CLINICAL STUDY

Initial experience with lung transplantation in Slovakia — an example for successful bilateral cooperation between countries

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Abstract

Objective: To review initial experiences, results of single lung transplantation (SLT) and double lung transplantation (DLT) on the basis of bilateral cooperation between Slovakia and Austria.
Patients and methods: During the period between July 1998 and January 2003 ten patients from Slovakia underwent lung transplantation in Vienna, Austria. There were 7 males and 3 females with an age range from 21 to 48 years. Eight patients underwent double lung transplantation, two patients had single lung transplantation. Indications were: pulmonary fibrosis in 2, cystic fibrosis in 2, emphysema in 2, primary pulmonary hypertension (PPH) in 4 cases. In the PPH patients (n=4) and in the patients with cystic fibrosis (n=2), bilateral lung transplantation under ECMO support was performed. One patient (n=1) with postradiative pulmonary fibrosis and intracardial myxoma underwent bilateral lung transplantation under cardiopulmonary bypass. Only three patients (e.i. the two with emphysema and one with pulmonary fibrosis) underwent lung transplantation without any intraoperative circulatory support.
Results: No perioperative mortality was recorded. Two patients died in late postoperative period: one due to multiorgan failure on 93rd day after DLT, the other one – on a liver failure caused by cirrhosis after 2.5 years after LTX. All the remaining eight patients, but the two ones who underwent LTX several days ago, are with improved functional status in full work activity. The follow up period for all patients ranges between 10 days and 54 months.
Conclusion: Both unilateral and bilateral lung transplantations are accepted treatment modalities in patients with end-stage pulmonary disease. Bilateral cooperation for such countries as Slovakia (with limited possibilities) offers a unique example of possible and successful way how to deal with such demanding procedures. (Tab. 3, Fig. 2, Ref. 19.)
Key words: initial experience, lung transplantation, bilateral cooperation between countries.

Almost forty years passed since the first human lung transplantation was performed by Doctor James Hardy at the University of Mississippi in 1963 (Hardy JD, 1999). After the first dissapointing decades, in the 90ths Lung Transplantation (LTX) becomes a fully accepted and acknowledged treatment modality, and nowadays it is already a routine practise with a constantly increasing number of transplanted patients with more improving and more improved results.

As other countries, Slovakia has already its experience with LTX. It is almost five years since the first Slovak patient underwent successful lung transplantation in Vienna, Austria on 9 July 1998. Since that time further patients underwent LTX, the results of which are getting better; cooperation with Vienna Transplant Centre is progressing. Right at the very beginning it must be emphasized that for the above-mentioned activities and successes Vienna Lung Transplant Group (VLTG) and mainly the Director of this program – Professor Walter Klepetko must be thanked. It is important to mention that lung transplantation from the very beginning is based on the fruitful cooperation between

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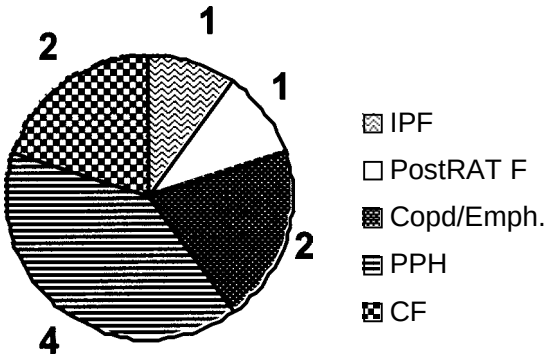

Fig. 1. Indications of LTX.

the two departments in AKH, Vienna and Slovak National Respiratory Diseases Hospital.

The objective and the main goal of this paper is to review initial experiences, results of single lung transplantation (SLT) and double lung transplantation (DLT) on the basis of bilateral cooperation between Slovakia and Austria.

Patients and methods

Patients demographic

During the period between July 1998 and January 2003 ten patients from Slovakia underwent lung transplantation in Vienna, Austria. There were 7 males and 3 females with an age range from 21 to 48 years (mean 29.5). The cause of their lung disease was idiopathic pulmonary fibrosis (IPF, n=1), postradiative pulmonary fibrosis (PostRAT F, n=1), cystic fibrosis (CF, n=2), emphysema (n=2), primary pulmonary hypertension (PPH, n=4) (Fig. 1). These ten patients underwent various forms of LTX, including SLT and DLT, as well as split lung – bilateral lobar transplantation (Blobar) in one case (Fig. 2).

