 CARDIAC PROCUREMENT AND PRESERVATION

Cardiac donor procurement starts with median sternotomy and longitudinal pericardial incision. The heart is inspected and palpated for any evidence of injury and if nothing unusual is found, the recipient surgical team is informed so they can proceed with their operation. 30000 units of heparin is infused intravenously and the heart is prepared for explantation. Then, heart is arrested with a single flush of cardioplegic solution and copious amounts of cold saline are poured into the pericardium to achieve rapid cooling effect. Once all arteries and veins are dissected, heart is explanted and checked if there is patent foramen ovale, which should be closed at that time, or some valvular anomalies. If allograft is intact, it is put into the sterile container and transported to the recipient's hospital as soon as possible. Safe cardiac ischemic time is 4-6 hours. Factors that influence on postoperative myocardial dysfunction are hypothermia, ischemia- reperfusion injury and depletion of energy stores. The heart should be

stored on a temperature between 4 and 10°C. Timing of donor and recipient cardiectomies is critical to minimize allograft ischemic time and recipient bypass time. [1]

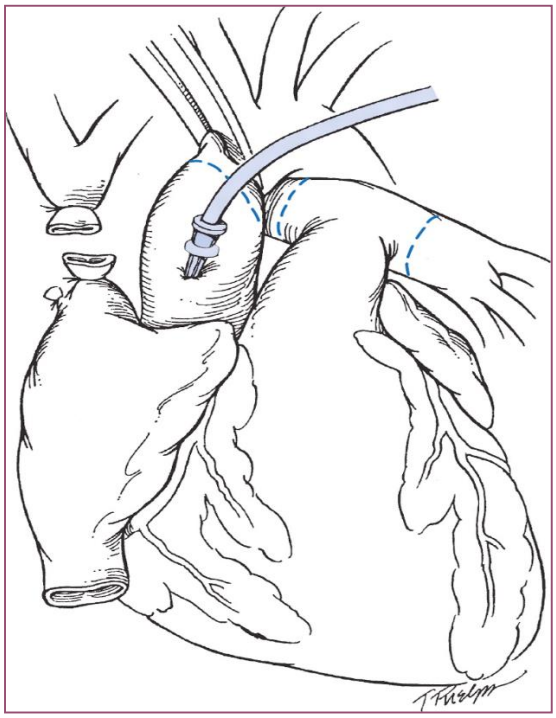

Figure 1: Donor cardiectomy; indicating incision lines[1]

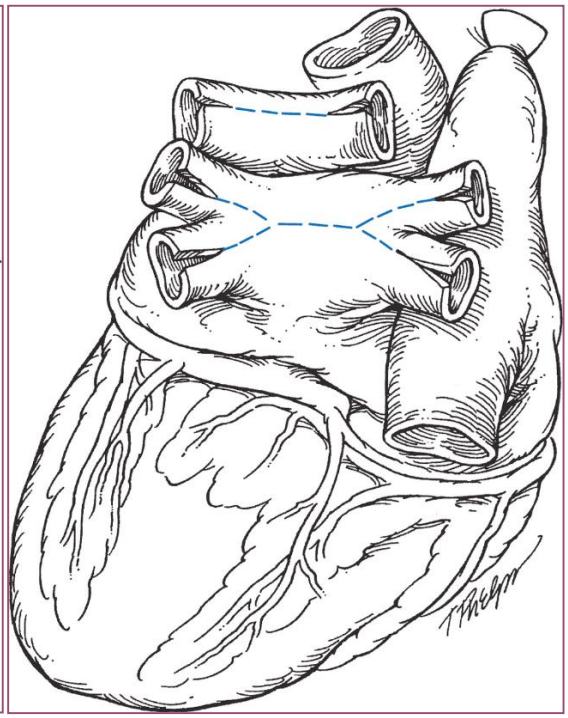

Figure 2: Donor allograft preparation; pulmonary vein orifices are joined to form left atrial cuff[1]

1.8 SURGICAL PROCEDURE

There are two types of heart transplantation procedures, orthotopic where the heart is implanted into its usual site and heterotopic where the heart is implanted in some other part of the body, most commonly right pleural space. Nowadays, only orthotopic one is performed (95%) with a few exceptions, when patients have irreversible pulmonary hypertension or when there is a significant donor- recipient size mismatch. Orthotopic surgical procedure starts with a median sternotomy and a vertical pericardiotomy. Then, the patient is heparinized and prepared for a cardiopulmonary bypass. When bypass is initiated, the patient is cooled down to a 28°C and the ascending aorta is clamped. Ideally, recipient

cardiectomy is completed just before arrival of the cardiac allograft. No irreversible surgical maneuvers should be performed before donor organ has safely arrived. Although biatrial technique introduced by Lower and Shumway was widely used as a standard method, nowadays the bicaval Whythenshawe anastomotic method is more commonly employed because it results in shorter hospital stay and improved post- transplant survival. This technique preserves the anatomical integrity of the donor atria and combines the standard left atrial anastomosis with a separate bicaval anastomosis. Since recipient's right atrium is excised completely and the donor's right atrium is left intact, atrial contractility is preserved and sinus node and valvular competence is not lost, which results in decreased incidence of post- transplant valvular insufficiency and arrhythmias. Preserved atrial contraction is important because it boosts pump function and contributes 15-20% of the net stroke volume. When the heart is implanted, a warm substrate enhanced reperfusion solution is administered, the aortic cross-clamp is removed and the patient's cardiopulmonary bypass is stopped. Half of the patients require electrical defibrillation and some need temporary pacing. Inotrope infusion is initiated. Temporary epicardial atrial and ventricular bipolar wires are placed in the donor right atrium and ventricle. After insertion of mediastinal and pleural tubes, median sternotomy is closed. [1,25]

