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# Novel Goal-Directed Hemodynamic Optimization Therapy Based on Major Vasopressor during Corrective Cardiac Surgery in Patients with Severe Pulmonary Arterial Hypertension: A Pilot Study

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## ABSTRACT

**Introduction:** Pulmonary arterial hypertension (PAH) is a common and fatal complication of congenital heart disease (CHD). PAH-CHD increases the risk for postoperative complications. Recent evidence suggests that perioperative goal-directed hemodynamic optimization therapy (GDHOT) significantly improves outcomes in surgery patients. Standard GDHOT is based on major solution volume, vasodilators and inotropic therapy, while novel GDHOT is based on major vasopressor and inotropic therapy. Therefore, we tested whether standard or novel GDHOT improves surgical outcomes in PAH-CHD patients.

**Methods:** Forty PAH-CHD patients with a ventricular septal defect (VSD) and mean pulmonary arterial pressure (mPAP) >50 mmHg, who were scheduled for corrective surgery, were randomly assigned to 2 groups: SG (study group, n = 20) and CG (control group, n = 20). SG patients received perioperative hemodynamic therapy guided by novel GDHOT, while CG patients received standard GDHOT. Outcome data were recorded up to 28 days postoperatively. Ventilator time, length of ICU stay, and mortality were the primary endpoints.

**Results:** There were no significant differences in preoperative data, surgical procedure, and hospital mortality rates between the 2 groups. Time of mechanical ventilation and length of ICU stay were significantly shorter in SG patients compared to CG patients ($P < .05$, n = 20). Patients in SG showed a significantly increased systemic vascular resistance index and decreased cardiac index, but no change in pulmonary vascular resistance index at 12 and 24 hours after surgery compared to the controls ($P < .05$). Patients in SG had significantly decreased PAP, pulmonary arterial pressure/systemic arterial pressure (Pp/Ps), and RVSWI (right ventricular stroke work index) at 12 and 24 hours after surgery ($P < .05$, respectively). Patients in SG also showed significantly decreased central venous pressure at 4, 12, and 24 hours after surgery compared to those treated with standard protocol ($P < .05$).

**Conclusion:** Our study provides clinical evidence that perioperative goal-directed hemodynamic optimization therapy based on major vasopressor is associated with reduced duration of postoperative respiratory support, and length of ICU stay in PAH-CHD patients undergoing elective surgery. These outcomes, then, may be linked to improved hemodynamics and preservation of right ventricular dynamic function.

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a common and fatal complication of congenital heart disease (CHD). Not surprisingly, then, cardiac surgery patients who present with pre-existing PAH are at an increased risk for developing postoperative complications. Indeed, despite advances in cardiac surgery and expanding options in PAH-specific therapy, the mortality rate for PAH-CHD cardiac surgery patients remains unacceptably high at 22.2-54.5% [Beghetti 2010; Haworth 2009]. Moreover, optimal strategies for managing these patients are still debated [Minai 2013; Thunberg 2013].

Goal-directed hemodynamic optimization therapy (GDHOT) stabilizes cardiac output and hemodynamic parameters by optimizing intravenous fluid and inotropic/vasopressor therapy [Salzwedel 2013]. This approach involves adjusting cardiac contractility and cardiac preload and afterload to balance oxygen delivery with oxygen demand. GDHOT substantially improves clinical outcomes in non-cardiac surgery patients [Salzwedel 2013], and reduces mortality among patients with severe sepsis or septic shock [Rivers 2001]. Standard GDHOT is based on major solution volume, vasodilators and inotropic therapy, while novel GDHOT is based on major vasopressor and inotropic therapy. However, the effect of GDHOT on postoperative outcome in PAH-CHD patients has not yet been studied. Thus, we conducted a randomized controlled trial to test whether standard or

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novel GDHOT benefits patients with severe PAH who are undergoing corrective cardiac surgery.

## PATIENTS AND METHODS

With the approval of the Institutional Research Ethics Committee of Beijing Anzhen Hospital, the study was performed from 2009 to 2015 as a prospective, single-center, randomized trial to investigate the benefit of standard or novel GDHOT for PAH-CHD patients undergoing corrective cardiac surgery.

