In-Parallel Attachment of a Low-Resistance Compliant Thoracic Artificial Lung Under Rest and Simulated Exercise

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Background. Previous thoracic artificial lungs (TALs) had blood flow impedance greater than that of the natural lungs, which could cause abnormal pulmonary hemodynamics. New compliant TALs (cTALs), however, have an impedance lower than that of the natural lung.

Methods. In this study, a cTAL of new design was attached between the pulmonary artery (PA) and the left atrium (LA) in 5 sheep (60.2 ± 1.9 kg). A distal PA band was placed to control the percentage of cardiac output (CO) routed to the cTAL. Rest and exercise conditions were simulated using a continuous dobutamine infusion of 0 and 5 μg/kg/min, respectively. At each dose, a hemodynamic data set was acquired at baseline (no flow to the cTAL), and 60%, 75%, and 90% of CO was shunted to the cTAL.

Results. Device resistance did not vary with blood flow rate, averaging 0.51 ± 0.03 mm Hg/(L/min). Under all conditions, CO was not significantly different from baseline. Pulmonary system impedance increased above baseline only with 5 μg/kg/min of dobutamine and 90% of CO diverted to the cTAL.

Conclusions. Results indicated minimal changes in pulmonary hemodynamics during PA–LA cTAL attachment for high device flows under rest and exercise conditions.


The only long-term solution for chronic lung disease is lung transplantation; however, organ donation is limited and cannot supply the demand [1]. There is a need for a device that can serve as a bridge to lung transplantation for patients with end-stage lung disease. Thoracic artificial lungs (TAL) are being developed for these patients and would ideally allow patients to be awake and ambulatory while awaiting lung transplantation.

TALs are attached to the pulmonary circulation, and thus their blood flow is provided by the right ventricle (RV). It is essential that these devices have low blood flow resistance to prevent overloading the RV and causing decreases in cardiac output (CO). Several studies have shown that CO decreases linearly with the pulmonary system zeroth harmonic pulmonary input impedance, $Z_0$ [2, 3], a measure of right ventricular afterload [4]. During TAL use, $Z_0$ is influenced by the TAL attachment mode and the resistance of the TAL, device inlet graft anastomosis, and native lung [5, 6].

The most commonly proposed TAL attachment modes are in parallel or in series with the natural lungs. During in-parallel attachment, blood flow is routed from the pulmonary artery (PA), through the TAL, and then returned to the left atrium (LA). In patients with pulmonary hypertension, this attachment mode is ideal because it reduces $Z_0$ for the combined TAL and natural lung system and thus unloads the RV. In this setting, TAL attachment should ideally result in a pulmonary system $Z_0$ that is as close as possible to the healthy natural lung. To accomplish this, the combined resistance of the TAL and the anastomoses used to attach it must also be close to that of the healthy natural lung.

This article presents the first in vivo test of a new, ultralow-resistance compliant TAL (cTAL) that is designed to meet that goal. The device has a gradual blood inlet and outlet and a compliant housing that reduces blood flow recirculation. The housing is combined with a low-resistance fiber bundle designed to arrive at an overall low device resistance. This study examined pulmonary hemodynamics and cTAL function during in-parallel attachment in sheep with up to 90% of CO through the cTAL both at rest and during simulated exercise.

Material and Methods

Compliant Thoracic Artificial Lung

A cTAL, consisting of a compliant Biospan (DSM PTG, Berkeley, CA) housing and polypropylene fiber bundle, was used in this study (Fig 1). In this device, blood flows into the inlet conduit, expands into the inlet manifold, flows through the fiber bundle at the center of the device,
and then travels through the outlet manifold and exits through the outlet conduit. To create the fiber bundle, woven mats of polypropylene fibers with a fiber diameter of 210 μm were wound into compact bundles with porosity, path length, and frontal area of 0.75, 0.038, and 0.013 m², respectively.