Two patients were preoperatively hospitalized in intensive care unit (ICU), none from the total of ten patients was preoperatively resuscitated or bridged by any circulatory supports systems to LTX. All patients were preoperatively oxygen dependent.

LTX technique

All donor lungs were harvested en bloc as part of a multiorgan procurement. The organs were preserved in a low potassium dextran extracellular solution in 7 cases, and in a hyperosmolar intracellular solution in 3 cases. LTX was performed by standard technique (Taghavi et al, 1999; Pereszlényi et al, 1999; 2000), approached through anterior thoracotomies in 9 recipients, through a longitudinal sternotomy in 1 recipient. This sternotomic approach was chosen because the 25 yrs old female patient had an intracardial myxoma at her original disease of postradiative pulmonary fibrosis (PostRAT F), and this procedure was performed under cardiopulmonary bypass (CPB). This TX was performed as bilateral lobar transplantation (Blobar) – split lung, because of the small, thin chest of this recipient. Tab.1

From the remaining 9 patients, seven underwent DLT and two patients SLT. All single lung transplantations (n=2) and a double lung transplantation in case of emphysema (n=1) were performed without any intraoperative circulatory support. In 6 recipients: PPH patients (n=4) and patients with cystic fibrosis (n=2), bilateral lung transplantation under extracorporeal membrane oxygenation (ECMO) support was performed (Tab. 1 and Fig. 2).

ECMO was set up through the femoral venoarterial route after induction of anaesthesia in all cases but one (in this case the ECMO was set up centrally by cavo-aortal route). The whole ECMO apparatus was obtained from Medtronic Inc., and consisted of a Medtronic Carmeda heparin bound system, a Medtronic Maxima hollow-fiber oxygenator, a Bio-Medicus BP-80 centrifugal pump, a flow probe and 3/8-inch internal diameter heparin-bound tubing. As the tubing set was already heparinized, systemic administration of heparin was not used, except for an intravenous bolus of 50 IU/kg before cannulation.

Human albumin (5 %, 500 ml) with physiological saline (500 ml) supplemented with 1000 IU of Heparin was used as a priming solution. Oxygen saturation, respiration and circulation parameters as well as complete haemodynamics was continuously monitored on-line. The ECMO was discontinued immediately after the conclusion of the operation, or was prolonged postoperatively, depending on the clinical situation (Pereszlényi et al, 2002 a, b).

Immunosuppression and postoperative management

The early postoperative management at the intensive care unit (ICU) principally does not differ from the management of other complicated postoperative cases.

Immunosuppressive therapy is introduced immediately after transplantation. Nowadays more protocols of immunosuppressive therapy are known (Pereszlényi et al, 2000, 2002). Our ten patients were treated according to the Vienna Lung Transplant Group's (VLTG) immunosuppressive protocol, of course.

Cyclosporin (CyA)/ tacrolimus, mycophenolat mophetil (MMF) and prednisone were applied to all our patients. Methylprednisolone at a dose of 1000 mg i.v. was given intraoperatively and followed by 125 mg every 8 hours in three doses postoperatively. Immunosuppressive dose was adjusted to achieve a through level of 350–450 ng/ml for CyA and 15–18 ng/ ml for tacrolimus, respectively.

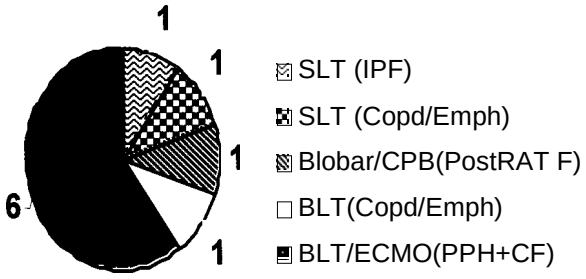

Fig. 2. LTX procedures.

Tab. 1. Patient demographics (Complex table).

