The Heart Surgery Forum 2022-4569
25 (2), 2022 [Epub April 2022]
doi: 10.1532/hsf.4569

Online address: http://journal.hsforum.com

Perioperative Use of Pituitrin after Cardiac Defect Repair in Adult Patients with Severe Pulmonary Hypertension

Yuntao Li, MD,[1] Mingwui Tung, MD,[1] Jianping Xu, MD,[1,2] Guangyu Pan, MD,[1] Rui Jiang, MD[2,3]

[1]Department of Cardiac Surgery, Peking University International Hospital, Beijing, China; [2]Adult Cardiac Surgery Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; 3Key Laboratory of Pulmonary Vascular Medicine, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ABSTRACT

Background: Vasopressin can constrict peripheral arteries without constricting the pulmonary artery. Theoretically, vasopressin is suitable for the perioperative treatment of pulmonary hypertension. Few studies have investigated the use of pituitrin (a substitute for vasopressin) after cardiac defect repair surgery. This study aimed to analyze the effect of pituitrin on hemodynamics and to determine whether pituitrin can be used after surgical repair in adult patients with pulmonary arterial hypertension-congenital heart disease (PAH-CHD).

Methods: A pulmonary artery catheter was used in all the patients for hemodynamic monitoring. Hemodynamic parameters were recorded before and at 0.5 h, 1 h, 6 h, 12 h and 24 h after pituitrin administration. The changes in the hemodynamic parameters before and after pituitrin use were analyzed through repeated measures analysis of variance.

Results: A total of 110 patients with PAH-CHD underwent repair surgery; 23 patients were included in further analysis, including 11 with atrial septal defect, 9 with ventricular septal defect, and 3 with patent ductus arteriosus. Ten (43.5%) were men, with a mean age of 29.4 ± 6.8 years. Hemodynamic parameters before and after the oxygen test were as follows: radial artery oxygen saturation, 91.5% ± 4.4 vs. 97.9 ± 2.4%; pulmonary vascular resistance, 10.5 ± 1.8 Wood units (wu) vs. 5 ± 1.2 wu; systemic-pulmonary blood flow ratio (QP/QS), 1.1 ± 0.2 vs. 2.1 ± 0.9. With prolonged use, the systolic blood pressure of the radial artery increased significantly (P = 0.001), that of the pulmonary artery decreased significantly (P = 0.009), and RP/s decreased significantly (P < 0.001).

Conclusion: Pituitrin as an alternative to vasopressin can increase arterial pressure, decrease pulmonary artery pressure, and reduce the pulmonary artery pressure/arterial pressure ratio after repair surgery in adult patients with PAH-CHD.

Received January 18, 2022; accepted February 27, 2022.

Correspondence: Yuntao Li, MD, Peking University International Hospital, Beijing, China, (e-mail: lyt19203@163.com).

INTRODUCTION

Pulmonary arterial hypertension (PAH) is common in patients with congenital heart diseases (CHD). Approximately 10% of CHD patients present with PAH (PAH-CHD), and the incidence of PAH increases with age [van Riel 2014; Lowe 2011]. According to recent guidelines for the diagnosis and treatment of pulmonary hypertension (PH), PAH-CHD is categorized as the first major category of PH, which is hemodynamically characterized by precapillary pulmonary hypertension and is defined as mean pulmonary arterial hypertension (mPAP) ≥25 mmHg, pulmonary vascular resistance (PVR) >3 Wood units (wu), and pulmonary artery wedge pressure (PAWP) ≤15 mmHg [Galie 2016]. Morbidity and mortality are significantly increased in patients with CHD once they develop PAH [Lowe 2011; Smilowitz 2019; Sommer 2008]. In China, many patients with congenital heart disease do not close their defects during childhood, resulting in PH in adulthood.

Over the past decade, crucial success has been achieved in the development of PAH-targeted medications and perioperative management of PAH-CHD. Many symptomatic adults with severe PAH-CHD suffer from late diagnosis and hence may be considered inoperable due to irreversible PAH in developing countries. Patients who were previously considered inoperable may still benefit from repair surgery with targeted therapy and improved right ventricular function [Bradley 2019; Bradley 2013], based on the results from long-term follow up.

