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VASOPRESSIN IN VASODILATORY SHOCK FOR BOTH LEFT AND RIGHT HEART ANOMALOUS PEDIATRIC PATIENTS AFTER CARDIAC SURGERY

Zhongyuan Lu,* Xu Wang,* Juxian Yang,* Shoujun Li,† and Jun Yan†

**PICU, Pediatric Cardiac Center, Fuwai Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China; and †Surgery Department, Pediatric Cardiac Center, Fuwai Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China*

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ABSTRACT—Although the use of vasopressin has become commonplace in pediatric patients with vasodilatory shock after cardiac surgery, its efficacy and hemodynamic effects have not been systematically documented. Furthermore, previous studies were mainly limited patients with left heart anomalies. To date, the use of vasopressin in patients with right heart anomalies has not yet been reported. To clarify the hemodynamic effects of vasopressin on pediatric patients with vasodilatory shock after cardiopulmonary bypass, 70 consecutive patients, most of whom with right heart anomalies, were retrospectively analyzed in Fuwai Hospital from October 2013 to September 2015. Vasopressin was administered continuously at a dose of 0.0002 to 0.002 u/kg/min. Hemodynamics, urine output, and catecholamine vasopressor doses were compared before and after vasopressin initiation. Results showed that besides the significant increase in blood pressure at 2 h after vasopressin administration, the systemic vascular resistance index also prominently elevated from 894.3 ± 190.8 dyn/s to 1138.2 ± 161.4 dyn/s per cm^5 per m^2, while the heart rate, right atrial pressure, pulmonary artery pressure had a trend of decline. Subsequently, the fluid requirement, the catecholamine vasopressor requirement both decreased and urine output increased. Lactate concentration showed a later remarkable decline at 12 h since vasopressin administration. All the 70 patients survived to hospital discharge. In conclusion, low dose of vasopressin administration was associated with great and timely hemodynamic improvement for pediatric patients with vasodilatory shock after cardiac surgery without any significant adverse effects.

KEYWORDS—Cardiac surgery, pediatric, right heart anomaly, vasodilatory shock, vasopressin

Vasodilatory shock is a well-known phenomenon which can potentially occur after cardiac surgery with cardiopulmonary bypass (CPB). It is a state of profound low systemic arterial pressure despite normal or high cardiac output and adequate fluid resuscitation characterized by markedly low systemic vascular resistance (SVR). The recent reported incidence ranged from 5% to 25% (1–4). It leads to inadequate tissue perfusion and metabolic acidosis. It is often refractory to traditional vasopressors such as catecholamine, resulting in high morbidity and mortality. The current investigations suggest a beneficial use of vasopressin in adult patients with vasodilatory shock (5–9), but little is known for children who underwent cardiac surgery (10–15). Furthermore, previous studies were mainly limited in left heart anomalous patients, whereas application in right heart anomalous patients has not yet been reported. Besides, the quantified monitoring of systemic vascular resistance index during vasopressin administration was seldom. The purpose of the present study was to systemically evaluate the efficacy and hemodynamic effects of low dose of vasopressin administration for pediatric patients with vasodilatory shock after cardiac surgery.

METHODS

Patients' characteristics and postoperative management

Medical records of a total of 70 consecutive pediatric patients who suffered from vasodilatory shock after cardiac surgery under CPB and treated with vasopressin in Fuwai Hospital from October 2013 to September 2015 were retrospectively analyzed. The study protocol was reviewed and approved by the local institutional ethic committee. Patients' characteristics were shown in Table 1. Sixty-six were cyanotic congenital heart disease, while four were acyanotic. Fifty-nine patients with right heart anomaly, while 11 patients with left heart anomaly. Sixteen patients with single ventricle (SV) underwent total cavopulmonary connection (TCPC) procedure, nine patients with CTGA/PAA/VSD/ASD/post-Glenn procedure underwent one and a half ventricle repair in which Glenn was preserved, the others all underwent double-ventricular repair.