Experimental Procedure
A total of 5 male sheep averaging 60.2 ± 1.9 kg were used in this study. All sheep received humane care in compliance with the Guide for the Care and Use of Laboratory Animals, and all methods were approved by the University of Michigan Committee for the Use and Care of Animals. Anesthesia was induced with 6 to 9 mL/kg of propofol and was then maintained after endotracheal intubation with 1% to 3% inhaled isoflurane. Sheep were then given sodium heparin to maintain active clotting times of greater than 300 seconds.

The cTAL was primed with heparanized saline (10 U/mL) and then connected to the PA (device inlet) and LA (device outlet) grafts (Fig 2). An ultrasonic flow probe (Transonic 14PXL; Transonic Systems, Inc) was placed around the inflow conduit and connected to a flow meter (T400; Transonic Systems, Inc) to measure device flow (Q_{cTAL}). Pressure transducers were connected to the device inlet and outlet to acquire device inlet and outlet pressure (P_{in} and P_{out}). A suction line was attached to the cTAL gas outlet and 95%:5% O₂:CO₂ with 2% to 3% vaporized isoflurane was used as the sweep gas through the gas inlet. Sweep gas flow was adjusted during cTAL use to maintain PaCO₂ between 35 and 45 mm Hg. A Hoffmann clamp was placed around the cTAL outlet conduit to restrict flow through the device. After cTAL attachment, clamps on the cTAL inlet and outlet conduits were removed, and the Hoffmann clamp was slowly loosened until Q_{cTAL} = 1 L/min was achieved. This flow was maintained for 10 minutes for equilibration of fluid volumes and any inflammatory response. After device attachment, central venous pressure (CVP) decreased relative to the systemic inflammatory response, and 500 mL of hetastarch and 500 to 1000 mL of crystalloid were administered to restore CVP back to baseline values. Thereafter, the device conduits were clamped off and baseline data was obtained, marking the start of the experiment.

A hemodynamic data set of Q_{PA}, Q_{cTAL}, P_{art}, P_{CV}, P_{PA} P_{in} P_{out} was digitally acquired for 10 seconds at a sampling frequency of 250 Hz through a BIOPAC data acquisition system (BIOPAC, Goleta, CA). Before attaching the cTAL, an animal baseline data set was acquired. Rest and exercise conditions were simulated using a continuous dobutamine infusion of 0 μg/kg/min and then 5 μg/kg/min, respectively. At each dose, the hemodynamic data set was acquired at baseline (Q_{cTAL} = 0 L/min) and conditions of 60%, 75%, and 90% of CO shunted to the cTAL (100 * Q_{cTAL}/Q_{PA}), created by tight-
en the Rommel tourniquet around the PA. At each condition, 10 minutes was allowed for equilibration before data were obtained. Also, at each condition, a device exit gas sample was taken along with blood samples from the animal, device inlet, and device outlet.

**Data Analysis**

The zeroth harmonic pulmonary input impedance modulus, $Z_0$, was calculated at each flow condition:

$$Z_0 = \frac{P_0}{Q_0}$$

(1)

where $P_0$ is the mean PA pressure and $Q_0$ is the mean PA blood flow rate.

Device resistance, $R$, was calculated using the formula:

$$R = \frac{P_{in} - P_{out}}{Q_{cTAL}}$$

(2)

where $P_{in}$ is the cTAL inlet pressure, $P_{out}$ is the cTAL outlet pressure, and $Q_{cTAL}$ is cTAL flow. Comparisons were performed on the rest and exercise data sets separately with SPSS, version 19 (SPSS Inc, Chicago, IL). A mixed model was used, with sheep number as the subject variable and flow condition (percentage of flow to the cTAL) as the fixed, repeated-measure variable. All data are reported as mean ± standard error with a $p$ value of 0.05 or less being considered statistically significant.

