Respiratory dialysis: Reduction in dependence on mechanical ventilation by venovenous extracorporeal CO_2 removal*

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Objectives: **Mechanical ventilation is injurious to the lung. Use of lung-protective strategies may complicate patient management, motivating a search for better lung-replacement approaches. We investigated the ability of a novel extracorporeal venovenous CO_2 removal device to reduce minute ventilation while maintaining normocarbia.**

Design: **Prospective animal study.**

Setting: **Government laboratory animal intensive care unit.**

Subjects: **Seven sedated swine.**

Interventions: **Tracheostomy, volume-controlled mechanical ventilation, and 72 hrs of round-the-clock intensive care unit care. A 15-F dual-lumen catheter was inserted in the external jugular vein and connected to the Hemolung, an extracorporeal pump-driven venovenous CO_2 removal device. Minute ventilation was reduced, and normocarbia ($Paco_2$ 35–45 mm Hg) maintained. Heparinization was maintained at an activated clotting time of 150–180 secs.**

Measurements and Main Results: **Minute ventilation (L/min), CO_2 removal by Hemolung (mL/min), Hemolung blood flow, O_2 consumption (mL/min), CO_2 production by the lung (mL/min), $Paco_2$, and plasma-free hemoglobin (g/dL) were measured at baseline (where applicable), 2 hrs after device insertion, and every 6 hrs thereafter. Minute ventilation was reduced from 5.6 L/min at baseline to 2.6 L/min 2 hrs after device insertion and was maintained at 3 L/min until the end of the study. CO_2 removal by Hemolung remained steady over 72 hrs, averaging 72 ± 1.2 mL/min at blood flows of 447 ± 5 mL/min. After insertion, O_2 consumption did not change; CO_2 production by the lung decreased by 50% and stayed at that level ($p < .001$). As the arterial PCO_2 rose or fell, so did CO_2 removal by Hemolung. Plasma-free hemoglobin did not change.**

Conclusions: **Venovenous CO_2 removal enabled a 50% reduction in minute ventilation while maintaining normocarbia and may be an effective lung-protective adjunct to mechanical ventilation. (Crit Care Med 2011; 39:1382–1387)**

KEY WORDS: lung-protective ventilation; mechanical ventilation; extracorporeal circulation; CO_2 removal; respiratory dialysis; swine

Acute respiratory distress syndrome (ARDS) has a 30%–50% mortality, affects about 150,000 patients per year, and together with chronic lung failure causes one in every seven deaths in the United States (1). Acute lung injury and ARDS are also significant combat casualty care problems stemming from trauma and resuscitation (2, 3), smoke inhalation and burns (4), pulmonary contusion (5), chemical weapons such as mustard agent (6), and blast injury (7). Toxic industrial chemicals such as chlorine can also lead to ARDS (8) and have been used with improvised explosive devices in a recent conflict (9). Civilian events such as the H1N1 pandemic have the potential to overwhelm the available pool of mechanical ventilators, thus signifying the need for alternative lung support therapies (10).

Although it is the mainstay of current acute lung injury/ARDS therapy, mechanical ventilation is itself injurious, causing ventilator-induced lung injury (11–16). A recent retrospective study conducted by Wunsch et al (17) using data from six U.S. states found that mechanical ventilation is associated with a high (34.5%) in-hospital mortality rate. Low-tidal-volume lung-protective strategies in ARDS decreased inflammatory mediator levels (12, 15), end-organ dysfunction (15, 18) and mortality (15). Consequences of low-tidal-volume ventilation, however, may include cardiovascular instability, use of high FIO_2, hypoventilation, alveolar derecruitment, hypercarbia, and acidosis and have led to a search for other lung-protective approaches (1). In addition, the low-tidal-volume strategy, although accepted as a standard of care for ARDS, has in clinical practice been implemented in a variable fashion (19–24).

