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Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension

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Abstract

Low systemic vascular resistance (SVR) hypotension concomitant with pulmonary hypertension (PH) is difficult to manage postoperatively because they are often catecholamine-resistant. So, we applied arginine vasopressin (AVP), which is a potent vasoconstrictor in a specific condition, for post-cardiotomy refractory low SVR hypotension concomitant with PH. We treated nine cases of postoperative refractory vasodilatory hypotension concomitant with PH even after conventional treatment that included nitric oxide inhalation and/or intraaortic balloon pump. AVP was administrated with 0.05∼0.1 U/min intravenously. After AVP administration, the mean systemic arterial pressure increased from 47.3±9.5 to 76.5±12.2 mmHg ($P<0.01$) and SVR increased from 488.1±92.7 to 1188±87 dynes·s·cm^{-5} ($P<0.01$). Fortunately, even though the cardiac index decreased, it remained in a normal range. Alteration in the PVR was not significant, but the Pp/Ps became somewhat lower (0.66±0.2 to 0.47±0.16, $P<0.01$). AVP increased the urine output and improved oxygenation. AVP improved systemic circulation (increased systemic blood pressure with maintaining cardiac output) without deterioration of pulmonary hypertension. AVP is an ideal drug for treating refractory low SVR hypotension concomitant with PH. But its indication must be limited.

Keywords: Arginine vasopressin; Low systemic vascular resistance; Pulmonary hypertension; Post-cardiac surgery management

1. Introduction

Postoperative low systemic vascular resistance (SVR) hypotension is one of the major consequences of cardiac surgery because it leads to delayed extubation and prolonged stay in an intensive care unit [1, 2]. If pulmonary hypertension (PH) is additionally involved with low SVR hypotension, circulation management will be much more complicated. These cases are often cathecolamine-resistant and a vasoconstrictive drug may worsen PH. On the other hand, a medication used to reduce PH may lead to a worsening of the systemic hypotension.

Here, we report a successful effort in treating low SVR hypotension concomitant with PH using arginine vasopressin (AVP), a potent vasoconstrictor. Our treatment gave priority to treating systemic blood pressure over coping with PH.

2. Patients and methods

Definitions of PH, SVR, pulmonary vascular resistance (PVR) and vasodilatory hypotension are given in Table 1. Between January 2000 and May 2006, we carried out 1766 cases of adult cardiac surgery. In this series, we encountered refractory vasodilatory hypotension after cardiac surgery under cardiopulmonary bypass (CPB) and treated it with AVP administration in nine cases. The indication for AVP administration was a prolonged period of low SVR hypotension (SVR <800 dyne·s·cm^{-5} and systolic systemic blood pressure (s-BP) <80 mmHg or mean systemic blood pressure (m-BP) <65 mmHg) even after conventional treatment (undertreatment with proper preload, dopamine+dobutamine >20 μg/kg/min, and/or noradrenaline >0.1 μg/kg/min). Intraaortic balloon pump (IABP) and nitric oxide (NO) inhalation were applied if necessary. Intravenous AVP administration was started at 0.05 U/min and was continuously infused at 0.05∼0.1 U/min.

All data are expressed as the mean±standard deviation. A matched pair *t*-test analysis was used when appropriate. A *P*-value <0.05 was considered significant.

3. Results

Profiles of the nine cases are described in Table 2. Redo-cardiac surgery (4 cases), preoperative left ventricular dysfunction (Cardiac Index, CI <1.8 l/min/m² or left ventricular ejection fraction <40% by catheter examination (4 cases), preoperative PH (6 cases) and preoperative oral medical treatment with an angiotensin-converting enzyme

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Table 1
Definitions

- Pulmonary hypertension
  Pp/Ps (mean) >0.4, or systolic PA >45 mmHg
- Systemic vascular resistance (SVR)
  SVR=(mean BP-CVP)×80/CO dynes·s·cm^{-5}
- Pulmonary vascular resistance (PVR)
  PVR=(mean PA-PCWP)×80/CO dynes·s·cm^{-5}
- Vasodilatory systemic hypotension
  SVR <800 dynes·s·cm^{-5} and, systolic BP <80 mmHg or mean BP <65 mmHg

inhibitor or an angiotensin II receptor blocker (7 cases) were frequently observed.