No	Diagnosis	Age	Sex	Date of TX	Technique	Compl	Follow-up
1	IPF	29	F	9.7.1998	SLT		54 mo
2	Postrad F	25	F	20.12.1998	Blobar/CPB MOF		+93rd day
3	Copd/Emph	48	M	19.3.1999	BLT	Cirrhosis	+29 mo
4	PPH	22	M	1.12.1999	BLT/ECMO		38 mo
5	PPH	28	M	9.8.2000	BLT/ECMO	Hemothorax	29 mo
6	CF	28	M	5.6.2001	BLT/ECMO		19 mo
7	PPH	34	F	14.5.2002	BLT/ECMO		8 mo
8	Copd/Emph	27	M	1.11.2002	SLT	Pneumothorax	3 mo
9	PPH	27	M	30.11.2002	BLT/ECMO	Hemothorax	1 mo
10	CF	27	M	6.1.2003	BLT/ECMO		10 days

Induction therapy consisted of rabbit antithymocyte globulin (ATG) at a dose of 2.5 mg/ kg maintained for 6 days (adjusted for white blood cell and platelet count) in 4 patients, and daclizumab in three patients. The daclizumab group received an infusion of daclizumab of 1mg/ kg intraoperatively before reperfusion of the graft, and again on days 14, 28, 42, and 56 in three patients. The remaining three patients received no induction immunosuppression.

Results

Perioperative mortality

No perioperative mortality was evidenced in our group of patients.

Late mortality

Two patients (n=2) died in late postoperative period: one due to multiorgan failure on 93rd day after DLT, the other one – because of a liver failure due to cirrhosis after 2.5 years after LTX (Tab. 1). All the remaining eight patients, but the two ones who underwent LTX several days ago, are with improved functional status in full work activity.

The follow up period for all patients ranges between 10 days and 54 months.

Perioperative morbidity

Two patients with severe PPH (from ECMO group) underwent reoperation for hemothorax. Further complication, which appeared in one of these patients, was lymph fistula due to exposure of the cannulated femoral vessels. The complication was succesfully treated by radiation therapy and healed completely within 2 weeks.

Tab. 2. Recipient selection — General guidelines.

Clinically and physiologically severe disease
Medical therapy ineffective or unavailable
Limited life expectancy, usually less than 12 to 18 mo (when listed)
Ambulatory with rehabilitation potential
Acceptable nutritional status, usually 80–120 % of ideal body weight
Satisfactory psychosocial profile and support system

There were no vascular problems in the repaired femoral vessels in all cannulated ECMO patients (Tab. 1).

The other patient with emphysema had reoperation for tension pneumothorax developed in native left lung. After this operation his further postoperative period was uneventful (Tab. 1).

Two patients: one with PostRAT F, and one with severe PPH (who underwent LTX only several days ago), developed renal insufficiency, which had to be treated by haemodialysis.

Late functional outcome

The incidence of rejection during the first 100 days was 0.2 per patient. The overall incidence of infection during the same period was 0.5 per patient (bacterial infections 0.3, viral 0.1 and fungal 0.1, respectively).

All the remaining eight patients, but the two ones, who underwent LTX several days ago, are alive and well with improved functional status in full work activity. The follow up period for all patients ranges between 10 days and 54 months.

Discussion

The most frequent indications for LTX are the following diagnosis: chronic obstructive pulmonary disease (COPD), Alfa 1-antitrypsin deficiency emphysema, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF) and primary (PPH) and secondary pulmonary hypertension (Eisenmenger's syndrome) (Arcasoy and Kotloff, 1999; Pereszlényi et al, 2000).

Less common indications have included bronchiectasis, sarcoidosis, lymphangioleiomyomatosis, and eosinophilic granuloma of the lung.

According to the newest official data provided by the International Society for Heart and Lung Transplantation (ISHLT): 14 588 lung transplantations (LTX), 2935 combined heart-lung transplantations (HLT) and 61 533 heart transplanations were performed worldwide until the end of 2001 (Hosenpud et al, 2001).

In its begining lung transplantation was offered to patients with idiopathic lung fibrosis (IPF) only. After initial experiences, indications for lung transplantation were rapidly widened for all forms of infectious and non infectious parenchymal lung diseases, as well as vascular diseases in their different forms of pri-

Tab. 3. Recipient selection — Contraindications.

Acutely ill or unstable clinical status
Uncontrolled or untreatable pulmonary or extrapulmonary infection
Uncured neoplasm
Significant dysfunction of other vital organs, especially liver, kidney and central nervous system
Significant coronary disease or left ventricular dysfunction
Active cigarette smoking
Drug or alcohol dependency
Unresolvable psychosocial problems or noncompliance with medical management

mary and secondary pulmonary hypertension (Aigner and Klepetko, 2002).

Indications for LTX for Slovak patients were: pulmonary fibrosis – in 2 cases, cystic fibrosis in 2, emphysema in 2, and the most frequent – PPH was in 4 cases (Fig. 1).