An alternate approach to treating acute respiratory insufficiency, for avoiding ventilator-induced lung injury, and for achieving "lung rest," is to perform gas exchange *via* an extracorporeal device (25–31). Such "respiratory dialysis," arguably, may make it possible to avoid mechanical ventilation altogether in se-

***See also p. 1576.**

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Dr. Batchinsky conducted previous research involving the Hemolung device, during which travel and lodging were funded by the device manufacturer. He has nothing to disclose as pertinent to the work presented in this manuscript. Dr. Federspiel is cofounder of ALung Technologies, manufacturer of the Hemolung device; holds equity interest, stock ownership, and options in ALung Technologies; and has a pending patent from ALung Technologies. The remaining authors have not disclosed any potential conflicts of interest.

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lected patients (32). Extracorporeal membrane oxygenation (ECMO) has, to date, been too costly for routine use as a lung rest strategy in adult ARDS patients, although calls for revisiting this technology are emerging (33). Zwischenberger and colleagues (27, 28, 34, 35) developed a less invasive arteriovenous CO_2 removal ($AVCO_2R$) system that improved survival in animal studies (27, 28, 34) and has been used safely in clinical studies (35). $AVCO_2R$ requires an adequate cardiac output and blood pressure as well as separate arterial catheterization, which may lead to limb ischemia (36).

The purpose of the current study was to investigate the potential of a new motor-driven extracorporeal venovenous CO_2 removal device (V_2CO_2R) that allows for CO_2 removal at relatively low blood flow rates (400–600 mL/min) (Hemolung, ALung Technologies, Pittsburgh, PA). This technology has high gas exchange efficiency per relatively small membrane surface area (0.59 m^2). The invasiveness of this device is reduced by use of a dual-lumen catheter and a single-stick venous cannulation, comparable to catheterization for dialysis. Hemolung utilizes a computer-controlled pump, which allows for use in low cardiac output states. In this first report involving the Hemolung, we tested its ability to reduce the need for ventilatory requirements in healthy mechanically ventilated swine over 72 hrs. We hypothesized that Hemolung permits a significant reduction in minute ventilation while maintaining normocarbia and thus could have potential as an adjunct to mechanical ventilation.

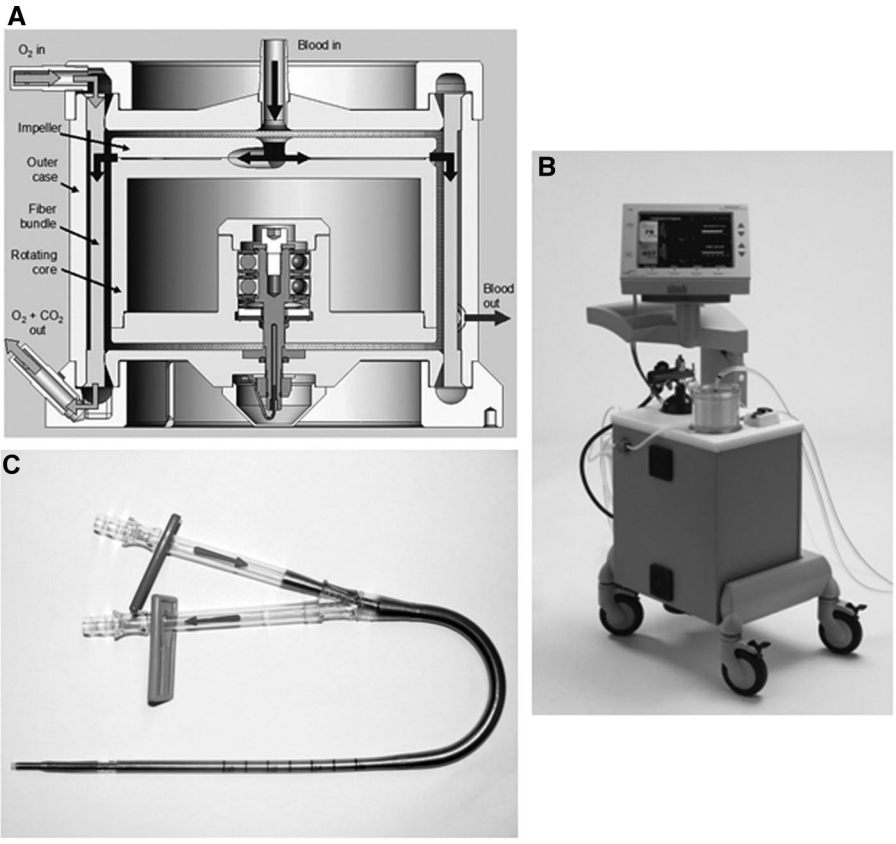

Figure 1. *A*, Hemolung unit. *B*, Controller. *C*, Dual-lumen catheter.

