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Hemodynamic Design Requirements for In Series Thoracic Artificial Lung Attachment in a Model of Pulmonary Hypertension

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Abstract

Recent thoracic artificial lung (TAL) prototypes have impedances lower than the natural lung. With these devices, proximal pulmonary artery to distal pulmonary artery (PA-PA) TAL attachment may be possible in patients without right ventricular dysfunction. This study examined the relationship between pulmonary system impedance and cardiac output (CO) to create TAL design constraints. A circuit with adjustable resistance and compliance (C) was attached in a PA-PA fashion with the pulmonary circulation of seven sheep with chronic pulmonary hypertension. The pulmonary system zeroth harmonic impedance modulus (Z_0) was increased by 1, 2.5, and 4 mmHg/(L/min) above baseline. At each Z_0 , C was set to 0, 0.34, and 2.1 mL/mmHg. The change in pulmonary system zeroth and first harmonic impedance moduli (ΔZ_0 and ΔZ_1), the percent change in CO ($\% \Delta CO$), and the inlet and outlet anastomoses resistances were calculated for each situation. Results indicate that ΔZ_0 ($p < 0.001$) but not ΔZ_1 ($p = 0.5$) had a significant effect on $\% \Delta CO$ and that $\% \Delta CO = -7.45 * \Delta Z_0$ ($R^2 = 0.57$). Inlet and outlet anastomoses resistances averaged 0.77 ± 0.16 and 0.10 ± 0.19 mmHg/(L/min), respectively, and the relationship between $\% \Delta CO$ and TAL resistance, R_T , in mmHg/(L/min) was determined to be $\% \Delta CO = -(7.45f) * (R_T + 0.87)$, in which f = the fraction of CO through the TAL. Thus, newer TAL designs can limit $\% \Delta CO$ to less than 10% if $f < 0.75$.

Keywords

Right Ventricle; Impedance; Afterload; Pulmonary Hypertension; Artificial Lung

Introduction

Blood flow through thoracic artificial lungs (TALs) is driven by the right ventricle, and thus, TALs can cause significant changes in right ventricular (RV) function. Recently, laboratory studies have demonstrated successful long-term use of these devices when attached to the pulmonary circulation in parallel with the native lung. In-parallel attachment can significantly reduce pulmonary pressures and unload the right ventricle.^{1–4} Thus, this is the preferred method for artificial lung attachment in lung transplant candidates with significant pulmonary hypertension and resultant RV dysfunction.

However, a significant subset of lung transplant candidates do not have pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg). This includes 69% of candidates with idiopathic pulmonary fibrosis,⁵ 50% with chronic obstructive pulmonary

disease,⁶ and 37% with cystic fibrosis.⁷ These patients may tolerate a small increase in pulmonary system impedance without RV dysfunction. If so, pulmonary artery (PA) to PA TAL attachment might be possible. The advantages of this attachment method are that emboli cannot escape into the systemic circulation to damage other major organs and that the entire cardiac output flows through the native lungs, allowing full processing of vasoactive molecules by the lungs.⁸⁻⁹

The major disadvantage of this attachment mode is that it automatically increases the impedance that the right ventricle must pump against, leading to decreased cardiac output in the short term and, potentially, RV failure. Thus, for PA-PA attachment to be feasible, TALs need to be designed with extremely low impedances. Recently, Schewe et al., reported artificial lung designs with resistances approximately one-third of previously reported devices.^{10,11} It is unclear, however, if this reduction is sufficient for PA-PA attachment. The goal of this study, therefore, was to examine the design constraints of TALs for PA-PA attachment in a model of mild pulmonary hypertension. Accordingly, this study first examined the effect of pulmonary system impedance on short-term RV function in sheep with chronic pulmonary hypertension. Second, this study quantified the contribution of the pulmonary artery anastomoses and grafts to the impedance of the pulmonary system during artificial lung attachment. From these results, design constraints for the artificial lung were created for patients with mild pulmonary hypertension.