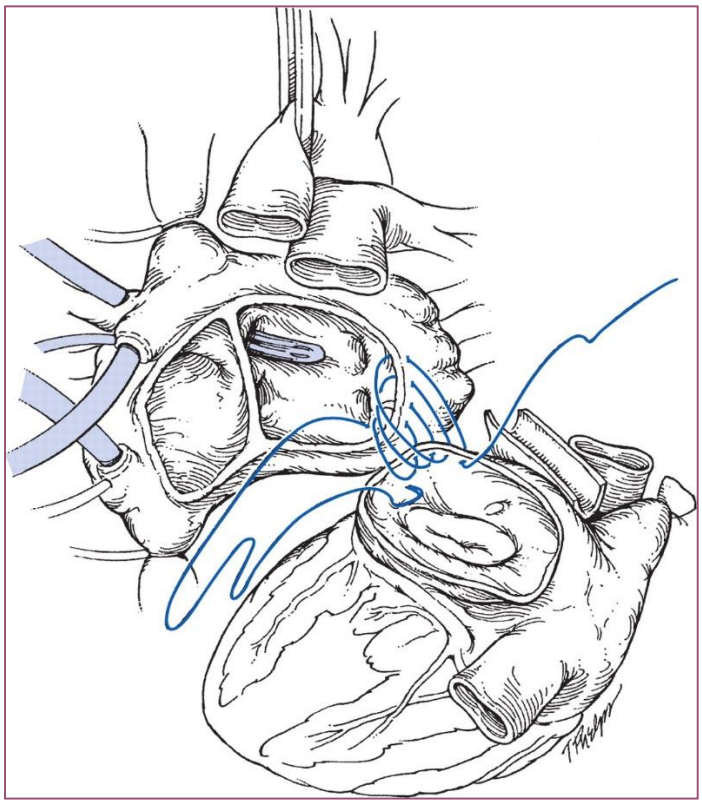

Figure 3: Shumway technique: left atrial anastomosis; the first suture is placed at the level of the recipient' left superior pulmonary vein and then through the donor left atrial cuff near the base of the atrial appendage. [1]

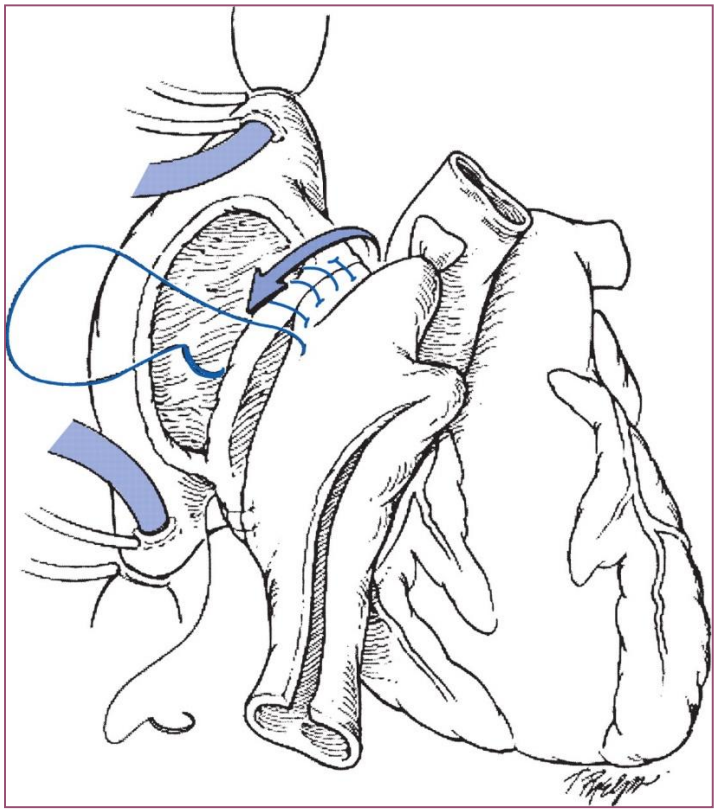

Figure 4: Shumway technique: inter-atrial anastomosis. [1]

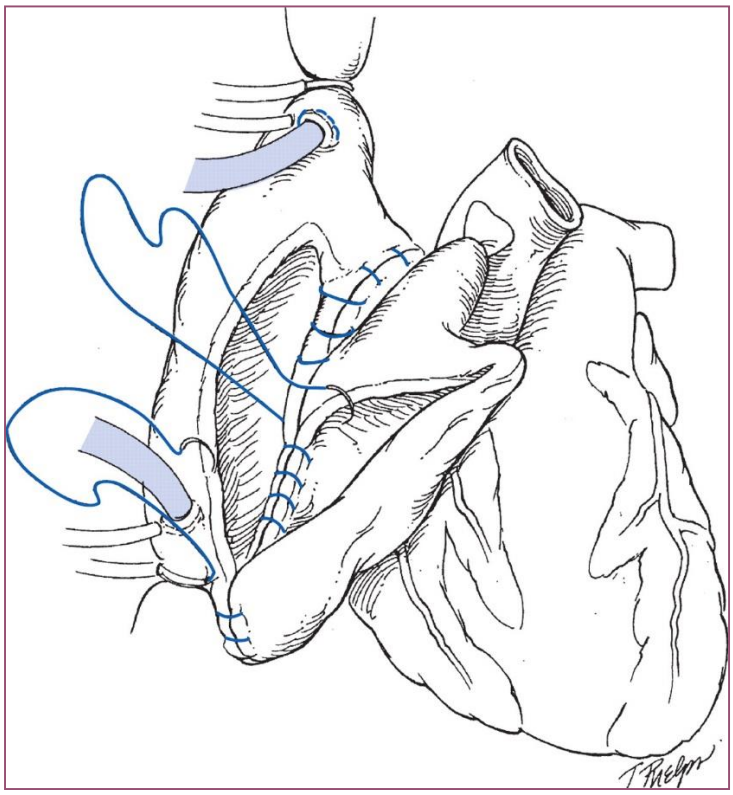

Figure 5: Shumway technique: right atrial anastomosis. [1]

