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Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study

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Abstract *Objective:* To evaluate the safety and efficacy of pumpless extracorporeal arteriovenous carbon dioxide removal ($AVCO_2R$) in subjects with acute respiratory failure and hypercapnia.
Design: A phase I within-group time series trial in which subjects underwent up to 72 h of support with $AVCO_2R$ in intensive care units of two university hospitals.
Patients: Eight patients with acute hypercapnic respiratory failure or hypoxemic respiratory failure managed with permissive hypercapnia.
Interventions: Extracorporeal CO_2 removal was achieved through percutaneous cannulation of the femoral artery and vein, and a simple extracorporeal circuit using a commercially available membrane gas exchange device for carbon dioxide exchange.
Measurements and results: Measurements of hemodynamics, blood gases, ventilatory settings, and laboratory values were made before initiation of $AVCO_2R$, and at subsequent intervals for 72 h. $PaCO_2$ decreased significantly from 90.8 ± 7.5 mmHg to 52.3 ± 4.3 and 51.8 ± 3.1 mmHg at 1 and 2 h, respectively. This decrease occurred despite a decrease in minute ventilation from a baseline of 6.92 ± 1.64 l/min to 4.22 ± .46 and 3.00 ± .53 l/min at 1 and 2 h. There was a normalization of pH, with an increase from 7.19 ± .06 to 7.35 ± .07 and 7.37 ± .05 at 1 and 2 h. These improvements persisted during the full period of support with $AVCO_2R$. Four subjects underwent apnea trials in which $AVCO_2R$ provided total carbon dioxide removal during apneic oxygenation, resulting in steady-state $PaCO_2$ values from 57 to 85 mmHg. Hemodynamics were not significantly altered with the institution of $AVCO_2R$. There were no major complications attributed to the procedure.
Conclusion: Pumpless extracorporeal $AVCO_2R$ is capable of providing complete extracorporeal removal of carbon dioxide during acute respiratory failure, while maintaining mild to moderate hypercapnia. Applied in conjunction with mechanical ventilation and permissive hypercapnia, $AVCO_2R$ resulted in normalization of arterial PCO_2 and pH and permitted significant reductions in the level of mechanical ventilation.

Keywords Acute respiratory failure · Respiratory insufficiency · Carbon dioxide · Hypercapnia · Extracorporeal membrane oxygenation · Extracorporeal circulation

Table 1 Characteristics of the study subjects (*COPD* chronic obstructive pulmonary disease, *ARDS* acute respiratory distress syndrome)

Subject	Age (years)	Sex	Weight (kg)	Duration (hours)	Outcome	Cause of respiratory failure
1	44	M	82	72	S	Pneumonia, restrictive lung disease
2	67	M	68	72	S	COPD exacerbation
3	29	F	62	72	D	ARDS, sepsis
4	35	F	77	72	S	ARDS, aspiration
5	66	F	62	68	D	Pneumonia
6	41	M	65	56	D	Pneumonia, sepsis
7	49	M	64	72	D	ARDS, pneumonia, sepsis
8	21	M	75	72	S	ARDS, bowel perforation, sepsis

Introduction

It has become increasingly evident over the past three decades that the manner in which patients with acute lung injury are supported with mechanical ventilation may contribute to progression of the underlying lung injury process. A series of compelling animal studies provides strong support for this argument [1, 2, 3, 4, 5, 6]. Furthermore, recent clinical trials demonstrate that limitation of lung inflation [7] and ventilation based on measurement of pulmonary mechanical properties [8] are associated with improved outcome from severe acute respiratory failure. Since hypercapnia usually accompanies these approaches, management of hypercapnia through extracorporeal removal may enhance the application of these ventilatory strategies and reduce the complications of hypercapnia.

Extracorporeal techniques for the removal of carbon dioxide, such as extracorporeal CO_2 removal, have not been widely adopted. Controlled clinical trials of venoarterial extracorporeal membrane oxygenation [9] and venovenous extracorporeal CO_2 removal [10] have failed to demonstrate an improvement in survival. Pumpless arteriovenous CO_2 removal ($AVCO_2R$) using percutaneous cannulation is an alternative to traditional pumped extracorporeal systems. We have previously demonstrated in both mathematical and animal models that $AVCO_2R$ can remove clinically significant amounts of carbon dioxide [11, 12, 13] and permit significant reduction in ventilatory volumes and pressures [14, 15, 16]. Mathematical modeling has suggested that total carbon dioxide removal in humans is possible with the use of physiologically tolerable arteriovenous blood flow and the existing gas exchange capabilities of currently available membrane oxygenators [13]. $AVCO_2R$ is a simple extracorporeal technique that involves the insertion of a membrane gas exchange device in an arteriovenous shunt using percutaneous cannulation. Since the extracorporeal circuit does not require the use of a blood pump, hematological effects are expected to be minimal [17].

In this study our objective was to evaluate the safety and efficacy of percutaneous $AVCO_2R$ in a pilot study in adults with moderate to severe hypercapnia due to severe respiratory failure during mechanical ventilation with lung protective strategy for hypoxemic respiratory failure and in patients with hypercapnic respiratory failure requiring mechanical ventilation.

Methods and materials

This was a collaborative phase I safety and efficacy study performed in the intensive care units of Louisiana State University Health Sciences Center in Shreveport, Louisiana, and the University of Texas Medical Branch at Galveston, Texas, USA. The Institutional Review Boards at each institution reviewed and approved the study protocol and consent form. Informed consent was obtained in each subject from a legally authorized representative for all research procedures.

Subject selection

Eight patients were enrolled in the study between March 1997 and June 1999 and contributed to the analysis. Inclusion criteria were (a) mechanical ventilation for acute respiratory failure of at least 72 h expected duration, (b) cardiopulmonary stability for least 6 h prior to enrollment (defined as absence of need for changes in mechanical ventilation, fluid therapy, vasopressors or inotropes, and (c) hypercapnia, with $PaCO_2$ greater than 55 mmHg. Hypercapnia could be due to either permissive hypercapnia during treatment of hypoxemic respiratory failure, or hypercapnic respiratory failure due to reversible airways disease or extrapulmonary causes. Exclusion criteria included (a) hemodynamic instability or hypotension requiring significant vasopressor support (> 10 μg/kg per minute dopamine), (b) contraindication to systemic heparinization, (c) class 3 or 4 heart failure (New York Heart Association classification), (d) significant peripheral vascular disease or previous surgery precluding percutaneous femoral arterial cannulation, (e) myocardial infarction in the previous 6 months, (f) prior venous thrombosis or pulmonary embolism, or (8) uncontrolled coagulopathy. There was no attempt to capture a representative sampling of all patients with acute respiratory failure. Characteristics of the subject and the causes of acute respiratory failure are listed in Table 1. One patient had hypercapnic respiratory failure due to obstructive airways disease, and the remaining had permissive hypercapnia during mechanical ventilation with lung protective strategies (low tidal volume).