All the 70 children were intubated and supported by mechanical ventilation with BIPAP model when transferred to pediatric intensive care unit (PICU) from operation room. The peak inspiratory pressure was adjusted to reach a tidal volume goal with 8 mL/kg to 10 mL/kg. Multiple vasoactive agents mainly including catecholamine drugs were continuously pumped to maintain a stable hemodynamics for these patients. Hemodynamic parameters were immediately monitored, which was introduced in detail in the following part. Thus, the cardiac function and circulatory blood volume status were obtained. Target-oriented treatment was implemented. Adequate fluid supplement was given if the blood volume was deficient. Dosage of vasoactive agents was adjusted according to hemodynamic response by physician on duty.

Criterion of vasodilatory shock and monitoring

Vasodilatory shock was characterized by significant hypotension, high or normal cardiac outputs with satisfied surgical correction, low SVR and increased requirements for vasopressors. Hypotension can be recognized by blood pressure (BP) monitoring. Cardiac output and satisfied surgical correction were confirmed by echocardiography, while ejection fraction greater than 50% was defined as normal or high cardiac output. Dopamine or dobutamine $\geq$ 10 ug/kg/min and epinephrine $\geq$ 0.1 ug/kg/min were categorized as increased requirements of vasopressors. Any patient with increased vasopressors requirements, normal or high cardiac outputs, satisfied cardiac surgical correction, adequate fluid resuscitation, but still with profound hypotension was identified as vasodilatory shock with low SVR, and then vasopressin were administered. Proper fluid resuscitation was defined as isotonic fluid $\geq$ 30 mL/kg in 2 h. Vasopressin was infused continuously at a dose of 0.0002 u/kg/min to 0.002 u/kg/min under close monitoring, and the initiation time was all within 48 hours after cardiac surgery.

The hemodynamic parameters and other indicators including invasive BP, heart rate (HR), center venous pressure (CVP), fluid requirement, urine output, catecholamine vasopressor doses were monitored and recorded for all the patients. The superior CVP and inferior CVP were measured respectively for the patients with Glenn or TCPC procedure. Left atrial pressure (LAP)

Address reprint requests to Xu Wang, MD, Department of PICU, Pediatric Cardiac Center, Fuwai Hospital, 167 Beilishi Road, Xi Cheng District, Beijing, China 100037. E-mail: fwpicu@163.com

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Table 1. **Patients' preoperative characteristics**

Variable	Value
Male/female (n)	40/30
Age (m)	24.5 (0.3–156.0)
Weight (kg)	13.0 ± 6.5
Hemoglobin	163.3 ± 39.5
Time of CPB (min)	179.9 ± 88.2
Time of ACC (min)	108.6 ± 48.6
Diagnosis (n)	
TOF	20
PAA/VSD	6
SV	16
CTGA/PAA/VSD/ASD/post-Glenn procedure	9
TGA/VSD/ASD/PS	6
DORV/TECD	4
PAA/DORV	2
TAPVC/cor triatriatum	1
Ebstein malformation	1
AOPA	1
TGA/IVS	1
Taussig-bing syndrome	1
VSD/ASD	2

CPB indicates cardiopulmonary bypass; ACC, aortic cross clamping; TOF, tetralogy of Fallot; PAA, pulmonary artery atresia; VSD, ventricular septal defect; SV single ventricle; CTGA, corrected transposition of great arteries; ASD, atrial septal defect; TGA, transposition of great arteries; PS, pulmonary stenosis; DORV, double outlet of right ventricle; TECD, total endocardial cushion defect; TAPVC, total anomlous of pulmonary venous connection; AOPA, anomalous origin of pulmonary artery; IVS, intact ventricular septum.

was additionally measured for the rest 43 complex CHD patients through a specialized slim catheter that was placed during the open heart operation pass through jugular vein and atrial septum. The inotrope score of catecholamine was calculated by dosages of dopamine × 1 + dobutamine × 1 + epinephrine × 100 + norepinephrine × 100 (16). All dosages were expressed in micrograms per kilogram per minute. The systemic vascular resistance index (SVRI) was monitored noninvasively with ICON (cardiotronic, Osypka Medical Inc, Berlin, Germany) by electrical cardiometry technology for 13 patients who received the operations under CPB at the late period of this study.

To evaluate treatment efficacy, we observed the changes of hemodynamics continuously and compared the systolic BP, diastolic BP, HR, CVP, and SVRI just before and 2 h after vasopressin initiation. Data for each patient at any study time point were taken the average value of three times measurements within 2 min. To assess the changes on organ perfusion, mean urine volume 2 h before and after vasopressin administration, plasma lactate concentration at baseline, 2, 6, 12 h after vasopressin administration were compared. Inotrope score of catecholamine and fluid requirement at baseline, 2, 6, 12 h after vasopressin administration were also compared. The side effects associated with vasopressin infusion and the clinical outcomes were recorded and evaluated.

