Published in final edited form as:

ASAIO J. 2016 ; 62(1): 110–113. doi:10.1097/MAT.0000000000000291.

“Large Animal Model of Pumpless Arteriovenous Extracorporeal CO₂ Removal Using Room Air Via Subclavian Vessels”

Lucas Witer, MD^{1,2}, Ryan Howard, BA¹, John Trahanas, MD^{1,3}, Benjamin S. Bryner, MD¹, Fares Alghanem, BS¹, Hayley R. Hoffman, BS¹, Marie S. Cornell, BS¹, Robert H. Bartlett, MD¹, and Alvaro Rojas-Peña, MD^{1,4}

¹Department of Surgery Extracorporeal Life Support Laboratory, University of Michigan, Ann Arbor, MI, USA

²Department of Surgery, Beaumont Health Systems, Royal Oak, MI, USA

³Department of Surgery, Columbia University Medical Center, New York NY

⁴Department of Surgery, Section of Transplantation, University of Michigan, MI, USA

Abstract

End-stage lung disease (ESLD) causes progressive hypercapnia, dyspnea, and impacts quality of life. Many extracorporeal support (ECS) configurations for CO₂ removal resolve symptoms but limit ambulation. An ovine model of pumpless ECS using subclavian vessels was developed to allow for ambulatory support.

Vascular grafts were anastomosed to the left subclavian vessels in four healthy sheep. A low-resistance membrane oxygenator was attached in an arteriovenous (AV) configuration. Device function was evaluated in each animal while awake and spontaneously breathing, and while mechanically ventilated with hypercapnia induced. Sweep gas (FiO₂=0.21) to the device was increased from 0-15 L/min and arterial and post-device blood gases, as well as post-device air, were sampled.

Hemodynamics remained stable with average AV shunt flows of 1.34±0.14 L/min.. In awake animals, CO₂ removal was 3.4±1.0 mL/kg/min at maximum sweep gas flow. Respiratory rate decreased from 60±25 at baseline to 30±11 breaths per minute. In animals with induced hypercapnia, PaCO₂ increased to 73.9±15.1. At maximum sweep gas flow, CO₂ removal was 3.4±0.4 mL/kg/min and PaCO₂ decreased to 49.1±6.7 mmHg. Subclavian AV access is effective in lowering PaCO₂ and respiratory rate, and is potentially an effective ambulatory destination therapy for ESLD patients.

Keywords

Ovine model; extracorporeal support; CO₂ removal; pumpless; subclavian access

Corresponding Author: Alvaro Rojas-Peña MD, ECLS Laboratory B560 MSRB II, 1150 W. Medical Center Drive- Ann Arbor, MI 48109, Phone: (734) 615-5357, Fax (734) 615-4220, alvaror@med.umich.edu.

Conflict of Interest Statement: The above authors stipulate there are no conflicts of interest existing for the attached manuscript.

End-stage lung disease, caused by chronic obstructive pulmonary disease (COPD) is a major public health problem and is the third most common cause of death in the United States.¹ The pathophysiology of COPD is very large alveolar dead space caused by the primary disease leading to CO₂ retention, hyperventilation, and ultimately exhaustion from severe dyspnea and tachypnea. Lung transplantation remains the definitive treatment, however demand for transplantable organs far outweighs availability: in 2010, COPD accounted for more than 130,000 deaths in the United States, while less than 2,000 lung transplants were performed. Due to organ scarcity, median wait time for a transplant is four months, and 15.4% of patients die while awaiting transplant.² Many other patients suffering from COPD may not be eligible for transplantation due to comorbidities or poor functional status.

Extracorporeal support (ECS) for CO₂ removal was first proposed by Kolobow in 1978³ and is currently utilized as a bridge to transplantation and for relief of exacerbations of respiratory failure. Our laboratory is developing implantable artificial lungs meant for destination therapy in transplant ineligible patients with severe lung disease. The goal of destination therapy for COPD is palliation. Extracorporeal CO₂ removal should decrease patients' ventilatory drive alleviate tachypnea both at rest and with exercise. The challenges in developing a permanent implantable lung for COPD are: device design and efficiency, anticoagulation, management with an air pump as opposed to oxygen, easy access (paracorporeal) for device evaluation and potential change out, infection, and vascular access.^{4,5} This study was designed to evaluate the subclavian vessels as a vascular access for a permanent artificial lung for CO₂ removal in a large bovine model.

Normal O₂ and CO₂ exchange in awake, standing sheep is 4-5 mL/kg/min and 250-300 mL/min, respectively. Thus, the theoretical blood flow required to remove sufficient CO₂ for palliative care is 1.0L/min. These long-term use devices should allow ambulation, easy access to evaluate function and changes, minimal risk of systemic embolism, low resistance, and minimal anticoagulation therapy. Since artificial lungs for COPD must be developed in large animal models we evaluated subclavian AV access in adult sheep.

