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RIGHT VENTRICULAR UNLOADING AND RESPIRATORY SUPPORT WITH A WEARABLE ARTIFICIAL PUMP-LUNG (APL) IN AN OVINE MODEL

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Abstract

Background—Device availability of mechanical circulatory or respiratory support to the right heart has been limited. The purpose of this study was to investigate the effect of right heart unloading and respiratory support with a wearable integrated artificial pump-lung (APL).

Methods—The APL device was placed surgically between the right atrium and pulmonary artery in seven sheep. Anticoagulation was performed with heparin infusion. Its ability to unload the right ventricle (RV) was investigated by echocardiograms and right heart catheterization at different bypass flow rates. Hemodynamics and Echo data were evaluated. The device flow and gas transfer rates were also measured at different device speeds.

Results—Hemodynamics remained stable during APL support. There was no significant change in systemic blood pressure and cardiac index. Central venous pressure, RV pressure, RV end-diastolic dimension and RV ejection fraction were significant decreased when APL device flow rate approached 2 L/min. The linear regression showed significant correlative trends between the hemodynamic and cardiac indices and the device speed. The oxygen transfer rate increased with the device speed. The oxygen saturation from APL outlet was fully saturated (>95%) during the support. The impact of the APL support on blood elements (plasma free hemoglobin and platelet activation) was minimal.

Conclusion—The APL device support significantly unloaded the right ventricle with increasing device speed. The APL device provided stable hemodynamic and respiratory support in terms of

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blood flow and oxygen transfer. The right heart unloading performance of this wearable device need to be evaluated in the animal model with right heart failure for a long term support.

Keywords

right heart unloading; respiratory support; artificial pump lung; in vivo

Introduction

Mechanical circulatory support (MCS) therapy has evolved into a standard therapy for patients with advanced heart failure (HF), not only as a bridge to myocardial recovery or cardiac transplantation but also as a destination therapy (1–3). The number of patients receiving MCS therapy has quadrupled over the last five years. The majority of MCS devices have been specifically designed as a left ventricular assist device (LVAD) for left heart failure (LHF). MCS devices for appropriate right heart support are limited. Although right heart failure (RHF) is not frequent as LHF, it happens commonly, complicated with left heart dysfunction or primary pulmonary hypertension which usually presents with overloaded congestive heart failure (4, 5). RHF also occurs in 20–50% of LVAD patients and negatively impacts their morbidity and mortality (6, 7). In spite of medical advances the medical therapy does not work well in the end stage RHF. Heart transplantation or heart and lung transplantation are optimal choices for endstage RHF patients, but limited by the shortage of organ donors (8, 9). MCS devices designed for the left heart and extracorporeal membrane oxygenation (ECMO) systems have been occasionally used to relieve RHF symptom, including pulsatile and continuous VADs (10–13). But these techniques have their own shortcomings, including no respiratory support function in VADs or poor long term biocompatibility, low efficiency of unloading, complex and bulky components in ECMO systems.

Over the last decade, the concepts of ambulatory respiratory/cardiopulmonary support and percutaneous right heart support has emerged and gained acceptance among physicians and surgeons (14, 15). An ultra-compact integrated artificial pump-lung (APL) is currently being developed for ambulatory respiratory or cardiopulmonary support (16). The APL consists of a uniquely configured hollow fiber membrane (HFM) bundle integrated with a magnetically levitated centrifugal impeller pump. The overall size of the APL is comparable to a 12-ounce soda can. It can function either as a respiratory support device or partial cardiopulmonary support device with maximal flexibility of application in the broad spectrum of heart/lung diseases. The APL device can not only supply cardiac support but also have gas exchange function. Therefore, the APL device might be an optimal alternative for RHF. The objective of this study was to evaluate the effect of right ventricular unloading and respiratory support function of the APL device in an acute ovine model.