Methods

Circuit and Compliance Chamber

The test circuit was connected to the pulmonary system via vascular graft anastomoses to the pulmonary artery as shown in Figure 1. The circuit is made of 5/8 inch ID, 7/8-inch OD non-compliant PVC tubing and a variable compliance chamber, which has been described elsewhere.¹²⁻¹³ The compliance was varied using springs that give $C = 0.34$ and 2.1 mL/mmHg. To create a $C = 0$ situation, the chamber was bypassed during testing with an extra length of 5/8 inch ID, 7/8 inch OD PVC tubing.

Pulmonary Hypertension Model

A large animal model of pulmonary hypertension with right ventricular hypertrophy was created using pulmonary embolization in adult male sheep. This model is characterized in detail elsewhere.¹⁴ In brief, 0.75 gm of Sephadex G-50 (100-300 μ m) beads (Sigma-Aldrich CO, St. Louis, MO) were injected into the pulmonary circulation every other day for 60 days. Mean PA pressures in these sheep were 28 ± 2 mmHg during surgery just prior to initiating the experimental procedure below.

Experimental Procedure

Seven hypertensive sheep (65-75 kg) were used. All sheep were cared for in compliance with the Guide for the Care and Use of Laboratory Animals. Anesthesia was induced with an intravenous injection of 7-10 mg/kg sodium thiopental (Abbot Laboratories, North Chicago, IL). Mechanical ventilation, anesthesia, arterial and venous pressure monitoring, and left thoracotomy followed previously published methods.³

Following thoracotomy, sheep were anticoagulated with 100 IU/kg of intravenous sodium heparin (Baxter Healthcare Corporation, Deerfield, IL). The inflow conduit was anastomosed in an end-to-side fashion to the proximal PA, and the outflow conduit was anastomosed in the same fashion to the distal PA. The conduits for the artificial lung were 18 mm, low porosity woven Dacron vascular grafts (Boston Scientific, Natick, MA) bonded to five-eighths inch ID PVC tubing. Angiocatheters (16 gauge) were inserted into the

proximal PA immediately distal to the valve and distal PA immediately distal to the circuit outlet anastomosis and attached to fluid-coupled pressure transducers (Abbot Critical Care Systems, Chicago, IL). These were then used to record continuous proximal and distal PA pressures (P_{pPA} and P_{dPA} , respectively). An ultrasonic flow probe (Transonic 24AX, Ithaca, NY) was placed around the proximal PA, immediately distal to the proximal PA angiocatheter before the inlet conduit to measure instantaneous PA flow (Q_{PA}) using a flow meter (Transonic TS420, Ithaca, NY).

Clamps on the inlet and the outlet conduits were removed, and the segment of PA between the proximal and distal PA anastomoses was snared to divert CO through the artificial circuit. An ultrasonic flow probe (Transonic 14XL, Ithaca, NY) was placed on the outflow conduit tubing and connected to a flow meter (Transonic TS410, Ithaca, NY) to record circuit flow, Q_C . Blood was allowed to flow through the circuit for 10 minutes for equilibration before the circuit was clamped off again and a baseline hemodynamic data set was recorded. This data set consisted of P_{pPA} , P_{dPA} , Q_{PA} , and Q_C . Data were digitally acquired at a sampling frequency of 250 Hz via a 16-channel circuit board using LabVIEW software (National Instruments, Austin, TX).

The pulmonary system zeroth harmonic input impedance modulus (Z_0 , see *Data Analysis*) was increased by first snaring the main PA between the two grafts to divert flow into the artificial circuit. Then, after the full cardiac output was diverted, the variable resistance, Hoffman clamp was tightened at the distal end of the artificial circuit. The Z_0 was increased by 1, 2.5, and 4 mmHg/(L/min) greater than baseline. At each Z_0 , C was set at 0, 0.34 and 2.1 ml/mmHg in order to vary the pulmonary system first harmonic input impedance modulus (Z_1 , see *Data Analysis*). Each condition was held for ten minutes prior to recording data. No inotropes, pressors, or volume support was used at any point in the experiment so as to highlight hemodynamic changes. At the end of the study, the animal was euthanized with an intravenous injection of pentobarbital (Fatal-Plus, 90-150 mg/kg, Vortech Pharmaceuticals, Dearborn, MI).