MATERIALS AND METHODS

This study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee and was carried out in accordance with the guidelines set forth by the Animal Welfare Act, other federal statutes and regulations, and the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council.

Animal Preparation. Seven female Yorkshire pigs weighing 54.2 kg ± 0.8 SEM were fasted for 24 hrs, induced with isoflurane (2–4 volume %) via mask, and intubated. Next, total intravenous anesthesia (ketamine, 200–500 μg/kg/min; and midazolam, 10–20 mg/hr) was started through an ear vein, and femoral arterial and venous catheters were aseptically placed for blood pressure monitoring, intravenous access, and sample collection. The animals were volume-control ventilated using a Siemens Servo 300A ventilator (Siemens-Elema, Göteborg, Sweden) with room air at a tidal volume (V_T) setting of 12 mL/kg and respiratory rate of 8–9 breaths per minute. (This baseline V_T setting is standard practice in this animal facility and was not intended to conform with current guidelines for low-tidal-volume ventilation in adults with ARDS [15]). The respiratory rate was adjusted at baseline to maintain normocarbia ($Paco_2$ 35–45 mm Hg). Each animal received a maintenance rate of lactated Ringer's solution to maintain urine output at 0.5–1 mL/kg/hr.

Hemolung Description and Insertion. The Hemolung system consists of a unit in which gas exchange takes place (Fig. 1*A*) and an integrated control console (Fig. 1*B*). The system is interfaced with the patient through a custom dual-lumen 15-F catheter similar to a dialysis catheter. The catheter is designed to offer low flow resistance and superior kink resistance compared to off-the-shelf dialysis catheters (Fig. 1*C*). The Hemolung pump withdraws venous blood from the superior vena cava, which after CO_2 removal is reinfused into the right atrium through the distal openings. Inside the Hemolung unit, blood flows centrally into a rotating core, is radially pumped through a stationary annular fiber bundle, and returns to the patient via an outlet port (Fig. 1*A*). Unlike conventional passive oxygenators, the core uses a motor-driven rotational motion to increase gas exchange efficiency. This motion increases the amount of CO_2 removed relative to the surface area (0.59 m^2) of the fiber bundles. This increased efficiency permits blood-flow rates comparable to those used in dialysis (300–600 mL/min).

After 1 hr of baseline stabilization of the animals, the Hemolung unit was primed with 300 mL of normal saline containing 5000 units of heparin. The right jugular vein was aseptically exposed via a cut-down. After a 20-u/kg intravenous bolus of heparin, each animal underwent placement of the 15-F catheter through the external jugular vein. The catheter was positioned so that the proximal set of openings was situated in the superior vena cava and the distal tip (with another set of openings) was placed in the right atrium. Upon catheter placement, plastic tubing provided by the manufacturer was immediately connected to each of the two ports of the catheter using the wet-to-wet technique, and the Hemolung unit was started. Placement of the catheter was confirmed via fluoroscopy. The rationale for device insertion in the superior vena cava/right atrium junction was to achieve optimal mixing of the returned "ventilated" blood with systemic blood and to ensure maximal separation of the inflow (into the proximal set of catheter holes) and the outflow (from the distal set of holes). This was based on manufacturer recommendations.

