PREDICTING IDEAL, ARTIFICIAL LUNG ATTACHMENT MODE WITH PRE-ATTACHMENT, RIGHT VENTRICULAR FUNCTION INDICES

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INTRODUCTION

Thoracic artificial lungs (TALs) are being developed as a treatment for acute respiratory failure and as a bridge to lung transplantation. *In vivo* experiments with TALs have demonstrated gas transfer rates capable of nearly full support of adult humans for up to seven days [1,2]. Despite the success in respiratory support, all current TALs possess higher impedances than the natural pulmonary circulation, and *in vivo* testing of these devices has lead to cases of increased right ventricular hydraulic power output and right ventricular dysfunction [1,3,4]. These experiments have all been performed with either healthy animals or animals with, at worse, acute lung failure and near normal pulmonary hemodynamics. Clinically, these devices will be used with patients with a wide variety of disease states and pulmonary hemodynamics. All patients will possess some degree of pulmonary hypertension. For some, the hypertension may be long-term and accompanied by right ventricular dysfunction, making it more difficult for the right ventricle (RV) to support increased workloads without a significant reduction in cardiac output (CO). Thus, a means is required to pre-operatively assess a patient to ensure that TAL implantation does not cause a deleterious decrease in CO.

Right ventricular function is predominantly affected by natural and artificial lung resistances; the TAL attachment mode, in series or parallel; and the percentage of the CO going to the artificial lung. Clinically, the natural and artificial lung resistances will be fixed, whereas the attachment mode and percentage of CO going to the TAL can be varied to maintain proper RV function. In-parallel attachment can reduce the overall pulmonary system resistance (PSR) and work requirements of the RV and lead to improved RV function. Some blood, however, bypasses the natural lungs, limiting performance of their non-respiratory functions and possibly allowing passage of harmful emboli to the systemic circulation. In-series attachment has the advantage that the entire CO flows through the natural lungs, allowing for filtration and performance of non-respiratory functions. In-series attachment, however, increases the overall PSR and RV power requirements, and this increase is proportional to the percentage of CO going to the TAL.

The effect of PSR on RV function make it desirable to have a pre-operative means to determine which TAL attachment mode is ideal for each patient. We are currently examining four possible indices for predicting the ideal attachment mode: maximum right ventricular output power (RVOP), maximum cardiac index (CI), RVOP reserve, and CI reserve. These indices have several advantages over contractility measurements in the prediction and assessment of RV function during TAL implantation. First, unlike contractility, they are good relative and absolute measurements [5] and can be compared between patients and to numerical models of the pulmonary circulation with or without a TAL. Second, the left ventricle's ability to generate flow or power increases with the health of a heart [5, 6], and this may also hold true for the right ventricle. Dobutamine-induced, maximum average left ventricular output power has been used successfully to predict survival of patients with left ventricular failure with greater than 87% accuracy [5,7]. Both maximum RVOP and CI can be determined through progressive stimulation of the heart by dobutamine while measuring real-time PA flow and pressure. As dobutamine infusion rates increase, CI and RVOP rise, reach a plateau, and then fall. We believe the peak and reserve values of both may be predictive of the RV's reaction to elevated PSR.

METHODS

Two groups are proposed to determine if pre-implantation, dobutamine-induced RVOP or CI can be used to predict the effect of elevated PSR on right ventricular function. The first group consists of healthy sheep with three different treatments: in-parallel implantation, in-series implantation, or pulmonary artery banding. The second group consists of sheep with simulated, long-term, respiratory disease with the same three treatments. In these sheep, 50 g of sephadex G-50 beads were injected into the pulmonary circulation over the course of one year. The beads lodge within the pulmonary arterioles, blocking flow and leading to increased pulmonary resistance. The initial studies reported here include six animals. Two sheep are healthy with a TAL

attached in series, two are healthy with a TAL attached in parallel, and two are bead-injected with a TAL attached in parallel. The TAL used in all experiments is the MC3 Biolung®.