**Results**

**Animal Physiology**

Before cTAL attachment, average animal baseline CO, mean arterial pressure (MAP), mean PA pressure (mPAP), CVP, and $Z_0$ were 6.4 ± 0.59 L/min, 87.7 ± 8.08 mm Hg, 18.2 ± 1.34 mm Hg, 6.83 ± 1.22 mm Hg, and 2.99 ± 0.41 mm Hg/(L/min), respectively. The effect of cTAL attachment on the sheep’s CO is shown in Fig 3. Without dobutamine, the baseline CO was 5.5 ± 0.65 L/min and was maintained at or above this level until 90% flow to the cTAL. At 90% flow to the cTAL, there was
a negligible 0.33% decrease in CO from baseline, which was not significant (p = 0.94). At 5 μg/kg/min of dobutamine, baseline CO was 7.23 ± 0.70 L/min and was maintained at greater than this level until it decreased to 6.88 ± 0.69 L/min at 90% flow to the cTAL. This 5.6% drop was also not significant (p = 0.36).

Fig 4 displays Z₀ for increasing flow to the cTAL. For both rest and dobutamine-simulated exercise conditions, Z₀ decreased from baseline with 60% flow to the cTAL. Without dobutamine, Z₀ remained below baseline at all conditions. At 5 μg/kg/min of dobutamine, baseline Z₀ decreased because of increased blood flow to the natural lungs. As more flow was diverted to the TAL, Z₀ was initially relatively constant but began to rise at 75% flow. As the natural lung was increasingly excluded, Z₀ then rose toward the same Z₀ as without dobutamine. At 90% flow, Z₀ had increased to 50% greater than the 5 μg/kg/min dobutamine baseline and was almost equivalent to all 0 μg/kg/min conditions. This increase was significant (p = 0.049) when compared with baseline.

MAP and mPAP for both dobutamine levels are displayed in Table 1 at each target and actual percent flow to the cTAL. The mean baseline PA pressure at 0 μg/kg/min dobutamine was 25.1 ± 5.31 mm Hg, with no significant change at 60%, 75%, and 90% flow to the cTAL (p = 0.35, 0.46, and 0.86, respectively). At 5 μg/kg/min dobutamine, mPAP increased from 20.5 ± 1.48 mm Hg at baseline to 29.4 ± 3.61 mm Hg at 90% flow to the cTAL; however, this increase approached significance but was not significant (p = 0.09). Baseline MAP was 78.4 ± 12.6 mm Hg with no dobutamine and decreased slightly to 73.1 ± 7.82 mm Hg at 90% flow to the cTAL. With 5 μg/kg/min of dobutamine, baseline MAP was 78.5 ± 4.98 mm Hg and decreased to 67.3 ± 6.92 mm Hg at 90% flow to the cTAL; however, this decrease was not significant (p = 0.16).

**Device Performance**

Device resistance at various flow rate ranges is shown in Fig 5. Resistance of the cTAL remains relatively constant at all tested flow rates. Device resistance averaged 0.51 ± 0.01 mm Hg/(L/min), ranging from 0.50 ± 0.01 mm Hg/(L/min) at 2 to 3 L/min to a maximum of 0.55 ± 0.02 mm Hg/(L/min) at 5 to 6 L/min. Accordingly, device flow did not significantly affect resistance (p = 0.29). Although this was not primarily a gas exchange experiment, the cTAL also exchanged gas effectively. Arterial Po₂, Pco₂, and pH, along with cTAL O₂ and CO₂ gas transfer rates (Vo₂ and Vco₂) are displayed in Table 2 for each device flow condition. The device outlet oxyhemoglobin saturations were greater than 99% at every flow condition, although venous conditions were not sufficient to challenge the device. A typical hemoglobin and device inlet Po₂ was 75 and 80 mm Hg, respectively. Even with this higher inlet Po₂, Vo₂ rates ranged from 85.7 ± 7.7 mL/min at 0 μg/kg/min dobutamine and 60% CO to the cTAL to 155.5 ± 8.8 mL/min at 5 μg/kg/min dobutamine and 90% CO to the cTAL. Finally, at the conclu-
sion of the experiment, there was no visible clot formation in the device.

