Annals of Academy of Romanian Scientists
Online edition Series: Medical Sciences
ISSN 2285-4150 Volume 1, Number 2/2010

Original Article

HEART AND LUNG TRANSPLANTATION

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Abstract

Thoracic organ transplantation (Tx) has become clinical routine for the treatment of end-stage heart and lung disease. The article discusses the current guidelines for the indication of thoracic transplantation. It provides furthermore a brief summary about listing procedures, allocation, post-operative care and the long-term results after heart or lung transplantation.

Ischemic cardiomyopathy and the heterogeneous group of dilative cardiomyopathy represent up to 40% of the causes that lead to heart failure and finally, to heart transplantation (HTx). Other indications for HTx are valvular diseases or congenital heart failure that cannot be corrected surgically.

In the decision for Tx are equally involved the cardiologist, the cardiovascular surgeon and the patient. The main objectives are the quality of life and the success of the transplantation. The time point for placing the patient into the waiting list has to be estimated by considering the individual risk and the expected waiting time. HTx is not an operation to be performed in emergency, because patients on the waiting list must be optimally prepared.

Keywords: *heart transplantation, lung transplantation, immunosuppression*

Rezumat

Transplantul organelor toracale reprezintă în prezent o metodă terapeutică de rutină pentru boli cardiace şi pulmonare în stadiu terminal. Articolul prezintă un ghid practic de indicaţii pentru transplantul de organe toracice, tipurile de tehnică chirurgicală şi tratamentul postoperator, precum şi supravieţuirea la distanţă după transplantul de cord şi de plămân.

Cardiomiopatia ischemică şi grupul heterogen al cardiomiopatiilor dilatative, reprezintă 40% din cauzele ce duc la insuficienţă cardiacă şi, in final, la transplantul cardiac (HTx). Alte indicaţii sunt bolile valvulare şi malformaţiile congenitale cardiace, care nu pot fi corectate chirurgical.

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Decizia pentru transplant cardiac trebuie luată în comun de către cardiolog şi chirurg cardio-vascular şi de către pacient. Obiectivele sunt, în aceeaşi măsură, calitatea vieţii şi succesul transplantului. La momentul înscrierii pacientului pe lista de aşteptare, trebuie evaluat bine riscul individual până la momentul operator.

Transplantul organelor toracale nu este o operaţie adecvată pentru a fi realizată în urgenţă, deoarece pacienţii listaţi trebuie pregătiţi în condiţii optime.

Cuvinte-cheie: *Transplantul de cord, transplantul de plămân, imunosupresie*

Thoracic organ transplantation (Tx) has become clinical routine for the treatment of end-stage heart and lung disease. The article discusses the current guidelines for the indication of thoracic transplantation. It provides furthermore a brief summary about listing procedures, allocation, post-operative care and the long-term results after heart or lung transplantation.

Ischemic cardiomyopathy and the heterogeneous group of dilative cardiomyopathy represent up to 40% of the causes that lead to heart failure and finally, to heart transplantation (HTx). Other indications for HTx are valvular diseases or congenital heart failure that cannot be corrected surgically.

In the decision for Tx are equally involved the cardiologist, the cardiovascular surgeon and the patient. The main objectives are the quality of life and the success of the transplantation. The time point for placing the patient onto the waiting list has to be estimated by considering the individual risk and the expected waiting time. HTx is not an operation to be performed in emergency, because patients on the waiting list must be optimally prepared.

The classic indication for HTx is irreversible end-stage heart failure (NYHA III / IV), with a survival probability of less than 50% at one year. The International Society for Heart and Lung Transplantation states, that in patients with a maximum oxygen uptake (VO2max) of 12 ml/kg/min, indicated by spiroergometry, HTx is recommended (1, 2).

Table 1: Main indications for heart transplantation.

I) Absolute indications:
- VO2max < 12 ml/kg/min - Angina pectoris refractory to therapy - Ischemia refractory to therapy with no option of revascularisation - Ventricular arrhythmias refractory to therapy
II) Possible indications
- VO2max < 14 ml/kg/min with severe limitation of physical activity - Recurrent unstable angina pectoris without option of revascularisation - Unstable fluid balance and impaired renal function despite a good compliance - Left ventricular ejection fraction < 20%

Other prognostic factors to be taken into account in the decision for Tx are: stage IV NYHA heart failure, serum sodium < 135 mmol/L, complex ventricular arrhythmias, brain natriuretic peptide (BNP) > 200 pg/ml, end diastolic left ventricular diameter > 75 mm, end systolic left ventricular diameter > 65 mm, end diastolic left ventricular pressure > 20 mmHg, a cardiac index < 2.0 L/min/m^2, pulmonary hypertension, as well severe liver and kidney impairment (3).

