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Extracorporeal Respiratory Support with a Miniature Integrated Pediatric Pump-Lung device (PediPL) in an Acute Ovine Respiratory Failure Model

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Abstract

Purpose—Respiratory failure is one of the major causes of mortality and morbidity all over the world. Therapeutic options to treat respiratory failure remain limited. The objective of this study was to evaluate the *gas transfer* performance of a new newly developed miniature portable integrated *pediatric pump-lung device* (PediPL) with small membrane surface for respiratory support in an acute ovine respiratory failure model.

Methods—The respiratory failure was created in six adult sheep using intravenous anesthesia and reduced mechanical ventilation at 2 breaths/min. The PediPL device was surgically implanted and evaluated for respiratory support in a veno-veno configuration between the right atrium and pulmonary artery. The hemodynamics and respiratory status of the animals during support with the device gas transfer performance of the PediPL were studied for four hours.

Results—The animals exhibited respiratory failure after 30 minutes after mechanical ventilation was reduced to 2 breaths/min, indicated by low oxygen partial pressure, low oxygen saturation and elevated carbon dioxide in arterial blood. The failure was reversed by establishing respiratory support with the PediPL after 30 minutes. The rates of O₂ transfer and CO₂ removal of the PediPL were 86.8 ml/min and 139.1 ml/min, respectively.

Conclusions—The results demonstrated that the PediPL (miniature integrated pump-oxygenator) has the potential to provide respiratory support as a novel treatment of both hypoxia and hypercarbia. The compact size of the PediPL could allow portability and potentially be used in many emergency settings to rescue patients suffering acute lung injury.

Keywords

Respiratory failure; artificial lung; integrated pump-oxygenator; animal model

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Introduction

Respiratory failure is one of the major causes of mortality and morbidity all over the world [1]. It is estimated that the incidence of acute lung injury is nearly 320,000 cases per year in the United States with an in-hospital mortality rate of 25 to 55% [2, 3]. In addition to acute lung injury, chronic obstructive pulmonary disease (COPD) is also a major cause of disability, and it's the third leading cause of death in the United States [4]. Mortality with current therapy for severe COPD is over 26% in 1 year after diagnosis [5]. There is a significant opportunity and the need to improve current management and treatment of respiratory failure. While oxygenation failure secondary to diseases such as acute respiratory distress syndrome (ARDS) is devastating, the majority of deaths from respiratory failure are secondary to CO₂ retention and respiratory acidosis in lung diseases such as COPD.

The standard respiratory therapies for patients experiencing acute exacerbation of COPD and ARDS include supplemental oxygen and mechanical ventilation. Although the current noninvasive ventilatory strategies for respiratory failure, *such as intermittent positive pressure ventilation*, have been demonstrated to be effective and improved survival, invasive mechanical ventilation is still required for a significant portion of patients [6]. The increased barotrauma with ventilation can contribute to alveolar inflammation and impede recovery. As an alternative, extracorporeal membrane oxygenation (ECMO) has infrequently been used to support patients suffering life-threatening respiratory failure either in emergency medical conditions or after all other treatment options have been exhausted. ECMO recently has received renewed interest as an adjunct or alternative to invasive mechanical ventilatory support for patients suffering from respiratory failure [7]. However, conventional ECMO is a bulky system with complicated circuit, with which patient mobility is reduced and complications increase. High complication rates and limited duration of use are significant disadvantages of the traditional ECMO therapy [8, 9].

In the recent years ECMO entered a new era of rapid evolution as the progress in understanding of therapeutic principle and complications has been made and newer equipment and components, including console, pump, oxygenator and cannulae, are emerging. The risks associated with extracorporeal life support have been gradually reduced. The option for early ECMO use in acute lung failure, long-term ECMO support (>14 days) and ambulatory ECMO support are being explored in light of the recent progress [10-12]. The portable integrated *pediatric pump-lung (PediPL)* is a miniaturized integrated pediatric pump-oxygenator designed for respiratory or cardiopulmonary support for patients weighing 5-20 kg to allow mobility and extended use for 30 days [13]. The PediPL device was designed *to* operate at a low flow range (<2.5L/min) with a small surface area of the gas exchange membranes (0.3 m²). The PediPL has been demonstrated to be capable of providing cardiopulmonary support with long-term reliability and good biocompatibility over the 30 day duration [14]. The objective of this study was to evaluate the *gas exchange* performance of the PediPL for respiratory support in an acute respiratory failure ovine model.

