Special Report

Interventional Lung Assist: A New Concept of Protective Ventilation in Bridge to Lung Transplantation

Stefan Fischer,* Marius M. Hoeper,† Thomas Bein,‡ Andre R. Simon,* Jens Gottlieb,† Wilfried Wisser,§ Lorenz Frey,¶ Dirk Van Raemdonck,‖ Tobias Welte,† Axel Haverich,* and Martin Strueber*

On March 22, 2006, the first Interventional Lung Assist (ILA) Consensus Meeting was held in Hannover, Germany, hosted by the Hannover Thoracic Transplant and Cardiac Assist Program at the Hannover Medical School. Leading experts in the field of lung transplantation, respiratory and critical care medicine, lung injury, mechanical ventilation, extracorporeal life support, and oxygenator engineering were formally invited to participate. The main goal was to translate previous clinical experience with the ILA into a consensus for the use of the ILA as a bridge to lung transplantation. *ASAIO Journal* 2008; 54:3–10.

According to the World Health Organization (WHO),[1] lung disease is the third leading cause of death in developed countries. Consequently, the number of patients listed for lung transplantation (LTx) is continuously rising as is the proportion of patients listed for high-urgency (HU) LTx. The proportion of HU transplant procedures has increased from 10% in 2000 to 60% in 2004 (Rahmel A, personal communication, 2005). High-urgency patients often require ventilatory support. This, however, is still seen as a contraindication for LTx by many leading LTx programs, because the reported outcomes after LTx have been poor.

The annual number of lung transplants worldwide has been increasing during the past decade.[2] Although a remarkable increase in the acceptance rate of donor lungs has been noticed,[3] particularly because of widening the selection criteria for lung donors by some major programs,[4] a relative shortage of donor organs still exists. Regarding the waiting list mortality,[5] this situation creates enormous pressure for transplant programs and an urgent need for solutions to enable successful bridging of end-stage lung patients to LTx, including the development of alternative strategies for long-term lung support.

From the *Division of Thoracic and Cardiovascular Surgery, Hannover Thoracic Transplant and Cardiac Assist Program; †Division of Respiratory Medicine, Hannover Medical School; ‡Department of Anesthesiology, Regensburg University Hospital, Germany; §Department of Cardiothoracic Surgery, Vienna Lung Transplant Program, Medical University Vienna, Austria; ¶Department of Anesthesiology, Grosshadern University Hospital, Ludwig Maximilian University, Munich, Germany; and ‖Department of Thoracic Surgery, Leuven Lung Transplant Program, University Hospitals Leuven, Belgium.

Submitted for consideration March 2007; accepted for publication in revised form April 2007.

Presented at First Interventional Lung Assist Consensus Meeting, March 22, 2006, Hannover, Germany.

Reprint Requests: Dr. Martin Strueber, Division of Thoracic and Cardiovascular Surgery, Hannover Thoracic Transplant and Cardiac Assist Program, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany.

DOI: 10.1097/MAT.0b013e318161d6ec

Ventilator-Associated Lung Injury (VALI)

There are two modes of acute respiratory failure: 1) hypoxic/hypocapnic respiratory failure caused by alveolar collapse leading to a ventilation/perfusion mismatch. The main treatment strategy is pressure-controlled ventilation with high-positive end-expiratory pressure (PEEP). 2) hypoxic/hypercapnic respiratory failure caused by respiratory muscle insufficiency leading to alveolar hypoventilation. Primary hypercapnic failure is found in the weaning period after long-term mechanical ventilation. The appropriate treatment is volume application by noninvasive or invasive mechanical ventilation.

Many post-LTx patients suffer from normocapnic/hypocapnic ventilation failure because of alveolar collapse. Welte pointed out that invasive positive-pressure ventilation is the only treatment option in these patients, but it has the potential to damage the lung significantly. Two forms of damage caused by ventilation can be differentiated: biophysical trauma including barotrauma, volutrauma, biochemical trauma, and atelectrauma.

Barotrauma

The concept that high airway pressures in positive-pressure ventilation can cause gross injury has been investigated since the classical study by Macklin in 1939.[6] It was realized that high inspiratory pressure (HIP) is the main reason for complications, such as pneumothorax and pneumomediastinum. However, from findings by Petersen and Baier[7] and Weg *et al.*,[8] it was concluded that absolute airway pressure *per se* does not directly lead to injury.

Volutrauma

Dreyfuss and Saumon[9] postulated that high-volume ventilation leads to regional overinflation, leading to increased microvascular permeability, pulmonary edema, alveolar flooding, and ultimately a reduction in lung distensible volume. Parker *et al.* provided molecular insight into this concept,[10] and Dreyfuss *et al.*[11] showed that albumin sequestration as a marker for pulmonary edema formation correlates with the applied tidal volume. Animals in the HIP/low tidal volume (LOV) group therefore did not develop pulmonary edema.

Biochemical Trauma

In contrast to the above, Ranieri *et al.*[12] demonstrated that high ventilatory volume application is responsible not only for pulmonary edema but also for cytokine sequestration and upregulation of proinflammatory cytokines in the lung.