Study design

The study was designed as a within-group time series study of AV-CO_2R for up to 72 h in which each subject served as control. After enrollment each subject underwent baseline (time 0) measurement of hemodynamics, arterial blood gases, ventilatory support parameters (patient and ventilator), and laboratory assessment (coagulation, blood cell counts, complement levels, plasma free hemoglobin). Subsequent measurements were obtained 1, 2, 4, and 8 h after initiation of support, then at 8-h intervals until termination of support (up to 72 h). Additional measurements were made one and 4 h after discontinuation.

Complications were recorded for all patients, and were classified as major or minor. Complications were considered as major if they required device removal, resulted in therapeutic intervention (except fluid administration or changes in vasopressors), physical injury or death, or prolonged the stay of the intensive care or hospital course. Major complications included transfusion, infection, heart failure, air embolism, and venous thromboembolism. All other complications were considered minor, and included minor cannula site bleeding, hypothermia, oxygenator failure, clotting or failure of the extracorporeal circuit.

Extracorporeal procedures

The femoral area was prepared with aseptic technique. The femoral artery and vein of seven subjects were cannulated with 12 and 14- to 15 F percutaneous cannulae (Biomedicus, Medtronic, Eden Prairie, Minn., USA). The first subject was cannulated with a 10-F arterial cannula, but flow was lower than desirable. Heparin at 100–200 mg/kg was administered at the time of cannulation. The cannulae were connected to an uncoated hollow fiber polypropylene membrane oxygenator (Affinity, Medtronic) that had been primed with heparinized crystalloid (Normosol-R, Abbott). Flow was permitted spontaneously through the subjects' natural arteriovenous pressure difference. Heparin was infused into the systemic circulation to maintain an activated coagulation time (ACT) of 200–250 s. Oxygen was used as the sweep gas, and the gas:blood flow ratio was maintained at 5:1 or greater using a calibrated flowmeter. The oxygenator was changed as required for the development of clotting within the oxygenator and reduction in flow. The heat exchanger of the oxygenator was not used for temperature control at the initiation of support but was available if the subject developed a decrease in body temperature.

Measurements

Blood gases were measured using a commercial blood gas analyzer (model 288, CIBA-Corning, Medfield, Mass., USA). Oxygen saturation was measured by spectrophotometry (model 270, CIBA-Corning). Measurement of carbon dioxide concentration in the oxygenator exhaust gas was performed with mass spectrometry, and CO_2 removal rates were calculated as the product of sweep gas flow and CO_2 concentration. Inlet gas flow was controlled with a calibrated flowmeter. Due to the high gas flow rate used, inlet and exhaust gas flow differences were assumed to be negligible.

Cardiac output was determined in triplicate by the thermodilution method with pulmonary artery catheters. Extracorporeal blood flow was measured in the extracorporeal limb with an ultrasonic flow meter (model HT109, Transonics Systems, Ithaca, N.Y., USA). Blood pressure was measured using intra-arterial catheters in the femoral artery, and the remaining pressure measurements were made with the pulmonary artery catheter. Temperature was measured by thermistor in the pulmonary artery.

Total CO_2 removal

Apnea trials were conducted in four subjects who were pharmacologically paralyzed as part of their underlying treatment to assess the capability of the system for total carbon dioxide removal. The subjects were placed on a FIO_2 of 1.0 for 30 min, and then placed on continuous positive airway pressure with no spontaneous or mechanical ventilator breaths for 60 min. Exhaust gas PCO_2 was monitored continuously to verify the attainment of a steady-state condition. Measurement of arterial blood gases was performed at the end of the apnea trial to determine steady-state $PaCO_2$ during total carbon dioxide removal.

Ventilator management

Prior to entry into the study, subjects were managed on mechanical ventilation using strategies aimed at reducing secondary pulmonary injury, including pressure-controlled ventilation, limitation of tidal volumes (6–8 ml/kg), reduction in respiratory frequency (< 12 breaths/min), and management of positive end-expiratory pressure to maintain alveolar recruitment [18]. Over the first 2 h following the introduction of AVCO_2R, $PaCO_2$ decreased as a result of extracorporeal CO_2 removal. This allowed further reductions in rate and tidal volume. All subjects were maintained on controlled mechanical ventilation with sedation and neuromuscular blockade for at least 24 h. Following this period subjects were switched to pressure support ventilation with spontaneous ventilatory effort if their condition permitted.

Statistical analysis

Observed continuous variables at various time points were compared using two-way fixed-effects analysis of variance in which the subject represented a common effect. Comparisons of means in significant analysis of variance models were performed with Tukey's test using two-sided confidence intervals and multiple comparisons against a control (baseline measurement). Identification of variables contributing to carbon dioxide transfer was performed using stepwise multiple regression from a subset of plausible dependent variables. The type I error was set at 0.05. All statistical and graphic procedures were performed with S-Plus (S-Plus 2000 Professional, MathSoft, Seattle, Wash., USA).

