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1.1 History of lung transplantation:

**Worldwide:**
In 1963 the first human lung transplantation (LTx) was performed at the University of Mississippi in the United States\(^1\). Between 1963 and 1974, 36 patients received a LTx but the medical results of this treatment were disappointing. The median survival rate at that period was less than 10 days\(^2\). In the following period, human LTx were only sporadically performed. The current era of successful human organ transplantation began in the early nineteen eighties following the introduction of cyclosporine as an immunosuppressive agent. In this period, only heart-lung transplantations were performed\(^3\). In the following years, single\(^4\) and bilateral\(^5\) lung transplantations became more and more popular. Currently, worldwide more than 15,000 (heart-) lung transplantations have been performed (about 2,700 heart-lung, 6,500 single lung and 4,600 double lung procedures)\(^6\). In the last 10 years, the number of heart-lung transplantations has declined, while the number of lung transplantations performed in the last 5 years has more than doubled.

**The Netherlands/ Groningen:**
The strong interest of the University Hospital Groningen in LTx dates from the nineteen sixties, when the first lung transplants were performed on dogs. At that time, the research questions were mainly related to clinical-technical and physiological aspects of LTx. From this research, among others, the power of cyclosporine as an immunosuppressive agent became clear\(^7\)\(^8\). In 1989 the St. Antonius Hospital in Nieuwegein performed the first clinical LTx in the Netherlands. Shortly thereafter, in November 1990, the University Hospital Groningen performed its first LTx. Until August 2002, about 218 patients were transplanted for end-stage pulmonary disease with LTx in the Netherlands. Of these 200 LTx, 194 were performed in the University Hospital Groningen (148 bilateral lung transplantations, 37 unilateral lung transplantations, 7 heart-lung transplantations and 2 liver-lung transplantations).

1.2 Lung transplantation program:

**Worldwide:**
LTx has become an accepted therapeutic option for patients with end-stage lung disease\(^9\). The number of transplantation centres performing (heart)-lung transplantations nowadays amounts to approximately one hundred. These centres all report improvements in survival rates, functional results and health-related quality of life (HRQL) after LTx in comparison with the situation on the waiting list before LTx. During the last decade, survival rates after LTx have slightly improved. Registry data from the International Society for Heart and Lung Transplantation (ISHLT) shows that the 1-year survival rate after LTx in the periods 1988-1992, 1993-1996 and 1997-2000 was 68%, 72% and 74% respectively\(^10\). The 5-year survival rates in the periods 1988-1992 and 1993-1996 were about 41% and 43% respectively. These figures are based on cumulative data from centres all over the world.
This improvement in survival rates may be caused by increasing surgical or clinical experience or by improvement of the surgical techniques. The long-term effect on survival rates of patients using new immunosuppressive medicine in trials remains unclear for the time being.

Functional results also improve after LTx. After a successful bilateral LTx, ventilatory function usually improves until 80-90% of predicted values, which are based on the height, gender and age of the recipient. After unilateral LTx, the original lung disease of the native lung influences parameters in pulmonary function and are usually lower after unilateral LTx than after bilateral LTx. The maximum exercise capacity improves after LTx, but the exercise capacity between unilateral and bilateral LTx is not different\textsuperscript{1}, since this parameter in most patients is limited because of muscle function\textsuperscript{12} and not because of pulmonary or cardiac function. The muscle function may be limited due to the influence of cyclosporine-induced mitochondrial myopathy\textsuperscript{13}. In only a few patients lung(s) or heart is the limiting factor.

Measuring HRQL has been increasingly accepted as an important outcome measure in new treatments. Previous studies focused on the health-related quality of life showing significant improvements between the situation before and after lung transplantation\textsuperscript{14}.

Figure 1: Flowchart of the Dutch lung transplantation program (1 July 1990 - 1 April 1999). Patients were either removed from the program when they died, rejected because of a serious contra-indication, withdrew from the program or were lost to follow-up if there was no contact with the LTx-team for more than 12 months.

( ) =numbers between brackets indicate the number of patients who are still in a specific phase
Chapter 1

The Netherlands/ Groningen:
The following phases in the lung transplantation program in the University Hospital Groningen can be distinguished: referral, outpatient screening, inpatient screening, waiting list, transplantation (peri-operative and intensive care), inpatient follow-up and outpatient follow-up. The patient flow and the number of patients for the first 10 years until April 1, 1999 in the different phases of the transplantation program are described in a flowchart (Figure 1).