Statistical analysis

Data are expressed as mean ± standard deviation or median (minimum–maximum) when appropriate. Paired variables were analyzed by the Student paired *t* test while more than two groups were analyzed using repeated measure analysis of variance (ANOVA) test with various post-tests whenever required. All the statistics was analyzed with the software of SPSS version 17.0 for Windows (SPSS Inc, Chicago, Ill). $P \leq 0.05$ was considered a significant statistical difference.

RESULTS

Seventy patients were identified with vasodilatory shock and treated with vasopressin at a dosage of 0.0002 u/kg/min to 0.002 u/kg/min continuously after cardiac surgery under cardiopulmonary bypass. Fifty-three (76%) patients received vasopressin within 12 h after surgery, nine patients within 12 to 24 h, and the other eight patients within 24 to 48 h. The mean duration of vasopressin was 49.8 h, while the shortest was 2 h and the longest was 322 h. The mean maximum dose is 0.0008 ± 0.0004 u/kg/min. When the highest of 0.002 u/kg/min vasopressin was used, the duration was less than 4 hours.

Table 2 shows the hemodynamic changes since vasopressin initiation.

At baseline, the systolic blood pressure (SBP) was low and rose 12% at 2 h after administration of vasopressin from 73 ± 11 mm Hg to 82 ± 10 mm Hg ($P < 0.001$). Before initiation of vasopressin, the SBP was 2 SD below the mean for age and sex (17) in 38 patients and 1 SD below the mean in 24 others. However, 2 h after vasopressin infusion, only eight had SBP < 1 SD below the mean and no one had SBP < 2 SD below the mean. Diastolic blood pressure (DBP) increased 14%, from 44 ± 8 mm Hg to 50 ± 9 mm Hg ($P < 0.001$).

The HR was in high level with 166 ± 27 beats per minute at baseline, and came down apparently to 156 ± 20 at 2 h after vasopressin administration, more close to normal.

As the inferior CVP could represent the pressure of right atrium in patients with Glenn procedure, just the same as CVP in patients with double-ventricular anatomical correction, these can be collectively described as right atrial pressure (RAP). Thus, the RAP at baseline was 11.2 ± 4.1 mm Hg, while 36 patients with high level above 10 mm Hg and 18 patients with normal level below 10 mm Hg. Two hours later, the RAP came down to 10.6 ± 2.9 mm Hg totally, with a trend of decrease though without significant statistical difference ($P = 0.090$). However, respectively speaking, for the 36 patients with high level RAP at baseline, it decreased apparently from 13.6 ± 3.0 mm Hg to 12.0 ± 2.5 mm Hg ($P = 0.001$), with great statistical difference, while for the rest 18 patients with normal level at baseline, the RAP maintained normal.

As the superior CVP represent the pressure of pulmonary artery in patients with Glenn procedure (shown in Fig. 1), just the same as CVP in patients with TCPC procedure, we all called them pulmonary artery pressure (PAP) under these two conditions. Thus, the PAP decreased apparently from 13.9 ± 2.4 mm Hg to 13.0 ± 2.2 mm Hg ($P = 0.009$) completely. While for the 14 cases with high level of PAP (≥15 mm Hg) at baseline,

Table 2. **Hemodynamics improvement since vasopressin initiation**

Hemodynamics	Baseline	2 h later	*P*
SBP (mm Hg)	73 ± 11	82 ± 10	<0.001
DBP (mm Hg)	44 ± 8	50 ± 9	<0.001
HR (beats/min)	166 ± 27	156 ± 20	0.001
RAP (mm Hg, n = 54)	11.2 ± 4.1	10.6 ± 2.9	0.09
RAP≥10 (mm Hg, n = 36)	13.6 ± 3.0	12.0 ± 2.5	0.001
PAP (mm Hg, n = 25)	13.9 ± 2.4	13.0 ± 2.2	0.009
PAP≥15 (mm Hg, n = 14)	16.0 ± 1.2	14.2 ± 2.1	0.003
SVRI (dyn/s per cm^5 per m^2, n = 16)	894.3 ± 190.8	1138.2 ± 161.4	<0.001

Each data for each patient at any study time point were taken the average value of three times measurements within 2 min.
SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; SVRI, systemic vascular resistance index.