After written informed consent was obtained and preoperative right-heart catheterization was performed, 40 patients, 8-18 years old, with ventricular septal defect and mean pulmonary arterial pressure (mPAP) >50 mmHg, were enrolled and randomized to receive novel GDHOT based on major vasopressor (as study group [SG]) or standard care based on major solution volume (as control group [CG]). Fifteen subjects also had patent ductus arteriosus. All patients were no syncope and physical activity was not limited.

All patients received pethidine IM (1 mg/kg) for pre-anesthesia sedation. All operations were performed under general anesthesia induced by fentanyl (10 μg/kg) and midazolam (0.1 mg/kg) IV. Anesthesia was maintained with fentanyl (5 μg/kg) and sevoflurane (0.5-2%). Pancuronium (0.1-0.15 mg/kg) was administered for muscle relaxation.

A Swan-Ganz catheter was placed in each patient to monitor mPAP and cardiac index after anesthesia induction. Intraoperative transesophageal echocardiography (TEE) was also used in all patients to identify any residual leaks.

Corrective surgery was performed in all patients via a midline sternotomy using cardiopulmonary bypass (CPB) at a non-pulsatile perfusion flow rate of body surface area × 2.4 L/min/m2, and moderate hypothermia (28-32°C) with alpha-stat cooling and conventional ultrafiltration during rewarming. After aortic cross-clamping, the heart was arrested using intermittent cold-blood cardioplegia. Upon weaning from CPB, patients received standard GDHOT (n = 20) or novel GDHOT (n = 20), as follows.

After removing the aorta cross-clamp, the hemodynamic status in the standard GDHOT group (CG) was managed according to institutional protocol. Upon weaning from CPB, continuous infusion of glycerol trinitrate 0.3-0.5 μg/kg/min and prostaglandin E1 5-15 ng/kg/min was initiated in all CG patients. Hemodynamics were stabilized by fluid resuscitation and by continuous infusion of dopamine 3-8 μg/kg/min and/or dobutamine 3-8 μg/kg/min and/or adrenaline 0.05-0.15 μg/kg/min to maintain a cardiac index ≥2.5 L/min/$m^2$, mean arterial pressure (MAP) of 50-80 mmHg, heart rate of 100-140 beats/min, urine output of 1-2 mL/kg/h, continuous mixed venous oximetry ($SvO_2$) >70%, and central venous pressure (CVP) of 6-10 mmHg. If the value of CVP was <6 mmHg, fluids were given until the preset target was reached. If the cardiac index was <2.5 L/min/$m^2$, and/or MAP was <50 mmHg, the inotropic agents noted above were given in a stepwise additive fashion, at the discretion of the attending anesthesiologist, until the preset targets for MAP and cardiac index were reached.

In the novel GDHOT group (SG), continuous infusion of glycerol trinitrate and/or prostaglandin E1 was not started upon weaning from CPB. The preset range for hemodynamic parameters was similar: cardiac index 2.5-3 L/min/$m^2$, MAP 50-80 mmHg, heart rate 100-140 beats/min, urine output 1-2 mL/kg/h, $SvO^2$ >70%, and CVP 6-8 mmHg. As in CG patients, hemodynamic status was maintained by continuous infusion of dopamine 3-8 μg/kg/min and/or dobutamine 3-8 μg/kg/min and/or adrenaline 0.05-0.15 μg/kg/min. If the cardiac index was < 2.5L/min/$m^2$ and/or CVP was <6 mmHg, fluids and inotropic agents were given until the preset target was reached. If the cardiac index was >3 L/min/$m^2$, inotropic agents were limited. If the values of the cardiac index and CVP were in the preset range, and MAP was still <50 mmHg, vasoconstrictors were used to maintain MAP in the preset range. Vasoconstriction was achieved by continuous infusion of noradrenaline 0.05-0.4 μg/kg/min, with or without hypophysin 0.01-0.2 μg/kg/h.

In all patients, packed cell transfusion was used to maintain hematocrit values at or above 30%. Postoperatively, all patients were transferred to the intensive care unit (ICU), and were mechanically ventilated to achieve pulse oximetry ($SpO_2$) >95%, blood pH of 7.35-7.45, and partial pressure of arterial carbon dioxide ($PaCO_2$) of 35-45 mmHg. All patients received midazolam infusion (1-5 μg/kg/min) with small increments of fentanyl and 20 ppm inhaled nitric oxide (NO).

