Summary, conclusions, perspectives and recommendations
9.1 Introduction

In 1990 the first lung transplantation in Groningen was carried out. In the present thesis the experiences and limitations of the Groningen Lung Transplant Group in the past 10 years are described. The following aspects are summarised and discussed:

- the major pre-transplantation limitation i.e. donor organ shortage: waiting list priorities and allocation of donor lungs (chapters 2 and 3).
- the major limitation after lung transplantation i.e. the occurrence of bronchiolitis obliterans syndrome: early onset of bronchiolitis obliterans syndrome after single and after double lung transplantation (chapters 4, 5 and 6).
- the cost-effectiveness of the lung transplantation program in comparison with the heart- and liver transplantation program and the main findings of the evaluation of the lung transplantation protocol and the influence on the cost-effectiveness of the lung transplantation program (chapters 7 and 8).
- the long-term quality of life after lung transplantation (chapter 9).

This chapter concludes with perspectives and recommendations for further research and suggestions for further improvement of the results of lung transplantation.

9.2 Summary and conclusions

Chapter 2

The number of organ transplantations has declined in the past few years. This is mainly caused by a decline in available donor organs. Donor organ shortage causes long waiting lists and a high mortality on the waiting list. The waiting list survival for lung transplantation is not equal for different indications: the probability of receiving a donor lung for patients with rapidly vs. slowly progressive diseases is different. In our actual lung transplantation program the allocation system is based on blood group, height and waiting time. Mainly the patients with chronic obstructive pulmonary disease take advantage of this situation. Although chronic obstructive pulmonary disease can be severe and debilitating, the mortality from this disorder without lung transplantation is not as high as that from other indications for lung transplantation. International data confirm these findings. Previous investigations showed that patients with chronic obstructive pulmonary disease usually only gain health-related quality of life without a survival benefit after lung transplantation. On the contrary, patients with cystic fibrosis and pulmonary fibrosis have a much higher benefit in survival by a lung transplantation. Because of this imbalance, we explored in a simulation model the possibilities of prioritization of patients with the most life threatening diseases i.e. a significantly increased risk to die on the waiting list. These diseases were primary pulmonary hypertension, cystic fibrosis, and pulmonary fibrosis. For these diagnoses, the relative risks of death on the waiting list were used for prioritization in the simulation model by multiplying the waiting time with the relative risk. Hereafter, the waiting list was sorted in the order of prioritized waiting time. Starting at the top of the patient list, a matching patient was sought for each donor taking into account the actual data of availability of donor lungs and listing of patients. As expected, the percentage of prioritized diagnoses after lung transplantation increased and the percentage non-prioritized diagnosis after transplantation decreased. After prioritization, the distribution of diagnoses after lung transplantation was close to the distribution of

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diagnoses on the waiting list. In conclusion: the results after prioritization show a more equal and fair distribution of donor lungs.

Chapter 3
Size matching is important in the allocation of donor lungs. The allocation of donor lungs is based on height, blood group and waiting time on the waiting list. A subject of discussion is the possible range in height by the allocation donor lungs. For an exact allocation of a three-dimensional organ like a donor lung, one value like height may be insufficient. Many approaches have been followed in the past, for example by matching chest X-rays. The best approach to donor-recipient size matching has not been determined so far.
In the present study the predicted Total Lung Capacity (TLC) was used, which is dependent on height and gender. This parameter represents the volume of the thoracic cavity. The influence of gender on the allocation of donor lungs was retrospectively evaluated by calculating both the height donor/recipient (D/R) ratio as well as the predicted TLC D/R ratio. Since an increased range in TLC D/R ratio was expected, we also investigated if an increased range has led to clinical (pneumothorax/atelectasis) and/or functional (exercise capacity) complications.
The results showed that the allocation of donor lungs based upon height alone as used in daily practice led to a substantial mismatch in TLC, which is mainly caused by gender mismatch. In case of gender mismatch the allocation on height alone is therefore not sufficient. The results also suggested that liberalisation of height matching may be possible since mismatch in Total Lung Capacity did not lead to clinical and functional complications.
These results may have practical consequences. Most lung transplantation centres have long waiting lists because of donor organ shortage. Therefore, donor lungs can usually be allocated. However, in case of a special blood group, in case of an unusual height or in case of seriously ill patients listed for high urgency, height mismatch may preclude proper allocation.
In Germany, the allocation of donor lungs that was based on height alone (like in the Netherlands) has been changed recently. New legislation of the German court of law determined that the patient who is most seriously ill should be transplanted first. If the other lung transplantation centres within Eurotransplant or in other countries follow this new legislation in Germany, liberalisation of height matching and the influence of gender mismatch on the allocation of donor lungs may become of more importance.