Data Analysis

Calculation of Z_0 , Z_1 , and CO are described in detail elsewhere.^{15,16} The change in Z_0 and Z_1 from baseline (ΔZ_0 , ΔZ_1) was also calculated for each situation as $\Delta Z_i = Z_i - Z_{i,BL}$, in which $Z_{i,BL}$ is Z_i at baseline. To ensure the compliance chamber was functioning properly, the change in pulsatility across the circuit was calculated. The pulsatility of blood flow, $\mathcal{P}$, in both the pulmonary artery and circuit outlet was calculated according to previous methods.¹³ The pulsatility decrease, $\Delta \mathcal{P}$, caused by the compliance chamber was calculated as pulmonary artery $\mathcal{P}$ minus circuit outlet $\mathcal{P}$.

The resistance of the inlet anastomosis was calculated as $R_i = (\bar{P}_{pPA} - \bar{P}_i) / \bar{Q}_C$, in which $\bar{P}_{pPA}$ is the average proximal PA pressure, $\bar{P}_i$ is the average circuit inlet pressure, and $\bar{Q}_C$ is the average circuit blood flow rate. The resistance of the outlet anastomosis was calculated as $R_o = (\bar{P}_o - \bar{P}_{dPA}) / \bar{Q}_C$, in which $\bar{P}_o$ is the average circuit outlet pressure and $\bar{P}_{dPA}$ is the average distal pulmonary artery pressure.

The relationship between impedance, right ventricular power output, and cardiac output was examined by calculating the stroke power output from the right ventricle. Three conditions were examined to capture the loading extremes in the study: baseline (low ΔZ_0 and low ΔZ_1); $\Delta Z_0 = 4$ mmHg/(L/min), $C = 0$ (high ΔZ_0 , high ΔZ_1); and $\Delta Z_0 = 4$ mmHg/(L/min), $C = 2$ (high ΔZ_0 , low ΔZ_1). In all cases, total power, POW_T , was calculated as

$$POW_T = \frac{1}{T} \int_0^T Q_{PA} P_{PA} dt, \quad (6)$$

in which T is the data period. The power present in the zeroth and first harmonic (POW_0 and POW_1) were calculated as $Q_0^2 Z_0$ and $Q_1^2 Z_1 \cos^2 \phi_{Z_1}$, respectively.¹⁷ The percentage of power in the i th harmonic is thus calculated as $100 * POW_i / POW_T$.

Data Analysis – Statistics

Statistical analyses utilized SPSS (Chicago, IL). Mixed model analysis was utilized to determine if ΔZ_0 and ΔZ_1 had a significant effect on dependent variables $\% \Delta CO$, MAP, CVP, and HR. The sheep number was the subject variable; ΔZ_0 was a fixed, independent variable; and ΔZ_1 was a covariate. Based upon this statistical analysis (see **Results**), linear regression was performed within SPSS to generate the following relationship:

$$\% \Delta CO = m \Delta Z_0. \quad (7)$$

Lastly, linear regression was performed to relate the inlet and outlet anastomoses resistances (R_i and R_o) to the flow rate through the TAL, $\bar{Q}_C$.

Data Analysis – Relationship Between TAL Resistance and Cardiac Output

The correlation $\% \Delta CO = m \Delta Z_0$ relates $\% \Delta CO$ to the impedance change of the entire pulmonary system. In order to isolate the acceptable TAL resistance during PA-PA attachment, R_T , a relationship was created between R_T and $\% \Delta CO$; the fraction of blood flow going to the TAL, f ; and the impedance due to the anastomoses. Figure 2 presents a diagram of PA-PA attachment, in which Z_b , Z_{ia} , Z_{oa} , and Z_T are the impedances of the PA band, the inlet anastomosis, the outlet anastomosis, and the TAL. If one assumes the impedance of the natural lung is unchanged by TAL attachment, the change in the impedance of the system due to the TAL, ΔZ , is:

$$\Delta Z = \frac{Z_b (Z_{ia} + Z_{oa} + Z_T)}{Z_b + Z_{ia} + Z_{oa} + Z_T}. \quad (8)$$