High-volume/non-PEEP-ventilated animals showed an increase in all proinflammatory parameters considered to be the main mediators in acute respiratory distress syndrome (ARDS). Changing to low volume ventilation reduced the concentration of proinflammatory cytokines.[13] In addition, Imai *et al.*[14] showed a significant increase in cell apoptosis in lung, intestine, and kidneys in animals ventilated with high tidal volumes. These intriguing findings might help to explain why high-volume ventilation often leads to multiorgan failure (MOF).[15,16]

Atelectrauma

Again, Dreyfuss *et al.*[11] observed in animals ventilated with LOVs that atelectasis was much more pronounced in the low-volume ventilation group. This process, called atelectrauma, leads to a repetitive open-close cycle of distal lung units in the ventilated lung with shear forces acting on the epithelial layer and is also responsible for an increase in proinflammatory cytokines and for VALI seen in long-term ventilated patients. Van Kaam *et al.*[17] used a porcine ARDS model of transbronchial administration of *streptococcus* B to study the effects of high- and low-volume ventilation. A major focus of this study was the translocation of infection. High-volume ventilation led to proinflammatory stimulus and to an increase in infectious disease complications.

Conclusions of this discussion: 1) identification of the mode of respiratory failure predicts the mode of ventilation. 2) Positive-pressure ventilation is a significant trigger for VALI mainly in patients with normocapnic (or hypocapnic) respiratory failure. 3) Hypercapnia plays a major role in pulmonary edema development and therefore is involved in the inflammatory response in normocapnic respiratory failure, which leads to apoptosis and fibrotic modifications of the lung. 4) New strategies/devices are necessary to reduce tidal volume, hypercapnia, and inflammation to allow a more protective form of ventilation and, ultimately, improve the clinical outcome.

Clinical Experience with Mechanical Ventilation in Lung Transplant Candidates

Noninvasive ventilatory support (NIPPV) is a useful strategy for bridge to LTx. However, in lung transplant candidates who do not respond to noninvasive ventilatory support, mechanical ventilation is used to improve gas exchange, particularly in the case of rapidly deteriorating lung function, *e.g.*, because of infections. Frey presented three selected cases (listed for LTx) from Munich, all of which developed ventilation-refractory lung failure. In the first candidate, the Novalung (Interventional Lung Assist, ILA, Novalung GmbH, Hechigen, Germany) was used, whereas the other two were supported by venovenous ECMO.

Case 1

A 56-year-old female patient suffering from severe chronic obstructive pulmonary disease (COPD) developed rapid respiratory failure. After 9 days on NIPPV, adequate gas exchange could no longer be achieved, and she had to be mechanically ventilated. Blood gas analysis after 4 days showed a Pa_{O_2}/F_{IO_2} of 110 and a Pa_{CO_2} of 106 mm Hg. The Novalung (ILA) device was implanted but, surprisingly, HU status was denied by EuroTransplant. After 18 days of ILA support the patient developed sepsis and died from MOF.

Case 2

A female patient (44 years) with post-ARDS interstitial fibrosis was mechanically ventilated for 8 weeks, then transferred to the Munich Lung Transplant Program. Blood gas analysis showed: p_{CO_2} 52 mm Hg, p_{O_2} 44 mm Hg and pH 7.23. After futile attempts were made to reduce the ventilatory pressures, she was put on venovenous ECMO. High-urgency status was denied by EuroTransplant. After 43 days of support, ECMO was discontinued because of recurrent septical episodes and no prospects of achieving adequate conditions for transplantation.

Case 3

A 34-year-old-female patient with acute interstitial fibrosis was ventilated for 48 days and had a F_{IO_2}/Pa_{O_2} of 44. She was put on venovenous ECMO support and was accepted for HU LTx. After 18 days on ECMO, LTx was successfully performed.

Bridge to Recovery: The Regensburg Experience

To minimize the risk of ventilation-associated organ dysfunction, the reduction of tidal volume and peak pressure are mandatory, which reflects the concept of protective ventilation. The tidal volume should be 6 ml/kg body weight (BW) in protective ventilation.[18] Bein presented a study from the Regensburg Critical Care Program on ventilated patients (n = 160) with acute lung failure. Although all patients were initially ventilated with a tidal volume of 6 ml/kg, a gradual increase in tidal volume was seen over time.

At the Regensburg University Hospital, a pumpless extracorporeal lung assist device was designed which allows for extracorporeal carbon dioxide elimination during lung protective ventilation. This device is characterized by a low resistance and, therefore, can be perfused by the left ventricular output through an arteriovenous shunt with no additional support by a blood pump.[19] The corresponding commercially available device is the Novalung ILA system.[20]

This device has been used in more than 130 patients at the Regensburg Critical Care Program as a bridge to recovery from acute lung failure, as reported by Bein *et al.*,[21] previously. Briefly, the aim of this retrospective analysis was to examine the effectiveness and complication rate of ILA in patients with severe ARDS and persistent hypoxemic/hypercapnic lung failure.

Between 1996 and 2004, a total of 90 patients were treated with ILA for more than 24 hours. Indications for ILA application were established according to the "slow entry" and "fast entry" criteria described by Lewandowski *et al.*[22] Diagnoses leading to respiratory failure are summarized in **Table 1**. Thirty-seven patients (41%) survived the initial hospital stay which is a lower mortality rate (59%) than expected from the Sequential Organ Failure Assessment (SOFA) Score. Information on survivors and nonsurvivors is listed in **Table 2**.