The results for survival rates after transplantation in the Dutch lung transplantation program are given in Figure 2. These data show that survival rates after transplantation over the period January 1995-April 1999 are better than survival rates over the period 1990 – 1995, although not statistically significant (log rank p=0.629). The overall survival after lung transplantation of the Dutch lung transplantation program is higher than in most other countries. The ISHLT-registry reports a two-year survival rate of 60% and subsequently a decrease in survival rate of almost 5% a year.

Figure 2: The survival rates after LTx: 1990 until 1-1-1995 versus 1-1-1995 until 1-4-1999 of the Dutch lung transplantation program (Kaplan-Meier analysis).

Functional results after LTx investigated in Groningen showed significant improvements already within one month after transplantation\textsuperscript{15}. Parameters investigated were the FEV\textsubscript{1} percentage of predicted the arterial oxygen pressure, the exercise capacity and the 6-minute walking distance test.

From the start of the lung transplantation program in 1990, much effort has been spent in creating a database with data about the health-related quality of life of patients on the waiting list and after lung transplantation. Usage of this database resulted already in several international publications\textsuperscript{16,17,18}. 

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1.3 Limitations in the lung transplantation program:

Limitations pre-transplantation: donor organ shortage
Of all types of transplantations, the need for donor organs is especially urgent in lung transplantation because of the large discrepancy between the number of acceptable donor lungs on the one hand and recipients on the other hand. For end-stage pulmonary failure, no temporary support mechanism, such as dialysis for end-stage renal failure, is available. The annual demand for lung transplantation has been rising steadily despite new therapeutic options like lung volume reduction surgery for emphysema and prostacyclin treatment for patients with pulmonary hypertension\textsuperscript{19}. The shortage of donor organs has proven to be one of the major limitations of lung transplantation. Since 1998, the worldwide number of donor organs and the number of lung transplantations has decreased about 25%\textsuperscript{6}. Moreover, in only 10% of the multi-organ procedures the donor lungs can be used for transplantation because of the vulnerability of these organs\textsuperscript{20}. As a consequence the number of patients who die on the waiting list amounts more than 20%\textsuperscript{21}.

Limitations post-transplantation: bronchiolitis obliterans syndrome
Chronic rejection is the most important impediment to better medium and long-term survival rate (post-LTx)\textsuperscript{22,23}. It is diagnosed histologically (obliterative bronchiolitis (OB)) or physiologically by airflow limitation (bronchiolitis obliterans syndrome (BOS)).
OB is characterized by obliteration of the terminal and respiratory bronchioli. The term BOS is used to connote graft deterioration secondary to progressive airway disease for which there is no other cause\textsuperscript{24}. BOS is defined, according to the gradation of the International Society for Heart and Lung Transplantation, as a fall of the FEV\textsubscript{1} of at least 20% from the baseline value (Table 1)\textsuperscript{25}. The baseline value is defined as the average of the two highest FEV\textsubscript{1}’s obtained at least 3-6 weeks apart. Infection or acute rejection may not cause this decline in FEV\textsubscript{1}. The cause of this syndrome is still unknown. Although much research on several target areas has been made to discover its pathophysiology, the precise mechanism remains unclear. Late acute rejection, lymfocytic bronchiolitis, a decreased immunosuppression, CMV-pneumonitis, number of acute rejections and bronchial hyperreactivity are identified in several studies as principal risk factors for chronic rejection\textsuperscript{26,27,28,29,30,31,32}.

Table 1: International Society for Heart and Lung Transplantation for the staging of BOS.

<table>
<thead>
<tr>
<th>Original classification</th>
<th>Current proposition</th>
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<tr>
<td>BOS 0 FEV\textsubscript{1} 80% or more of baseline</td>
<td>BOS 0 FEV\textsubscript{1} &gt;90% of baseline and FEF\textsubscript{25-75} &gt;75% of baseline</td>
</tr>
<tr>
<td></td>
<td>BOS 0-p FEV\textsubscript{1} 81%-90% of baseline and/or FEF\textsubscript{25-75} \leq 75% of baseline</td>
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<tr>
<td>BOS 1 FEV\textsubscript{1} 66%-80% of baseline</td>
<td>BOS 1 FEV\textsubscript{1} 66%-80% of baseline</td>
</tr>
<tr>
<td>BOS 2 FEV\textsubscript{1} 51%-65% of baseline</td>
<td>BOS 2 FEV\textsubscript{1} 51%-65% of baseline</td>
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<tr>
<td>BOS 3 FEV\textsubscript{1} 50% or less of baseline</td>
<td>BOS 3 FEV\textsubscript{1} 50% or less of baseline</td>
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BOS, bronchiolitis obliterans syndrome; FEF\textsubscript{25-75} ≤mid-expiratory flow rate; FEV\textsubscript{1}, forced expiratory flow in one second.