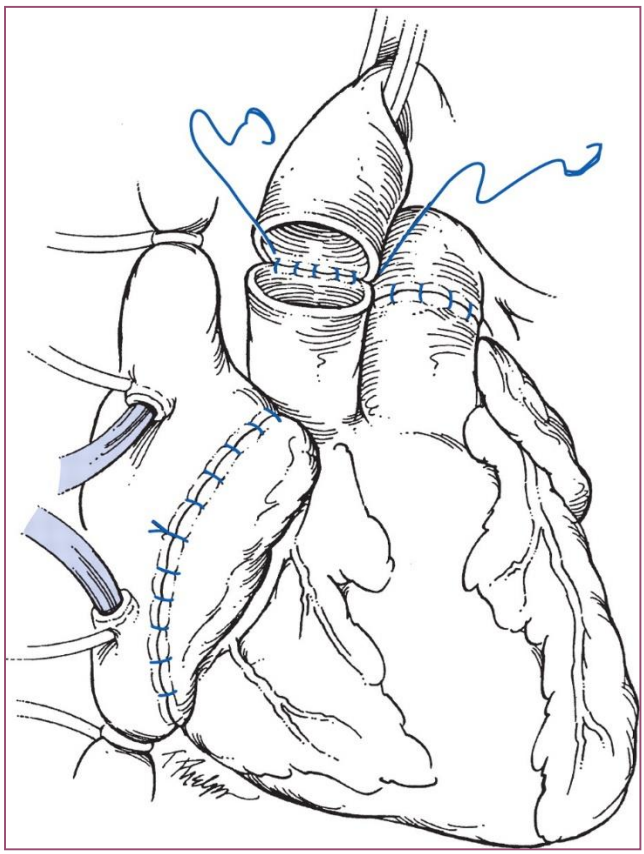

Figure 6: Shumway technique: aortic anastomosis. [1]

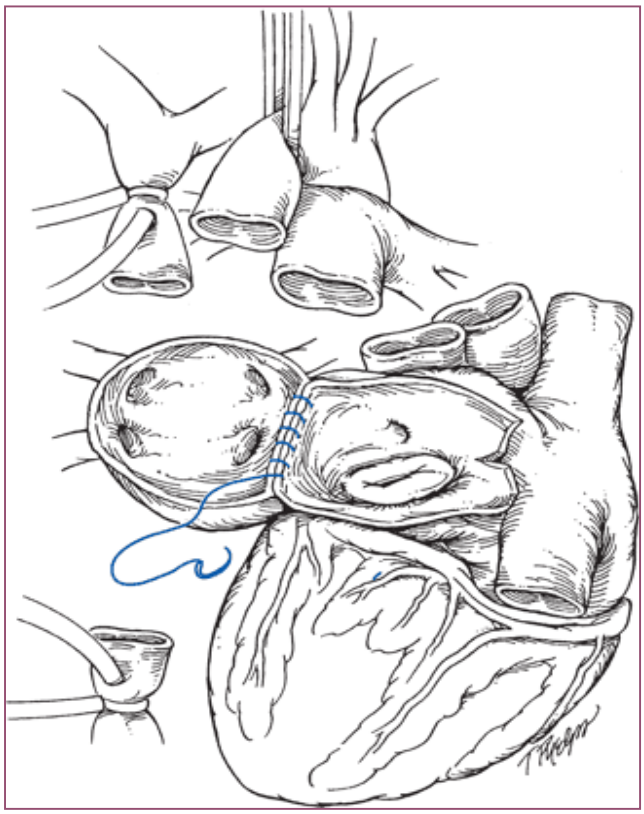

Figure 7: Whythenshave technique: bicaval on left atrium cuff. [1]

1.9 POSTOPERATIVE MANAGEMENT

It is important to notice that the transplanted heart is denervated which leads to its altered physiology. Denervation causes loss of autonomic nervous system of the heart and alters its response to therapeutic interventions which act through autonomic nervous system. Therefore, high doses of inotropic therapy are required for a few days after the surgery. In some patients, atrial fibrillation, atrial flutter and other supraventricular arrhythmias can occur and should be treated with low doses of antiarrhythmic agents. Ventricular tachycardia and ventricular fibrillation can also occur and are thought to be the cause of sudden and unexplained deaths. Systemic hypertension should also be treated in the early postoperative period with intravenous sodium nitroprusside to prevent afterload stress on the allograft. The causes of early allograft failure are myocardial dysfunction due to donor instability, pulmonary hypertension, ischemic injury during preservation and sometimes acute rejection. The leading

cause of early mortality is right- sided heart failure due to recipient's elevated pulmonary vascular resistance. Right- sided heart failure is treated with pulmonary vasodilators. If PH is refractory to medical treatment, intra-aortic balloon pump or RVAD are other options. Renal function should also be carefully monitored in the postoperative period. Some patients develop acute calcineurin inhibitor- induced renal insufficiency which usually resolves with the reduction of the dose. Concurrent administration of mannitol may reduce their nephrotoxicity. [1]

1.10 COMPLICATIONS

1.10.1 CARDIAC ALLOGRAFT REJECTION

A rejection reaction against a transplanted organ occurs when a recipient's immune system recognizes the donor organ as foreign. There are two types of cardiac allograft rejection, cell- mediated and humoral (also called antibody-mediated rejection). Most can be reversed with administration of corticosteroids.