Perioperatively, patients are prone to sudden pulmonary artery constriction due to pain, tracheal intubation, stress response, extracorporeal circulation, endothelial cell injury, systemic inflammatory response syndrome, and reduced nitric oxide (NO) synthesis, leading to pulmonary hypertensive crisis and right heart failure [Lindberg 2002; Adatia 2009]. For patients with PH crisis and severe right heart insufficiency, vasoconstriction aims to increase coronary perfusion pressure and hence right ventricular blood supply thus improving right heart function [Adatia 2009; Olsson 2018]. Catecholamines and vasopressin (AVP) raise systemic vascular resistance (SVR), systolic arterial pressure (SAP), and pulmonary arterial pressure (PAP), but only AVP reduces the ratio of PAP and SAP (PAP/SAP) [Siehr 2016]. Previous studies support that AVP can significantly improve oxygenation

Table 1. Demographics and treatment process data of patients

	Mean	SD
Age (y)	29.4	6.9
Sex (M %)	10/23 (43.5)	
Height (cm)	165.6	8.6
Body weight (kg)	56.5	11.6
BMI (kg/m^2)	20.5	3.2
CPB (min)	101.3	48.6
Clap time (min)	63.6	30.9
PO-LOS (d)	9.3	4.4
Ventilation time (h)	44.3	30.9
ICU-LOS (h)	83.1	39.4
BNP (pg/ml)	58.6	92.9
UCG LA (mm)	35.2	5.6
LVEDD (mm)	43.6	9.4
LVEF (%)	66.8	8

BMI, body mass index; CPB, cardiopulmonary bypass; PO-LOS, postoperative length of stay; ICU-LOS, intensive care unit length of stay; UCG, ultrasound cardiography; LA, left atrium; LVEDD, left ventricular end; LVEF, left ventricular ejection fraction; SD, standard deviation

Table 2. Types of CHDs in this study

Type of CHD	No. (%)
ASD	11/23 (48%)
VSD	9/23 (39%)
PDA	3/23 (13%)

CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect, PDA, patent ductus arteriosus

and elevate SAP [Mohamed 2014] and increase NO synthesis via the pulmonary V1 receptor pathway, thereby reducing pulmonary artery pressure [Hoeper 2011; Evora 1993]. However, the role of the perioperative use of AVP in patients with severe PAH-CHD remains unclear. We used pituitrin as an alternative to AVP in clinical practice in mainland China. This retrospective study aimed to determine the effect of intravenous pituitrin on pulmonary and systemic circulatory pressures in patients with PAH-CHD.

MATERIALS AND METHODS

Patient selection: We retrospectively reviewed adults with severe PAH-CHD who underwent repair surgery between January 1, 2020, and December 31, 2020, in our institution.

Table 3. Hemodynamic parameters before and after OT

Hemodynamic parameters	Before OT (mean ± SD)	After OT (mean ± SD)
SaO_2 (%)	91.5 ± 4.4	97.9 ± 2.4
SPAP (mmHg)	109.087 ± 17.6	100.7 ± 17.3
DPAP (mmHg)	53.7 ± 13	45.3 ± 13.1
MPAP (mmHg)	73.9 ± 11.4	66.7 ± 12.9
PVR	10.5 ± 1.8	5 ± 1.2
QP/QS	1.1 ± 0.2	2.1 ± 0.9

OT, oxygen test; SaO_2, oxygen saturation; SPAP, systolic pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; QP/QS, systemic-pulmonary blood flow ratio

Table 4. Dosage of vasoactive drugs during perioperative stage

Vasoactive agents	mean	SD
DAmax (μg/kg.min)	4.1	1.7
NEmax (μg/kg.min)	0.2	0.15
Pitmax (u/h)	2.5	2.6
NEbase (μg/kg.min)	0.16	0.1

DAmax, dopamine maximum dose; NEmax, norepinephrine maximum dose; Pitmax, pituitrin maximum dose; NEbase, baseline norepinephrine (norepinephrine dosage at the beginning of pituitrin administration)

The inclusion criteria were as follows: 1) age ≥18 years; 2) surgery under extracorporeal circulation, and 3) continuous use of intravenous pituitrin after surgery. Exclusion criteria included patients without a preoperative pulmonary artery catheter (PAC) and inhaled oxygen test (OT, 100% oxygen inhaled for 10 min at 10 L/min) and those without a PAC for hemodynamic monitoring during the surgery.

All patients were treated preoperatively with ambrisentan 10 mg/day and tadalafil 20 mg/day until the day of surgery. Postoperative PAP was recorded before PAC removal. Conventional sternotomy with general anesthesia and cardiopulmonary bypass was performed during the repair surgery. This study was approved by the local ethics committee in compliance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective design of this study, and all investigations were performed for routine clinical care.

