Hemodynamic Effects of Phenylephrine, Vasopressin, and Epinephrine in Children With Pulmonary Hypertension: A Pilot Study*

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Objectives: During a pulmonary hypertensive crisis, the marked increase in pulmonary vascular resistance can result in acute right ventricular failure and death. Currently, there are no therapeutic guidelines for managing an acute crisis. This pilot study examined the hemodynamic effects of phenylephrine, arginine vasopressin, and epinephrine in pediatric patients with pulmonary hypertension.

Design: In this prospective, open-label, nonrandomized pilot study, we enrolled pediatric patients previously diagnosed with pulmonary hypertensive who were scheduled electively for cardiac catheterization. Primary outcome was a change in the ratio of pulmonary-to-systemic vascular resistance. Baseline hemodynamic data were collected before and after the study drug was administered.

Patients: Eleven of 15 participants were women, median age was 9.2 years (range, 1.7–14.9 yr), and median weight was 26.8 kg (range, 8.5–55.2 kg). Baseline mean pulmonary artery pressure was 49 ± 19 mm Hg, and mean indexed pulmonary vascular resistance was 10 ± 5.4 Wood units. Etiology of pulmonary hypertensive varied, and all were on systemic pulmonary hypertensive medications.

Interventions: Patients 1–5 received phenylephrine 1 μg/kg; patients 6–10 received arginine vasopressin 0.03 U/kg; and patients 11–15 received epinephrine 1 μg/kg. Hemodynamics was measured continuously for up to 10 minutes following study drug administration.

Measurements and Main Results: After study drug administration, the ratio of pulmonary-to-systemic vascular resistance decreased in three of five patients receiving phenylephrine, five of five patients receiving arginine vasopressin, and three of five patients receiving epinephrine. Although all three medications resulted in an increase in aortic pressure, only arginine vasopressin consistently resulted in a decrease in the ratio of systolic pulmonary artery-to-aortic pressure.

Conclusions: This prospective pilot study of phenylephrine, arginine vasopressin, and epinephrine in pediatric patients with pulmonary hypertensive showed an increase in aortic pressure with all drugs although only vasopressin resulted in a consistent decrease in the ratio of pulmonary-to-systemic vascular resistance. Studies with more subjects are warranted to define optimal dosing strategies of these medications in an acute pulmonary hypertensive crisis. (*Pediatr Crit Care Med* 2016; 17:428–437)

Key Words: epinephrine; pediatric; phenylephrine; pulmonary hypertension; vasopressin

Pulmonary hypertension (PH) is characterized by an elevation in mean pulmonary artery pressure and pulmonary vascular resistance (PVR). During a pulmonary hypertensive crisis, if interventions are not timely and/or appropriate, the marked increase in PVR and right ventricular afterload can result in acute right ventricular failure, leading to cardiogenic shock and death.

Acute, inpatient PH crises are generally managed with a combination of pulmonary vasodilators to decrease right ventricular afterload and systemic vasoconstrictors to maintain systemic vascular resistance (SVR) and augment coronary artery perfusion. Research on the direct effect of these drugs in this patient population is limited. Inhaled nitric oxide, IV prostacyclin, dobutamine, and milrinone have the greatest support in the adult literature for ongoing treatment of PH crises although they are not first choice for resuscitation (1).

*See also p. 465.

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Pediatric patients with idiopathic pulmonary arterial hypertension (IPAH) or PH associated with congenital heart disease are at high risk of periprocedural cardiac arrest and pulmonary hypertensive crises (2–4). There are no data to support a "best" treatment in an acute crisis although (5) epinephrine remains the first-line therapy for pediatric advanced life support in the cardiac arrest algorithm. Given that cardiac output in children is heart rate dependent, epinephrine with its chronotropic effect and ability to vasoconstrict and maintain SVR would seem ideally suited. However, this has not been specifically studied in the treatment of PH crisis.

There is concern that despite its ability to raise SVR, epinephrine could be detrimental in PH patients because it can cause a concomitant increase in PVR and increase the heart rate, which could further reduce coronary perfusion. Hence, our institutional practice had been to use phenylephrine for acute pulmonary hypertensive crises based on published data in the adult literature (6). Phenylephrine, a powerful α-agonist, is a systemic vasoconstrictor, maintains SVR, and shifts the interventricular septum rightward to improve left ventricular filling. More recently, case reports in the pediatric literature on the use of vasopressin in children with PH led us to examine its use prospectively (7–10).

The purpose of this pilot study was to examine the hemodynamic effects, specifically the effect on the PVR and SVR, of phenylephrine, arginine vasopressin (AVP), and epinephrine in pediatric patients with PH. A primary outcome of the change in the PVR-to-SVR ratio (Rp:Rs) was chosen.

METHODS

This prospective, open-label, nonrandomized pilot study was approved by the Institutional Review Board at Stanford University. The protocol was registered at clinicaltrials.gov as ID number SU-10142011-8534, and written parental consent for participation and participant assent when applicable were obtained.

Children under 18 years old with PH and scheduled for elective, follow-up, hemodynamic cardiac catheterization were eligible for participation. In order to theoretically subselect for patients at higher risk of pulmonary hypertensive crises, the inclusion criteria also included an indexed PVR (PVRi) greater than or equal to ≥ 6 Wood units (WU) by previous cardiac catheterization at our institution. Patients without a prior cardiac catheterization were not eligible for inclusion.

Patients were then sequentially assigned, based on the order of enrollment, in groups of five to one of the three medications—patients 1–5 received 1 μg/kg IV phenylephrine as a bolus over 10 seconds, 6–10 received 0.03 U/kg IV AVP over 5 minutes as an infusion, and 11–15 received 1 μg/kg IV epinephrine, administered as a bolus over 10 seconds. Given our limited experience with AVP administration as a rapid bolus, it was administered as an infusion on the recommendation of the institutional pharmacy. However, since the conclusion of this study, rescue doses of AVP are administered as a bolus in our institution. The order of patient assignment/drug administration was arbitrary.