Hyperacute rejection occurs if blood groups from donor and recipient do not match or from preformed donor- specific antibodies in the recipient. The onset is within minutes to several hours. This is a rare complication due to ABO blood group and PRA screening. The allograft becomes dark red and on histologic examination there are characteristic global interstitial hemorrhage and edema without lymphocytic infiltrate. The prognosis is bad, immediate plasmapheresis, IVIG and mechanical support are indicated and sometimes retransplantation is the only other option. [10,16]

Classical signs of acute rejection are: low- grade fever, malaise, leukocytosis, pericardial friction rub, supraventricular arrhythmias, low cardiac output, reduced exercise tolerance and signs of congestive heart failure. Since the introduction of the immunosuppressive therapy, most of allograft rejections became insidious and patients remain asymptomatic until the advanced stage of rejection. The gold standard for diagnosing acute rejection is endomyocardial biopsy of the right ventricle. This is performed percutaneously through the right IJV. The sample of endocardium is evaluated according to the ISHLT grading

system. The severity of rejection is determined depending on pattern and density of lymphocyte infiltration and presence or absence of myocyte necrosis. Every transplant center has a endomyocardial biopsy schedule. Immediately postoperatively, biopsies are done every 7 to 10 days until 1 month. Then they are tapered down to 3- to 6- month intervals after the first year. Acute rejection is treated with 3 drugs; cyclosporine or tacrolimus, mycophenolate mofetil and a corticosteroid. When the therapy is finished, another biopsy must be done to see if the treatment of acute rejection was successful. [1]

Immunosuppressive drugs are primarily responsible for the present success of transplantation. They are used to control rejection caused by antigen differences remaining after tissue typing and donor recipient matching. Successful immunosuppression began in the early sixties with the discovery of anti- cancer agent azathioprine. This therapy was soon combined with corticosteroids to achieve an additive effect. In the early eighties, a new anti-rejection agent cyclosporine was discovered and thereafter, many other immunosuppressive drugs were developed like tacrolimus and monoclonal antibodies. [3]

1.10.2 INFECTIONS

Infection is the leading cause of morbidity and mortality in the cardiac transplantation patients. Infections can develop secondary to donor transmission, reactivation of latent recipient infection or reinfection with a different strain. One of the most serious ones is CMV infection because firstly, it is indirectly associated with acute rejection episodes, acceleration of CAV and post-transplant lymphoproliferative disease and secondly, it causes reduction in leukocytes which can lead to superinfections with other pathogens. Prevention is very important, therefore, screening of both donor and recipient is performed and prophylaxis of 2-3 weeks with intravenous ganciclovir is indicated. Patients are at greatest risk of life- threatening infections in the first 3 months after the transplantation. The most common gram negative bacterial infections are caused by Escherichia coli and Pseudomonas aeruginosa which result in pneumonia or urinary tract infections and the most common gram positive bacterial infections

are caused by Staphylococcus species, which can cause mediastinitis or catheter- associated bacteremia. Mucocutaneous candidiasis is not uncommon and is treated with topical antifungal agents. Aspergillus is an opportunistic pathogen that causes a serious pneumonia and can lead to a fatal outcome therefore, aggressive therapy with either amphotericin B or itraconazole is given. Toxoplasmosis in heart transplant recipients is usually a reactivation of latent disease in seropositive donor organ and is treated with either pyrimethamine with sulfadiazine or clindamycin. [5,21,22,24]

1.10.3 CHRONIC COMPLICATIONS

Cardiac allograft vasculopathy is a unique rapidly progressive form of atherosclerosis that is characterized by concentric intimal proliferation and luminal stenosis, occlusion of small arteries and myocardial infarction. CAV can be angiographically detected in up to 50% of patients 5 years after heart transplantation. It begins within several weeks after the surgery and progresses insidiously. The only definitive treatment for CAV is retransplantation, therefore prophylactic management such as reducing cold ischemia time and improving myocardial preservation is very important. [5,9]

Renal dysfunction is a very common complication because immunosuppressive therapy with cyclosporine is nephrotoxic. Therefore, to slow down the progression of renal failure, the dosage of cyclosporine is lowered and another immunosuppressive agent such as MMF or tacrolimus is added. The risk of death after heart transplantation is markedly increased by the development of end- stage renal failure.

Moderate to severe hypertension affects more than half of cardiac transplant recipients. The causes are peripheral vasoconstriction and fluid retention.

Chronic immunosuppression is associated with increased incidence of cancer. The occurrence is much higher than in general population. Lymphoproliferative disorders and skin cancer are most commonly found. Treatment options include reduction in immunosuppression and conventional

cancer therapies such as chemotherapy, radiotherapy and surgical removal. [5,7,8,14]

Other complications are: hyperlipidemia, osteoporosis, obesity or cachexia, GI problems and cholelithiasis.

2. AIM OF THE STUDY

To evaluate a single centre 10-year experience and outcome of patients who underwent heart transplantation. Despite great advances in medical treatment and other surgical alternatives heart transplantation remains the golden standard for end- stage heart failure. The aim of this study is to examine long- term results of heart transplantation in Clinical Hospital Dubrava and compare it to those reported by the International Society of Heart and Lung Transplantation.

3. PATIENTS AND METHODS

This is a retrospective review of patients who had heart transplantation surgery at the University Hospital Dubrava in Zagreb.

The study population consists of 140 heart transplant recipients who had the surgery between January 2008 and December 2018. There were far more men among recipients; 116 (82,9%) out of 140 and only 24 (17,1%) were female. The mean recipient age at the time of transplantation was 54 ± 9 (the range is between 22 and 66). Dilated cardiomyopathy was present in 99 (70,7%) recipients, ischemic cardiomyopathy in 37 (26,4%) recipients and 4 (2,9%) were other causes. LVAD as a bridge to transplant was implanted in 5 (3,6%) patients, 3 men and 2 women. The highest number of heart transplantations is in age group between 50 and 59, followed by those between 60 and 69. The average number of heart transplantations per year during this 10- year period is 14 transplantations per year (range 4-20). It is interesting to notice that 34 (24,3%) patients had pulmonary hypertension, 12 of them died already.

