CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

PERCUTANEOUS EXTRACORPOREAL ARTERIOVENOUS CARBON DIOXIDE REMOVAL IMPROVES SURVIVAL IN RESPIRATORY DISTRESS SYNDROME: A PROSPECTIVE RANDOMIZED OUTCOMES STUDY IN ADULT SHEEP

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Objective: Arteriovenous carbon dioxide removal (AVCO₂R) uses a simple arteriovenous shunt for CO₂ removal to minimize barotrauma/volutrauma from mechanical ventilation. We performed a prospective randomized outcomes study of AVCO₂R in our new, clinically relevant model of respiratory distress syndrome.

Methods: Adult sheep (n = 18) received an LD₅₀ severe smoke inhalation and 40% third-degree burn. When respiratory distress syndrome developed (Pao₂/Fio₂ < 200 at 40 to 48 hours), animals were randomized to the AVCO₂R (n = 9) or sham group (n = 9) for 7 days. Ventilator management protocols mandated reductions in minute ventilation, first tidal volume to peak inspiratory pressure less than 30 cm H₂O, then respiratory rate when Paco₂ was less than 40 mm Hg. Pao₂ was kept above 60 mm Hg by adjusting Fio₂. When Fio₂ was 0.21, animals were weaned.

Results: The study required 2946 animal-hours of critical care with 696 AVCO₂R hours. One died in each group during model development. AVCO₂R flow from 820 mL/min to 970 mL/min (11% to 14% cardiac output) removed CO₂ at a rate of 92 to 116 mL/min (mean 103 mL/min; 93%-97% of CO₂ production). Heart rate, mean arterial pressure, cardiac output, and pulmonary arterial wedge pressure remained relatively constant. Within 48 hours, AVCO₂R allowed significant ventilator reductions versus baseline in the following measurements: tidal volume (420 to 270 mL), peak inspiratory pressure (25 to 14 cm H₂O), minute ventilation (13 to 5 L/min), respiratory rate (26 to 16 breaths/min), and Fio₂ (0.88 to 0.35). Ventilator-free days with AVCO₂R were 3.9 versus 0.2 (*P* < .01) for sham animals, and ventilator-dependent days with AVCO₂R were 2.4 versus 6.2 (*P* < .01) for the 3 sham survivors. All 8 AVCO₂R animals and 3 of 8 sham animals survived 7 days after randomization.

Conclusions: Percutaneous AVCO₂R achieved significant reduction in airway pressures, increased ventilator-free days, decreased ventilator-dependent days, and improved survival in a sheep model of respiratory distress syndrome. (*J Thorac Cardiovasc Surg* 2001;121:542-51)

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Despite recent advances in critical care, the overall mortality of adult respiratory distress syndrome (ARDS) remains approximately 50%.^{1,2} Mechanical ventilation can cause iatrogenic injury to the lungs by inflicting barotrauma and volutrauma³⁻⁶ to the small fraction of compliant alveoli and by the activation of inflammatory mediators, which may aggravate ARDS.⁷⁻⁹ By way of reducing ventilator-induced lung injury, recent trends in ventilator management limit inflation pressures and tidal volumes, often with a rise in systemic arterial carbon dioxide (CO₂),¹⁰ termed “permissive hypercapnia.” Lung protective ventilator strategies have

Fig 1. Schematic of model using the simple AVCO₂R circuit with low-resistance membrane gas exchanger in mechanically ventilated smoke/burn-injured sheep.

been shown to reduce the incidence of barotrauma/volutrauma and possibly improve survival in ARDS.^{11,12}