Oxygenation improvement, carbon dioxide elimination, hemodynamic parameters, and the amount of vasopressor sub-

Table 1. Diagnosis Leading to Acute Respiratory Distress Syndrome

Diagnosis	Percent (n = 90)
Pneumonia	33
Multiple trauma	17
Pancreatitis, peritonitis	12
Sepsis	12
Postsurgery	11
Brain injury	9
Other	6

Table 3. Frequency of Side Effects and Complications (24% of 90 Patients)

Side Effects and Complications	n
Ischemia of lower limb after cannulation (surgical intervention) (amputation in one patient)	7
Cannulation site bleeding	4
Compartment syndrome	5
Bleeding after nonsurgical cannula removal	4
Intracerebral hemorrhage	1
Hemolysis	1

stitution were documented before, as well as 2 and 24 hours after ILA initiation. The ILA led to an acute and moderate increase in arterial oxygenation; hypercapnia was promptly and markedly reversed within 2 hours, which allowed a less aggressive ventilation strategy by reducing tidal volume, PEEP, and peak inspiratory pressure. The incidence of complications was 24% (**Table 3**). Switching from initially 19F cannulae to the currently used 15 or 17F cannulae has resulted in fewer ischemia problems.

Bein suggested an algorithm for lung protection with the use of the ILA (**Figure 1**). In patients who range between ALI and ARDS according to the lung injury score (LIS) of approximately 2.5, and who are ventilated in a lung protective mode for 6–12 hours, an ILA should be implanted if blood gas analysis does not improve (pH <7.25). The underlying idea for this strategy is to prevent progressive deterioration and VALI. Characteristics of the ILA are: 1) very effective CO_2 removal, 2) moderate but statistically significant oxygenation improvement, 3) ease of handling, 4) relatively low costs in comparison with ECMO, 5) long-term setting application (up to 100 days has been reported), 6) lower acceptable Activated coagulation time (ACT) levels than for ECMO.

Options for Bridge to LTx

Mechanical Ventilation Before LTx

The most frequently used approach to bridging acute lung failure patients to recovery or to LTx is the use of noninvasive or even invasive ventilatory support. During the past two decades, positive-pressure ventilation has helped to improve survival in patients with acute lung failure, but VALI remains a significant problem. **Table 4** summarizes the advantages and disadvantages of mechanical ventilation. There is evidence that mechanical ventilation before LTx is a significant risk factor for post-LTx mortality[23] and often leads to MOF.[24] As a consequence, many transplant centers consider mechanical ventilation a contraindication for transplantation with only 3% undergoing LTx finally after being bridged by mechanical ventilation.[25] At the final consensus panel discussion, the following main concerns regarding LTx in ventilated patients were identified: 1) ventilation-associated airway colonization may increase the risk of postoperative pneumonia. 2) Ventilation-associated complications, *e.g.*, sinusitis, thromboembolism, hemodynamic compromise, and others may increase the risk of LTx and negatively impact on the outcome. 3) Prolonged sedation and ventilation lead to muscular wasting with delayed recovery, critical illness polyneuropathy and myopathy, and development of other infection sites such as skin ulceration. 4) Emergency intubation for acute hypoxemia or mechanical resuscitation (cardiopulmonary resuscitation; CPR) may lead to an unclear neurological situation before LTx. 5) Complications of a prolonged artificial airway may lead to post-LTx complications, such as swallowing dysfunction, tracheomalacia, and tracheal stenosis.

Mechanical Ventilation Before LTx: The Hannover Experience

Absolute and relative contraindications in mechanically ventilated HU LTx candidates according to the Hannover Thoracic Transplant Program (HTTP) protocol were presented by Gottlieb and Simon and are depicted in **Table 5**. Patients that show three of the delineated relative or one of the absolute contraindications are not considered to be appropriate LTx candidates.

The HTTP differentiates between three scenarios to evaluate mechanically ventilated patients before LTx (**Table 6**). These scenarios are based on the Hannover experience (n = 750 LTx procedures) as well as on outcomes reported in the literature. According to previous reports, only "scenario C" patients ("unstable" mechanical ventilation) have a significantly reduced post-LTx survival. A retrospective analysis of data from patients with "unstable" pre-LTx mechanical ventilation (scenario C) from January 2000 to September 2005 at the HTTP revealed an increase in the proportion of patients with "unstable" mechanical ventilation before LTx from 5% to 17%. Of these 39

Table 2. Comparison of Survivors and Nonsurvivors

Variable	All Patients (n = 90), avg (range)	Survivors (n = 37), avg (range)	Nonsurvivors (n = 53), avg (range)	*p*
Age (yr)	44 (26–59)	32 (22–49)	49 (33–60)	0.009
BMI	25.4 (23–30)	24.1 (23–26)	27.7 (24–31)	0.001
Ventilation before iLA (d)	3 (1–10)	1 (1–8)	4 (1–14)	0.034
SOFA score	11 (8–13)	10 (7–11)	11 (8–14)	0.016
Lung injury score	3.5 (3.5–3.8)	3.7 (3.3–3.8)	3.5 (3.3–3.8)	NS

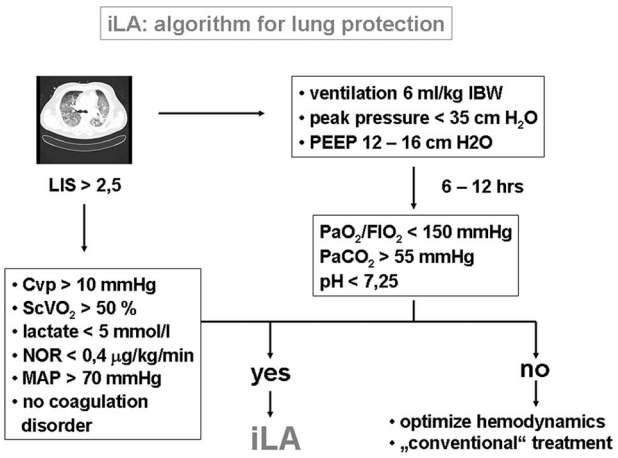

Figure 1. The Regensburg algorithm for lung protection with the interventional lung assist (ILA).

scenario C patients (19 women, 20 men), 35% received additional extracorporeal gas exchange. The 1-year survival in the total cohort was 45%.