At the end of surgery (T1), and at 4 hours (T2), 12 hours (T3), and 24 hours (T4) after surgery, we recorded hemodynamic parameters, blood lactic acid, mechanical ventilation time, and pulmonary complications. Primary endpoints of this clinical trial were ventilator time, length of ICU stay, and mortality.

### *Statistical Analysis*

The group size (n = 20) was assigned to have sufficient power to detect a difference in ventilator time between the 2 groups of PAH-CHD patients (study group and control group) undergoing corrective surgery for ventricular septal defect. Based on data from the 40 patients studied, the power was 80% for a type I error of 5% (Power Analysis and Sample Size, PASS V11.0, NCSS, LLC; Kaysville, Utah, USA).

Statistical analyses were performed using SPSS version 22 software. The results are presented as mean ± SD. Quantitative variables are presented as mean ± SD or median (interquartile range [IQR]), and categorical variables are presented as frequencies and percentages. All normally distributed continuous variables were compared using 2-tailed Student t test, while the data that were not normally distributed were analyzed by Wilcoxon rank sum test. Discrete data were compared using Pearson chi-square test or Fisher exact test, as appropriate. *P* values < .05 were considered statistically significant.

## RESULTS

Preoperatively, there were no significant differences between the standard GDHOT group and the novel GDHOT group with respect to mPAP with or without oxygen, $SpO_2$, pulmonary vascular resistance index with or without oxygen,

Table 1. Operative Data from Patients Receiving Standard or Novel GDHOT

| | Standard | Novel | *P* |
|---|---|---|---|
| Age, y | 13.8 ± 4.5 | 13.5 ± 4.2 | .881 |
| Weight, kg | 43.0 ± 5.0 | 46.0 ± 11.0 | .542 |
| VSD, mm | 17.8 ± 3.5 | 16.6 ± 4.5 | .714 |
| Hb, g/L | 133.0 ± 11.0 | 129.0 ± 12.0 | .775 |
| mPAP, mmHg | 85.0 ± 12.0 | 83.0 ± 14.0 | .708 |
| mPAP with oxygen, mmHg | 77.0 ± 13.0 | 75.0 ± 18.0 | .730 |
| mABP, mmHg | 85 ± 10 | 87 ± 10 | .828 |
| Pp/Ps | 1.0 ± 0.2 | 1.0 ± 0.1 | .896 |
| PVRI, dynes • sec • $m^2/cm^5$ | 1330 ± 704 | 1408 ± 669 | .726 |
| PVRI with O2 , dynes • sec • $m^2/cm^5$ | 345 ± 156 | 365 ± 154 | .918 |
| SVRI, dynes • sec • $m^2/cm^5$ | 1052 ± 110 | 998 ± 132 | .401 |
| Resting $SPO_2$ ,% | 96 ± 4 | 95 ± 5 | .736 |
| Resting $SPO_2$ with $O_2$,% | 99 ± 1 | 99 ± 1 | .981 |
| Qp/Qs | 1.3 ± 0.4 | 1.4 ± 0.3 | .773 |
| Duration of CPB, min | 69 ± 6 | 72 ± 5 | .415 |
| Duration of aortic cross-clamp, min | 44 ± 8 | 48 ± 5 | .376 |
| Postoperative Intravenous therapy, mL | 990 ± 336 | 745 ± 193 | .195 |
| Volume of urine and drainage, mL | 1158 ± 379 | 1024 ± 337 | .532 |

Data are presented as mean ± SD; n = 20. mABP indicates mean aortic blood pressure; CPB, cardiopulmonary bypass; Hb, hemoglobin; mPAP, mean pulmonary arterial pressure; Pp/Ps, pulmonary arterial pressure/systemic arterial pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, pulmonary blood flow/systemic blood flow; $SPO_2$, oxyhemoglobin saturation; SVRI, systemic vascular resistance index; VSD, ventricular septal defect. Intravenous therapy includes transfusion of allogeneic red blood cells and allogeneic blood plasma within 24 hours after surgery. Drainage is the volume of draining blood within 24 hours after surgery.

systemic vascular resistance index, pulmonary arterial pressure/systemic arterial pressure (Pp/Ps), or pulmonary blood flow/systemic blood flow (QpQs). Further, aortic cross-clamp time and CPB time were not significantly different between the 2 groups (Table 1), and no residual shunt was confirmed by TEE at the end of surgery. Demographic data, ventricular septal defect types, and associated congenital heart lesions are summarized in Table 1.