Methods

Device Description

The PediPL is an extracorporeally placed respiratory/cardiopulmonary support device and a single-use integrated pump oxygenator mounted on a reusable motor drive system (Figure 1). The pumping function of the PediPL was designed based on the magnetically levitated bearingless impeller/motor technology which was previously implemented in the Levitronix CentriMag® blood pump, a continuous-flow, centrifugal-type rotary blood pump. The magnetic levitation motor and control system used in the PediPL are the same as used for Levitronix CentriMag® blood pump, but the flow path of the PediPL was completely redesigned [13]. Blood from the failing heart and lungs of a patient can be directed to the inlet of the PediPL via an inlet cannula. Blood exits through the outlet of the PediPL and ultimately returns to the patient's circulation through an outlet cannula. The PediPL system is comprised of the single-use PediPL device, a motor drive, a primary drive console, and a set of cannulae [13, 14]. The *expected mechanical and biological capabilities* for the PediPL include:

- Durable – The intended duration of use up to 30 days without exchange
- Hemocompatible – Free of thrombus at explant
- Minimal hemolysis – less than 15 mg/dL under normal operation
- Competitive hemodynamic capability: 2.5 LPM with 150 mmHg pressure head
- Competitive gas exchange:
 - At least 95% O₂ saturation at 2.5 LPM
 - At least 100 ml/min removal of CO₂ at 2.5 LPM
 - Small, membrane surface area < 0.3 m² and priming volume < 100 ml
- Transportable

Surgery

Six Dorset hybrid sheep (45~65 kg) bred for laboratory research (Thomas Morris, Reisterstown, MD) were used in this study. All surgical procedures and animal care were carried out according to the protocol approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Maryland School of Medicine. Additionally, all animals received humane care in accordance with the Guide for Care and Use of Laboratory Animals (NIH publication 86-23, revised 1996) throughout the experiment.

The study animal was pre-anesthetized with atropine (0.02 mg/kg, IM) and glycopyrrolate (0.01 mg/kg, IM), followed by Ketamine (10-15 mg/kg, IM) for sedation. Anesthesia was induced with propofol (2-4 mg/kg, IV) and maintained with 1-4% isoflurane after endotracheal intubation. Sheep were mechanically ventilated with a tidal volume of 10-20mL/kg at a rate of 12-20 breaths per minute with 3-5 mmHg positive end-expiratory pressure (PEEP). A left lateral thoracotomy was performed through the 4th intercostal space. The 4th rib was removed and the pericardium opened to expose the main pulmonary artery

and the right atrial appendage. A 20-mm transonic flow probe was placed around the pulmonary artery for monitoring cardiac output (T401; Transonic Systems). Systemic anticoagulation was achieved by intravenous heparin injection to achieve an activated clotting time (ACT) of 200 seconds (100 Units/kg). A custom-made 10 mm arterial outflow cannula with a fused graft tip was anastomosed to the main pulmonary artery of the sheep in an end-to-side fashion with 5/0 Prolene running suture. Two 3/0 Prolene purse-strings pledgeted sutures were placed in the right atrial appendage. A malleable single stage venous inflow cannula (Medtronic DLP® 32 CB67316) was inserted into the right atria about 3.5 cm deep through the right atrial appendage and secured with the purse string sutures (Figure 1C). The two cannulae were de-aired, connected to the PediPL device. The bypass flow path from the right atrium to pulmonary artery was established to evaluate the PediPL device for respiratory support (Figure 1D).

An arterial line was established to monitor the arterial blood pressure (ABP) by percutaneous puncture of the femoral artery and followed with placement of a 5 Fr catheter. A Swan-Ganz catheter was placed in the jugular vein through an 8Fr catheter for monitoring pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) during the surgery. Flow probes (Transonic System, Ithaca, NY) were placed around the main pulmonary artery and the outflow graft or tubing to measure the cardiac output (CO) and the PediPL device-generated flow.