The fraction of the cardiac output flowing to the artificial lung, f , is characterized by:

$$f = \frac{Z_b}{Z_b + Z_{ia} + Z_{oa} + Z_T}. \quad (9)$$

Substituting, equation 9 into 8 and solving for Z_T gives:

$$Z_T = \frac{\Delta Z}{f} - Z_{ia} - Z_{oa} \quad (10)$$

The equation retains its form considering the zeroth harmonic only:

$$Z_{T,0} = \frac{\Delta Z_0}{f} - Z_{ia,0} - Z_{oa,0} \quad (11)$$

Substituting in equation 7 yields:

$$Z_{T,0} = \frac{\% \Delta CO}{mf} - Z_{ia,0} - Z_{oa,0}. \quad (12)$$

The zeroth harmonic impedances for the TAL and anastomoses are equal to their resistances, R_T , R_i , and R_o . Thus, the desired relationship between R_T and $\% \Delta CO$ is:

$$R_T = \frac{\% \Delta CO}{mf} - R_i - R_o. \quad (13)$$

Results

Confirmation of Study Design

Tables 1 and 2 show the actual average ΔZ_0 and ΔZ_I , respectively, of each hemodynamic situation. Values for ΔZ_0 were close but typically a bit lower than our goals. Table 2 shows that ΔZ_I increases with increasing ΔZ_0 and decreasing C . Overall, changes in ΔZ_I were small for $C = 0.3$ ml/mmHg and $\Delta Z_0 = 1$ mmHg/(L/min) but markedly increased for $C=0$ and $\Delta Z_0 = 2.5$ mmHg/(L/min). Figure 3 shows representative P_{PA} and Q_{PA} waveforms for baseline (BL) and $\Delta Z_0 = 4$ mmHg/(L/min) at $C = 0$ and 2.1 ml/mmHg. Figure 4 demonstrates the decrease in pulsatility between Q_{PA} and Q_C . The decrease in pulsatility increases with compliance, indicating the compliance chamber is functioning appropriately.

Effect of Impedance on Hemodynamics

Table 3 demonstrates the effect of each ΔZ_0 and ΔZ_I condition on heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP). Neither ΔZ_0 nor ΔZ_I has a significant effect on HR ($p = .17$ and 0.54 , respectively) or MAP ($p = 0.97$ and 0.98 , respectively). CVP, however, increases significantly with increasing ΔZ_0 ($p < 10^{-5}$) but does not change significantly with C ($p = 0.28$). Figure 5 demonstrates the effect of ΔZ_0 on cardiac output at varying C . The percentage change in cardiac output decreases linearly with ΔZ_0 , but C does not affect cardiac output. Accordingly, the effect of ΔZ_0 is statistically significant ($p < 0.001$), whereas the effect of ΔZ_I is not ($p = 0.5$). A curve fit yields the relationship $\% \Delta CO = -7.45 \Delta Z_0$ ($R^2 = 0.57$).

Figure 6 demonstrates the percentage of the stroke power from the heart in the zeroth and first harmonic at baseline and when $\Delta Z_0 = 4$ mmHg/(L/min) at $C = 0$ and 2 ml/mmHg. The percentage of stroke power in the zeroth and first harmonics range from 82-85% and 5-9% respectively. Thus, it can be seen that the work load of the RV is dominated by the zeroth harmonic within relevant ranges of loading conditions.

Anastomosis Resistances

Linear regression between R_i and R_o and $\bar{Q}_C$ demonstrated weak relationships with a large degree of scatter ($R^2 = 0.10$ and 0.05 , respectively). Therefore, physical differences in anastomosis construction and pressure catheter placement appear to have as great an effect on resistance as flow rate. Therefore, all anastomosis resistances were regarded as constants and averaged across device flow rates ranging from 2.5-5.2 L/min, leading to $R_i = 0.77 \pm 0.16$ mmHg/(L/min) and $R_o = 0.10 \pm 0.19$ mmHg/(L/min).