These prognostic parameters are not applicable to all cardiac diseases, such as congenital heart defects, amyloidosis, sarcoidosis, malignancies, etc.

Mortality on the waiting list is about 20% (Eurotransplant countries). Leading causes of death are cardiac arrhythmias. Therefore, patients on the waiting list should receive a defibrillator. There are also telemetry systems available, that continuously transmit hemodynamic data (4).

Contraindications

There are few absolute contraindications for HTx. The main contraindication is pulmonary hypertension that is unresponsive to drug therapy. Patients are eligible for Tx with a maximum pulmonary resistance of less than 4 Wood units (320 dyn×s×cm^5) or a transpulmonary gradient of less than 12 mmHg. In cases of elevated pulmonary resistance, response to nitric oxyde or prostanoids must be tested. These criteria gain relevance, because nowadays the indication for HTx is often made when secondary pulmonary hypertension is already evident, as a result of modern heart failure and pacemaker therapy.

Relative contraindications are co-morbidities, which may reduce the chances for a successful transplant, such as diabetes, chronic or acute infectious diseases, tumors that cannot be treated curatively, severe systemic disease (amyloidosis, sarcoidosis), severe renal and hepatic insufficiency, advanced pulmonary disease, cerebrovascular or peripheral artery disease, severe obesity (BMI > 40), low compliance, nicotine and alcohol dependency, as well as psychiatric diseases. Current studies show, that nicotine abuse both before and after Tx is a risk factor for posttransplant survival (5).

The patient's age alone does not represent a contraindication and the decision has to be made by considering the biological age.

It is generally agreed, that the maximum age for HTx is 70 years, although there are many experiences with good results beyond this limit (6, 7).

Examinations before listing for heart transpaIntation

Before being placed onto the waiting list, it should be clarified from a health perspective, that the patient is suitable for HTx [see Table 2].

Chronic infections or malignant diseases must be excluded. In addition, it is also necessary to test the pulmonary function and pulmonary vascular resistance as a key indicator for adverse outcome.

Operability of the patient must be evaluated by the anesthesiologist. Patients must also be investigated for psychiatric and psychosomatic diseases. After completion of these investigations, the patient can be put on the waiting list.

Table 2: Summary of the necessary investigations.

I. Laboratory investigations	
Coagulation tests	Blood group, blood count, platelets, INR, PTT, fibrinogen, CRP
Renal function	Electrolytes, creatinine (clearence), urea, urinary status
Liver function	Total bilirubine, AST, ALT, GGT, LDH, AP, CK, amylase, lipase, serum protein electrophoresis
Metabolism and endocrinology	Cholesterole, Triglyceride, LP(a), serum lipoprotein electrophoresis, T3/T4/TSH, glucose profile, HbA1c
Immunology	Panel reactive antibodies (PRA) test, HLA typing, cold agglutination test, antinuclear antibodies
II. Microbiology	
Bacteriology	Urine culture
Virology	Coxsackie, Herpes simplex, Varicella zoster, Herpes zoster, Cytomegalovirus, EBV, HIV, hepatitis virus A, B, C
Serology	Mycoplasmosis, toxoplasmosis, candida, syphilis
III. Imaging	
12 channel ECG, echocardiogram, abdominal ultrasound, computed tomography of thorax and abdomen, Chest x-ray, right heart catheterization, spiroergometry, blood gas analysis, cerebral CT	
IV. Specialized expertise	
Dentistry, ENT, gastroenterology, psychiatry, urology, gynecology, anesthesia, neurology, endocrinology	

Listing for heart transplantation and the waiting time

In the presence of end-stage heart failure (NIHA III / IV) the patient can be put onto the waiting list after possible contraindications are ruled out.
Mandatory is a thorough preliminary discussion with a transplant specialist is about the risks and prospects of Tx, about the surgical procedure and possible risks, about the social and psychological impact of Tx, about immunosuppression and its secondary effects, as well as the necessity and frequency of regular controls after successful Tx.

A cardiologic checkup is scheduled at least every three months during the entire waiting time. In addition, right heart catheterization should be performed every six months. The transplant center has to be informed in case of transient diseases, such as an infectious febrile syndrome.

Heart transplantation

The technique is based on scientific experiments of Lower and Shumway [8]. According to Lower and Shumway's biatrial method, the recipient heart is excised at the atrial level. Furthermore, the ascending aorta and the trunk of the pulmonary artery are separated. Implantation begins at the left atrium and continues with the right atrium and ends with the anastomoses of the pulmonary artery and the ascending. In the bicaval modified implantation technique, the right atrium is completely resected, preserving the posterior wall of the left atrium. The advantages of this method are a better geometrical integrity of the tricuspid valve and a later reduction in the need for pacemaker implantation (8, 9, 10, 11). Stenosis of the anastomoses of the inferior and superior caval veins is the main disadvantage of this method.

