Published in final edited form as:

ASAIO J. 2017 ; 63(5): 644–649. doi:10.1097/MAT.0000000000000627.

Fourteen Day *In Vivo* Testing of a Compliant Thoracic Artificial Lung (cTAL)

David J. Skoog, PhD^{*}, Joshua R. Pohlmann, BS[†], David S. Demos, MD^{†,‡}, Christopher N. Scipione, MD[†], Amit Iyengar, BS^{*}, Rebecca E. Schewe, PhD^{*}, Ahmed B. Suhaib, BS^{*}, Kelly L. Koch, MD[†], and Keith E. Cook, PhD^{*,†}

^{*}Department of Biomedical Engineering, University of Michigan

[†]Department of Surgery, University of Michigan

[‡]Department of General Surgery, Henry Ford Health System

Abstract

The compliant Thoracic Artificial Lung (cTAL) has been studied in acute in vivo and in vitro experiments. The cTAL's long term function and potential use as a bridge to lung transplantation are assessed presently. The cTAL without anti-coagulant coatings was attached to sheep (n=5) via the pulmonary artery and left atrium for 14 days. Systemic heparin anticoagulation was utilized. cTAL resistance, cTAL gas exchange, hematologic parameters, and organ function were recorded. Two sheep were euthanized for non-device related issues. The cTAL's resistance averaged 1.04 ± 0.05 mmHg/(L/min) with no statistically significant increases. The cTAL transferred 180 ± 8 mL/min of oxygen with 3.18 ± 0.05 L/min of blood flow. Except for transient surgical effects, organ function markers were largely unchanged. Necropsies revealed pulmonary edema and atelectasis, but no other derangements. Hemoglobin levels dropped with device attachment but remained steady at 9.0 ± 0.1 g/dL thereafter. In a fourteen day experiment, the cTAL without anti-coagulant coatings exhibited minimal clot formation. Sheep physiology was largely unchanged, except for device attachment related hemodilution. This suggests that patients treated with the cTAL shouldn't require multiple blood transfusions. Once tested with anti-coagulant coatings and plasma resistant gas exchange fiber, the cTAL could serve as a bridge to transplantation.

Keywords

Artificial lung; ECMO; Bridge to lung transplantation; Destination therapy

Introduction

In the United States approximately 127,000 people die annually from chronic respiratory diseases.¹ The only long term cure is lung transplantation. However, donor lung shortages only allow approximately 1800 transplantations annually.² Extracorporeal membrane oxygenation (ECMO) can be used as a bridge to lung transplantation in a variety of patients

and configurations ranging from cystic fibrosis patients with veno-venous ECMO to pulmonary hypertension (PH) patients with veno-arterial ECMO.^{3–6} However, ECMO offers limited patient ambulation^{4,5,7,8} and biocompatibility issues lead to patient deterioration over time.^{6,9,10} Blood damage and activation that necessitate blood product transfusions and greater anticoagulation, greatly affect biocompatibility.^{6,9,10} Thus, a longer term treatment that would circumvent these shortcomings is needed as a bridge to transplantation and destination therapy.

Thoracic artificial lungs (TALs) may be suitable as a bridge to transplantation or destination therapy for patients with chronic lung disease. TALs consist of a low resistance gas exchanger attached in a pulmonary artery to left atrium (PA-LA) or pulmonary artery to pulmonary artery configuration. Flow through the TAL is driven by the right ventricle, avoiding the large ECMO circuit and pump that can damage and activate formed elements in blood.^{11–13} Although TAL systems have the potential to increase system biocompatibility and lower PA pressures of some patients, their attachment requires invasive surgical procedures. Thus, TAL's are better suited towards long term treatment of chronic respiratory disease rather than acute conditions, such as Acute Respiratory Distress Syndrome. A commercial gas exchanger designed originally for use in arterio-venous carbon dioxide removal, the Novalung iLA, has been utilized as a TAL in a small number of patients. However, as the Novalung iLA was not designed for this purpose, its relatively high resistance, low gas exchange capabilities, and relatively short device lifespan limited its use as a TAL. The MC3 Biolung, with its low 1.8 mmHg/(L/min) resistance¹⁴ was designed specifically as a TAL, and has been tested in sheep in 7 day and 30 day experiments.^{15,16} Without employing anti-thrombogenic coatings, the MC3 Biolung was able to support sheep for a period of 30 days.¹⁶ However, in 30 day studies Biolung replacement was performed every 9.5 days on average due to thrombus formation, and in 7 day studies one of the devices exhibited near total occlusion from thrombus formation on Day 7.^{15,16} The Biolung has not been used clinically as a TAL.