Respiratory failure model

The acute respiratory failure animal model was created using intravenous anesthesia and reduced mechanical ventilation at 2 breath/min. Continuous intravenous ketamine and propofol were administered to sedate sheep suppressing spontaneous respiration. The anesthetic depth was evaluated by jaw laxity, movement, limb muscle tone, tachycardia and/or hypertension. Positive end-expiratory pressure was maintained at 5–10 mmHg to mimic continuous positive airway pressure. Tidal volume was set at 450 ml and respiratory rate at 2 breaths/min to minimize the gas exchange through mechanical ventilation. FIO₂ was set at 0.4. About 30 min after the reduced mechanical ventilation, the animals exhibited the symptom of acute respiratory failure with low oxygen saturation and partial pressure in arterial blood. Once the respiratory failure was induced, the respiratory support with the PediPL device was initiated and continued for 4 hours while the animals remained to be ventilated at 2 breaths/min. Hemodynamic data was recorded every 15 minutes during the study. The Saturation of Peripheral Oxygen (SPO₂) was monitored using a pulse oximeter attached at the edge of the mouth. Arterial and venous blood samples were collected for blood gas analysis at baseline, the time of respiratory failure, 30 minutes after device respiratory support, and every 1 hour thereafter. End-tidal CO₂ was recorded with Microstream CO₂ Extension monitor (Oridion Medical, Ltd).

Device performance evaluation for respiratory support

Blood gas analysis was performed for blood samples collected from the device inlet and outlet 30 minutes and every hour after respiratory support was initiated. The following equations were used to calculate the gas transfer performance of the PediPL:

$$mO_2 = (13.4 \times Hgb \times [SO_{2out} - SO_{2in}] + k \times 10^3 [PO_{2out} - PO_{2in}]) \times Qb$$

$$mCO_2 = 22.3 \times (TCO_{2in} - TCO_{2out}) \times Qb$$

where mO_2 = oxygen transfer rate (mL/min); mCO_2 = carbon dioxide transfer rate (mL/min); Hgb = hemoglobin concentration (g/dL); k = solubility of oxygen in blood (mL/Ml.mmHg); Qb = blood flow rate (L/min); SO_{2in} = oxygen saturation of blood at inlet; SO_{2out} = oxygen saturation of blood at outlet; PO_{2in} = oxygen partial pressure of blood at inlet (mmHg); PO_{2out} = oxygen partial pressure of blood at outlet (mmHg); TCO_{2in} = total blood carbon dioxide content of blood at inlet (mmol/L); and TCO_{2out} = total blood carbon dioxide content of blood at outlet (mmol/L).

Results

Acute Respiratory Failure

After the animals were anesthetized and mechanically ventilated with pure oxygen at a rate of 12 breaths/min. The animals had a normal respiratory status as indicated by the normal blood gases and pH value. Oxygen partial pressure (PO_2), oxygen saturation (SO_2) and carbon dioxide partial pressure (PCO_2) in both the venous and arterial blood samples were in the normal range (Table 1). The rate of mechanical ventilation was subsequently reduced to 2 breaths/min. The animals experienced acute respiratory failure and became hypercapnia after 30 minutes on reduced mechanical ventilation. The PO_2 and SO_2 in the arterial blood dropped significantly from 254.3 mmHg and 99.2% to 72.7 mmHg and 81.2%, respectively ($p < 0.05$). The PCO_2 elevated significantly from 36.1 ± 5.1 mmHg to 92.1 ± 24.1 mmHg ($p < 0.05$) (Table 1).

Respiratory Support with PediPL

Once acute respiratory failure was established in the animals, the early implanted PediPL device was turned on. The operating speed was adjusted to produce an average bypass flow rate from the right atrium to pulmonary artery between 2.0 and 3.0 liters/min with an average rate of 2.6 ± 0.5 L/min. Pure oxygen was used as the sweep gas through the PediPL. The ratio of the sweep gas flow to the PediPL flow was set at 1:1. The Animal respiratory parameters at baseline, before and during PediPL support are listed in Table 1.

Systemic O_2 consumption and supplementation by PediPL

At baseline, the arterial blood PO_2 (PaO_2) was 254.3 ± 110.8 mmHg and arterial O_2 saturation (SaO_2) was $99.2 \pm 0.5\%$ under full mechanical ventilation with pure oxygen. They dropped to 72.7 ± 16.4 mmHg and $81.2 \pm 11.0\%$ under respiratory failure, respectively. During the PediPL support, the average PaO_2 and SaO_2 increased to 113.8 ± 20.6 mmHg and $97.0 \pm 1.9\%$, respectively. To see the tendency of efficiency of oxygen supply, the arterial and venous PO_2 , SaO_2 at different time points during PediPL support was shown in Figures 2 (A, B). After 30 minutes of the PediPL support, the PO_2 increased to 100 mmHg and remained above this level with the PediPL device support thereafter (Figure 2). Correspondingly, the SO_2 of the arterial blood increased to $97.2 \pm 1.6\%$ (Figure 3). The venous blood SaO_2 and PO_2 had no significant changes during the study. The *average*