Aortic cross-clamp and extracorporeal circulation times were 135.3±50.6 min and 213.6±68.5 min, respectively. The average lowest rectal temperature was 29.9±4.0 °C, and one case underwent a deep hypothermia operation (<20 °C, Case 9). Transfusion of blood products were relatively large: MAP 10.6±8.2 U, FFP 9±4.2 U, Platelet 3.8±5.2 U during operations; and MAP 2.9±3.7 U and FFP 7.2±5 U postoperatively. Two cases were managed without transfusions perioperatively.

All nine patients had been suffering from low SVR hypotension even after the maximum conventional treatment (m-BP 47.3±9.5 mmHg, SVR 488.1±92.7 dyne·s·cm^{-5}) (Fig. 1). An IABP was applied in five patients (three of them were prophylactic use since preoperatively). Despite the application of NO inhalation for all patients, PH was prolonged mean pulmonary artery pressure (m-PA) 30.3±9.4 mmHg, PVR 205.1±103.3 dyne·s·cm^{-5}.

Following AVP infusion, the plasma AVP level increased from 16.8±25.4 to over 100 pg/ml. Rapid systemic vasoconstractive effect was observed within 15 min. One hour after AVP administration, m-BP increased from 47.3±9.5 to 76.5±12.2 mmHg ($P<0.05$), and SVR increased from 488.1±92.7 to 1188±87 dyne·s·cm^{-5} ($P<0.001$). Fortunately, the cardiac index decreased (CI 3.51±0.61 to 3.09 to 0.64 l/min/m^2, $P<0.05$), the CI was maintained in a normal range. Four patients could be weaned from noradrenaline administration within 2 h after the AVP com-

Table 2
Profile of nine cases

	Diagnosis	Preoperative status	Operative procedures
1	58-year-old, male		
	Prosthetic valve endocarditis	CTR 58%, BP100/55	Re-re MVR
	(Mitral position)	PA 38/20, PCW 22	
	Post MVR+AVR	CVP11, CI 2.8, EF58%	
	Post reMVR+AVR		
2	35-year-old, male		
	OMI+MR	CTR 46%, BP86/59	CABG+MVR
		PA 73/30, PCW 24	Prophylactic-IABP
		CVP7, CI 1.8,	
		EF32%	
3	65-year-old, male		
	Constrictive pericarditis	CTR 68%, BP106/73	Pericardiectomy re
	Paravalvular leakage	PA 76/40, PCW 33	AVR
	(Aortic position)	CVP33, CI 1.7, EF56%	Prophylactic-IABP
	Post resection of sinus of		
	Valsalva aneurysm+AVR		
4.	67-year-old, male		
	MR, TR, OMI	CTR 64%, BP90/62	MVR+TAP
	Post CABG+MAP+TAP	PA 84/36, PCW 26	Prophylactic-IABP
		CVP14, CI 2.0, EF35%	
5	51-year-old, male		
	DCM, MR, TR	CTR 58%, BP90/62	MVP+TAP
		PA 45/25, PCW 22	IABP
		CVP10, CI 2.3, EF32%	
6	64-year-old, male		
	MR, TR	CTR 72%, BP80/56	MVP+TAP
		PA 36/18, PCW 18	
		CVP14, CI 2.7, EF54%	
7	64-year-old, female		
	MR, TR	CTR 61%, BP100/60	MVR+TAP
	Post AVR+Asc Aorta Replace	PA 73/23, PCW 22	
	Chronic renal failure on HD	CVP10, CI 2.5, EF67%	
8	70-year-old, male		
	AR, MR	CTR 69%, BP122/50	AVR+MVP+TAP
		PA 30/16, PCW 20	
		CVP6, CI 2.5, EF43%	
9	63-year-old, male		
	AS, MS, Calcified Asc Aorta	CTR 46%, BP150/70	AVR+MVR+TAP
		PA 60/30, PCW 28	Asc Aorta Replace
		CVP9, CI 4.4, EF73%	