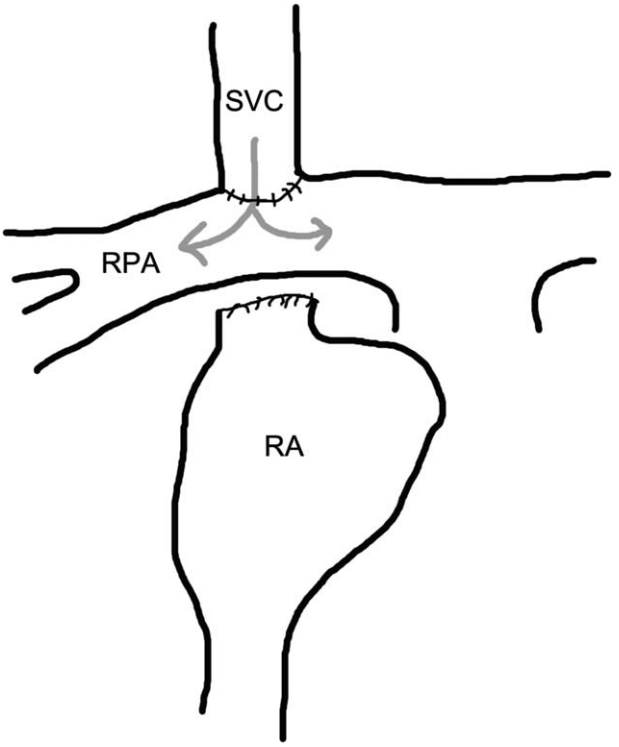

FIG. 1. **Diagram of bidirectional Glenn procedure.** In this procedure, SVC was connected to the right branch of the pulmonary artery. The main pulmonary artery was divided or tied up. So venous blood from the head and upper limbs would pass directly to the lungs, bypassing the right ventricle. The venous blood from the lower half of the body however would continue to enter the heart. A central venous catheter was respectively put into the SVC and IVC through internal jugular vein or femoral vein. So the SCVP and ICVP could be measured respectively. The SCVP reflected the PAP and the ICVP reflected the RAP in this procedure. SVC indicates superior vena cava; IVC, inferior vena cava; SCVP, superior central venous pressure; ICVP, inferior central venous pressure; PAP, pulmonary artery pressure; RAP, right artial pressure.

the difference was more significant from 16.0 ± 1.2 mm Hg down to 14.2 ± 2.1 mm Hg at 2 h later ($P = 0.003$).

All the measured LAP in 43 patients was nearly unchanged since vasopressin infused (shown in Fig. 2).