ECMO: The Vienna Experience

ECMO was introduced as a clinical application of extra pulmonary lung assistance in 1972 and, until recently, was the only treatment option for patients with ventilation-refractory lung failure. Although occasionally successful as a bridge to recovery or transplant,[33] ECMO is associated with a range of severe complications.[34] Potential treatment time with ECMO is very limited, and reported survival of patients that undergo LTx off ECMO is extremely poor with a 1-year survival of 40% or less.[35]

Wisser focused on peri- and postoperative management of lung transplant patients in which ECMO has been applied electively. Three main indications for the use of ECMO are: first, as a rescue therapy after LTx (primary organ failure); second, as a bridge to transplantation; and last as a protective concept intraoperatively or intra- and postoperatively during transplantation, as previously reported by the Vienna group in patients with pulmonary hypertension (PH).[36]

According to the Vienna experience, intraoperative elective application of ECMO or cardiopulmonary bypass provides hemodynamically stable conditions throughout the implantation period of both lungs and allows for controlled reperfusion of the grafts. This strategy prevents the so-called "first lung syndrome," which occurs because of hyperperfusion of the first implanted lung during implantation of the second lung.

Table 4. Advantages and Disadvantages of Mechanical Ventilation

Promechanical ventilation
To support ventilation during muscle fatigue
To restore adequate gas exchange
Contra mechanical ventilation
Lung injury (VALI) and remote organ failure
Atelectasis
Pneumonia
Muscle fatigue

Table 5. Contraindications for LTx in Ventilated Patients

Absolute contraindications
Unclear neurological condition
Extrapulmonary organ failure (isolated LTx)
Severe sepsis/septic shock
Active malignancy
Morbid obesity (BMI >32)
Relative contraindications
Burkholderia cepacia colonization without effective antibiotic coverage
Age >65 yr
Sigmoid diverticulosis
Systemic diseases with severe extrapulmonary impairment
Severe muscular deconditioning
BMI >27 kg/m^2
Coronary artery disease
Extracorporeal membrane oxygenation (ECMO)
Significant degree of osteoporosis
Redo-LTx
"Unstable" ventilation
Hemodynamic instability

The commonly seen right ventricular hypertrophy in patients with PH may add to this phenomenon.

Briefly, between 1999 and 2001, 17 patients with PH underwent bilateral LTx at the Vienna Lung Transplant Program. Femoral venoarterial ECMO support was set up. The flow was 50% of predicted cardiac output and there was prolonged ECMO support for the first 8 hours to allow protective ventilation and prevent overflow to the lungs in the early period after transplantation. Weaning was initialized after 4 hours, ECMO stepwise reduced, and after 8 hours explanted. This experience resulted in excellent initial organ function. Underlying mechanisms may include the concept of controlled reperfusion combined with protective ventilation.

In another study at the Vienna LTx Program, between 2001 and 2006 ECMO was used in a total of 146 of 308 LTxs (247 bilateral lung transplantation (BLTX), 59 single lung transplantation (SLTX), 2 heart-lung transplantation (HLTX)). In 77 patients intraoperative and in 54 patients intra- and postoperative support was applied. The complications that occurred are

Table 6. Pre-LTx "Ventilation Scenarios"

Scenario A
Noninvasive ventilation
Success depends on the underlying disease (COPD > cF ≫ iPF)
Chronic *vs.* acute on chronic
Fewer infectious complications
1 yr survival >70%[26]
Scenario B
"Stable" mechanical ventilation
Frequently long-term tracheostomy, patient is ambulatory
Intermittent and/or partial respiratory support
No continuous sedation
Extrapulmonary organ failure uncommon
1 yr survival 70%–87%[27–29]
Scenario C
"Unstable" mechanical ventilation (most common situation)
Extrapulmonary organ failure common
Continuous sedation: neurological status unclear
1 yr survival 25%–61%*[30–32]

* The survival rates differ widely because most of these studies did not specifically distinguish between stable and unstable patients.

Table 7. ECMO-Related Complications

Complications	n
Thrombosis at lower extremity cannulation site	13
Lymph fistula	9
Vascular injuries	4
Intracerebral bleeding	2
Pericardial tamponade	1
Bleeding requiring surgical reexploration	3
Compartment syndrome, fasciotomy	1

listed in **Table 7**. Three-month and 1-year survival curves are shown in **Figures 2** and **3**.

Bridge to LTx With Extracorporeal Ventilation: The Hannover Experience

Fischer presented the Hannover experience on the first application of ILA (**Figure 4**) as a bridge to LTx in a prospective observational study.[37] Briefly, between March 2003 and March 2005, 176 LTx were performed at the HTTP including 54 HU LTx. Approximately 25% of HU listed patients at the HTTP require invasive mechanical ventilatory support. Twelve patients meeting HU criteria, who developed severe ventilation-refractory hypercapnia and respiratory acidosis despite maximal conventional ventilatory support, received ILA implantation in an arterialvenous femorofemoral position.