MVR, mitral valve replacement; AVR, aortic valve replacement, OMI, old myocardial infarction; CABG, coronary artery bypass grafting; TR, tricuspid valve regurgitation; DCM, dilate cardiomyopathy; Asc Ao Replace, ascending aorta replacement; MS, mitral valve stenosis; HD, hemodialysis.

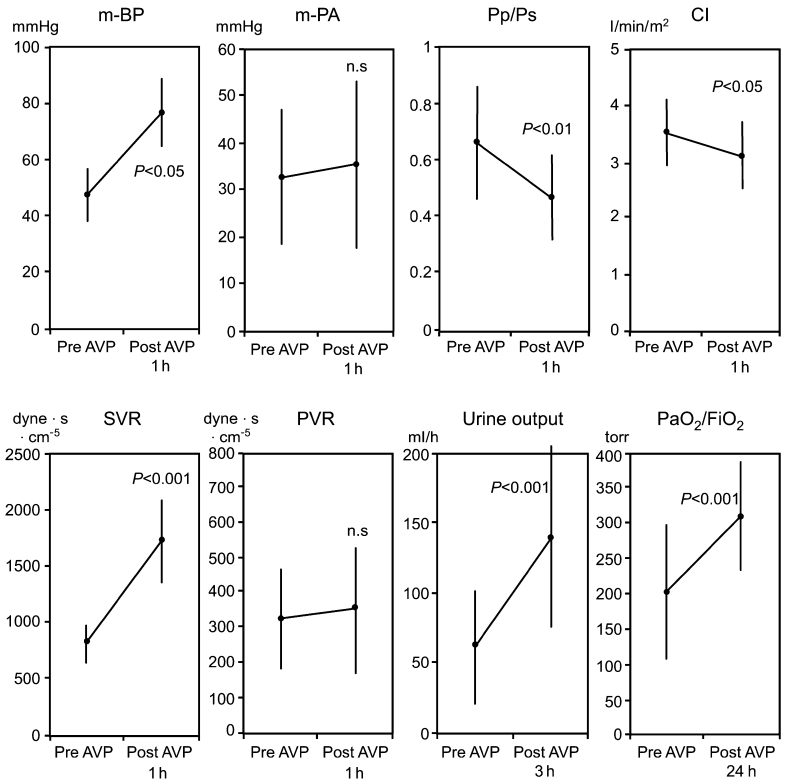

Fig. 1. Effects of Arginine Vasopressin. mBP, mean systemic blood pressure; mPA, mean pulmonary artery pressure; Pp/Ps, systemic blood pressure/pulmonary artery pressure; CI, cardiac output index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. The values of mBP, SVR, urine output, and PaO_2/FiO_2 increased, and Pp/Ps decreased significantly. The values of mPA and PVR were not changed.

menced. Alterations in PA and PVR were not significant, but Pp/Ps lowered significantly (0.66 ± 0.2 to 0.47 ± 0.16, $P < 0.01$). No RV failure was observed in any cases.

Furthermore, RV failure was not observed in any cases. Fortunately, AVP enhanced urine output (62.1 ± 40.1 to 140 ± 55.5 ml/min at 3 h after AVP, $P < 0.001$) and subsequently improved the water balance. The respiratory function was also improved (PaO_2/FiO_2 of 201.8 ± 94.8 to 310.8 to 76.2 at 24 h after AVP, $P < 0.001$). The duration of AVP administration and ICU stay were 4.0 ± 2.3 days and 15.8 ± 16.5 days. Continuous hemodiafiltration was applied in three cases (Case 5, 7, 9), which included a chronic hemodialisis patient since preoperatively (Case 9). One patient was suffering from pericarditis, which required creating a pericardial fenestration (Case 9). Two patients died due to sepsis (Case 3, POD 56) and sustained ventricular fibrillation (Case 5, POD 14).