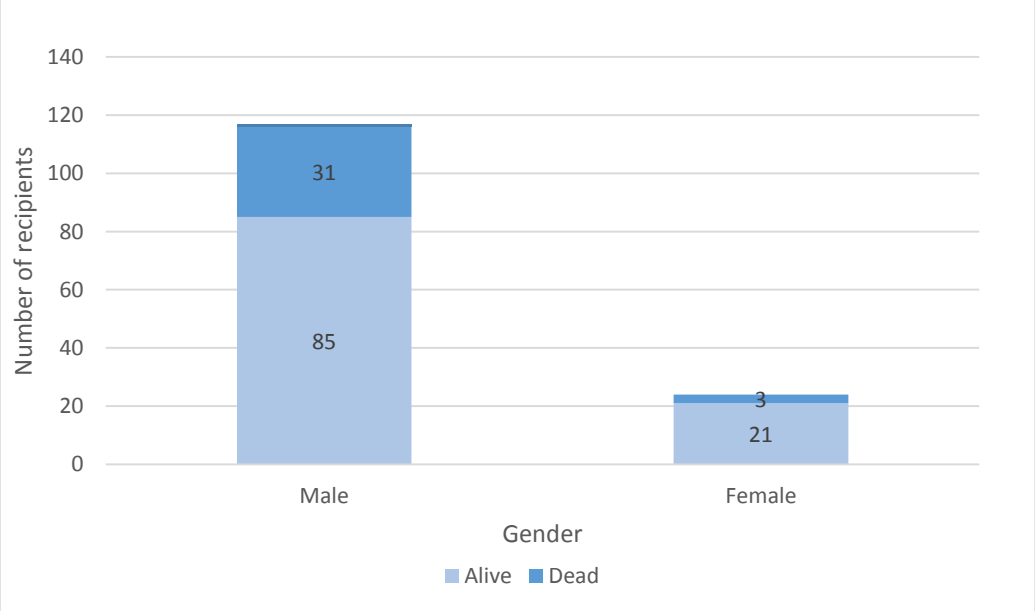

Figure 8: Number of heart transplant recipients, alive and dead, according to gender