Chapter 4
Onset of bronchiolitis obliterans syndrome (BOS) is the major limitation of the survival after lung transplantation. An early diagnosis of BOS after lung transplantation is of major importance to try to stop further decline in lung function, e.g. by changing the immunosuppressive regimen. The adjunctive value of flow markers like the FEV\textsubscript{1}, FEF\textsubscript{25}, FEF\textsubscript{50}, FEF\textsubscript{75}, MMEF\textsubscript{75/25}, was investigated in patients after bilateral lung transplantation in relation to occurrence of BOS.
In order to avoid improper extrapolation from the normal population, first the coefficient of variation (V\textsubscript{coef}) for the above mentioned lung function parameters was calculated from a group of stable lung transplantation-recipients without BOS. The observed variations appeared to correspond with those found in healthy volunteers.
Subsequently, a lower limit percentage for each of the mentioned parameters was calculated by using the formula (100 - 1.64*V\textsubscript{coef})%, the factor 1.64 being the lower 5\textsuperscript{th} percentile of the
normal distribution. A persistent and significant decrease in FEV$_1$, FEF$_{25}$, FEF$_{50}$, FEF$_{75}$ and MMEF$_{75/25}$ below the lower limit was observed in 23, 24, 30, 32 and 29 patients, respectively. This indicates that the majority of lung transplantation-recipients will develop pulmonary dysfunction in time, as defined by all markers tested here. Since potentially all lung transplantation-recipients may develop BOS, an arbitrary, but clinically useful follow-up period of 120 days for the calculation of positive predictive values was chosen between a significant decline of the respective flow markers below the lower limit and the occurrence of BOS grade 1. By using the lower limit of the FEV$_1$, in the present study calculated as 93.3% of baseline, an early diagnosis of BOS grade I seemed possible by 71 days (median). Persistent decline below this lower limit showed a positive predictive value for developing BOS grade 1 within 120 days of almost 90%.

These data suggest that the margin of BOS of 20% decline in FEV$_1$ in the ISHLT-classification of BOS is conservative and that the diagnosis of BOS and a persistent decrease of FEV$_1$ is preceded by persistent decreases of small airway parameters in the expiratory flow. From a clinical perspective, a significant decline of FEF$_{75}$ may be used as an early warning sign for the development of BOS. However, the clinician should be aware that the probability of developing BOS within 120 days is approximately 35%.

In practice, the composite finding of declining values of FEF$_{75}$ and FEV$_1$ below the lower limit may urge additional diagnostic procedures including transbronchial biopsies to obtain insight in the cause of transplant dysfunction. The role of flow-volume measurements should be of more importance in the search for early signs of OB. It is an easy, cheap and non-invasive method in contrast with obtaining histology or very sophisticated lung function tests.

Chapter 5

The value of ventilation scintigraphy after single lung transplantation was evaluated in relation to an early diagnosis of BOS. In case of single lung transplantation, a decrease of FEV$_1$ as a diagnostic criterion for BOS might be significantly influenced by the presence of the native lung. By multiplying the measured FEV$_1$ with the ventilation percentage of each lung, a separate FEV$_1$-value can be calculated for the native lung and for the graft. For the patient groups with obstructive lung disease, restrictive lung disease and pulmonary vascular disease, the contribution of the ventilatory capacity of the native lung to the total FEV$_1$ before and after single lung transplantation was separately calculated. Subsequently, by taking the contribution of the native lung into account, onset of early graft dysfunction was investigated in individual patients. Therefore first a baseline value (see also chapter 4) and secondly a gradation of BOS for the graft alone was calculated. The results showed that the function of the native lung was low in patients with obstructive lung disease, compared to patients with restrictive lung disease or pulmonary vascular disease. The FEV$_1$ post-transplantation of the native lung was for all investigated patient groups stable in time.