All these LTX candidates fulfiled the recipient selection criteria and were listed in Vienna Lung Transplantation's international waiting list. General recipient selection criteria are itemized in Tables 2 and 3, respectively (Maurer et al, 1998; Pereszlényi et al, 2000).

The median waiting time for organ availability was almost 7 months (7.4 Mo), no mortality on waiting list for Slovak patients was recorded. None of our patients had to be announced as „High Urgency" case.

Generally, the optimum age to perform HLT is less than 45 yrs, to perform DLT is less than 55 yrs, and to perform SLT is less than 60 yrs (Klepetko et Birsan, 1997; Pereszlenyi et al, 1999).

The mean age of the Slovak patients was almost 30 years (29.5) and ranged from 21 to 48 years. So, our patients, who underwent DLT and SLT, were younger. No HLT had to be performed in our group of patients, there was also no pediatric indication for lung transplantation.

From our 10 patients, two had single lung transplantation and eight double lung transplantation. Out of these eight patients – one underwent bilateral lobar (Blobar) lung transplantation under cardio-pulmonary bypass (CPB); six underwent bilateral lung transplantation with ECMO support and one had double lung transplantation with no intraoperative circulatory support. All single lung transplantations (n=2) and the double lung transplantation in one case of emphysema (n=1) were performed without any intraoperative circulatory support (Tab. 1 and Fig. 2).

The usage of cardiopulmonary support systems is still the matter of active discussion among the experts. Uni – as well as bilateral lung transplantation can be performed without cardiopulmonary bypass (CPB) support in haemodynamical stable patients with lack of excessive pulmonary vascular resistance (Sherdan et al, 1998). For bilateral lung transplantation this implies that the first transplanted lung is exposed to the completed cardiac output during implantation of the second lung, with potentially consecutive damaging effects (Aigner et Klepetko, 2002; Pereszlényi et al, 2002). Therefore several centres prefer the routine use of CPB for bilateral lung transplantations (Rao et al, 2000). An alternative to CPB is the use of heparin-bounded ECMO systems. Several authors reported DLT in patients with severe PPH on intraoperative and postoperatively prolonged ECMO support (Ko et al, 2001; Pereszlényi et al, 2002). With this approach the need for complete heparinisation was avoided. Furthermore ECMO also offers less invasive mild ventilation and fully controlled prolonged reperfusion of the lung allograft (Aigner and Klepetko, 2002; Pereszlényi et al, 2002).

Results and functional outcome of our lung transplanted patients are presented in a complex Table 1. No perioperative mortality was recorded. Two patients died in late postoperative period. All the remaining eight patients, but the two ones who underwent LTX several days ago, are with improved functional status in full work activity. It is evident that summarizing the results from such a small number of patients can be bound with significant statistical inaccuracy. Despite this fact, we are convinced, that our first results are very encouraging, and we appreciate that this treating modality can also be offered to our Slovak patients. Needless to say that great thanks must go to Professor Klepetko and his Team, as without him we would never reach the above-mentioned results.

Both unilateral and bilateral lung transplantations are accepted treatment modalities in patients with end-stage pulmonary disease. Successful transplantation can offer the patient incomparably better quality of life, which is the main motivation as for the patient so for the Transplant Staff.

In Slovakia we also tried to offer better quality of life for patients suffering from those pulmonary diseases. Since 1998 these Slovak patients are being introduced to Vienna Lung Transplant Group. Because, while we have a number of obstacles to be able to start the whole sufficient Lung Transplant Program in Slovakia ourselves, this bilateral cooperation with Vienna means for us (the country with limited possibilities) at present a unique example of a possible and successful way how to deal with such demanding process.