Immunosuppression

Critical for the success of Tx is an appropriate and individually controlled therapy. In earlier days immunosuppression consisted of cyclosporine A, azathioprine and prednisolone. The immunosuppression induction with mono- and polyclonal antibodies (such as OKT III or ATG) or with interleukin-2 receptor antagonists is currently performed in approximately 50% of the transplant centers. Its use is still controversial. Nowadays immunosuppression consists of tacrolimus or cyclosporine A in combination with mycophenolate mofetil (12). Steroids are not used as regular long term medication, but in the immediate post transplant period or as rejection treatment. New substances such as sirolimus or everolimus, part of mTOR inhibitors group are new immunosuppressive drugs. They may be used to prevent kidney failure caused by calcineurin inhibitors (13). The combination and the dosage of immunosuppressive drugs should result in a balance between the risk of graft rejection and the risk of opportunistic infections and adverse side effects. The extent of the immunosuppressive therapy after Tx can be reduced consecutively in most of the patients during follow-up.

Additional medication

In addition to the immunosuppressive medication, other drugs are used regularly. They should protect the body against infections or they should reduce immunosuppressant toxic side effects. Therefore, the protocol of additional medication administration depends on the needs of each patient. Diuretics stimulate renal function immediately after Tx. Furthermore, diuretics can stimulate renal function, in case of immunosuppressive nephrotoxicity. Statins (HMG-CoA reductase inhibitors) are routinely prescribed after Tx. Many of the immunosuppressive drugs, especially sirolimus and everolimus lead to increased cholesterole and triglyceride levels. Statins can increase survival in cardiac transplant patients. They are therefore administered routinely in some centers, even at a normal level of cholesterole. Besides pre-existing hypertension,

calcineurin inhibitors, may increase blood pressure. Antihypertensive therapy consists of ACE inhibitors, angiotensin receptor antagonists and calcium antagonists. Beta blockers may be prescribed but they are often not tolerated. Furthermore, calcineurin inhibitors may induce post-transplant diabetes mellitus. Therefore, antidiabetic therapy may be indicated.

Transmission or reactivation of cytomegalovirus (CMV) is common among transplant recipients. Antiviral prophylaxis (especially with ganciclovir) is used especially in exposed patients (CMV negative recipients of CMV positive grafts). Regular monitoring of blood CMV-PCR is routinely performed in the transplant centers. The optimal duration of antiviral therapy is widely discussed. Costs and side effects, such as myelotoxicity and nephrotoxicity play an important role. On the other hand, an early CMV infection can cause early vascular dysfunction. Patients should receive cotrimoxazole twice a week in order to prevent Pneumocystis jiroveci pneumonia (Pneumocystis carinii) infection. The duration of the prophylaxis varies between two and twelve months after Tx.

There are many drug interactions with immunosupessive drugs. Antibiotics, antiepileptic medication, calcium antagonists and even grapefruit are metabolized via Cytochrome P450 Isoenzyme CYP 3A4, which is the key enzyme for tacrolimus and cyclosporine A metabolism. Therefore thorough evaluation of trough levels after changes in medication are mandatory.

Graft rejection

As a consequence of the effective immunosuppressive therapy acute graft rejection has become a rare complication. Besides a good prevention, early diagnosis plays an important role. Possible signs of rejection are nonspecific and may be limited to dyspnea, edema, cardiac arrhythmias, and sometimes fever. Endomyocardial biopsy represents the gold standard for the diagnosis of rejection after heart transplantation. After a clinical or histological diagnosis of acute rejection, steroid treatment should be started immediately. Rejection refractory to steroids is rare and can be treated with ATG antibodies.

The exact cause of chronic rejection or cardiac allograft vasculopathy (CAV) is not finally elucidated. It may be related to immunological processes that cause or maintain the changes. 5-10% per year of the cardiac transplant patients develop new-onset CAV, and after 5 years, 30-50% show signs of CAV. Therefore, coronary angiography should be performed regularly by an experienced cardiologist familiar to HTx.

The main objective of CAV is not the early diagnosis, but a good prevention. The elimination of risk factors such as rejection, viral infections, hypertension, hyperlipoproteinemia, and diabetes mellitus are crucial. The new generation of immunosuppressants, such as sirolimus and everolimus, possess inhibitory effect on the development of CAV.

Results

After data provided by the ISHLT, survival after HTx during 2002-2006 is 85% at 1 year and 75% at 5 years. The risk factors for mortality in the first year are reproduced in Table 3.