4. Comment

Low SVR hypotension occurred in 5%~22% of post-cardiac surgery cases [1, 2]. Various causes may be attributed for it: the hypothermia and duration of CPB, the total cardioplegic volume infused, reduced left ventricular function, preoperative treatment with angiotensin-converting enzyme inhibitors, and systemic inflammatory response syndrome [1, 2]. Not only these mechanisms, but also inappropriate low AVP secretion may be another important factor in producing low SVR hypotension, as we describe later.

Unfortunately, the effectiveness of pressor catecholamines is limited in cases of low SVR hypotension because their action is interrupted due to cellular acidosis, opening of ATP sensitive channels, efflux of K and hyperpolarization of the myocytes, which prevents voltagegated Ca channels from opening so that Ca influx into the cells and smooth muscle contraction is halted [1−4]. In addition, high dose cathecolamine often leads to significant toxic effects, such as tachyarrythmia. If PH is additionally involved, circulatory management becomes much more difficult. Because the conventional drugs that reduce PVR − for example, prostaglandin E1 and phosphodiesterase inhibitor − have the potential to cause life-threatening systemic hypotension. Before we began this study, we had a hard time overcoming this conflict. We used to reluctantly accept low SVR hypotention and high cardiac output and had made great efforts to treat PH instead of increasing the systemic blood pressure, if a certain level organ perfusion pressure is maintained. Because decreasing the LV after load and maintaining a certain output is a basic management for a poor LV function case. However, even if we used the maximum conventional treatment, including NO inhalation and IABP, the systemic hypotension with PH did not improve. The trial, using phosphodiesterase inhibitor for right-sided, and infusing norepinephrine for left-sided to counterbalance, was also a limited success. Then, we changed out policy. We took priority to maintain the systemic pressure (normalize the SVR) over to reduce PH. Subsequently, we selected AVP, which is a potent vasoconcentrator used for shock states.

What is AVP? Endogenous AVP is released from the posterior pituitary in response to increased serum osmolality or reduced plasma volume. Under normal conditions, the major physiological role of vasopressin is the regulation of water balance. It does not appear to play a major role in the vascular regulation of blood pressure. In shock states, however, the release of endogenous vasopressin is an important vasoconstrictor mechanism and vascular response to 'exogenous' AVP is markedly enhanced [2−6].

Understanding the association between the AVP level and CPB is not simple. Post-CPB hypotension is typically associated with a marked increase in AVP levels to concentrations of over 100 pg/ml [6]. On the other hand, there is a report which focused on vasodilatory shock after cardiac surgery that indicated that AVP level was inappropriately low for the degree of systemic hypotension that was present; it was in the normal osmoregulatory range for healthy normotensive subjects [2]. Another report showed that inappropriately low levels of AVP (8∼34 pg/ml) often exist in hypotension after a left ventricular assist device implantation [6]. These reports indicate that a long-term congestive heart failure may lead to exhaustion of AVP secretion and that a relative deficiency in AVP correlates with episodes of vasodilatory shock [2, 6]. Therefore, the supplementary AVP infusion results in an improved and stable hemodynamic state. Dünser et al. reported a prospective randomized study, where the combination infusion of AVP and noradrenarine are superior to infusion of noradrenarine alone in the treatment of cardiocirculatory failure in catheholamine-resistant vasodilatory shock [3]. Luckner et al. also described the effectiveness of supplementary AVP infusion in advanced vasodilatory shock, and recommended to initiate the AVP infusion before norepinephrine requirements >0.6 μg/kg/min [4].