The hospital mortality rate was 10% in patients treated with the standard protocol; one patient died from right heart failure complicated with more organ failure, and the other died from severe lung infections complicated with more organ failure. However, one of the patients (5%) treated with novel GDHOT died from severe lung infection complicated with more organ failure (Table 2). Further, the time of mechanical ventilation and the duration of ICU stay were much shorter in novel GDHOT-treated patients ($P < .05$, n = 20), as shown in Table 2.

Table 2. Postoperative Outcomes in Patients Treated with Standard or Novel GDHOT

| Endpoints | Standard | Novel | *P* |
|---|---|---|---|
| Ventilator time, h | 115 ± 14 | 68 ± 7 | .001** |
| ICU stay, days | 8 ± 1 | 5 ± 1 | .001** |
| Alveolar consolidation, %* | 20 | 10 | .661 |
| Hospital mortality (%) | 10 | 5 | .687 |

Data are presented as mean ± SD; n = 20.
*Alveolar consolidation >1 quadrant was determined by X-ray at 24 hours after surgery.
**$P < .01$.

Postoperatively, both patient groups had high cardiac output and low resistance at the end of surgery. However, patients treated with novel GDHOT showed a significantly increased systemic vascular resistance index and decreased cardiac index, but no change in pulmonary vascular resistance index at 12 and 24 hours after surgery compared to the controls ($P < .05$, n = 20). Further, patients treated with novel GDHOT had significantly decreased PAP, Pp/Ps, and RVSWI (right ventricular stroke work index) at 12 and 24 hours after surgery ($P < .05$, respectively). Finally, patients treated with novel GDHOT showed significantly decreased central venous pressure at 4, 12, and 24 hours after surgery compared to those treated with standard GDHOT ($P < .05$, n = 20).

## DISCUSSION

Here, we studied the effects of novel GDHOT in patients with severe pulmonary arterial hypertension and congestive heart disease (PAH-CHD) who underwent corrective cardiac surgery. Patients who received novel GDHOT showed improved outcome compared to those who received standard GDHOT, as evidenced by significantly shortened mechanical ventilation time and length of ICU stay.

Severe PAH secondary to CHD is one of the main challenges in pediatric cardiac surgery, especially in cases with a bi-directional shunt, cyanosis, and concurrent organic changes in the pulmonary vessels. Sustained increase in the pulmonary arterial pressure (PAP) may lead to progressive pulmonary vascular remodeling, and eventually result in irreversible changes, including extensive intimal injury, adventitial fibrosis, and smooth muscle cell proliferation [Krishnan 2013; Frank 2015; Galiè 2016], which at last causes right heart failure [Barst 2014]. Preserved right ventricular function is the most important determinant of outcome, particularly in corrective cardiac surgery patients.

Current standard practice emphasizes the continuous use of vasodilators to reduce pulmonary vascular resistance and mPAP postoperatively. However, according to Table 3, there were no effects of pulmonary artery pressure and pulmonary vascular resistance. This practice also dilates systemic vessels,

Table 3. Perioperative Hemodynamics in Patients Treated with Standard or Novel GDHOT