Data collection and follow-up: General demographic characteristics were collected for all patients, including a detailed description of the preoperative right heart catheterization parameters, preoperative hemodynamics from echocardiography, duration of mechanical ventilation, length of intensive care unit (ICU) stay, and duration of extracorporeal

Table 5. Pressures at different time points

	T1	T2	*P*	T3	*P*	T4	*P*	T5	*P*	T6	*P*
SAP	88.2 ± 13.2	95.2 ± 11.8	0.773	99 ± 11.2	0.076	98.7 ± 8	0.065	100.3 ± 8.5	0.027	100.2 ± 7.3	0.017
DAP	53.6 ± 8.2	57 ± 7.6	0.442	58.7 ± 7.9	0.06	59 ± 5.8	0.151	59.1 ± 6.6	0.334	59.4 ± 7.1	0.205
SPAP	74.1 ± 24.8	75.8 ± 24.8	1	76.7 ± 21.4	1	74.7 ± 19.9	1	62.7 ± 14.9	0.06	65.3 ± 20.1	1
DPAP	44.3 ± 14.8	43.7 ± 12.9	1	43.6 ± 11	1	40.7 ± 10.3	1	35.6 ± 9	0.003	36.3 ± 10.8	0.013
Rp/s	0.84 ± 0.23	0.8 ± 0.25	1	0.78 ± 0.23	0.518	0.76 ± 0.18	0.909	0.63 ± 0.13	<0.001	0.65 ± 0.19	0.024

Pressures before using intravenous pituitrin (T1) and at different time points: at 0.5 h (T2), 1 h (T3), 6 h (T4), 12 h (T5), and 24 h (T6) after pituitrin administration

circulation. Radial artery pressure and pulmonary artery pressure were collected at baseline (T1), 0.5 h (T2), 1 h (T3), 6 h (T4), 12 h (T5), and 24 h (T6) after using pituitrin.

Statistical analysis: Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as numbers (percentages). Differences in categorical data were evaluated using the chi-squared test. Repeated measurement data were statistically analyzed using repeated-measures analysis of variance. Statistical significance was set at a two-tailed P-value of 0.05. Statistical analyses were performed using SPSS software (version 23.0, IBM, Corp., Armonk, NY, USA).

RESULTS

Patient characteristics: A total of 110 patients with PAH-CHD underwent repair surgery; 25 (22.7%) patients were treated perioperatively with pituitrin; one patient with complex congenital malformation was excluded due to the absence of the OT, and one case without PAC was excluded due to severe tricuspid regurgitation. A total of 23 patients with PAH-CHD, with a mean age of 29.4±6.8 years, were included for further analysis. Demographics and treatment process data are shown in Table 1. (Table 1) Ten (43.5%) patients were men, and 11 had an atrial septal defect (ASD), 9 had a ventricular septal defect (VSD), and 3 had patent ductus arteriosus (PDA). (Table 2)

The following changes in hemodynamics were observed before and after the OT: radial artery oxygen saturation (SaO2), 91.5 ± 4.4% vs. 97.9 ± 2.4%; PVR, 10.5 ± 1.8 wu vs. 5 ± 1.2 wu; systemic-pulmonary blood flow ratio (QP/QS), 1.1 ± 0.2 vs. 2.1 ± 0.9. (Table 3)

Two deaths (8.7%) occurred on postoperative day two and five, both from a pulmonary hypertensive crisis. The mean length of ICU stay was 83.1 ± 39.4 h, and the mean ventilation time was 44.3 ± 30.1 h (Table 1). Postoperatively, dopamine (DA), norepinephrine (NE), and pituitrin were administered to all patients, with a maximum dosage of 4.1 ± 1.7 μg/kg.min for DA and 0.2 ± 0.15 μg/kg.min for NE. As a second line vasoactive drug, pituitrin is used when the dosage of NE is large and blood pressure is still low; pituitrin was initiated with a NE dosage (NE base) of 0.16 ± 0.1 μg/kg.min, and the maximum pituitrin was administered was 2.5 ± 2.6 U/h. Dobutamine and epinephrine were used in two patients. (Table 4)

Relationships between intravenous pituitrin and artery pressures: After pituitrin administration, the differences in SAP at different time points were statistically significant ($P = 0.001$). The SAP was elevated by 7 mmHg after 0.5 h (T2) without statistical significance ($P = 0.773$). However, significant elevation in SAP was observed at 12 h (T5) and 24 h (T6); the SAP increased by 12.1 mmHg ($P = 0.027$) and 12 mmHg ($P = 0.017$) at 12 h and 24 h, compared to that at the baseline, respectively. (Figure 1A) (Figure 1B)

There was no statistically significant difference in DAP at each time point ($P = 0.11$); however, there was an increasing trend over time (Figure 2A) (Figure 2B) (Table 5)

Relationships between pituitrin and pulmonary artery pressures: The SPAP after pituitrin use at each time point did not significantly increase compared to that at the baseline (T1) (P values: 1, 1, 1, 0.06, and 1, respectively). However, the SPAP at T5 decreased by 13 mmHg, 13.9 mmHg, and 12 mmHg compared to that at T2, T3, and T4, respectively, with statistically significant differences (P values of 0.021, 0.005, and 0.001, respectively) (Figure 3A) (Figure 3B)