During the catheterization, patients were monitored and anesthetized per institutional guidelines, which include standard noninvasive monitoring of blood pressure, ECG, pulse oximeter, and end-tidal Co_2. The standard anesthetic regimen included a propofol-ketamine infusion with sevoflurane, spontaneous ventilation, and breathing room air, unless patient was on home oxygen therapy as previously described (11). After obtaining femoral arterial and venous access, right heart cardiac catheterization was performed in the standard fashion, obtaining oxygen saturation and/or pressure measurements in the superior vena cava, right atrium, right ventricle, pulmonary arteries, and pulmonary artery occlusion locations. Cardiac index was measured using the thermodilution method, averaging the results of three room temperature saline injections.

The study protocol was then initiated. Repeat baseline measurements of pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output were obtained. The study drug was then administered, and pulmonary artery pressure and systemic blood pressure were monitored continuously at a sampling rate of 240 points per second. Pressures were recorded for 10 minutes after the drug administration to ensure that all effects of the drug had worn off and pressures returned to baseline. A moving average filter was used to represent the changes in systolic aortic and pulmonary artery pressures. Two minutes after the drug was delivered (or infusion initiated), a pulmonary artery occlusion pressure and cardiac output were measured.

For analysis, baseline systolic, diastolic, and mean aortic and pulmonary artery pressures were determined by averaging the data for the 30 seconds immediately prior to the administration of study drug. The peak drug effect was defined as the highest systemic blood pressure and the simultaneous pulmonary artery pressure after administration of study drug. The ratio of systolic pulmonary artery pressure-to-systolic systemic blood pressure was calculated at baseline and peak drug effect.

The primary outcome variable was a change in Rp:Rs after drug administration. Secondary outcomes were the changes in systemic and pulmonary artery pressure, pulmonary artery occlusion pressure, PVR, SVR, and cardiac index after study drug administration.

Statistics

Statistical comparisons of continuous variables within groups before and after drug administration were made using a paired *t* test (IBM SPSS Statistics, Armonk, NY); statistical significance was set at a *p* value of less than 0.05.

TABLE 1. Baseline Patient Characteristics

ID	Sex	Age (yr)	Weight (kg)	Diagnosis	New York Heart Association Class	Cardiac Index (L/min/m^2)	Mean Pulmonary Artery Pressure (mm Hg)	Pulmonary Artery Occlusion Pressure (mm Hg)	Indexed Pulmonary Vascular Resistance (Wood Units)	Ratio of Pulmonary-to-Systemic Vascular Resistance	Medical Therapy
1	Female	6.8	18.6	IPAH	2–3	3.4	90	20	20.6	2.0	PDE5, ERA, prostin, O_2
2	Female	6.1	20	Juvenile idiopathic arthritis	2	4.8	40	11	6	0.4	PDE5, ERA
3	Female	14.1	55.2	IPAH	1	3.6	27	5	6.1	0.3	PDE5, ERA
4	Female	13.8	54	IPAH	2	3.5	37	10	7.7	0.5	PDE5, ERA, prostin, O_2
5	Male	10.4	20	Left heart disease	2–3	3.6	51	21	8.3	0.6	Prostin
6	Female	12.2	33.6	IPAH	1	4.3	38	9	6.7	0.7	PDE5, prostin
7	Female	13.9	45.4	IPAH	3	3.3	86	12	22.4	1.1	PDE5, ERA, prostin, O_2
8	Female	3	13.2	CHD	1	3.7	38	10	7.6	0.4	PDE5
9	Female	14.9	53.7	IPAH	2–3	3.9	41	11	7.7	0.6	PDE5, ERA, prostin, O_2
10	Male	8.3	26.8	CHD	1	4.5	74	14	12	1.1	PDE5, ERA, prostin
11	Female	2.3	9.6	CHD	1	5.2	29	10	3.5	0.3	PDE5
12	Male	1.7	8.5	CDH	1–2	3.9	48	9	10	0.6	PDE5, O_2
13	Female	12.9	39.2	IPAH	1	4.3	40	10	7	0.7	ERA
14	Male	9.2	30.7	CHD	2–3	2.8	54	12	15	0.9	PDE5, ERA, prostin
15	Female	7.8	20.1	CHD	1–2	3.9	46	12	8.7	0.5	PDE5, ERA, prostin, O_2

IPAH = idiopathic pulmonary arterial hypertension, CHD = congenital heart disease, CDH = congenital diaphragmatic hernia, NYHA = New York Heart Association, PDE5 = phosphodiesterase inhibitor, ERA = endothelin receptor antagonist, O_2= oxygen.

RESULTS

Fifteen pediatric patients with PH were enrolled between January 2012 and July 2014. Demographic information and baseline hemodynamics are shown in **Table 1**. Eleven of the participants were women, the median age at the time of cardiac catheterization was 9.2 years (range, 1.7–14.9 yr), and median weight was 26.8 kg (range, 8.5–55.2 kg). Baseline mean pulmonary artery pressure was 49 ± 19 mm Hg, and mean PVRi was 10 ± 5.4 WU. The etiology of PH varied—seven had IPAH, five had PAH associated with congenital heart disease, one patient had PH because of left heart disease, one had PH secondary to lung disease, and one had PH associated with rheumatologic disease. All patients were on systemic medications to treat PH, including phosphodiesterase inhibitors (n = 13), endothelin receptor antagonists (n = 10), and/or prostacyclins (n = 8); five were on home oxygen therapy. All hemodynamic results are indexed to body surface area unless otherwise noted.