Methods

All animals received proper care following the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*. This study was approved by the University Committee on Use and Care of Animals (UCUCA) at the University of Michigan, Ann Arbor, MI.

Sedation and Anesthesia

Four healthy sheep (61.3±6.2 kg) were anesthetized following our laboratory protocols, and maintained with 1-3% inhaled isoflurane throughout the procedure.⁶

AV Access

Two 6 mm ringed expanded polyester gelatin polypropylene vascular grafts (Terumo/Vaskutek Gelsoft, Ann Arbor, MI) were anastomosed in end-to-side fashion to the subclavian vessels, then cannulated with 17Fr Novalung[®] cannulae (GmbH, Hechingen, Germany) which were linked by $\frac{3}{8}$ inch tubing (Tygon, Akron, OH) to create an AV shunt. Cannulae were secured and tunneled subcutaneously to exit the animal's upper back. A

Swan-Ganz catheter (Edwards Lifesciences, Munich, Germany) was also placed in the right internal jugular vein using Seldinger technique. Following surgery, sheep were recovered, extubated, and transferred to our animal ICU for extended monitoring. Once stabilized, the AV shunt tubing was clamped and cut to length, and a low-resistance membrane oxygenator (Novalung® GmbH, Hechingen, Germany) was primed and attached to the AV shunt according to the manufacturer specifications.

Study design

Heparin infusion was titrated to maintain activated clotting time (ACT) between 250-300 seconds. The animals were followed for the next two days, evaluating cardiac function, membrane lung function, ambulation, ease of access, CO₂ removal over a range of sweep flows, respiratory rate, and PaCO₂ under ambient conditions. On the second day the animals were anesthetized paralyzed and ventilated. Hypercarbia was induced by decreasing minute ventilation from 120 to 27 mL/kg/min, and gas exchange measured. The membrane lung was ventilated with air over a wide range of sweep flows.

Data Collection

Blood gases were taken pre- and post-device and analyzed using a blood gas analyzer (ABL 800 Flex, Radiometer, Westlake, OH). Flow through the AV shunt was measured using a $\frac{3}{8}$ inch tubing flow probe and a TS420 console (Transonic Systems Inc, Ithaca, NY).

Device CO₂ removal was calculated as:

$$(CO_2 \text{ in sweep gas exhaust}) \times (\text{Sweep gas flow})$$

Device resistance was calculated as:

$$\frac{(Pre - \text{device } MAP) - (Post - \text{device } MAP)}{\text{Circuit flow}}$$

Results

All four animals completed the study protocol, with no operative, technical or infectious complications in these short experiments. None of the animals exhibited any sign of upper extremity swelling or functional impairment, and the animals were able to ambulate (video available on request). The AV shunt did not negatively affect systemic hemodynamics during the experiment. Flow through the AV shunt and membrane lung averaged 21.9±8.1 mL/kg/min (1.34±0.14 L/min) throughout the experiments, which represents 14% of the cardiac output. Device resistance throughout the study was 3.6±1.1 mmHg/min/L.

CO₂ Clearance

The CO₂ clearance with a range of sweep flow to blood flow ratios is shown in Figure 1. In the awake standing sheep high levels of sweep flow resulted in 180 mL/min CO₂ clearance and a change in spontaneous respiratory rate from 60±25 to 30±11 breaths per minute. At the end of the two day experiment the sheep were anesthetized and hypoventilated to create

hypercarbia in the range of PaCO_2 73.9 ± 15.1 mmHg after minute ventilation was gradually decreased as described above. As sweep gas flow was increased, CO_2 removal increased to a maximum of 3.4 ± 0.4 mL/kg/min at 15 L/min of sweep gas flow. At this rate of flow, PaCO_2 decreased to 49.1 ± 6.7 mmHg (Figure 2).

Upon necropsy, both grafts in all animals were secure, and all anastomoses were revealed to be patent and intact.

Discussion

Extracorporeal gas exchange, particularly CO_2 removal is effective in the management of CO_2 retention in end stage COPD.⁷ Both animal and clinical trials have focused on short term normalization of blood gases using venovenous access with a pump or using pulmonary artery (PA) to left atrium (LA) direct vascular access.^{6,8-14} PA/LA access allows perfusion of the device by the right ventricle and can provide full oxygenation as well as CO_2 removal. However, it requires thoracotomy for placement and runs the risk of systemic embolism because of blood return to the left atrium. Arterio-venous access for CO_2 removal has been evaluated with many laboratory and clinical trials and is a very effective way of achieving CO_2 removal at relatively low blood flow.