The compliant thoracic artificial lung (cTAL) utilizes a flexible Biospan polyurethane (DSM, Berkeley, CA) housing with 45 degree inlet and outlet sections (Figure 1), and a 2.4 m² surface area, polypropylene fiber bundle.¹⁷ This design maximizes spatial and temporal blood flow uniformity in an effort to reduce blood flow resistance, improve gas exchange efficiency, and limit device thrombosis.¹⁷ The cTAL's rated flow exceeds 7 L/min, and its 0.5 mmHg/(L/min) resistance^{17,18} was able to unload the right ventricle in an animal model of PH using a PA-LA attachment.¹⁸ The present 14 day study examines whether the cTAL can maintain the gas exchange and resistance characteristics demonstrated during acute *in vitro* and *in vivo* studies, while maintaining normal animal physiology.

Material and Methods

Surgery

The cTAL was attached to five sheep weighing 60–65 kg. All received humane care in compliance with the Guide for the Care and Use of Laboratory Animals and the Principles of Laboratory Animal Care. Sheep were administered transdermal fentanyl (100 µg/hour) 24 hours pre-surgery, and anesthesia was induced with propofol (400–600 mg, IV). Left

thoracotomy, instrumentation, graft attachment, and closure proceeded according to previous methods.^{18,19} Blood inflow and outflow graft-conduits with a combined prime volume of 116 mL were fabricated by bonding vascular grafts (Maquet Getinge, Wayne, NJ, or Terumo Cardiovascular, Ann Arbor, MI) to PVC tubing using previous methods.²⁰ These were attached to the PA and LA for cTAL connection. Initially, graft patency was maintained by connecting the inlet and outlet grafts with 5/8" tubing, and limiting blood flow to 1 L/min using a Hoffman clamp. To protect the cTAL during recovery, it was attached 6–40 hours post-surgery. Nafcillin (1000 mg, IV), gentamicin (120 mg, IV), heparin (77–123 Units/kg, IV), buprenorphine (0.6 mg, IM), and flunixin (60 mg, IV) were administered. Continuous heparin was supplied to the distal end of the inlet conduit to maintain a targeted systemic activated clotting time (ACT) of 200–280 seconds, as measured with glass particle activated P214 Hemochron reagent tubes (Accriva Diagnostics, San Diego, CA). Sheep were recovered according to previous methods.¹⁶

cTAL Attachment

The cTAL was placed into a protective holder that eliminated shunt flows around the fiber bundle. The first holder version, used in Sheep 1, clamped the fiber bundle sides with high pressure. The second version, used in all subsequent sheep, held the cTAL with minimal pressure. The cTAL was primed with 1.3 L lactated Ringers solution, 50 mL albumin (25% solution), 92 Units/kg heparin, and 500 mg methylprednisolone. Heparin (77–123 Units/kg) and methylprednisolone (500 mg) were also administered intravenously. The shunt was then replaced with the cTAL. A 5 L/min oxygen (O₂) sweep gas was supplied to the cTAL gas inlet to allow for adequate oxygen exchange and clearing of condensation and plasma from the gas exchange fiber lumen. Attaching a vacuum to the gas outlet and maintaining a gas inlet pressure between negative 15–30 mmHg prevented air embolus. Lastly, blood flow was initiated through the device. Due to excessive carbon dioxide (CO₂) transfer, CO₂ (6.9+/-0.3%) was blended into the sweep gas to maintain normal arterial pCO₂ and respiratory rate.