In case of a high contribution of the native lung like in restrictive lung disease and pulmonary vascular disease, BOS could be detected earlier ($p=0.018$), when the FEV$_1$ was corrected for the contribution of the native lung. Progression of BOS from grade 1 to BOS grade 2 or 3 was observed earlier as well. When the function of the native lung was low due to the original lung disease, such as obstructive lung disease, the correction did not contribute to either the numbers of patients developing BOS or an early diagnosis of BOS.

From the study can be concluded that early detection of BOS in single lung transplantation is enhanced when correcting for the contribution of the native lung in those diseases where the
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pre-transplant FEV$_1$ is significant. This study emphasised the importance of ventilation scintigraphy after single lung transplantation including calculation of ventilation values for the left and the right lung.

Chapter 6

We describe a case report of a patient after single lung transplantation for idiopathic pulmonary fibrosis. In this patient, the effect of the graft on the pulmonary improvement was only temporary, as the patient developed graft dysfunction resulting in complete destruction of the graft. This patient, however, is still alive 6 years after obliterative bronchiolitis was diagnosed, apparently as a consequence of improvement of the native lung by the combination of triple immunosuppressive medication.

This case is of interest for several reasons. First, it shows that pulmonary fibrosis may respond to intensive immunosuppressive therapy and that special attention should be given to protocols of triple immunosuppression for treatment of idiopathic pulmonary fibrosis in the future. Secondly it demonstrates that ventilation scintigraphy is useful in addition to pulmonary function tests in estimating the actual function of the graft after single lung transplantation, and thirdly it appears that the gradation of bronchiolitis obliterans syndrome after single lung transplantation may overestimate the true function of the graft. Our patient could never have developed BOS grade 3 because of the influence of the native lung despite absence of ventilation and perfusion of the graft. This case report also shows the importance of ventilation scintigraphy in case of a decline in FEV$_1$ after SLTX.

Chapter 7

A comparison of the cost-effectiveness of the Dutch lung, heart and liver transplantation programs was made, based on the results from three Dutch transplant studies. Therefore, some adjustments for the methods and differential timing of the studies were necessary. The present analysis showed that the cost-effectiveness of lung transplantation is unfavourable compared to the cost-effectiveness of heart and liver transplant recipients. There are two main reasons for this unfavourable cost-effectiveness. First, the survival gain (survival after transplantation minus survival on the waiting list) is relatively small for lung transplant recipients compared to the other programs. This is partly due to the relatively short survival after lung transplantation, because of the high risk of infection and the invariably high risk of BOS. Another reason for the low survival gain is the relatively "long" survival of the lung transplant patients on the waiting list, resulting in a rather good survival of the control-group. An explanation for the high survival on the waiting list is the relatively large proportion of patients with chronic obstructive pulmonary disease (usually with long survival) and the difficulty of determining the optimal point of time to place these patients on the waiting list for lung transplantation.

A second reason for the unfavourable cost-effectiveness of lung transplantation compared to the cost-effectiveness of heart and liver transplantation are the high follow-up costs of lung transplant recipients compared to heart and liver transplant recipients. Both survival and high follow-up costs are mainly caused by the frequent infection and rejection problems of lung transplantation recipients, which regularly involve hospitalisation and high medical costs.
Chapter 8

The Minister of Health Affairs allowed inclusion of lung transplantation in the Dutch benefit package in 1998. She also requested initiation of a cost-effectiveness study to explore the possibilities of improving the cost-effectiveness ratio of the lung transplantation-program. The basis for this evaluation was the protocol for lung transplantation, originally formulated in 1990. The diagnostic gain of routinely performed tests in this protocol was evaluated to establish a more favourable ratio between costs and effects. Subsequently, in sensitivity analyses, the influence of a 20% change in survival, number of transplantations, program costs in different phases, costs of medication and hospitalisation on the actual cost-effectiveness were calculated. The purpose was to determine the influence of these costs on the cost-effectiveness of the lung transplantation-program separately.