We¹³ have shown that arteriovenous CO₂ removal (AVCO₂R) allows significant reductions in ventilator pressures without hypercapnia or the complex circuitry and monitoring required for extracorporeal membrane oxygenation (ECMO) in sheep. Arterial percutaneous cannulas of 10F to 14F allow adequate blood flow to achieve near total CO₂ removal without incurring hypercapnia in adult sheep.^{14,15} In this current study, we used our recently established, clinically relevant LD₅₀ large animal model of respiratory distress syndrome (ARDS) induced by a 40% full-thickness cutaneous flame burn and a moderately severe smoke inhalation injury.¹⁶ To evaluate algorithm-directed, pressure-limited ventilator management with and without percutaneous AVCO₂R, we designed a prospective randomized nonblinded outcomes study with the primary end points of ventilator-free/ventilator-dependent days and survival. Secondary end points included AVCO₂R flow and CO₂ removal, hemodynamic parameters (heart rate, mean arterial pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output), ventilator parameters (tidal volume, peak inspiratory pressure, respiratory rate, and inspired oxygen fraction [FiO₂]), complications, and necropsy findings.

Materials and methods

All animals received humane care according to the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources,

National Research Council, and published by the National Academy Press, revised 1996. The study was approved by the Institutional Animal Care and Use Committee (IACUC) of The University of Texas Medical Branch, Galveston, Texas, with strict adherence to IACUC guidelines regarding humane use of animals.

Adult Suffolk ewes (n = 18, 29.5–45 kg) were instrumented with femoral arterial and venous catheters and a pulmonary arterial catheter 2 days before injury. Baseline variables including heart rate, cardiac output, mean arterial pressure, pulmonary artery pressure, central venous pressure, pulmonary artery wedge pressure, and arterial and venous blood gases were obtained immediately before injury.

After endotracheal intubation, 1% to 2.5% halothane was administered via an anesthesia ventilator (Ohmeda 7000; BOC Health Care, Liberty Corner, NJ). To induce ARDS, we performed a third-degree cutaneous flame burn on 40% of the total body surface area (20% on each side of the animal) with 36 breaths of cotton smoke insufflation delivered between the two burn episodes.¹⁶ Animals recovered from anesthesia and were mechanically ventilated (Servo 900C; Siemens-Elema, Sweden). Initial post-injury ventilator settings were as follows: respiratory rate 25 to 30 breaths/min, tidal volume 15 mL/kg, FiO₂ 1.0, and positive end-expiratory pressure 5 cm H₂O. Fluid resuscitation used lactated Ringer's solution as determined by the Parkland formula.¹⁷ FiO₂ was reduced (once carboxyhemoglobin was below 10% of baseline) to maintain a Pao₂ more than 60 mm Hg. Arterial and mixed venous blood gases were measured every 6 hours, with minute ventilation and FiO₂ adjusted to maintain arterial pH 7.35 to 7.45, Pao₂ more than 60 mm Hg, and Paco₂ less than 40 mm Hg. Hemodynamic variables and ventilator settings, including minute ventilation and peak inspiratory pressure, were recorded every 6 hours. Airway suctioning and lavage were performed every 4 to 6 hours to remove proteinaceous bronchial casts.

Fig 2. Management algorithm for ventilator reductions with AVCO₂R. ARDS, Adult respiratory distress syndrome; P/F, Pao₂/Fio₂ ratio; TV, tidal volume; PIP, peak inspiratory pressure; RR, respiratory rate; PEEP, peak end-expiratory pressure; CPAP, continuous positive airway pressure.

Animals were randomized to AVCO₂R (n = 9) or sham (n = 9) groups when they met entry criteria for ARDS (Pao₂/Fio₂ < 200), generally within 40 to 48 hours of injury. Animals randomized to the AVCO₂R group were reanesthetized, systemically anticoagulated (300 IU/kg bovine lung heparin; Upjohn, Kalamazoo, Mich), and started on antibiotic therapy (ampicillin, 1 g; gentamicin, 80 mg/mL). Animals then underwent cannulation of the left carotid artery (percutaneous 10F TF018LH; Research Medical, Midvale, Utah) and the left jugular vein (percutaneous 14F TF022L; Research Medical). A commercially available, low-resistance membrane gas exchanger (Affinity; Avecor Cardiovascular, Plymouth, Minn) was primed with normal saline solution (270 mL) and connected to the vascular cannulas (Fig 1). Activated clotting time (ACT, Hemochron 400; International Technidyne, Edison, NJ) was maintained between 300 and 500 seconds with a continuous heparin infusion throughout the study. The animal was then placed on a volume-controlled ventilator (Bear 1000 Ventilator; Bear Medical Systems, Inc, Riverside, Calif) before initiation of AVCO₂R. Animals randomized to the sham group underwent the identical management and operative exposure, with ligation of the carotid artery and jugular vein, but were not cannulated for AVCO₂R.