Animal Management

The sheep were awake, and analgesia was accomplished through buprenorphine (0.6 mg, IM) every four to six hours, and flunixin (60 mg, IV) every twelve hours or toradol (60 mg, IM) every six hours, with adjustment as needed. Sheep were administered nafcillin (500 mg IV) every six hours and gentamicin (120 mg IV) every eight hours for three days and then as needed. To reduce the effects of pulmonary edema and hemodilution, Furosemide (40 mg, IV) was administered every 12 hours until day 7 and 9 for Sheep 4 and 5, respectively. Heparin administration continued as before attachment. Sheep 4 was transfused on day 6 to correct low hemoglobin, but transfusion lysis occurred over the following days due to an unmatched blood type.

If fever was observed, bacterial cultures were performed. After 14 days, animals were euthanized using sodium pentobarbital (16 mL, IV), and necropsied. The PA, LA, and inlet and outlet grafts were inspected for thrombus formation. The heart, kidneys, and liver were inspected for signs of gross infarct. The lungs were inspected for atelectasis and edema.

Data Collection and Analysis

Blood gas analysis and ACTs were taken every 1–6 hours. Aspartate aminotransferase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine, white blood cell counts (WBC), and platelet counts (Plt) were measured approximately every other day post-surgery. The WBC and Plt were corrected for hemodilution using standard methods.²¹ Mean arterial pressure (MAP) was recorded hourly from pressure transducers coupled with a patient monitor (Solar 8000, Marquette Electronics, Milwaukee, WI). CTAL blood inlet and outlet pressures were measured with pressure transducers (ICU Medical, San Clemente, CA) coupled with a data acquisition system (Biopac Systems, Goleta, CA), and cTAL flowrate was measured via an ultrasonic flow meter and probe (TS410 with 14PXL, Transonic, Ithaca, NY). The cTAL blood flow resistance and oxygen transfer rate (VO_2) were calculated once and twice daily using standard methods, respectively.²²

Data represented as pre-device (PD) was averaged over six hours pre-device attachment, and data represented as baseline (BL) was averaged over six hours post-attachment. All other data was averaged over 24 hour periods post-attachment. The exception to this are the veterinary labs (AST, ALT, BUN, Creatinine, WBC, and Plt). These baseline samples were measured at animal intake and averaged over 3 day periods post-attachment. Sheep 2 had no intake labs. Statistical comparisons were performed with SPSS (IBM, Armonk, NY) using a mixed model with the sheep number as the subject variable and time as the fixed, repeated measure variable.¹⁶ Post-hoc analysis using a Bonferroni-corrected confidence interval was employed to compare variables to baseline data to examine changes with time.¹⁶

Results

Three of the five sheep survived the entire experiment, and no device exchanges were performed. Sheep 2 was euthanized on day 6 due to a bradycardic arrhythmia that was evident prior to device attachment but worsened thereafter. Sheep 5 was euthanized on day 11 after a blood conduit connection fractured.

Sheep Physiology

Physiology was largely normal and unchanged throughout the experiment. The daily average PO_2 , PCO_2 , and MAP can be seen in Figure 2. The MAP was 84 ± 12.8 mmHg pre-device and averaged 103 ± 0.8 mmHg thereafter, with no statistically significant comparisons to baseline ($p=0.24$). Arterial PCO_2 was 33 ± 1.0 mmHg pre-device averaged 40 ± 0.4 mmHg thereafter, and was only statistically greater than baseline on Day 6 ($p<0.05$). Pre-device PO_2 was significantly lower than baseline (65 ± 4 mmHg vs. 138 ± 13 mmHg, $p<10^{-8}$), but PO_2 did not vary significantly thereafter (average = 130 ± 1.1 mmHg, $p=0.99$).