Results

Blood gases and ventilator support

Substantial improvement in blood gases resulted from the introduction of extracorporeal support. $PaCO_2$ decreased significantly from 90.8 ± 7.5 mmHg to 52.3 ± 4.3 and 51.8 ± 3.1 mmHg at 1 and 2 h, respectively. This decrease occurred despite a decrease in minute ventilation from a baseline of 6.92 ± 1.64 l/min to 4.22 ± .46 and 3.00 ± .53 l/min at 1 and 2 h. Following initiation of AVCO_2R the pH normalized, with an increase from

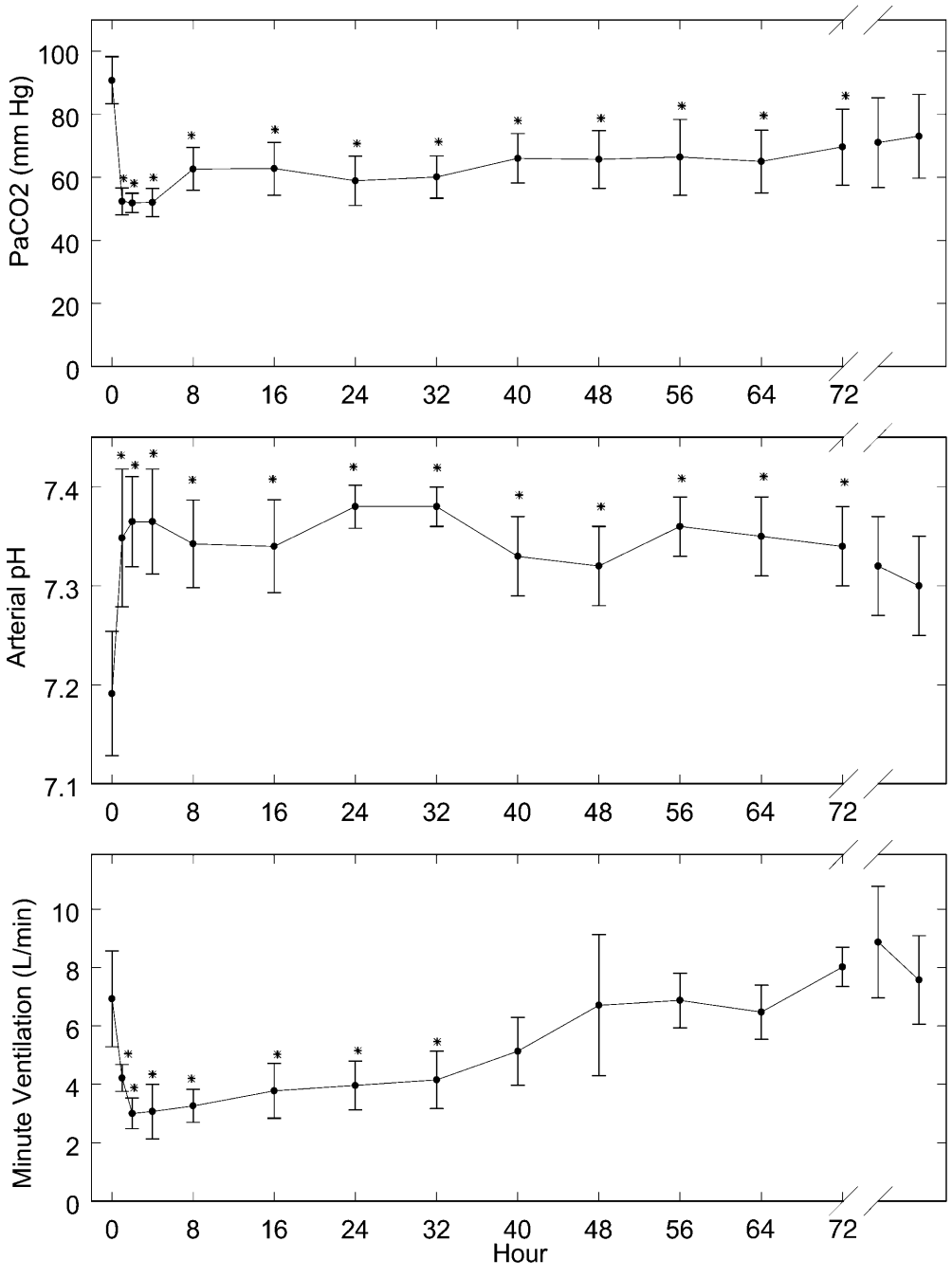

Fig. 1 $PaCO_2$, pH and minute ventilation over the 72-h course of $AVCO_2R$ support and 4 h following termination of support. Hour 0 represents baseline measurements. The post-support measurements were made 1 and 4 h after termination of $AVCO_2R$. $PaCO_2$ and pH were returned to near normal levels following initiation of $AVCO_2R$, and remained significantly improved compared to baseline throughout the support interval. Minute ventilation was reduced significantly for 32 h; following that time some subjects were switched from controlled to supported ventilation. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$) and 72 h ($n = 6$)

7.19 ± .06 to 7.35 ± .07 and 7.37 ± .05 at 1 and 2 h, respectively. These improvements were statistically and clinically significant for the duration of support (Fig. 1). The reduction in minute ventilation was significant for the first 32 h of support. Following that time, the level of mechanical ventilation increased in some subjects, as the subjects were allowed to breathe with a spontaneous ventilatory support mode (pressure support) if their condition warranted.

Hemodynamic

No significant hemodynamic changes developed at initiation of $AVCO_2R$ or during the remainder of the study period. Mean blood pressure and heart rate remained stable during the course of the study (Fig. 2). There were no significant changes in cardiac output or mixed venous oxygen saturation remained stable throughout the course of support (Fig. 3). Two subjects had mild de-

