

Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure

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Clinical application of extracorporeal carbon dioxide removal (ECCOR) for acute hypercapnic respiratory failure was first reported in 1979.¹ Initial reports on patients with severe acute respiratory distress syndrome (ARDS) who were not responding to conventional ventilation and were treated using ECCOR appeared to be encouraging.^{2,3} However, when subjected to a randomised controlled trial, ECCOR appeared to offer no benefit compared with conventional ventilation.⁴ Several reasons were proposed for this lack of benefit, including the complexity of the technology of ECCOR, the circuit design, anticoagulation management and case selection.⁵ These factors have restricted the use of ECCOR in routine clinical practice until recently.

Several minimally invasive extracorporeal respiratory support systems with substantial improvements in technology have recently been introduced into clinical practice. These aim to enable lung-protective ventilation while preventing hypercapnic acidosis in patients with ARDS.⁶⁻⁹ Minimally invasive extracorporeal systems usually have a short, heparin-coated circuit with an integrated centrifugal pump, an efficient gas exchanger and a small priming volume to avoid haemodilution.¹⁰ They are distinguished from more invasive extracorporeal membrane oxygenation (ECMO) by reduced blood flow (0.4–0.6 L/min v 3–5 L/min), smaller cannulae (14–15.5 Fr v 21–31 Fr) and avoidance of arterial cannulation and its associated complications.

Abbreviations

ACT	activated clotting time
APACHE	Acute Physiology and Chronic Health Evaluation
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
BOS	bronchiolitis obliterans syndrome
COPD	chronic obstructive pulmonary disease
ECCOR	extracorporeal carbon dioxide removal
ECMO	extracorporeal membrane oxygenation
ICC	intercostal catheter
ICU	intensive care unit
IQR	interquartile range
LPV	lung-protective ventilation
PIP	peak inspiratory pressure
RAS	Respiratory Assist System
TGA	Therapeutic Goods Administration
VATS	video-assisted thoracoscopic surgery

ABSTRACT

Background: Recent advances in the technology of extracorporeal respiratory assist systems have led to a renewed interest in extracorporeal carbon dioxide removal (ECCOR). The Hemolung is a new, low-flow, venovenous, minimally invasive, partial ECCOR device that has recently been introduced to clinical practice to aid in avoiding invasive ventilation or to facilitate lung-protective ventilation.

Objective: We report our early experience on use, efficacy and safety of the Hemolung in three Australian intensive care units.

Methods: Retrospective review of all patients with acute or acute-on-chronic respiratory failure (due to chronic obstructive pulmonary disease [COPD] with severe hypercapnic respiratory failure when non-invasive ventilation failed; acute respiratory distress syndrome; COPD; or asthma when lung-protective ventilation was not feasible due to hypercapnia) for whom the Hemolung was used.

Results: Fifteen patients were treated with ECCOR. In four out of five patients, the aim of avoiding intubation was achieved. In the remaining 10 patients, the strategy of instituting lung-protective ventilation was successful. The median duration for ECCOR was 5 days (interquartile range, 3–7 days). The pH and Pco₂ improved significantly within 6 hours of instituting ECCOR, in conjunction with a significant reduction in minute ventilation. The CO₂ clearance was 90–100 mL/min. A total of 93% of patients survived to weaning from ECCOR, 73% survived to ICU discharge and 67% survived to hospital discharge.

Conclusion: Our data shows that ECCOR was safe and effective in this cohort. Further experience is vital to identify the patients who may benefit most from this promising therapy.

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The use of ECCOR has been reported to facilitate ultra-protective lung ventilation, with tidal volume reduced to less than 6 mL/kg — an outcome that could not be achieved with mechanical ventilation alone.^{8,9} It has been suggested that these devices could have a positive impact on the management of refractory acute respiratory failure.^{11,12}

The Hemolung Respiratory Assist System (RAS) (ALUNG Technologies) is a new, minimally invasive, low-flow ECCOR device. Other ECCOR devices were introduced as an adjunct to ARDS management, but the clinical use of the Hemolung was first reported in a series of 20 patients with chronic obstructive pulmonary disease (COPD) and failure to wean from mechanical ventilation.¹³ That report only showed data until 30 days and provided no hospital discharge data.

The use of complex extracorporeal respiratory support systems, such as ECMO, has traditionally been restricted to large centres with a cardiothoracic service. However, the currently available, minimally invasive extracorporeal respiratory assist systems may be successfully used in intensive care units that do not have cardiac surgical services but are familiar with other extracorporeal therapies, such as renal replacement therapy.

With this clinical context, we retrospectively analysed the data on the use of the Hemolung in three Australian ICUs with varying casemixes and expertise in extracorporeal therapies. We analysed the data to assess the efficacy of the Hemolung in CO₂ clearance, and feasibility and safety in managing patients with acute or acute-on-chronic hypercapnic respiratory failure.

Methods

Ethics approval and consent

The human research and ethics committees of all ICUs approved the use of the Hemolung. Approval was also obtained from the Australian Therapeutic Goods Administration (TGA) for 11 patients, as these patients were treated with the Hemolung before formal TGA approval of this device in Australia. The human research ethics committees of Peninsula Health (QA/16/PH/4), St Vincent's Hospital (file number 10/218) and Gold Coast Health Service District (HREC/16/QGC/78) reviewed the study proposal and waived the requirement for full ethics committee application. This was because the study was seen as a retrospective audit of data routinely collected for patient care and was not experimental research. Consent from individual patients was not required, as the research was limited to the use of information previously collected in the course of normal care and the patients were not identifiable.

Centres

The three centres where the Hemolung was used were Frankston Hospital, Melbourne, Australia (Centre 1), which is a metropolitan hospital with no cardiac surgery or ECMO services; St Vincent's Hospital, Sydney, Australia (Centre 2), where cardiac surgery and ECMO services are available; and the Gold Coast University Hospital, Gold Coast, Australia

(Centre 3), which offers cardiac surgery services but no ECMO service (at the time of the study).

Patients

We included all patients with acute or acute-on-chronic hypercapnic respiratory failure who were managed with ECCOR in the three ICUs. The Hemolung was used either to avoid intubation or to institute lung-protective ventilation.

Patients were managed with the Hemolung at the discretion of the intensivist if they had severe hypercapnic respiratory failure, were on non-invasive mechanical ventilation for at least 1 hour and were not responsive to non-invasive mechanical ventilation (defined as having a pH < 7.25, Pco₂ > 55 mmHg and/or a high likelihood of requiring invasive mechanical ventilation).

We also included patients who were on invasive mechanical ventilation but could not be ventilated with lung-protective ventilation (tidal volumes ≤ 6 mL/kg of ideal body weight) due to hypercapnic respiratory failure (pH < 7.2).

Contraindications to ECCOR included:

- limited anticoagulation (heparinisation to achieve an activated partial thromboplastin time [APTT] of 50–70 seconds or an activated clotting time [ACT] of 150–180 seconds)
- platelet count < 75 000/mm³
- patients who had treatment limitations in place.

Outcome measures

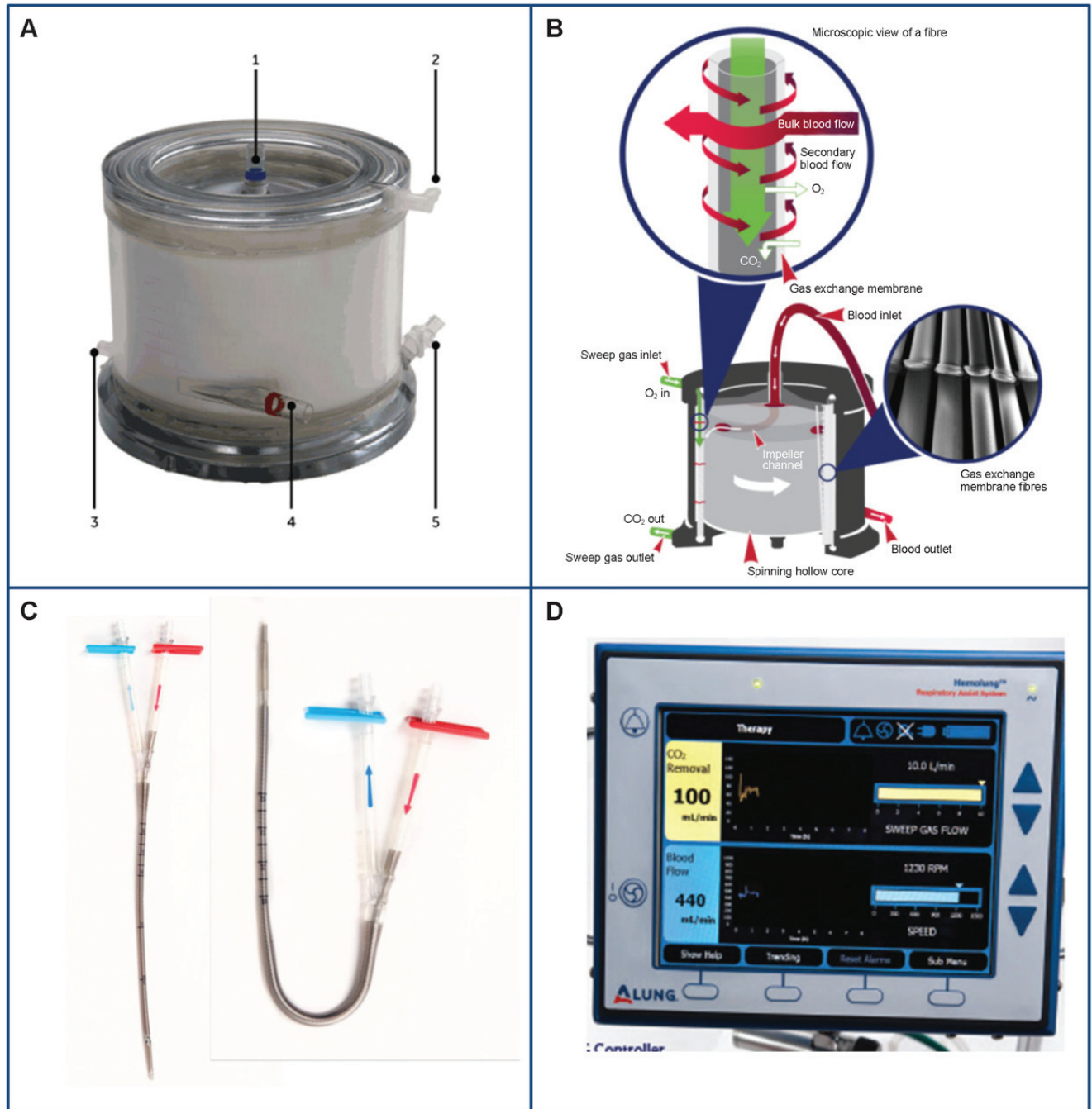
The primary outcome measure was clearance of CO₂ and change in pH with the use of ECCOR. Secondary outcome measures included complications associated with Hemolung use, survival to weaning from Hemolung, and survival to ICU and hospital discharge.

Equipment

The Hemolung RAS is a minimally invasive partial ECCOR device including an integrated gas exchanger, centrifugal blood pump, and low prime volume circuit with a dual lumen 15.5 Fr venous access cannula. A detailed description of Hemolung and its management has been published previously.^{6,13} The device consists of three main components including a catheter, cartridge and controller (Figure 1).

A 15.5 Fr double-lumen catheter (Figure 1) that could be inserted via the jugular vein (catheter length, 17 cm) or the femoral vein (catheter length, 26 cm) was used. The Hemolung cartridge consists of an integrated pump and a membrane that facilitates gas exchange. The hollow-core pump spins within a cylindrical bundle of hollow-fibre membranes, integrating pump and gas exchanger within a single component. This design aims to offer simplicity

Figure 1. Components of Hemolung Respiratory Assist System



A. Cartridge: (1) blood flow inlet, (2) sweep gas inlet, (3) sweep gas outlet, (4) blood flow outlet, (5) seal flush port with one-way valve. B. Cross-section of cartridge showing blood flow and gas exchange in cartridge. C. Femoral catheter (15.5 Fr, 17 cm) on left; jugular catheter (15.5 Fr, 26 cm) on right. D. Controller.

Source: ALung Technologies.

with no need for a heat exchanger and a more efficient gas exchange than the traditional extracorporeal respiratory support devices. The controller shows pump speed, blood flow rate, gas flow and the amount of CO₂ that is being

cleared, as real-time data. Two control settings are available, one to change pump speed to adjust the blood flow rate, and a second one to adjust sweep gas flow (0–10 L of air or oxygen) that determines the amount of CO₂ removal.

Patient management

Catheter insertion was performed using real-time ultrasound guidance. Heparin was used for anticoagulation, aiming for an APTT of 50–70 seconds or an ACT of 150–180 seconds. The Hemolung circuit was then connected to the catheter and ECCOR was initiated. Blood flow was established at a rate between 450 mL/min and 550 mL/min. Sweep gas was gradually increased to 10 L/min to provide ECCOR of about 90–100 mL/min, as measured by the Hemolung controller. The sweep gas was subsequently titrated to ensure adequate CO₂ clearance, as determined by the patient's blood gas levels and the ventilator settings. After lung recovery (at the discretion of the treating clinician), Hemolung weaning was initiated by reduction in sweep gas flow, thereby reducing the amount of CO₂ removal to zero. After confirming adequate respiratory function without sweep gas flow, the Hemolung was disconnected from the patient and the cannula removed.

There was no pre-specified protocol for management of mechanical ventilation across the three centres, but all centres used low-volume, low-pressure ventilation for patients with ARDS.¹⁴ Mechanical ventilation for asthma was provided with a low tidal volume (5–7 mL/kg), a low respiratory rate (10–12 breaths/min) and a short inspiratory time associated with prolonged expiratory time to avoid dynamic hyperinflation.

Statistical analysis

All data analyses were performed using SAS, version 9.4 (SAS Institute) and SPSS, version 22 (IBM SPSS). We assessed changes in pH, P_{CO₂}, P_{O₂}, peak inspiratory pressure (PIP) and minute ventilation from baseline values before initiation of Hemolung and at successive time points. To account for repeat measures, data were analysed using the PROC MIXED procedure in SAS, with each patient treated as a random effect. Results are presented as means and standard errors. Time was treated as a categorical variable to facilitate specific comparisons. A two-sided *P* < 0.05 was chosen to indicate statistical significance.

Results

Fifteen patients were treated in three intensive care units, and their data are shown in Table 1. The primary diagnoses were ARDS in five patients and COPD in five patients, with acute severe asthma in two patients, cardiac arrest due to COPD in one patient, cardiac arrest due to asthma in one patient, and bronchiolitis obliterans syndrome (BOS) in one patient.

In five patients (four with COPD and one with BOS), the indication was to avoid intubation, and this was achieved in four patients. In 10 patients (five with acute lung injury

or ARDS, three with asthma and two with COPD), the indication was to institute lung-protective ventilation, and this strategy was successful in all patients, as shown by a reduction in PIP, tidal volume and minute ventilation. The median age of patients was 61.5 years (interquartile range [IQR], 44.7–68.7 years) and 12 patients (80%) were men. The median Acute Physiology and Chronic Health Evaluation III score was 85 (IQR, 44–98), and the most common access site was the jugular vein (10 patients, 67%). The median duration of ECCOR was 5 days (IQR, 3–7 days). Six patients were on concurrent renal replacement therapy.

The clearance of CO₂ and return of P_{CO₂} to near-normal levels was achieved within 6 hours (Table 2, Figure 2). The pH correction matched the return of the P_{CO₂} level to normal. With the institution of the Hemolung, a significant reduction in minute ventilation and peak airway pressures was achieved (Figure 3, Table 2). There was no significant change in P_{O₂} (Table 2, Figure 2). The CO₂ clearance was 90–100 mL/min and the blood flow rates were about 450 mL/min (Figure 4).

Complications

Haemorrhage occurred in seven patients, most of which was minor and stopped with reduction of anticoagulant agents and administration of blood products. Haemorrhages included catheter site insertion bleeding, haematuria, gastrointestinal bleeding, and a haemothorax that required video-assisted thoracoscopic surgery for drainage. Packed red cells were used in 12 patients (80%), with a median transfusion volume of two packed cell units (IQR, 1–7 units).

Four patients had thrombocytopenia requiring platelet transfusion. Haemodynamic instability was noted at the time of initiation of ECCOR in two patients, both of whom required inotropic support that they were subsequently weaned off.

One patient developed compartment syndrome during Hemolung support and associated anticoagulation therapy, after a cannulation attempt of the brachial artery for arterial access.

Survival

Overall, 93.3% of the patients survived to discontinuation of ECCOR, 73.3% to ICU discharge and 66.6% to hospital discharge. All patients treated for ARDS and acute severe asthma were discharged from hospital. Three out of five patients treated for COPD (60%) were discharged from hospital. Both patients who had a cardiac arrest were successfully weaned from ECCOR support but both patients died in hospital due to severe anoxic brain injury. The patient with BOS could not be weaned from the Hemolung and died while on Hemolung support (see Table 1). No patient died due to a complication from the Hemolung.

Table 1. Summary of data for patients managed with Hemolung Respiratory Assist System

Centre no.	Age (years)	Diagnosis	ECCOR indication	Intubated	ECCOR duration (days)	ECCOR complications	Survival to ECCOR removal	Survival to ICU discharge	Survival to hospital discharge	Cause of death
1	74	COPD exac.	AI	No	8.4	Catheter site bleeding	Yes	No	No	COPD
2	59	COPD exac.	AI	No	4.0	NA	Yes	Yes	Yes	–
2	37	Stage 3 BOS	AI	No	1.0	Seizure	No	No	No	BOS
2	63	COPD exac.	AI	No	2.1	NA	Yes	Yes	Yes	–
1	68	COPD exac.	AI	Yes	5.7	Haematuria	Yes	Yes	Yes	–
1	60	Asystolic cardiac arrest secondary to COPD	LPV	Yes	2.7	NA	Yes	No	No	Severe anoxic brain injury
1	44	Asthma exac.	LPV	Yes	5.8	Haemothorax after ICC insertion requiring VATS	Yes	Yes	Yes	–
1	49	Cardiac arrest secondary to asthma	LPV	Yes	2.6	NA	Yes	Yes	No	Severe anoxic brain injury
1	66	Resp. arrest with COPD exac.	LPV	Yes	6.2	NA	Yes	No	No	Candida sepsis and multi-organ failure
1	23	Aspiration pneum.	LPV	Yes	1.9	Gastric bleeding	Yes	Yes	Yes	–
2	–	ARDS, pneum.	LPV	Yes	4.0	NA	Yes	Yes	Yes	–
2	45	Influenza B, asthma	LPV	Yes	5.0	Compartment syndrome, haematoma	Yes	Yes	Yes	–
3	64	ARDS, pneum.	LPV	Yes	6.9	NA	Yes	Yes	Yes	–
3	71	ARDS, pneum.	LPV	Yes	9.7	Haemorrhage, thrombocytopenia	Yes	Yes	Yes	–
3	71	ARDS, pneum.	LPV	Yes	6.6	Haemorrhage	Yes	Yes	Yes	–

ECCOR = extracorporeal carbon dioxide removal. ICU = intensive care unit. COPD = chronic obstructive pulmonary disease. exac. = exacerbation. AI = avoiding intubation. NA = not applicable. BOS = bronchiolitis obliterans syndrome. LPV = lung-protective ventilation prevented by management of severe hypercapnia. ICC = intercostal catheter. VATS = video-assisted thoracoscopic surgery. Resp. = respiratory. pneum. = pneumonia. ARDS = acute respiratory distress syndrome.

Discussion

In our study, we discuss the use of the Hemolung in 15 patients in three ICUs with different expertise in the management of extracorporeal support systems. Our primary aim was to assess the efficiency of CO₂ clearance. This ECCOR device was effective in correcting hypercapnia and improving pH, in conjunction with a significant reduction in minute ventilation and PIPs.

In our limited experience, its use appears to be safe and it appears to have no major complications (such as circuit clotting due to inadequate anticoagulation, or fatal retroperitoneal bleeding during catheterisation, as in earlier reports¹²). Most of the complications we noted were minor and did not require withdrawal from the Hemolung.

Intracranial bleeding is one of the most serious complications of extracorporeal life supports. A recent study by Luyt and colleagues,¹⁵ on neurological events during venovenous ECMO, showed an association between

rapid reduction in Pco₂ and intracranial bleeding. Given the limited experience with the Hemolung and other similar low-flow extracorporeal devices, it is difficult to ascertain such association with these devices. No patients in our cohort suffered intracranial bleeding.

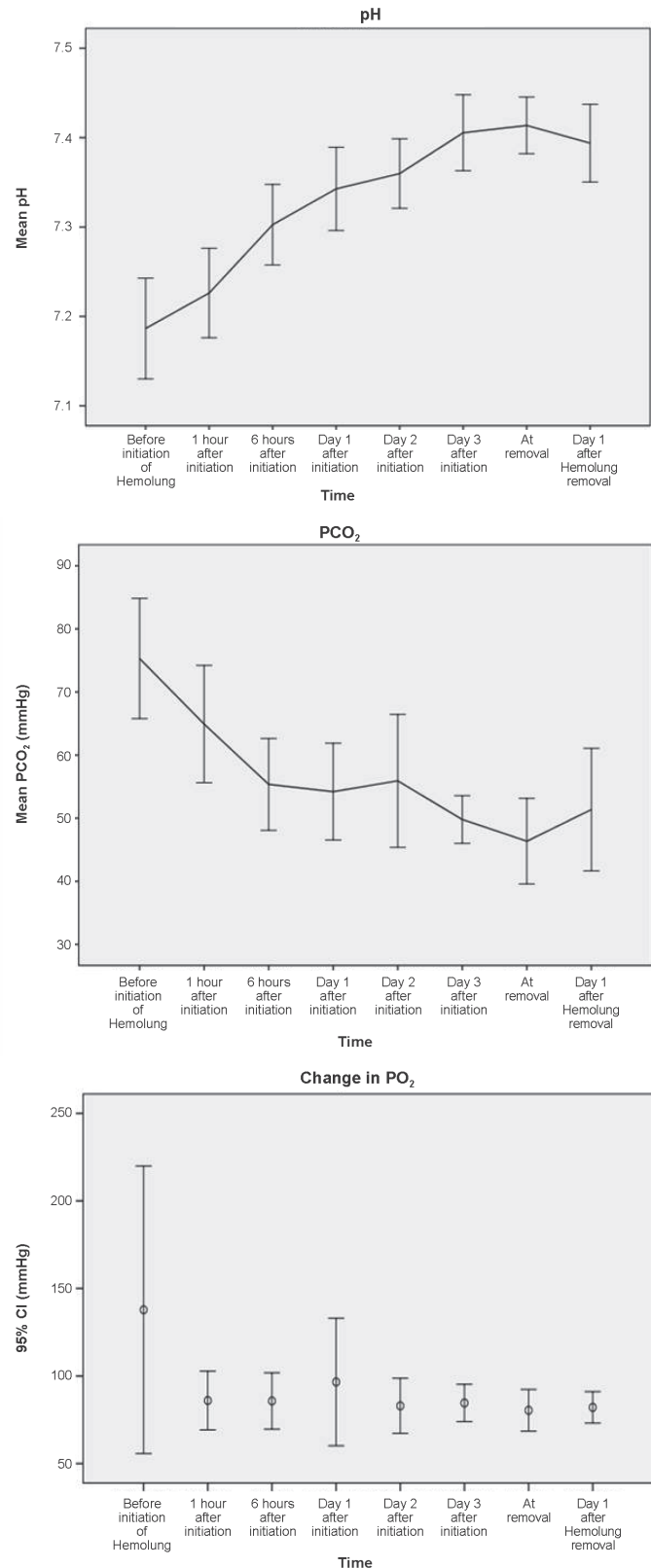
The proportion of patients who required blood transfusions was 80% (median volume, 2 units of packed red cells). While this proportion appeared to be lower than blood transfusion requirements reported with comparable low-flow partial respiratory support systems,¹⁶ further experience in the use of the Hemolung and anticoagulation management is essential to reduce the need for blood and blood products. Furthermore, six of our patients were on renal replacement therapy concurrently with the Hemolung. Replacement of circuits during renal replacement therapy is known to be associated with blood loss,¹⁷ and this may have contributed to the requirement for blood transfusions.

The prediction of potential reversibility is an important aspect in patient selection when instituting advanced

Table 2. Estimated mean changes in minute ventilation, peak inspiratory pressure, P_aCO₂, P_aO₂ and pH before initiation and at successive time points

Variable	Estimated change from before initiation	Standard error	P
Minute ventilation			
1 hour	3.145	1.188	0.010
6 hours	3.632	1.214	0.004
Day 1	3.618	1.230	0.005
Day 2	3.454	1.231	0.007
Day 3	2.126	1.271	0.099
At removal	-0.407	1.216	0.739
24 hours after removal	-1.981	1.231	0.113
Peak inspiratory pressure			
1 hour	3.429	2.256	0.134
6 hours	4.070	2.347	0.088
Day 1	4.602	2.402	0.060
Day 2	7.562	2.465	0.003
Day 3	6.023	2.538	0.021
At removal	6.220	2.465	0.014
24 hours after removal	9.723	2.621	< 0.0001
P_aCO₂			
1 hour	9.653	3.515	0.007
6 hours	19.844	3.590	< 0.0001
Day 1	18.967	3.515	< 0.0001
Day 2	19.077	3.670	< 0.0001
Day 3	24.826	3.869	< 0.0001
At removal	27.916	3.590	< 0.0001
24 hours after removal	23.771	3.672	< 0.0001
P_aO₂			
1 hour	44.287	27.381	0.110
6 hours	37.502	27.471	0.176
Day 1	33.700	27.381	0.222
Day 2	44.538	27.567	0.110
Day 3	40.537	27.815	0.149
At removal	45.180	27.471	0.104
24 hours after removal	43.663	27.571	0.117
pH			
1 hour	-0.029	0.018	0.112
6 hours	-0.096	0.019	< 0.0001
Day 1	-0.131	0.018	< 0.0001
Day 2	-0.167	0.019	< 0.0001
Day 3	-0.211	0.021	< 0.0001
At removal	-0.219	0.019	< 0.0001
24 hours after removal	-0.212	0.019	< 0.0001

Figure 2. Changes in pH, P_aCO₂ and P_aO₂ before initiation and at successive time points



Error bars: 95% CIs.

Figure 3. Changes in peak inspiratory pressure and minute ventilation before initiation of Hemolung and at successive time points

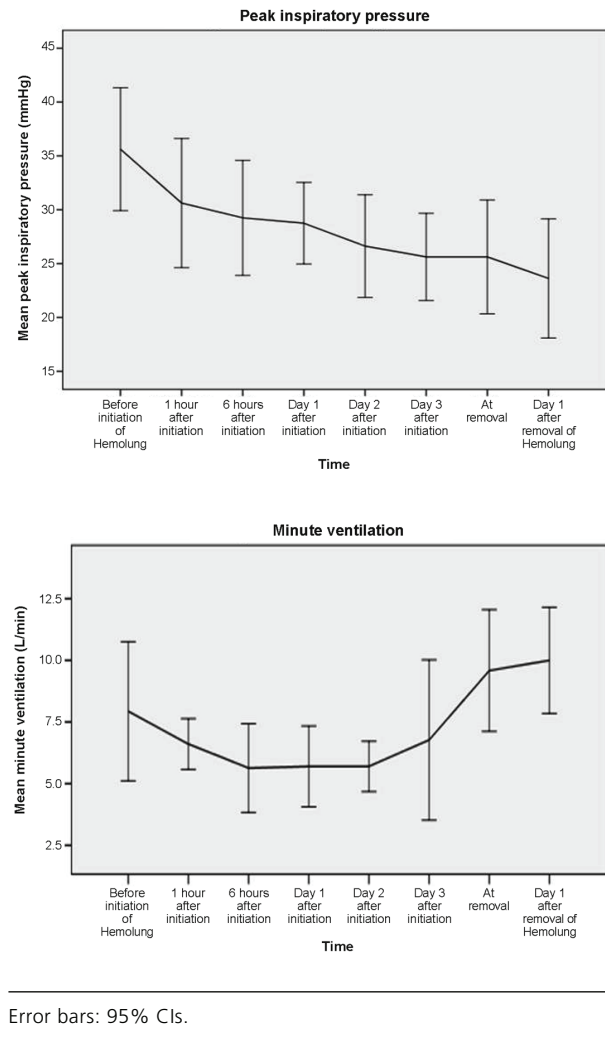
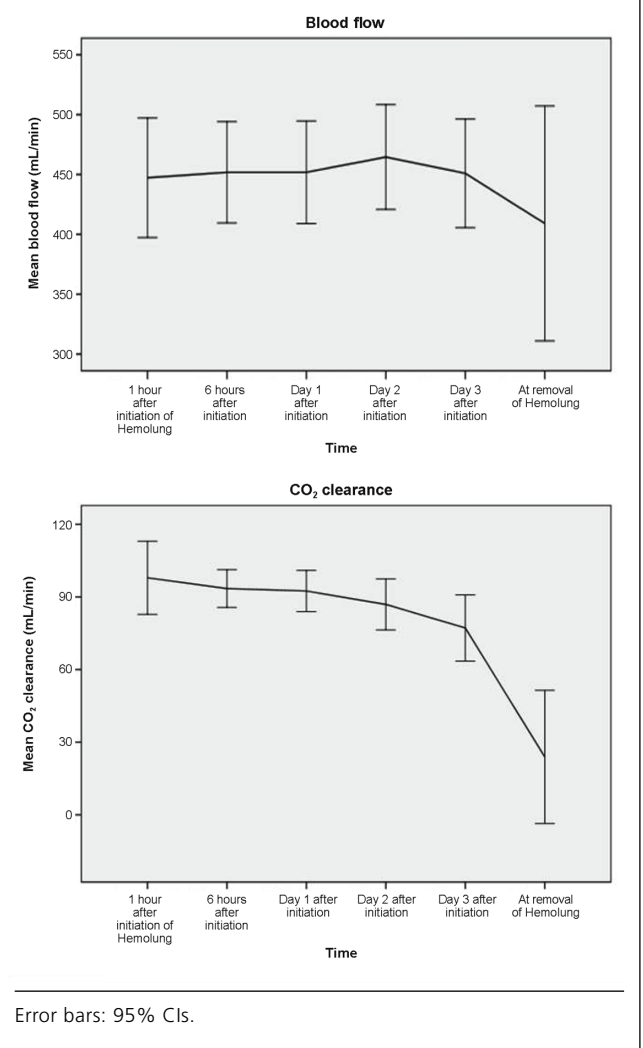