After device insertion, the ventilator settings were reduced according to an algorithm to test the CO_2 removal capacity of the Hemolung. The algorithm did not pursue de-

Table 1. Ventilatory data, blood gas data, and key Hemolung parameters

Variable	Value at					*p*			
	BL	2 hrs	24 hrs	48 hrs	72 hrs	BL vs. 2 hrs	BL vs. 24 hrs	BL vs. 48 hrs	BL vs. 72 hrs
Minute ventilation, L/min	5.6 ± 0.3	2.6 ± 0.3[a]	3.0 ± 0.1[a]	3.1 ± 0.2[a]	3.3 ± 0.2[a]	.02	.0004	.0003	.0002
Respiratory rate, bpm	9	5[a]	5[a]	5[a]	5[a]	.0002	.0004	.001	.003
Tidal volume, mL	650 ± 14	556 ± 24	576 ± 9	574 ± 15	578 ± 15	.087	.084	.16	.18
Pao_2, mm Hg	96 ± 2	77 ± 5[a]	103 ± 8	97 ± 16	112 ± 8	.04	.94	.55	.08
$Paco_2$, mm Hg	39 ± 0.8	43 ± 2.2	42 ± 1.0	44 ± 1.2[a]	46 ± 5.8[a]	.52	.08	.01	.0003
pH	7.46 ± 0.0	7.41 ± 0.0	7.47 ± 0.0	7.45 ± 0.0	7.44 ± 0.0	.14	.98	1.0	.99
CO_2 removal by the Hemolung device, mL/min	n/a	76 ± 3.0	73 ± 1.2	69 ± 2.7	65 ± 2.6[a]	n/a	.62[b]	.17[b]	.03[b]
Blood flow through the Hemolung device, mL/min	n/a	422 ± 11	471 ± 24	445 ± 29	431 ± 21	n/a	.42[b]	.77[b]	.67[b]

BL, baseline.

[a]Significant difference vs. baseline at $p < .05$; [b]comparison of time point data to 2-hr postinsertion time point. All data are means ± SEM. Statistics by one-way analysis of variance with repeated measures and adjustment to multiple comparisons.

creases in V_T as the primary mechanism for reducing minute ventilation as recommended for ARDS patients (12, 15, 18), because this study focused on assessing the Hemolung's CO_2 removal capacity, without regard to how the decrease in minute ventilation was achieved. First, respiratory rate was reduced to the minimum setting allowed by the ventilator (5 breaths per minute) and kept there unless hypercarbia above the target level ($Paco_2$ 35–45 mm Hg) developed. Further decreases in minute ventilation were sought via reduction in V_T in 2 mL/kg steps as verified by blood gas analysis (Roche, CO Bas B 221, Indianapolis, IN). CO_2 removal by the Hemolung was assessed by comparing data from the time point immediately after device insertion (hour 2) to data from the subsequent time points in the study. After device insertion, animals were maintained for 72 hrs with round-the-clock care in an animal intensive care unit.

Measurements. Heparin was given continuously during the study and assessed by the activated clotting time (in seconds) using a Hemochron Jr Signature Microcoagulation System (International Technidyne, Piscataway, NJ). The target level for heparinization was a relatively low activated clotting time of 150–180 secs (37). Heart rate (beats per minute), systolic arterial pressure (mm Hg), minute ventilation (V_E, L/min), respiratory rate (breaths/minute), and V_T (mL/min) were recorded. Pulmonary oxygen consumption (mL/min) and CO_2 production (mL/min) were measured using a Deltatrac II metabolic cart (Sensor Medics, Yorba Linda, CA) and were adjusted for body surface area. Hemolung blood flow (L/min), CO_2 removal rate (mL/min) and sweep gas flow (mL/min) were recorded from the Hemolung console. Arterial tension of oxygen (Pao_2, mm Hg) and CO_2 ($Paco_2$, mm Hg) were measured at baseline, 2 hrs after insertion of the Hemolung and every 6 hrs thereafter.

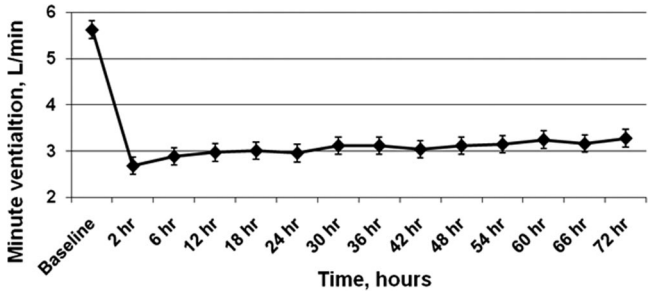

Figure 2. Changes in minute ventilation over time. For statistical significance, see Table 1.