The DPAP showed statistically significant differences at different time points after pituitrin use ($P < 0.001$). Compared with the DPAP at T1, DPAP decreased by 8.7 mmHg and 8 mmHg at time points T5 and T6, respectively (P values of 0.0037 and 0.013, respectively) (Table 5). (Figure 4A) (Figure 4B)

Relationships between pituitrin and Rp/s: Multivariate tests showed statistically significant differences in the Rp/s at different time points after pituitrin use ($P < 0.001$). No significant change in Rp/s was observed at 0.5 h (T2), 1 h (T3), and 6 h (T4) compared to that at the baseline (T1) ($P = 1$, 0.518, and 0.909, respectively). A significant decrease in the Rp/s occurred at T5 and T6 ($P < 0.001$ and 0.016, respectively) (Table 5).

DISCUSSION

This study showed that in the early postoperative period of adult patients with PAH-CHD, pituitrin can elevate SAP and

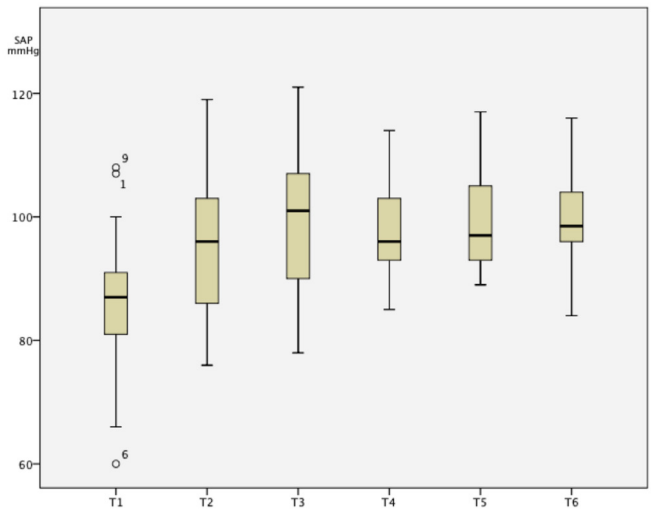

Figure 1A. SAP at different time points after Pituitrin use.

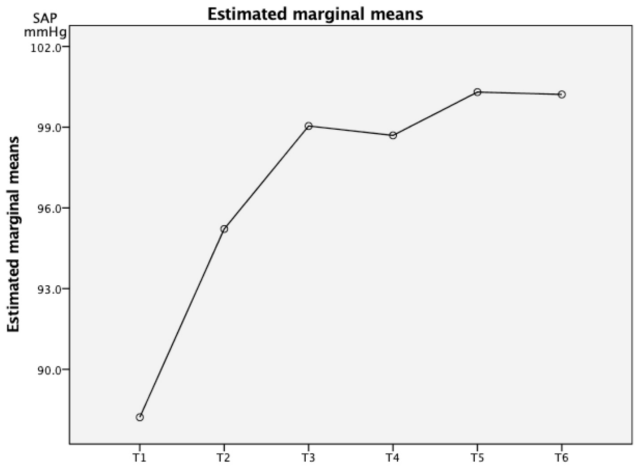

Figure 1B. SAP trends over time after Pituitrin use.

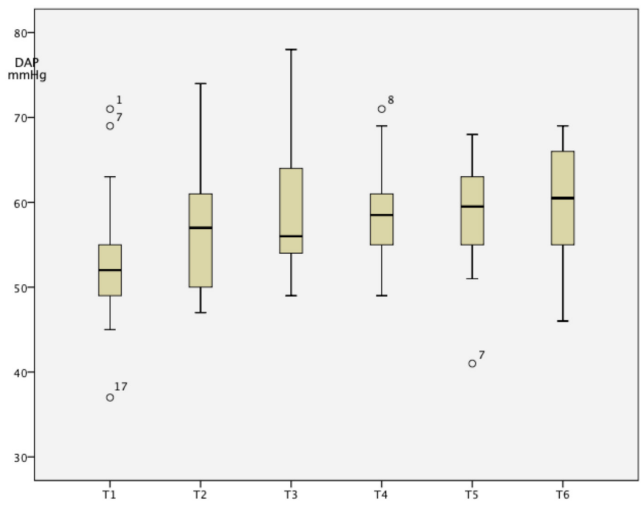

Figure 2A. DAP at different time points after Pituitrin use.