Detection of BOS using flow-volume measurements is an easy, cheap and non-invasive method in contrast with very sophisticated lung function tests or with obtaining histology.
Previous studies have suggested the usefulness of markers other than the FEV$_1$ like the specific airway conductance or markers representing the small airways as functional indicators of OB$^{33-36}$. Since the precise mechanism of development of chronic rejection is still unknown, we focused on early diagnosis of BOS in lung function. The importance of BOS in our population is given in Figure 3.

Figure 3: freedom from BOS after lung transplantation in the University Hospital Groningen by October 1, 2001 (actual analysis)

censored = end of follow up or patient died
1.4 Medical Technology Assessment of Lung Transplantation:

**Worldwide:**
Medical Technology Assessment (MTA) emerged with rapid developments in health care technologies, for example new and expensive diagnostic tests, new drugs and therapies. The fundamental aim of all MTA's is to provide information to those individuals and organizations who take profit from new health technology (patients), those who will pay for it (payers) and those who make health care decisions (providers), concerning the effectiveness, costs, unwanted health effects, and ethical and social consequences of health technologies. MTA is a multidisciplinary profession requiring combined expertise in clinical medicine, epidemiology, biostatistics, bioengineering, health economics, administration, psychology, sociology, ethics and legal science. While many aspects may be evaluated in an MTA, the central part usually consists of an economic evaluation in which the costs and effects of a new diagnostic or therapeutic developments are assessed.

**The Netherlands/Groningen:**
The Dutch National Health Insurance Board initiated in 1991 an MTA, which should provide information on costs, clinical effectiveness, quality of life, cost-effectiveness of LTx and the number and supply of donor organs. Furthermore, an economic evaluation was performed from a lifetime and societal perspective. In this economic evaluation, the additional costs and effects of LTx were evaluated. To assess the additional (or incremental) costs and effects, a comparison was made between the costs and effects in the situation with and without a transplantation program. This resulted in 1996 in the “Evaluation report lung transplantation”. In October 1997 the Minister of Health Affairs decided to incorporate LTx in the Dutch benefit package by January 1, 1998 because of the proven efficacy of LTx reflected both as survival benefit and benefit in health related quality of life. From the Evaluation report it was concluded that the costs per life year gained were remarkably high. In comparison to the cost-effectiveness of heart- and liver transplantation, the cost-effectiveness of LTx was unfavourable. Therefore, the Minister of Health Affairs requested at the end of 1997 the start of a second cost-effectiveness study of the Dutch LTX-program. The key question was how adjustments of the protocol and/or change in the patient flow could lead to a more favourable ratio of costs and effects in the LTx-program.

1.5 Aim and outline of the this:
LTex has come of age. The survival rates and health related quality of life are improving after LTx. However, the limitations have become apparent. The key question to be addressed in this thesis is: In which way does adjusting the LTx protocol lead to further improvement of the LTx-program?
More specifically, the following subjects of research will be addressed in this thesis.

Part I: Improvements in the lung transplantation program:

Pre-transplantation: waiting list and allocation by studying:
1) Simulated waiting list prioritization for equitable allocation of donor lungs. Chapter 2
2) Size matching in lung transplantation using predicted Total Lung Capacity. Chapter 3

Post-transplantation: early occurrence of bronchiolitis obliterans syndrome by studying:
1) Bronchiolar airflow impairment after lung transplantation: an early and common manifestation. Chapter 4
2) Selective monitoring and early diagnosis of bronchiolitis obliterans syndrome after single lung transplantation. Chapter 5
3) Long-term survival despite early loss of graft function after single lung transplantation. Chapter 6

Part II: Cost-effectiveness and utility of lung transplantation by studying:
1) The cost-effectiveness of lung transplantation compared to heart- and liver transplantation in the Netherlands. Chapter 7
2) Improving the cost-effectiveness of the lung transplantation program. Chapter 8
3) Long-term quality of life in patients surviving at least 55 months after lung transplantation. Chapter 9

References: