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Extracorporeal Lung Support Technologies - Bridge to Recovery and Bridge to Lung Transplantation in Adult Patients

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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List of Abbreviations

ARDS	Acute respiratory distress syndrome
CESAR Trial	Conventional Ventilation or ECMO for Sever Adult Respiratory Failure
COPD	Chronic obstructive pulmonary disease
ECMO	Extracorporeal membrane oxygenator
FiO_2	Fraction of inspired oxygen
HIMOX	Highly integrated membrane oxygenator
H-LTx	Heart and lung transplantation
IVOX	Intravascular oxygenator
LTx	Lung transplantation
MAP	Mean arterial pressure
MOF	Multiple organ failure
MV	Minute ventilation
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PEEP	Positive end expiratory pressure
PGD	Primary graft dysfunction
V_T	Tidal volume

Executive Summary

For cases of acute respiratory distress syndrome (ARDS) and progressive chronic respiratory failure, the first choice or treatment is mechanical ventilation. For decades, this method has been used to support critically ill patients in respiratory failure. Despite its life-saving potential, however, several experimental and clinical studies have suggested that ventilator-induced lung injury can adversely affect the lungs and patient outcomes. Current opinion is that by reducing the pressure and volume of gas delivered to the lungs during mechanical ventilation, the stress applied to the lungs is eased, enabling them to rest and recover. In addition, mechanical ventilation may fail to provide adequate gas exchange, thus patients may suffer from severe hypoxia and hypercapnea. For these reasons, extracorporeal lung support technologies may play an important role in the clinical management of patients with lung failure, allowing not only the transfer of oxygen and carbon dioxide (CO_2) but also buying the lungs the time needed to rest and heal.

Objective

The objective of this analysis was to assess the effectiveness, safety, and cost-effectiveness of extracorporeal lung support technologies in the improvement of pulmonary gas exchange and the survival of adult patients with acute pulmonary failure and those with end-stage chronic progressive lung disease as a bridge to lung transplantation (LTx).The application of these technologies in primary graft dysfunction (PGD) after LTx is beyond the scope of this review and is not discussed.

Clinical Applications of Extracorporeal Lung Support

Extracorporeal lung support technologies [i.e., Interventional Lung Assist (ILA) and extracorporeal membrane oxygenation (ECMO)] have been advocated for use in the treatment of patients with respiratory failure. These techniques do not treat the underlying lung condition; rather, they improve gas exchange while enabling the implantation of a protective ventilation strategy to prevent further damage to the lung tissues imposed by the ventilator. As such, extracorporeal lung support technologies have been used in three major lung failure case types:

1) As a bridge to recovery in acute lung failure – for patients with injured or diseased lungs to give their lungs time to heal and regain normal physiologic function.
2) As a bridge to LTx – for patients with irreversible end stage lung disease requiring LTx.
3) As a bridge to recovery after LTx – used as lung support for patients with PGD or severe hypoxemia.

Ex-Vivo Lung Perfusion and Assessment

Recently, the evaluation and reconditioning of donor lungs *ex-vivo* has been introduced into clinical practice as a method of improving the rate of donor lung utilization. Generally, about 15% to 20% of donor lungs are suitable for LTx, but these figures may increase with the use of *ex-vivo* lung perfusion. The *ex-vivo* evaluation and reconditioning of donor lungs is currently performed at the Toronto General Hospital (TGH) and preliminary results have been encouraging (Personal communication, clinical expert, December 17, 2009). If its effectiveness is confirmed, the use of the technique could lead to further expansion of donor organ pools and improvements in post-LTx outcomes.

Extracorporeal Lung support Technologies

ECMO

The ECMO system consists of a centrifugal pump, a membrane oxygenator, inlet and outlet cannulas, and tubing. The exchange of oxygen and CO_2 then takes place in the oxygenator, which delivers the reoxygenated blood back into one of the patient's veins or arteries. Additional ports may be added for haemodialysis or ultrafiltration.

Two different techniques may be used to introduce ECMO: venoarterial and venovenous. In the venoarterial technique, cannulation is through either the femoral artery and the femoral vein, or through the carotid artery and the internal jugular vein. In the venovenous technique cannulation is through both femoral veins or a femoral vein and internal jugular vein; one cannula acts as inflow or arterial line, and the other as an outflow or venous line. Venovenous ECMO will not provide adequate support if a patient has pulmonary hypertension or right heart failure. Problems associated with cannulation during the procedure include bleeding around the cannulation site and limb ischemia distal to the cannulation site.

ILA

Interventional Lung Assist (ILA) is used to remove excess CO_2 from the blood of patients in respiratory failure. The system is characterized by a novel, low-resistance gas exchange device with a diffusion membrane composed of polymethylpentene (PMP) fibres. These fibres are woven into a complex configuration that maximizes the exchange of oxygen and CO_2 by simple diffusion. The system is also designed to operate without the help of an external pump, though one can be added if higher blood flow is required. The device is then applied across an arteriovenous shunt between the femoral artery and femoral vein. Depending on the size of the arterial cannula used and the mean systemic arterial pressure, a blood flow of up to 2.5 L/min can be achieved (up to 5.5 L/min with an external pump). The cannulation is performed after intravenous administration of heparin.

Recently, the first commercially available extracorporeal membrane ventilator (NovaLung GmbH, Hechingen, Germany) was approved for clinical use by Health Canada for patients in respiratory failure. The system has been used in more than 2,000 patients with various indications in Europe, and was used for the first time in North America at the Toronto General Hospital in 2006.

Evidence-Based Analysis

The research questions addressed in this report are:

1. Does ILA/ECMO facilitate gas exchange in the lungs of patients with severe respiratory failure?
2. Does ILA/ECMO improve the survival rate of patients with respiratory failure caused by a range of underlying conditions including patients awaiting LTx?
3. What are the possible serious adverse events associated with ILA/ECMO therapy?

To address these questions, a systematic literature search was performed on September 28, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to September 28, 2008. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Studies in which ILA/ECMO was used as a bridge to recovery or bridge to LTx
- Studies containing information relevant to the effectiveness and safety of the procedure
- Studies including at least five patients

Exclusion Criteria

- Studies reporting the use of ILA/ECMO for inter-hospital transfers of critically ill patients
- Studies reporting the use of ILA/ECMO in patients during or after LTx
- Animal or laboratory studies
- Case reports

Outcomes of Interest

- Reduction in partial pressure of CO_2
- Correction of respiratory acidosis
- Improvement in partial pressure of oxygen
- Improvement in patient survival
- Frequency and severity of adverse events

The search yielded 107 citations in Medline and 107 citations in EMBASE. After reviewing the information provided in the titles and abstracts, eight citations were found to meet the study inclusion criteria. One study was then excluded because of an overlap in the study population with a previous study. Reference checking did not produce any additional studies for inclusion. Seven case series studies, all conducted in Germany, were thus included in this review (see Table 1).

Also included is the recently published CESAR trial, a multicentre RCT in the UK in which ECMO was compared with conventional intensive care management. The results of the CESAR trial were published when this review was initiated. In the absence of any other recent RCT on ECMO, the results of this trial were considered for this assessment and no further searches were conducted. A literature search was then conducted for application of ECMO as bridge to LTx patients (January, 1, 2005 to current). A total of 127 citations on this topic were identified and reviewed but none were found to have examined the use of ECMO as bridge to LTx.

Quality of Evidence

To grade the quality of evidence, the grading system formulated by the GRADE working group and adopted by MAS was applied. The GRADE system classifies the quality of a body of evidence as high, moderate, low, or very low according to four key elements: study design, study quality, consistency across studies, and directness.

Results

Trials on ILA

Of the seven studies identified, six involved patients with ARDS caused by a range of underlying conditions; the seventh included only patients awaiting LTx. All studies reported the rate of gas exchange and respiratory mechanics before ILA and for up to 7 days of ILA therapy. Four studies reported the means and standard deviations of blood gas transfer and arterial blood pH, which were used for meta-analysis.

Fischer et al. reported their first experience on the use of ILA as a bridge to LTx. In their study, 12 patients at high urgency status for LTx, who also had severe ventilation refractory hypercapnea and respiratory acidosis, were connected to ILA prior to LTx. Seven patients had a systemic infection or sepsis prior to ILA insertion. Six hours after initiation of ILA, the partial pressure of CO_2 in arterial blood significantly decreased ($P < .05$) and arterial blood pH significantly improved ($P < .05$) and remained stable for one week (last time point reported). The partial pressure of oxygen in arterial blood improved from 71 mmHg to 83 mmHg 6 hours after insertion of ILA. The ratio of PaO_2/FiO_2 improved from 135 at baseline to 168 at 24 hours after insertion of ILA but returned to baseline values in the following week.

Trials on ECMO

The UK-based CESAR trial was conducted to assess the effectiveness and cost of ECMO therapy for severe, acute respiratory failure. The trial protocol were published in 2006 and details of the methods used for the economic evaluation were published in 2008. The study itself was a pragmatic trial (similar to a UK trial of neonatal ECMO), in which best standard practice was compared with an ECMO protocol. The trial involved 180 patients with acute but potentially reversible respiratory failure, with each also having a Murray score of ≥ 3.0 or uncompensated hypercapnea at a pH of < 7.2. Enrolled patients were randomized in a 1:1 ratio to receive either conventional ventilation treatment or ECMO while on ventilator. Conventional management included intermittent positive pressure ventilation, high frequency oscillatory ventilation, or both. As a pragmatic trial, a specific management protocol was not followed; rather the treatment centres were advised to follow a low volume low pressure ventilation strategy. A tidal volume of 4 to 8 mL/kg body weight and a plateau pressure of < 30 cm H_2O were recommended.

Conclusions

ILA

Bridge to recovery

- No RCTs or observational studies compared ILA to other treatment modalities.
- Case series have shown that ILA therapy results in significant CO_2 removal from arterial blood and correction of respiratory acidosis, as well as an improvement in oxygen transfer.
- ILA therapy enabled a lowering of respiratory settings to protect the lungs without causing a negative impact on arterial blood CO_2 and arterial blood pH.
- The impact of ILA on patient long-term survival cannot be determined through the studies reviewed.
- In-hospital mortality across studies ranged from 20% to 65%.
- Ischemic complications were the most frequent adverse events following ILA therapy.
- Leg amputation is a rare but possible outcome of ILA therapy, having occurred in about 0.9% of patients in these case series. New techniques involving the insertion of additional cannula into the femoral artery to perfuse the leg may lower this rate.

Bridge to LTx

- The results of one case series (n=12) showed that ILA effectively removes CO_2 from arterial blood and corrects respiratory acidosis in patients with ventilation refractory hypercapnea awaiting a LTx
- Eight of the 12 patients (67%) awaiting a LTx were successfully transplanted and one-year survival for those transplanted was 80%

Since all studies are case series, the grade of the evidence for these observations is classified as “LOW”.

ECMO

Bridge to recovery

Based on the results of a pragmatic trial and an intention to treat analysis, referral of patient to an ECMO based centre significantly improves patient survival without disability compared to conventional ventilation. The results of CESAR trial showed that:

- For patients with information about disability, survival without severe disability was significantly higher in ECMO arm
  - Assuming that the three patients in the conventional ventilation arm who did not have information about severe disability were all disabled, the results were also significant.
  - Assuming that none of these patients were disabled, the results were at borderline significance
- A greater, though not statistically significant, proportion of patients in ECMO arm survived.
- The rate of serious adverse events was higher among patients in ECMO group

The grade of evidence for the above observations is classified as "HIGH".

Bridge to LTx

- No studies fitting the inclusion criteria were identified.

There is no accurate data on the use of ECMO in patients awaiting LTx.

Economic Analysis

The objective of the economic analysis was to determine the costs associated with extracorporeal lung support technologies for bridge to LTx in adults. A literature search was conducted for which the target population was adults eligible for extracorporeal lung support. The primary analytic perspective was that of the Ministry of Health and Long-Term Care (MOHLTC). Articles published in English and fitting the following inclusion criteria were reviewed:

- Full economic evaluations including cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-benefit analyses (CBA);
- Economic evaluations reporting incremental cost-effectiveness ratios (ICER) i.e. cost per quality adjusted life year (QALY), life years gained (LYG), or cost per event avoided; and
- Studies in patients eligible for lung support technologies for to lung transplantation.

The search yielded no articles reporting comparative economic analyses.

Resource Use and Costs

Costs associated with both ILA and ECMO (outlined in Table ES-1) were obtained from the University Health Network (UHN) case costing initiative (personal communication, UHN, January 2010). Consultation with a clinical expert in the field was also conducted to verify resource utilization. The consultant was situated at the UHN in Toronto. The UHN has one ECMO machine, which cost approximately $100,000. The system is 18 years old and is used an average of 3 to 4 times a year with 35 procedures being performed over the last 9 years. The disposable cost per patient associated with ECMO is, on average, $2,200. There is a maintenance cost associated with the machine (not reported by the UHN), which is currently absorbed by the hospital's biomedical engineering department.

The average capital cost of an ILA device is $7,100 per device, per patient, while the average cost of the reusable pump $65,000. The UHN has performed 16 of these procedures over the last 2.5 years. Similarly, there is a maintenance cost not that was reported by UHN but is absorbed by the hospital's biomedical engineering department.

Table ES-1: Resources Associated with Extracorporeal Lung Support Technologies

Resource	Unit	Cost	Comments
		ECMO	
Capital	per machine	$100,000	UHN has one machine; 18 years old; used 3-4 times a year; 35 procedures in the last 9 years
Disposables	per patient	$2,210	Cannulas, tubings, etc.
Maintenance cost		NR	Hospital incurs a cost for maintenance
		ILA	
Capital	per device/per patient	$7,100	ILA device plus disposables; 16 procedures in the last 2.5 years
Reusable pump	per lifetime	$65,000	Reusable; pump is 3 years old
Maintenance cost		Not Reported	Hospital incurs a cost for maintenance

Hospital costs associated with ILA were based on the average cost incurred by the hospital for 11 cases performed in the FY 07/08 (personal communication, UHN, January 2010). The resources incurred with this hospital procedure included:

- Device and disposables
- OR transplant
- Surgical ICU
- Laboratory work
- Medical imaging
- Pharmacy
- Clinical nutrition
- Physiotherapy
- Occupational therapy
- Speech and language pathology
- Social work

The average length of stay in hospital was 61 days for ILA (range: 5 to 164 days) and the average direct cost was $186,000 per case (range: $19,000 to $552,000). This procedure has a high staffing requirement to monitor patients in hospital, driving up the average cost per case.

Background

For cases of acute respiratory distress syndrome (ARDS) and progressive chronic respiratory failure, the first choice or treatment is mechanical ventilation. For decades, this method has been used to support critically ill patients in respiratory failure. Despite its life-saving potential, however, several experimental and clinical studies have suggested that ventilator-induced lung injury can adversely affect the lungs and patient outcomes. (1-3) Current opinion is that by reducing the pressure and volume of gas delivered to the lungs during mechanical ventilation, the stress applied to the lungs is eased, enabling them to rest and recover. (1) In addition, mechanical ventilation may fail to provide adequate gas exchange, thus patients may suffer from severe hypoxia and hypercapnea. For these reasons, extracorporeal lung support technologies may play an important role in the clinical management of patients with lung failure, allowing not only the transfer oxygen and carbon dioxide (CO_2) but also buying the lungs the time needed to rest and heal.

Objective

The objective of this analysis was to assess the effectiveness, safety, and cost-effectiveness of extracorporeal lung support technologies in the improvement of pulmonary gas exchange and the survival of adult patients with acute pulmonary failure and those in end stage chronic progressive lung disease as a bridge to lung transplantation (LTx). The application of these technologies in primary graft dysfunction (PGD) after LTx is beyond the scope of this review and is not discussed.

Clinical Need and Target Population

Extracorporeal lung support technologies [i.e., Interventional Lung Assist (ILA) and extracorporeal membrane oxygenation (ECMO)] have been advocated for use in the treatment of patients with respiratory failure. These techniques do not treat the underlying lung condition; rather, they improve gas exchange while enabling the implementation of a protective ventilation strategy to prevent further damage to the lung tissues imposed by the ventilator. As such, extracorporeal lung support technologies have been used in three major lung failure case types:

1. As a bridge to recovery in acute lung failure – for patients with injured or diseased lungs to give their lungs time to heal and regain normal physiologic function.
2. As a bridge to LTx – for patients with irreversible end stage lung disease requiring LTx.
3. As a bridge to recovery after LTx – used as lung support for patients with PGD or severe hypoxemia.

Ex-Vivo Lung Perfusion and Assessment

Recently, the evaluation and reconditioning of donor lungs *ex-vivo* has been introduced into clinical practice as a method of improving the rate of donor lung utilization. (4-6) Generally, 15% to 20% of donor lungs are suitable for LTx, but these figures may increase with the use of *ex-vivo* lung perfusion. The *ex-vivo* evaluation and reconditioning of donor lungs is currently performed at the Toronto General Hospital (TGH) and preliminary results have been encouraging (personal communication, clinical expert, December 17, 2009). If its effectiveness is confirmed, the use of the technique could lead to further expansion of donor organ pools and improvements in post-LTx outcomes.

Global Incidence of Acute Respiratory Failure

Acute respiratory failure, defined as the necessity for mechanical ventilation, occurs at an annual incidence rate of 78 to 88 cases per 100,000 persons. Similarly, the respective incidences of ARDS and acute lung injury are reportedly 1.5 to 13.5 and 18 to 70 per 100,000 persons annually. (7)

Ontario Context

The TGH holds the distinction of being the location of the world's first successful human LTx in 1983. In 1986, it also became the first hospital to carry out the first successful double LTx. (8) Now, approximately 10 to 15 patients a year at the TGH will require extracorporeal lung support. Two-thirds of these cases will be for bridge to recovery after LTx, while the remaining are bridge to recovery in ARDS or lung injury cases. Approximately 100 LTx cases per year are performed in Ontario, with the majority (~95%) being adult cases (personal communication, clinical expert, December 17, 2009).

According to the London Health Sciences Centre (LHSC), a total of 852 organ transplants were performed in Ontario during 2008, 82 of which were LTx. Over the same year, 131 LTx (single or double) were performed in Canada. (9) Examining Ontario specifically, data from the Canadian Institute of Health Information (CIHI) showed that for the first half of 2009, four single LTx (all in patients 18 years or older) and 49 double LTx (46 in patients 18 years or older) were performed in the province. (10) At that point, no patients under 18 years of age were waiting for LTx while 30 patients 18 years or older were waiting for a single LTx and 20 for a double LTx. (11)

A 10-year history of LTx through the Trillium Gift of Life Network has shown that the number of LTx procedures performed has doubled over the past decade, from 54 in 2000 to 101 in 2009 (see Figure 1). According to the Network, 98 of these procedures in 2009 were LTx, while the remaining were three heart-lung transplants. As of January 2010, 51 patients were on the waiting list for LTx. (12)

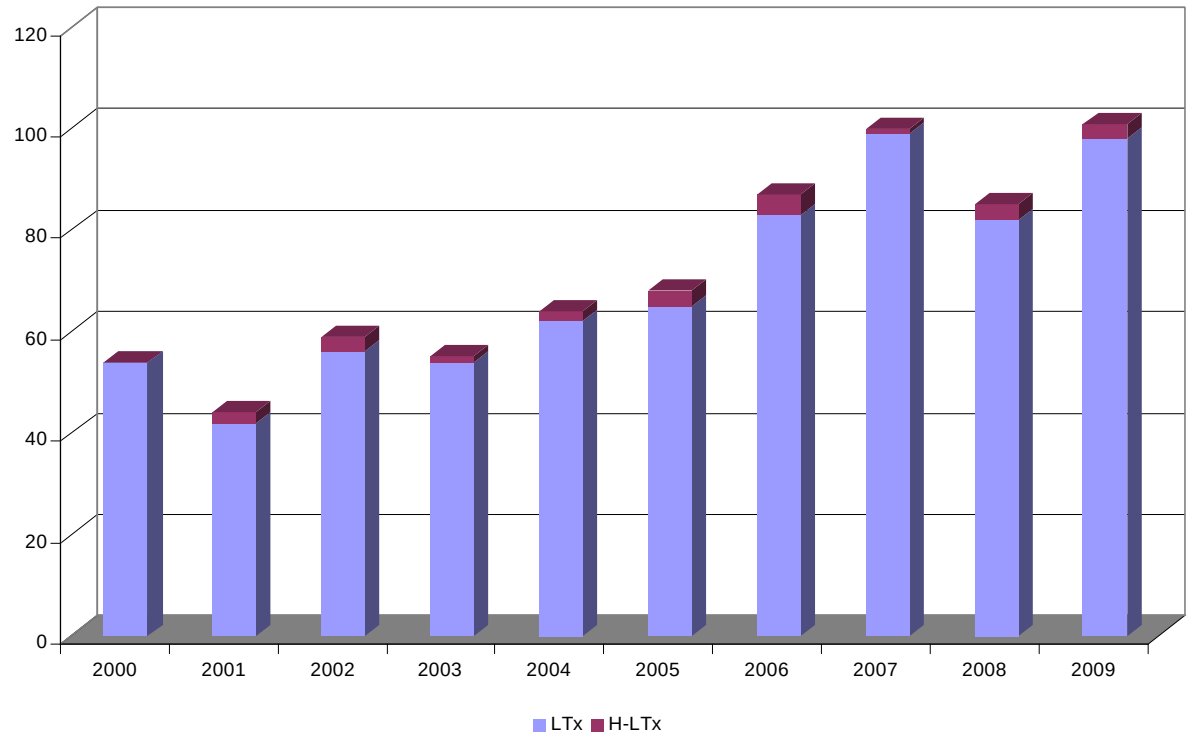

Figure 1: Lung transplantation through the Trillium Gift of Life Network – 10 year history

Artificial Lungs

There are three major classifications for artificial lungs: extracorporeal, paracorporeal, and implantable. (13) With extracorporeal artificial lungs, gas exchange is performed externally through an artificial lung. In contrast, with paracorporeal artificial lungs, the patient's right heart is used as a pump. The device is surgically attached to the pulmonary circulation using different attachment modes: parallel, series, or hybrid. (13)

Implantable artificial lungs are the ultimate goal of all artificial respiration but such technology may be years away from clinical use. (13) The first intravascular oxygenator (IVOX) was applied in 1994 by Conrad et al. and in 2004, a group from Germany introduced a second implantable artificial lung named the "highly integrated membrane oxygenator" (HIMOX).

Extracorporeal Lung Support Systems

The word "ECMO" has become a general term encompassing a range of methods for extracorporeal blood oxygenation and CO_2 removal. In the 1970's, ECMO referred to a high-flow venoarterial bypass system aimed primarily at blood oxygenation. By the 1980's, the term 'extracorporeal CO_2 removal' ($ECCO_2R$) was used to cover a low-flow venovenous bypass technique and replaced ECMO to underscore the importance of CO_2 removal. Later in the mid-1980's, 'partial extracorporeal CO_2 removal' ($PECO_2R$) emerged with the development of a technique used to eliminate only part of the body's CO_2 for patients with chronic lung disease. In 1987, a Japanese working group then introduced the term 'extracorporeal lung assist (ECLA)' to describe a venovenous low-flow bypass system. 'Extracorporeal life support' was then introduced to describe techniques that provide prolonged but temporary support for the lungs and heart. (7) The most accurate way of characterizing these methods, however, is by distinguishing their particular method of vascular access, the proportion of cardiac output pumped, and the ventilatory regimen used.

Despite these various changes in terminology and delivery, ECMO has remained the best known extracorporeal system in use, providing cardiac and respiratory support for patients with severe cardiopulmonary conditions. (13) The technique involves connecting the patient's circulatory system to an external blood pump and an artificial lung. In this manner it acts as a temporary life support system, though it does not treat the underlying pathology. Examples of adult conditions that can benefit from ECMO are:

- Acute respiratory distress syndrome
- Pneumonia
- Pulmonary embolism
- Inhalation injury
- Trauma
- Graft failure after lung transplantation
- Drowning
- Cardiac failure

Patients with terminal illnesses are not candidates for ECMO as even if they survive respiratory failure, they often succumb due to other reasons. (14) ECMO is contraindicated in patients in whom heparin cannot be used because of potential hemorrhagic complications.

ECMO System

ECMO connects the patient's circulation to an external blood pump and artificial lung for temporary life support. The system consists of a centrifugal pump, a membrane oxygenator, inlet and outlet cannulas, and tubing. The exchange of oxygen and CO_2 takes place in the oxygenator, which delivers the reoxygenated blood back into one of the patient's veins or arteries. Additional ports may be added for haemodialysis or ultrafiltration.

Two different techniques may be used to introduce ECMO: venoarterial and venovenous. In the venoarterial technique, cannulation is through either the femoral artery and the femoral vein, or through the carotid artery and the internal jugular vein. In the venovenous technique cannulation is through both femoral veins or a femoral vein and internal jugular vein; one cannula acts as inflow or arterial line, and the other as an outflow or venous line. Venovenous ECMO will not provide adequate support if a patient has pulmonary hypertension or right heart failure. (14) Problems associated with cannulation during the procedure include bleeding around the cannulation site and limb ischemia distal to the cannulation site.

Randomized Controlled Trials on ECMO

Although the use of ECMO to support neonatal patients with severe respiratory failure has been supported by RCT evidence demonstrating its effectiveness in improving the patient survival rate without severe disability (15), its use in adult patients remained controversial. Until recently, only two RCTs had examined the use of ECMO in adults. (16;17) The first was conducted by the US National Institute of Health (NIH) in the early days of extracorporeal life support. (16) The study (n=90) showed no difference in survival between patients who received ECMO and those who had received conventional treatment with both groups fairing poorly (around 8% to 10% survival). The second study (n=40) compared pressure controlled inverse ratio ventilation (PCIRV) with ECMO. (17) No significant difference in survival was found between the two groups (42% in PCIRV versus 33% in ECMO, P = .8). The authors recommended that ECMO should not be used for the treatment of ARDS in adult patients. A considerable amount of criticism was, however, levelled against this study in relation to the ECMO methodology used and most reviewers agreed that modern standards were not employed. (7) Although both RCTs did not find significant differences in the survival rate between their respective ECMO and control groups, the overall survival rate had improved when comparing results of the two RCTs.

ILA System

Interventional Lung Assist (ILA) is used to remove excess CO_2 from the blood of patients in respiratory failure. The system is characterized by a novel, low-resistance gas exchange device with a diffusion membrane composed of polymethylpentene (PMP) fibres. These fibres are woven into a complex configuration that maximizes the exchange of oxygen and CO_2 by simple diffusion. (18) The system is also designed to operate without the help of an external pump, though one can be added if higher blood flow is required. The device is then applied across an arteriovenous shunt between the femoral artery and femoral vein. Depending on the size of the arterial cannula used and the mean systemic arterial pressure, a blood flow of up to 2.5 L/min can be achieved (up to 5.5 L/min with an external pump). The cannulation is performed after intravenous administration of heparin.

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Evidence-Based Analysis

Research Questions

The research questions addressed in this report are:

1. Does ILA/ECMO facilitate gas exchange in the lungs of patients with severe respiratory failure?
2. Does ILA/ECMO improve the survival rate of patients with respiratory failure caused by a range of underlying conditions including patients awaiting LTx?
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- Correction of respiratory acidosis
- Improvement in partial pressure of oxygen
- Improvement in patient survival
- Frequency and severity of adverse events

The literature search yielded 107 citations in Medline and 107 citations in EMBASE. After reviewing the information provided in the titles and abstracts, eight citations were selected. Reviewing the full articles of the selected studies resulted in exclusion of one due to an overlap in the study population with a previous study. (19) Reference checking did not produce any additional studies for inclusion. Seven case series studies (20-26), all conducted in Germany, were included in this review (see Table 1). Also included was the recently published CESAR trial, a multicentre RCT in the UK in which ECMO was compared with conventional intensive care management. (21)

Table 1: Quality of Evidence of Included Studies

Study Design	Level of Evidence†	No. of Eligible Studies	
		ILA	ECMO
Large RCT, systematic review of RCTs	1	0	1
Large RCT unpublished but reported to an international scientific meeting	1(g)	0	0
Small RCT	2	0	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0	0
Non-RCT with contemporaneous controls	3a	0	0
Non-RCT with historical controls	3b	0	0
Non-RCT presented at international conference	3(g)	0	0
Surveillance (database or register)	4a	0	0
Case series (multisite)	4b	0	0
Case series (single site)	4c	4	0
Retrospective review, modelling	4d	3	0
Case series presented at international conference	4(g)	0	0
	Total	**7**	**1**

RCT refers to randomized controlled trial;

Literature Search for ECMO

The results of the CESAR trial on ECMO for severe ARDS were published when this review was initiated. In the absence of any other recent RCT on ECMO, the results of this trial were considered for this assessment and no further searches were conducted. A literature search was conducted for application of ECMO as bridge to LTx patients. A total of 127 citations on this topic were identified and reviewed but none were found to have reported the use of ECMO as bridge to LTx.

Statistical Analysis

Meta-analysis technique, using Review Manager (RevMan) 5, was used for the analysis of statistical significance and graphical presentations of the outcomes comparing pre- and post-ILA institution over the following time frames: before ILA, 2-6 hours after, 24 hours after, and up to 7 days after institution of ILA. The included in the meta-analysis were: the partial pressure of CO_2 in arterial blood ($PaCO_2$), the ratio of PaO_2/FiO_2 (Partial pressure of oxygen/fraction of inspired oxygen), and arterial blood pH. Changes in other variables were demonstrated through EXCEL graphs.

The extracted data included study characteristics, patient characteristics, variables indicating gas exchange ($PaCO_2$, PaO_2, PaO_2/FiO_2, arterial blood pH), respiratory parameters, hemodynamic parameters, adverse events, and mortality or survival.

Quality of Evidence

To grade the quality of evidence, the grading system formulated by the GRADE working group (27) and adopted by MAS was applied. The GRADE system classifies the quality of a body of evidence as high, moderate, low, or very low according to four key elements: study design, study quality, consistency across studies, and directness (see Appendix 2). The definition of categories of quality of evidence as stated by the GRADE Working Group is:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Any estimate of effect is very uncertain

Results of Evidence-Based Analysis: ILA

Of the seven studies identified, six (20-24;26) involved patients with ARDS caused by a range of underlying conditions; the seventh (25) included only patients awaiting LTx . All studies reported the rate of gas exchange and respiratory mechanics before ILA and up to 7 days during ILA therapy. Four studies (20;23;25;26) reported the mean and standard deviation of blood gas transfer and arterial blood pH, which were used for meta-analysis. One (24) reported the outcomes for survivors and non-survivors separately. Mortality outcome was reported in six case series, of which only three reported the number of patients who died during ILA therapy. The characteristics of the included studies are summarized in Table 2.

Mean Duration of Therapy

No patients received ILA therapy for more than 33 days, with the exception of four in Weber-Carstense et al.'s 2009 study. (22) Figure 2 displays the mean duration of ILA therapy among the studies reviewed.

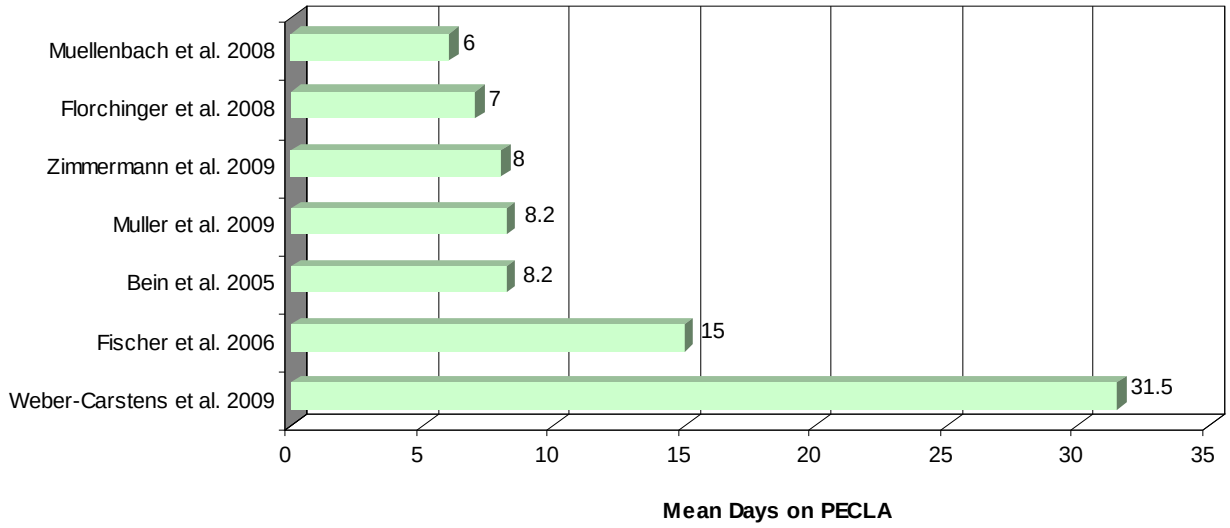

Figure 2: Mean duration of ILA therapy in reviewed studies

Fischer et al. reported their first experience on the use of ILA as a bridge to LTx. In their study, 12 patients at high urgency status for LTx, who also had severe ventilation refractory hypercapnea and respiratory acidosis, were connected to ILA prior to LTx. Seven patients had a systemic infection or sepsis prior to ILA insertion. Six hours after initiation of ILA, the partial pressure of CO_2 in the arterial blood significantly decreased ($P < .05$), while arterial blood pH significantly improved ($P < .05$) and remained stable for one week (last time point reported). The partial pressure of oxygen in arterial blood improved from 71 mmHg to 83 mmHg 6 hours after insertion of ILA. The ratio of PaO_2/FiO_2 improved from 135 at baseline to 168 at 24 hours after insertion of ILA but returned to baseline in the following week.

Table 2: Characteristics of the Studies Included in the Review: Case Series Studies on ILA

*Author, Year	Country/City	Study Design	No. Patients	Male/ Female	Mean Age ± SD, Years (Range)	Indication	Mean Days on ILA ± SD (Range)
Müller et al. 2009 (20)	Germany Regensburg	Prospective	96	NR	22.8 ± 5.6	Brain injury and chest trauma due to traffic accidents	8.2 ± 3.2
Zimmermann et al. 2009 (21)	Germany Regensburg	Prospective	51	43/8	52 (40-59)	ARDS due to pneumonia, trauma, or sepsis (51)	Survivors: 8 (6-10) Non-survivors: 8 (4-16)
Weber-Carstens et al. 2009 (22)	Germany Berlin	Retrospective	10	6/4	54 ± 10.75	Pulmonary fibrosis due to medication (3) Pneumonia of different types (6) Invasive aspergillosis after renal transplantation (1)	31.5 (7-77)
Florchinger et al. 2008 (23)	Germany Regensburg	Prospective	159	121/38	44 ± 17 (7-78)	ARDS (112) Pneumonia (45) End stage cystic fibrosis waiting for lung transplantation (2)	7±6.2 (0-33)
Muellenbach et al. 2008 (24)	Germany Wuerzburg	Retrospective	22	20/2	31 ± 15	Trauma (11) Pneumonia (6) Aspiration (4) COPD (1)	Survivors: 6 (4.8-7.3) Non-survivors: 4.5 (1.5-9)
Fisher et al. 2006 (25)	Germany Hannover	Prospective	12	NR	NR	ARDS as bridge to LTx	15 ± 8 (4-32)
Bein et al. 2005 (26)	Germany Regensburg	Retrospective	5	4/1	22.8 ± 5.6	ARDS and brain injury	8.2 ± 3.2

ILA, interventional lung assist; ARDS, Acute respiratory distress syndrome; COPD, Chronic obstructive pulmonary disease; LTx, Lung transplantation

* Include one study as bridge to LTx;

Gas Exchange

Removal of CO_2 and Correction of Respiratory Acidosis

Most studies reported a significant reversal of hypercapnea and severe respiratory acidosis within 2 to 6 hours of initiating ILA. Partial pressure of CO_2 in arterial blood and arterial blood pH remained in the normal range until termination of ILA (see Figure 3).

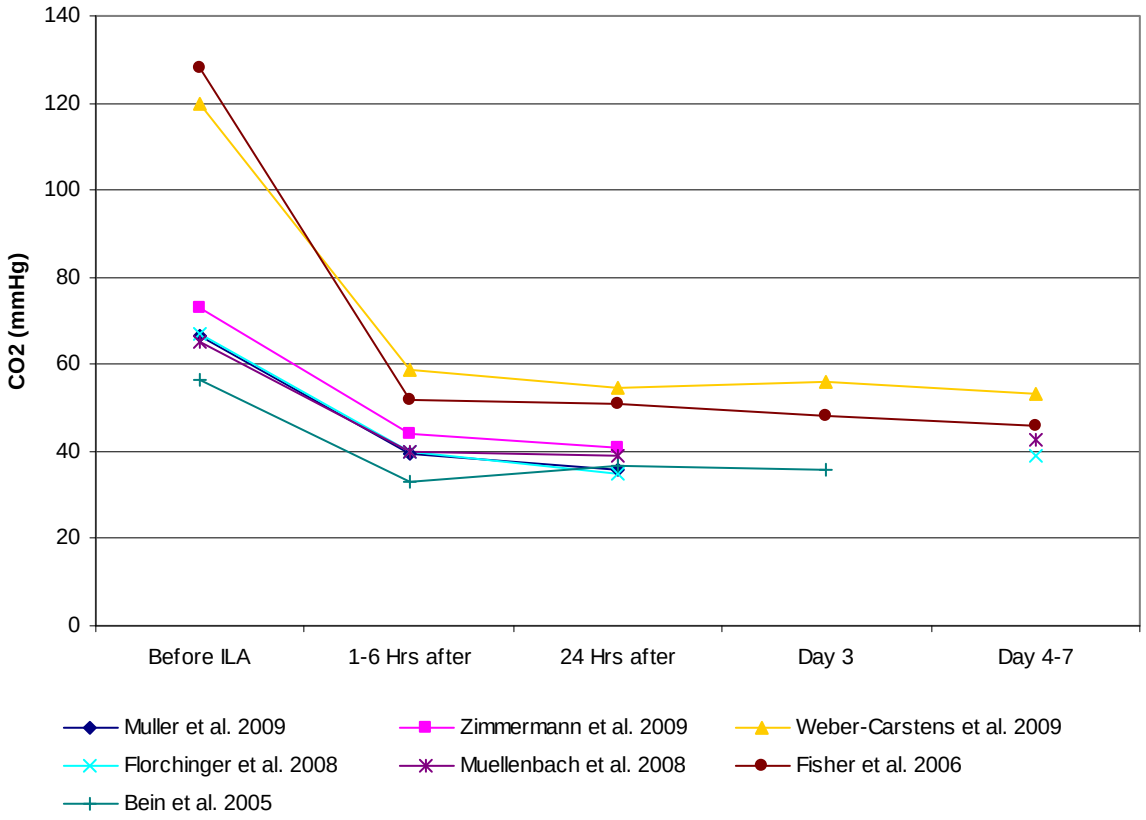

Figure 3: Reduction in partial pressure of CO_2 in arterial blood

The results of meta-analysis of the partial pressure of CO_2 in arterial blood demonstrated that instituting ILA resulted in a significant decrease in partial pressure of CO_2 in arterial blood; a decrease of 31.49 mmHg within 2-6 hours, 31.80 mmHg within 24 hours, and 39.78 mmHg within 2-7 days compared to the baseline values (see Figure 4). The p-value remained significant at all three time points the study by Fischer et al. was excluded (results not shown).

The studies also reported reductions in respiratory acidosis after instituting ILA as removing CO_2 from the blood improves blood pH (see Table 3 and Figure 5). These results were corroborated by a meta-analysis of arterial blood pH values, which showed significant improvement following ILA (Figure 6). The p-value again remained significant at all three time points when the Fischer et al. study was excluded.

Table 3: Blood Gas Analyses Before and After Instituting ILA

Author, Year	Time Frame	$PaCO_2$ (mmHg)	Arterial pH	PaO_2 (mmHg)	FiO_2 (mmHg)	PaO_2/FiO_2 (mmHg)
Müller et al. 2009 (20)	Pre-ILA:	66.7±25	7.24±0.13	NR	NR	68.9±29.9
	2 Hrs after:	39.5±12.1*	7.41±0.12*			93.7±48.4*
	24 Hrs after:	35.8±7.6*				
	After termination:	49.8±14.7	7.36±0.09			
Zimmermann et al. 2009 (21)	Pre-ILA:	73 (61-86)	7.23 (7.16-7.30)	NR	1 (0.8-1)	75 (62-130)
	2 Hrs after:	44 (36-54)*	7.38 (7.32-7.46)*		0.8 (0.7-1)*	102 (70-127)*
	24 Hrs after:	41 (34-48)*	7.44 (7.37-7.49)*†		0.7 (0.6-0.9)*†	110 (86-160)*
Weber-Carstens et al. 2009 (22)	Pre-ILA:	120 (81.9-154.5)	7.06 (6.9-7.3)	NR	1 (1-1)	121.5 (79.3-178.3)
	6 Hrs after:	58.7 (50.5-68.8)	7.39 (7.15-7.54)		0.78 (0.66-1)	87.5 (74.3-174)
	12 Hrs after:	60.3 (52.5-69)	7.38 (7.48-8.18)		0.88 (0.66-1)	87 (73-139.3)
	Day 2:	54.8 (45.9-64.5)	7.34 (7.29-7.44)		0.83 (0.66-1)	124.9 (85.8-229.7)
	Day 3:	56.1 (52.1-61)	7.41 (7.27-7.45)		0.8 (0.55-0.95)	108.5 (80.3-247)
	Day 4:	53.4 (48.2-58.4)*	7.37 (7.3-7.43)		0.73 (0.66-0.94)*	91.5 (78.5-145.5)
Florchinger et al. 2008 (23)	Pre-ILA:	67±24	7.25±0.13	66±24	0.96±0.11	72±37
	2 Hrs after:	40±12	7.40±0.12	81±33	0.89±0.14	95±52
	24 Hrs after:	35±7*	7.44±0.09	79±19	0.77±0.17	111±46
	Before termination:	39±17	7.43±0.07	91±17*	0.48±0.13*	203±61
	Day 1 after termination:	48±14	7.38±0.09	96±19	0.5±0.13	202±69
Muellenbach et al. 2008 (24)	Pre-ILA:			NR	NR	
	Survivors:	65.4 (54.1-72.2)	7.25 (7.22-7.29)			61.6 (47.4-85.7)
	Non-survivors:	75.2 (52.6-97.7)	7.12 (7.03-7.27)			95.5 (57.9-163.9)
	1 Hr after:					
	Survivors:	39.8 (35.3-41.4)*	7.39 (7.3-7.42)			72.9 (65.4-111.3)
	Non-survivors:	54.1 (38.3-63.9)	7.23 (7.13-7.24)			57.1 (50.4-69.9)
	24 Hrs after:					
	Survivors:	39.1 (35.3-42.1)*	7.42 (7.38-7.44)			142.1 (109.8-170.7)*
	Non-survivors:	42.9 (35.3-45.1)*	7.36 (7.35-7.43)			65.4 (54.9-148.9)
	Before termination:					
	Survivors:	39.8 (39.1-42.1)*	7.40 (7.4-7.42)			263.2 (227.1-324.1)
	Non-survivors:	33.8 (33.1-33.8)	7.43 (7.42-7.43)			229.3 (209.8-248.1)
	1 Hr after termination:					
	Survivors:	42.9 (39.8-45.1)	7.42 (7.4-7.45)			276.7 (242.9-333.1)
	Non-survivors:	38.3 (38.3-39.1)	7.45 (7.45-7.45)			233.1 (215-248.9)
Fisher et al. 2006 (25)	Pre-ILA:	128±42	7.12±0.1	71±27	NR	135±33
	6 Hrs after:	52±5*	7.34±0.1*	83±17*		150±24
	24 Hrs after:	51±33	7.38±0.2	124±42		168±42
	72 Hrs after:	48±8	7.37±0.1	113±28		145±24
	7 days after:	46±5	7.39±0.1	114±36		139±22
Bein et al. 2005 (26)	Pre-ILA:	56.6±12.28	7.29±0.13	NR	NR	99±34.54
	2-4 Hrs after:	33.2±4.38	7.44±0.07			113.8±38.04
	24 Hrs after:	36.6±6.47	7.43±0.04			180±72.77
	48 Hrs after:	35.6±4.83	7.43±0.04			195.8±47.19

NR, Not reported; $PaCO_2$, Partial pressure of CO_2 in arterial blood; PaO_2, Partial pressure of oxygen in arterial blood; FiO_2, Fraction of inspired oxygen; ILA, Interventional lung assist;
*Statistically significant in comparison with pre-ILA values;
†Statistically significant in comparison with 2 hours after ILA insertion

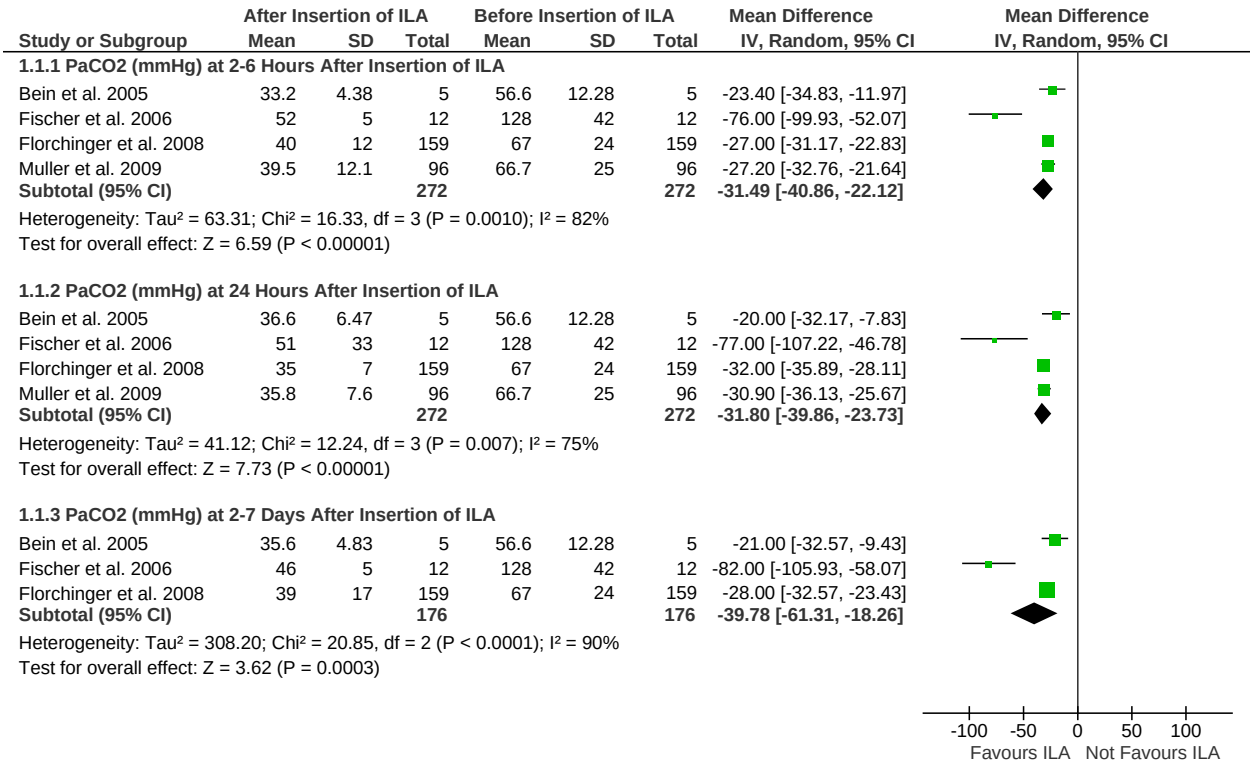

Figure 4: Reduction in Partial Pressure of CO_2 in Arterial Blood

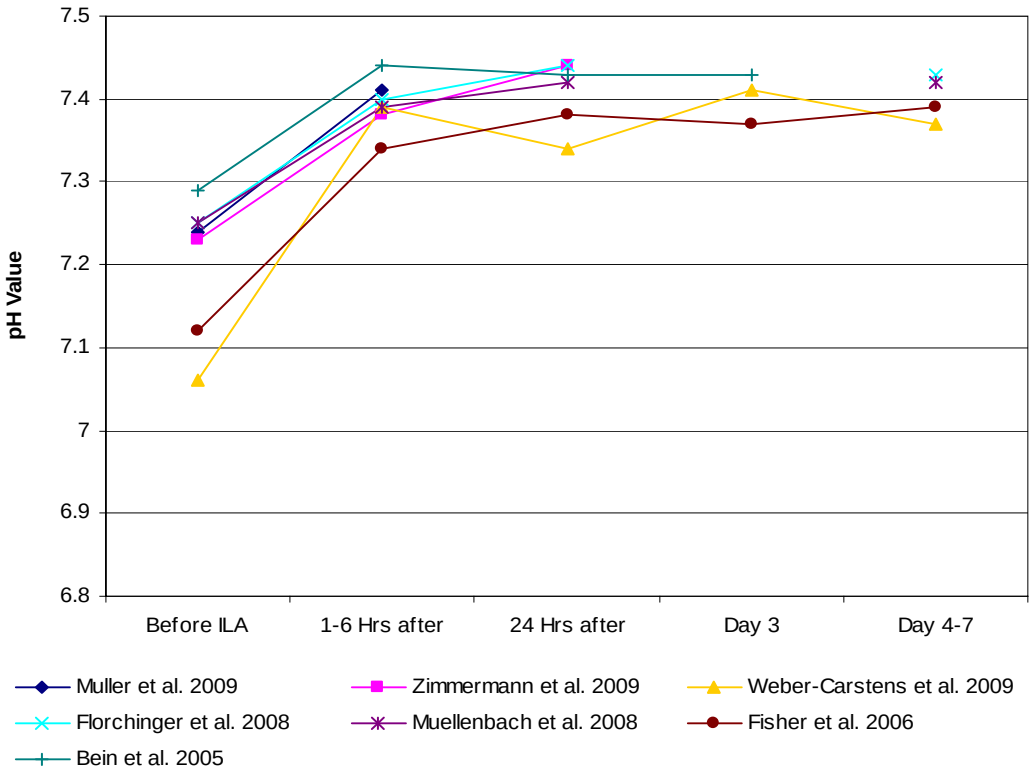

Figure 5: Changes in arterial blood pH and correction of respiratory acidosis

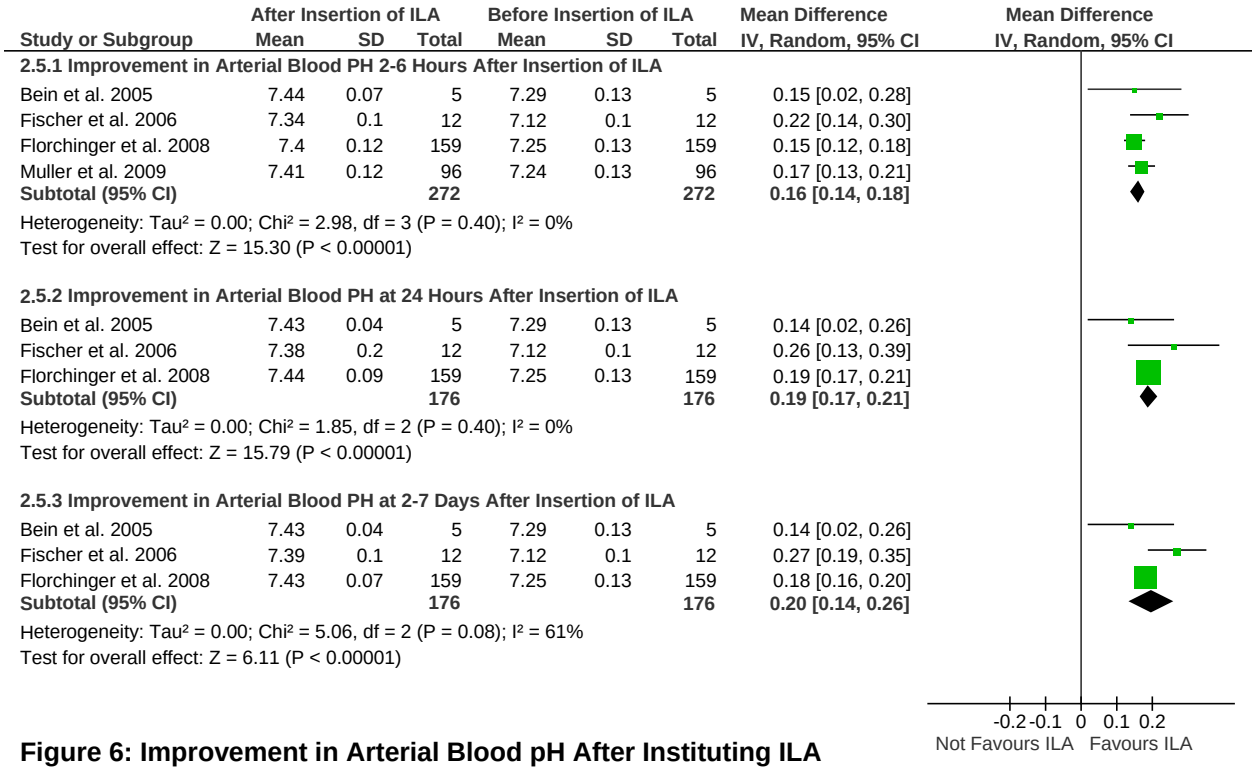

Figure 6: Improvement in Arterial Blood pH After Instituting ILA

Improvement in Arterial Blood Oxygenation

All studies reported improvements in the ratio of PaO_2/FiO_2 after institution of ILA (see Table 3 and Figure 7). Meta-analysis showed a significant improvement in the ratio of PaO_2/FiO_2 a few hours after the institution of ILA, but these results were not significant beyond the first day (see Figure 8). When the Fischer et al. study was excluded, however, the p-values at all three time points were significant (results not shown).

Respiratory Settings

Significant improvements in CO_2 removal and oxygenation of the arterial blood allowed the tidal and minute volumes to be set to lower levels during ILA, thus the peak inspiratory pressure and plateau inspiratory pressure during ILA therapy were reduced without any negative impact on arterial blood CO_2 or arterial blood pH. There were also trends toward lowering the PEEP. Table 4 and Figures 9 to 13 display the respiratory settings before and after the institution of ILA.

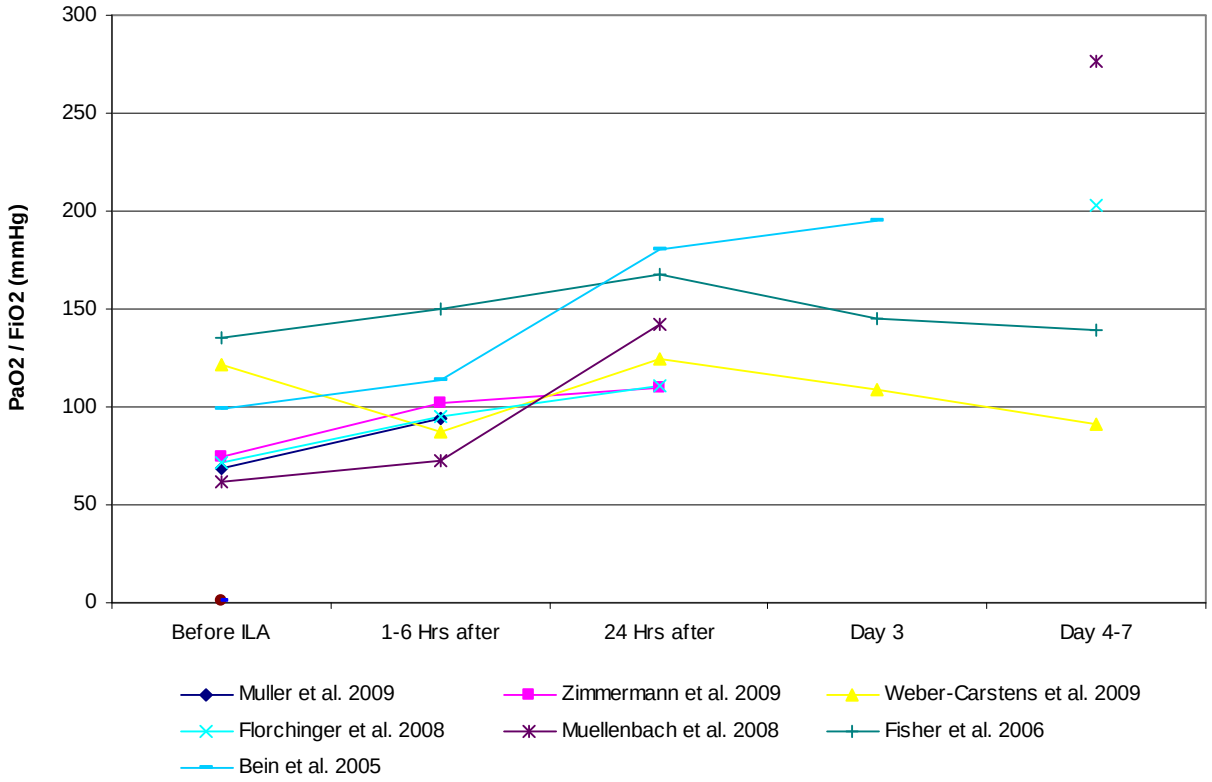

Figure 7: Improvement in Ratio of PaO_2/FiO_2 After Instituting ILA

Study or Subgroup	After ILA Mean	SD	Total	Before ILA Mean	SD	Total	Mean Difference IV, Random, 95% CI
3.1.1 PaO2/FiO2 at 2-6 Hours After Insertion of ILA							
Bein et al. 2005	113.8	38.04	5	99	34.54	5	14.80 [-30.24, 59.84]
Fischer et al. 2006	150	24	12	135	33	12	15.00 [-8.09, 38.09]
Florchinger et al. 2008	95	52	159	72	37	159	23.00 [13.08, 32.92]
Muller et al. 2009	93.7	48.8	96	68.9	29.9	96	24.80 [13.35, 36.25]
Subtotal (95% CI)			**272**			**272**	**22.74 [15.69, 29.78]**
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 3 (P = 0.88); I² = 0%							
Test for overall effect: Z = 6.33 (P < 0.00001)							
3.1.2 PaO2/FiO2 at 24 Hours After Insertion of ILA							
Bein et al. 2005	180	72.77	5	99	34.54	5	81.00 [10.40, 151.60]
Fischer et al. 2006	168	42	12	135	33	12	33.00 [2.78, 63.22]
Florchinger et al. 2008	111	46	159	72	37	159	39.00 [29.82, 48.18]
Subtotal (95% CI)			**176**			**176**	**39.14 [30.43, 47.85]**
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%							
Test for overall effect: Z = 8.80 (P < 0.00001)							
3.1.3 PaO2/FiO2 at 2-7 Days After IInsertion of ILA							
Bein et al. 2005	195.8	47.19	5	99	34.54	5	96.80 [45.54, 148.06]
Fischer et al. 2006	139	22	12	135	33	12	4.00 [-18.44, 26.44]
Florchinger et al. 2008	203	61	159	72	37	159	131.00 [119.91, 142.09]
Subtotal (95% CI)			**176**			**176**	**77.04 [-16.95, 171.03]**
Heterogeneity: Tau² = 6628.35; Chi² = 99.01, df = 2 (P < 0.00001); I² = 98%							
Test for overall effect: Z = 1.61 (P = 0.11)							

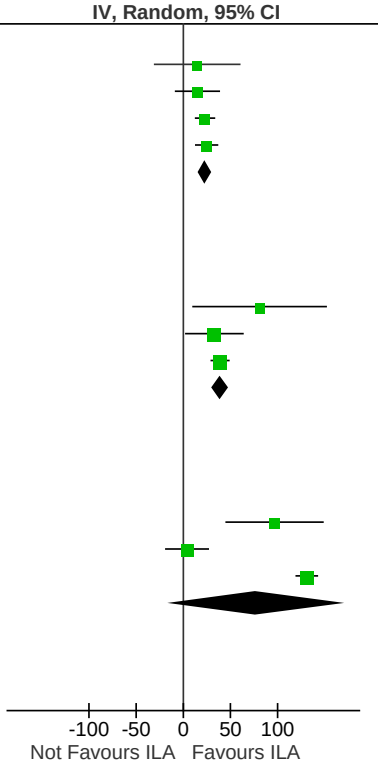

Figure 8: Improvement in Ratio of PaO_2/FiO_2 After Instituting ILA

Table 4: Changes in Respiratory Settings

Author, Year	Time Frame	Minute Ventilation (L/min)	V_T (ml/kg BW/PBW)	Peak Inspiratory Pressure (cm H_2O)	Inspiratory Plateau Pressure (cm H_2O)	PEEP (cm H_2O)
Müller et al., 2009 (20)		NR	458±131		38±6	16±5
Zimmermann et al. 2009‡ (21)	Pre-ILA:	11.5 (9.3-12.5)	6.6 (5.3-7.2)		35 (31-38)	17 (14-20)
	2 Hrs after:	8.6 (6.4-10.5)*	5 (4-6.4)*		34 (30-37)	15 (11-19)*
	24 Hrs after:	6.6 (5.5-8.3)*†	4.4 (3.4-5.4)*†		30 (26-34)*	17 (14-20)
Weber-Carstens et al. 2009 (22)	Pre-ILA:	NR	5.2 (4.4-5.9)		39 (34.8-43.3)	14 (12.75-17)
	6 Hrs after:		4 (3.1-4.6)		32 (29.3-35.3)	15 (13.5-16.25)
	24 Hrs after:		3.5 (2.7-4.1)		31.5 (30.3-34.3)	16 (13.5-17)
	Day 3:		3.4 (2.6-4.1)		31 (28.5-32.3)	15.5 (13.5-16.25)
	Day 4:		3.0 (1.8-3.7)*†		30 (28.5-32.3)*	16 (13.25-16.5)
Florchinger et al. 2008 (23)			Tidal volume, mL:			
	Pre-ILA:	13.8±4.8	453±134	37.7±6.3		15±5
	2 Hrs after:	11.7±5.3	404±126	36±7.4		15±5
	24 Hrs after:	11.6±7.6	402±144	34.5±7.2		14±5
	Before termination:	9.8±4.8	450±152	29.6±6		12±4
	Day 1 after termination:	11.6±4.2	497±146	30±6		11±4
Muellenbach et al. 2008 (24)		NR	Tidal volume, mL:	Survivors:		Survivors:
	Pre-ILA:		450 (400-542.5)	40 (36-46)		24 (21-29)
	2 Hrs after:		240 (200-272.5)*	35 (33-36)		26 (22-28)
	24 Hrs after:		210 (150-250)*	34 (32-35)		24 (23-25)
	Before termination:		300 (250-440)	29 (26-32)		16 (15-19)
	1 Hr after termination:		450 (450-500)	29 (26-32)		16 (15-20)
				Non-survivors:		Non-survivors:
	Pre-ILA:			41 (37-44)		24 (21-25)
	2 Hrs after:			34 (33-36)		28 (25-30)
	24 Hrs after:			35 (34-35)		26 (21-29)
	Before termination:			32 (31-33)		17 (16-17)
	1 Hr after termination:			32 (31-32)		17 (16-17)
Fisher et al. 2006 (25)	Pre-ILA:	NR	NR	61.2±6.8		17.7±1.4
	2 Hrs after:			61.2±6.8		17.7±1.4
	24 Hrs after:			43.5±4.1		8.2±1.4
	3 days after			40.8±6.8		6.8±2.7
	7 days after			38.1±8.2		8.2±1.4
Bein et al. 2005 (26)			Tidal volume, mL:	NR		NR
	Pre-ILA:	13.18±4.59	495.8±112.46			
	2-4 Hrs after:	10±3.73	513.8±203.18			
	24 Hrs after:	8.06±2.94	518.8±123.19			
	48 Hrs after:	8.74±2.86	524±54.13			

V_T, Tidal volume; BW, Body weight; PBW, Predicted body weight; PEEP, Positive end expiratory pressure
*Significant in comparison with pre-ILA; †Significant in comparison with 2 hours after insertion; ‡Reported median;