After the initiation of AVCO₂R flow with extracorporeal CO₂ removal, minute ventilation was reduced in a stepwise fashion according to our algorithm (Fig 2). Initial reductions were made in tidal volume (20% reduction) to reduce the peak inspiratory pressure below 30 cm H₂O. Once targeted airway pressures were achieved, respiratory rate was incrementally reduced to allow a longer respiratory cycle and gentle inspiratory flow if Paco₂ was 40 mm Hg or less. To minimize atelectasis, the re-

spiratory rate was not reduced below 2 breaths per minute. Concurrently, Fio₂ was reduced as Pao₂ remained above a threshold of 60 mm Hg. Positive end-expiratory pressure was kept at 5 cm H₂O throughout the study. When Pao₂ could be maintained above 60 mm Hg on an Fio₂ of 0.21 and a continuous positive airway pressure of 7 cm H₂O, animals were weaned from the ventilator. Daily measurements of heart rate, cardiac output, mean arterial pressure, pulmonary artery pressure, blood flow, peak inspiratory pressure, and CO₂ removal were recorded, and systemic and pulmonary vascular resistance were calculated and compared with baseline measurements.

AVCO₂R blood flow was monitored by an ultrasonic flow probe (model H6X; Transonic Systems, Ithaca, NY) on the arterial cannula interfaced with a real-time flowmeter (model HT 109; Transonic Systems) with digital display. The arteriovenous pressure gradient across the gas exchanger was calculated on the basis of difference between the inlet and outlet pressures. Sweep gas flow (100% oxygen) was controlled by an in-line regulator and set at 1.5 to 2.0 times blood flow. CO₂ removal by the device was calculated as the product of gas flow and its exhaust CO₂ concentration measured by an inline capnometer (SaraTrans, Lenexa, Kan). CO₂ removal by the native lungs was calculated as the product of minute ventilation and the CO₂ concentration in the expired gas collected in a Douglas bag. Blood and expired gases were measured with a blood gas system (System BG3 and Co-Oxymeter 482; Instrumentation Laboratory, Lexington, Mass). The animals received 24-hour bedside care and remained mechanically ventilated for 7 days or until successfully weaned from ventilator support. The management of both groups of animals was reviewed by a pulmonologist/intensivist (A.B.) for consistency of care and adherence to the algorithm.

Fig 3. AVCO₂R blood flow (*Qb*) and cardiac output remained stable while AVCO₂R flow ranged from 821.4 ± 55.4 mL/min to 970.2 ± 45.1 mL/min and averaged 869.9 ± 23.2 mL/min or 13.2% ± 0.7% of the cardiac output.

Data are expressed as mean ± SEM and were displayed and analyzed by SigmaPlot and SigmaStat (Jandel Scientific, San Rafael, Calif). Comparisons with baseline (before injury) were made by 1-way analysis of variance with Dunnett's test, with time treated as repeated measures. Survival, ventilator-free days, and ventilator-dependent days as primary end points and applicable secondary end points were compared between the 2 groups of animals with the Student *t* test.

Results

A total of 2946 animal-hours of bedside critical care and 696 total hours of AVCO₂R were required for this study. Ninety percent compliance with the study protocol was maintained during the trial. There were no significant changes in hemodynamics throughout the study despite the arteriovenous shunt. In the AVCO₂R group, there was no significant change in blood flow or pressure gradient across the device (always less than 10 mm Hg) throughout the experiment. For the primary end points, the AVCO₂R group averaged 3.9 ventilator-free days compared with 0.2 for the sham group ($P < .05$). Likewise, the AVCO₂R group averaged 2.4 ventilator-dependent days whereas all 3 survivors in the sham group were still ventilator dependent at day 7 (average 6.2 [$P < .05$]). All 8 animals in the AVCO₂R group survived the 7-day study, whereas only 3 of 8 animals in the sham group survived 7 days ($P < .05$). One animal died in each group from technical complications during model development and both were excluded from analysis. One AVCO₂R animal had minor bleeding from the neck, which was relieved with pressure.