Figure 4. Changes in blood flow and CO₂ clearance before initiation of Hemolung and at successive time points



respiratory support systems such as ECMO and ECCOR. The use of ECMO for ARDS over the past three decades, in conjunction with established registries (such as the Extracorporeal Life Support Organization), have contributed to intensivists gaining significant experience in patient selection. This experience has led to the development of scoring systems that may be useful in predicting the appropriateness of these devices for patients with ARDS.^{5,18,19} Therefore, the use of extracorporeal respiratory support devices such as ECCOR may now prove to be more successful than previously reported devices. The use of ECCOR in patients with COPD and other chronic respiratory conditions is very limited, and further experience is vital to understand the role of ECCOR in COPD and other causes of acute-on-chronic respiratory failure.

The mortality of patients with ARDS is reducing with modern intensive care practice,²⁰ but mortality is still

high.^{20,21} Further mortality and morbidity reduction appears to be feasible if driving pressures and tidal volume ventilation can be reduced.^{9,22} Technologies working in conjunction with mechanical ventilation may be required to achieve this reduction. In severe ARDS, the introduction of ECMO has been shown to improve outcome.⁵ In the context of mild-to-moderate ARDS, such treatment is not indicated because of its invasiveness and the associated risk of complications. Minimally invasive and effective devices such as the Hemolung may aid in lung-protective ventilation with a lower risk. It is encouraging to note that none of our patients with ARDS died, and no device-related complications were reported.

The use of the Hemolung and other similar ECCOR systems has been reported in patients with chronic respiratory failure such as COPD.^{13,23} Although the reports are early and further data are vital to evaluate the role of the Hemolung

in COPD management, we believe this system has the potential to influence the management of exacerbations of COPD patients in whom prolonged mechanical ventilation may increase mortality and morbidity.²⁴ The use of the Hemolung may aid in avoiding intubation, facilitate lung-protective ventilation and hasten liberation of patients from mechanical ventilation. An observational study by Del Sorbo and colleagues²³ suggests that the risk of intubation could be reduced, compared with a propensity score-matched historic control. Kluge and colleagues reported similar results in their retrospective series.²⁵ Furthermore, a retrospective ancillary cost analysis of using arteriovenous ECCOR in COPD patients suggests that the costs are comparable to conventional management, due to shorter ICU and hospital lengths of stay when ECCOR is used.²⁶ However, the retrospective nature of these studies only provides limited evidence, and further experience is vital for patient selection to evaluate the role of ECCOR in this population.

Acute asthma that is refractory to conventional therapies may necessitate the use of ECMO,²⁷ but the use of ECMO is invasive and not available in most centres. Two of our patients had severe asthma that was resistant to conventional pharmacological and mechanical ventilation management and could have potentially required the use of ECMO (not available at that centre). In both patients, ECCOR was successfully instituted with no requirement for transfer to an ECMO centre. More data are needed to establish the role of low-flow ECCOR in asthma treatment, but it appears from our results that ECCOR use may prevent the need for ECMO in patients with severe asthma, especially if the patients are not profoundly hypoxic.

In this study, the Hemolung was used in two patients with cardiac arrest when the severity of anoxic brain injury could not be assessed at the time of instituting the Hemolung. Both patients had severe hypercapnic respiratory failure associated with severe respiratory acidosis, and it was considered vital to treat the severe hypercapnia to optimise neuroprotection.^{28,29} The use of the Hemolung ameliorated severe hypercapnia and respiratory acidosis and aided in reducing the time to assess the brain injury by avoiding prolonged use of sedation and muscle relaxants, which would have been required in these difficult-to-ventilate patients. The earlier clinical assessment probably led to a reduced duration of ICU stay for these patients, thus reducing prolonged futile treatment and associated health care costs.

Conclusion

The Hemolung appears to be effective, safe and feasible for managing hypercapnic respiratory failure of various aetiologies. Further experience is vital to identify the types

of patients who may benefit most from this promising therapy. Considering the minimally invasive nature of the Hemolung, in conjunction with its efficient removal of CO₂, we believe it has a promising place in the management of hypercapnic respiratory failure.

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Competing interests

Hergen Buscher was an invited speaker at an Alung Technologies-sponsored meeting in 2014.

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