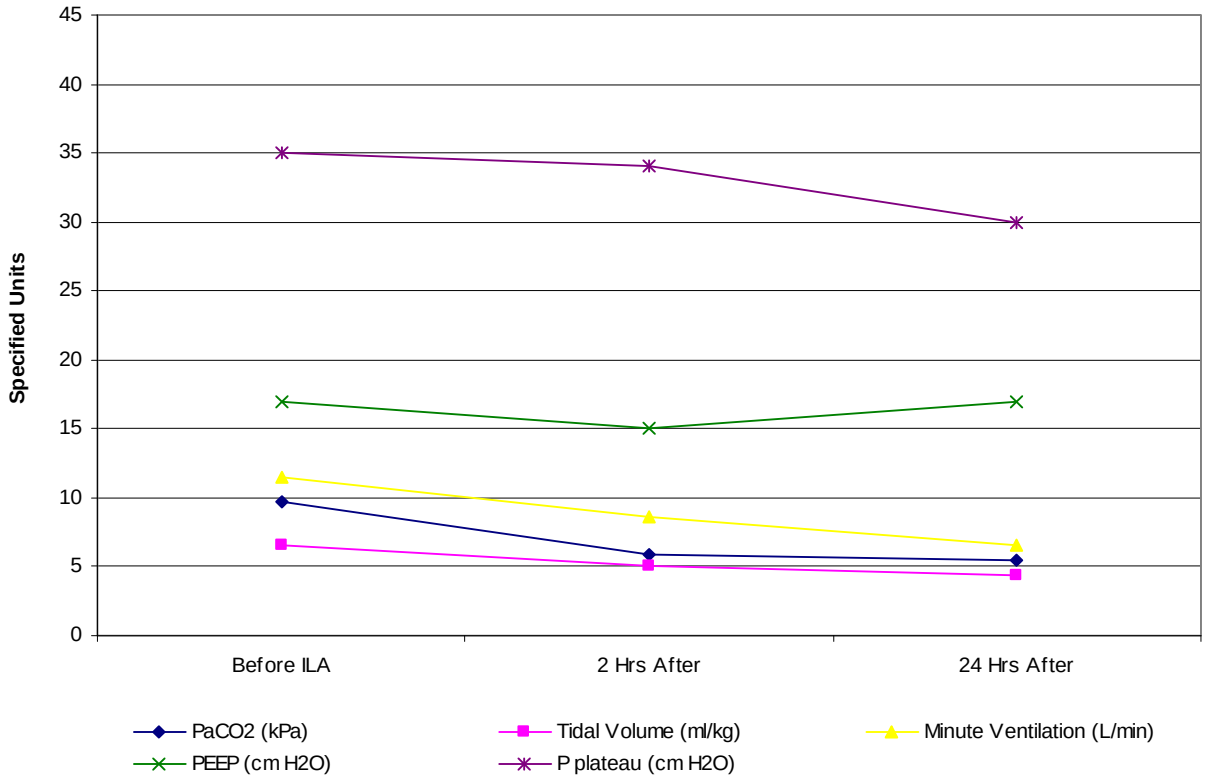

Figure 9: Changes in Respiratory Settings, Zimmermann et al. 2009

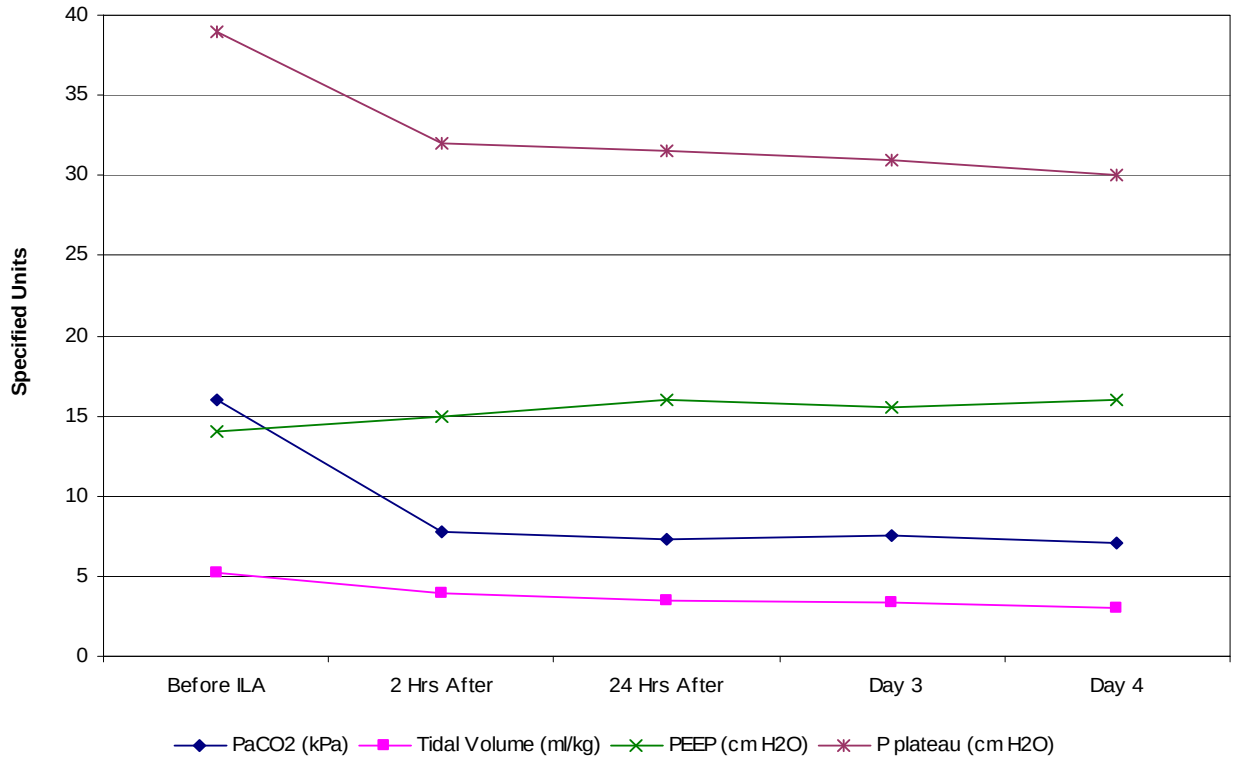

Figure 10: Changes in Respiratory Settings, Weber-Carstens et al. 2008

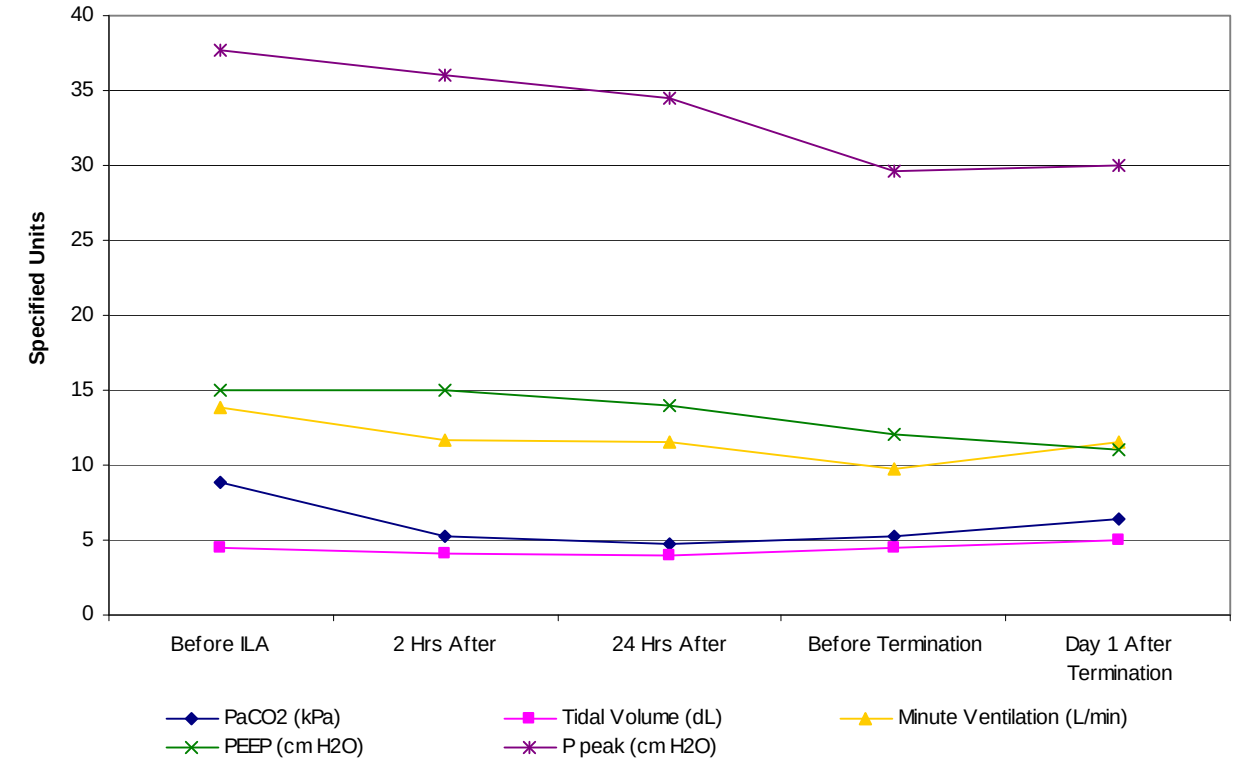

Figure 11: Changes in respiratory settings, Florchinger et al. 2008

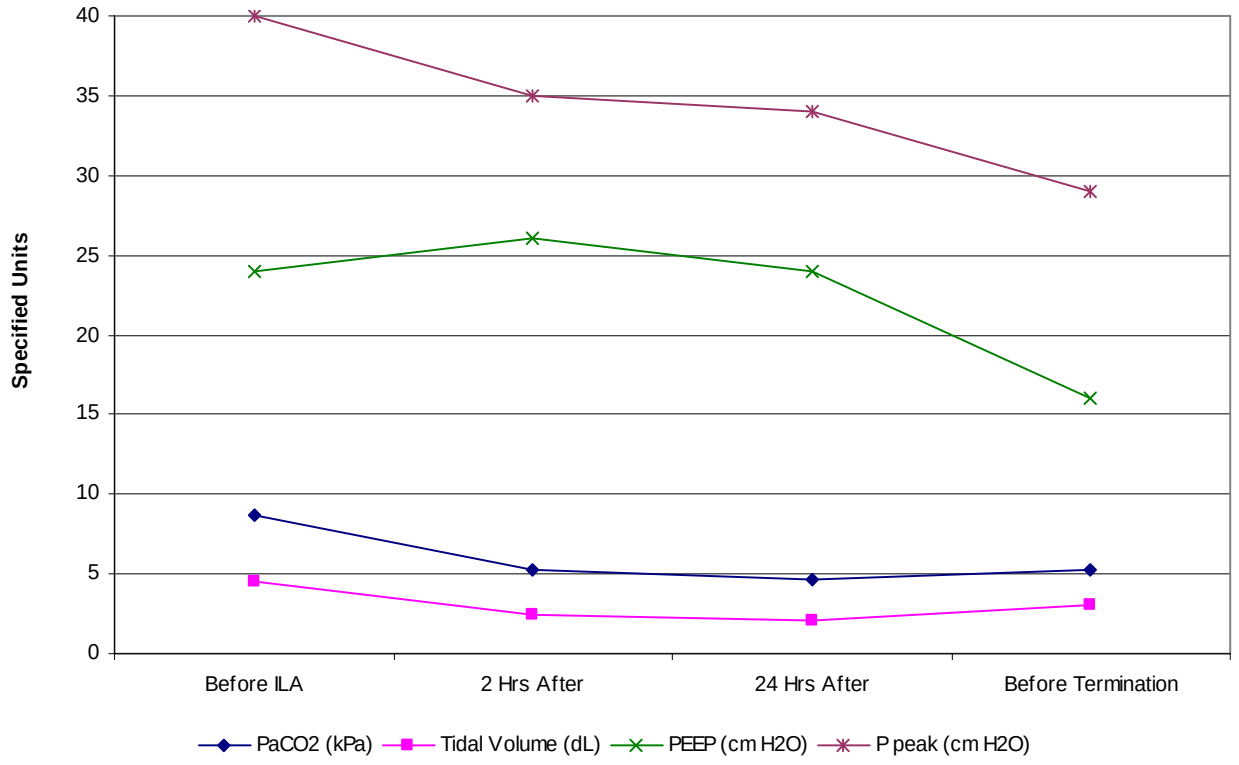

Figure 12: Changes in respiratory settings, Muellenbach et al. 2008

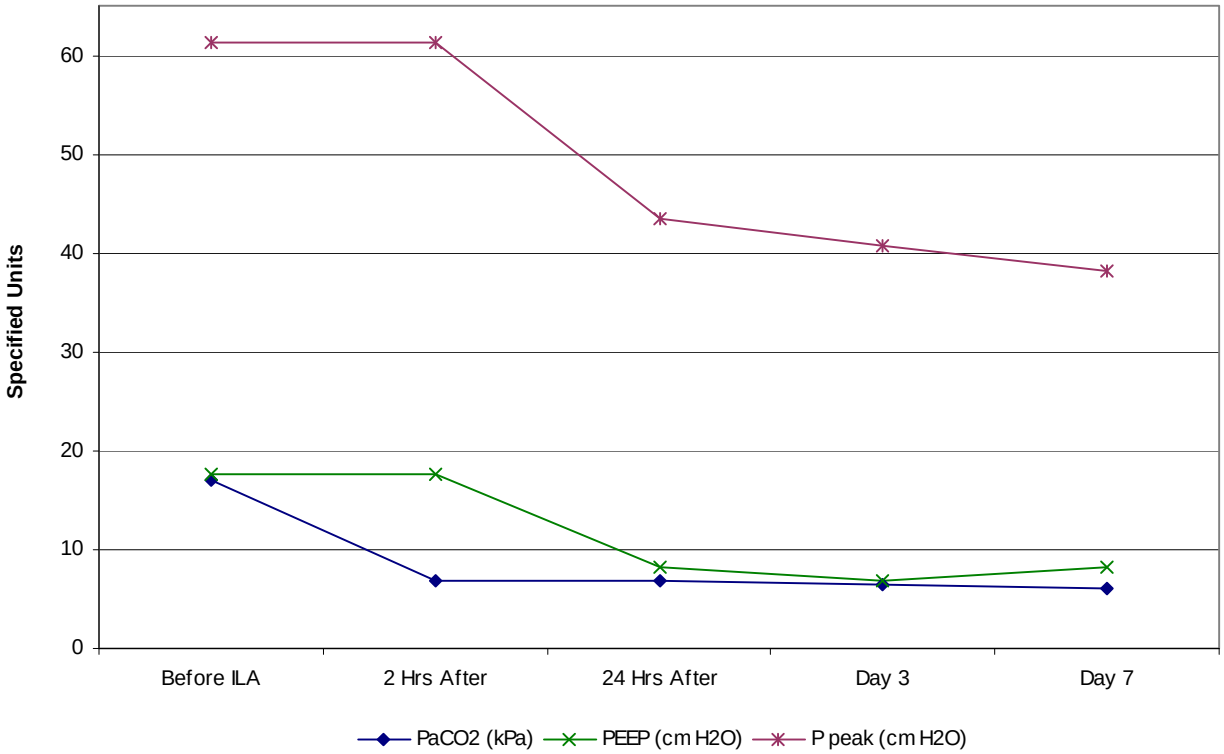

Figure 13: Changes in respiratory settings, Fischer et al. 2006

Changes in Hemodynamic Parameters

All studies reported that the institution of ILA did not result in hemodynamic instability. Three also reported that the mean arterial pressure remained stable when the amount of catecholamine use was lowered (Table 5). (21;23;24)

Table 5: Changes in Hemodynamic Parameters

Author, Year	Time Frame	Cardiac Output (L/min)	Mean Arterial Pressure (mmHg)	Noradrenaline (µg/kg/min)
Müller et al. 2009 (20)	Pre-ILA: 2 Hrs after: 24 Hrs after: 48 Hrs after:	8.76±2.6 9.45±2.6*	85±16.6 85.3±14.7 89.6±15.4* 87.8±16.4	mg/h 1.67±2.18
Zimmermann et al. 2009‡ (21)	Pre-ILA: 2 Hrs after: 24 Hrs after:	NR	73 (65-80) 83 (75-91)* 81 (76-90)	0.16 (0.04-0.35) 0.11 (0.03-0.28) 0.09 (0.02-0.24)*
Weber-Carstens et al. 2009 (22)	Pre-ILA: 6 Hrs after: 12 Hrs after 24 Hrs after: Day 3: Day 4:	NR	NR	0.2 (0.06-0.7) 0.02 (0-0.13)
Florchinger et al. 2008 (23)	 Pre-ILA: 2 Hrs after: 24 Hrs after: Before termination Day 1 after termination:	 8.7±2.8 9.7±2.7 9.3±2.1 8.5±2.5 6.8±3.3	 74±14 87±17 89±15 84±13 80±14	mg/h 2.0±1.9 2.0±2.4 1.3±1.3 0.6±0.8 0.5±0.8
Muellenbach et al. 2008 (24)	Pre-ILA: Survivors: Non-survivors: 1 Hrs after: Survivors: Non-survivors: 24 Hrs after: Survivors: Non-survivors: Before termination: Survivors: Non-survivors: 1 hour after termination: Survivors: Non-survivors:	NR	88 (81-99) 87 (78-97) 96 (89-99) 95 (90-97) 96 (91-98) 	 38 (19-90) 188 (156-238) 35 (23-78) 200 (163-200) 22 (12-38) 105 (58-258) 8 (0-12) 7 (6-9) 9 (0-13) 6 (4-8)
Fisher et al. 2006 (25)	Pre-ILA: 2 Hrs after: 24 Hrs after: 72 Hrs after: 7 days after:	NR	72±8 74±7 78±8 77±6 75±5	NR
Bein et al. 2005 (26)	Pre-ILA: 2-4 Hrs after: 24 Hrs after: 48 Hrs after:	NR	86.2±11.58 92.6±7.44 92.4±5.98 94±5.7	NR

NR, Not reported;
‡Reported median

Mortality Rate and Frequency of Complications

Overall, 56.4% of patients died in hospital due to a variety of reasons. Mortality rate was the highest among patients in the study by Florchinger et al. (23) in which 75 died during ILA therapy and 29 after the therapy. Three studies reported the number of patients who died while on ILA (50%, 50%, and 72% of deaths). (22;23;25) Florchinger et al. (23) reported that one third of deaths during ILA therapy occurred within the first 24 hours of ILA insertion. Zimermann et al. (21) reported that non-survivors had a significantly higher age compared to survivors (see Table 6 and Figure 14).

Table 6: Mortality Rate and Frequency of Complications

Author, Year	Hospital Mortality, N (%)	Limb Ischemia, N (%)	Compartmental Syndrome, N (%)	Cannula Thrombosis, N (%)	Leg Amputation, N (%)	Other N (%)
Müller et al., 2009 (20)	NR	NR	NR	NR	NR	NR
Zimmermann et al., 2009 (21)	25 (49)	3 (5.9)	1 (1.9)	1 (1.9)	0	1 (1.9)
Weber-Carstens et al., 2009 (22)	6 (60) 3 died during ILA	NR	NR	NR	NR	NR
Florchinger et al., 2008 (23)	104 (65.4) 75 died during ILA	13 (8.2)	4 (2.5)	2 (1.6)	1 (0.6)	0
Muellenbach et al., 2008 (24)	6 (27.3)	2 (9.1)	0	0	1 (4.5)	2 (9.1)
Fisher et al., 2006 (25)	4 (33) 2 died during ILA 2 died after LTx	NR	NR	NR	NR	NR
Bein et al., 2005 (26)	1 (20)	NR	NR	NR	NR	NR

NR, Not reported; LTx, Lung transplantation

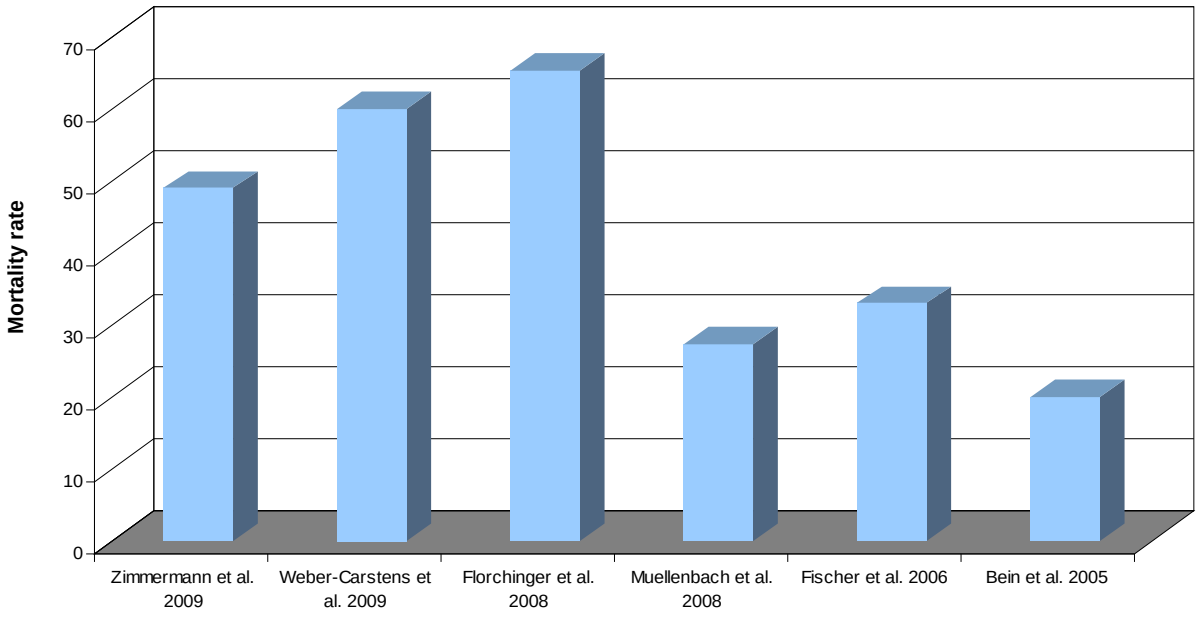

Figure 14: In-Hospital Mortality Rate

Only three studies reported adverse events from ILA therapy. (21;23;24) The most frequent adverse event was limb ischemia, which occurred in 7.8% of patients and led to amputation of the affected leg in two patients (0.9%). The current method used to prevent such ischemias is to insert an extra cannula into the femoral artery to perfuse the leg. Following limb ischemia, compartmental syndrome and cannula thrombosis were the most prevalent adverse events, occurring in 2.2% and 1.3% of patients, respectively (Figure 15).

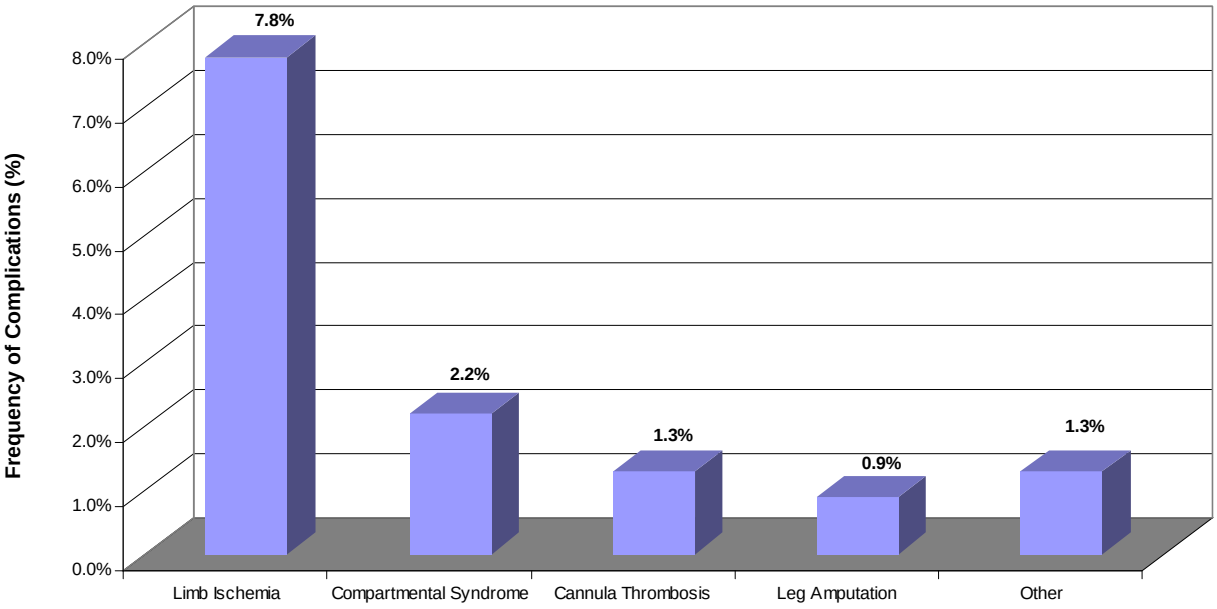

Figure 15. Frequency of Complications

Fischer et al. (25) were the first to apply ILA as a bridge to LTx. In this study, 12 patients at high urgency status to receive LTx and who had severe ventilation refractory hypercapnea and respiratory acidosis were connected to ILA prior to LTx. Seven of these patients had systemic infection or sepsis. Six hours after insertion of ILA partial pressure of CO_2 in their arterial blood significantly decreased ($P < .05$) and arterial blood pH significantly increased ($P < .05$) and remained stable for one week (last time point reported). The partial pressure of oxygen in arterial blood improved from 71 mmHg to 83 mmHg 6 hours after insertion of ILA, while the PaO_2/FiO_2 ratio improved from 135 at the baseline to 168 at 24 hours after insertion (returning to baseline values one week after). Twenty-four hours after the insertion of ILA, the peak ventilatory pressure was lowered from 61 cm H_2O to 43.5 H_2O, while the PEEP was lowered from 17.7 cm H_2O to 8.2 H_2O.