Fig 4. CO₂ removal and resultant PaCO₂ on AVCO₂R. The decreasing *n* is due to animals improving and weaning from AVCO₂R. Six of 8 animals were off AVCO₂R by the end of day 3. For the 1 animal that required AVCO₂R to day 7, AVCO₂R flow was weaned during days 5 to 7. ARDS, Adult respiratory distress syndrome.

Despite the arteriovenous shunt, the measured parameters of heart rate, mean arterial pressure, cardiac output, and pulmonary artery wedge pressure remained relatively constant and were not statistically different from baseline at any time point during the study. The extracorporeal flow rate and cardiac output are seen in Fig 3. Blood flow through the oxygenator ranged from 821.4 ± 55.4 mL/min to 970.2 ± 45.1 mL/min and averaged 869.9 ± 23.2 mL/min or 13.2 ± 0.7% of the cardiac output. As seen in previous studies, the pressure gradient across the device was less than 10 mm Hg throughout the study. CO₂ removal in relation to PaCO₂ is shown in Fig 4. CO₂ removal via AVCO₂R (up to day 5) ranged from 91.5 ± 22.1 to 116.4 ± 13.7 mL/min (93%-97% of CO₂ production) while maintaining normocapnia (PaCO₂ ≤ 40 mm Hg). As tidal volume was reduced during the study, AVCO₂R was sufficient to maintain normocapnia. Animals were weaned from AVCO₂R beginning after day 2 until only 1 animal still required AVCO₂R after day 4. This animal, however, was weaned from AVCO₂R over days 5 to 7 and was off AVCO₂R by the end of day 7.

Changes in peak inspiratory pressure during AVCO₂R, compared with the sham group, are shown in Fig 5. Incremental ventilator reductions in rate and tidal volume decreased peak inspiratory pressure by 41% as compared with baseline ($P < .05$) while maintaining normocapnia (day 3). Peak inspiratory pressures in AVCO₂R animals were significantly lower than in sham animals throughout the study. AVCO₂R also allowed significant reductions in minute ventilation as

Fig 5. Reduction in peak inspiratory pressure during AVCO₂R. Incremental ventilator reductions in rate and tidal volume decreased peak inspiratory pressure by 41% as compared with baseline ($P < .05$) while maintaining normocapnia (day 3). Peak inspiratory pressure in AVCO₂R animals was consistently less than in sham animals throughout the study. The decreasing n is due to animals being weaned from mechanical ventilation (AVCO₂R) or dying of respiratory failure (sham).

compared with the sham group (Fig 6). Significant reductions were seen at days 1 to 4 ($P < .05$). At 48 hours, AVCO₂R allowed significant reductions compared with onset of ARDS entry criteria (PAO_2/FIO_2 ratio < 200) in minute ventilation (12.4 ± 1.5 to 6.5 ± 0.6 L/min), tidal volume (398.8 ± 42.1 to 274.0 ± 7.5 mL), peak inspiratory pressure (23.4 ± 2.9 to 18.8 ± 0.8 cm H₂O), respiratory rate (24.0 ± 1.7 to 17.0 ± 2.0 breaths/min), and FIO_2 (0.88 to 0.35 ± 0.1) while normocapnia was maintained. Fig 7 shows improvement in the PAO_2/FIO_2 ratio once AVCO₂R was used, allowing a reduction in FIO_2 commensurate with an improvement in arterial oxygenation. The PAO_2/FIO_2 ratio improved from 151.5 ± 40.0 at the introduction of AVCO₂R to more than 200 over 36 hours, with further improvement to more than 300 (320.0 ± 17.8) by 72 hours. The PAO_2/FIO_2 ratio in the 3 surviving sham animals improved in a similar pattern.