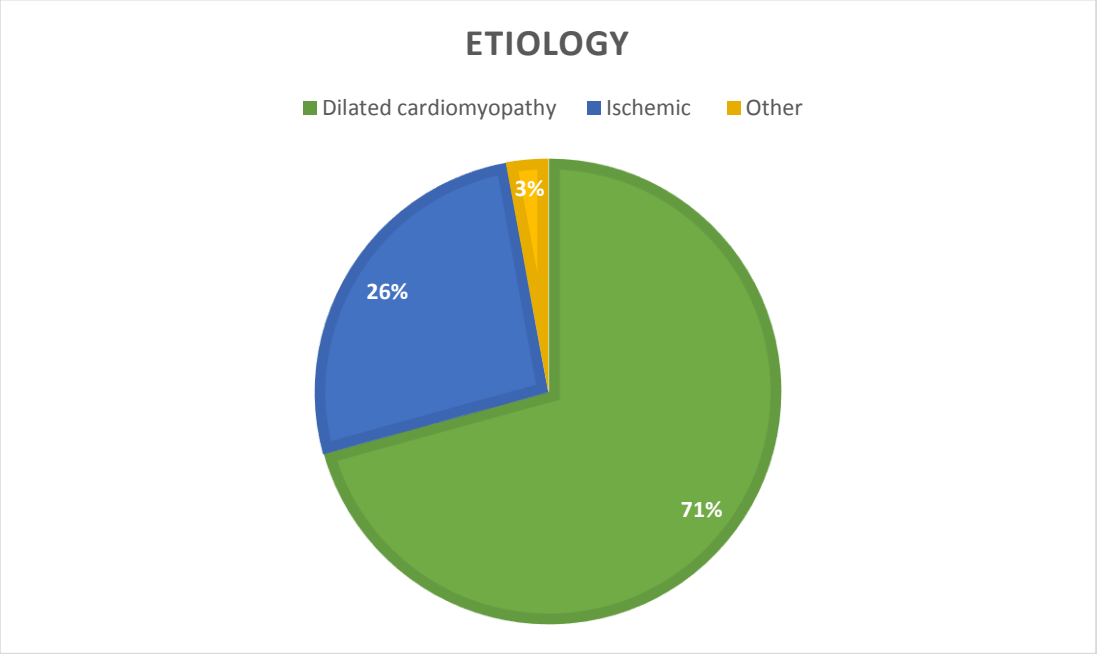

Figure 9: Aetiology of end- stage heart failure

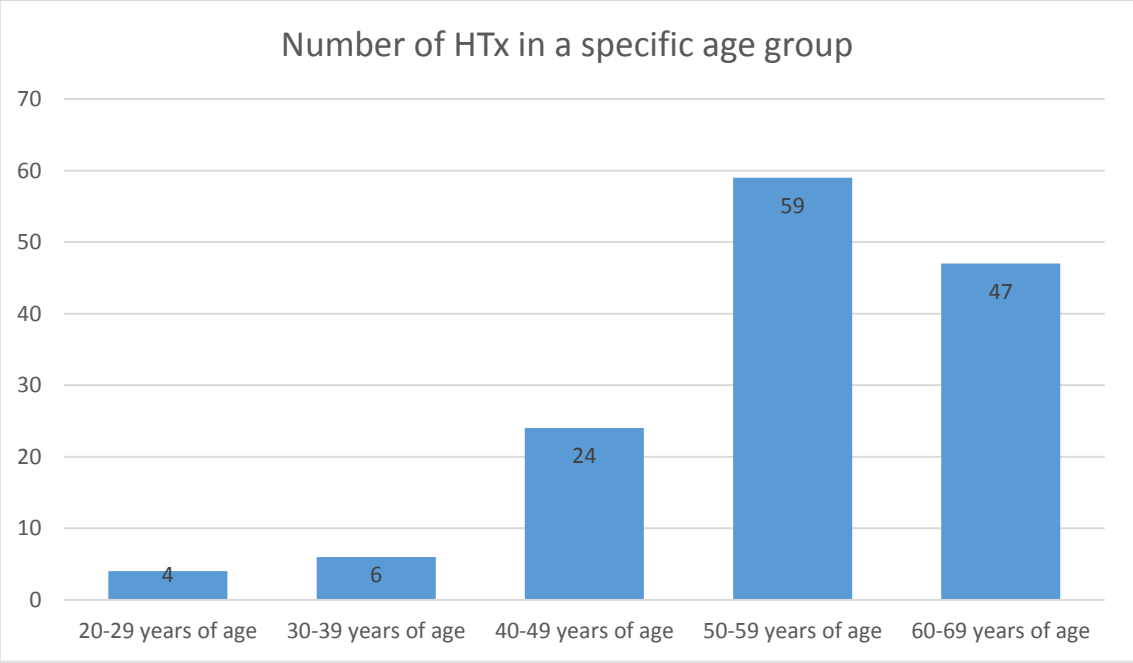

Figure 10: Number of heart transplantations in a specific age group

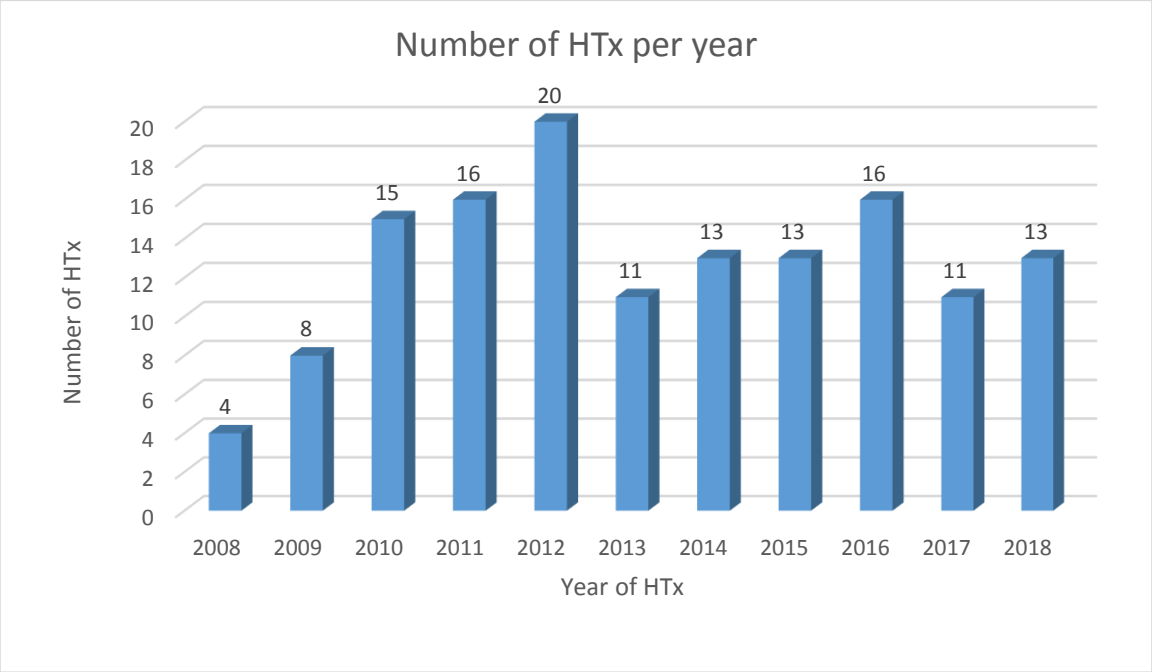

Figure 11: Number of heart transplantations per year

4. RESULTS

Even though heart transplantation program in Croatia has started in year 1988 already, I decided to take a sample of heart transplantations that were performed in a 10-year period from beginning of January 2008 to the end of December 2018. The reason why I chose to do so is because in year 2007 Croatia entered Eurotransplant organization and since then, the number of transplants per year has increased a lot, which makes it a better study population.

30-day mortality was 9%. Median follow- up was 1132 days. Survival rate was studied using Kaplan- Meier curves. Survival rates at 1, 5, and 10 years were 78%, 72%, and 63% respectively. The mean survival is 1530 days (4,2 years).