Initial clinical trials were conducted with femoral artery and vein access but the risk of femoral artery injury or exsanguination and the limitation of ambulation has resulted in the use of pumped venovenous access for selective CO_2 removal in modern practice.¹⁵ Limited potential for ambulation prevents patients from participating in rehabilitative therapies which in recent years have been shown to be highly beneficial for ECLS.¹⁴

Peripheral vessels represent a more attractive access option for ambulatory and long-term therapy. Axillary and subclavian vessel cannulation for extracorporeal oxygenation has been demonstrated, both via direct cannulation and also via end to side “chimney graft.”^{13,16-20}

A permanent implantable artificial lung designed for COPD palliation requires moderate blood flow, and a device capable of achieving a CO_2 content inlet/outlet difference of 10-15 mL/dL. (We define an implantable device as a device dependent on permanent vascular access, as opposed to an intravascular removable cannula). These studies show that subclavian AV access is feasible, results in blood flow which would allow high levels of CO_2 removal, and that efficient CO_2 removal can be accomplished in an awake animal using a commercial membrane lung.

We identified the following limitations in our study: 1) The use of a relatively low sample size. It became clear that results were reproducible, and feasibility had been demonstrated with these 4 animals. However, a larger sample size might uncover potential technical complications after graft or device attachment; 2) Anticoagulation regimen, high ACT goals were targeted in this study given the increased thrombogenicity of sheep relative to humans. While we did not observe any hematoma formation, a low incidence is to be expected. In human subjects we would target lower ACTs, and postoperatively transition to oral antiplatelets and anticoagulants would be similar to the one given to patients with ventricular assist devices; 3) The need for mechanical ventilation in order to show a reduction in

PaCO₂. Healthy animals drastically lowered respiratory rate in response to CO₂ removal, thus preventing profound hypocapnea. Our goal with ambulatory CO₂ removal is to provide a long-term solution to chronic lung disease, therefore it would be more applicable to evaluate CO₂ removal in a chronic disease model.

Further studies will evaluate: development of an animal model of end stage COPD, development of an anticoagulation protocol, development of a membrane lung specifically designed for this purpose, and chronic subclavian access .

Conclusions

Subclavian arteriovenous access results in flow of 10-20% of the cardiac output which has no deleterious effects on the heart in normal animals but allows perfusion of a membrane lung sufficient to remove large amounts of CO₂. In both normal and hypercarbic conditions. CO₂ removal via subclavian AV access is sufficient to remove enough CO₂ to decrease the resting respiratory rate by 50% under ambient conditions in adult healthy sheep. Finally, subclavian AV access is a reasonable starting point for further studies on development of a permanent implantable artificial lung for end stage COPD.

Acknowledgements

The described research was sponsored by National Institutes of Health 2RO1 HD015434-29. Authors thank: Terumo Cardiovascular Group for contribution of graft material to our animal experiment, The University of Michigan Undergraduate Research Opportunity Program (UROP), the Cardiovascular Center Summer Undergraduate Research Fellowship & The Esperance Family Foundation for supporting our visiting undergraduate summer student Alejandra Macias who helped with post-operative care of some animals. Finally, the authors acknowledge the efforts of Cindy Cooke for review and preparation of the manuscript.

Source of Funding: Dr. Rojas-Peña is an independent consultant and advisor for Terumo CVS, specifically to endoscopic vascular harvesting (EVH) and cardiopulmonary bypass (CPB) products.

REFERENCES

1. Zielinski J, MacNee W, Wedzicha J, et al. Causes of death in patients with COPD and chronic respiratory failure. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo. 1997; 52:43–7.
2. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2013; 61:1–117.
3. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE. An alternative to breathing. The Journal of thoracic and cardiovascular surgery. 1978; 75:261–6. [PubMed: 625133]
4. Lick SD, Zwischenberger JB. Artificial lung: bench toward bedside. ASAIO journal. 2004; 50:2–5. [PubMed: 14763484]
5. Vincent JL, Bihari DJ, Suter PM, et al. EPIC International Advisory Committee. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA: the journal of the American Medical Association. 1995; 274:639–44. [PubMed: 7637145]
6. Sato H, Hall CM, Lafayette NG, et al. Thirty-day in-parallel artificial lung testing in sheep. Ann Thorac Surg. 2007; 84:1136–43. discussion 43. [PubMed: 17888959]
7. Abrams D, Roncon-Albuquerque R Jr, Brodie D. What's new in extracorporeal carbon dioxide removal for COPD? Intensive care medicine. 2015; 41:906–8. [PubMed: 25643904]