Hematology

Normalized WBC and normalized Plt are summarized in Table 1. Neither normalized WBC nor normalized platelet counts ($p=0.27$, and $p=0.75$, respectively) varied significantly from baseline. Hemoglobin was 10.3 ± 0.4 g/dL pre-device, dropped to 8.9 ± 0.6 g/dL at baseline after device attachment, and was stable thereafter (average = 9.0 ± 0.1 g/dL). The hemoglobin drop from pre-device attachment to baseline was the only statistically significant comparison

($p < 0.01$). The ACT was 211 ± 7.3 sec pre-device, 310 ± 71 sec at baseline, averaged 238 ± 2.1 g/dL thereafter, and did not vary significantly with time ($p = 0.99$). Bacterial cultures were analyzed from Sheep 3, 4, and 5, and all were negative.

Device Function

The cTAL flowrate, resistance, cTAL inlet oxyhemoglobin saturation (SO_2), cTAL outlet SO_2 , and VO_2 didn't vary significantly from baseline ($p = 0.68$, $p = 0.99$, $p = 0.51$, $p = 0.07$, and $p = 0.27$, respectively). Blood flow through the cTAL was 3.46 ± 0.15 L/min at baseline and averaged 3.18 ± 0.05 L/min thereafter (Figure 3). CTAL resistance was 0.99 ± 0.07 mmHg/L/min at baseline and averaged 1.04 ± 0.05 mmHg/L/min thereafter (Figure 3). In sheep 3, resistance increased over days 12–14, despite minimal visual thrombus formation in this device (Figure 4) and no drop in device blood flowrate. Blood flow averaged 3.48 L/min for days 1–11 and 3.40 L/min for days 12–14. This suggests a faulty pressure drop reading due to the thrombus formation in the transducer stopcock or a failure of the transducer itself. CTAL VO_2 was 206 ± 27 mL/min at baseline and averaged 180 ± 8 mL/min thereafter (Figure 5). cTAL inlet SO_2 and outlet SO_2 were 57.8 ± 6.1 % and 98.6 ± 0.9 % at baseline, and averaged 52.7 ± 1.0 % and 96.0 ± 0.7 % thereafter, respectively (Figure 5). At approximately day 7, plasma leakage was observed in the gas outlet of most cTALs. After the onset of plasma leakage, cTAL inlet and outlet SO_2 trended downwards. Periodic gas flow rate increases were utilized to clear bulk plasma from the fiber lumen.

Explanted devices from 14 day survivors had varying amounts of thrombus formation depending on which device holder was employed (Figure 4). Sheep 1's cTAL employed the first generation holder and had thrombus formation where the fiber bundle was clamped. The remaining devices employed the second generation holder and had minimal thrombus formation. The bundles were largely clear of thrombus formation from the inlet to the outlet, with a small section of thrombus at device corners and thrombus formation on the side of the bundle stemming from a section of tape used during cTAL fabrication (Figure 4 - bottom).

Organ Function

Neither BUN, creatinine, ALT, nor AST varied significantly from baseline (Table 1). Liver enzymes increased immediately post-surgery, but fell thereafter and stayed within normal ranges. At day 13–14 there was a non-significant increase in the AST.

Necropsy

Necropsy organ inspections were unremarkable with the exception of the lungs. The lungs typically exhibited edema throughout, and atelectasis in the upper lobes and the areas around the chest tubes and blood conduits. There were visual signs of infection around the blood conduits of Sheep 4 due to inadequate tissue in-growth and chest wall sealing.

Discussion

These studies were performed to determine if the uncoated cTAL could maintain the gas exchange and resistance characteristics demonstrated during short-term *in vitro* and *in vivo* studies while maintaining normal animal physiology for 14 days.^{18,19} Overall, the cTAL

demonstrated its capability to be used for at least two weeks without anti-coagulant coatings, and likely longer with more sophisticated biomaterials approaches. The device maintained a low, constant resistance. Plasma leakage through the gas exchange fiber resulted in some decrease in cTAL outlet SO_2 . Animal physiology was, in general, normal with initial changes due to surgical effects and a trend back towards normal values thereafter, with the exception of elevated AST levels in one sheep, increasing WBC, and pulmonary edema and atelectasis at necropsy.