Figure 1 provides examples for each drug of representative changes in aortic and pulmonary artery pressure during drug administration. There are two plots for each drug—one in a patient with baseline subsystemic pulmonary artery pressure and one in a patient with systemic or suprasystemic pulmonary artery pressure to demonstrate the drug effects in the setting of different baseline hemodynamics. In patients with subsystemic pulmonary artery pressure, all three drugs resulted in an increase in aortic pressure with phenylephrine and AVP resulting in only a slight increase in pulmonary artery pressure, whereas epinephrine resulted in a substantial increase in pulmonary artery pressure. In patients with

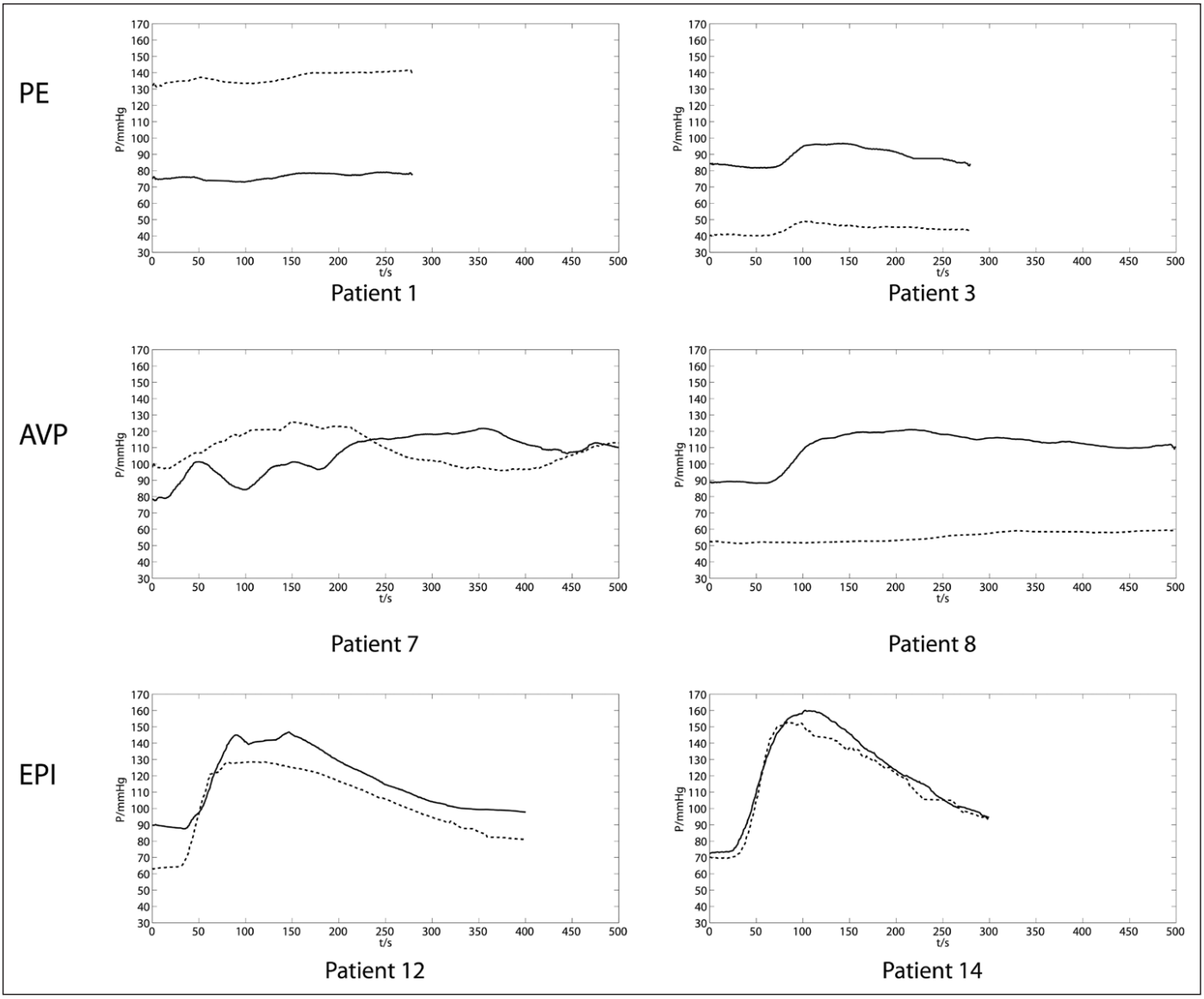


Figure 1. Representative pressure tracings of aortic (*black*) and pulmonary artery (*dashed line*) pressures for selected patients from each drug group. Time is shown in *x*-axis and pressure in *y*-axis. AVP = arginine vasopressin, EPI = epinephrine, PE = phenylephrine.

systemic or suprasystemic pulmonary artery pressure, phenylephrine had no effect on aortic or pulmonary artery pressures, AVP resulted in an increase in aortic pressure with a decrease in pulmonary artery pressure, and epinephrine resulted in a substantial increase in both aortic and pulmonary artery pressures. **Table 2** summarizes the hemodynamic data for each patient.

Pressures

Figure 2*A* shows the change in systolic aortic pressure compared with baseline for each patient. All three drugs resulted in an increase in systolic aortic pressure (epinephrine 185% ± 25% > AVP 147% ± 18% > phenylephrine 118% ± 8%).

Figure 2*B* shows the change in systolic pulmonary artery pressure compared with baseline for each patient. Epinephrine resulted in a substantial increase (191% ± 27%) at peak drug effect in all patients. Phenylephrine resulted in a small increase or no change (109% ± 11%), and the effect of AVP was mixed, with only slight increases or decreases (96% ± 13%) noted.

The ratio of systolic pulmonary artery pressure-to-systolic aortic pressure for each patient compared with baseline for each patient is shown in **Figure 2*C***. Phenylephrine resulted in a decrease in ratio in four patients (89% ± 11%); AVP resulted in a decreased ratio in all patients (57% ± 13%); epinephrine resulted in no change in the ratio (104% ± 21%).