Comment

To date, there is no commercially available TAL. Over 18 years of development, these devices have always featured excellent gas exchange, and research has thus focused on developing devices with progressively lower blood flow resistance and improved hemodynamics during in vivo attachment [7–9]. Ideally, TALs should be able to provide the majority of the gas exchange while being able to maintain normal pulmonary hemodynamics.

Because there is no commercial device for this application, a few groups have investigated clinical PA-LA attachment in cases of severe pulmonary hypertension using the lowest resistance gas exchanger on the market, the Novalung ILA (NovaLung, Heilbronn, Germany). Two patients treated this way had primary pulmonary hypertension and 4 had pulmonary venoocclusive disease. Five of the patients (87%) underwent successful bridging to transplantation. Despite this success, the Novalung’s gas exchange capabilities are low for the application, and the resistance is approximately 5 to 6 mm Hg/(L/min) at blood flow of 2 to 2.5 L/min [10–12]. To support patients with chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and sepsis, greater gas exchange will be required. Moreover, in cases of marked pulmonary hypertension, it would be ideal to be able to fully unload the RV and eliminate the need for inotropic agents.

In the current study, the new cTAL design was tested in healthy animals with normal PA pressure. Therefore, the goal for this study was to maintain normal PA pressures and CO with up to 90% of CO diverted to the cTAL. Results indicate that these goals were met. cTAL attachment caused only minimal, statistically insignificant decreases in CO and increases in PA pressure from baseline at all conditions. At the most extreme condition, simulated exercise with 90% of the CO diverted to the cTAL, CO decreased 5.6% and PA pressure increased 8.8 mm Hg. This, however, represents an extreme case. A more typical, and advisable [13], condition would likely be 75% of CO. In this case, CO was identical to baseline values, and PA pressure decreased at rest and increased a small amount during simulated exercise.

Maintenance of normal pulmonary hemodynamics was the result of very low cTAL resistance. Average resistance for the range of flows tested was 0.51

Table 2. Arterial Po2, Pco2 and pH, and cTAL O2 and CO2 Gas Transfer Rates (V\textsubscript{O2} and V\textsubscript{CO2}) for Varied Percentages of CO to the cTAL

<table>
<thead>
<tr>
<th>Dobutamine Dose</th>
<th>% CO to cTAL</th>
<th>Arterial Po\textsubscript{2} (mmHg)</th>
<th>Arterial Pco\textsubscript{2} (mmHg)</th>
<th>Arterial pH</th>
<th>cTAL V\textsubscript{O2} (mL/min)</th>
<th>cTAL V\textsubscript{CO2} (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 µg/kg/min</td>
<td>60%</td>
<td>439 ± 57</td>
<td>38.9 ± 1.3</td>
<td>7.40 ± 0.01</td>
<td>85.7 ± 7.7</td>
<td>213.6 ± 17.1</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>460 ± 49</td>
<td>38.7 ± 1.3</td>
<td>7.41 ± 0.01</td>
<td>96.0 ± 6.8</td>
<td>238.6 ± 58.1</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>442 ± 35</td>
<td>37.1 ± 3.6</td>
<td>7.40 ± 0.01</td>
<td>109.1 ± 8.2</td>
<td>277.5 ± 21.5</td>
</tr>
<tr>
<td>5 µg/kg/min</td>
<td>60%</td>
<td>399 ± 37</td>
<td>43.6 ± 1.6</td>
<td>7.37 ± 0.02</td>
<td>103.3 ± 11.1</td>
<td>326.0 ± 16.6</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>442 ± 35</td>
<td>45 ± 1.8</td>
<td>7.36 ± 0.02</td>
<td>120.7 ± 10.9</td>
<td>369.5 ± 31.4</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>422 ± 38</td>
<td>44.4 ± 1.3</td>
<td>7.36 ± 0.01</td>
<td>155.5 ± 8.8</td>
<td>424.0 ± 31.5</td>
</tr>
</tbody>
</table>

CO = cardiac output; cTAL = compliant thoracic artificial lung; V\textsubscript{CO2} = CO\textsubscript{2} gas transfer rate; V\textsubscript{O2} = O\textsubscript{2} gas transfer rate.