Despite the lack of anti-coagulant coatings, there wasn't a significant resistance increase over 14 days. There was a consistent resistance spike after one day but the resistance returned to baseline thereafter. This likely reflects some initial, transient protein or cellular binding that then resolves. Gross visual thrombus formation was minimal in all cTALs except the single device that was clamped excessively by its holder. Clamping led to stasis regions and clot formation on the sides of this fiber bundle. There was some thrombus formation stemming from a piece of tape that will be eliminated when manufacturing future cTALs. Overall, the cTAL proved more biocompatible than similar devices. The uncoated MC3 Biolung had a tripling of resistance over an average of 9.5 days during 30 day studies.¹⁶ A more comparable Biolung study, where devices weren't replaced, demonstrated a more than six-fold resistance increase by day seven.¹⁵ The anti-coagulant coated iLA membrane ventilator in a PA-LA configuration lasts 14–21 days before replacement is required.^{23–26} The uncoated cTAL would have functioned beyond 14 days, and the application of anti-coagulant coatings could potentially extend its lifespan beyond a month.

Previous *in vitro* and acute *in vivo* experiments demonstrated a 0.5 mmHg/(L/min) cTAL resistance.^{17–19} However, the baseline resistance in this study was 1 mmHg/(L/min). In previous studies, the device was positioned ideally, sitting flat on the animal. In these long-term studies, the device was placed on its side at the animal's flank. This can cause lower pressure and housing collapse in the superior regions of the device, and may limit blood flow through these regions, raising resistance. Despite this, the cTAL's resistance was lower than healthy lungs and the next least resistive devices (iLA membrane ventilator - 6 mmHg/(L/min), MC3 Biolung - 1.8 mmHg/(L/min)).^{14,27,28}

CTAL VO_2 was maintained throughout the experiment, but cTAL outlet SO_2 decreased after the onset of plasma leakage through the gas exchange fiber. When gas exchange performance degraded, bulk plasma was cleared from the fiber lumen by temporarily doubling the sweep gas flowrate. Plasma leakage susceptible polypropylene fibers were used in the cTAL, since nonporous polymethylpentene fibers are not commercially available with an outer diameter under 380 microns and it was believed that plasma leakage didn't occur in sheep. For clinical prototypes, small outer diameter PDMS coated (1–2 micron coating thickness) polypropylene fibers will be necessary to prevent plasma and air leakage while maintaining sufficient gas exchange surface area.^{29–31}

Physiology was largely normal during the experiment. The MAP and arterial blood gasses normalized after device attachment. The kidneys functioned normally. Liver enzyme levels showed some dysfunction post-surgery, but they trended back towards normal levels throughout the experiment. One exception was a non-significant increase in the AST on the

last two day period. This was largely the effect of early euthanasia of sheep with lower AST and a single animal AST increase. Necropsy organ inspections revealed no derangements besides atelectasis and edema throughout the lungs. Common after lung surgery, pulmonary edema resulted from single-lung ventilation of the right lung and direct manipulation and inflammation of the packed away left lung. Atelectasis resulted from a low respiratory drive. Another factor that likely contributed to these findings was some level of patient discomfort following surgery. Local anesthetics and opioid analgesia are utilized, but sheep likely experience some thoracic discomfort post-operatively when taking deep breaths. Thus, their breathing is fairly shallow, and we cannot encourage them to breathe deeply, as we would a patient using an incentive spirometer. Adding CO₂ into the sweep gas can aid in promoting deeper breathing. However, since respiratory rate can also increase to aid in removing the excess CO₂, this method is imperfect and doesn't fully solve the issue.