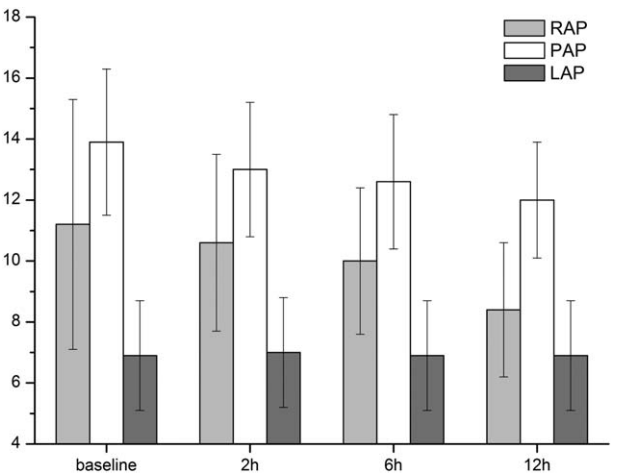

FIG. 2. **RAP, PAP, LAP changes after vasopressin administration.**

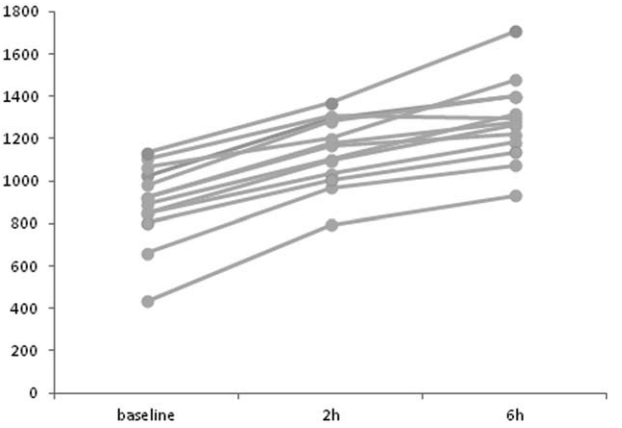

FIG. 3. **SVRI changes after vasopressin administration.**

SVRI of 13 consecutive patients at the late study period were monitored. It showed that all these patients were in low systemic vascular resistance state at baseline with SVRI of 894.3 ± 190.8 dyn/s per cm^5 per m^2, while 2 h later, all SVRI got a tremendous increase since vasopressin pumping, up to 1138.2 ± 161.4 dyn/s per cm^5 per m^2 ($P < 0.001$). And then SVRI gradually reached and maintained at a normal range (Fig. 3).

All children received multiple vasopressors and inotropes support, including dopamine ($n = 70$, 7.8 ± 1.8 ug/kg/min), epinephrine ($n = 67$, 0.11 ± 0.07 ug/kg/min), dobutamine ($n = 56$, 7.5 ± 1.9 ug/kg/min), and norepinephrine ($n = 16$, 0.08 ± 0.06 ug/kg/min) before vasopressin was given. The inotrope score of catecholamine at baseline was 24.6 ± 10.0, decreased to 23.3 ± 7.9 and 22.3 ± 6.3 at 2 and 6 h, respectively ($P = 0.057$, $P = 0.035$). All the norepinephrine was ceased within 2 h after vasopressin initiation (Fig. 4). Meanwhile, the fluid requirement was also decreased significantly from 15.8 ± 6.2 mL/kg/h at baseline to 9.1 ± 3.2 mL/kg/h at 2 h, 4.7 ± 1.2 mL/kg/h at 6 h (all $P < 0.001$).

Urine output and plasma lactate concentration were used to reflect the status of organ perfusion. We calculated the mean urine volume of 2 h just before and after vasopressin administration. It showed a significant statistical difference, elevated from 2.6 ± 1.7 mL/kg/h to 4.4 ± 3.1 mL/kg/h ($P < 0.001$), although the urine output was not increased in 15 patients.

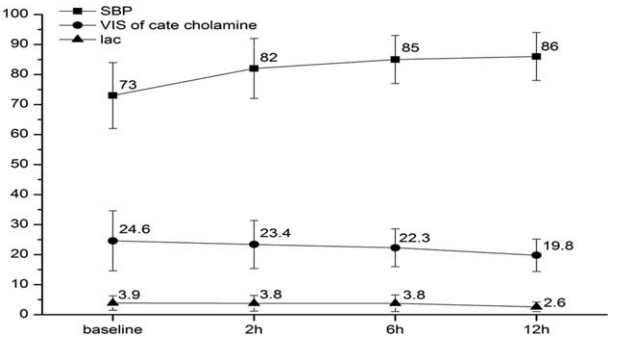

FIG. 4. **Catecholamine inotrope score and lactate concentration modification since BP improvement after vasopressin administration.**

Sixteen patients still needed the peritoneal dialysis or hemofiltration after vasopressin initiation because of unsatisfied negative fluid balance or oliguria. Comparing with the urine output, the plasma lactate concentration showed a delayed decline until 12 h later, manifested with 3.9 ± 2.4 mmol/L at base line, 3.8 ± 2.6 mmol/L at 2 h, 3.8 ± 2.8 mmol/L at 6 h, 2.6 ± 1.4 mmol/L at 12 h since vasopressin administration (Fig. 4).

No serious side effects were observed when vasopressin infused. Two patients who received angiography and collateral artery occlusion through femoral artery at the same day of operation presented with mild peripheral limb ischemia when vasopressin infusion with 0.001 u/kg/min for 12 h. After lowering down the dose to 0.0004 u/kg/min immediately and a small amount of heparin and papaverine were used, the symptom of limb ischemia was gradually disappeared within 2 days. No myocardial infarction, ventricular arrhythmias, gastrointestinal hemorrhage, hyponatremia, anaphylaxis, bronchospasm, or venous thrombosis (18, 19) associated with vasopressin infusion was observed. All the patients were survived to hospital discharge. The time of ventilation support was 92.1 ± 93.5 h, while the ICU stay was 13.3 ± 11.0 days.