Discussion

Hickling, Henderson, and Jackson¹⁸ first published retrospective data on 50 patients with severe ARDS managed with permissive hypercapnia, significantly lowering the hospital mortality rate predicted by the APACHE* II scores (26.4% vs 53.3%, $P = .004$).¹¹

*Acute Physiology and Chronic Health Evaluation.

Fig 6. Reduction in minute ventilation during AVCO₂R as compared with sham. Significant reductions were made at days 1 to 4 (* $P < .05$).

Amato and colleagues¹⁹ compared “protective ventilation” at 6 mL/kg tidal volume with “conventional” ventilation at 12 mL/kg tidal volume in patients with ARDS. Protective ventilation allowed 66% of the patients to be weaned from ventilators compared with 29% with conventional ventilation; clinical barotrauma was 7% versus 42%, and hospital mortality was 38% versus 71%. Despite early reported success, the impact of “protective lung ventilation” on patients’ outcomes needed clarification because some studies reported an improved outcome whereas several randomized controlled studies could not demonstrate significant beneficial effects.²⁰⁻²² The recent National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) ARDS Clinical Network on Ventilator Management of ALI and ARDS study of low tidal volume (a randomized, controlled trial on 12 vs 6 mL/kg tidal volume) was terminated after 861 patients because the outcome of patients in the low tidal volume group was significantly improved by approximately 25%.²³ Likewise, the American Thoracic Society International Consensus Conference on Ventilator-Associated Lung Injury in ARDS recently reaffirmed that ventilator-induced lung injury is an important determinant of mortality in patients with ARDS.²⁴ Our study was not designed to evaluate the strategy of low tidal volume with “permissive hypercapnia” versus AVCO₂R. Instead, the goal of this particular study was to compare the strategy of “protocol-driven” pressure-limited ventilation versus AVCO₂R. We plan future studies to specifically evaluate the low tidal volume pressure-limited ventilation at different levels of hypercapnia (60s vs 80s), with and without blood pH normalization versus AVCO₂R.

ECMO provides complete gas exchange and improves survival in neonates,²⁵ pediatric patients,^{26,27} and selected adult patients.^{28,29} More than 15,000 cases of ECMO, to date, reveal an 81% survival in neonates, 49% in children, and 38% in adults in patient populations estimated to have more than an 80% mortality.³⁰ ECMO, however, involves intensive monitoring, high cost in labor and equipment, and frequent complications.³¹ To eliminate the need for an extracorporeal circuit, Mortensen and Berry³² developed an intravenacaval device (IVOX) designed to provide oxygenation and CO₂ removal. Intracorporeal membrane oxygenation and CO₂ removal provide 30% of CO₂ removal to significantly reduce the ventilatory requirements due to surface area limitations.³³ The technique, although innovative, was unsuccessful because clinical trials revealed a surface area limitation for sufficient gas exchange³⁴ and no impact on mortality.

AVCO₂R was developed to minimize the foreign surface interactions and blood element shear stress (inherent in an extracorporeal circuit with a pump) and allow a gas exchange membrane of sufficient surface area for total CO₂ removal.³⁵⁻³⁷ Recent developments in computational fluid dynamics have led to newly designed, low-resistance oxygenators.³⁸ We coupled such a low-resistance gas exchanger with percutaneous arterial and venous cannulas selected for the flow ranges necessary for total CO₂ removal for the treatment of respiratory failure.¹⁵ The extremely low resistance of the circuit and gas exchanger (<10 mm Hg) allowed a blood flow of up to 14% of the cardiac output at a mean arterial blood pressure in the 90 mm Hg range. We achieved approximately 970 mL/min of flow with a transdevice resistance consistently less than 10 mm Hg, to achieve near total CO₂ removal.