In all animals, the carotid artery and jugular vein were cannulated for monitoring of arterial and central venous pressures, respectively. A left thoracotomy was performed for TAL implantation and placement of a flow probe around the proximal PA and a Millar pressure transducer into the PA. All pressure and flow values were then digitally acquired. Each hemodynamic data set was taken twice, at 250 Hz for eight seconds, with a five minute interval between samples. After baseline measurements, increasing rates of dobutamine were infused into the central venous line. The initial infusion rate was 2.5 μg/kg/min for five minutes, followed by increases of 1.25 μg/kg/min every five minutes. Infusion was ceased when the CO reached a maximum and began to fall. Hemodynamic data were acquired immediately prior to each change in the infusion rate. The TAL was attached following cessation of dobutamine. The attachment process took over an hour to perform, allowing the remaining dobutamine to be metabolized. The animal received 100 units/kg of heparin, and the TAL inlet conduit was anastamosed to the PA. For in-series and in-parallel attachment, the TAL outlet conduits were anastomosed to the distal PA and left atrium, respectively.

For in-parallel implantation, a clamp on the device outflow is released incrementally such that flow increases at 10-25% intervals. When the clamp is fully released, a PA band is tightened incrementally to further increase flow at 10-25% intervals. Hemodynamic data were acquired at each interval. When TAL flow reached 70-80% of the cardiac output, hemodynamic data were taken again, and both clamp and band were incrementally tightened such that the percentage of CO to the TAL was constant but overall PSR increased. The resistance was increased incrementally such that each tightening caused approximately a 10% reduction in CO. At each reduction, hemodynamic data were acquired. When CO fell by 50%, hemodynamic data were repeated, and all clamps were released. For in-series implantation, a PA band was used to incrementally increase the CO going to the TAL as above. When TAL flow reached 100%, overall pulmonary system resistance was increased by clamping the outlet of the artificial lung. The CO was incrementally decreased and data was acquired as during in-parallel implantation.

All baseline and dobutamine data were analyzed to determine CI, PSR, and steady and pulsatile values of RVOP. The CI equals the CO divided by the sheep's weight. The PSR equals average PA pressure divided by the average PA flow rate. The steady RVOP equals the product of average PA flow and pressure. The pulsatile RVOP equals the product of PA flow and pressure integrated over time and divided by the time span of the integral. The RVOP reserve, steady or pulsatile, and RV CI reserve were calculated as the difference between maximum and baseline RVOP and maximum and baseline CI. Cardiac index is graphed vs. resistance to determine the relationship between CI and PSR. Lastly, CI reserve, RVOP reserve, maximum CI, and maximum steady and pulsatile RVOP were graphed vs. the change in resistance necessary to reach a certain CI.

RESULTS AND DISCUSSION

Cardiac indices were found to decrease linearly with PSR in each sheep when cardiac indices were below normal, healthy values (CI < 0.098 L/min/kg). The PSR change to reach any given CI could thus be determined using this linear relationship. Graphs of the various RV performance indices vs. this PSR change indicate that peak CI is the only index capable of effectively predicting the PSR change required to reach a given CI. Figure 1 shows the PSR change that would bring each sheep to a CI of 0.075 L/min/kg. In these initial results, any sheep with a peak CI greater than 0.15 should be able to tolerate some degree of in-series attachment, and those at or below this level should be implanted in parallel instead. The percentage of CO that can safely flow through the TAL can then be determined by calculating the resistance changes using simple electrical circuit analogues. Therefore, initial results suggest that pre-operative determination of peak CI could be an effective method of determining which attachment modes is ideal for a given patient.

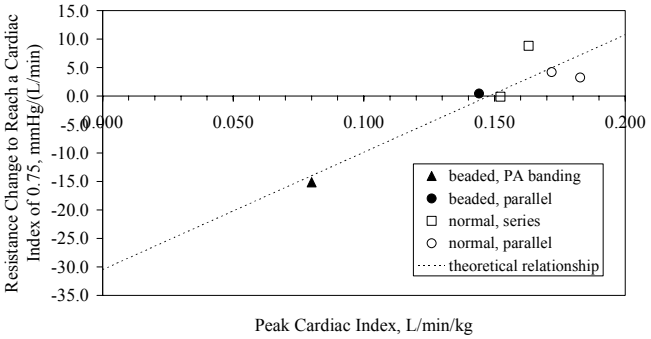

Figure 1: Effect of peak cardiac index, L/min/kg on the change in resistance necessary to reach a target cardiac index of 0.075 L/min/kg.

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