There were hemodilatory effects of device attachment due to the large system prime volume of 1416 mL, (1300 mL cTAL, 116 mL grafts) but hematologic parameters remained consistent or rebounded the longer the cTAL was attached. Hemodilution was offset by the cTAL's minimal blood product consumption, evidenced from the stable hemoglobin and rising Plt throughout the experiment. In clinical use, patients treated with the cTAL may need an initial transfusion after device attachment, but shouldn't need further transfusions. This contrasts to ECMO, where reported blood product median daily transfusions can range from 0.16–2 units/day for red blood cells and from 0–3 units/day for platelets.^{3,10,27,32} These transfusion requirements can be particularly high for patients with PH or other conditions that necessitate veno-arterial ECMO.⁶ However, for a true comparison of hemolysis and blood product needs, the cTAL would have to be tested versus a commercial ECMO circuit in an identical animal model. It is expected that in the ECMO case, the high resistance ECMO circuit would result in high shear stresses in the ECMO pump and, in turn, blood damage and activation would occur.^{11–13} The cTAL prime volume and resulting hemodilution can be reduced by shrinking the size of the device and/or compressing its housing during priming. When the cTAL is primed, its flexible housing expands well beyond its post-attachment volume. Once the device is attached, housing relaxes down to conform to the blood pressure in the device, resulting in excess prime and a fluid bolus to the patient. In future testing and clinical use, the housing could be compressed to its post attachment volume during priming to prevent excessive prime volume from being delivered to the patient.

The ultimate goal for the cTAL will be its use as a long term bridge to lung transplantation and destination therapy. To progress towards this goal, the cTAL will be reduced in prime volume, utilize a solid walled fiber to reduce plasma leakage and air embolism risk, and anti-coagulant coatings will be applied to all device surfaces. The cTAL's superior fluid dynamic design coupled with these coatings may allow the cTAL to be used for months without replacement, and longer with replacement. The lack of blood damage and need for continuing blood transfusions further indicates the cTAL's potential long term use.

The long term efficacy experiments of the uncoated cTAL demonstrated the device's ability to support a patient for two weeks without major thrombus formation and subsequent device failure. The cTAL's gas exchange performance was reduced after the onset of plasma

leakage. During cTAL support, there were no major physiological derangements and the device had minimal blood product consumption. Even without anti-coagulant coatings, the cTAL could have functioned beyond the current 14 day experimental time. 60 day studies of the improved cTAL with anti-coagulant coatings and plasma resistant gas exchange fiber will be performed to demonstrate its utility as a long term therapy.

Acknowledgments

Conflicts of Interest and Source of Funding

This work was supported with a federal R01 grant, NIH/NHLBI R01 HL089043. Dr. Cook and Dr. Skoog are equity owners of Advanced Respiratory Technologies LLC. Advanced Respiratory Technologies LLC was founded after this work was completed and has no rights in regard to its publication.

References

1. Association AL. Lung disease data: 2008. Focus: Clean Air and Lung Disease. 2008. Retrieved from <http://www.lungusa.org>
2. Valapour M, Paulson K, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: Lung. Am J Transplant. 2013; 13:149–177. [PubMed: 23237700]
3. Javidfar J, Brodie D, Iribarne A, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation and recovery. J Thorac Cardiovasc Surg. 2012; 144(3):716–721. [PubMed: 22795457]
4. Hayes D Jr, Kukreja J, Tobias JD, Ballard HO, Hoopes CW. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. J Cyst Fibros. 2012; 11(1):40–45. [PubMed: 22035707]
5. Mangi AA, Mason DP, Yun JJ, Murthy SC, Pettersson GB. Bridge to lung transplantation using short-term ambulatory extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg. 2010; 140(3):713–715. [PubMed: 20381081]
6. Shafii AE, Mason DP, Brown CR, et al. Growing experience with extracorporeal membrane oxygenation as a bridge to lung transplantation. ASAIO J. 2012; 58(5):526–529. [PubMed: 22929896]
7. Bermudez CA, Rocha RV, Sappington PL, Toyoda Y, Murray HN, Boujoukos AJ. Initial Experience With Single Cannulation for Venovenous Extracorporeal Oxygenation in Adults. Ann Thorac Surg. 2010; 90(3):991–995. [PubMed: 20732530]
8. Garcia JP, Iacono A, Kon ZN, Griffith BP. Ambulatory extracorporeal membrane oxygenation: a new approach for bridge-to-lung transplantation. J Thorac Cardiovasc Surg. 2010; 139(6):e137–e139. [PubMed: 20219215]
9. Cheung P-Y, Sawicki G, Salas E, Etches PC, Schulz R, Radomski MW. The mechanisms of platelet dysfunction during extracorporeal membrane oxygenation in critically ill neonates. Crit Care Med. 2000; 28(7):2584–2590. [PubMed: 10921599]
10. Ang A, Teo D, Lim C, Leou K, Tien S, Koh M. Blood transfusion requirements and independent predictors of increased transfusion requirements among adult patients on extracorporeal membrane oxygenation—a single centre experience. Vox Sang. 2009; 96(1):34–43. [PubMed: 19121196]
11. Anai H, Wakisaka Y, Nakatani T, Taenaka Y, Takano H, Hadama T. Relationship between pump speed design and hemolysis in an axial flow blood pump. Artif Organs. 1996; 20(5):564–567.
12. Cook, KEM., LF. Biocompatibility of artificial lungs. In: Vaslef, SNA., RW, editors. The artificial lung. Austin, TX: Landes Bioscience; 2002.
13. Kawahito K, Mohara J, Misawa Y, Fuse K. Platelet Damage Caused by the Centrifugal Pump: In Vitro Evaluation by Measuring the Release of α -Granule Packing Proteins. Artif Organs. 1997; 21(10):1105–1109. [PubMed: 9335369]