First the costs of the original protocol dating from 1990 were indexed and adapted to the patient flow and patient survival in the year 2000. Secondly, the savings in costs in the future protocol (assuming a stable patient flow and survival) were calculated. The cost-effectiveness (CE) was discounted with 5% a year. Indexation and adaptation of patient flow and survival resulted in a cost-effectiveness ratio per life year gained of US $84,500 in 2000. A number of routine investigations showed that showed no diagnostic gain. As a result of this evaluation of the original protocol, the cost-effectiveness improved to US $68,500 per life year gained. Sensitivity analyses showed that the best way to improve the cost-effectiveness of lung transplantation is by trying to improve the survival and decrease the follow-up costs after lung transplantation.

Chapter 9

Health-related quality of life is a topic, which is considered more and more as an important outcome measurement. In the present study, the health-related quality of life was evaluated until 55 months after lung transplantation.

The results showed that the health-related quality of life improved already within 4 months after lung transplantation. The calculated health-related quality of life scores were close to the reference values, which apply for these questionnaires. From 4 months until 43 months after lung transplantation, the health-related quality of life remained stable in time. After 43 months a clear and significant decline in health-related quality of life is visible. This decrease is mainly caused by co-morbid conditions like drug treated diabetes mellitus, drug treated hyperlipidemia, decrease in kidney function and an increased occurrence of BOS.

9.3 Perspectives and recommendations

In this thesis, three major problems related to lung transplantation are described. First, the major limitation on the waiting list i.e. donor organ shortage. Secondly, the major limitation after lung transplantation i.e. bronchiolitis obliterans syndrome and thirdly, the high cost-effectiveness ratio of lung transplantation. In the following paragraph recommendations and suggestions are given for these problems.
1. Donor organ shortage
Decrease of donor organ shortage or improvement of the number of lung transplantations may be realised by:

**Improvement of the recruitment of donors**
This is one of the most important issues for both governmental and non-governmental institutions. The Government in the Netherlands tried to improve donor organ shortage by developing new legislation, resulting in the beginning of 1998 in the Dutch law organ donation (Wet op de Orgaandonatie). This law requires that every Dutch person above 18 years will be asked if he/she want his or her organs put at someone's disposal after decease, a so-called permission system with voluntary registration during life. The acquirement of donor organs after initiating this new law is until now for all types of organs beneath expectations and is low compared to the situation in other countries. Except for several, always available cultural and organisational differences, it seems that the difference between the number of donor lungs in the Netherlands and in for example Belgium can be explained by differences in legislation (in the Netherlands the permission system with voluntary registration during life and in Belgium a ‘non-objection-system’).

**Recognition of donor lungs**
In the period June 1996 until July 1998 the maximal donor organ potential in the Netherlands was investigated (Don Quichot report). The results showed that shortage of donor organs also is caused by the fact that only a small percentage of potential donors are recognised by medical doctors. The number of donor organs may be doubled at least in the actual situation. After notifying the results of this report, the Minister of Health Affairs appointed so called “donor co-ordinators”. The donor co-ordinators are trained in searching for potential donors at intensive care units in hospitals to minimise this loss of organs. Recently, the work of the donor co-ordinators was evaluated and the Minister of Health Affairs decided to expand both the number of donor co-ordinators and the number of participating hospitals.

**Transplantation capacity**
In the University Hospital Groningen, over 190 lung transplantations have been performed since 1990 (until 1/8/2002). This hospital was until 2001 the only centre in the Netherlands, which performed lung transplantations.