Figure 3, ***A*–*C*** show average change compared with baseline for each drug in the systolic aortic pressure, systolic pulmonary

TABLE 2. Hemodynamic Data Predrug and Postdrug Administration for Each Patient

		Mean Pulmonary Artery Pressure (mm Hg)		Mean Aortic Pressure (mm Hg)		Indexed Pulmonary Vascular Resistance (WU)		Ratio of Pulmonary-to-Systemic Vascular Resistance		Pulmonary Artery Occlusion Pressure (mm Hg)		Cardiac Index (L/min/m²)	
ID	Drug	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	Phenylephrine	89	89	53	53	20.3	NA	2.1	2.1	20	20	3.4	NA
2	Phenylephrine	40	47	73	92	6	7.2	0.4	0.4	11	14	4.8	4.6
3	Phenylephrine	25	34	69	80	5.6	7.7	0.3	0.3	5	7	3.6	3.5
4	Phenylephrine	36	38	63	92	7.4	6.8	0.5	0.3	10	12	3.5	3.8
5	Phenylephrine	50	54	49	54	8.1	NA	0.7	0.5	21	30	3.6	NA
6	AVP	39	40	49	90	3.2	5.5	0.4	0.3	9	14	4.3	4.7
7	AVP	94	78	71	90	24.8	24.1	1.3	0.8	12	8	3.3	2.9
8	AVP	38	39	75	104	7.6	7.6	0.4	0.3	10	10	3.7	3.8
9	AVP	43	42	57	91	8.2	8.6	0.7	0.4	11	12	3.9	3.5
10	AVP	69	64	60	88	12.2	10.6	1.1	0.6	14	14	4.5	4.7
11	Epinephrine	24	41	55	108	2.7	3	0.3	0.2	10	19	5.2	7.3
12	Epinephrine	47	99	77	129	9.7	NA	0.5	0.7	9	12	3.9	NA
13	Epinephrine	42	56	56	125	7.4	6.6	0.7	0.3	10	24	4.3	4.9
14	Epinephrine	44	104	58	121	15.4	20	0.9	0.8	12	12	2.8	4.6
15	Epinephrine	48	108	68	117	9.2	17.6	0.6	1	12	12	3.9	5.5

AVP = arginine vasopressin, NA = not applicable.
Baseline predrug mean pulmonary artery and aortic pressures are calculated from 30 s of recording immediately before drug effect.

pressure, and ratio of systolic pulmonary-to-systolic aortic pressure, respectively.

Phenylephrine resulted in a change in mean aortic pressure from 61 ± 10 to 74 ± 20 mm Hg ($p = 0.2$). AVP and epinephrine resulted in a significant increase in mean aortic pressure from 62 ± 11 to 93 ± 6 mm Hg ($p < 0.01$) and 63 ± 9 to 120 ± 8 mm Hg ($p < 0.01$), respectively. Phenylephrine and AVP resulted in no change in mean pulmonary artery pressure from 48 ± 25 to 52 ± 22 mm Hg ($p = 0.8$) and 57 ± 24 to 53 ± 18 mm Hg ($p = 0.8$), respectively. Epinephrine resulted in a significant increase in mean pulmonary artery pressure from 43 ± 12 to 82 ± 31 mm Hg ($p = 0.03$).

The following changes were seen in pulmonary artery occlusion pressure following drug administration—phenylephrine: 13.4 ± 6.9 to 16.6 ± 8.8 mm Hg ($p = 0.5$); AVP: 11.2 ± 1.9 to 11.6 ± 2.6 mm Hg ($p = 0.8$); and epinephrine: 10.6 ± 1.3 to 15.8 ± 5.5 mm Hg ($p = 0.07$).

SVR and PVR

Phenylephrine and AVP significantly increased SVRi from 14 ± 3.7 to 21.3 ± 2.1 WU ($p = 0.02$) and 14.2 ± 4.4 to 22.4 ± 5.2 WU ($p = 0.03$), respectively. Epinephrine resulted in no change in SVRi from 14 ± 4 to 19.9 ± 4.9 WU ($p = 0.09$). The following changes were seen in PVRi following drug administration—phenylephrine: 9.5 ± 6.1 to 7.3 ± 0.5 WU ($p = 0.6$); AVP: 11.1 ± 8.1 to 11.3 ± 7.4 WU ($p = 1$); epinephrine: 8.9 ± 4.6 to 11.8 ± 8.3 WU ($p = 0.5$).

Rp:Rs is compared from baseline to peak drug effect for each patient in **Figure 4*A*** and as an average for each drug in **Figure 4*B***. Overall, the following changes were seen in Rp:Rs following drug administration—phenylephrine: 0.8 ± 0.7 to 0.73 ± 0.77 ($p = 0.9$); AVP: 0.75 ± 0.41 to 0.49 ± 0.24 ($p = 0.3$); epinephrine: 0.61 ± 0.23 to 0.6 ± 0.34 ($p = 1$). Phenylephrine resulted in a decrease in Rp:Rs in three patients, no change in one patient, and an increase in one patient. AVP resulted in a decrease in Rp:Rs in all five patients. Epinephrine administration resulted in a decrease in Rp:Rs in three patients and an increase in two patients.

Cardiac Index and Heart Rate

The following changes were seen in cardiac index following drug administration—phenylephrine: 3.8 ± 0.6 to 4 ± 0.6 L/min/m² ($p = 0.7$); AVP: 3.9 ± 0.5 to 3.9 ± 0.8 L/min/m² ($p = 1$); epinephrine: 4 ± 0.9 to 5.6 ± 1.2 L/min/m² ($p = 0.06$). Cardiac index by thermodilution was not performed post drug administration in three patients (20%) because of patient instability and/or catheter malfunction.