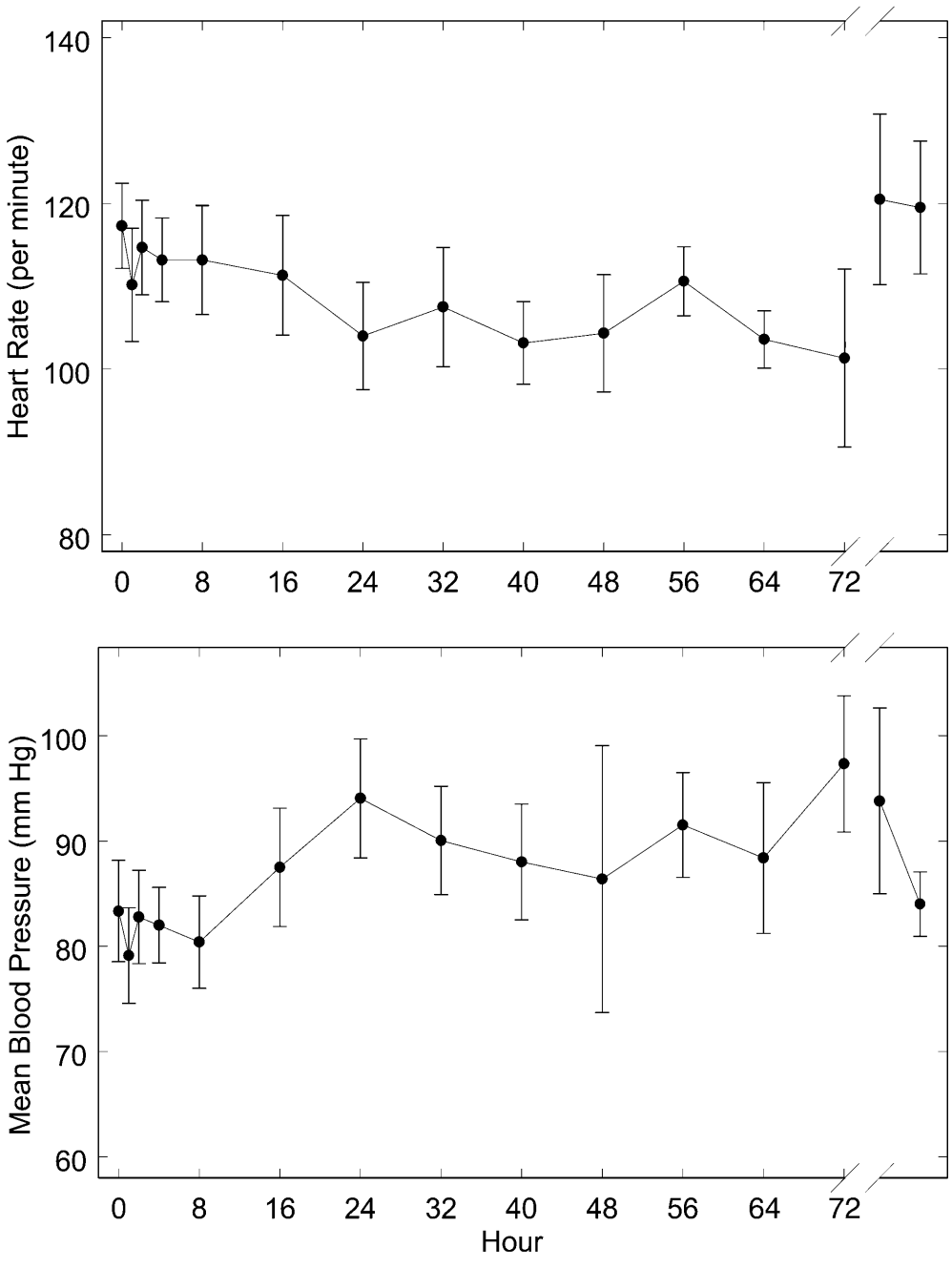

Fig. 2 Heart rate and blood pressure over the 72-h course of $AVCO_2R$ support and 4 h following termination of support. Hour 0 represents baseline measurements. The postsupport measurements were made 1 and 4 h after termination of $AVCO_2R$. There were no clinically or statistically significant changes in heart rate or blood pressure from baseline during the support interval. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$) and 72 h ($n = 6$)

creases in blood pressure that responded to fluid administration. One subject required an increase in dopamine from 5–8 μg/kg per minute. Four other subjects on vasopressor support did not have adverse effects following initiation of $AVCO_2R$ and did not require dose changes. No patient showed signs of perfusion deficit or circulatory failure.

Apnea trials

Four subjects underwent evaluation for total carbon dioxide removal during apnea. Each of the four subjects tolerated the trial with apneic oxygenation and total extracorporeal CO_2 removal for 1 h without hemodynamic or gas exchange complications. All four subjects attained steady-state conditions as determined by continuous monitoring of exhaust gas PCO_2. Steady-state $PaCO_2$ levels were 85, 57, 75, and 82 mmHg, respective-