oxygen transfer rate was 85.1 ± 13.9 ml/min during support. The oxygen transfer rate was higher during the first half hour of support (initial state) than it during the rest hours (steady state). (108.8 ± 57.6 ml/min vs. 81.3 ± 28.0 ml/min, $P < 0.05$).

Systemic CO₂ distension /removal

The average PCO₂ was 39.4 ± 4.2 mmHg in venous blood and 36.1 ± 5.1 mmHg in arterial blood at baseline. Under respiratory failure, the venous PCO₂ increased to 92.1 ± 24.1 mmHg and arterial PCO₂ increased to 87.6 ± 18.4 mmHg. *During the PediPL support, the average PCO₂ in arterial blood and in venous blood were 63.8 ± 11.5 mmHg and 56.3 ± 8.6 mmHg, respectively.* The arterial and venous PCO₂ at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours of PediPL support was shown in Figure 3. After initiation of the respiratory support with the PediPL, the device removed CO₂ quickly. In 30 minutes, the venous PCO₂ decreased to 66.2 ± 11.9 mmHg and the arterial PCO₂ to 58.9 ± 14.6 mmHg. Gradually the venous PCO₂ decreased to 59.5 ± 6.8 mmHg and the arterial PCO₂ to 52.1 ± 4.0 mmHg in 4 hours (Figure 4). EtCO₂ increased to over 99% under the respiratory failure and decreased to a normal level ($\sim 55\%$) 4 hours after initialing of the respiratory support with the PediPL, indicating decreased CO₂ retention (Figure 5). The average CO₂ removal rate was 133.6 ± 45.6 ml/min during support. During the first half hour of support, the CO₂ removal rate (initial state) was significantly higher than during the rest hours (steady state) (214.4 ± 69.6 ml/min vs. 113.4 ± 79.4 ml/min, $P < 0.05$).

The pH value and lactate

The pH value at baseline was 7.53 ± 0.03 in the venous blood and 7.55 ± 0.06 in the arterial blood. Under respiratory failure, the pH value decreased to 7.15 ± 0.03 in the venous blood and to 7.13 ± 0.06 in the arterial blood. With the PediPL support, the pH increased gradually to 7.36 ± 0.03 in the venous blood and to 7.39 ± 0.03 in the arterial blood. Lactate increased under respiratory failure. But the increase was not statistically significant. There was no significant change of Lactate during the PediPL support.

Hemodynamic effect of the respiratory support with PediPL

The heart rate of the animals increased from 92.5 ± 10.4 beats/min at the baseline to 120 ± 17.3 beats/min under respiratory failure (Table 2). After being supported with the PediPL, the heart rate decreased to the baseline level within 1 hour. Although the systemic blood pressures (systolic ABP, diastolic ABP, and mean ABP) decreased under the respiratory failure condition, the differences were not statistically significant. The blood pressures remained stable throughout the study. Pulmonary artery pressure increased from 13.7 ± 2.4 mmHg to 21.3 ± 5.3 mmHg under respiratory failure and remained elevated during support due to the hemodynamic support of the device to the pulmonary artery. The CVP, PCWP, and CO had no statistical changes during the study.

Right ventricular unloading effect of PediPL Support

The PediPL was connected between the RA and the pulmonary artery. The blood was partially bypassed from the right heart. Therefore, the right ventricle (RV) could be unloaded with the PediPL support. Figure 6 shows the reduction of the RV area on a short-axis view

plane when the bypass flow rate was increased from 0.5 L/min to 3.5 L/min. The diastolic RV area is $11.9 \pm 3.2 \text{ cm}^2$ and the systolic RV area is $8.1 \pm 3.0 \text{ cm}^2$ at baseline. The average cardiac output at baseline was $7.8 \pm 2.1 \text{ L/min}$. During the PediPL support, with the increase of the operating speed the RV areas decreased with the increase of the flow rate. The cardiac output didn't change significantly during the support. When the bypass flow was 3 L/min (~40% of the cardiac output), the diastolic RV area was reduced to $7.5 \pm 3.2 \text{ cm}^2$ and the systolic RV area to $5.3 \pm 2.3 \text{ cm}^2$.