The mechanisms by which exogenous AVP normalizes the vascular tone are speculated as follows. First, AVP activates the second messenger system of inositol triphosphate and diacylglycerol in vascular smooth muscle cells, causing a rise in cytoplasmic Ca^{2+} [7]. Second, AVP inhibits the NO-induced accumulation of cyclic guanosine monophosphate in vascular smooth muscles [8]. Third, AVP closes K^{+}ATP channels if open, halting the efflux of K^{+} and promoting myocyte depolarization. This depolarization enables Ca^{2+} to enter the myocytes and cause contraction [9]. The relative deficiency in AVP accompanied by sustained hypotension, hypoperfusion, and lactic acidosis results in NO production and hyperpolarization of myocytes. The exogenous AVP helps to repolarize the myocytes and inhibits NO production. This allows catecholamines to synergistically work with AVP to bring about a stable hemodynamic state.

In addition, the AVP's minimum effect on pulmonary vascular bed, not as like as on systemic artery, is preferable. Animal experiments have shown that AVP selectively vasodilates the pulmonary vasculature under hypoxic conditions through an endothelium (not the smooth muscle cells, which induces vasoconstriction) V1 receptor-mediated release of NO [10]. Tagawa et al. reported that AVP-induced vasodilatation was mediated by the NO induction through a V2 receptor [11]. They also suggested that AVP has a unique biphasic effect on the vascular resistance; vasoconstriction at lower doses and vasodilatation at higher doses. On balance, therefore, the vasoconstriction of vascular smooth muscle cells and the vasodilatation of NO induction determine the actual degree of vasoconstriction. Our data show that the organ-specific vasoreaction by AVP is favorable in treating low SVR hypotension with PH.

An increase in urine output is also a favorable effect, even though AVP is known as an antiduretic hormone. Similar results from AVP administration have been shown in cases of hemorrhage, sepsis, and severe heart failure [2, 5]. Increased systemic blood pressure contributes to the glomerular filtration volume. Furthermore, AVP receptors in the renal vasculature are concentrated in the efferent arterioles, in contrast to catecholamine receptors, which are concentrated on the afferent arterioles [12]. Therefore, unlike catecholamine vasoconstriction, which causes a decreased filtration fraction, AVP causes an increase in the filtration fraction and the urinary output [12, 13].

After significant urine output has occurred, the respiratory condition improves as a secondary result. In addition, AVP is more effective than epinephrine in the early post-resuscitation phase in improving pulmonary gas exchange because it is less likely to induce a ventilation-perfusion mismatch [14].

The possible adverse reactions are cardiovascular (hypertension, bradycardia, arrhythmias, venous thromosis, angina), neurologic ('pounding' of the head, diaphoresis, fever, vertigo, tremors), dermatologic (urticaria, circumoral pallor), and gastrointestinal (flatus, abdominal cramps, nausea, emesis, hyperbilirubinemia) [4, 5]. Fortunately, we did not encounter any complications associated with AVP administration. Although the mortality was high (2 out of 9) in this series, it does not seem due to AVP administration but poor systemic condition since preoperatively. In order to prevent a possible complication, strictly maintaining the proper dose must be essential.

4.1. Study limitation

Since this study was a retrospective analysis, preoperative AVP levels were not available. However, we speculated that the objective patients had been relatively exhausted of AVP preoperatively because they had suffered from poor LV function and PH over a substantial period. In addition, the absolute AVP level may not be so important, while the relative AVP level against the circulatory status is meaningful.

5. Conclusion

We treated postoperative refractory low SVR hypotension concomitant with PH by AVP administration. Exogenous AVP normalized SVR and increased the systemic arterial pressure with a minimum effect on PVR. Subsequently, AVP enhanced urine output and improved respiratory function. AVP is an ideal drug for treating refractory low SVR hypotension concomitant with PH.

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