TAL Resistance Requirements

Results for m , R_i , and R_o were substituted into equation 10 to yield $\% \Delta CO = -(7.45f)(R_T + 0.87)$ or, solving for R_T , $R_T = -\% \Delta CO / (7.45f - 0.87)$. Figure 7 shows the resistance requirements for the TAL graphed vs. $-\% \Delta CO$ at $f = 0.5, 0.75$, and 1.0 . If one would like to limit the drop in CO to less than 10%, for example, one must hold the TAL resistance less than 1.81, 0.92, and 0.47 for 50, 75, and 100% blood flow to the TAL.

Discussion

The goal of this study was to create a relationship between cardiac output and impedance of the artificial lung during PA-PA attachment with the natural lungs. The first major finding of this study is that the first harmonic impedance modulus, Z_1 , has no effect on cardiac output in a model of chronic pulmonary hypertension. Thus, in a clinical setting, artificial lung compliance should not significantly affect cardiac output. The implications of this finding are that one can design thoracic artificial lungs by focusing solely on minimizing Z_0 or, equivalently, TAL resistance.

The finding that Z_1 has no effect on CO appears to contradict a decade worth of research in this area. Studies by several authors have demonstrated lower right ventricular workloads and improved cardiac output using an inlet compliance chamber.^{1,2,12,13} Most notably, Sato et al.¹³ attached the MC3 Biolung PA-PA with 100% of CO flowing through the TAL, and found that cardiac output fell 42% with $C = 0.5$ ml/mm Hg but only 25% when $C = 1.0$ ml/mm Hg. Under these conditions ΔZ_0 was approximately 4 mm Hg/(L/min). Kuo et al., performed experiments similar to those in this paper in normal sheep and found a small but statistically significant effect of Z_1 on CO.¹⁶

The major difference between those two studies and the current one is that they were conducted using normal sheep. The sheep pulmonary hypertension model utilized here has RV hypertrophy and normal cardiac output despite mean PA pressures of 35 mmHg when awake.¹⁴ It is likely, therefore, that the hypertrophied RV is less affected by the ΔZ_1 than the normal RV. Furthermore, as Figure 6 demonstrates, the first harmonic adds less than 10% to RV stroke power requirements and thus only a small change in the oxygen consumption requirements. Due to study design, this study was not able to determine the total power requirements of the RV, including dissipated power, but it is likely that the contribution of Z_1 remains very small.

Ultimately, this means that the artificial lung design requirements can focus only on the zeroth harmonic and system resistances. The relationship between cardiac output, TAL resistance, and the fraction of cardiac output going to the TAL was thus found to be $\% \Delta CO = -(7.45f)(R_T + 0.87)$. One previous study¹⁵ examined the relationship between $\% \Delta CO$ and ΔZ_0 alone in both healthy and hypertensive sheep, generating the relationship $\% \Delta CO = 0.215 \Delta Z_0^2 - 7.14 \Delta Z_0 + 2.94$. The effect of Z_1 was not considered. As in Figure 7, one can use this relationship to determine the relationship between $\% \Delta CO$ and R_T . That relationship is:

$$\% \Delta CO = 0.215 f^2 (0.87 + R_T)^2 - 7.14 f (0.87 + R_T) + 2.94. \quad (14)$$

In that study, if the design goal was $\% \Delta CO < 10\%$, R_T would need to be less than 1.05 and 1.70 with 100 and 75% of cardiac output flowing through the TAL, respectively. The current study predicts a more conservative estimate for the design requirements of the TAL, with $R_T < 0.47$ and 0.92 under the same conditions. Even under the more conservative estimate from this study, it should be possible to achieve a PA-PA attachment that offers significant oxygen transfer with $\% \Delta CO < 10\%$. Schewe et al. presented the lowest impedance TAL in the literature, a solid shell TAL with $R_T = 0.69 \pm 0.13$ mmHg/(L/min).¹¹ The predicted drop in cardiac output is 8.8% for PA-PA attachment with 75% of cardiac output flowing to this TAL.