Table 3: Risk factors for 1-year-mortality (all heart transplants in the world between 2002 and 2006, n = 8823)

Factor	Relative risk	p-value	Confidence Interval 95%
Extracorporal circulation / assist device / ECMO pre HTx	3.19	< 0.0001	2.32 - 4.37
Diagnosis: congenital vs. cardiomyopathy	1.89	0.0002	1.35 - 2.64
Mechanical ventilation	1.50	0.0044	1.13 - 1.98
Pre-transplant hemodialysis	1.48	0.0021	1.15 - 1.19
Infection with antibiotics i.v. in the 2 weeks pre-HTX	1.30	0.0047	1.08 - 1.56
AB0-unidentical (ex. 0 to A)	1.25	0.0067	1.06 - 1.46
Blood transfusions	1.19	0.0432	1.01 - 1.41
Diagnosis: ICM vs. DCM	1.16	0.0431	1.00 - 1.35
i.v. inotropes pre-transplant	0.85	0.0282	0.73 - 0.98
Recipient age		< 0.0001	
donor age		< 0.0001	
Donor BMI		0.0288	
Center volume		0.0032	
Ischemic time		0.0060	
Pulmonary pressure		0.0004	
Serum bilirubine		0.0006	
Serum creatinine		0.0001	

Lung transplantation

Lung transplantation (LTx) has become a routine therapeutic procedure for lung diseases that cannot be cured conservatively, now counting around 20.000 cases in the world (14).

Indications

The indications for LTx cover a broad spectrum. Depending on the primary disease, some patients reveal a rapid deterioration or a rather stable course. Therefore, the timing in putting the patient onto the waiting list is essential. The Interational Society for Heart and Lung Transplantation (ISHLT) (14) has developed strict criteria for listing for LTx, as summarized in Table 4.

Table 4: Indications for lung transplantation

COPD/ Emphysema
BODE-Index > 7 or one of the following states: ☐ FEV1 < 20% after bronchodilation and DLCO < 20% or a homogeneous distribution of emphysema. ☐ Multiple hospitalizations due to increasing hypercapnia ($PaCO_2$> 55 mmHg) ☐ Secondary pulmonary hypertension under oxygen substitution
Idiopathic pulmonary fibrosis
Histological or radiological diagnosis of one of the following criteria: ☐ DLCO < 40% predictive value ☐ decrease of vital capacity > 10% in 6 months ☐ saturation of oxygen < 88% at 6 minute test ☐ honeycomb lung in the high-resolution CT
Cystic fibrosis (Mucoviscidosis)
☐ FEVI < 30% predictive value after bronchodilation or sudden drop in FEV1 ☐ Hypercapnia ☐ PaO2 < 55 mmHg at rest ☐ Secondary pulmonary hypertension despite oxygen substitution
Pulmonary hypertension
Heart failure NYHA III-IV
Shortening (<350m) or sudden drop of the walking distance
CVP > 15 mmHg
Cardiac index < 2 L/min/m2
Failure of drug therapy

Single lung transplantation (SLTx) is in principle possible and indicated in patients without infectious complications or pulmonary hypertension. In the later double lung transplantation (DLTx) is recommended. Accompanying right heart failure or congenital heart defects, with Eisenmenger reaction, require a

combined heart-lung transplantation. The bilateral sequential technique for DLTx has replaced the en-block-DLTx technique. The two lobes are implanted one after another. This decreases the necessity for the usage of the heart-lung-machine.

Immunosuppression

The established immunosuppressant combination therapy after LTx is a triple therapy, consisting of tacrolimus, mycophenolate mofetil and steroids. Proliferation signal inhibitors (PSI) such as sirolimus or everolimus, should not be administered immediately after LTx, because they interfere with the healing of the bronchial anastomoses. If PSI's can prevent bronchiolitis obliterans, is currently under investigation and there are some encouraging data. There are no consistent data concerning the advantage of an induction therapy after Ltx.

Results

According to the ISHLT data (14), survival after LTx has improved between 1994 - 2006 up to 88% at 3 months, 78% at 1 year and 51% at 5 years. DLTx leads to better results compared to SLTx. Chronic rejection presenting as bronchiolitis obliterans syndrome (BOS) is still the major limiting factor for long-term success after LTx. The prevalence of BOS is 9.2% after 1 year, 33.8% after 5 years and 46.3% after 10 years.

Posttransplant care

Regular ambulatory checkups are necessary in the early stage after Tx. After HTx, endomyocardial biopsies are usually performed on a monthly basis followed by annually performed coronary angiograms.

After LTx lung function testing on a regular basis is mandatory for the early detection of BOS. Trough level monitoring and dose adjustments of the immunosuppressive medication should always be in the hands of a specialized transplant centre.

The importance of a close relation between the patient and the transplantation centre cannot be underestimated and is a key to long-term survival.

The four corner stones in the long-term care of patients after heart and/or lung transplantation are:

- ☐ Close monitoring of the immunosuppressive therapy
- ☐ Early recognition and treatment of drug side effects
- ☐ Recognition and treatment of acute or chronic rejection
- ☐ Psychological support of patients and their families

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