Brief summary of findings: 1) duration of ILA support was 15 ± 8 days (4–32 days). Interventional Lung Assist was explanted in all cases at the end of the LTx procedure. 2) ACT was 160–180 seconds after injection of a bolus of 10,000 IU heparin followed by continuous infusion. 3) Three patients required change of the device because of accidental clotting levels at ACT <150 seconds. 4) Four patients died from MOF (two before LTx, two on day 16 and day 30, respectively, after successful bridging to LTx with ILA). 5) Six hours after ILA implantation $Paco_2$ levels decreased and pH increased significantly and remained stable. Further data are summarized in **Table 8**. 6) Only a slight, but statistically insignificant rise in oxygenation was noted. 7) All patients were hemodynamically stable throughout the bridging process.

The Hannover study showed the applicability of the ILA as a bridge to LTx in patients with end-stage lung failure who could not be sufficiently supported by mechanical ventilation.

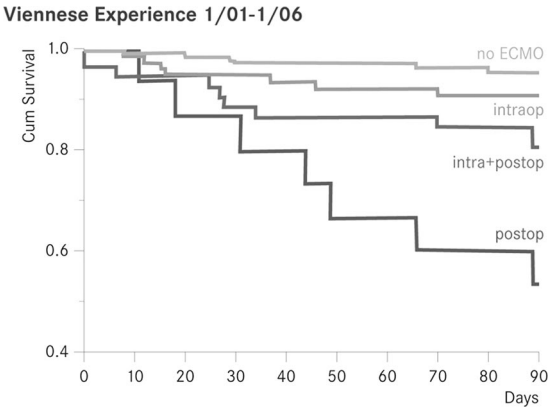

Figure 2. Three-month survival curve of lung transplantation (LTx) patients with or without ECMO support (intra + postop, transplant procedure performed on ECMO intraoperatively plus prolonged postoperative ECMO support, for allowing prolonged controlled reperfusion; postop, postoperative use of ECMO because of severe initial graft failure after exploiting all other therapeutical strategies).

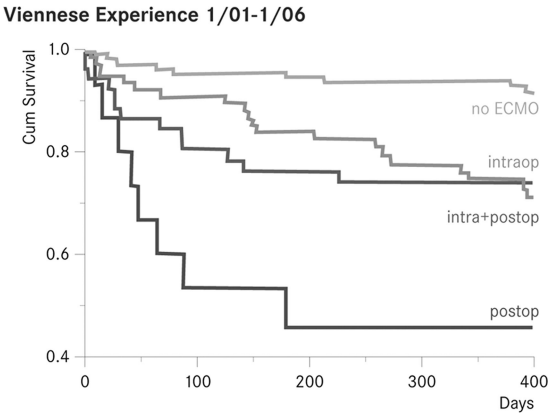

Figure 3. One-year survival curve of LTx patients with or without ECMO support (intra + postop, transplant procedure performed on ECMO intraoperatively plus prolonged postoperative ECMO support, for allowing prolonged controlled reperfusion; postop, postoperative use of ECMO because of severe initial graft failure after exploiting all other therapeutical strategies).

Alternative Strategies: Controlled Reperfusion of Nonheart Beating Donor (NHBD) Lungs

Despite improvements in organ preservation, reperfusion injury remain a major cause of morbidity and mortality after LTx. According to International Society for Heart and Lung Transplantation Registry, graft failure is responsible for approximately 30% of deaths during the first 30 days after LTx.[39] Bhabra *et al.*[40] first demonstrated in a rat model the need for lower initial reperfusion pressure to limit ischemia reperfusion injury. Van Raemdonck stated that controlled ventilation of a cold ischemic lung also is important. De Perrot *et al.*[41] ameliorated ischemic reperfusion injury in a rat lung transplant

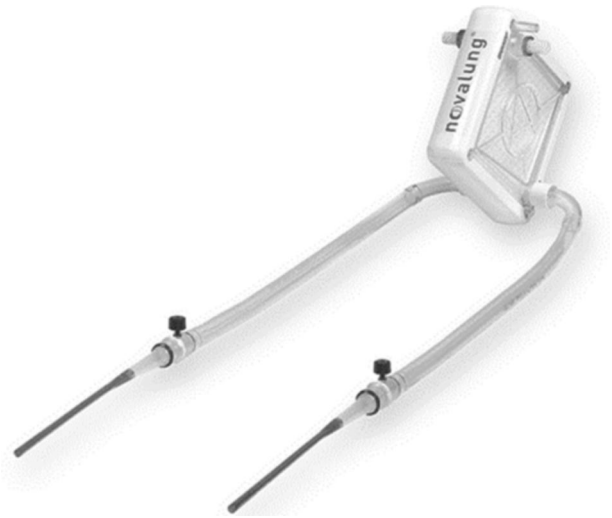

Figure 4. The Novalung ILA membrane ventilator.