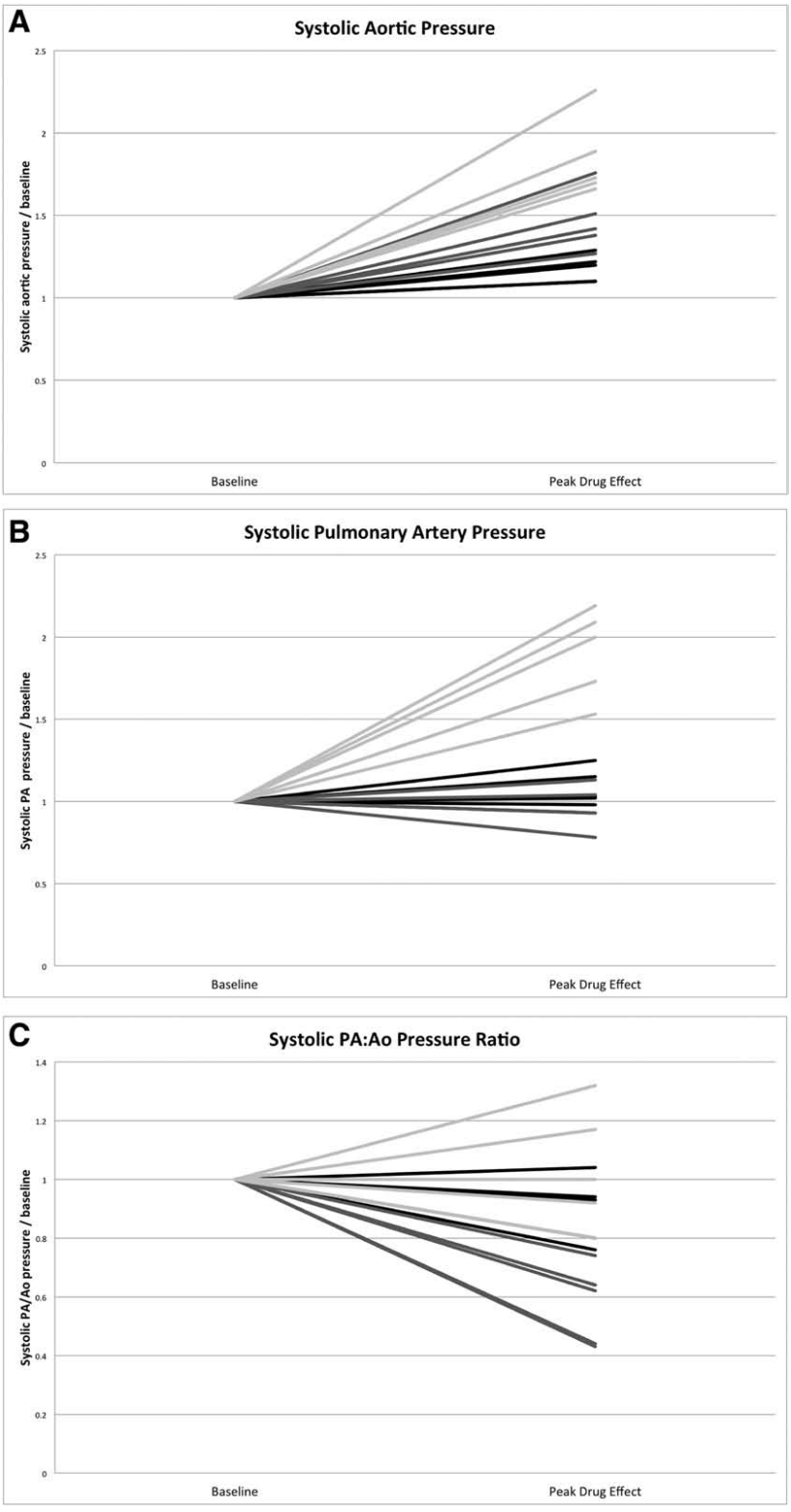


Figure 2. Peak drug effects on systemic and pulmonary artery (PA) pressures and vascular resistance (systolic aortic [Ao] pressure [**A**], systolic PA pressure [**B**], and ratio of systolic PA-to-Ao pressure [**C**]) at peak drug effect indexed to baseline for phenylephrine (*black*), arginine vasopressin (*gray*), and epinephrine (*light gray*) for each patient.

Phenylephrine and AVP resulted in a mixed effect on the heart rate with an average change of –6% ± 10% and –15% ± 15%, respectively. Epinephrine resulted in an increase in the heart rate in all patients with an average change of 24% ± 20%.

Adverse Events

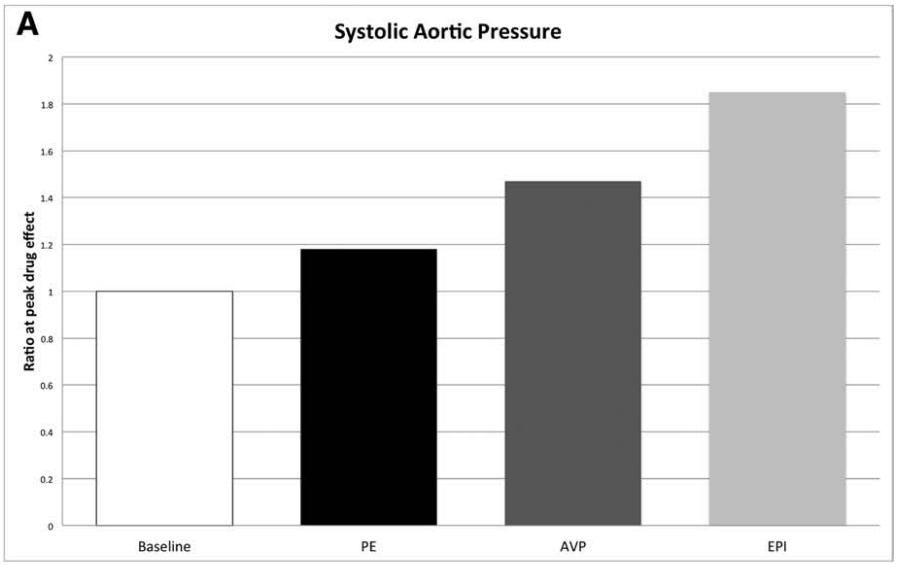
Two patients had a transient arrhythmia following epinephrine administration: one patient had brief atrial bigeminy and another had ventricular ectopy followed by ventricular bigeminy. Neither arrhythmia was hemodynamically significant and did not require treatment.