Material and Methods

Device description

The APL device is 117 mm in length and 89 mm in diameter. Its priming volume is 115 ml. The combined weight of the APL device and the motor/controller unit is only 0.54 kg. It was

designed to be a fully integrated pump-lung for respiratory and heart failure support. The APL design combines a magnetically levitated centrifugal pump and a hollow fiber membrane bundle to form one single compact system capable of both pumping and oxygenation. The pumping function of the APL was designed based on a continuous-flow, and centrifugal-type rotary blood pump supported by the magnetically levitated bearingless impeller/motor technology. The oxygenation component is made of micro porous hollow fiber membranes (HFM). To achieve the most effective use of the fiber membranes, maximum gas exchange and elimination of deleterious flow stagnancy, a cylindrically HFM bundle with a unique circumferential-radial uniform outside-in flow path design is employed. Figure 1A shows the sectional view of the flow path inside the APL. Venous blood is drawn from the patient into the APL pump chamber from a central cylindrical tube through a drainage cannula. Driven by a magnetically levitated rotating centrifugal pump impeller, the blood is propelled through the diffuser section and flows toward the space between the outer housing and the polymethylpentene HFM (Oxyplus; Membrana, Wuppertal, Germany) bundle. While the blood passes through the HFM bundle, the oxygen is transferred from the fiber lumen to the blood and the carbon dioxide is removed from the blood. The oxygenated blood is collected at the space between the HFM bundle and the center tube and returned back to the patient through the return cannula. The sweep gas enters the lumens of individual hollow fibers of the potted HFM bundle from the top and exits the device at the bottom through the channels imbedded in the diffuser fins. The APL device and its controller and motor drive were showed in Figure 1B. The detailed construction and operating principle were described previously (14, 16).

Animal preparation

Seven Dorset crossbred sheep (56.6 kg, weigh range from 51.3–62.4 kg) were used in the study. Prior to surgery, the animals were pre-medicated with atropine (0.05 mg/kg, intramuscular) followed by initial anesthetic induction with ketamine hydrochloric acid (25 mg/kg, intramuscular). Endotracheal intubation was achieved under direct visualization. Anesthesia was achieved using isoflurane (1–3% to effect) followed by the placement of an oral–gastric tube for abdominal decompression. Monitoring lines were placed in the left external jugular vein (IV) and femoral artery. A Swan-ganz catheter was put into the pulmonary artery by left external jugular vein. The blood samples were collected for baseline laboratory tests. All the surgical procedure and animal care were carried out according to the approved protocol by the Institutional Animal Care and Use Committee (IACUC) of the University Of Maryland School Of Medicine. During the course of the animal experiments, all animals received humane care in accordance with the Guide for Care and Use of Laboratory Animals (NIH publication 86–23, revised 1996).

Surgical procedure

After the general anesthesia and preoperative preparation, a left thoracotomy incision was made in the fourth intercostal space and the fourth rib was excised. The pleural space was opened and the left lung gently tucked out of the way. The pericardium was horizontally and vertically incised to expose the pulmonary artery and right atrial appendage. Heparin was injected through the IV line (100U/kg). The main pulmonary artery (PA) was partially clamped by a side clamp. Then a custom-made graft fixed outflow cannula was anastomosed

on PA with a prolene 5/0 using an end-to-side approach. Two purse-strings were placed on the right atrial appendage (prolene 3/0) with pledget felt. The inflow Cannula (Medtronic DLP Single Stage Venous Cannula 32 Fr. CB67316) was placed into the right atrial about 3 cm and secured with the purse string sutures using the push-pull method (Figure 1C). The two cannulae were rinsed and de-aired and then capped or clamped. The inlet and outlet of the APL device was connected to the two cannulae. The APL drew the blood from the right atrium, oxygenated venous blood, bypassed the right ventricle and returned oxygenated blood to the pulmonary artery (Figure 1D).

Hemodynamic variables

Hemodynamic data were recorded after the implant surgical procedure. Hemodynamic parameters (pressures and flows) were collected with the outflow cannula being clamped without APL support, and then with APL support at nine different operating speeds (2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000RPM). The hemodynamic parameters included heart rate (HR), systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP), mean arterial blood pressure (MABP), central venous pressure (CVP), pulmonary arterial systolic pressure (PASP), pulmonary arterial diastolic pressure (PADP), pulmonary arterial mean pressure (PAMP), pulmonary capillary wedge pressure (PCWP), right ventricular systolic pressure (RVSP), right ventricular diastolic pressure (RVDP), right ventricular mean pressure (RVMP) and cardiac index (CI).