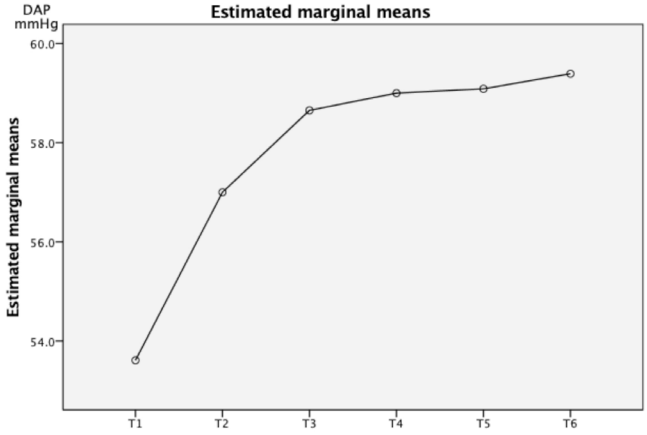

Figure 2B. DAP trends over time after Pituitrin use.

reduce pulmonary artery pressure and Rp/s when the dose of vasoactive drugs is large, and circulation is unstable. Thus, it may be able to prevent and treat pulmonary hypertensive crisis.

The main causes of perioperative mortality in patients with severe PAH-CHD are related to pulmonary hypertensive crisis, leading to right heart failure. Comprehensive management of hemodynamic stability, including continued use of targeted drugs, ensuring oxygenation, reducing volume load, prolonged sedation, adequate analgesia, prevention of infection, and ensuring ventricular perfusion are needed in the perioperative period after surgical repair [Adatia 2009]. Inhalation of nitric oxide (NO) can selectively decrease pulmonary artery pressure [Miller 2000], and it is the preferred treatment method for severe postoperative PH in many centers. However, there is no inhaled NO system approved for medical use in China; therefore, we cannot use this effective treatment.

Right ventricular (RV) perfusion is another key factor in perioperative management of PAH-CHD. Conventional pulmonary vasodilators, such as nitroglycerin, milrinone, levosimendan, and prostacyclin decrease PVR, while SVR [Mullens 2008; Colucci 1986; Comin-Colet 2018; Bouchez 2018], which is associated with perioperative factors, such as systemic inflammatory response and infection, is more likely to cause hypotension after surgery [Ortoleva 2020; Singer 2016], then decrease RV perfusion, and further aggravate right heart failure. Therefore, drugs that raise the SAP and increase myocardial perfusion play an important role in these highly selected patients [Konstam 2018]. Pulmonary and systemic arterial walls contain catecholamine receptors, and catecholamine drugs, such as norepinephrine, epinephrine, and phenylephrine significantly elevate the SPAP and SAP, increase Rp/s, and increase RV afterload [Siehr 2016].

Vasopressin is an alternative vasoconstricting agent. There are three types of AVP receptors in the human body: V1 receptors, mainly distributed in body parts such as vascular smooth muscle cells, platelets, and the liver; V2 receptors,

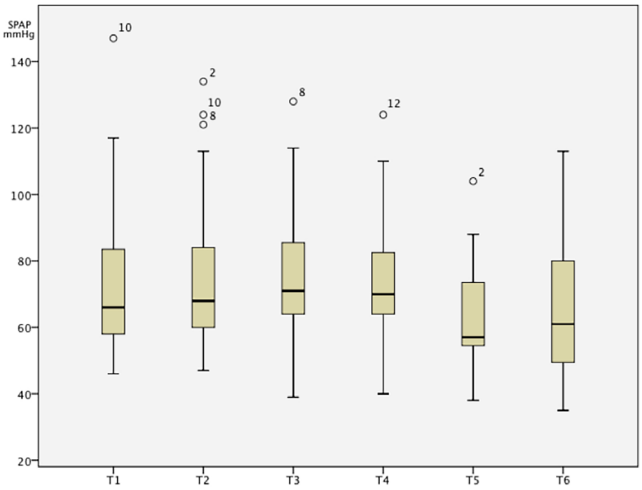

Figure 3A. SPAP at different time points after Pituitrin use.

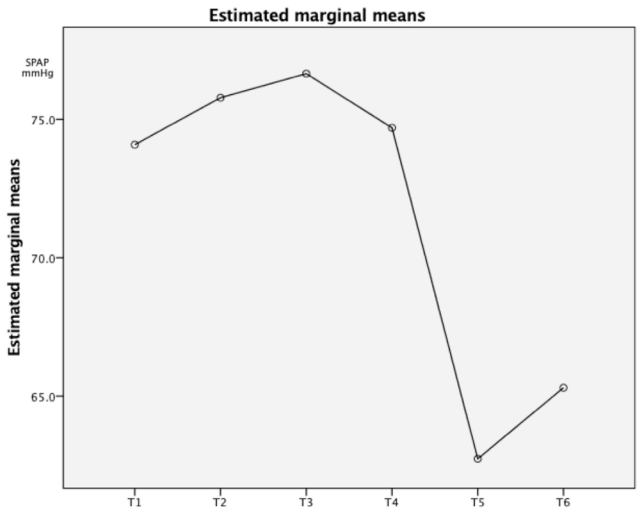

Figure 3B. SPAP trends over time after Pituitrin use.