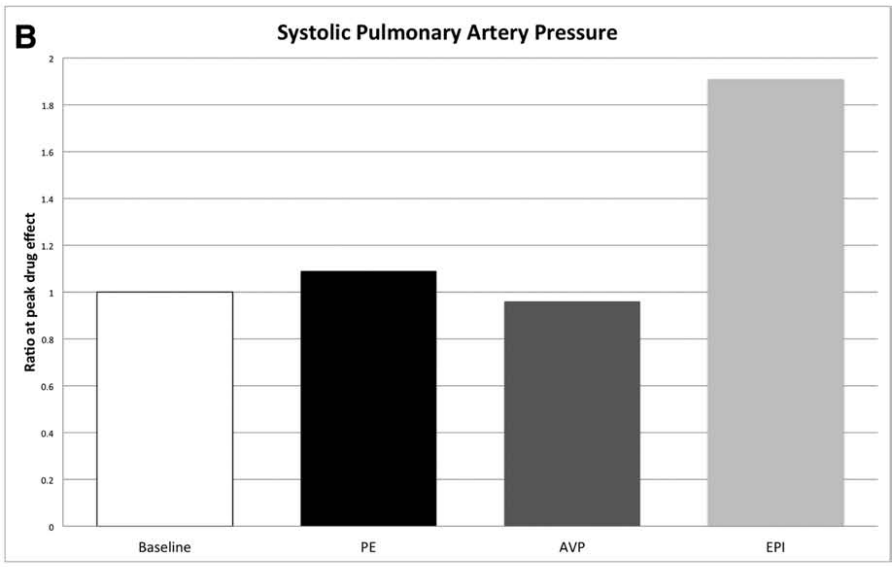
DISCUSSION

This prospective, pilot study of phenylephrine, AVP, and epinephrine in pediatric patients with PH demonstrated a decrease in Rp:Rs at peak drug effect following vasopressin infusion in all patients. All three drugs resulted in an increase in SVR, but only AVP consistently decreased the ratio of systolic pulmonary artery-to-aortic pressure.

Phenylephrine is a pure α-agonist that may increase both PVR and SVR without an increase in the heart rate, theoretically improving coronary artery perfusion through an increase in SVR. Studies of phenylephrine in adults show that phenylephrine increases systolic blood pressure and coronary perfusion pressure but decreases cardiac output and right ventricular systolic function while raising pulmonary artery pressure (12, 13). In our study, phenylephrine decreased Rp:Rs in three patients, increased Rp:Rs in one patient, and resulted in no change in one patient. Based on these results, phenylephrine may be beneficial in some patients with PH, but this was not consistent, especially in patients with suprasystemic pulmonary artery pressures.

Epinephrine, the first-line drug in most advanced cardiac life support algorithms, is appealing because it is easily available and familiar to most practitioners. However, as a combined α- and β-agonist, it may not be favorable to use as it can induce tachycardia and increase myocardial oxygen demand, further reducing effective coronary blood flow. In this study, all patients demonstrated an increase in the heart rate following its administration. However, the inotropy provided by epinephrine might be beneficial in





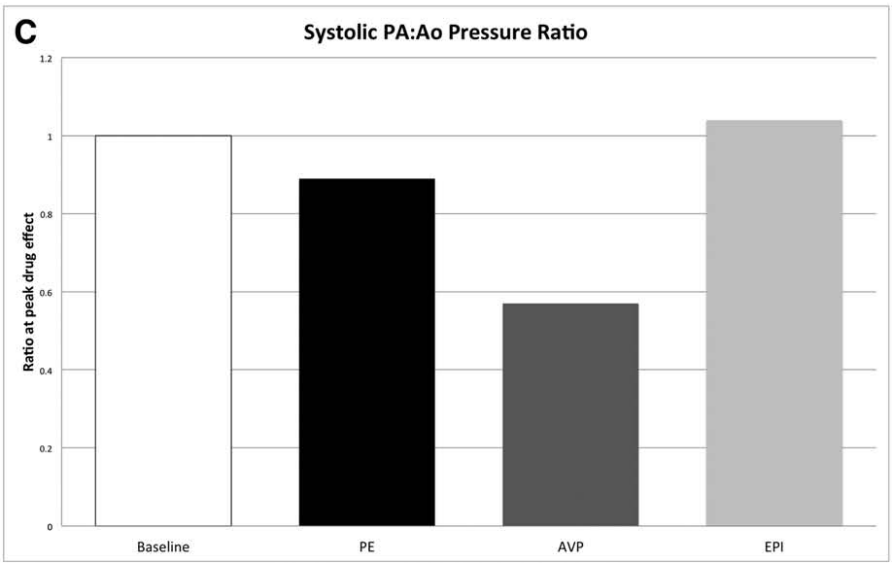


Figure 3. Average (systolic aortic [Ao] pressure [**A**], systolic pulmonary artery [PA] pressure [**B**], and ratio of systolic PA-to-Ao pressure [**C**]) at peak drug effect indexed to baseline for phenylephrine (PE) (*black*), arginine vasopressin (AVP) (*gray*), and epinephrine (EPI) (*light gray*).

a failing right ventricle. There are no trials of epinephrine during an acute pulmonary hypertensive crisis or in treatment of cardiogenic shock in patients with PH. In this study, epinephrine resulted in increases in pulmonary artery pressure in all five patients, but Rp:Rs decreased in only three patients. In addition, the only arrhythmias noted during the study were in two patients after an epinephrine bolus, but these were resolved without treatment.