14. McGillicuddy JW, Chambers SD, Galligan DT, Hirschl RB, Bartlett RH, Cook KE. In vitro fluid mechanical effects of thoracic artificial lung compliance. *ASAIO J.* 2005; 51(6):789–794. [PubMed: 16340369]
15. Sato H, Griffith GW, Hall CM, et al. Seven-day artificial lung testing in an in-parallel configuration. *Ann Thorac Surg.* 2007; 84(3):988–994. [PubMed: 17720415]
16. Sato H, Hall CM, Lafayette NG, et al. Thirty-Day In-Parallel Artificial Lung Testing in Sheep. *Ann Thorac Surg.* 2007; 84(4):1136–1143. [PubMed: 17888959]
17. Schewe RE, Khanafer KM, Arab A, Mitchell JA, Skoog DJ, Cook KE. Design and In Vitro Assessment of an Improved, Low-Resistance Compliant Thoracic Artificial Lung. *ASAIO J.* 2012; 58(6):583–589. [PubMed: 23103694]
18. Schewe RE, Scipione CN, Koch KL, Cook KE. In-parallel attachment of a low-resistance compliant thoracic artificial lung under rest and simulated exercise. *Ann Thorac Surg.* 2012
19. Scipione CN, Schewe RE, Koch KL, Shaffer AW, Iyengar A, Cook KE. Use of a low-resistance compliant thoracic artificial lung in the pulmonary artery to pulmonary artery configuration. *J Thorac Cardiovasc Surg.* 2013
20. Akay B, Reoma JL, Camboni D, et al. In-parallel artificial lung attachment at high flows in normal and pulmonary hypertension models. *Ann Thorac Surg.* 2010; 90(1):259–265. [PubMed: 20609788]
21. Amoako KA, Montoya PJ, Major TC, et al. Fabrication and In vivo Thrombogenicity Testing of Nitric Oxide Generating Artificial Lungs. *J Biomed Mater Res.* 2013; 101(12)
22. Cook KE, Perlman CE, Seipelt R, Backer CL, Mavroudis C, Mockros LF. Hemodynamic and gas transfer properties of a compliant thoracic artificial lung. *ASAIO J.* 2005; 51(4):404–411. [PubMed: 16156307]
23. de Perrot M, Granton JT, McRae K, et al. Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. *J Heart Lung Transplant.* 2011; 30(9):997–1002. [PubMed: 21489818]
24. Schmid C, Philipp A, Hilker M, et al. Bridge to lung transplantation through a pulmonary artery to left atrial oxygenator circuit. *Ann Thorac Surg.* 2008; 85(4):1202–1205. [PubMed: 18355495]
25. Strueber M, Hoepfer MM, Fischer S, et al. Bridge to Thoracic Organ Transplantation in Patients with Pulmonary Arterial Hypertension Using a Pumpless Lung Assist Device. *Am J Transplant.* 2009; 9(4):853–857. [PubMed: 19344471]
26. Camboni D, Philipp A, Arlt M, Pfeiffer M, Hilker M, Schmid C. First Experience With a Paracorporeal Artificial Lung In Humans. *ASAIO J.* 2009; 55(3):304–306. DOI: 10.1097/MAT.0b013e31819740a0 [PubMed: 19282751]
27. Müller T, Lubnow M, Philipp A, et al. Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. *Eur Respir J.* 2009; 33(3):551–558. [PubMed: 19010979]
28. Flörchinger B, Philipp A, Klose A, et al. Pumpless Extracorporeal Lung Assist: A 10-Year Institutional Experience. *Ann Thorac Surg.* 2008; 86(2):410–417. [PubMed: 18640306]
29. Sato H, Odeleye ME, Chambers SD, Hirschl RB, Bartlett RH, Cook KE. Thoracic artificial lung (TAL) development: Determining the most suitable fiber for TAL. *ASAIO J.* 2005; 51(2):51A.
30. Eash HJ, Jones HM, Hattler BG, Federspiel WJ. Evaluation of plasma resistant hollow fiber membranes for artificial lungs. *ASAIO J.* 2004; 50(5):491–497. [PubMed: 15497391]
31. Keller K, Shultis K. Oxygen permeability in ultrathin and microporous membranes during gas-liquid transfer. *ASAIO J.* 1979; 25(1):469–472.
32. Javidfar J, Brodie D, Wang D, et al. Use of bicaval dual-lumen catheter for adult venovenous extracorporeal membrane oxygenation. *Ann Thorac Surg.* 2011; 91(6):1763–1769. [PubMed: 21619973]