To evaluate the effect of our newly designed AVCO₂R circuit on regional organ/tissue perfusion at varying levels of AVCO₂R flow, we injected colored microspheres in a conscious adult sheep. At up to a 25% arteriovenous shunt, vital organ perfusion (brain, heart, kidney, mesentery) was well maintained within 80% of baseline in the conscious animal. We conclude that organ blood flow distribution is only mildly affected with an arteriovenous shunt of sufficient magnitude to allow total CO₂ removal.³⁹ To determine hemodynamic tolerability of prolonged AVCO₂R, we subjected adult sheep to a severe smoke inhalation injury to induce ARDS and then applied AVCO₂R at sufficient shunt flow for total CO₂ removal to evaluate the effect of sustained AVCO₂R flow on critical hemodynamic variables over 7 days.⁴⁰ Our data confirmed that despite up to a 25% cardiac shunt through the AVCO₂R circuit for 7 days, there was no instability in the hemodynam-

Fig 7. PaO₂/FiO₂ after smoke inhalation and cutaneous flame burn injury and after placement of AVCO₂R. Entry criteria (PaO₂/FiO₂ < 200) was met at 48 hours (194.8 ± 25.9). At the time AVCO₂R was initiated, PaO₂/FiO₂ was 151.5 ± 40.0. After 36 hours, PaO₂/FiO₂ had improved to more than 200, and after 72 hours PaO₂/FiO₂ was more than 300 (320.0 ± 17.8). The 3 (of 8) surviving sham animals improved in a similar pattern.

ic profile, specifically heart rate, cardiac output, mean arterial pressure, pulmonary artery pressure, or AVCO₂R flow.

To establish a clinically relevant model of severe respiratory failure in adult sheep, we developed a smoke dose-dependent smoke/burn model of ARDS of predictable severity.¹⁶ We found an inhalation injury of 36 breaths of smoke coupled with a 40% (20% each flank) third-degree cutaneous burn could create an LD₅₀ model to allow evaluation of the utility of AVCO₂R during ARDS.

Percutaneous AVCO₂R involves much simpler monitoring and maintenance than conventional ECMO. The simplicity of percutaneous femoral vessel cannulation with relatively small cannulas, the substantially reduced foreign body blood interface, and elimination of the shear forces of a blood pump all greatly simplify the extracorporeal circuit with the potential for decreased complications. The AVCO₂R circuit does not eliminate the gas exchange device (oxygenator) and so still requires systemic heparinization with the potential for bleeding complications. In the laboratory setting, the higher heparin doses (ACT 300-500 seconds) were easier to maintain over the 7-day study than tightly titrated lower ACTs. We⁴¹ have presented our data on the use of heparin-coated AVCO₂R circuits to allow decreased dosing of systemic heparin to ACTs of less than 200 seconds. Although the sheep in this 7-day outcomes study demonstrated no hemodynamic instability

during AVCO₂R, patients with concomitant cardiac disease or pre-existing hemodynamic instability may not tolerate the 11% to 14% arteriovenous shunt. Our upcoming prospective randomized clinical trials are designed to address these issues.

This current prospective randomized outcomes study required 2946 total animal-hours of bedside critical care and 696 total hours of AVCO₂R in a laboratory setting. Although "unblinded" for obvious reasons, the fact that all management was directed by a study algorithm with 90% compliance compares very favorably with other algorithm-directed ventilator management studies.⁴² Only one AVCO₂R animal experienced minor bleeding (relieved with pressure) from the incision site at the neck. Our technique of AVCO₂R still requires systemic anticoagulation with heparin and, therefore, imposes additional risks of bleeding. Heparin anticoagulation alone may improve outcome of smoke inhalation injury if administered immediately on injury.⁴³ However, this study used clinical entry criteria for ARDS ($\text{PaO}_2/\text{FIO}_2 < 200$ mm Hg). Therefore, 40 to 48 hours were required for ARDS to develop in these animals as seen clinically. This late in the course of ARDS, heparin alone contributes little to improving outcome.⁴⁴ Future developments of coated circuits and gas exchangers may decrease the blood/foreign surface interactions and decrease the need for anticoagulation.