More recently, AVP has been studied as an alternative to phenylephrine and epinephrine as it provides systemic vasoconstriction and pulmonary vasodilation, making it an attractive drug for acute pulmonary hypertensive crisis. Vasopressin acts at the pulmonary artery vascular endothelium by V_1 receptor–mediated release of nitric oxide. In a recent study on human radial and pulmonary artery specimens, norepinephrine and phenylephrine produced dose-dependent vasoconstriction of both radial and pulmonary arteries. Vasopressin, on the other hand, produced potent vasoconstriction of the radial artery but had no effect on the pulmonary artery (14). The effect on the pulmonary artery has been shown in several studies on canine pulmonary endothelium to be dependent on nitric oxide synthesis (13, 15). However, pulmonary artery vasodilation has not been consistently shown in all human studies (16). One study demonstrated deleterious effects of pulmonary vasoconstriction with vasopressin on right ventricular function with a 31% decrease in right ventricular contractility (17). In our group of patients, we only looked at pressures and did not directly measure right ventricular function.

Following cardiopulmonary bypass, cardiac intensive care patients with systemic hypotension and PH showed a favorable

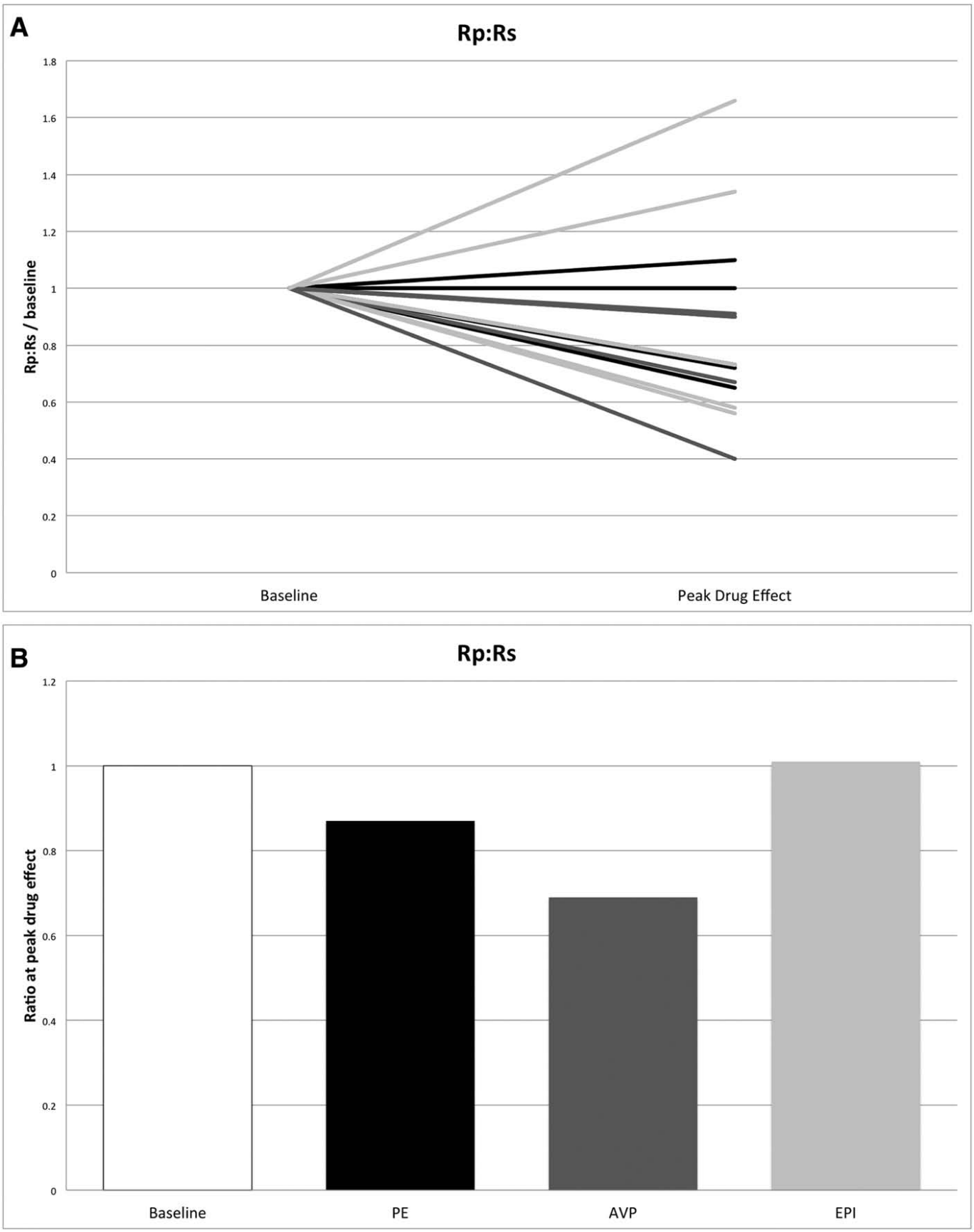


Figure 4. A, Ratio of pulmonary-to-systemic vascular resistance (Rp:Rs) at peak drug effect indexed to baseline for each patient. **B**, Average Rp:Rs at peak drug effect indexed to baseline for phenylephrine (PE) (*black*), arginine vasopressin (AVP) (*gray*), and epinephrine (EPI) (*light gray*).

response to vasopressin through an increase in SVR and reduction in the ratio of pulmonary artery pressure-to-systemic blood pressure without any effect on PVR (7). A series of neonates with persistent PH of the newborn responded favorably to vasopressin with improved oxygenation index and the ability to reduce inhaled nitric oxide dose (8). There are case reports of the successful use of vasopressin in acute pulmonary hypertensive crisis (9, 18) and its analog terlipressin (19) in a neonate with congenital diaphragmatic hernia with reduction in pulmonary artery pressure. In this study, the effect of vasopressin on PA pressure was variable, but Rp:Rs was reduced at peak drug effect in all patients, suggesting a greater increase in systemic pressure in the subjects.