Fig 5. Compliant thoracic artificial lung (cTAL) resistance at varying ranges of blood flow rate.
mm Hg/(L/min), much less than that of the natural lung. Moreover, the resistance of the device did not change significantly as flow increased. The low cTAL resistance in turn maintained low Z_{op}. Previous studies have shown that Z_{op} is the dominant variable affecting CO during TAL attachment, with CO decreasing as Z_{op} increases [5, 6, 14].

In this study, Z_{op} was lower than baseline at 60% flow to the cTAL because of the second parallel flow path provided by the cTAL and the minimal banding of the PA at that condition. As the PA was banded further, the natural lung portion of the system was closed, the percentage of flow to the cTAL increased, and Z_{op} increased slightly. However, since device resistance remained low, the resulting Z_{op} remained small and similar to that of healthy natural lungs. At 5 \mu g/kg/min of dobutamine, however, high CO and PA pressure led to lower baseline Z_{op}. As flow was diverted to the cTAL, Z_{op} then increased to the same level seen in the case of 0 \mu g/kg/min dobutamine.

Based on these results, the cTAL will be able to completely unload the RV in vivo during PA-LA attachment in patients with any degree of pulmonary hypertension. To examine this, one can use the equation P_{PA} = CO \cdot R + P_{LAV}, where P_{PA} is the PA pressure, P_{LAV} is the left atrial pressure, and CO is cardiac output. R is the resistance of the parallel natural lung and the artificial lung system. If there is no PA banding, R = [R_N \cdot (R_P + R_A)]/[R_N + R_P + R_A], in which R_N is the natural lung resistance, R_P is the TAL resistance, and R_A is the resistance of the TAL anastomoses or cannulas. For CO = 6 L/min, P_{LAV} = 6 mm Hg, R_P = 0.5 mm Hg/(L/min), R_A = 0.87 mm Hg/(L/min), and R_N = 9 mm Hg/(L/min) [14], the PA pressure before attaching the TAL would be 60 mm Hg. With the cTAL, it falls to 13 mm Hg. In comparison, under the same conditions the Novalung ILA (R_F = 6 mm Hg/(L/min)) would reduce PA pressure to 29 mm Hg.

The other experimental TAL in development is the Biolung (Michigan Critical Care Consultants [MC3], Ann Arbor, MI). The hard-shell Biolung was tested in a study similar to this one. The only exception was that Akay and colleagues [15] simulated rest (no dobutamine), ambulatory (2 \mu g/kg/min dobutamine), and exercise (5 \mu g/kg/min dobutamine) conditions. Results showed that CO was maintained as the percentage of CO to the device increased at resting and ambulatory conditions. At exercise conditions, CO decreased with increasing flow to the TAL up to 23% ± 5% at 90% flow diverted through the TAL. Direct comparison between these 2 studies is difficult, as the baseline Z_{op} and baseline cardiac response to dobutamine varied greatly. In the Biolung study, baseline Z_{op} was lower, and as a result baseline CO was greater at the same dobutamine doses. Therefore, the easiest means of comparison between these studies is the Z_{op} with 90% of CO through the artificial lung. In this case, hemodynamics are largely unaffected by natural lung resistance. At 90%, Z_{op} ranged from 4.5–4.9 in the Biolung study and 4.1–4.5 in the cTAL study. This small difference is similar to what one would predict by the difference in TAL resistances in these studies. The cTAL resistance is approximately 0.3 mm Hg/(L/min) smaller, with flow rates of 2 to 3 L/min and approximately 0.65 mm Hg/(L/min) lower at flow rates of 5 to 6 L/min. Thus the Biolung should provide slightly less but similar unloading.