Echocardiography

In parallel with the hemodynamic data collection, echocardiography was performed under the same conditions. Echocardiograms were recorded without APL support and with APL support at nine different operating speeds. The right ventricular end-diastolic dimension (RVESD), right ventricular end-systolic dimension (RVESD) and right ventricular ejection fraction (RVEF) were analyzed.

Oxygen transfer

Blood samples at the inlet and outlet of the APL were collected at different operating speeds for blood gas analysis using a blood gas analyzer (Stat Profile Phox Plus L; Nova Biomedical, Waltham, MA). The oxygen transfer rate was calculated according to the published method (17). Because 95% oxygen mixed with 5% carbon dioxide was used as the sweep gas, the carbon dioxide transfer rate could not be reliably evaluated and was not presented.

Assessment of plasma free hemoglobin and platelet activation

Blood samples were collected at baseline and then every two hours for determination of complete metabolic panel, complete blood count, plasma free hemoglobin (PFH), and platelet activation markers (percentage of P-selectin positive platelets and plasma soluble P-selectin) for twelve hours. The PFH was measured using a modified cyanomethemoglobin method. Expression of P-selectin (CD62p) on platelets was quantified with flow cytometry. Plasma soluble P-selectin levels were measured by enzyme-linked immunosorbent assay developed in our laboratory specifically for ovine(18).

Statistics

All data were analyzed using the statistical package for social science (SPSS) 18.0 for Windows (IMB, Chicago, IL). All data were given as mean $\pm$ standard deviation (SD). Two-way ANOVA was used to compare differences between hemodynamic and echocardiographic data at the different device speed. *F*-test and linear regression were used to describe the relationship between the hemodynamic and echocardiographic data and the different device speeds. All data were analyzed using the normality test. The statistical significance was accepted at *p* value < 0.05 .

Results

The implant surgical procedure was completed less than 50 minutes in all the animals. No uncontrolled bleeding occurred. All the animals survived until the study endpoint. There were no complications during the acute study. All the implanted APL devices functioned normally during the study. There was no leaking, uncontrolled clotting or other mechanical complication of the APL devices.

Hemodynamic data

The hemodynamics in all the animals was stable during the study. The APL device flow rates were increased correspondingly with increasing the speed. Linear regression showed an excellent relative curve between them ($r^2 = 0.9216$, $P < 0.001$) (Figure 2). The heart rate varied slightly between 75–95 beats/min when the device speed was adjusted. There was no significant change in systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP) and mean arterial blood pressure (MABP) when the device speed was changed from low to high. The cardiac indexes (CI) were stable in the range of 2.5 to 3.4 L/min/m², and there were no significant change with the increase of the speed (Table 1). However, the central venous pressure (CVP) was significant decreased with the increased device speed over 3500RPM (Table 1). The linear regression showed a significant correlative trend between CVP and device speed ($p < 0.01$) (Figure 3A). There were similar trends observed for the right ventricular systolic pressure (RVSP), right ventricular diastolic pressure (RVDP) and right ventricular mean pressure (RVMP) (Table 1). The linear regressions showed significant correlative trends between RVSP, RVDP, RVMP and device speed ($p < 0.01$) (Figure 3B, C, D).

Echocardiographic data

The parallel response of the right ventricular function to the APL support was observed with the change of device speed by echocardiography. The right ventricular end-diastolic dimension (RVEDD) was decreased with the increased device speed over 3500RPM (Table 1). Linear regression showed a significant correlative trend between RVEDD and device speed ($p < 0.01$) (Figure 4A), although there were no significant difference among RVEDD in different device speed by two-way ANOVA. The right ventricular end-systolic dimension (RVESD) remained unchanged with the increase of the device speed. Linear regression showed no significant correlative trend between RVESD and device speed ($p = 0.3155$) (Figure 4A). The right ventricular ejection fraction (RVEF) was significantly decreased with the increase of the device speed over 3500RPM (Table 1). A significant correlative trend

was described between RVEF and device speed by linear regression ($p < 0.01$) (Figure 4B). Figure 5 showed the representative 2-D echocardiographic images showing the changes of right ventricular area with increasing device speed on a typical short axis view at end diastole.