The annual reports of Eurotransplant showed the last few years a net export of donor lungs from the Netherlands to foreign countries. This means that with the actual donor potential the annual number of lung transplantations can be increased in the Netherlands. However, acceptance and rejection criteria of donor lungs differ in various lung transplantation centres. Based on the Eurotransplant figures, an annual number of about 30 lung transplantations (conservatively estimated) may be possible in the Netherlands. By an increase of the capacity (at the moment between 15 and 20 transplantations in one year) in the University Hospital Groningen or by expansion of the number of lung transplantation centres in the Netherlands the number of transplantations may increase. Since 2001, the University Hospital Utrecht and University Hospital Rotterdam co-operate and perform also lung transplantations. Until 1/8/2002 14 lung transplantations have been performed.

**Shift of priorities**
Another possibility for an increase of the transplantation capacity may be a shift of priorities in favour of lung transplantation. The problem is that thoracic surgeons who perform lung transplantations are dealing with different types of urgent patients and with different waiting times.
lists. With the actual demand to regular thoracic surgical treatments and the possibilities therefore, this seems for the time being a theoretical option.

**Acceptation of ‘marginal donors’**
Using donor lungs with marginal or lower qualitative characteristics is defendable and justifiable considering the long waiting list for lung transplantation and the high waiting list mortality. Despite data with successful outcome, sufficient capacity after lung transplantations with marginal donors is of even more importance because of the probably increased risk on complications and an increased post-operative hospitalisation.

**Non-heart-beating lung transplantation**
The value of this method of lung transplantation will be obvious in the nearby future and deserves a chance to be developed, considering the pre-clinical work and the recently published paper of the first successful non-heart-beating lung transplantation. During the first 5 months of follow-up, the function of the transplanted lung has been good.

**Single lung transplantation**
A shift to performing more single lung transplantations for emphysema patients instead of double lung transplantation will contribute to an increase of the number of transplanted patients in the Netherlands. However, international experience shows that the long-term results after single lung transplantations lag behind compared those after double lung transplantation. In Groningen in the last few years there already has been a shift towards performing more single lung transplantations (1/6 of the number of lung transplantations had been unilateral; at the moment (April 2002) about 1/2 of the actual waiting list is listed for an unilateral lung transplantation). Performing two single lung transplantations in one centre at the same time in one hospital is logistically difficult to organise. By opening of a second or even a third lung transplantation centre, performance of two single lung transplantations at the same time from one donor is possible.

**Development of new therapies**
The past few years, possibly also stimulated by the donor organ shortage, new therapies for end-stage pulmonary and vasculary diseases are developing fast. For example: lung volume reduction surgery for patients with emphysema and treatment with prostacyclin for patients with pulmonary hypertension. However, lung volume reduction surgery hardly influenced the inflow of the number of patients with emphysema in the lung transplantation program. On the other hand, the treatment with prostacyclin resulted in a significant decrease of the inflow of patients with primary pulmonary hypertension on the waiting list and even patients already on the waiting list with primary pulmonary hypertension were removed. Whether both methods of treatment will lead to a permanent decrease of influx of patients in the future is at this time unclear.

From the above it becomes clear that multiple measures are necessary to increase the number of lung transplantation. The problems associated with donor organ shortage are a joint responsibility in general for the whole population and in particular: the government, hospital organisations, and medical and nurse professions.

The two other limitations described in this thesis are the occurrence of BOS and the unfavourable cost-effectiveness of lung transplantation. These subjects are closely related to each other since BOS is the most important impediment to long-term survival after lung transplantation and the cost-effectiveness of lung transplantation can be influenced best by
improving the survival of patients after lung transplantation. Therefore, insights in onset and time course of BOS are of major importance for prevention strategies and treatment in the future in an attempt to improve survival.

2. The major limitation post-transplantation: Bronchiolitis Obliterans Syndrome

Current efforts are directed at delineation of the pathophysiology of this heterogeneous syndrome, at immunohistology, at broncho-alveolar lavage studies and at the development of early diagnostic (this thesis) and prognostic markers of BOS. The effects of these studies on the survival of patients after lung transplantation will become obvious in the next few years.