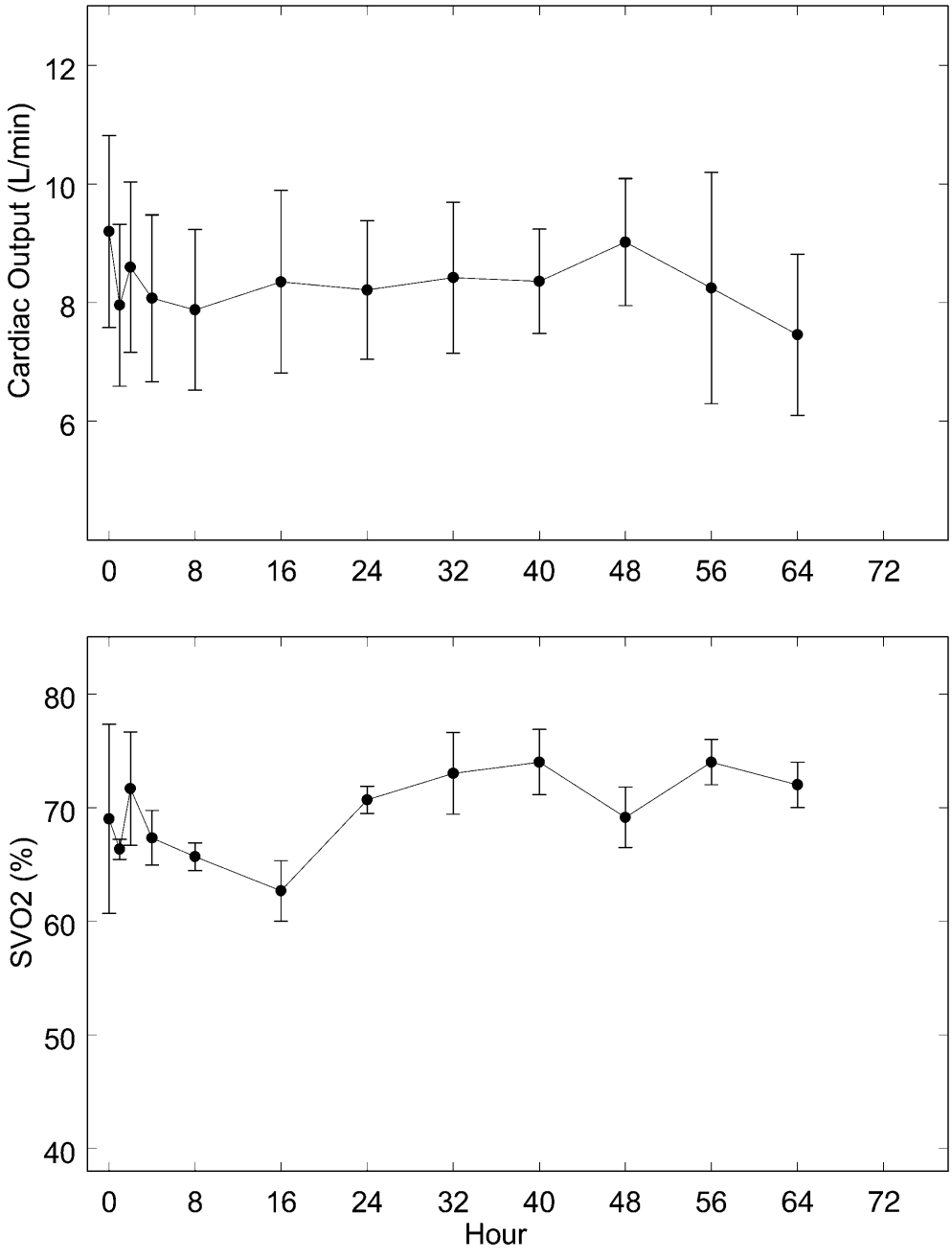

Fig. 3 Cardiac output and mixed venous oxygen saturation (SVO_2) over the 72-h course of $AVCO_2R$ support and 4 h following termination of support. Hour 0 represents baseline measurements. There were no clinically or statistically significant changes in cardiac output or SVO_2 from baseline during the support interval. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$) and 72 h ($n = 6$)

ly, indicating that total carbon dioxide removal by arteriovenous extracorporeal circulation is feasible and physiologically tolerable.

Laboratory and hematological effects

Hemoglobin decreased approximately 1 g/dl over the first 8 h following initiation of $AVCO_2R$. Hemodilution from the circuit may have contributed to this decrease. No subject had any significant blood loss or required transfusion because of bleeding complications or anemia. Two subjects received blood transfusions by the attending physician during the first 24 h unrelated to the research protocol.

Platelets decreased gradually but continuously over the initial 24-h period but remained stable afterward (Fig. 4). While this may be partially due the critical nature of the subjects, platelet deposition on the fibers of the gas exchange device may have contributed to the de-

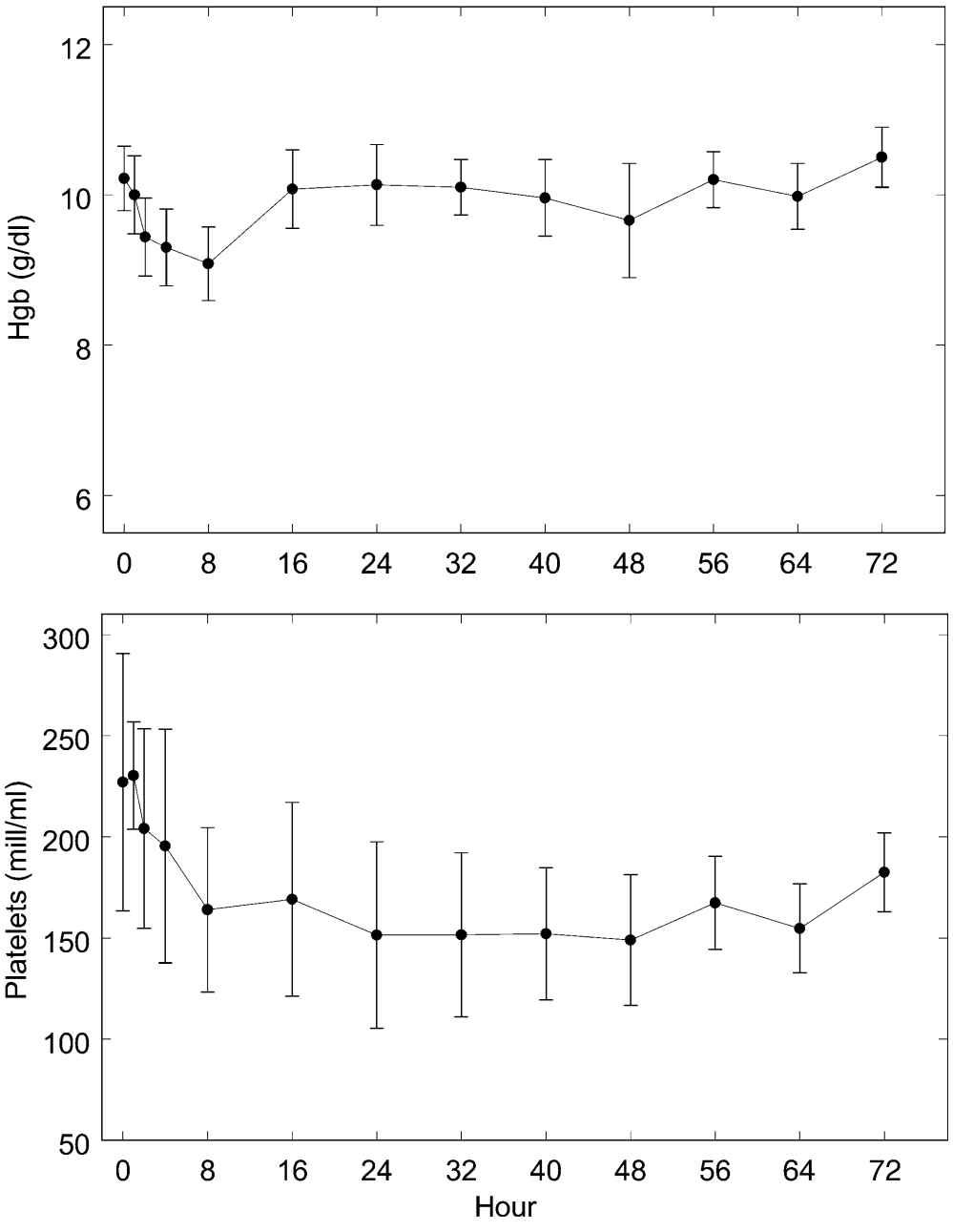

Fig. 4 Hemoglobin *(Hgb)* and platelet count over the 72-h course of $AVCO_2R$ support and 4 h following termination of support. Hour 0 represents baseline measurements. There was a slight but nonsignificant drop in hemoglobin, possibly related to hemodilution from the extracorporeal circuit. Platelets decreased over the initial 24 h of support (possibly related in part to platelet deposition in the circuit), but remained stable following that time. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$) and 72 h ($n = 6$)

crease in platelet count. No patient developed clinically significant thrombocytopenia or required platelet transfusion.