Percutaneous AVCO₂R in combination with low-frequency mechanical ventilation allowed significant reductions in minute ventilation, peak inspiratory pressures, and ventilator-dependent days, while achieving a significant improvement in survival in our ovine model of ARDS. The improved results in survival and ventilator-free/dependent days may be directly related to the reduction in tidal volume and airway pressures. Because the sham animals were managed to match the blood gas values of AVCO₂R animals, resultant blood gases were similar in both groups. As AVCO₂R allowed immediate reductions in minute ventilation and peak inspiratory pressure, lung rest was achieved, presumably contributing to the improved survival.

Along with the decreased ventilatory requirements associated with the use of AVCO₂R, there was a concomitant improvement in arterial oxygenation.⁴⁵ As shown in Fig 7, similar improvement in $\text{PaO}_2/\text{FIO}_2$ ratio was seen among surviving animals—all 8 AVCO₂R animals but only 3 of 8 sham animals. As described by Bone and coworkers,⁴⁶ the $\text{PaO}_2/\text{FIO}_2$ ratio remains a reliable predictor of survival from ARDS, regardless of the therapeutic modality. Most interestingly, AVCO₂R, a treatment modality that

reduces ventilatory requirements by extracorporeal removal of CO₂ manifested improved survival with improvements in $\text{PaO}_2/\text{FIO}_2$ ratio. This improvement in arterial oxygenation with AVCO₂R is likely due to three separate effects. With resolution of noncardiogenic pulmonary edema associated with the lung injury, one would expect a decrement in the right-to-left shunt fraction. Second, the use of AVCO₂R improves the central mixed venous oxygen tensions, due to the admixture of well-oxygenated blood from AVCO₂R with the venous return to the right atrium. Finally, AVCO₂R allows the use of low peak airway pressures and tidal volumes to accomplish gas exchange, improving the ventilation/perfusion relationship and preventing further barotrauma/volutrauma from mechanical ventilation. Our data indicate that the PaO_2 in AVCO₂R animals was successfully managed above 60 mm Hg by adjusting FIO_2 and maintaining positive end-expiratory pressure at 5 cm H₂O. Thus, near-apneic oxygenation coupled with lung rest proved to be sufficient for oxygen exchange even in the presence of ARDS. Percutaneous AVCO₂R, therefore, can be an effective treatment, not only for CO₂ retention syndromes, but also during ARDS with poor oxygenation.

We have reported the application of AVCO₂R in 5 patients with unresponsive severe ARDS and CO₂ retention as a safety and feasibility study.⁴⁷ Via percutaneous access, AVCO₂R achieved approximately 70% CO₂ removal and allowed decreased barotrauma/volutrauma without hemodynamic compromise. All 5 patients were successfully cannulated for AVCO₂R at the bedside and completed the 72-hour trial. Three of the 5 patients were eventually discharged from the hospital. On the basis of our favorable initial patient experience and this prospective randomized outcomes study in sheep, we plan three prospective randomized ARDS trials using percutaneous AVCO₂R in humans: (1) smoke/burn-induced ARDS in children; (2) ARDS in adults; and (3) acute CO₂ retention syndromes in adults. The control arm of each of these studies will use the gentle ventilation strategies as outlined in the recent NIH/NHLBI ARDS network trial.

In conclusion, in a prospective randomized outcomes study of ARDS in sheep, AVCO₂R significantly reduced minute ventilation and peak airway pressure during mechanical ventilation for ARDS, significantly increased ventilator-free days and decreased ventilator-dependent days, and significantly improved survival. In addition to the clinical trials outlined, we plan further studies on optimization of gas exchange during AVCO₂R and studies on pathophysiology of ARDS.

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Discussion

Dr Robert H. Bartlett (*Ann Arbor, Mich*). If you have ever tried to do an acute animal experiment for 7 hours, you know how difficult it is, and you have some appreciation of the work that was involved in doing acute animal experiments for 7 days. Very few studies have been conducted on any type of prolonged extracorporeal support (or, for that matter, ventilator support) in animals with acute lung injury. I dare say they have all been done by either Ted Kolobow or Jay Zwischenberger, and you just heard the best one done to date.