Discussion

While oxygenation failure secondary to diseases such as acute respiratory distress syndrome (ARDS) is devastating, many deaths are secondary to CO_2 retention and respiratory acidosis in chronic obstructive pulmonary disease [15]. Current management of acute respiratory failure includes mechanical ventilation and ECMO combined with medical management. Although current ventilatory strategies for acute respiratory failure have reduced mortality, in severe cases, the increased barotrauma of ventilation can contribute to alveolar inflammation and impede recovery. We have been developing a miniature integrated pump oxygenator for pediatric patients, the pediatric pump-lung (PediPL), for pediatric cardiac or cardiopulmonary support. The PediPL device was designed to operate at a low flow range ($<2.5 \text{ L/min}$) with a very small surface area of the gas exchange membranes. This study demonstrated the ability of the PediPL device to remove CO_2 from blood, normalize pH, transfer O_2 to blood, improve hemodynamics as well as unload the RV in an animal model of acute respiratory failure.

Expanding Gattinoni's original concept of using CO_2 removal to reduce barotrauma and ventilatory requirements, the PediPL device may represent a significant improvement beyond current CO_2 removal strategies [16]. In an effort to avoid use of a full ECMO circuit, interventional lung assist (iLA) techniques have used temporary percutaneous cannulation and pumpless hollow fiber membrane devices such as the NovaLung to remove CO_2 in decompensating COPD patients. This approach has been successful in resolving hypercarbic crises and improving survival in patients bridged to transplantation [17]. In addition, iLA is capable of allowing lung protective ventilation, sequential lung deflation in the setting of COPD exacerbation and decreasing systemic inflammation [18-19]. Given this precedent and the results of this current study, it is reasonable to predict that the PediPL device might similarly allow lung rest and recovery through CO_2 removal. Based on the unique circumferential-radial, uniform outside-in flow path and the magnetically bearingless motor technology, the PediPL was developed with a membrane surface area of 0.3 m^2 . Even for our adult pump-lung device, membrane surface area is only 0.80 m^2 , remarkably smaller than the membrane surface area of iLA (1.3 m^2) with a prime volume of 175 ml. We were able to achieve a rated flow of 2.5 L/min with a prime volume of 110 ml for the PediPL. The main limitation of pumpless respiratory support is the femoral A-V cannulation approach has to be employed. The femoral AV cannulation also lack the ability to provide oxygenation. Relying on the heart to pump blood through the circuit limits iLA to those with a mean arterial pressure over 60 mmHg. The femoral A-V fistula created with iLA cannulation adds a risk of peripheral limb ischemia and hemodynamic instability when iLA is initiated. In this

study the PediPL was able to remove CO₂, improve pH and oxygenation without risk of peripheral embolism or hemodynamic instability.

Similarly to ECMO or iLA, the possible applications of the compact PediPL, include acute resuscitation and acute respiratory failure. In validating its ability not only to improve oxygenation but also to remove CO₂ in this study, the PediPL device significantly broadens its possible target population to include those with ventilatory failure and CO₂ retention. Additionally, the V-A cannulation approach can be employed with the PediPL and does not exclude patients with pulmonary arterial hypertension as does the V-V mode. As expected, the PediPL support was able to unload the right heart. The device placement in parallel to the right heart serves to unload volume reaching the right heart and will likely prevent or recover the right heart failure that can often complicate mechanical circulatory support. This is supported by evidence of increased survival and bridge to transplantation seen in V-A ECMO and PA-LA iLA patients with PA hypertension and right heart failure [20]. Building on the current surgical support option, an alternative strategy is to establish the V-V support by using the bicaval dual lumen cannula, such as the Wang-Zwische patented cannula [21, 22]. With this cannula, the PediPL device can be used by the completely percutaneous placement and avoid the open chest surgery, especially under emergency circumstance.

There are several limitations in the present study. The nature of our disease model, created through hypoventilation, incorporated no direct lung injury or inflammation that could be resuscitated with the removal of CO₂. The duration of the experiment was relatively short and also created a need for longer measurement of CO₂ removal.