Plasma hemoglobin, a sensitive measure of red cell destruction in extracorporeal circuits, remained well within normal values (< 10 mg/dl; Fig. 5). There was no evidence of device-related hemolysis. Complement 3 levels decreased slightly but not significantly decrease following the introduction of $AVCO_2R$, suggesting a mild activation of complement but remained stable afterward. There was no change in complement 4 levels. The contribution of the device to the activation of complement is unknown. No clinically detectable complement-activation sequelae were identified.

Device performance

Figure 6 gives the median and ranges of CO_2 transfer by the extracorporeal circuit. The level of carbon dioxide transfer with partial support remained constant at over 100 ml/min for the duration of support, except for a

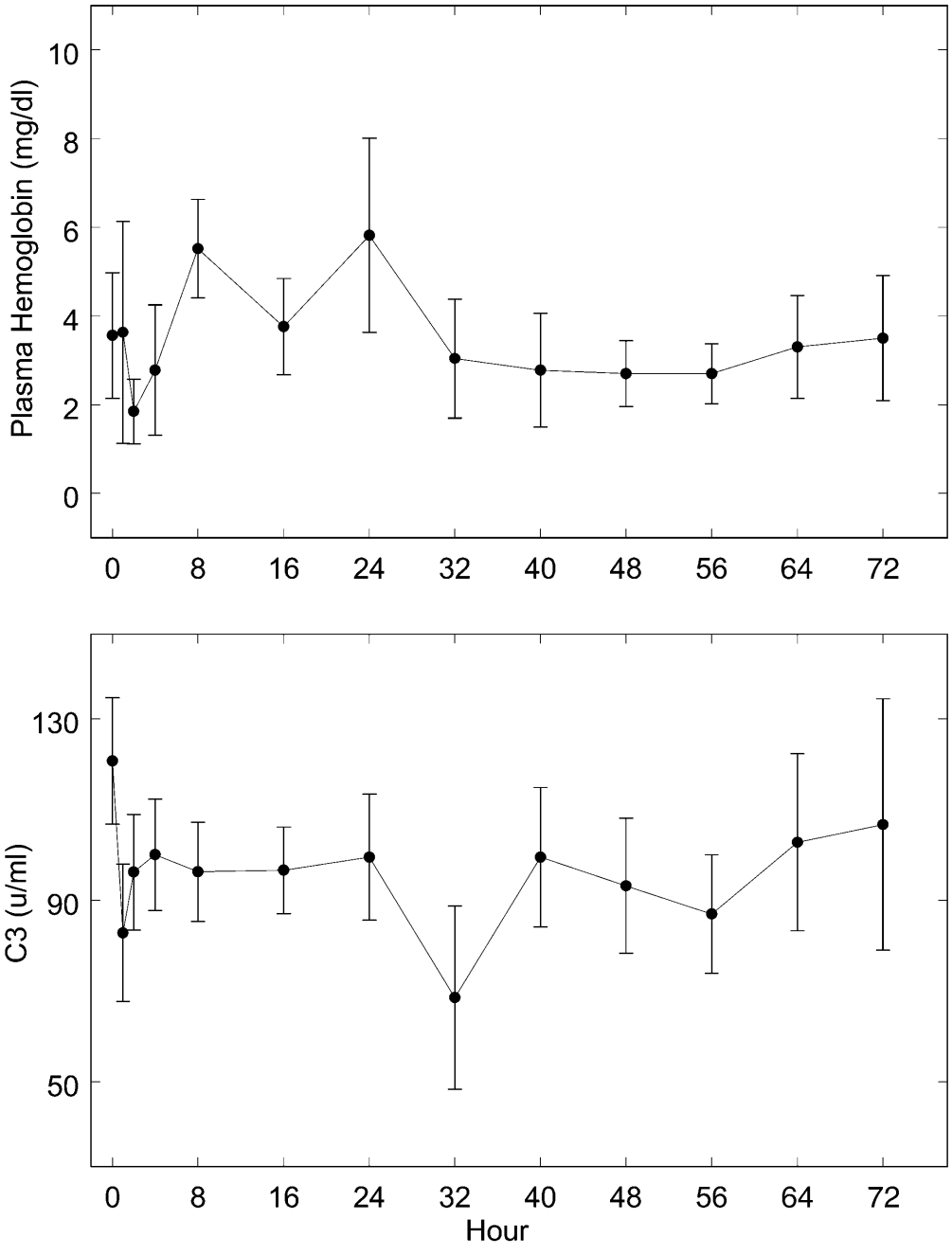

Fig. 5 Plasma free hemoglobin and complement 3 *(C3)* levels over the 72-h course of AV-CO_2R support and 4 h following termination of support. Hour 0 represents baseline measurements. There was no elevation in plasma hemoglobin, indicating the absence of hemolysis. C3 levels decreased slightly immediately following initiation of $AVCO_2R$, but this decrease was not statistically or clinically significant and levels remained constant subsequent to that. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$ subjects) and 72 h ($n = 6$)

slightly lower value at 72 h. Analysis of contributing factors was performed with stepwise multiple regression with the following dependent variables: extracorporeal blood flow, sweep gas flow, arterial blood gases, and ventilatory parameters. The analysis revealed a significant regression on the following variables: blood flow, sweep gas flow, arterial PO_2, and arterial pH (Table 2).

Blood flow in the extracorporeal circuit is driven by the pressure differential between the arterial and venous circulations. The relationship of blood flow with systemic blood pressure was evaluated with linear regression (Fig. 7). Since venous pressure in the iliac vessels could not be measured, it was not included in the model. A first-order linear model revealed a nonsignificant intercept term, and therefore so the model was fit without an intercept (consistent with the underlying physical principles of blood flow). Given the cannula sizes used in this study, blood flow of approximately 8-9 ml/mmHg per minute can be expected from the circuit.