Oxygen transfer

The oxygen transfer performance of the APL device is shown in Figure 6. The oxygen transfer rate increased with device speed (Figure 6A). A linear trend could be observed between the oxygen transfer rate and device speed. This is consistent with the linear increase of the device blood flow rate with the device speed (Figure 2). The highest oxygen transfer rate was 188 ml/min at a device speed of 7000RPM with a blood flow rate around 4 L/min. Figure 6B shows the oxygen saturation at the inlet and outlet of the APL device during the study. In spite of varying inlet blood conditions, the oxygen saturation of the blood at the device outlet was always above 95%.

Plasma free hemoglobin (PFH) and Platelet activation

The plasma free hemoglobin (PFH) was within the normal range (<20 mg/dL) during the study (Figure 7A). The platelet activation was minimal under 6% during the study (Figure 7B). The platelet activation was comparable to the pre-surgical baseline level. The damage to blood was negligible during the study according to these results.

Discussion

The knowledge of the right heart function and failure has lagged behind that of the left heart. There were limited therapeutic options to treat the end-stage RHF (19). The end-stage heart dysfunction usually presents congestive heart failure. The RHF is always complicated with left heart dysfunction and chronic pulmonary hypertension or primary pulmonary hypertension. For patients with end-stage left heart failure, a LVAD can provide effective circulatory support. However, the dysfunction of right side heart could be more complicated and fatal after implantation of LVAD (10, 12, 13). The total artificial pulsatile heart assist device with double chambers supplies an alternative. Previous studies also implemented the bi-ventricular support using two axial ventricular assist devices in animal models (20). The APL is designed as an ambulatory cardiopulmonary assist device for chronic use. It can function as a respiratory support device or as a partial cardiopulmonary support device. In this study, we only focused on its function of right heart support. According to our results, hemodynamic data showed that CVP, RVSP, RVDP and RVMP were significant decreased when device speed over 3500RPM with about 2 L/min flow. The echocardiogram showed that RVEDD and RVEF had a correlatively decreasing trend with increasing the device speed. These results suggest that the APL device could decrease the preload for right heart significantly at appropriate device speeds with blood flow rate of more than 2L/min.

Patients with RHF are usually accompanied with respiratory failure. Therefore, the ideal right ventricular assist device should have compatible function with both circulatory and respiratory support for these patients. In this study, with the performance of right heart unloading function, the APL device showed the reliable oxygen transfer function. The

oxygen transfer performance of the APL device was stable with a rate of 100mL/min at a flow rate of 2 L/min. The rate increased with the device speed. The highest oxygen transfer rate reached 188 ml/min at 4 L/min flow, which is about 75% of the normal oxygen consumption. This rate should provide patients with adequate ambulatory cardiopulmonary support. The oxygen saturation from outlet of the APL device was always over 95% during the study. These results indicated the stable oxygen transfer function of the APL device, which could supply a reliable respiratory support for respiratory dysfunction complicated with RHF.

Patients with the end-stage RHF complicated with chronic hypoxia, for example, some congenital heart disease often need long term cardiopulmonary support, which may bridge them to heart and lung transplantation or recovery. The ideal long term support system should allow patients to be ambulatory with the ability to exercise. Tamesue and his co-workers tried use traditional extracorporeal membrane oxygenation (ECMO) to support animal model with right heart failure (21). Apparently, this is not an optimal choice for long term right heart support. With the current ECMO systems, patients are usually bedridden, resulting in muscular atrophy and wasting syndrome that may affect patients' survival. Wang and his co-workers designed a different support system with separated oxygenator and blood pump, and evaluated the performance of their system in ovine model (22, 23). Although the device was wearable and allowed animal standing, dinking and eating, the system was still complex and bulky. The APL device is a portable device with combined oxygenator and blood pump. The portable size allows it to be used as ambulatory device. The long term support for 30 days of The APL device had been demonstrated previously (24). The APL device had stable oxygen transfer function and biocompatibility for the 30-day support. Therefore, it is reasonable to make the assumption that the APL device can supply an encouraged function of right heart unloading with respiratory support for long term.