Abbreviations

LTX	— Lung Transplantation
TX	— Transplantation (in general)
SLT	— Single Lung Transplantation
HLT	— Heart-Lung Transplantation
DLT	— Double Lung Transplantation
VLTG	— Vienna Lung Transplantation Group
AKH	— General Hospital Vienna (Allgemeines Krankenhaus Wien)
ISHLT	— International Society for Heart and Lung Transplantation
CPB	— Cardiopulmonary Bypass
ICU	— Intensive Care Unit
COPD	— Chronic Obstructive Pulmonary Disease
CF	— Cystic Fibrosis
IPF	— Idiopathic Pulmonary Fibrosis
PPH	— Primary Pulmonary Hypertension

PostRAT F — Postradiative Pulmonary Fibrosis
ECMO — Extracorporeal Membrane Oxygenation
CyA — Cyclosporine A, immunosuppressant
MMF — Mycophenolate Mofetil, imunosuppressant
ATG — Anti-thymocyte Globulin, immunosuppressant
Blobar — Bilateral Lobar Transplantation
BOS/OB — Bronchiolitis Obliterans Syndrome/ Obliterative Bronchiolitis

References

Aigner C, Klepetko W. Lung Transplantation: State of the Art. J Cardiovasc Surg 2002; 43 (Suppl 1), 6: 22—28.

Arcasoy SM, Kotloff RM. Lung Transplantation. New Engl J Med 1999: 340: 1081—1091.

Hardy JD. The first lung transplant in man (1963) and the first heart transplant in man (1964). Transplant Proc 1999; 31: 25—29.

Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: eighteenth Official Report-2001. J Heart Lung Transplant 2001; 20 (8): 805—815.

Klepetko W, Birsan T. Lungentransplantation: State of the Art (Abstract): Jahrestagung der Österreichischen Gesellschaft für Transplantation, Transfusion und Genetik (29.10.-1.11.1997, Saalfelden am Steinernen Meer, Austria).

Ko WJ, Chen YS, Luh SP, Chu SH. Extracorporeal membrane oxygenation support for single-lung transplantation in patients with primary pulmonary hypertension. Transplantation Proc 1999; 31: 166—168.

Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. J Heart Lung Transplant 1998: 17: 703—709.

Pereszlényi Jr. Á, Klepetko W, Haruštiak S. Transplantácia pľúc — súčasný stav. Stud Pneumol Phthiseol 1999; 59 (6): 255—259.

Pereszlényi Jr. Á, Haruštiak S, Taghavi S, Birsan T, Huber E, Deviatko E, Klepetko W. Lung Transplantation Today. Bratisl Lek Listy 2000; 101 (2): 63—70.

Pereszlényi Jr. Á, Haruštiak S, Klepetko W. Indikácie a kontraindikácie pľúcnej transplantácie. Stud Pneumol Phthiseol 2000; 60 (4): 163—167.

Pereszlényi Jr. Á, Haruštiak S, Klepetko W. Circumstances of bronchiolitis obliterans development after lung transplantation: Analysis of risk factors. Bratisl Lek Listy 2000; 101 (12): 633—638.

Pereszlényi Jr. Á, Haruštiak S, Taghavi S, Birsan T, Huber E, Klepetko W. The current state of lung transplantation. Med Thorac 2000; 53 (4): 129—136.

Pereszlényi Jr. Á, Lang G, Steltzer H, Hetz H, Kocher A, Neuhauser P, Wisser W, Klepetko W. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Europ J Cardio Thorac Surg 2002; 21: 858—863.

Pereszlényi Jr. Á, Haruštiak S, Klepetko W. Extracorporeal membrane oxygenation in lung transplantation. Bratisl Lek Listy 2002; 103 (1): 34—38.

Pereszlényi Jr. Á, Haruštiak S, Klepetko W. Prostacyclins in pulmonary hypertension treatment. Bratisl Lek Listy 2002; 103 (4—5): 179—184.

Pereszlényi Jr. Á, Klepetko W, Haruštiak S. Skúsenosti s transplantáciou pľúc počas pobytu na transplantačnej Klinike vo Viedni. Stud Pneumol Phthiseol 2002; 62 (4): 150—155.

Rao JN, Hasan A, Parry G, Wardle J, Corris P, Dark JH. Routine cardiopulmonary bypass (CPB) for bilateral lung transplantation. Abstract, presented at 14th Annual Meeting of EACTS, Frankfurt, Germany, 7-11 October 2000.

Sherdan BC, Hodges TN, Zamora MR, Lynch DL, Brown JM, Campbell DN et al. Acute and chronic effects of bilateral lung transplantation without cardiopulmonary bypass on the first transplanted lung. Ann Thorac Surg 1998; 66: 1755—1758.

Taghavi S, Birsan T, Pereszlényi Jr. Á, Kupilik N, Deviatko E, Wisser W, Steltzer H, Klepetko W. Bilateral lung transplantation via two sequential anterolateral thoracotomies. Europ J Cardio-thorac Surg 1999; 15: 658—662.

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