Table 8. Changes in Blood Gases, Hemodynamics, and the Ventilatory Regimen[38]

	Before iLA BL (n = 12)	After iLA Implantation			
			24 ± 5 h (n = 12)	72 ± 6 h (n = 10)	7 ± 0.5 d (n = 7)
MAP (mm Hg)	72 ± 8	74 ± 7	78 ± 8	77 ± 6	75 ± 5
Pa_{O_2} (mm Hg)	71 ± 27	83 ± 17	124 ± 42	113 ± 28	114 ± 36
Pa_{CO_2} (mm Hg)	128 ± 42	52 ± 5	51 ± 33	48 ± 8	46± 5
pH	7.121 ± 0.1	7.344 ± 0.1	7.378 ± 0.2	7.368 ± 0.1	7.392 ± 0.1
P_{O_2}/F_{IO_2}	135 ± 33	150 ± 24	168 ± 42	145 ± 24	139 ± 22
Peak VP (mm Hg)	45 ± 5	45 ± 5	32 ± 3	30 ± 5	28 ± 6
PEEP (mm Hg)	13 ± 1	13 ± 1	6 ± 1	5 ± 2	6 ± 1

iLA, interventional lung assist device; BL, baseline before interventional lung assist device implantation; MAP, mean arterial blood pressure; F_{IO_2}, fraction of inspired oxygen; VP, ventilatory pressure; PEEP, positive end-expiratory pressure.

model by ventilating the ischemic graft in a controlled ventilatory mode (**Table 9**).

Van Raemdonck dedicated the second part of his talk to the topic of *ex vivo* lung perfusion. Fewer than 25% of all available multiorgan donors have lungs suitable for transplantation.[43] Alternative sources such as organs from so-called NHBD might increase the potential donor pool. Steen *et al.*[44] performed the first successful single LTx with a lung from an NHBD after a warm ischemic interval of 65 minutes. In a porcine *ex vivo* model, lungs from NHBDs were transplanted into healthy recipient pigs and retained normal function during a 24-hour observation period.[45] Rega *et al.*[46] demonstrated that interim *ex vivo* evaluation of NHBD lungs is a valid and safe method to assess graft function.

Van Raemdonck and his group hypothesized that, if the quality of inferior donor lungs could be improved outside the donor, some of them might still become suitable for transplantation. They performed a feasibility study[47] in which human lungs rejected for transplantation were considered for *ex vivo* reperfusion. Starting in 2002, 20 double lungs in total were preserved, explanted, packed, and stored in an ice box until preparation. The stored lung was unpacked and cannulated. Blood from a reservoir passed an oxygenator used as a deoxygenator by sending nitrogen through the membranes. The deoxygenated blood passed a leukocyte filter and then entered a plastic box with the (heart-)lung block that was ventilated with 50% oxygen. Finally, the oxygenated blood flowed back. Assessments were performed on the inflow and outflow lines. Controlled reperfusion of the lung was performed. Composition of the reperfusion solution: Steen solution, deleukocyted red blood cell (15% hct), $NaHCO_3$ (0.8 M) 45 ml/L, $CaCl_2$ 10 mg/ml, heparin 10.000 IU/L, nitroglycerine 2 mg/L, Tienam 500 mg. To limit alveolar injury from mechanical shear stress the lung was ventilated in a controlled manner.

Table 9. Recommendations Published by de Perrot[42] for Reperfusion and Reventilation after Lung Transplantation

Controlled reperfusion
Low PA pressure
Slowly releasing PA clamp over 10-min period
Reperfusion on CBP
Controlled reventilation
Limited peak airway pressure 20–25 cm H_2O
F_{IO_2} <50%
PEEP 5 cm H_2O

The following graft parameters were measured during 2 hours: 1) pulmonary vascular resistance (dynes × sec × cm^{-5}), pulmonary arterial flow (PAF) L/min, mean arterial pressure (MAP) and pulmonary arterial pressure (PAP) cm H_2O, oxygenation index: P_{O_2}/F_{IO_2} (mm Hg), wet-to-dry weight ratio. During the 2-hour period, there was no significant change in the measured parameters, meaning that the *ex vivo* system was not deteriorating. Results of this study indicated that it is technically feasible to reperfuse lungs for at least 2 hours; the system is stable for at least 2 hours; the system might serve as a model for further studies.

As a perspective, *ex vivo* lung perfusion may be a method to: 1) predict graft function in NHBDs I–II, 2) reassess graft function in HBD, 3) optimize inferior quality of lungs, 4) prolong the cold ischemic interval, 5) condition lungs against early and long-term graft dysfunction.

Perspectives

Extracorporeal ventilation in LTx brings new light to the concept of protective ventilation. Experimental and first clinical studies were able to show a potential role and benefit of extracorporeal ventilation, although it has to be underscored that controlled data are currently not available. The major indications seem to be bridge to transplantation, bridge to recovery in patients with primary graft dysfunction, and controlled reperfusion during transplantation, which requires the additional use of a blood pump. Future studies therefore have to be carefully designed, which may be reasonably performable in a multi-institutional setting only given the relatively small number of patients.

Fischer presented the outline of a phase I clinical investigation of safety and efficacy of the ILA as a bridge to lung transplant, which currently is being performed at the University of Toronto, Canada in a single-center trial. This study evaluates the safety of the Novalung (ILA) by collecting performance data on the device during extracorporeal lung support and by calculating the complication and failure rates observed with the device.

Appendix: Important Questions and Answers

Bridge to Lung Transplantation: What are the Options?

Patients with end-stage lung failure on the waiting list for transplantation can be treated with intermittent and long-term

noninvasive ventilatory support using a mask or a helmet. In severe cases, mechanical ventilation is an additional option, but it is well known to be a risk factor for post-LTx mortality and should therefore be avoided if possible. If mechanical ventilation fails, extracorporeal gas exchange such as ECMO or, more recently the use of lung assist devices (*e.g.*, Novalung) can be considered for bridge to lung transplantation in selected patients.

What is the Role of Extracorporeal Support Before LTx? What Are the Entry Criteria?

