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Horizon Scanning Technology Prioritising Summaries

Pumpless extracorporeal lung assist system (Novalung)

June 2006
(Updated August 2007)



ASERNIP/S

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**



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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by Mr. Luis Zamora from the Australian safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).



Name of Technology:

Pumpless extracorporeal interventional lung assist (iLA) system (Novalung® GmbH, Hechingen, Germany).

Purpose and Target Group:

The Novalung iLA system is a gas exchange device that provides pulmonary support for patients suffering from acute respiratory distress syndrome. The system is designed to improve carbon dioxide elimination in combination with a lung protective mechanical ventilation strategy (Bein *et al.* 2005).

Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Not yet emerged in Australia

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely diffused
Europe		✓	
Canada		✓	

Impact Summary:

Background

Acute respiratory distress syndrome (ARDS), or adult respiratory distress syndrome, is a life threatening breathing dysfunction associated with a variety of conditions (Anatomica 2001). ARDS is not a specific disease itself, although it can be associated with various conditions including pneumonia, shock, sepsis, trauma, fluid overload, narcotic overdose and burns (Anatomica 2001).

ARDS causes both lungs to become inflamed. Often the inflammation is severe, resulting in damage to alveoli and surrounding capillaries that affects their ability to exchange oxygen and carbon dioxide (Ware and Matthay 2000). This leads to fluid leaks from capillaries (oedema), which causes the alveoli to collapse or fill with fluid and further reduces the capacity of the lungs for gaseous exchange. Continued inflammation leads to fibrosis as the lungs attempt to heal themselves (Ware and Matthay 2000). The result is a life threatening condition marked by respiratory failure.



Currently the precise cause of ARDS is unknown. Two mechanisms, however, have been associated with its onset (ARDS Support Center, Inc. 2006; National Heart, Lung, and Blood Institute 2006).

- Direct physical or toxic injury of the lungs, such as severe bruising of the lungs or the inhalation of toxic fumes.
- Indirect injury to the lungs through events such as sepsis, trauma to some part of the body, massive transfusion and some types of drug overdose.

Providing sufficient oxygen to and removing carbon dioxide from the blood of an ARDS patient is a crucial part of treatment. Depending on the patient's condition, this can be achieved in various ways, including mechanical ventilation, antibiotics, analgesics, sedatives, cardiovascular approaches and muscle relaxants (Ware and Matthay 2000; ARDS Support Center, Inc. 2006).

Mechanical ventilators are one of the most effective ways of treating ARDS. They can breathe for the patient or assist the patient to breathe. In both instances the goal is to maintain sufficient gaseous exchange while the lungs heal (ARDS Support Center, Inc. 2006). The use of mechanical ventilation, however, remains controversial because the tidal volume required for ARDS patients is higher than for healthy individuals at rest and can lead to ventilator-associated lung injury in some patients (Ware and Matthay 2000). Inflation pressure and tidal volume can both be limited to minimise the high airway pressure and associated lung trauma, but only at the cost of permissive hypercapnia, which carries its own complications (e.g. respiratory acidosis) (Zwischenberger *et al.* 1999).

Extracorporeal lung assist (ECLA) devices can be used to complement mechanical ventilation and reduce the risk of ventilator-associated lung injury during ARDS treatment. ECLA devices are an invasive alternative that work by establishing either a venovenous or venoarterial shunt comprising a roller or pump, a membrane for gaseous exchange and a heat exchanger to maintain blood temperature (Liebold *et al.* 2002). However, this technique also has drawbacks. In particular, the significant blood trauma caused by ECLA devices can lead to haemolysis and coagulation disorders.

In an attempt to overcome many of the limitations of conventional pump driven ECLA devices, the pumpless extracorporeal interventional lung assist (iLA) device was developed. The iLA system consists of three main components (Novalung 2006):

- a heparin coated biocompatible diffusion membrane for gaseous exchange;
- cannulae for femoral access via the Seldinger technique; and
- a monitoring device for measuring volumetric blood flow.

The iLA acts as an extra-pulmonary gas exchange system that uses the patient's arteriovenous pressure gradient as the driving force for the extracorporeal circuit, thus eliminating the need for a pump (Liebold *et al.* 2002; Zimmermann *et al.* 2006).



The system is implanted by inserting cannulae into the femoral artery and femoral vein. These are connected to the membrane apparatus and blood allowed to flow from the artery, through the apparatus and then into the venous cannula (Zimmermann *et al.* 2006). An oxygen supply line is connected to the membrane apparatus to provide oxygen for gaseous exchange, and a bidirectional ultrasound sensor is attached to the venous cannula to monitor volumetric blood flow. The iLA system is easy to handle and does not require continuous support from technical staff. Once implanted the entire system can be placed anywhere that is convenient but this is most often between the patient's legs.

Clinical Need and Burden of Disease

Currently there are no precise figures for the incidence of ARDS (Ware and Matthay 2000). People being treated for serious illness and those who have suffered major injuries are most at risk of developing ARDS (National Heart, Lung, and Blood Institute 2006). It is estimated that 150,000 people are affected by ARDS in the United States (ARDS Support Center, Inc. 2006, National Heart, Lung, and Blood Institute 2006). Estimates of the incidence of ARDS in the United States have been put at 75 per 100,000 population per year (Ware and Matthay, 2000). No figures regarding the incidence or prevalence of ARDS in Australia were found.

ARDS is a very serious condition and usually requires treatment in an intensive care or critical care unit of a hospital. However, only a small fraction of people with conditions that can lead to ARDS actually develop ARDS. For those who do develop ARDS though, mortality rates have been reported to be between 40% and 50% (Ware and Matthay 2000; ARDS Support Center, Inc. 2006).

Estimated Speed and Geographic and Practitioner Use Patterns of Diffusion in the Health System

The Novalung iLA received approval from Health Canada on August 30, 2005. It also received the CE Mark in Europe in 2003. The Novalung iLA, however, is currently not approved by the United States Food and Drug Administration and is not listed in the Australian Register of Therapeutic Goods.

Existing Comparators

- Volume controlled mechanical ventilation
- Pump driven EDLA devices

Estimated Cost Impact

The costs associated with the use of the Novalung iLA were not revealed in our searches. The iLA system is designed to be used in conjunction with lung protective mechanical ventilation strategies. The Medicare Benefits Schedule item numbers, reimbursements and number of claims between July 2004 and June 2005 for mechanical ventilation support of a patient are outlined in Table 1.



Liebold *et al.* (2002) noted that the iLA is a cheaper alternative than pump driven ECLA because it does not need a pump, blood warming device or external power source, and can be used for a longer period of time.

Table 1 Summary of Medicare Benefits Schedule data for mechanical ventilation support.

Category	Item Number	Benefit (AUD)	Number of Claims July 2004 to June 2005
Airway access, establishment of and initiation of mechanical ventilation in an Intensive Care Unit	13881	\$126.70	0
Airway access, establishment of and initiation of mechanical ventilation outside an Intensive Care Unit for subsequent support in an Intensive Care Unit	13857	\$126.70	730
Ventilatory support management in an Intensive Care Unit	13882	\$99.75	44,244

Efficacy and Safety Issues

List of Studies Found

Total number of studies	4
Case series studies	4

The studies included in this summary are highlighted in bold in the reference list. Safety and efficacy data from four case series studies were selected for inclusion in this summary as no randomised controlled trials or comparative studies were available.

Efficacy

Fischer *et al.* (2006) documented the use of the iLA as a bridge to lung transplantation in 12 patients suffering from severe ventilation-refractory hypercapnia and respiratory acidosis. Arterial blood samples were taken from each patient prior to implantation of the iLA, as well as six, 24 and 72 hours and seven days after implantation. The patients received support from the iLA for a mean of 15 days (range 4 to 32 days). Implantation of the iLA had no significant impact on mean arterial blood pressure, which remained stable throughout the implantation period. A significant ($p < 0.05$) reduction in mean carbon dioxide levels in the blood was observed after iLA implantation, with the arterial level of CO₂ (PaCO₂) decreasing from 128 mmHg to 52 mmHg after 6 hours of iLA therapy. This was maintained for the duration of iLA therapy. Oxygenation also improved from a PaO₂ of 71 mmHg to 83 mmHg at six hours and 124 mmHg 24 hours after iLA therapy. These improvements remained stable throughout the seven days of therapy, but were not statistically significant.



The mean blood pH, which was 7.1 at baseline, improved to 7.3 six hours after initiation of the iLA system ($p < 0.05$). This effect was maintained for up to seven days. The use of the iLA system in these patients allowed for a more lung protective mechanical ventilation strategy to be adopted and helped to successfully bridge 10/12 patients to lung transplant by improving severe hypercapnia and acidosis of the blood.