Ultimately, this study suggests that the cTAL is capable of being used clinically in parallel with the native lungs and under high-flow conditions. Minimal decreases in CO were seen at 90% flow to the device at both dobutamine levels, indicating exercise would be possible during cTAL attachment. Since cTAL resistance is small, flow would route preferentially through the device. This attachment mode could be used in any patient with chronic respiratory insufficiency but would be ideal for patients with high pulmonary vascular resistance (PVR) because the device resistance would be much lower than the native lung resistance. Approximately 57% of CO went through the cTAL with no PA banding in these sheep with normal PVR. Assuming PVR = 2.25 mm Hg/(L/min) in patients with pulmonary hypertension, about 70% of the CO would flow through the cTAL with no PA banding.

Further long-term testing (≥ 14 days) of in-parallel attachment of the cTAL is necessary in healthy sheep and sheep with pulmonary hypertension. These studies would focus on the biocompatibility of the device in a fashion similar to the studies of Sato and colleagues [16, 17] with the Biolung. Those studies used simple heparin anticoagulation with active clotting times (ACTs) from 180 to 220 seconds. That said, future studies with this device should examine various surface coatings as well as different anticoagulation strategies, including aspirin to inhibit platelets as is sometimes used with the Novalung ILA [10]. Although farm sheep tend to be more procoagulant than humans, these studies may help to define clinical anticoagulation strategies.

In conclusion, the cTAL resistance is lower than the natural lung, averaging 0.51 ± 0.03 mm Hg/(L/min). Use of the cTAL in a PA-LA configuration caused no change in CO under rest and exercise conditions. Thus the cTAL can provide PA-LA respiratory support without significant changes in pulmonary hemodynamics in healthy sheep and will be capable of unloading the RV in patients with pulmonary hypertension.

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References

The need for lung replacement therapy owing to critical pulmonary failure was recognized long ago. Following the pioneering work of Hardy and Cooper, lung transplantation programs have been established all over the world. But like in the other fields of solid organ transplantation, the need cannot be met. Oxygenators came into play with the development of heart-lung machines used as extracorporeal circulation devices for open heart surgery in the mid 1950. Isolated pulmonary support based on venovenous extracorporeal membrane oxygenation (ECMO) was devised in the early 1970s, but only now does intensive care medicine face a gradual acceptance of adult venovenous ECMO.

In 2006, the concept of a total artificial lung was successfully realized for the first time in a patient with pulmonary hypertension by the Regensburg group in Germany based on a low-resistance oxygenator [1]. Although it was clinically efficient to bridge patients to lung transplantation, the handling was difficult. For example, elevating the oxygenator above a certain height increased the risk of gas embolism, and the cannulation site at the left atrium was prone to thrombus formation.

Accordingly, research to improve total artificial lung concepts is imperative. The study by Schewe and colleagues nicely demonstrates that the in-parallel attachment of low-resistance oxygenators allows deviation of greater than 90% of blood flow from the lung without altering pulmonary system impedance [2]. As the oxygenator resistance of the compliant thoracic artificial lung (cTAL) was even lower than in a native lung, mechanical support of patients without pulmonary hypertension may become feasible. This would be a tremendous success. However, I doubt the statement that cTAL will be able to completely unload the right ventricle in patients with any degree of pulmonary hypertension. First, a normal sheep lung probably does not exactly reflect the situation of a severely diseased human lung. Second, the ventricle will never be completely unloaded; this can be achieved only with a pump-driven system such as the Bio Lung. Third, ongoing unloading of the pulmonary vascular bed may lead to vasoconstriction, shunting, and other unknown adverse events. Additional problems for long-term support include the need for anticoagulation to lower the deposition of fibrin clots and to prevent the seeding of endothelial cells on the oxygenator surface. Percutaneous device placement and miniaturization will be additional tasks for the future to improve quality of life of the unfortunate patients with critical lung failure. Nevertheless, Schewe and colleagues [2] have to be congratulated for their outstanding efforts to develop long-term mechanical pulmonary support and for their brilliant results.

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