Conclusion

An acute respiratory failure was reproduced in a clinically relevant large animal model. The respiratory failure was reversed by establishing the device based respiratory support with the PediPL device. The study demonstrated the potential of the PediPL support as a novel and improved treatment of both hypoxia and hypercarbia for respiratory failure patients. While the study for demonstrating the long-term oxygenation capability of the PediPL device is ongoing, this study highlights the potential of the PediPL with very small membrane surface for CO₂ removal application. In possibly providing benefit to COPD patients and representing an improved bridge to transplantation, this compact device may offer support to patients suffering from respiratory failure.

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Figure 1.
The PediPL for respiratory support in the sheep. A – the flow path of the PediPL device (arrows); B – The disposable PediPL device; C - the cannulation site for the PediPL device; and D - the complete respiratory support system. The inserted picture showed the color difference in blood between the inflow and outflow cannulae of the PediPL device placed on the motor drive.

Figure 2.
Arterial and venous PO₂ before and during support by the PediPL.

Figure 3.
Arterial and venous SaO₂ before and during support by the PediPL.

Figure 4.
Arterial and venous P_{CO2} before and during support by the PediPL.

Figure 5.
CO₂ concentration in the endotracheal tube before and during support by the PediPL.

Figure 6.
Right ventricular unloading effect evaluated by echocardiography.

Table 1

Animal respiratory status

	Baseline	Respiratory Failure	During PediPL Support
PvO ₂ (mmHg)	46.8±6.3	60.9±6.5	53.9±7.3
PaO ₂ (mmHg)	254.3±110.8	72.7±16.4 *	113.8±20.6 *
PvCO ₂ (mmHg)	39.4±4.2	87.6±18.4 *	63.8±11.5 *
PaCO ₂ (mmHg)	36.1±5.1	92.1±24.1 *	56.3±8.6 *
SvO ₂ (%)	73.7± 9.5	69.2±6.4	72.3±11.6
SaO ₂ (%)	99.2 ±0.5	81.2±11.0 *	97.0 ±1.9
<i>pH_v</i>	<i>7.53±0.03</i>	<i>7.15±0.03 *</i>	<i>7.36±0.03</i>
<i>pH_a</i>	<i>7.55±0.06</i>	<i>7.13±0.06 *</i>	<i>7.39±0.03</i>

Parameters (mean ± SD), PvO₂ - O₂ partial pressure in venous blood; PvCO₂ - CO₂ partial in venous blood; SvO₂ - O₂ saturation in venous blood; PaO₂ - O₂ partial pressure in arterial blood ; PaCO₂ - CO₂ partial in arterial blood; SaO₂ - O₂ saturation in arterial blood; *pH_v*- *pH value in venous blood*; *pH_a* - *pH value in arterial blood*.

* P<0.05 compared to baseline

Table 2

Hemodynamic effect of the artificial lung device in respiratory failure conditions

	Baseline	RF	30 mins	1 hour	2 hour	3 hour	4 hour
HR(beat/min)	92.5±10.4	120±17.3 [*]	102±11.5	94.8±9.0	87.7±9.3	95±10.6	93.7±14.2
sABP (mmHg)	90.8±8.6	76.7±14.4	84±13	77.8±10.6	76.8±7.4	82±16.1	83±13.1
dABP(mmHg)	58.2±11.0	48±11.0	53.6±11.3	50±14.6	45.5±6.9	56.3±13.5	45.6±7.6
mABP(mmHg)	71.6±9.4	61.2±12.2	66.3±9.9	61.6±9.9	59±4.9	67.6±11.5	61.6±7.6
CVP(mmHg)	5.2±2.8	7.7±2.4	5.2±2.6	5.8±2.9	5.8±2.8	6±2.6	5.7±3.1
PCWP(mmHg)	8.2±3.1	10.2±3.5	9.5±2.9	11±2.5	9.8±2.9	10±2	10.7±2.1
PAP(mmHg)	13.7±2.4	21.3±5.3 [*]	22.5±5.6 [*]	23±4.8 [*]	23±3.7 [*]	22.3±4.2 [*]	21.3±3.2 [*]
CO(liter/min)	7.8±2.1	9.4±0.8	8.8±1.0	6.5±1.5	6.2±1.3	6.6±1.1	6.0±1.0

RF, respiratory failure; HR, heart rate; sABP, systolic arterial blood pressure; dABP, diastolic arterial blood pressure; mABP, mean arterial blood pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; CO, cardiac output.

^{*} P<0.05 compared to baseline.