DISCUSSION

Vasodilatory shock after cardiac surgery in children is usually refractory to routine therapy which includes administration of volume and high doses of catecholamine pressors. It is considered the results from the inappropriate activation of vasodilator mechanisms and the failure of vasoconstrictor mechanisms (1). Our study showed great improvements in hemodynamic parameters (BP, HR, CVP, PAP) after the use of vasopressin in vasodilatory shock after pediatric cardiac surgery, especially for patients with right heart anomaly.

When the low dose vasopressin were used, we found a significant increase in blood pressure, consistent with the previous report (10–15, 20). The change can be explained as the vasoconstriction of peripheral resistance vessels induced by vasopressin via V1 receptors (21). But it had seldom been quantified monitored in children in the previous study. In our study, SVRI of 13 consecutive patients with vasopressin infusion were monitored by ICON with electrical cardiometry technology. The results demonstrated a low systemic vascular resistance state at baseline and a great increase of SVRI as vasopressin infusion within just several hours. So it provided a strong evidence to initiate vasopressin treatment.

As the rising of BP, we found that other parameters including HR, CVP, and PAP did not increase simultaneously, different from catecholamine pressors' effect. Instead, these three parameters all came down, especially when they were in high level at baseline. Some studies demonstrated that the HR was essentially unchanged (10, 20) during vasopressin administration. Alten et al. (12) found a trend of HR decline, but without significant statistical difference. Compared with these reports, our results showed apparently HR decline. It can be explained as the nervous feedback regulation induced by BP increase.

Our study also showed a significant decrease in PAP since vasopressin infusion, consistent with the recent findings that vasopressin can decrease the ratio of pulmonary-to-systemic vascular resistance (22, 23). This may be explained as pulmonary vasculature dilation induced by vasopressin via V2 receptors or oxytocin receptors mediated the release of nitric oxide (24, 25). Subsequently, the right ventricle function improved as the PAP declined. Maybe, that is one reason why in our study the RAP also declined, especially when they were in high level at baseline. Furthermore, the decline of fluid requirement also contributed to this effect. Compared with the unchanged LAP at the same period, we draw a conclusion that vasopressin was associated with greater improvement on the right heart. More benefit may be obtained for the right heart anomaly patients.

To assess vasopressin effects on end organ perfusion, we analyzed several indicators such as urine output, plasma lactate concentration. It showed a significant increase in urine output and a delayed decline of lactate concentration since vasopressin initiation. All these proved that the organ perfusion was greatly improved. Agrawal et al. (19) suggested that the vasodilatation effect of vasopressin could take place not only in pulmonary, but also in renal and cerebral circulation, particularly when vasopressin infusion at low dose. A multicenter double-blind randomized controlled trial showed that vasopressin may reduce progression to renal failure and mortality in patients at risk of kidney injury who have septic shock (26).

As the initiation of vasopressin, catecholamine inotrope requirement declined significantly and it allowed weaning off other catecholamine vasopressors such as norepinephrine, which had potential side effect of increasing the tissue oxygen consumption. It is worth mentioning that the mean VIS at baseline was 28 in our study, which is much lower than other reports (10, 20, 27, 28). That means our timing of vasopressin initiation was much earlier, which contributed to good clinical outcomes.

However, there are several limitations that should be mentioned. The major limitation of this study is its retrospective nature vis-a-vis prospective study. First, it may introduce selection bias and information bias. Second, the maximum dose and duration of infusion titrated according to individual hemodynamic parameters and clinicians' experience may induce variability. Third, the SVRI was monitored only in 13 patients, the sample was relatively small. Last, all the patients in this study had normal left ventricular (LV) function. Effects of vasopressin administration on poor LV function patients still need to be explored.

In conclusion, low dose of vasopressin administration was associated with great and timely hemodynamic improvement for pediatric patients with vasodilatory shock after cardiac surgery without serious side effects. Maybe, more benefits could be obtained for the right heart anomalous pediatric patients. Further prospective, randomized studies are needed.

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