The reason these studies are so rare is they are so hard to do. You have to have a way of taking care of sick animals for days at a time, standardize the model, standardize everything except the intervention, and characterize the intervention. I do not have to describe to you how difficult it is. This is simply a beautiful study, which addresses a couple of very interesting questions.

We always teach the residents when they are managing severe respiratory failure to think about CO₂ clearance and oxygenation as very different issues. They overlap, to be sure, but oxygenation is a matter of alveolar inflation matching perfusion. CO₂ removal is a matter of breathing. If you just run around with your mouth open, you can oxygenate your blood. You breathe in and out just to clear carbon dioxide, and this study emphasizes that issue.

Dr Zwischenberger has used this novel technology to study the effect of mechanical ventilation on acute lung injury. This technique is simple. We want to know something about the clinical application of it.

Regarding mechanical ventilation in normal animals, there are a host of studies. The first one that I know of is by Greenfield and Ebert. They showed that if normal dogs are ventilated with a moderate inspiratory pressure (30 cm H₂O), severe lung injury will result in about 2 days.

Many studies since then by Kolobow, Dreyfus, West, and many others have shown that even moderate stretch injury to the lung causes severe lung injury.

A lot of human studies have shown that mechanical ventilation in lung-injured persons adds to the injury in a significant way. The first of these studies was by Gattinoni, demonstrating with computed tomographic scan that the volume of lung to be ventilated in an ARDS patient is much smaller than one might think, judging by the size of the patient. Studies by Hickling and Amato showed that if overdistention is avoided, survival outcome is better. Recently a large study done by the NIH/NHLBI ARDS network showed the same thing. If the lung is stretched even moderately in patients with severe respiratory failure, it adds significantly to the mortality. Of course, the ECMO studies in children, infants, and adults show the same thing. If the patient is simply taken off the ventilator or the settings are reduced to low settings, the outcome will be much better than if the ventilatory practices that have been taught for the past 35 years are used.

I congratulate Dr Zwischenberger on the quality of the study. I have 2 questions.

You referred briefly to clinical application, but I would like to know where those studies stand and what you plan to do with them.

Second (and to me much more interesting), on the basis of this information, why do you think that conventional mechanical ventilation, as you used in this study, caused higher mortality?

Dr Zwischenberger. You just heard the best 3-minute synopsis on respiratory failure I have ever been subjected to. Since Dr Bartlett has been my mentor for the past 20 years, I want to thank him for interesting this young investigator in the problem of respiratory failure.

What I can say is that lung protective strategies of ventilator management have been emphasized by this study. By removing CO₂, we are able to dramatically decrease the pressure and volume of ventilation and therefore impose even more lung protection. At first assessment, I believe the primary source of amelioration of the lung injury is the fact that we decrease peak inspiratory pressure, decrease mean airway pressure, and decrease minute ventilation. However, as we thought about respiratory failure, we were enthralled by the idea that perhaps homeostasis of CO₂ may have profound effects on the pathophysiology of ARDS. That is where our primary interest is now focusing. One option is to decrease the inflammatory mediators

of respiratory failure, such as tumor necrosis factor α , and we have significant preliminary data that this strategy does decrease the flame and the fuel that fire ARDS.

We have also noted that CO₂ homeostasis at the alveolar level may decrease macrophage activation of inflammatory mediators and influx of neutrophils in the inflammatory cellular response.

Last, at the alveolar level, achieving CO₂ homeostasis may allow decreased transfer of fluid or influx of fluid in the alveolus, which causes an abnormality of compliance. Decreasing aquaporin activity may contribute to this finding.

These competing theories are under investigation. The one we know we are able to achieve is decreasing ventilator-induced lung injury. Because of AVCO₂R technology and the fact that we have been able to demonstrate improved survival in animals and feasibility in human beings, we are now embarking on the 3 clinical trials that were described. Thanks to available funding, we have started a multicenter clinical trial on ARDS in children associated with burn injury. We have also appealed to funding agencies to do a multicenter clinical trial in adults. I am trying to avoid the use of commercial or entrepreneurial funding, so I am focusing on peer-reviewed sources to accomplish these trials.

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