Limitation

This study was performed in healthy animal models without pulmonary hypertension. The pulmonary hypertension and pulmonary vascular resistance should be considered if the APL device is used to support patients with right heart failure in the future. It has been reported that the right heart support by a Levitronix CentriMag led to bleeding in a patient with severe idiopathic pulmonary arterial hypertension. Then the venous arterial ECMO was performed to bridge the patient to heart -lung transplant. (6). Therefore, there is the potential of bleeding and/or hemoptysis if the MCS system was used as an RVAD support for RV failure with severe pulmonary hypertension. We are working on setting up the animal model with right heart failure and/or pulmonary hypertension recently. We will implant the APL device to this animal model to further understand its performance and limitation.

The cannulas and cannulation method used in this study was only for the purpose of our animal study and may not be the best alternative for clinical use.. A more convenient and minimal invasive cannulation and more reliable cannulas are recommended for clinical use.

Conclusion

The APL device provided reliable and effective right heart unloading and respiratory support when placed between the right atrium and pulmonary artery in an acute animal model.

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Figure 1.

(A) Cross-sectional view of the artificial pump-lung and flow path. (B) Description of The APL device. (C) Surgical implantation. (D) Total circulation of APL device. PA, pulmonary artery; RA right atrium.

Figure 2.

Relative curve between device speed and flow rate of APL in vivo ($P < 0.01$)

Figure 3.

Linear regression of hemodynamic data including CVP, RVSP, RVMP and RVDP. CVP, central venous pressure; RVSP, right ventricular systolic pressure; RVMP, right ventricular mean pressure; RVDP, right ventricular diastolic pressure.

Figure 4.

Linear regression of echocardiographic data. (A) RVED; (B) RVEF. RVED, right ventricular end dimension; RVEDD, right ventricular end-diastolic dimension; RVESD, right ventricular end-systolic dimension; RVEF, right ventricular ejection fraction.

Figure 5.

Representative 2-D echocardiography show the changes of right ventricular area at end diastole with increasing device speed by atypical short axes. (A) Pump off; (B) 2000RPM; (C) 2500RPM; (D) 3000RPM; (E) 3500RPM; (F) 4000RPM; (G) 4500RPM; (H) 5000RPM; (I) 5500RPM; (J) 6000RPM.

Figure 6.

Effects of respiratory support of The APL device. (A) Oxygen transfer rate with different device speed during the study. (B) Inlet and outlet oxygen saturation variation during the study. SO₂inlet, saturation of inlet; SO₂outlet, saturation of outlet.

Figure 7.
Variation of plasma free hemoglobin (PFH) and platelet activation during the study. (A) PFH; (B) Platelet activation.

Table 1

Hemodynamic data and Echo data with APL bypass in different pump speed (mean±SD)