| | Patients | T1 (0 h) | T2 (4 h) | T3 (12 h) | T4 (24 h) |
|---|---|---|---|---|---|
| CI, L/min/$m^2$ | | | | | |
| | CG | 4.5 ± 1.1 | 3.8 ± 1.2 | 4.9 ± 1.2 | 4.8 ± 1.6 |
| | SG | 4.3 ± 0.8 | 3.9 ± 0.8 | 2.6 ± 1.5* | 2.4 ± 0.7** |
| HR, beats/min | | | | | |
| | CG | 127 ± 18 | 132 ± 22 | 119 ± 16 | 121 ± 22 |
| | SG | 124 ± 16 | 129 ± 21 | 125 ± 17 | 128 ± 20 |
| mABP, mmHg | | | | | |
| | CG | 72 ± 16 | 85 ± 17 | 71 ± 9 | 72 ± 9 |
| | SG | 68 ± 12 | 91±11 | 82 ± 12 | 81 ± 11 |
| mPAP, mmHg | CG | 79 ± 7 | 78 ± 7 | 70 ± 3 | 69 ± 4 |
| | SG | 82 ± 6 | 81 ± 6 | 58 ± 5* | 58 ± 5* |
| Pp/Ps | | | | | |
| | CG | 1.1 ± 0.4 | 0.9 ± 0.3 | 1.0 ± 0.3 | 1.0 ± 0.3 |
| | SG | 1.2 ± 0.5 | 0.9 ± 0.4 | 0.7 ± 0.4* | 0.7 ± 0.4* |
| SVRI, dynes • sec • $m^2/cm^5$ | CG | 1226 ± 383 | 1189 ± 1 91 | 1266 ± 209 | 1317 ± 109 |
| | SG | 1178 ± 292 | 1226 ± 281 | 1759 ± 287* | 1959 ± 187** |
| PVRI, dynes • sec • $m^2/cm^5$ | CG | 371 ± 186 | 425 ± 256 | 482 ± 339 | 399 ± 196 |
| | SG | 424 ± 201 | 494 ± 226 | 462 ± 217 | 448 ± 224 |
| CVP, mmHg | CG | 7 ± 1 | 9 ± 3 | 10 ± 2 | 10 ± 3 |
| | SG | 7 ± 1 | 7 ± 2* | 6 ± 2* | 6 ± 3* |
| PAWP | CG | 12.5 ± 3.1 | 12.8 ± 2.7 | 13.2 ± 4.8 | 14.3 ± 3.9* |
| | SG | 12.1 ± 2.7 | 10.1 ± 1.9† | 10.1 ± 2.7† | 10.6 ± 1.9 |
| RVSWI × HR, g • $m/m^2$ | CG | 1478 ±169 | 1743 ± 911 | 1639 ± 161 | 1904 ±189 |
| | SG | 1642 ± 144 | 1832 ± 152 | 905 ± 131* | 813 ± 206** |
| Lactate levels, mmol/L | CG | 4.0 ± 1.6 | 2.1 ± 0.5 | 1.9 ± 0.5 | 1.9 ± 0.5 |
| | SG | 3.2 ± 1.8 | 1.9 ± 0.4 | 1.7 ± 1.9 | 1.7 ± 1.9 |
| $PaO_2/FiO_2$ | | | | | |
| | CG | 343 ± 120 | 364 ± 174 | 308 ± 132 | 363 ± 228 |
| | SG | 329 ± 124 | 340 ± 163 | 300 ± 109 | 364 ± 213 |
| $ERO_2$, % | CG | 0.29 ± 0.03 | 0.26 ± 0.07 | 0.25 ± 0.08 | 0.24 ± 0.09 |
| | SG | 0.29 ± 0.06 | 0.28 ± 0.05 | 0.29 ± 0.05 | 0.26 ± 0.07 |

Data are presented as mean ± SD. CG indicates control group (standard care); CI, cardiac index; $ERO_2$, oxygen extraction ratio; $FiO_2$, fraction of inspired $O_2$; HR, heart rate; mABP, mean aortic blood pressure; mPAP, mean pulmonary arterial pressure; $PaO_2$, partial pressure of $O_2$ in arterial blood; PAWP, pulmonary artery wedge pressure; Pp/Ps, pulmonary arterial pressure/systemic arterial pressure; PVRI, pulmonary vascular resistance index; RVSWI, right ventricular stroke work index; SG, study group (GDHOT); SVRI, systemic vascular resistance index; T1, end of surgery; T2, 4 hours after surgery; T3, 12 hours after surgery; T4, 24 hours after surgery.

*$P$ < .05; **$P$ < .01 vs CG group; †$P$ < .05 versus T1.

resulting in low systemic vascular resistance and a high cardiac output. A high cardiac output may not always be desirable in this subset of patients because it increases pulmonary blood volume and thus increases pulmonary arterial pressure and right ventricular workload, potentially leading to right heart failure after surgery [Strumpher 2011]. Only 3 factors can be responsible for increased mPAP: (1) increased pulmonary vascular resistance; (2) increased cardiac output (fluid overload and hyperdynamic states); and (3) increased left atrial pressure. Indeed, a recent study has shown that low cardiac output decreases right ventricular preload in the immediate postoperative period after corrective cardiac surgery with

CPB [Carrel 2000]. Therefore, in our opinion, perioperative management of PAH should focus on preserving and maximizing right ventricular function early in the postoperative period by using multimodal treatment strategies.