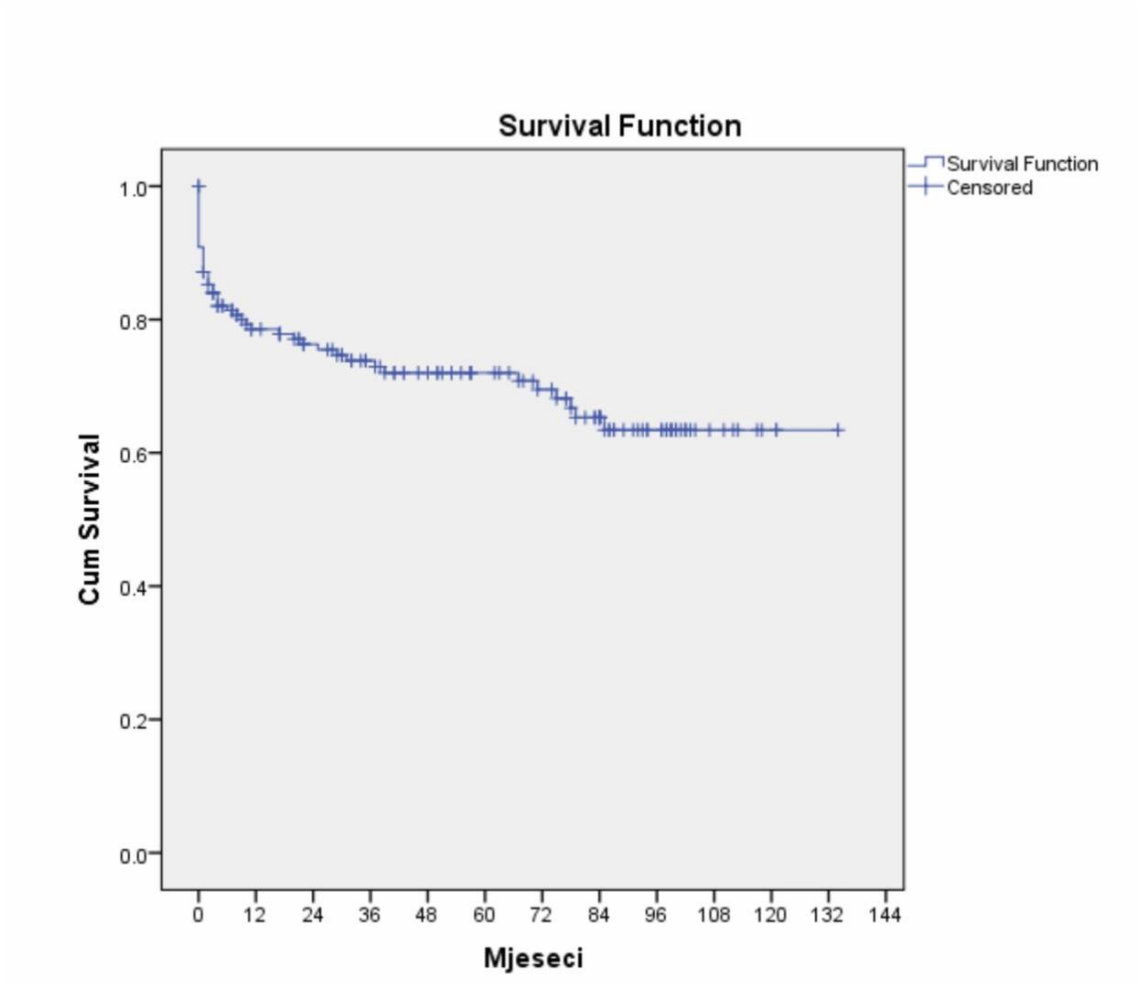

FIGURE 12: Survival rates at 1, 5 and 10 years using Kaplan- Meier curve

Table 1 shows that the main causes of death were infection (38,2%), cardiac causes (26,6%), allograft rejection (5,9%), vascular (2,9%) and renal (2,9%). It is important to notice that some causes of death were unknown (23,5%). This happened because some patients died in their home or their home- town hospital where cause of death was not determined or it was but the information was not passed down to the Clinical Hospital Dubrava. Table 2 shows most common complications that occurred in the transplanted patients. Most common were infections, from urinary tract infections (25,7%), sepsis (19,3%), pneumonia (10,0%) to sternum infections (7,9%). Cardiac problems, such as atrial fibrillation (18,6%) were also not so uncommon. Renal insufficiency was present in 13,6% of patients, delirium in 7,1% of patients and CVI in 5,0% of the transplanted patients.

Table 3: Causes of death in heart transplant recipients

Causes of death	Number of patients	%
Infection	13	38,2
Cardiac	9	26,6
Rejection	2	5,9
Vascular	1	2,9
Renal	1	2,9
N/A	8	23,5

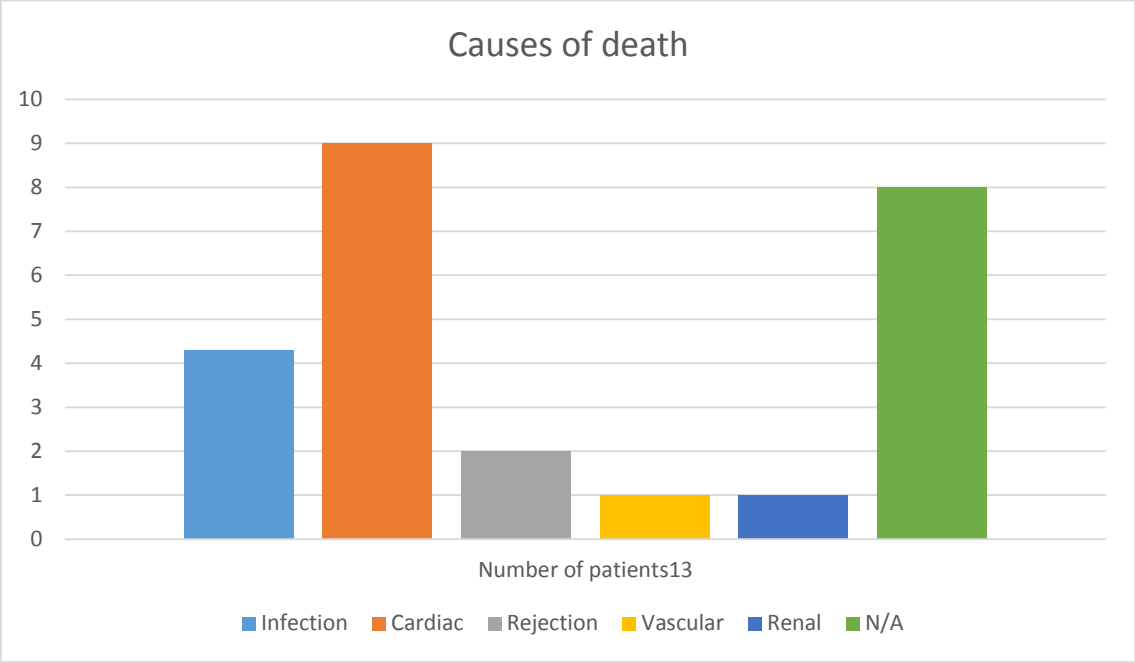

Figure 13: Causes of death in heart transplant recipients

Table 4: Number of patients who developed different complications

Complications	Number of pts	%
A. fib.	26	18,6
AV block	6	4,3
Infection of sternum	11	7,9
UTI	36	25,7
Sepsis	27	19,3
Pleural effusion	23	16,4
Renal insufficiency	19	13,6
Pericardial effusion	18	12,9
Pneumothorax	12	8,6
Pneumonia	14	10,0
Delirium	10	7,1
CVI	2	1,4
Multiple organ failure	7	5,0

5. DISCUSSION

Long- term results of heart transplantation are primarily affected by allograft rejection and side effects of immunosuppression, which lead to development of complications. Immunosuppressive agents used in the hospital are a combination of corticosteroids, cyclosporine and MMF, a so called triple immunosuppression regimen.

Therefore, it is expected that post-transplant patients develop different types of infections because as immunocompromised individuals they are at an increased risk of opportunistic viral and bacterial infections. Most common complication in my study is urinary tract infection, followed by sepsis, pneumonia and infection of the sternum. Renal problems are also a quite common complication, which may be a consequence of nephrotoxic cyclosporine.