8. Brunston RL Jr, Zwischenberger JB, Tao W, Cardenas VJ Jr, Traber DL, Bidani A. Total arteriovenous CO₂ removal: simplifying extracorporeal support for respiratory failure. *The Annals of thoracic surgery*. 1997; 64:1599–604. discussion 604–5. [PubMed: 9436542]
9. Brunston RL Jr, Tao W, Bidani A, Cardenas VJ Jr, Traber DL, Zwischenberger JB. Determination of low blood flow limits for arteriovenous carbon dioxide removal. *ASAIO journal*. 1996; 42:M845–9. [PubMed: 8945003]
10. Wang D, Lick SD, Campbell KM, et al. Development of ambulatory arterio-venous carbon dioxide removal (AVCO₂R): the downsized gas exchanger prototype for ambulation removes enough CO₂ with low blood resistance. *ASAIO journal*. 2005; 51:385–9. [PubMed: 16156304]
11. Conrad SA, Zwischenberger JB, Grier LR, Alpard SK, Bidani A. Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. *Intensive care medicine*. 2001; 27:1340–51. [PubMed: 11511947]
12. Zwischenberger JB, Conrad SA, Alpard SK, Grier LR, Bidani A. Percutaneous extracorporeal arteriovenous CO₂ removal for severe respiratory failure. *The Annals of thoracic surgery*. 1999; 68:181–7. [PubMed: 10421138]
13. Javidfar J, Brodie D, Costa J, et al. Subclavian artery cannulation for venoarterial extracorporeal membrane oxygenation. *ASAIO journal (American Society for Artificial Internal Organs)*. 1992; 2012; 58:494–8. [PubMed: 22929897]
14. Rehder KJ, Turner DA, Hartwig MG, et al. Active rehabilitation during extracorporeal membrane oxygenation as a bridge to lung transplantation. *Respiratory care*. 2013; 58:1291–8. [PubMed: 23232742]
15. Gander JW, Fisher JC, Reichstein AR, et al. Limb ischemia after common femoral artery cannulation for venoarterial extracorporeal membrane oxygenation: an unresolved problem. *Journal of pediatric surgery*. 2010; 45:2136–40. [PubMed: 21034934]
16. Abrams DC, Brodie D, Rosenzweig EB, Burkart KM, Agerstrand CL, Bacchetta MD. Upper-body extracorporeal membrane oxygenation as a strategy in decompensated pulmonary arterial hypertension. *Pulmonary circulation*. 2013; 3:432–5. [PubMed: 24015346]
17. Hysi I, Fabre O, Renaut C, Guesnier L. Extracorporeal membrane oxygenation with direct axillary artery perfusion. *Journal of cardiac surgery*. 2014; 29:268–9. [PubMed: 24131078]
18. Moazami N, Moon MR, Lawton JS, Bailey M, Damiano R Jr. Axillary artery cannulation for extracorporeal membrane oxygenator support in adults: an approach to minimize complications. *The Journal of thoracic and cardiovascular surgery*. 2003; 126:2097–8. [PubMed: 14688737]
19. Shafii AE, McCurry KR. Subclavian insertion of the bicaval dual lumen cannula for venovenous extracorporeal membrane oxygenation. *The Annals of thoracic surgery*. 2012; 94:663–5. [PubMed: 22818320]
20. Biscotti M, Bacchetta M. The “Sport Model”: Extracorporeal Membrane Oxygenation Using the Subclavian Artery. *The Annals of Thoracic Surgery*. 2014; 98:1487–9. [PubMed: 25282228]

Figure 1. Awake, Spontaneously Breathing Animals

(A). CO₂ removal increased as sweep gas flow was increased, reaching a maximum of 3.9 ± 1.7 mL/kg/min at 11 L/min; (B). PaCO₂ decreased from a baseline of 31.1 ± 6.2 to 26.7 ± 1.6 mmHg at 15 L/min; (C). Respiratory rate decreased from a baseline of 60 ± 25 to 30 ± 11 breaths per minute; (D). PaO₂ did not significantly deviate from baseline as sweep gas flow increased.

Figure 2. Hypercapnic, Anesthetized Animals

(A). Hypercapnia was induced by using the ventilator to reduce MV from 120 mL/kg/min at baseline to 26.6 ± 4.6 mL/kg/min; (B). As sweep gas flow was increased, CO₂ removal increased to a maximum of 3.4 ± 0.4 mL/kg/min at 15 L/min of sweep gas flow; (C). PaCO₂ increased from 37.4 ± 2.6 mmHg to 73.9 ± 15.1 mmHg after MV was gradually decreased, then decreased as sweep gas flow was increased, reaching 49.1 ± 6.7 mmHg at 15 L/min.