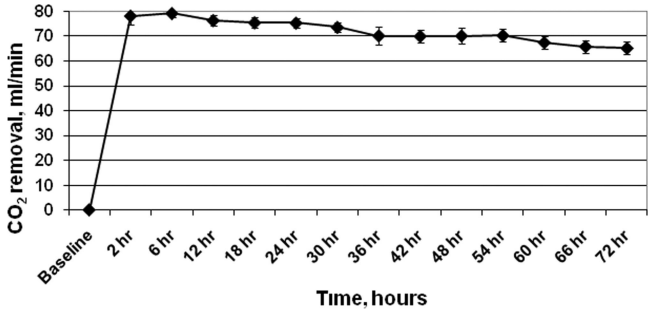

Figure 3. Changes in CO_2 removal over time. For statistical significance, see Table 1.

Plasma-free hemoglobin (g/dL) was determined using spectrophotometry (38).

Statistical Analysis. Statistical analysis by one-way analysis of variance with repeated measures and Dunnett's adjustment for multiple comparisons was performed using SAS v. 9.1. (SAS, Cary, NC). The data presented were normally distributed. Significance was accepted at $p < .05$.

RESULTS

A total of 504 hrs of intensive care unit care were provided in the conduct of this study. V_E and respiratory rate decreased 2 hrs after device placement and remained at 50% of baseline values throughout the duration of the study (Table 1, Fig. 2). V_T was about 75 to 100 mL lower at each time point compared to baseline values, but these changes were not significant. Pao_2 was lower at 2 hrs, whereas $Paco_2$ was higher at 48 and 72 hrs after insertion when compared to baseline values (Table 1). The pH was unchanged throughout the study. Mean CO_2 removal by Hemolung over the study duration was

Table 2. Hemodynamic and metabolic data

Variable	Value at					p			
	BL	2 hrs	24 hrs	48 hrs	72 hrs	BL vs. 2 hrs	BL vs. 24 hrs	BL vs. 48 hrs	BL vs. 72 hrs
Heart rate, bpm	100 ± 11	86 ± 11	77 ± 6[a]	89 ± 9	84 ± 6	.23	.02	.49	.89
Systolic arterial pressure, mm Hg	130 ± 8	125 ± 6	117 ± 6	114 ± 11	117 ± 15	.99	.55	.46	.50
Lung O_2 consumption, mL/min	313 ± 37	320 ± 39	259 ± 26	277 ± 33	262 ± 31	.98	.09	.56	.06
Lung CO_2 production, mL/min	262 ± 27	135 ± 15[a]	141 ± 13[a]	152 ± 17[a]	147 ± 18[a]	.0005	<.0001	<.0001	<.0001
Plasma-free hemoglobin, mg/dL	14.6 ± 2.4	10.5 ± 1.5	17.6 ± 5.8	10.9 ± 1.8	16.6 ± 2.8	.81	.99	.76	.98
Activated clotting time, secs	106 ± 4	186 ± 25	141 ± 24	150 ± 22	135 ± 25	.10	.69	.44	.57

BL, baseline.

[a]Significant difference vs. baseline at $p < .05$. All data are means ± SEM. Statistics by one-way analysis of variance with repeated measures and adjustment to multiple comparisons.