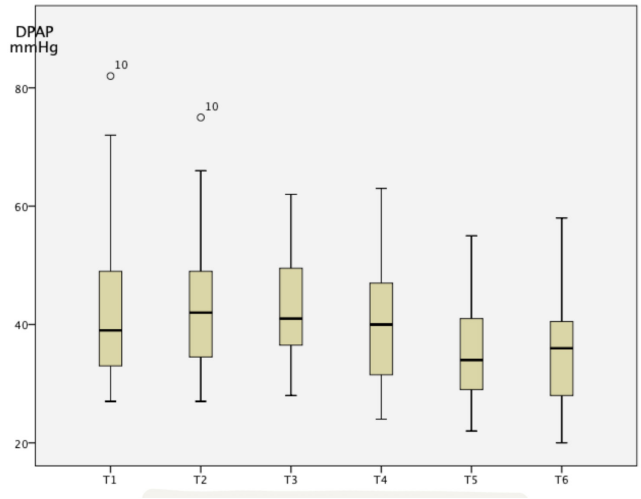

Figure 4A. DPAP at different time points after Pituitrin use.

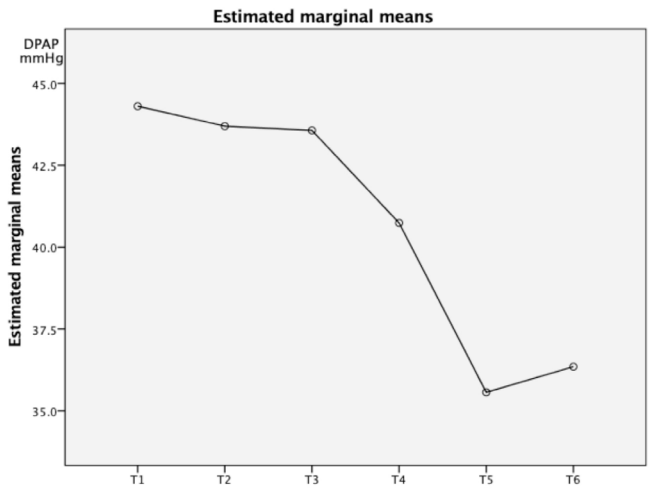

Figure 4B. DPAP trends over time after Pituitrin use.

mainly distributed in the cells of the renal collecting duct; and V3 receptors, mainly distributed in the central nervous system [Treschan 2006].

A previous study supported that supplementation with exogenous AVP elevates SVR [Buijk 1998], and animal and in vitro vascular experiments have found inconsistent effects of AVP on systemic and pulmonary arteries, with AVP constricting radial arteries but not pulmonary arteries [Currigan 2014]. Additionally, AVP agonizes V1 receptors in pulmonary arteries, causing pulmonary artery diastole via the NO pathway [Evora 1993]. The difference in the effects of AVP on the systemic and pulmonary arteries may benefit patients with severe PH. In the treatment of neonatal PH, AVP helps to increase the oxygenation index and reduce inhaled NO concentration [Mohamed 2014]. Vasopressin and its analog, terlipressin, reduce PAP, thereby reversing the pulmonary hypertensive crisis [Scheurer 2005].

Our study showed that there was a tendency to increase SAP immediately after 30 min of intravenous pituitrin use, and significantly decreased the SPAP and DPAP after 12 h compared with the values at the baseline. A similar improvement was observed for Rp/s. Of the 23 patients in this group, seven developed pulmonary hypertensive crisis (7/23), five reversed pulmonary hypertensive crisis after treatment, and two died due to irreversible pulmonary hypertensive crisis.

Although AVP is recommended for cardiac arrest [Panchal 2019] and no serious side effects have been found, a case of myocardial ischemia requiring percutaneous transluminal coronary angioplasty after terlipressin was reported in a patient with coronary artery disease [Medel 2001]. Coronary artery disease is a contraindication for terlipressin, as outlined in the package insert. Lower doses (0.03-0.07 U/min) are usually infused in patients with PH and RV failure [Crystal 2018; Price 2010]. However, studies using high-dose AVP instead