The novel GDHOT used in the current study maintained normal peripheral vascular resistance by using vasoconstrictors rather than vasodilators. This preserves the minimum cardiac output required for oxygen delivery, and thus decreases pulmonary blood volume and right ventricular workload, and the incidence of right cardiac failure after surgery [Mutlu 2004; Udeh 2012]. In our study, patients treated with novel GDHOT showed increased systemic vascular resistance, and decreased cardiac index and right ventricular stroke work in the immediate postoperative period, compared to patients receiving standard care. Yet, in contrast to an earlier report [Currigan 2014], goal-directed use of vasoconstrictors in the novel GDHOT group was not associated with increased pulmonary vascular resistance, but was actually associated with a gradual decrease in mPAP relative to the standard group throughout the postoperative course. Further, these beneficial effects were associated with a decreased right ventricular stroke work index, suggesting that routine administration of pulmonary vasodilators may be unfavorable, while judicious use of vasoconstrictors may even be helpful. The risk for right heart failure due to myocardial cell exhaustion is higher in infants compared to adults [Barst 2011]; therefore, reducing myocardial work may be particularly important in this population.

In the standard GDHOT group, administration of vasodilators caused a decrease in systemic vascular resistance and an increase in the cardiac index, thus requiring more fluid therapy, which in turn resulted in an increased volume of returned blood, and therefore increased pulmonary circulatory congestion. The high volume in the pulmonary circulation could increase pulmonary effusion, leading to pulmonary edema, and in severe cases may even cause a pulmonary hypertensive crisis. With decreasing capacity for pulmonary alveoli to dilate and contain air, the effective ventilation area and the permeation efficiency for gas exchange significantly decreases [Nomura 2013]. Pulmonary effusion is also an important predisposing factor to infection, a potentially serious pulmonary complication, and pulmonary complications can prolong postoperative ventilator support [Pullamsetti 2011].

In contrast, MAP was maintained by vasoconstrictors and limited volume in the novel GDHOT group, rather than by aggressive fluid resuscitation and more inotropic support. This strategy may allow us to control right heart cardiac output to limit the blood volume in pulmonary circulation and even to decrease mPAP. Therefore, novel GDHOT may effectively reduce pulmonary congestion, improve effective ventilation area, improve alveolar ventilation capacity, and reduce the incidence of pulmonary infection and other complications, as we observed in the current study.

A recent study indicated that controlled minimum cardiac output required $SvO_2$ >70% [Huh 2013]. Administration of vasoconstrictors may lead to decreased end-organ perfusion, especially in the splanchnic area. Therefore, to avoid such complications, it is critical to monitor $SvO_2$ and lactic acid levels to ensure adequate global oxygen supply/demand balance. In our study, $SvO_2$ and lactic acid levels were similar between groups. A previous report also showed that decreased blood flow within a certain range does not lead to organ hypoxia [Egi 2007].

Novel GDHOT should be administered early, adequately, and in a patient-specific manner. Based on our findings in this study, we propose that by maintaining minimum cardiac output required for oxygen delivery, reducing right ventricular work, and preserving right cardiac function, novel GDHOT can reduce the length of ventilator care and ICU stay, and may even reduce mortality rates in PAH-CHD surgery patients. Although our study provided evidence that supports the use of novel GDHOT, our study sample was small, and larger studies are needed to assess treatments for severe pulmonary hypertension.

This study had some limitations. Although the anesthesia and postoperative care providers were not aware that we were conducting this study, they could not be blinded to the treatment strategies. Also, inhaled NO was administered to all patients, and may have obscured any harmful effects of vasoconstrictors.

In conclusion, novel GDHOT based on major vasopressor and inotropic therapy may be beneficial in patients with severe PAH who are undergoing corrective surgery for ventricular septal defect. It improves hemodynamics, preserves right ventricular function, and reduces the duration of respiratory support and the length of ICU stay after surgery.

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