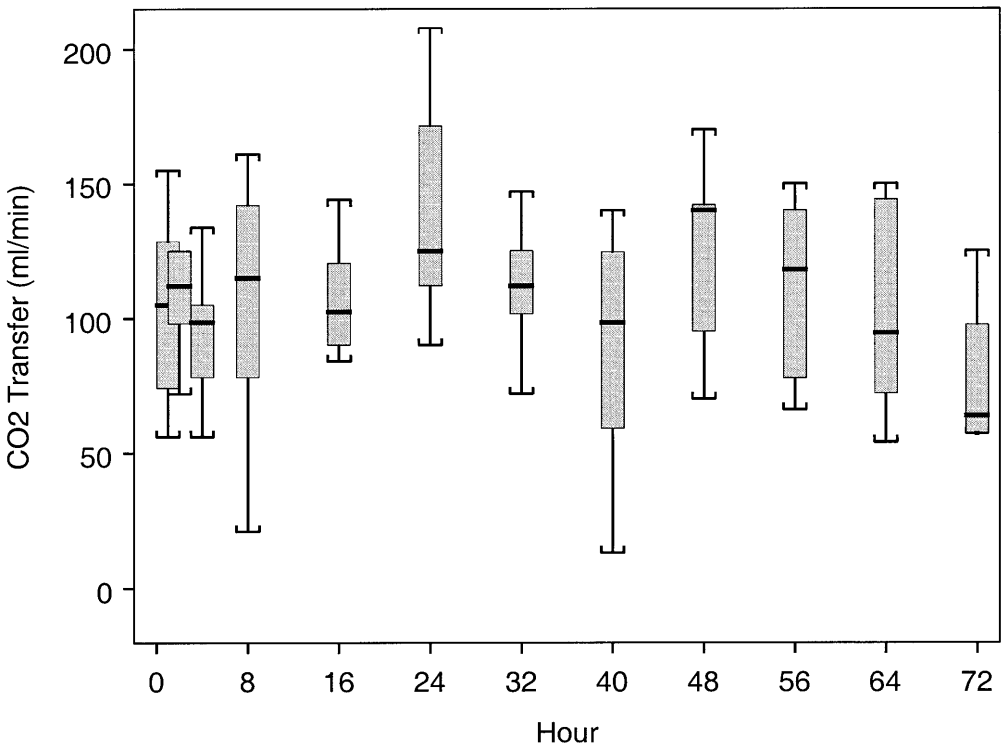

Fig. 6 Box plot of carbon dioxide transfer in ml/min over the course of partial support during mechanical ventilation. Median CO_2 removal rates exceeded 100 ml/min throughout most of the interval of support, and reached maximum levels of 210 ml/min. Values are presented as mean ± SEM. Observations from all eight subjects were included at each time point except for 68 h ($n = 7$) and 72 h ($n = 6$)

Table 2 Stepwise multiple regression on dependent variables affecting carbon dioxide removal rate (overall model: multiple $R^2 = 0.276$, $p = 0.0001$)

Dependent variable	Estimate	p
Blood flow (ml/min)	0.058	0.016
Gas sweep flow (ml/min)	0.008	< 0.001
Arterial PCO_2 (mmHg)	1.077	< 0.001
Arterial pH	113.9	0.018

The first two devices were sent to the manufacturer for mechanical and microscopic analysis. The fiber bundle was clean and without clot accumulation except for clot collection at the upper pole of the oxygenator. This clot collection was confined to the inner aspects of the fiber bundle, and resulted from the use of lower blood flows and longer duration than the rated specifications based on oxygenator design. There was no evidence of clot formation capable of embolization to the venous circulation. Deposits of fibrin and cellular elements was adherent to the external surface of some fibers, but not of sufficient magnitude to affect gas exchange.

Complications

No major complications were noted; specifically no occurrences of infection, air embolism, thromboembolism, heart failure, or refractory hypotension were identified. Minor complications included bleeding at the cannulation site in two patients that was controlled with application of pressure. One oxygenator developed thrombosis, resulting in decreased gas exchange. Five oxygenators required replacement during the course of $AVCO_2R$ support due to development of plasma leakage. One case of plasma leakage was temporally related to the administration of propofol in 10% lipid suspension. No patient developed hypothermia or required active temperature regulation through the heat exchanger of the oxygenator.

Discussion

Acute respiratory failure continues to be associated with a high mortality [19]. The mainstay of support is positive pressure mechanical ventilation, which improves gas exchange through effects on intrapulmonary shunting and ventilation-perfusion matching. In severe acute respiratory failure ventilation-perfusion abnormalities are profound and cannot be adequately overcome with positive pressure ventilation. The traditional approach in mechanical ventilation is to achieve normal arterial blood gas and pH values through the application of tidal volumes of 10–15 ml/kg, increased respiratory rates and short inspiratory times. These strategies, however, may lead to pulmonary overdistension.

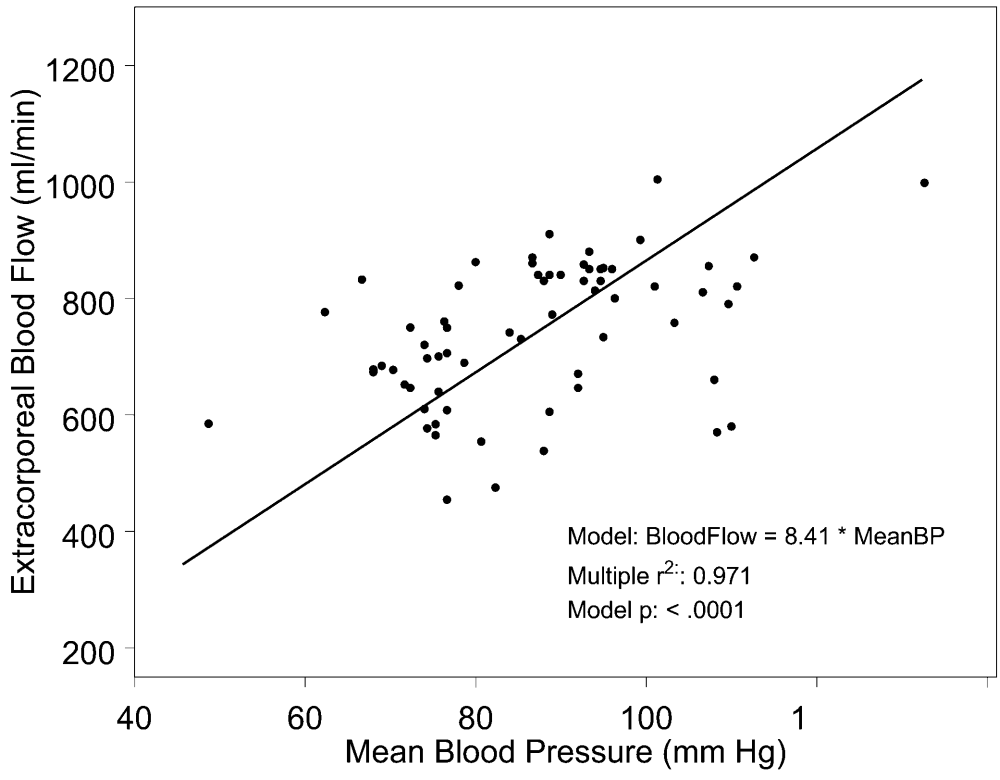

Fig. 7 Regression analysis of extracorporeal blood flow on mean arterial blood pressure. A significant relationship between blood pressure and blood flow was noted