According to the International Society for Heart and Lung Transplantation, survival rates at 1, 5, and 10 years were 81,7%, 69,3% and 52,5%. Comparing them to our study we can see that our 1-year survival rate is 3,7% below, 5- year survival rate is 2,7% above and 10- year survival rate is 10,5% above their results. We can conclude that our 1- year and 5- year survival rate results are very similar to the ISHLT results, however, our 10- year survival rate result is much better than the one reported by the ISHLT.

6. CONCLUSION

Heart transplantation has become a golden standard for treatment of patients with end- stage heart failure. Decades of experience has led us to development of excellent surgical procedure as well as perioperative and post- operative care. No other treatment option, such as medical therapy or mechanical devices, can compete with the successful results of heart transplantation, especially over the long- term.

Combined effort of different medical personnel, from cardiac surgeons to internists who follow- up patients after the transplant and all other medical staff such as nurses, lab technicians, social workers, psychologists, and nutritionists, as well as close relatives who provide emotional support to the patient, is what gives such great long- term results. Currently, the only unsolved problems which limit the success of heart transplantation are the consequences of immunosuppressive therapy and number of available donors. Therefore, a good transplant program is crucial to form an efficient donor network.

7. ACKNOWLEDGEMENTS

Foremost, I would like to express my sincere gratitude to my mentor Igor Rudež, MD, PhD for spending time and effort in helping me finish my thesis and guiding me in the right direction.

Besides my mentor, I would like to thank the rest of my graduate thesis committee: Joško Bulum, MD, PhD and Tomislav Meštrović, MD, PhD.

Last, but not least, I would like to thank my entire family and all my friends for the love and support they provided me with throughout my entire life, especially through the long years of my studies when they encouraged me in the pursuit of my dreams.

8. REFERENCES

1. Cohn LH, Adams DH; Cardiac surgery in the adult; fifth edition; McGraw-Hill Education 2018; p. 1299-1330
2. Coric V, Milicic D, Gasparovic H, Rajsman G, Siric F, Jelic I; Eighteen years of heart transplantation- a single center experience. Coll. Antropol. 2006; 30(4): 909-913
3. Eurotransplant; https://www.eurotransplant.org/cms/
4. International Society for Heart and Lung Transplantation; https://ishltregistries.org/registries/slides.asp
5. Wilhelm MJ. Long-term outcome following heart transplantation: current perspective. J Thorac Dis 2015;7(3):549-551.
6. Ramakrishna H, Jaroszewski DE, Arabia FA. Adult cardiac transplantation: A review of perioperative management (Part - II). Ann Card Anaesth 2009; 12:155-65
7. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. AmJ Transplant 2004; 4(2):222-230.
8. Rinaldi M, Pellegrini C, D'Armini AM, Aiello M, Negri M, Arbustini E, Ippoliti G. Vigano M. Neoplastic disease after heart transplantation: single center experience. Eur J Cardiothorac Surg; 2001; 19(5):696-701
9. Valantine H, Cardiac allograft vasculopathy after heart transplantation: risk factors and management. J Heart Lung Transplant. 2004; 23(5 Suppl): S187-193

10. Trento A. Hardesty RL, Griffith BP, Zerbe T, Kormos RL, Bahnson HT, Role of the antibody to vascular endothelial cells in hyperacute rejection in patients undergoing cardiac transplantation. J Thorac Cardiovasc Surg; 1988; 95(1): 37-41
11. Šoša T. Sutlić Ž. Stanec Z. Kirurgija. Zagreb, Naklada Ljevak, 2007
12. Steinman TI. Becker BN, Frost AE, Olthoff KM, Smart FW, Suki WN, Wilkinson AH. Guidelines for the referral and management of patients eligible for solid organ transplantation. Transplantation. 2001; 71(9):1189-1204.
13. Kellerman L, Neugut A, Burke B, Mancini D. Comparison of the incidence of de novo solid malignancies after heart transplantation to that in the general population. Am J Cardiol. 2009; 103(4):562-566
14. Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. J Am Coll Cardiol. 1996; 28(7): 1775-1780
15. Kirklin JK, Naftel DC, Kirklin JW, Blackstone EH, White- Williams C, Bourge RC. Pulmonary vascular resistance and the risk of heart transplantation. J Heart Transplant.1988; 7(5):331-336
16. Copeland JG, Emery RW, Levinson MM, Icenogle TB, Carrier M, Ott RA, Copeland JA, McAleer- Rhenman MJ et al. Selection of patients for cardiac transplantation. Circulation. 1987; 75(1):2-9.

17. Penn I. Cancers following cyclosporine therapy. Transplant Proc. 1987; 19(1 Pt 3): 2211-2213
18. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009; 53(15): e1-e90
19. Heart Failure Society, O.A. Surgical approaches to the treatment of heart failure. J Card Fail. 2006; 12(1): e76-79
20. Mehra M, Kobashigawa J, Starling R, Russel S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation Guidelines for the care of cardiac transplant candidates. J Heart Lung Transplant. 2006; 25(9): 1024-1042
21. Montoya JG, Giraldo LF, Efron B, Stinson EB, Gamberg P, Hunt S, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis. 2001; 33(5): 629-640
22. Rubin RH, Prevention and treatment of cytomegalovirus disease in heart transplant patients. J Heart Transplant. 2000; 19(8): 613-623
23. John R, Rajasinghe HA, Chen JM, Weinberg AD, Sinha P, Mancini DM, et al. Long- term outcomes after cardiac transplantation: an experience

based on different eras of immunosuppressive therapy. The Annals of Thoracic Surgery. 2001; 72(2):440-449

24. Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017; 17(4): 856-879
25. Morgan JA, Edwards NM. Orthotopic cardiac transplantation: comparison of outcome using biatrial, bicaval, and total techniques. J Card Surg. 2005; 20(1): 102-6