Pump Speed(RPM)	offpump	2000	2500	3000	3500	4000	4500	5000	5500	6000
HR(/min)	84±7	85±8	86±8	84±8	84±8	85±8	85±8	84±9	84±10	83±9
SABP(mmHg)	83.8±16.0	80.0±14.4	85.2±18.6	86.2±18.9	86.0±15.9	85.4±15.7	87.2±16.4	86.2±15.4	84.8±18.5	84.4±15.9
DABP(mmHg)	48.8±13.8	48.2±16.5	47.8±14.7	49.4±11.9	51.6±12.0	51.2±14.6	49.8±13.4	51.0±14.9	52.8±12.9	54.2±16.5
MABP(mmHg)	59.8±13.9	58.8±17.2	60.6±14.9	61.0±14.8	63.8±12.6	63.2±14.5	62.6±14.3	63.8±14.0	63.8±15.2	65.6±17.0
CVP(cmH ₂ O)	6.0±1.0	5.8±2.0	5.4±1.5	5.0±2.0	5.2±1.5	4.0±0.7*	3.0±0.7**	2.6±0.5**	1.6±0.5***	0.6±0.5***
PASP(mmHg)	28.4±8.1	29.6±8.8	27.8±10.9	28.4±7.7	27.0±7.5	28.4±8.2	28.0±8.6	27.6±10.5	27.0±8.1	31.2±5.8
PADP(mmHg)	7.0±5.71	6.4±5.01	6.4±5.31	6.4±5.11	7.4±5.61	7.8±5.2	7.8±4.2	7.6±4.9	7.2±4.5	7.2±4.7
PAMP(mmHg)	3.2±6.2	2.2±6.8	2.4±7.2	3.2±6.1	3.8±6.4	14.8±6.3	13.2±5.3	14.0±6.6	13.6±5.9	14.6±5.4
PCWP(mmHg)	11.0±5.7	11.6±6.0	11.8±6.5	13.0±4.8	10.2±4.1	11.6±4.5	11.8±4.5	11.4±5.9	11.4±6.2	11.4±4.4
RVSP(mmHg)	30.6±3.4	28.4±2.7	29.0±3.5	27.0±3.9	25.6±4.3	23.8±6.1	18.8±4.7*	15.2±3.4**	13.4±2.8**	11.6±2.4***
RVDP(mmHg)	7.4±1.8	7.0±1.2	6.4±0.9	5.2±0.4	3.0±1.6	2.6±1.3***	1.4±1.1***	0.0±1.2***	-1.2±1.3***	-3.4±0.9***
RVMP(mmHg)	14.4±1.8	13.4±1.3	13.0±1.9	11.8±0.8	9.4±2.1	9.2±2.7	6.6±1.9***	4.8±1.3***	3.6±1.5***	1.8±0.8***
SO ₂ (%)	98±1	100±1	99±1	99±1	99±1	98±1	99±1	99±1	99±1	99±1
Pump flow(L/min)	0	0.6±0.1	1.0±0.3	1.3±0.3	1.7±0.3	2.1±0.3	2.5±0.3	2.8±0.3	3.2±0.3	3.5±0.3
CI(L/min/m ²)	2.9±0.3	2.9±0.4	2.9±0.2	2.9±0.3	2.9±0.3	2.8±0.2	2.9±0.2	2.9±0.2	2.8±0.2	2.7±0.2
RVEDD(mm)	10.9±4.0	11.9±4.4	11.8±3.7	11.1±3.5	11.1±3.8	9.8±3.7	9.8±3.5	8.6±3.0	7.4±2.4	10.9±4.0
RVESD(mm)	6.1±3.1	7.6±4.1	7.5±2.6	6.5±1.7	7.3±2.8	7.1±2.9	7.4±3.3	5.9±2.3	5.7±2.5	6.1±3.1
RVEF(%)	55.2±3.8	54.6±3.8	53.6±4.6	50.0±4.9	48.4±5.5	44.4±3.8*	41.6±2.9**	39.6±3.3**	35.8±3.1***	31.0±6.0***

HR, heart rate; SABP, systolic arterial blood pressure; DABP, diastolic arterial blood pressure; MABP, mean arterial blood pressure; CVP, central venous pressure; PASP, pulmonary arterial systolic pressure; PADP, pulmonary arterial diastolic pressure; PAMP, pulmonary arterial mean pressure; PCWP, pulmonary capillary wedge pressure; RVSP, right ventricular systolic pressure; RVDP, right ventricular diastolic pressure; RVMP, right ventricular mean pressure; SO₂, arterial oxygen saturation; CI, cardiac index; RVEDD, right ventricular end-diastolic dimension; RVESD, right ventricular end-systolic dimension; RVEF, right ventricular ejection fraction.

* $P < 0.05$ vs offpump,

** $P < 0.05$ vs 2000RPM,

$P < 0.05$ vs 2500RPM.