Figure 1.

Top: The side view of the cTAL with inlet and outlet ports labeled. *Bottom:* The top view with the cTAL inlet taper angle labeled with θ_H .

Figure 2.
The arterial PO₂, PCO₂, and MAP.

Figure 3.
The cTAL resistance and blood flow rate.

Figure 4.

Thrombus formation in the explanted cTALs after 14 days of use. *Top*: The top view.

Middle: The side view of the non-taped side. *Bottom*: The side view of the taped side with the tape labeled.

Figure 5.
The cTAL oxygen transfer rate (VO₂), cTAL inlet SO₂, and cTAL outlet SO₂.

Table 1

Clinical Laboratory Hematology and Organ Function Parameters

Days	WBC (k/ μ L)	Plt (k/ μ L)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	CRE (mg/dL)
BL	6.2 $\pm$ 0.5	281 $\pm$ 36	23 $\pm$ 4	86 $\pm$ 9	11.5 $\pm$ 2.3	0.77 $\pm$ 0.06
1-3	5.6 $\pm$ 0.7	185 $\pm$ 25	100 $\pm$ 41	270 $\pm$ 87	10.3 $\pm$ 1.1	1.07 $\pm$ 0.14
4-6	7.6 $\pm$ 1.5	412 $\pm$ 96	50 $\pm$ 12	210 $\pm$ 74	12.0 $\pm$ 2.0	0.76 $\pm$ 0.15
7-9	7.1 $\pm$ 0.1	441 $\pm$ 120	37 $\pm$ 9	153 $\pm$ 40	13.3 $\pm$ 2.8	0.90 $\pm$ 0.05
10-12	10.9 $\pm$ 1.6	442 $\pm$ 148	30 $\pm$ 5	115 $\pm$ 17	12.3 $\pm$ 0.8	0.77 $\pm$ 0.06
13-14	12.9 $\pm$ 2.7	501 $\pm$ 153	39 $\pm$ 9	209 $\pm$ 59	13.3 $\pm$ 1.7	0.94 $\pm$ 0.14
Ave	6.8 $\pm$ 0.6	346 $\pm$ 81	62 $\pm$ 19	211 $\pm$ 34	11.9 $\pm$ 0.9	0.91 $\pm$ 0.09

NOTE. – WBC = white blood cell count normalized to baseline hemoglobin; Plt = platelet count normalized to baseline hemoglobin; ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRE = creatinine; Ave = average.

*
p < 0.05

**
p < 0.01