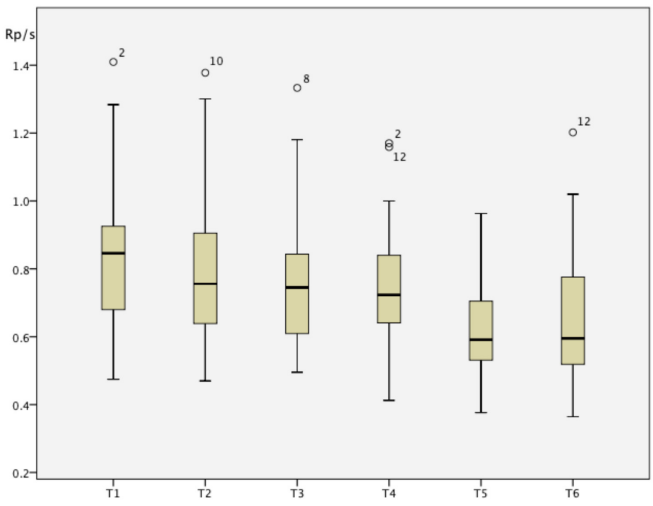

Figure 5A. Rp/s at different time points after Pituitrin use.v

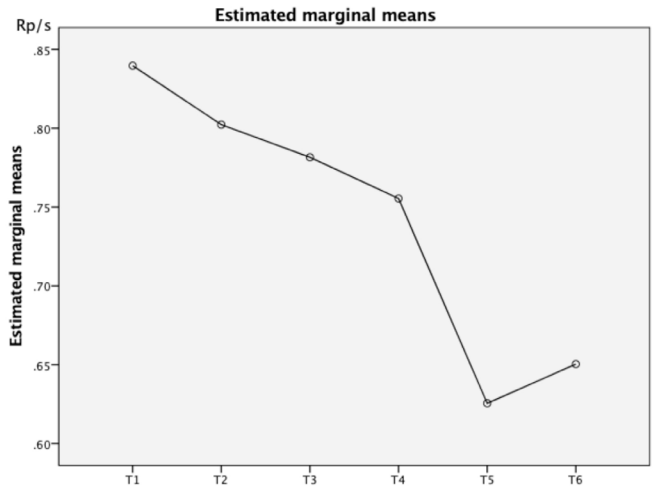

Figure 5B. Rp/s trends over time after Pituitrin use.

of NE in patients with infectious shock have shown that AVP significantly reduces cardiac output, decreases oxygen delivery, and decreases visceral blood supply compared with NE [Klinzing 2003; Dunser 2004]. The safe dose of AVP/pituitrin is not well known. The maximum dose of pituitrin used in this group was 2.5 ± 2.6 U/h. The maximum dose of pituitrin in the two deceased patients was 6 U/h and 5.76 U/h. No signs of myocardial perfusion deficits were observed in any of the included patients.

Norepinephrine mainly agonizes α1-adrenergic receptors and increases SVR but has a weak effect on β1-adrenergic receptors and increases myocardial contractility. All the patients in this group received DA and NE to maintain blood pressure after surgery, and 7 patients also received pituitrin. The other 16 patients started pituitrin only when circulation was difficult to maintain. The average dose of NE when starting vasopressin was 0.16 ± 0.1 μg/kg.min, and the maximum NE was 0.2 ± 0.15 μg/kg.min. It has been shown that a combination of NE and pituitrin enhances the vasoconstrictive effect of each of the two drugs. In our experience, when the amount of norepinephrine used is large (>0.1) and the blood pressure has not yet reached the target, the combined use of pituitrin can reduce the amount of NE and the adverse reactions caused by high-dose NE.

This single-center study included a small number of patients who had undergone repair surgery performed by a single surgeon. Moreover, other confounding factors of PAH, such as the prescription and duration of pituitrin use were not controlled because of the study design. The findings of this study may not be applicable to pediatric patients with PAH-CHD or patients with other forms of PAH because of the current inclusion criteria.

In conclusion, pituitrin can increase arterial pressure, decrease pulmonary artery pressure, and reduce Rp/s in patients with PAH-CHD after repair surgery. As an alternative to vasopressin, pituitrin can be safely used in the perioperative management of severe PAH-CHD.

REFERENCES

Adatia I, Beghetti M. 2009. Early postoperative care of patients with pulmonary hypertension associated with congenital cardiac disease. Cardiol Young. 19(4):315-319.

Bouchez S, Fedele F, Giannakoulas G, Gustafsson F, Harjola VP, Karason K, Kivikko M, von Lewinski D, Oliva F, Papp Z, et al. 2018. Levosimendan in Acute and Advanced Heart Failure: an Expert Perspective on Posology and Therapeutic Application. Cardiovasc Drugs Ther. 32(6):617-624.

Bradley EA, Ammash N, Martinez SC, Chin K, Hebson C, Singh HS, Aboulhosn J, Grewal J, Billadello J, Chakinala MM, et al. 2019. "Treat-to-close": Non-repairable ASD-PAH in the adult: Results from the North American ASD-PAH (NAAP) Multicenter Registry. Int J Cardiol. 291:127-133.