Two patients died of multiorgan failure before LTx but the remaining 10 underwent successful transplants from which eight survived. One year survival for those who underwent successful transplant was 80%.

Muller et al. found that blood flow through ILA was dependent on cannula size. The mean blood flow was 1.59±0.52 L/min^{-1} for cannulas of 15 Fr in size, 1.94±0.35 L/min^{-1} for 17 Fr cannulas, and 2.22±0.45 L/min^{-1} for 19 Fr cannulas. The study also showed a linear correlation between ILA blood flow and mean arterial pressure (MAP); r = 0.53, $P < .01$. CO_2 elimination was also dependent on the size of the cannula (r = 0.23, $P < .01$) as was oxygen transfer (r = 0.43, $P < .01$). For example, CO_2 removal was 135.6±30.2 mL/min^{-1} with 15 Fr cannulas, versus 144.1±68.6 mL/min^{-1} with 17 Fr cannulas, and 154.3±58.1 mL/min^{-1} with 19 Fr cannulas ($P < .001$).

Results of Evidence-Based Analysis: ECMO

Bridge to Recovery

The CESAR Trial

The "CESAR trial" was the only large RCT identified in the literature review. The study was conducted to assess the effectiveness and cost-effectiveness of ECMO therapy for severe acute respiratory failure. The primary hypothesis was that, compared to conventional treatment, an ECMO based protocol would increase survival without severe disability 6 months after randomization and would be cost effective. The trial's protocol were published in 2006 (28) and the economic evaluation methods in 2008 (29)

CESAR was a pragmatic trial, similar to a UK neonatal ECMO trial (15), in which the best standard practice was compared to an ECMO centered protocol. In it, 766 adult patients were screened and 180 eventually enrolled. Patients in this study were unconscious, intubated, and under mechanical ventilation. Therefore, they were not able to give consent for inclusion in the study at the time of randomization. This was instead provided by relatives on patients' behalf. Patients who became conscious were given the opportunity to withdraw from the study. Blinding of treating physicians and other staff to the arms of the study was not possible in the CESAR trial.

Eligible patients were in acute but potentially reversible respiratory failure with a Murray score ≥ 3.0 (the Murray score is a 0 to 4 grading system for ARDS; see Glossary) or uncompensated hypercapnea with pH < 7.2. The exclusion criteria were: high peak inspiratory pressure (> 30 cm H_2O), high FiO_2 (> 80%), and ventilation for > 7 days. Patients with intracranial bleeding or contraindications to heparin therapy or continuation of active treatment were also excluded. Enrolled patients were randomized in a 1:1 ratio to receive either conventional ventilation treatment or ECMO while on ventilator. Conventional management included intermittent positive pressure ventilation, high frequency oscillatory ventilation, or both. Since the study was a pragmatic trial, a specific management protocol was not followed, rather the treatment centres were advised to follow a low volume, low pressure ventilation strategy. A tidal volume of 4 to 8 mL/kg body weight and a plateau pressure of < 30 cm H_2O were recommended.

Overall, 103 hospitals obtained ethics committee approval to participate in the study (11 were referral hospitals); but in the end, all 180 enrolled patients were from 68 centres. Patients who were randomized to the ECMO arm (n=90) were treated in an ECMO based centre, while patients randomized to the conventional ventilation arm (n=90) were treated at conventional treatment centres. If ECMO patients were hemodynamically stable, a standard protocol was used for respiratory therapy. If a patient did not respond to the protocol within 12 hours or if they were hemodynamically unstable, they received ECMO therapy in addition to respiratory therapy. All ECMO treatments were venovenous with percutaneous cannulation. ECMO therapy was then continued until lung recovery or development of irreversible multiorgan failure.

The primary outcome was death or severe disability at 6 months after randomization or before discharge from the hospital. Severe disability was defined as confinement to bed and inability to wash or dress alone. No patient was disabled before they became ill but at the time of randomization, they were all disabled. Secondary outcomes were duration of ventilation, use of high frequency oscillation or jet ventilation, use of nitric acid, prone positioning, use of steroids, and ICU stay. Health status at 6 months after randomization was assessed by SF-36, EuroQol-5 dimensions (EQ-5D), St. George Hospital Respiratory Questionnaire, Hospital Anxiety and Depression Scale, and mini-mental state examination. Upper arm movements were examined, lung function was assessed by spirometry, and specific questions were asked about patients' sleep. During follow-up, if a home visit was not possible, patients were offered a telephone interview or postal questionnaire. For patients refusing this option, permission was requested to obtain information from their general practitioners.

Results

Six month follow-up was conducted at patients' homes by researchers blinded to the treatment allocation. (patients used a scarf to conceal their incision scars). A total of 22 patients assigned to the ECMO arm did not receive ECMO: five because they had died before or during transfer, one because of a contraindication to heparin, and 16 received only conventional ventilation. Therefore, only 68 (75%) of these 90 patients actually received ECMO. Overall, 90.6% of the study population complied with their randomized arm. A final total of 52 patients were assessed at 6 months follow-up in the ECMO arm and 32 in the conventional ventilation arm.

The CESAR trial preserved the randomized arms of the study and addressed the pragmatic hypothesis about the clinical utility of ECMO; therefore, an intention to treat analysis was used. A greater number of patients in the ECMO arm survived, but the difference did not reach statistical significance. The survival rate at 6 months was 63% in the ECMO arm and 50% in the conventional ventilation arm (relative risk: 0.73; 95% CI: 0.52 - 1.03; *P*=.07).

In the conventional ventilation arm, one patient became disabled and three did not have any information about severe disability. For patients with this information, 57 (63%) allocated to ECMO survived without severe disability at 6 months compared to 41 (47%) in the conventional ventilation arm (RR: 0.69; 95% CI: 0.05 - 0.97; *P*=.03). The absolute risk reduction was 16% and the number needed to treat was 6.25, meaning that for about every six ARDS patients referred to an ECMO centre, one's life will be saved and without severe disability. No analytical approach was reported for patients for whom there was no information regarding disability; however, the relative risk for two other possible case scenarios shows a survival benefit for patients referred to the ECMO centre:

- Assuming that three patients in the conventional ventilation arm who had no information on disability were all severely disabled, the relative risk would be 0.67 (95% CI: 0.48 - 0.94; *P*=.017).
- Assuming that none of these patients were severely disabled, the relative risk would be 0.72 (95% CI: 0.51 - 1.01; *P*=.051).

One death was related to ECMO therapy. Time from randomization to death was substantially shorter in the conventional ventilation group than the ECMO group (log-rank test *P*= 0.027). Most deaths in the conventional ventilation group were due to respiratory failure (60% of deaths in conventional ventilation versus 24% of deaths in ECMO group), while multiorgan failure was the cause of the majority of deaths in ECMO group (42% of deaths in ECMO group versus 33% of deaths in conventional ventilation group).

Hospital stay and ICU stay were longer in ECMO group than conventional ventilation group. Additional treatments such as steroid therapy and molecular albumin recirculating system for liver dysfunction were used more frequently for the ECMO patients than those in the conventional ventilation group (*P* = .001 and *P* < .0001 respectively).

Two serious adverse events resulting in the death of the patients were reported in ECMO group. One was a mechanical failure of the oxygen supply in the ambulance. The second was due to a vessel perforation during cannulation. There was also another death in ECMO group due to catastrophic pulmonary hemorrhage which was believed to be related to an underlying disease. No other serious complications were reported in either group.

Bridge to Lung Transplantation

No studies meeting the previously listed inclusion criteria were identified for the use of pumpless ECMO as bridge to LTx. Jackson et al. (30) reported the use of ECMO as bridge to LTx in three cases, along with a review of the literature. According to this report, there is no accurate data on the use of ECMO in patients awaiting LTx. Some authors indicated that pre-LTx ECMO negatively affects LTx outcomes.

Summary and Conclusions

ILA

Bridge to recovery

- No randomized controlled trial or observational studies compared ILA to other treatment modalities
- Case series have shown that ILA therapy results in significant CO_2 removal from arterial blood and correction of respiratory acidosis, as well as an improvement in oxygen transfer.
- ILA therapy enabled a lowering of respiratory settings to protect the lungs without causing a negative impact on arterial blood CO_2 and arterial blood pH
- The impact of ILA on patient long-term survival cannot be determined through the studies reviewed
- In-hospital mortality across studies ranged from 20% to 65%
- Ischemic complications were the most frequent adverse events following ILA therapy
- Leg amputation is a rare but possible outcome of ILA therapy and occurred in about 0.9% of patients in these case series. New techniques involving the insertion of additional cannula into the femoral artery to perfuse the leg may lower the rate of this complication.

Bridge to LTx

- The results of one case series (n=12) showed that ILA effectively removes CO_2 from arterial blood and corrects respiratory acidosis in patients with ventilation refractory hypercapnea awaiting a LTx
- Ten of the 12 patients awaiting a LTx were transplanted and one-year survival for those transplanted was 80%

Since all studies are case series, the grade of the evidence for these observations is classified as "LOW" (see Appendix 2).

ECMO

Bridge to recovery

Based on the results of a pragmatic trial and an intention to treat analysis, referral of patients to an ECMO based centre significantly improves patient survival without severe disability compared to conventional ventilation. The results of CESAR trial show that:

- For patients with information about disability, survival without severe disability was significantly higher in ECMO arm.
  - Assuming that three patients in the conventional ventilation arm who did not have information about severe disability were all disabled, the results were also significant.
  - Assuming that none of these patients were disabled, the results were at borderline significance.
- A greater, though not statistically significant, proportion of patients in ECMO arm survived.
- The rate of serious adverse events was higher among patients in ECMO group.

The grade of the evidence for the above observations is classified as "HIGH" (see Appendix 2)

Bridge to LTx

- No studies fitting the inclusion criteria were identified.
- There is no accurate data on the use of ECMO in patients awaiting a LTx.

Economic Analysis

DISCLAIMER

The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this project was to determine the costs associated with extracorporeal lung support technologies (i.e., ECMO and ILA) for bridge to LTx in adults.

Method

A literature search was conducted (described in Appendix 4) for which the target population was adults eligible for extracorporeal lung support. The primary analytic perspective was that of the Ministry of Health and Long-Term Care (MOHLTC). Articles published in English and fitting the following inclusion criteria were reviewed:

- full economic evaluations [cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA)];
- economic evaluations reporting incremental cost-effectiveness ratios (ICER), i.e., cost per quality adjusted life year (QALY), life years gained (LYG), or cost per event avoided; and
- studies conducted among patients eligible for lung support technologies for LTx.

No articles reporting comparative economic analyses were identified.

Resource Use and Costs

Costs associated with both ILA and ECMO were obtained (outlined in Table 7) from the University Health Network (UHN) case costing initiative (personal communication, UHN, January 2010). Consultation with a clinical expert in the field was also conducted to verify resource utilization. The consultant was situated at the UHN in Toronto. The UHN has one ECMO machine, which cost approximately $100,000. The system is 18 years old and used an average of 3 to 4 times a year with 35 procedures being performed in the last 9 years. The disposable cost per patient associated with ECMO is, on average, $2,200. There is a maintenance cost associated with the machine, however it was not reported by the UHN and it's currently absorbed by the hospital's biomedical engineering department.

The average capital cost of the ILA device is $7,100 per device, per patient, while the average cost of the reusable pump $65,000. The UHN has performed 16 of these procedures in the last 2.5 years. Similarly, there is a maintenance cost not reported by UHN but absorbed by the hospital's biomedical engineering department.

Table 7: Resources Associated with Extracorporeal Lung Support Technologies

Resource	Unit	Cost	Comments
		ECMO	
Capital	per machine	$100,000	UHN has one machine; 18 years old; used 3-4 times a year; 35 procedures in the last 9 years
Disposables	per patient	$2,210	Cannulas, tubings, etc.
Maintenance cost		NR	Hospital incurs a cost for maintenance
		ILA	
Capital	per device/per patient	$7,100	ILA device plus disposables; 16 procedures in the last 2.5 years
Reusable pump	per lifetime	$65,000	Reusable; pump is 3 years old
Maintenance cost		Not Reported	Hospital incurs a cost for maintenance

Hospital costs associated with ILA were based on average costs incurred at the hospital for 11 cases performed in the FY 07/08 (personal communication, UHN, January 2010). The resources incurred with this hospital procedure included:

- Device and disposables
- OR transplant
- Surgical ICU
- Laboratory work
- Medical imaging
- Pharmacy
- Clinical nutrition
- Physiotherapy
- Occupational therapy
- Speech and language pathology
- Social work

The average length of stay in hospital for ILA was 61 days (range: 5 - 164 days) and the average direct cost was $186,000 per case (range: $19,000 - $552,000). This procedure has a high staffing requirement to diligently monitor patients in hospital, driving up the average cost per case.

Conclusion

The average hospital cost of ILA is $186,000 per case, based on experiences at one hospital.