72 ± 1.2 mL/min. It remained not different from the postinsertion time point (hour 2) at all time points, other than at the 72-hr time point when it decreased to a mean of 65 mL/min (Table 1, Fig. 3). Mean blood flow through the Hemolung over the study was 447 ± 5 mL/min and remained steady (Table 1). Revolutions per minute of the motor remained steady in the 1200–1300 range throughout the 72 hrs (data not shown). Sweep gas flow averaged 8.6 L/min throughout the study and was kept constant to avoid the effect of changes on CO_2 removal (data not shown). Heart rate and systolic arterial pressure did not change after placement of the Hemolung unit at any time, except 24 hrs after Hemolung placement when heart rate decreased from 100 to 77 beats/min (Table 2). O_2 consumption did not change, whereas CO_2 production by the lung decreased significantly at all time points after device placement to nearly half of the baseline value (Table 2). Activated clotting time remained unchanged throughout the study. The plasma-free hemoglobin levels remained not different from baseline throughout the duration of the study (Table 2).

DISCUSSION

This the first report on *in vivo* use of the Hemolung V_2CO_2R device. Our aim was to benchmark this technology for its capacity to eliminate CO_2 and to permit a significant reduction in V_E. The main finding is that during a 72-hr experiment, the Hemolung removed an average of 72 mL/min of CO_2 at 450 mL/min blood flow through the device, and allowed for maintenance of normocarbia in spite of a 50% reduction in V_E. The Hemolung did not cause hemodynamic instability or erythrocyte destruction, suggesting that it may have a potential in supplementing mechanical ventilation while permitting the lung to heal (31) or even replacing the ventilator altogether (32).

Artificial lung support systems are medical devices designed to supplement or replace the respiratory function of the natural lung. ECMO was introduced for treatment of neonatal respiratory failure (39). ECMO is currently used in adults only in a few centers, requires highly trained staff, and is considered complicated and costly but effective for selected patients with severe pulmonary failure (10, 40, 41). Alpard, Zwischenberger, and colleagues (27, 28, 34, 42) developed a simpler extracorporeal $AVCO_2R$ system using a low-resistance ECMO oxygenator for gas exchange and showed that it permitted a reduction in minute ventilation, reduced airway pressure, improved Pao_2-to-FIO_2 ratio, and improved survival in animal models of ARDS. Another $AVCO_2R$ device, marketed in Europe as the Interventional Lung Assist device (NovaLung), has also shown promise in the treatment of acute lung failure and as a means of lung rest (29, 30, 36). However, compared to the Hemolung, currently available $AVCO_2R$ devices require a higher blood flow (500–1500 mL/min), rely on the arteriovenous pressure gradient (which could be difficult in hemodynamically unstable patients), and carry a risk of limb ischemia due to arterial cannulation (36).

Unlike passive oxygenators, which rely on the arteriovenous pressure gradient and require both arterial and venous cannulation for gas exchange (30), the Hemolung uses a single-stick dual-lumen venous cannula and an extracorporeal computer-driven pump. This motor, by increasing blood flow across the fibers, allows for optimized CO_2 elimination for a membrane surface area of only 0.59 m^2. Increased gas exchange efficiency in the Hemolung permits use of lower dialysis-level blood flow rates in the 300–750-mL/min range, compared to 500–1500 mL/min in the current $AVCO_2R$ devices (27, 30, 35, 43, 44). Our study also highlights several other features of the Hemolung when compared to other devices. First, in the present study a 15-F dual-lumen catheter was used, which is smaller than most currently used catheters and which permits for a single-stick venous insertion. Avoidance of arterial cannulation is a benefit of this system as it may lower the risk of lower limb ischemia, hemorrhage, and systemic thromboembolism. Second, Hemolung insertion and function did not lead to hemodynamic changes, as neither heart rate nor blood pressure changed clinically significantly at any time during the experiment. This feature may extend the applicability of this technology to hemodynamically unstable patients. Third, plasma-free hemoglobin did not change, indicating that the extracorporeal circuit did not cause erythrocyte lysis. Fourth, the Hemolung can be operated using only ambient air for sweep gas and CO_2 removal. This may make it amenable for use during transport, while reducing the need for oxygen tanks.

The present study did not pursue the minimal possible dose of heparin required for use with the Hemolung, but the activated clotting time values obtained (150–180 secs) are significantly lower than the systemic heparinization levels traditionally employed with similar technology (37, 43). Future work will explore the feasibility of avoiding systemic heparinization altogether. Cardenas et al (44), for example, recently described a CO_2 removal device in which regional heparinization (i.e., heparinization of the extracorporeal circuit

alone) was sufficient to achieve adequate device performance.