After onset of BOS, most studies are pointed at augmenting immunosuppression or at conversion of immunosuppressive medication to try to stop the decline in lung function. Augmented immunosuppression was studied in patients receiving azathioprine as third immunosuppressive agent showing a decline in the rate of progression of obliterative bronchiolitis compared to a group who did not receive augmented immunosuppressive therapy. The efficiency of cytolytic therapy on the course of BOS is variable. This therapy showed a stabilisation in pulmonary function in 5 patients, an improvement in 2 patients and continued to decline in 8 patients.

In the early nineties, the routine immunosuppressive therapy after lung transplantation consisted usually of cyclosporine, azathioprine and prednisolone. After occurrence of BOS, conversion of cyclosporine into tacrolimus in a non-randomised study showed a less progressive decline in lung function. Conversion of azathioprine into mycophenolate mofetil showed also a less progressive decline in lung function and is in general well tolerated. The effect of sirolimus on BOS is still unclear. A study with this immunosuppressive drug showed that a low dosage of sirolimus has a cyclosporine-sparing effect. The precise role of this drug in the treatment of BOS remains unclear, but the cyclosporine-sparing may be helpful to reduce kidney-failure. These results suggest that sirolimus may be indicated as an adjunct to the cyclosporine based immunosuppressive regimens.

Considering the fact that repeated acute rejection-episodes form the most important risk factors for the development of BOS, an increase of immunosuppression in the post-operative period until one year after lung transplantation may be helpful in preventing BOS (cave patients with chronic viral or bacterial infections). After onset of BOS and progression of BOS despite converting a patient to tacrolimus and/or mycophenolate mofetil, utilisation of new immunosuppressive drugs with proven effects in other types of organ transplantation as rescue therapy may be helpful. Therefore compliance of insurance companies with regard to the payment of this often not registered and expensive medication is necessary.
3. Cost-effectiveness of lung transplantation

From the sensitivity analyses in the cost-effectiveness study, it appears that improvement of survival rates, and reduction of the high follow-up costs, are the best possible ways for a positive influence on the cost-effectiveness of the lung transplantation-program. Newly introduced immunosuppressive medicine will be only cost-effective, if they result in a better survival rate and/or decrease the follow-up costs i.e. prevention of complications after lung transplantation. Improving survival rates is possible by prevention of BOS or by improving the treatment of BOS. Additional cost analyses in our program showed that BOS strongly influences the costs of follow-up\(^{30}\). These costs were mainly caused by an increase in the days that patients with BOS spent extra in the hospital. A decrease of the follow-up costs may also be established by a decrease in BOS, and further in prevention of the number of rejections, number of infections or co-morbidity. This may result in preventing expensive hospitalisation or medication. In all future attempts to reduce costs, the effect on survival rates and the follow-up costs should be considered.

Despite the earlier discussed bottlenecks, lung transplantation is nowadays an acceptable treatment with a satisfactory survival and acceptable chances for a reasonable quality of life. Science will continue and develop new methods and therapies to prevent, stabilise or cure diseases in relation to lung transplantation. Prevention of diseases may be found in recognition of diseases in the human genome, for instance in the case of cystic fibrosis. Stabilisation may be found in using new therapies in patients qualifying for lung transplantation and after lung transplantation in the treatment of BOS. Curation of the bottlenecks after lung transplantation may be found in the future in the field of the xenotransplantation or tolerance-induction. Decisions about how far doctors can go in these developments become more ethical decisions requiring a public point of view. The feasibility of these developments depends more and more on costs, which are still relatively high for lung transplantation. Whether the developments in lung transplantation in the next decade(s) will lead to an increased cost-effectiveness of lung transplantation is for the time being unclear. This type of organ transplantation will remain a dynamic subject in the future both in medical science and in the media.

References:

1. Wet op de orgaandonatie 22358, nr 46b vastgesteld op 20 februari 1996