Glossary

ARDS	Acute respiratory distress syndrome is a descriptive term that has been applied to many acute, diffuse infiltrative lung lesions caused by various underlying conditions such as sepsis, injury, etc.
Lung compliance	A measure of lung distensibility. Lung compliance can be calculated as tidal volume / Peak inspiratory pressure – PEEP
Minute Ventilation	The total amount of gas (in litres) expelled from the lungs in a minute. It is the product of tidal volume and respiration rate
FiO_2	Fraction of inspired oxygen, the percentage of oxygen that can be delivered to the patient during mechanical ventilation. Normal room air has a 21% oxygen content. High levels of FiO_2 for an extended period of time can be dangerous
Intention to treat analysis	A method of analyzing randomized controlled trial data. The method is used to preserve the randomization and to avoid baseline imbalances between the arms of the study. Therefore, the clinical effectiveness for each arm of the study is assessed based on the treatment initially assigned irrespective of compliance with the assigned treatment
Murray score	Murray score is a grading system for ARDS that uses four pieces of information graded 0-4 to score the severity of the disease. The data required to calculate Murray score are; PaO_2/FiO_2 in mmHg (while on 100% FiO_2 for at least 20 minutes), PEEP in cm H_2O, lung compliance in ml/cm H_2O, number of quadrants with infiltration seen on chest x-ray (1 point per quadrant)
Partial pressure of a gas	Partial pressure of a gas is the amount of pressure exerted by that gas in particular area. Gases always move from a high pressure area to the low pressure area; the difference in partial pressure of a gas in two areas (e.g. alveoli and blood) encourages its transfer.
Pragmatic trial	Pragmatic trials test whether an intervention works under “real-life” conditions as opposed to explanatory trials which test whether an intervention works under “ideal” conditions. Pragmatic trials are most useful for deciding what services should be provided but provide only limited insight into why the interventions works or do not work
Tidal volume	The volume of air inspired and expired with each breath. Tidal volumes can range from 4 - 12 ml/kg body weight
PEEP	Positive end-expiratory pressure refers to holding pressure in the lungs during the exhalation phase of mechanical ventilation. PEEP is usually set with the minimal positive pressure required to maintain an adequate PaO_2 with a safe FiO_2.

Appendices

Appendix 1: Literature Search Strategies for ILA

Search date: September 28, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to September Week 3 2009>
Search Strategy:

1 exp Extracorporeal Membrane Oxygenation/ or exp Oxygenators, Membrane/ or exp Extracorporeal Circulation/ or Extracorporeal membrane oxygenat*.mp. or ecmo.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (48684)
2 exp Pulmonary Gas Exchange/ or exp Respiration, Artificial/ or exp Ventilators, Mechanical/ (68171)
3 pumpless.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (104)
4 (1 or 2) and 3 (92)
5 ((lung* or pulmonary) adj5 (interventional or extracorporeal or arteriovenous) adj2 (membrane or assist*)).mp. (328)
6 (novalung or nova lung or novabreath or nova breath).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (23)
7 ((membrane adj2 ventilat*) or extracorporeal gas exchange).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (70)
8 (pecla or p-ecla or ECLS or AV-ECCO2R).ti,ab. (252)
9 or/4-8 (651)
10 limit 9 to (english language and humans and yr="2000 -Current") (186)
11 limit 10 to (case reports or comment or editorial or letter) (79)
12 10 not 11 (107)

Database: EMBASE <1980 to 2009 Week 39>
Search Strategy:

1 exp extracorporeal oxygenation/ (4174)
2 exp oxygenator/ (1647)
3 exp extracorporeal circulation/ (31253)
4 (Extracorporeal membrane oxygenat* or ecmo).mp. (3022)
5 exp ventilator/ (5180)
6 exp gas exchange/ (6527)
7 exp artificial ventilation/ (56606)
8 exp artificial lung/ (123)
9 exp assisted ventilation/ (54852)
10 exp lung gas exchange/ (4278)
11 or/1-10 (121315)
12 Pumpless.mp. (109)
13 ((lung* or pulmonary) adj5 (interventional or extracorporeal or arteriovenous) adj2 (membrane or assist*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (305)
14 ((membrane adj2 ventilat*) or extracorporeal gas exchange).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (73)
15 (pecla or p-ecla or ECLS or AV-ECCO2R).ti,ab. (247)
16 (novalung or nova lung or novabreath or nova breath).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (38)
17 11 and 12 (98)
18 (extracorporeal adj2 gas exchange).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (51)
19 or/13-18 (630)
20 limit 19 to (human and english language and yr="2000 -Current") (180)
21 limit 20 to (editorial or letter or note) (9)
22 case report/ (1056116)
23 20 not (21 or 22) (107)

Appendix 2: Literature Search Strategies for ECMO in Lung Transplantation

Search date: December 29, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to November Week 3 2009>
Search Strategy

1 exp Extracorporeal Membrane Oxygenation/ (2324)
2 (ecmo or Extracorporeal Membrane Oxygenat* or (extracorporeal adj2 lung* support)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2850)
3 1 or 2 (2850)
4 exp Lung Transplantation/ (6040)
5 ((lung* or pulmonary) adj2 (graft* or transplant*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7678)
6 4 or 5 (7678)
7 3 and 6 (119)
8 limit 7 to (english language and humans and yr="2005 -Current") (55)

Database: EMBASE <1980 to 2009 Week 52>
Search Strategy

1 exp extracorporeal oxygenation/ (4295)
2 (ecmo or Extracorporeal Membrane Oxygenat* or (extracorporeal adj2 lung* support)).mp. (3122)
3 1 or 2 (4862)
4 exp lung transplantation/ (10398)
5 ((lung* or pulmonary) adj2 (graft* or transplant*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (15889)
6 4 or 5 (15889)
7 3 and 6 (248)
8 limit 7 to (human and english language and yr="2005 -Current") (120)

Appendix 3: Grade of Evidence

Table A1: Grading System

Population	Outcome	No. of studies	Study Design	Quality of Studies	Consistency	Directness	Other Factors
			RCT= High Observational=Low Any other evidence=Low	Serious limitation (-1) Very serious (-2)	Important inconsistency (-1)	Some uncertainty (-1) Major uncertainty (-2)	Defined as*

*=Association: Strong (+1), very strong (+2)
Dose response gradient (+1)
All plausible confounders would have reduced the effect (+1)
Imprecise or sparse data (-1)
High probability of reporting bias (-1)

Table A2: GRADE Table for ILA

Population	Outcome	No. of studies	Study Design	Quality of Studies	Consistency	Directness	Other Factors
Patients with respiratory failure caused by a range of underlying diseases/conditions	Gas exchange	7	Case series=Low	No change	No change	No change	No change

Table A3: GRADE Table for ECMO

Population	Outcome	No. of studies	Study Design	Quality of Studies	Consistency	Directness	Other Factors
Patients with respiratory failure caused by a range of underlying diseases/conditions	Survival without severe disability	1	RCT=High	No change	No change	No change	No change

Appendix 4 - Economic Literature Search Strategy

Search date: October 29, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, EconLit

Database: Ovid MEDLINE(R) <1950 to October Week 3 2009>
Search Strategy

1 exp Extracorporeal Membrane Oxygenation/ or exp Oxygenators, Membrane/ or exp Extracorporeal Circulation/ or Extracorporeal membrane oxygenat*.mp. or ecmo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (48894)
2 exp Pulmonary Gas Exchange/ or exp Respiration, Artificial/ or exp Ventilators, Mechanical/ (68465)
3 pumpless.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (105)
4 (1 or 2) and 3 (93)
5 ((lung* or pulmonary) adj5 (interventional or extracorporeal or arteriovenous) adj2 (membrane or assist*)).mp. (329)
6 (novalung or nova lung or novabreath or nova breath).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (23)
7 ((membrane adj2 ventilat*) or extracorporeal gas exchange).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (70)
8 (pecla or p-ecla or ILA or AV-ECCO2R).ti,ab. (253)
9 or/4-8 (654)
10 limit 9 to (english language and humans and yr="2000 -Current") (186)
11 limit 10 to (case reports or comment or editorial or letter) (79)
12 10 not 11 (107)
13 exp Economics/ (415902)
14 exp Models, Economic/ (6869)
15 exp Resource Allocation/ (13121)
16 exp "Value of Life"/ or exp "Quality of Life"/ (83678)
17 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (185972)
18 ec.fs. (263342)
19 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (61663)
20 or/13-19 (705428)
21 9 and 20 (10)
22 limit 21 to (english language and yr="2000 -Current") (6)

Database: EMBASE <1980 to 2009 Week 43>
Search Strategy

1 exp extracorporeal oxygenation/ (4207)
2 exp oxygenator/ (1651)
3 exp extracorporeal circulation/ (31422)
4 (Extracorporeal membrane oxygenat* or ecmo).mp. (3041)
5 exp ventilator/ (5207)
6 exp gas exchange/ (6547)
7 exp artificial ventilation/ (56981)
8 exp artificial lung/ (123)
9 exp assisted ventilation/ (55239)
10 exp lung gas exchange/ (4319)
11 or/1-10 (122060)
12 Pumpless.mp. (109)

13 ((lung* or pulmonary) adj5 (interventional or extracorporeal or arteriovenous) adj2 (membrane or assist*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (305)
14 ((membrane adj2 ventilat*) or extracorporeal gas exchange).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (75)
15 (pecla or p-ecla or ILA or AV-ECCO2R).ti,ab. (247)
16 (novalung or nova lung or novabreath or nova breath).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (38)
17 11 and 12 (98)
18 (extracorporeal adj2 gas exchange).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (51)
19 or/13-18 (632)
20 limit 19 to (human and english language and yr="2000 -Current") (182)
21 limit 20 to (editorial or letter or note) (9)
22 case report/ (1060365)
23 20 not (21 or 22) (108)
24 exp "Health Care Cost"/ (110608)
25 exp Health Economics/ (242305)
26 exp Resource Management/ (15182)
27 exp Economic Aspect/ or exp Economics/ or exp Quality Adjusted Life Year/ or exp Socioeconomics/ or exp Statistical Model/ or exp "Quality of Life"/ (507934)
28 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (112404)
29 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (55312)
30 or/24-29 (582904)
31 limit 30 to yr="2000 -Current" (376009)
32 19 and 31 (24)
33 limit 32 to english language (20)

References

(1) Ricard JD, Dreyfuss D, Saumon G. Ventilator-induced lung injury. Curr Opin Crit Care 2002; 8(1):12-20.

(2) Dreyfuss D, Saumon G. From ventilator-induced lung injury to multiple organ dysfunction? Intensive Care Med 1998; 24(2):102-4.

(3) Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 1998; 157(1):294-323.

(4) Cypel M, Rubacha M, Yeung J, Hirayama S, Torbicki K, Madonik M et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. Am J Transplant 2009; 9(10):2262-9.

(5) Cypel M, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M et al. Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant 2008; 27(12):1319-25.

(6) Yeung JC, Cypel M, Waddell TK, Van RD, Keshavjee S. Update on donor assessment, resuscitation, and acceptance criteria, including novel techniques--non-heart-beating donor lung retrieval and ex vivo donor lung perfusion. Thorac Surg Clin 2009; 19(2):261-74.

(7) Lewandowski K. Extracorporeal membrane oxygenation for severe acute respiratory failure. Crit Care 2000; 4(3):156-68.

(8) Toronto General Hospital Multiorgan Transplant Program. Program achievements [Internet]. [updated 2001; cited 2010 Jan 15]. Available from: http://www.torontotransplant.org/programInfo/achievements.cfm

(9) London Health Sciences Centre. Multi-organ transplant program: statistics [Internet]. [updated 2009 Aug 18; cited 2010 Jan 10]. Available from: http://www.lhsc.on.ca/About_Us/MOTP/Statistics/index.htm

(10) Canadian Institute for Health Information. Table 1 A: Transplants by organ and donor type, province of treatment, Canada (Number) [Internet]. 2010 Jan 1. [cited: 2010 Feb 2]. Available from: http://secure.cihi.ca/cihiweb/en/downloads/corr_mid_year_tables_2009.pdf

(11) Canadian Institute for Health Information. Table 2 A: Patients waiting for transplants, province of treatment, Canada (Number) [Internet]. 2010 Jan 1. [cited: 2010 Feb 2]. Available from: http://secure.cihi.ca/cihiweb/en/downloads/corr_mid_year_tables_2009.pdf

(12) Trillium Gift of Life Network. Transplant 10-year history [Internet]. [updated 2010 Jan 14; cited 2010 Jan 10]. Available from: http://www.giftoflife.on.ca/page.cfm?id=27AB4669-F323-4ABC-8D4D-34AA102BF7C6

(13) Go T, Macchiarini P. Artificial lung: current perspectives. Minerva Chir 2008; 63(5):363-72.

(14) Furukawa S. Extracorporeal support of oxygenation and ventilation. Int Anesthesiol Clin 1997; 35(1):169-76.

(15) UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. UK

Collaborative ECMO Trail Group. Lancet 1996; 348(9020):75-82.

(16) Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979; 242(20):2193-6.

(17) Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Jr., Weaver LK et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. [erratum appears in Am J Respir Crit Care Med 1994 Mar;149(3 Pt 1):838]. Am J Respir Crit Care Med 1994; 149(2:Pt 1):t-305.

(18) Meyer A, Struber M, Fischer S. Advances in extracorporeal ventilation. Anesthesiol Clin 2008; 26(2):381-91.

(19) Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006; 34(5):1372-7.

(20) Muller T, Lubnow M, Philipp A, Bein T, Jeron A, Luchner A et al. Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. Eur Respir J 2009; 33(3):551-8.

(21) Zimmermann M, Bein T, Arlt M, Philipp A, Rupprecht L, Mueller T et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. Crit Care 2009; 13(1):R10.

(22) Weber-Carstens S, Bercker S, Hommel M, Deja M, MacGuill M, Dreykluft C et al. Hypercapnia in late-phase ALI/ARDS: providing spontaneous breathing using pumpless extracorporeal lung assist. Intensive Care Med 2009; 35(6):1100-5.

(23) Florchinger B, Philipp A, Klose A, Hilker M, Kobuch R, Rupprecht L et al. Pumpless extracorporeal lung assist: a 10-year institutional experience. Ann Thorac Surg 2008; 86(2):410-7.

(24) Muellenbach RM, Kredel M, Wunder C, Kustermann J, Wurmb T, Schwemmer U et al. Arteriovenous extracorporeal lung assist as integral part of a multimodal treatment concept: a retrospective analysis of 22 patients with ARDS refractory to standard care. Eur J Anaesthesiol 2008; 25(11):897-904.

(25) Fischer S, Simon AR, Welte T, Hoeper MM, Meyer A, Tessmann R et al. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. J Thorac Cardiovasc Surg 2006; 131(3):719-23.

(26) Bein T, Scherer MN, Philipp A, Weber F, Woertgen C. Pumpless extracorporeal lung assist (pECLA) in patients with acute respiratory distress syndrome and severe brain injury. J Trauma 2005; 58(6):1294-7.

(27) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454):1490.

(28) Peek GJ, Clemens F, Elbourne D, Firmin R, Hardy P, Hibbert C et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. BMC Health Serv Res 2006; 6:163.

(29) Thalanany MM, Mugford M, Hibbert C, Cooper NJ, Truesdale A, Robinson S et al. Methods of data collection and analysis for the economic evaluation alongside a national, multi-centre trial in the UK: conventional ventilation or ECMO for Severe Adult Respiratory Failure (CESAR). BMC Health Serv Res 2008; 8:94.

(30) Jackson A, Cropper J, Pye R, Junius F, Malouf M, Glanville A. Use of extracorporeal membrane oxygenation as a bridge to primary lung transplant: 3 consecutive, successful cases and a review of the literature. J Heart Lung Transplant 2008; 27(3):348-52.