Zimmermann *et al.* (2006) demonstrated the use of iLA for the transportation of eight patients with life threatening acute lung failure from tertiary hospitals to a specialised hospital. All eight patients suffered from severe pulmonary gas exchange impairment with hypoxemia and hypercapnia. Similar to Fischer *et al.* (2006), a significant ($p < 0.05$) improvement in carbon dioxide elimination was observed immediately after and 24 hours after iLA initiation. Mean (\pm standard deviation) values for PaCO₂ were: 8.9 ± 2.9 kPa before iLA initiation; 5.1 ± 0.93 kPa immediately after and 4.53 ± 1.2 kPa after 24 hours. Improved oxygenation was also observed, with the mean PaO₂ increasing from 6.7 ± 2.26 kPa to 10.4 ± 3.33 kPa after iLA. This effect became significant ($p < 0.05$) after 24 hours when the PaO₂ was 10.3 ± 5.46 kPa.

Bein *et al.* (2005) performed a retrospective analysis of the iLA system in five trauma patients suffering severe brain injury and ARDS. The patients were already receiving lung protective mechanical ventilation, so the iLA was used to avoid the detrimental effects of hypercapnia. Within the first four hours of iLA therapy, all five patients experienced a reduction in the levels of carbon dioxide in the blood. In four patients who had hypercapnia, the condition was alleviated completely for the duration of the iLA treatment. Slight improvements in arterial blood oxygenation, intracranial pressure and cerebral perfusion pressure were also observed, although none of these improvements were statistically significant.

Liebold *et al.* (2002) reported on the use of the iLA system under rescue conditions in 70 patients with severe ARDS who had previously been on aggressive mechanical ventilation. The patients received iLA therapy for a median duration of six days (range: one to 35 days). Prior to iLA therapy the mean PaO₂, PaCO₂ and fraction of inspired oxygen were 46 mmHg, 59 mmHg and 1.0 respectively. Within the first 24 hours of treatment all three parameters had improved to 85 mmHg, 32 mmHg and 0.8, respectively. Similar to other studies, improved oxygenation and elimination of carbon dioxide were observed with the iLA system, but these results were not confirmed statistically.

Safety

In the study by Fischer *et al.* (2006), two patients died before lung transplantation because of multi-organ failure. An additional two patients died after transplantation, also as a result of multi-organ failure. Eight patients were still alive one year after transplantation. Three patients required replacement of the iLA membrane as a result of clotting at activated clotting times of less than 150 seconds. Other adverse events noted included systemic infection or sepsis, as determined by blood cultures, in seven patients.



Zimmermann *et al.* (2006) reported that, although cannulation was successful in all eight patients, removal of the arterial cannula in two patients resulted in bleeding and necessitated surgical revision. In addition, transient ischemia of the lower limb was observed in one patient a few days after arterial cannulation. Importantly, during both air and ground transportation no major complications occurred. The length of the transportation period, however, was not stated. Four deaths occurred after iLA treatment as a result of multiple trauma or multiple organ treatment.

Bein *et al.* (2005) reported one death resulting from multi-organ failure. In another patient, stenosis and ulceration of the femoral artery led to acute leg ischemia after removal of the arterial cannula.

In Liebold *et al.* (2002), 36 (51%) patients were successfully weaned from iLA, while 34 (49%) died during iLA support. Of the 36 patients who were weaned, 25 survived a further period of less aggressive mechanical ventilation for a median of 16 days and were discharged home. The remaining 11 patients, however, did not survive to discharge and died as a result of irresolvable organ failure. Overall, the mortality rate was 64%. The authors also described technical problems arising from the use of the system, which occurred in 15 of the 70 patients. The most common was thrombus formation within the arterial cannula ($n = 5$), venous cannula ($n = 2$) and membrane ($n = 1$), which was successfully resolved in all cases. A further three patients experienced limb ischemia and required removal of the arterial cannula. Finally, plasma leakage from the membrane necessitated its replacement on five occasions. However, no deaths were related to use of the iLA or any of the technical difficulties.



2007 update

A search of relevant databases, online journals and the Internet was conducted in June 2007, following the recommendation in June 2006 that pumpless extracorporeal interventional lung assist using the Novalung system be monitored for 12 months. One case series study on the safety and effectiveness of this technology was identified. In addition, five case reports were also identified and retrieved (Elliot et al. 2007, Fischer et al. 2007, Mallick et al. 2007, Muellenbach et al. 2007, Zimmermann et al. 2007); however these were not included in this update.

Bein and colleagues (2006) reported their experience using the Novalung iLA in 90 patients recruited over eight years (1996 – 2004) suffering acute respiratory distress syndrome (Bein et al. 2006). The patients included in the study had previously undergone unsuccessful advanced optimised therapeutic strategies and were at risk for life threatening hypoxemia and/or excessive hypercapnia.