The adverse effects of pulmonary overdistension are now well recognized, and have been consistently produced in several animal species ranging from small to large. Rats ventilated to a peak pressure of 45 cmH_2O developed increased capillary permeability and alveolar edema [1, 2]. Hernandez et al. [3] demonstrated in rabbits that hyperinflation superimposed on existing lung injury was more deleterious than hyperinflation alone. Hyperinflation injury has also been demonstrated in dogs [4], swine [5], and sheep [6]. Histopathological data supporting ventilator-induced lung injury are lacking in humans. However, the conditions that predispose the lung to injury do exist in humans. Gattinoni et al. [20, 21] have demonstrated that the amount of recruited lung in severe respiratory failure is only a fraction of normal. Thus patients with existing pulmonary injury are especially subject to overdistension injury.

Clinical trials that targeted pulmonary mechanics as an end-point in ventilatory support, in a strategy that reduces secondary pulmonary injury, have suggested an improved outcome [8, 22]. A large multicenter trial of reduced tidal volume in acute respiratory distress syndrome in 861 patients demonstrated a significant reduction in mortality (31.0 vs. 39.8%, respectively) of a low tidal volume group (6 ml/kg) compared with subjects receiving 12 ml/kg [7]. These approaches, however, often lead to marked reduction in minute ventilation such that hypercapnia becomes manifest. While hypercapnia is tolerated (permissive hypercapnia), it nonetheless can be associated with significant pathophysiological effects [23, 24], which may be detrimental.

Pumped extracorporeal techniques are very effective at removing carbon dioxide [25]. Gattinoni and colleagues [26] demonstrated that pumped extracorporeal venovenous carbon dioxide removal is capable of sufficient CO_2 transfer during low-frequency positive pressure ventilation, and improved survival compared with historical controls. In a subsequent randomized controlled trial of low-pressure inverse ratio ventilation vs. low-pressure inverse ratio ventilation plus extracorporeal CO_2 removal by Morris et al. [10], however, there was no improvement in mortality. At the present time venovenous extracorporeal CO_2 removal, a modification of extracorporeal membrane oxygenation, requires a system that is resource intensive and has potential bleeding complications. Pumpless arteriovenous carbon dioxide removal is an alternative to pumped systems that is simpler, easier to initiate, and may be associated with fewer complications.

The first use of a membrane oxygenator for arteriovenous removal of carbon dioxide was by Barthelemy et al. [27]. A siliconized cellulose membrane oxygenator was used in a sheep model of hypercapnia induced by apneic oxygenation. These experiments established that total CO_2 removal was possible during apnea, resulting in moderate hypercapnia, but blood flows of

1200–1400 ml/min were required because of the poor efficiency of the oxygenator. Additional animal studies showing effective gas exchange using hollow fiber polypropylene membrane oxygenators have been reported by a number of other investigators [28, 29, 30, 31, 32, 33, 34].

This clinical trial of $AVCO_2R$ has been preceded by several preclinical studies from our laboratories. In collaboration with Zwischenberger and Bidani, Conrad et al. [13] developed a mathematical model to evaluate $AVCO_2R$, validated it in a small animal model, and determined operating characteristics required for $AVCO_2R$ to provide partial or total carbon dioxide removal. Brunston et al. [35] determined that $AVCO_2R$ did not adversely affect cardiac output or organ blood flow at extracorporeal shunt fractions up to 29%. Frank et al. [36] determined that vascular cannulae on the order of 10–14 F would provide sufficient flow for effective carbon dioxide removal; sizes which do not impose technical or safety barriers to percutaneous cannulation. The limits of blood flow predicted by mathematical modeling were confirmed in experimental studies by Brunston et al. [11]. Large animal studies confirmed that $AVCO_2R$ can transfer sufficient quantities of carbon dioxide to impact ventilatory support [14, 15].

This study demonstrates that $AVCO_2R$ is capable of total complete carbon dioxide removal during apneic oxygenation. Used in conjunction with mechanical ventilation for subtotal CO_2 removal, it permits clinically significant reductions in ventilatory support and near-normalization of blood gas homeostasis. In this series of eight patients there were no major safety issues. We could not identify any major impact on blood pressure, heart rate, or cardiac output, which supports experimental studies on hemodynamic effects of $AVCO_2R$ [30, 32]. Even patients with sepsis syndrome requiring low-dose vasopressor support (< 10 μg/kg dopamine per minute) tolerated the extracorporeal shunt well. In spite of the extracorporeal blood flow as high as 1 l/min, temperature control through the heat exchanger was not required.

The major drawback of $AVCO_2R$ is the need for systemic anticoagulation with its attendant risk of bleeding, and the development of plasma leakage in the microporous membrane. However, with advances in coating technology and biocompatible surfaces, it may be possible to develop a system that remains stable to plasma exposure and does not require the use of systemic anticoagulation, further improving the safety profile of $AVCO_2R$.

Extracorporeal techniques for support of gas exchange have not been widely adopted. Extracorporeal life support has been studied in two controlled trials in adults [9, 10], but has not been shown to impact outcome. However, neither of these trials adequately applied lung protective strategies to the degree that is now felt to be a fundamental component of effective management of severe acute respiratory failure. The potential advantages of $AVCO_2R$ include technical simplicity, low resource utilization, and safety. In addition to support of the patient with permissive hypercapnia, a potential role of $AVCO_2R$ is the support of the patient with hypercapnic respiratory failure from acute reversible airways disease, where it may even serve as a replacement for mechanical ventilation.

We conclude that in this series of subjects pumpless extracorporeal $AVCO_2R$ was capable of providing total carbon dioxide removal with mild to moderate hypercapnia. When used for partial support in conjunction with mechanical ventilation, it allowed significant reductions in ventilatory support and a return of pH to near normal values during hypercapnic respiratory failure or permissive hypercapnia.

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