V_2CO_2R is a relatively new form of extracorporeal lung support. Cardenas et al (44) used a modified ECMO system, a single-stick dual-lumen catheter, and a pump to perform V_2CO_2R in a manner similar to that used in our study. At comparable blood flows (500 mL/min), it achieved about the same CO_2 removal that we observed in the present study. By doubling the blood flow to 1000 mL/min and with a 15-L/min sweep gas flow (twice the settings of the present study), they reached a CO_2 elimination rate of 150 mL/min (44). Recently, a unique V_2CO_2R approach was tested in humans with ARDS, in which a pediatric ECMO system (membrane surface area 0.33 m^3) was connected in series with a dialysis circuit (45). V_T was reduced below the 6-mL/kg ARDSNet recommended target, and the resulting respiratory acidosis was successfully managed via the extracorporeal circuit. The authors concluded that their V_2CO_2R system allowed for safe use of lower-than-customary tidal volumes (45). Taken together, these studies and our experience support the concept that extrapulmonary CO_2 removal, by permitting a reduction in ventilator settings, can serve as a lung-protective strategy (47).

CO_2 removal rates were steady over the course of our experiment, especially considering the low blood flow rates used. In general, CO_2 removal is a function of three conditions: 1) $Paco_2$, in that an increase in $Paco_2$ leads to an increase in the extracorporeal VCO_2; 2) sweep gas flow rate (regulated by the user); and 3) blood flow through the device (a function of the catheter size and the device revolutions per minute). Because higher revolutions per minute may lead to hemolysis, more efficient gas exchange at lower rates is desirable. Device insertion was associated with a decreased (but still normal) Pao_2 at 2 hrs. This may represent the decrease in V_E, and/or transient changes in ventilation/perfusion matching in the lung.

In this study in animals with normal lungs, we did not attempt to duplicate ARDSNet low-tidal-volume recommendations, and we achieved decreases in V_E primarily by decreasing the respiratory rate. More work will be required to characterize the performance of this system in ARDS models.

The current study was designed to use the Hemolung in conjunction with mechanical ventilation to achieve a "normal" blood gas, defined as arterial oxygen saturation above 92% and $Paco_2$ of 35–45 mm Hg. By contrast, in the clinical care of patients with acute lung injury/ARDS, permissive hypercapnia is employed as long as the pH is within safe limits. The absence of hypercapnia in this study limited our ability to explore the maximal rate of CO_2 elimination. In bench studies by the Hemolung developers (46), the CO_2 removal by Hemolung of a prototype was estimated to be 250 mL/min/m^2 at 1500 rpm, assuming a membrane with a 0.4 m^2 surface area. We expect to challenge the Hemolung for its maximal CO_2 removal by Hemolung in follow-up studies involving animals with ARDS. Those studies will also pursue a less invasive femoral placement of the catheter as well as quantification of the oxygenation capacity by the Hemolung, which was not addressed in this experiment.

CONCLUSIONS

In summary, use of the Hemolung for V_2CO_2R in an uninjured porcine model allowed a significant and sustained reduction in V_E while maintaining normocarbia. The system performed about 50% of ventilatory function via percutaneous venous cannulation with a dual-lumen catheter similar to a dialysis catheter. Gas exchange efficiency was maintained for 72 hrs at low flow rates. No pronounced hemodynamic effects upon insertion and during operation were observed. Overt erythrocyte destruction was absent. Because of its ease of use, Hemolung may also make it possible to more rapidly initiate extracorporeal lung support in emergency departments and community intensive care units. V_2CO_2R, a relatively easy-to-employ extracorporeal lung support technology, may reduce levels of injurious mechanical ventilation and may even permit some patients to avoid mechanical ventilation entirely.

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We dedicate this work to Dr. Brack Hattler and his family. Dr. Hattler passed away in 2008. He was a pioneer of artificial lung support research and continues to be an inspiration to generations of physicians and scientists.

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