Thirty-seven patients survived treatment with the Novalung iLA (58.8% hospital mortality rate) which lasted 5 ± 5 days. Septic shock and persistent systemic inflammatory response were the major cause of death in the majority of patients ($n = 26$; 49%). The other cause of death included multiple organ failure in 13 patients (25%), cardiac failure in 10 patients (19%) and cerebral injury in four patients (7%). Analysis of various parameters demonstrated that patients who survived hospital treatment with the iLA were significantly younger ($p = 0.009$), had a lower body mass index ($p = 0.001$), had shorter pre-iLA ventilator periods ($p = 0.034$) and had a lower sequential organ failure assessment score ($p = 0.016$).

Treatment with the iLA resulted in significant carbon dioxide removal and a reduction in hypercapnia. Prior to treatment PaCO_2 was 60 mm Hg (IQR: 48 – 80) and reduced to 36 mm Hg (IQR: 30 – 44) two hours after iLA treatment had begun ($p < 0.05$). This further reduced to 34 mm Hg (IQR: 30 – 39) after 24 hours ($p < 0.05$, compared to baseline). Treatment with the iLA also led to an improvement in arterial oxygenation in the majority of patients. The $\text{PaO}_2/\text{FiO}_2$ significantly improved from a baseline of 58 mm Hg (IQR: 47 – 78) to 82 mm Hg (IQR: 64 – 103) at two hours after iLA initiation and 101 mm Hg (IQR: 74 – 142) after 24 hours ($p < 0.05$, compared to baseline). The authors reported that there was no difference in the amount of carbon dioxide removed or the level of additional arterial oxygenation between survivors and non-survivors. The pH level of blood also significantly ($p < 0.05$) improved two hours after iLA treatment from 7.27 (IQR: 7.18 – 7.36) to 7.42 (IQR: 7.35 – 7.52). This improvement was maintained at 24 hours with a pH of 7.45 (IQR: 7.41 – 7.50). Unfortunately, although the study was carried over an eight year period, only immediate post-procedural data are available. Therefore it is not possible to determine whether the improvements observed in the first 24 hours following iLA treatment were maintained during the entire iLA treatment period (5 ± 5 days).

In terms of complications, 22 patients (24.4 %) experienced serious complications. Ischemia of a lower limb after cannulation was the most common complication ($n = 9$) and led to amputation in one patient. In the remaining eight patients, the cannulae were removed and normal perfusion of the limb was restored. Other major complications reported included cannula thrombosis ($n = 4$), compartmental



syndrome in a lower limb (n = 4), hematoma/aneurysm at cannulation site (n = 2), hemolysis (n = 1), intracerebral haemorrhage (n = 1) and diffuse bleeding/shock syndrome during cannulation (n = 1) (Bein et al. 2006).

2007 HealthPACT action:

The Novalung iLA system appears to be capable of providing significant immediate improvement in patients with severe ARDS. Considering the fact that patients who receive iLA treatment are in a very serious condition, the iLA may be a valuable treatment option to improve/prevent hypercapnia and improve oxygenation in these patient. Given the lack of high quality studies and the limitation of small patient cohorts in current studies, it is recommended that the Novalung is monitored for an additional 12 months based on its potential benefits to ARDS patients.

Number of studies included

Total number of studies	1
Level IV intervention evidence	1

References

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Contraindications

- Low cardiac output (Fischer *et al.* 2006)
- Cardiogenic shock (Fischer *et al.* 2006)
- Advanced peripheral atherosclerosis (Fischer *et al.* 2006)
- Extensive coagulation disorders with acute bleeding (Zimmermann *et al.* 2006)

Ethical Issues

No issues were identified from the retrieved literature.

Cultural or Religious Considerations

No issues were identified from the retrieved literature.

Other Issues

No issues were identified from the retrieved literature.

Recommendation:

The Novalung iLA system is an interventional lung support device designed to provide pulmonary support for patients suffering ARDS. Limited evidence from small case series studies suggests that the iLA effectively removes carbon dioxide from the blood of patients with ARDS. Oxygenation of the blood was also demonstrated using the iLA, but to a lesser degree. No major recurrent safety issues were identified. However, due to the lack of literature documenting the use of the iLA in large numbers of patients, or in comparison to conventional pump driven ECLA devices, it is recommended that the Novalung iLA be monitored.

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| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

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Search Criteria:

A search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the UK National Research Register, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted in March 2006.

Search terms used were: 'interventional lung assist', 'iLA', 'Novalung', 'membrane lung', 'extracorporeal oxygenation', 'lung assist device'.

This Horizon Scanning Prioritising Summary was prepared by Mr Luis Zamora from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).