There are several limitations to this study. The largest one is the small number of patients, which precludes any meaningful statistical analysis either within or between groups. Furthermore, this was an open-label study, and this study did not include simple randomization or blinding of any investigators. This was a preliminary safety and feasibility study, and given the severity of disease, recruitment was slower than anticipated. However, completion of this study, albeit small, has altered clinical practice in our institution where AVP is now the drug of first choice when managing patients with severe PH under sedation and anesthesia in the operating room and/or ICU when hypotension or signs of right ventricular ischemia are noted. This preliminary study, performed without any major adverse events, could lead to larger, multicenter, dose-finding trials of one or more of the medications studied.

The second limitation is that patients received the study drugs during routine hemodynamic catheterization and not during a PH crisis; the same response may or may not occur similarly under both conditions. In addition, the inotropic effects of the drugs may have a different impact on the acutely failing right ventricle.

Third, as the drug effects were transient, it was impossible to measure all hemodynamic variables at once at peak drug effect. Hence, the measurement of cardiac index by thermodilution may not be as accurate as it was done after the recording of the pulmonary artery pressure and pulmonary artery occlusion pressure when the drug effect may have been on the wane. This can be overcome by studying loading dose followed by an infusion, which is how we currently administer AVP. In addition, only one dose was administered and there may be a dose- or dosing- (bolus vs continuous infusion) dependent effect of these agents. Finally, we did not perform transthoracic echocardiogram to demonstrate the effect of the medications on indices of right heart function.

Additional research is necessary to determine the best medication for patients with PH who experience an acute crisis. The ideal agent would increase SVR to maintain myocardial oxygenation with adequate coronary artery perfusion while decreasing PVR to reduce right ventricular afterload. Vasopressin is promising with its moderate systemic vasoconstrictor effects and its potential to lead to dilation of pulmonary arteries through release of nitric oxide although this latter effect is not consistent in animal models.

In conclusion, in this pilot, prospective study of phenylephrine, vasopressin, and epinephrine, vasopressin resulted in a decrease in Rp:Rs in all patients. Vasopressin may selectively reduce pulmonary artery pressure and the ratio of systemic-to-pulmonary artery pressure, making it a favorable choice although optimal dosing strategy has yet to be defined. Phenylephrine resulted in the smallest increase in aortic pressure with small changes in pulmonary artery pressure, suggesting that it might be a weak resuscitation agent in this patient population. Finally, epinephrine resulted in a substantial increase in both aortic and pulmonary artery pressures and caused transient arrhythmias in two patients, suggesting that it should be used with caution.

REFERENCES

1. Zamanian RT, Haddad F, Doyle RL, et al: Management strategies for patients with pulmonary hypertension in the intensive care unit. *Crit Care Med* 2007; 35:2037–2050
2. Carmosino MJ, Friesen RH, Doran A, et al: Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. *Anesth Analg* 2007; 104:521–527
3. Ramamoorthy C, Haberkern CM, Bhananker SM, et al: Anesthesia-related cardiac arrest in children with heart disease: Data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. *Anesth Analg* 2010; 110:1376–1382
4. van der Griend BF, Lister NA, McKenzie IM, et al: Postoperative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. *Anesth Analg* 2011; 112:1440–1447
5. Brunner N, de Jesus Perez VA, Richter A, et al: Perioperative pharmacological management of pulmonary hypertensive crisis during congenital heart surgery. *Pulm Circ* 2014; 4:10–24
6. Kwak YL, Lee CS, Park YH, et al: The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*. *Anaesthesia* 2002; 57:9–14
7. Tayama E, Ueda T, Shojima T, et al: Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interact Cardiovasc Thorac Surg* 2007; 6:715–719
8. Mohamed A, Nasef N, Shah V, et al: Vasopressin as a rescue therapy for refractory pulmonary hypertension in neonates: Case series. *Pediatr Crit Care Med* 2014; 15:148–154
9. Scheurer MA, Bradley SM, Atz AM: Vasopressin to attenuate pulmonary hypertension and improve systemic blood pressure after correction of obstructed total anomalous pulmonary venous return. *J Thorac Cardiovasc Surg* 2005; 129:464–466
10. Malikiwi A, Sasi A, Tan K, et al: Vasopressin as an adjunct therapy for pulmonary hypertension: A case report. *Eur J Pediatr* 2014; 173:1651–1654
11. Williams GD, Maan H, Ramamoorthy C, et al: Perioperative complications in children with pulmonary hypertension undergoing general anesthesia with ketamine. *Paediatr Anaesth* 2010; 20:28–37
12. Rich S, Gubin S, Hart K: The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. *Chest* 1990; 98:1102–1106
13. Evora PR, Pearson PJ, Schaff HV: Arginine vasopressin induces endothelium-dependent vasodilation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. *Chest* 1993; 103:1241–1245

14. Currigan DA, Hughes RJ, Wright CE, et al: Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: An in vitro study. *Anesthesiology* 2014; 121:930–936
15. Sai Y, Okamura T, Amakata Y, et al: Comparison of responses of canine pulmonary artery and vein to angiotensin II, bradykinin and vasopressin. *Eur J Pharmacol* 1995; 282:235–241
16. Smith AM, Elliot CM, Kiely DG, et al: The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension. *QJM* 2006; 99:127–133
17. Leather HA, Segers P, Berends N, et al: Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med* 2002; 30:2548–2552
18. Price LC, Forrest P, Sodhi V, et al: Use of vasopressin after Caesarean section in idiopathic pulmonary arterial hypertension. *Br J Anaesth* 2007; 99:552–555
19. Stathopoulos L, Nicaise C, Michel F, et al: Terlipressin as rescue therapy for refractory pulmonary hypertension in a neonate with a congenital diaphragmatic hernia. *J Pediatr Surg* 2011; 46:e19–e21