The first limitation of this study and these relationships is that only the short-term hemodynamic effect of attachment was examined. Further studies will need to be performed to determine the effect of attachment for a period of a few weeks to a month. It is unclear how long it would take for RV accommodation and whether pressor support would be

needed for a short period. Phenylephrine has been shown to increase cardiac output under similar high RV afterload conditions because it raises arterial pressures and coronary perfusion^{18,19} but has minimal effect on pulmonary vascular resistance. The second limitation of this study is that delivery of oxygenated blood to the pulmonary circulation may act to lower PVR. The extent to which this would ameliorate the effects of the added device resistance is unknown. The last limitation of this study is that PA-PA attachment in humans would be significantly more difficult than in sheep. The human main PA is very short in comparison to the sheep, and thus the outlet anastomosis would likely have to be placed upon a branch of the main PA. The effect of this change on total impedance should be small, however, as the impedance of the outlet anastomoses is small.

For use on the order of weeks, PA to LA attachment would be far more favorable due to the relatively small risk of systemic embolization. For longer term use, however, the lack of systemic embolization may outweigh risks of proximal PA to PA branch attachment. In PA to LA attachment of one month, uncoated TAL prototypes have demonstrated minimal changes to systemic hematology, despite clotting and subsequent device replacement after an average of 9.5 days, and there was no need to infuse blood products. Evidence of minor embolic events was present, however. If repeated, small embolic events are the greatest problem during long-term use, PA-PA use on the order of months may be beneficial.

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Figure 1.

Test circuit connected to the pulmonary system via vascular graft anastomoses to the proximal and distal pulmonary artery.

Figure 2.

A diagram of PA-PA attachment, in which Z_b , Z_{ia} , Z_{oa} , and Z_T are the impedances of the PA band, the inlet anastomosis, the outlet anastomosis, and the TAL.

Figure 3.

Representative pulmonary artery pressure and flow waveforms at different impedance conditions. A: baseline ($\Delta Z_0 = \Delta Z_F = 0$), B: $\Delta Z_0 = 4$ mmHg/(L/min), $C = 2$ ml/mmHg, C: $\Delta Z_0 = 4$ mmHg/(L/min), $C = 0$ ml/mmHg.

Figure 4. Pulsatility change from the proximal pulmonary artery flow, Q_{PA} , to the TAL outlet flow, Q_C

Figure 5.
Effect of ΔZ_0 on the percentage change in cardiac output, % ΔCO .

Figure 6.
Percent of stroke power in the zeroth and first harmonic.

Figure 7.

TAL resistance requirements, R_T , vs. the percent decrease in CO ($-\% \Delta CO$) with 50-100% of cardiac output through the TAL ($f = 0.5 - 1.0$).

Table 1 ΔZ_0 at each ΔZ_0 goal and C

	ΔZ_0 goal, mm Hg/(L/min)		
Compliance, ml/mmHg	1	2.5	4
C=0	0.90±0.08	2.39±0.14	3.66±0.19
C=0.34	0.96±0.17	2.66±0.47	3.76±0.24
C=2.1	0.92±0.09	2.48±0.16	3.84±0.16

Table 2 ΔZ_I at each ΔZ_0 goal and C

	ΔZ_0 goal, mm Hg/(L/min)		
Compliance, ml/mmHg	1	2.5	4
C=0	1.32±0.30	8.13±3.05	9.07±1.76
C=0.34	0.24±0.19	1.52±0.55	1.51±0.48
C=2.1	0.61±0.43	1.24±0.27	0.82±0.54

Table 3 Hemodynamic measurements at each ΔZ_0 goal and C

ΔZ_0 , mmHg/(L/min)	C, ml/mmHg	HR, bpm	MAP, mmHg	CVP, mmHg
Baseline		120.16±12.10	80.15±17.41	6.09±3.27
1	0	121.41±14.66	66.70±16.57	6.65±3.20
1	0.34	119.52±15.96	60.67±23.49	6.77±2.65
1	2.1	112.25±22.81	65.54±22.02	8.10±2.56
2.5	0	104.15±14.20	57.19±12.01	10.23±1.68
2.5	0.34	109.80±19.98	57.12±15.90	9.14±1.69
2.5	2.1	112.93±24.64	61.11±25.33	9.59±2.39
4	0	103.37±18.79	53.52±12.81	11.83±2.31
4	0.34	105.89±20.57	58.08±16.46	11.88±2.52
4	2.1	108.39±28.68	56.25±18.74	12.41±1.47