The Hannover study and additional case reports suggest that patients with pre-LTx ventilation-refractory hypercapnic lung failure can be supported with pumpless extracorporeal gas exchange and successfully bridged either to recovery or to transplantation. The contraindications for this type of support are severe arteriosclerosis and hemodynamic instability/shock. In patients with severe hypoxic failure, however, a pump-driven mode such as ECMO might be required. Extracorporeal gas exchange has been used for bridge to lung transplantation even in patients with systemic infection. Mechanical ventilation and/or extracorporeal gas exchange *per se* is no longer a contraindication for lung transplantation.

Are There Different Indications for ECMO and ILA?

Unlike ECMO, ILA is a pumpless device and a stable hemodynamic condition of the patient is a prerequisite. It removes carbon dioxide and thereby efficiently reverses hypercapnia. Hypoxemia is certainly not the primary indication, although the Regensburg group presented data on significantly improved oxygenation with the Novalung. The Hannover group, however, was not able to support this based on their experience.

What is the Success Rate of Different Bridging Strategies (MV, ILA, ECMO) in HU Lung Transplant Candidates?

There are no clinical data available comparing the outcome of ILA *versus* ECMO before lung transplantation. Mechanical ventilation before lung transplantation has been shown by the ISHLT Registry[2] to be a significant risk factor for postlung transplantation mortality.

Where is the Cutoff Point Between Protective Ventilation and Injurious Ventilation?

A clear cutoff point has not yet been defined. Reducing the invasiveness of mechanical ventilation by applying reduced tidal volume, reduced PEEP, and PIP as shown by the ARDS-Net Study significantly reduced mortality in mechanically ventilated patients, but some suspect that any positive pressure applied to the lung might be harmful.

What is the Role of ILA in Acute Graft Failure After LTx?

The role of ILA in acute lung failure after LTx has yet to be studied. However, the Toronto Lung Transplant Program has recently successfully used the Novalung ILA in a venoarterial mode supported by a centrifugal pump in a patient with primary graft dysfunction after single lung transplantation (Keshavjee S, personal communication 2006).

Is There an Indication for ILA Use in Nonintubated Patients? What Are the Criteria?

Although the application of ILA in nonintubated awake patients is an intriguing idea, it has not as yet been performed for bridge to lung transplantation. For this reason, no clinical criteria have been defined, and no evidence is available. This approach merits future investigation.

Acknowledgments

The members of the International iLA Study Group acknowledge the professional assistance in coordinating this manuscript by Ms. Maike Haas, Research Assistant at the Hannover Medical School.

References

1. World Health Organization: *The World Heath Report 1998. Life in the 21st Century. A Vision for All*. Geneva, World Health Organization, 1998.
2. Trulock EP, Edwards LB, Taylor DO, *et al*: Registry of the International Society for Heart and Lung Transplantation: Twenty-third official adult lung and heart-lung transplantation report—2006. *J Heart Lung Transplant* 25: 880–892, 2006.
3. de Perrot M, Bonser RS, Dark J, *et al*: ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction. Part III: Donor-related risk factors and markers. *J Heart Lung Transplant* 24: 1460–1467, 2005.
4. de Perrot M, Weder W, Patterson GA, Keshavjee S: Strategies to increase limited donor resources. *Eur Respir J* 23: 477–482, 2004.
5. Hosenpud JD, Bennett LE, Keck BM, *et al*: Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet* 351: 24–27, 1998.
6. Macklin CC: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. *Arch Intern Med* 64: 913–926, 1939.
7. Petersen GW, Baier H: Incidence of pulmonary barotrauma in a medical ICU. *Crit Care Med* 11: 67–69, 1983.
8. Weg JG, Anzueto A, Balk RA, *et al*: The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. *N Engl J Med* 338: 341–346, 1998.
9. Dreyfuss D, Saumon G: Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 157: 294–323, 1998.
10. Parker JC, Ivey CL, Tucker JA: Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. *J Appl Physiol* 84: 1113–1118, 1998.
11. Dreyfuss, D, Soler, P, Basset, G *et al*: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive endexpiratory pressure. *Am Rev Respir Dis* 137: 1159–1164, 1988.
12. Ranieri VM, Giunta F, Suter PM, Slutsky AS: Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 284: 43–44, 2000.
13. Stuber F, Wrigge H, Schroeder S, *et al*: Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. *Intensive Care Med* 28: 834–841, 2002.
14. Imai Y, Parodo J, Kajikawa O, *et al*: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 289: 2104–2112, 2003.
15. Vincent JL, Akca S, De Mendonca A, *et al*: SOFA Working Group: Sequential organ failure assessment. The epidemiology of acute respiratory failure in critically ill patients. *Chest* 121: 1602–1609, 2002.
16. Brochard L, Roudot-Thoraval F, Roupie E, *et al*: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial

Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 158: 1831–1838, 1998.
17. van Kaam AH, Lachmann RA, Herting E, *et al*: Reducing atelectasis attenuates bacterial growth and translocation in experimental pneumonia. *Am J Respir Crit Care Med* 169: 1046–1053, 2004.
18. Villar J, Kacmarek RM, Hedenstierna G: From ventilator-induced lung injury to physician-induced lung injury: Why the reluctance to use small tidal volumes? *Acta Anaesthesiol Scand* 48: 267–271, 2004.
19. Reng M, Philipp A, Kaiser M, *et al*: Pumpless extracorporeal lung assist and adult respiratory distress syndrome. *Lancet* 356: 219–220, 2000.
20. Fischer S, Strueber M: The Novalung ILA membrane ventilator: Technical aspects (CTSNet/Thoracic Portal). Available at: http://www.ctsnet.org/sections/thoracic/newtechnology/article-9.html. Accessed 2006.
21. Bein T, Weber F, Philipp A, *et al*: A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 34: 1372–1377, 2006.
22. Lewandowski K, Rossaint R, Pappert D, *et al*: High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. *Intensive Care Med* 23: 819–835, 1997.
23. Smits JM, Mertens BJ, Van Houwelingen HC, *et al*: Predictors of lung transplant survival in eurotransplant. *Am J Transplant* 3: 1400–1406, 2003.
24. Imai Y, Parodo J, Kajikawa O, *et al*: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 289: 2104–2112, 2003.
25. Taylor DO, Edwards LB, Boucek MM, *et al*: Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult heart transplant report–2005. *J Heart Lung Transplant* 24: 945–955, 2005.
26. Madden BP, Kariyawasam H, Siddiqi AJ, *et al*: Noninvasive ventilation in cystic fibrosis patients with acute or chronic respiratory failure. *Eur Respir J* 19: 310–313, 2002.
27. Massard G, Shennib H, Metras D, *et al*: Double-lung transplantation in mechanically ventilated patients with cystic fibrosis. *Ann Thorac Surg* 55: 1087–1091, 1993.
28. Baz MA, Palmer SM, Staples ED, *et al*: Lung transplantation after long-term mechanical ventilation: Results and 1-year follow-up. *Chest* 119: 224–227, 2001.
29. Bartz RR, Love RB, Leverson GE, *et al*: Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. *J Heart Lung Transplant* 22: 433–438, 2003.
30. Niedermeyer J, Hoffmeyer F, Strüber M, *et al*: Lungentransplantation bei beatmeten Patienten. *Intensivmed* 36: 183–189, 1999.
31. Meyers BF, Lynch JP, Battafarano RJ, *et al*: Lung transplantation is warranted for stable, ventilator-dependent recipients. *Ann Thorac Surg* 70: 1675–1678, 2000.
32. Adams DH, Cochrane AD, Khaghani A, *et al*: Retransplantation in heart-lung recipients with obliterative bronchiolitis. *J Thorac Cardiovasc Surg* 107: 450–459, 1994.
33. Jurmann MJ, Haverich A, Demertzis S, *et al*: Extracorporeal membrane oxygenation as a bridge to lung transplantation. *Eur J Cardiothorac Surg* 5: 94–97, 1991.
34. Fischer S, Bohn D, Rycus P, *et al*: Extracorporeal membrane oxygenation (ECMO) for primary graft dysfunction (PGD) after lung transplantation: Analysis of the Extracorporeal Life Support Organization (ELSO) Registry. *J Heart Lung Transplant* 25(suppl 2): A231, 2006.
35. Fischer S, Struber M, Haverich A: [Current status of lung transplantation: patients, indications, techniques and outcome]. *Med Klin (Munich)* 97: 137–143, 2002.
36. Wisser W, Marta G, Senbaklavaci O, *et al*: BLTX with intra- and postoperatively prolonged ECMO in patients with pulmonary hypertension: Beneficial effect on initial organ function. *J Heart Lung Transplant* 20: 224–225, 2001.
37. Fischer S, Simon AR, Welte T, *et al*: Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. *J Thorac Cardiovasc Surg* 131: 719–723, 2006.
38. Matheis G: New technologies for respiratory assist. *Perfusion* 18: 245–251, 2003.
39. Hertz MI, Mohacsi PJ, Taylor DO, *et al*: The registry of the International Society for Heart and Lung Transplantation: introduction to the Twentieth Annual Reports—2003. *J Heart Lung Transplant* 22: 610–672, 2003.
40. Bhabra MS, Hopkinson DN, Shaw TE, *et al*: Controlled reperfusion protects lung grafts during a transient early increase in permeability. *Ann Thorac Surg* 65: 187–192, 1998.
41. de Perrot M, Imai Y, Volgyesi GA, *et al*: Effect of ventilator-induced lung injury on the development of reperfusion injury in a rat lung transplant model. *J Thorac Cardiovasc Surg* 124: 1137–1144, 2002.
42. de Perrot M, Keshavjee S: Lung preservation. *Semin Thorac Cardiovasc Surg* 16: 300–308, 2004.
43. Egan TM, Boychuk JE, Rosato K, *et al*: Whence the lungs? A study to assess suitability of donor lungs for transplantation. *Transplantation* 53: 420–422, 1992.
44. Steen S, Sjoberg T, Pierre L, *et al*: Transplantation of lungs from a non-heart-beating donor. *Lancet* 357: 825–829, 2001.
45. Steen S, Liao Q, Wierup PN, *et al*: Transplantation of lungs from non-heart-beating donors after functional assessment ex vivo. *Ann Thorac Surg* 76: 244–252, 2003.
46. Rega FR, Jannis NC, Verleden GM, *et al*: Long-term preservation with interim evaluation of lungs from a non-heart-beating donor after a warm ischemic interval of 90 minutes. *Ann Surg* 238: 782–792, 2003.
47. Neyrinck A, Rega F, Jannis N, *et al*: Ex vivo reperfusion of human lungs declined for transplantation: A novel approach to alleviate donor organ shortage? (abstract) *J Heart Lung Transplant* 23: S172–S173, 2004.