Bradley EA, Chakinala M, Billadello JJ. 2013. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. Am J Cardiol. 112(9):1471-1476.

Buijk SE, Bruining HA. 1998. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation. 98(2):187.

Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. 1986. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. Circulation. 73(3 Pt 2):III175-183.

Comin-Colet J, Manito N, Segovia-Cubero J, Delgado J, Garcia Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, et al. 2018. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur J Heart Fail. 20(7):1128-1136.

Crystal GJ, Pagel PS. 2018. Right Ventricular Perfusion: Physiology and Clinical Implications. Anesthesiology. 128(1):202-218.

Currigan DA, Hughes RJ, Wright CE, Angus JA, Soeding PF. 2014. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an in vitro study. Anesthesiology. 121(5):930-936.

Dunser MW, Hasibeder WR, Wenzel V, Mayr AJ. 2004. Lessons learned from high-dosage vasopressin infusion in septic shock. Crit Care Med. 32(6):1433-1434; author reply 1434.

Evora PR, Pearson PJ, Schaff HV. 1993. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest. 103(4):1241-1245.

Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 2016. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 37(1):67-119.

Hoeper MM, Granton J. 2011. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 184(10):1114-1124.

Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A. 2003. High-dose vasopressin is not superior to norepinephrine in septic shock. Crit Care Med. 31(11):2646-2650.

Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, et al. 2018. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 137(20):e578-e622.

Lindberg L, Olsson AK, Jogi P, Jonmarker C. 2002. How common is severe pulmonary hypertension after pediatric cardiac surgery? J Thorac Cardiovasc Surg. 123(6):1155-1163.

Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ. 2011. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J Am Coll Cardiol. 58(5):538-546.

Medel J, Boccara G, Van de Steen E, Bertrand M, Godet G, Coriat P. 2001. Terlipressin for treating intraoperative hypotension: can it unmask myocardial ischemia? Anesth Analg. 93(1):53-55, TOC.

Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. 2000. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet. 356(9240):1464-1469.

Mohamed A, Nasef N, Shah V, McNamara PJ. 2014. Vasopressin as a rescue therapy for refractory pulmonary hypertension in neonates: case series. Pediatr Crit Care Med. 15(2):148-154.

Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, Taylor DO, Tang WH. 2008. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 52(3):200-207.

Olsson KM, Halank M, Egenlauf B, Fistera D, Gall H, Kaehler C, Kortmann K, Kramm T, Lichtblau M, Marra AM, et al. 2018. Decompensated right heart failure, intensive care and perioperative management in patients with pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 272S:46-52.

Ortoleva J, Shapeton A, Vanneman M, Dalia AA. 2020. Vasoplegia During Cardiopulmonary Bypass: Current Literature and Rescue Therapy Options. J Cardiothorac Vasc Anesth. 34(10):2766-2775.

Panchal AR, Berg KM, Hirsch KG, Kudenchuk PJ, Del Rios M, Cabanas JG, Link MS, Kurz MC, Chan PS, Morley PT, et al. 2019. 2019 American Heart Association Focused Update on Advanced Cardiovascular Life Support: Use of Advanced Airways, Vasopressors, and Extracorporeal Cardiopulmonary Resuscitation During Cardiac Arrest: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 140(24):e881-e894.

Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. 2010. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care. 14(5):R169.

Scheurer MA, Bradley SM, Atz AM. 2005. Vasopressin to attenuate pulmonary hypertension and improve systemic blood pressure after correction of obstructed total anomalous pulmonary venous return. J Thorac Cardiovasc Surg. 129(2):464-466.

Siehr SL, Feinstein JA, Yang W, Peng LF, Ogawa MT, Ramamoorthy C. 2016. Hemodynamic Effects of Phenylephrine, Vasopressin, and Epinephrine in Children With Pulmonary Hypertension: A Pilot Study. Pediatr Crit Care Med. 17(5):428-437.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 315(8):801-810.

Smilowitz NR, Armanious A, Bangalore S, Ramakrishna H, Berger JS. 2019. Cardiovascular Outcomes of Patients With Pulmonary Hypertension Undergoing Noncardiac Surgery. Am J Cardiol. 123(9):1532-1537.

Sommer RJ, Hijazi ZM, Rhodes JF, Jr. 2008. Pathophysiology of congenital heart disease in the adult: part I: Shunt lesions. Circulation. 117(8):1090-1099.

Treschan TA, Peters J. 2006. The vasopressin system: physiology and clinical strategies. Anesthesiology. 105(3):599-612; quiz 639-540.

van Riel AC, Schuuring MJ, van Hessen ID, Zwinderman AH, Cozijnsen L, Reichert CL, Hoorntje JC, Wagenaar LJ, Post MC, van Dijk AP, et al. 2014. Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol. 174(2):299-305.