Arginine vasopressin and paediatric cardiovascular surgery

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Abstract

Introduction

Arginine vasopressin has become an important part of the armamentarium available to paediatric cardiac intensive care physicians managing complex infants and children recovering from cardiovascular surgery. This therapy must be applied cautiously, however, as excessive afterload from its vasoconstrictive effects could be potentially detrimental to this patient population. Relative arginine vasopressin deficiency has been identified in some children recovering from cardiovascular surgery, and these children likely represent the ideal candidates for arginine vasopressin therapy. The aim of this critical review is to discuss arginine vasopressin and paediatric cardiovascular surgery.

Conclusion

Knowledge of endogenous plasma arginine vasopressin activity prior to initiation of therapy could therefore be helpful in clinical bedside decision making and should be the goal of future research.

Introduction

As the practice of paediatric cardiovascular surgery has evolved, the armamentarium of medical and technological therapies available to cardiac intensivists has expanded beyond traditional volume resuscitation and catecholamine administration (e.g. dopamine, dobutamine, epinephrine and norepinephrine). One of the most intriguing of these therapies is arginine vasopressin (AVP). AVP is a peptide hormone consisting of nine amino acids, endogenously produced by the supraoptico-paraventricular nuclei of the hypothalamus and stored in the posterior pituitary gland. It is released into the systemic circulation in response to numerous stimuli including, but not limited to, hyperosmolality, hypovolemia, hypoxia and hypotension. Consequently, AVP has an important role in the maintenance of adequate circulating blood volume and hemodynamic stability, which is achieved through its actions on various end-organ receptors, the predominant of which are systemic vasoconstriction via stimulation of the V1 receptor on vascular smooth muscle and free water retention via stimulation of V2 receptors on the renal collecting duct. The various actions of AVP are summarized in Table 1. In this review, we aim to discuss what is known in regards to endogenous production and release of AVP in infants and children requiring paediatric cardiac surgery. Based on these data and reports of exogenous AVP use in this patient population, we aim to define the role of AVP in their post-operative management.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Endogenous arginine vasopressin

Plasma AVP concentrations in healthy ‘normal’ children have been reported to be 1–7 pg/mL1–4. Price and colleagues noted significantly elevated plasma AVP concentrations

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Location</th>
<th>Principal effects</th>
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<tbody>
<tr>
<td>V1R</td>
<td>Vascular smooth muscle, Kidneys</td>
<td>Vasoconstriction, Renal efferent arteriolar constriction</td>
</tr>
<tr>
<td>V2R</td>
<td>Renal collecting duct, Endothelium, Myocardium</td>
<td>Anti-diuresis, Coagulation factor release, Inotropy</td>
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<tr>
<td>V3R</td>
<td>Pituitary</td>
<td>ACTH release</td>
</tr>
<tr>
<td>Oxytocin (OTR)</td>
<td>Reproductive tissue, Pulmonary Vascular endothelium, Heart</td>
<td>Uterine contractions, NO mediated vaso dilatation, ANP release</td>
</tr>
<tr>
<td>Purinergic (P2R)</td>
<td>Myocardium, Cardiac endothelium</td>
<td>Cardiac contractility, Coronary vasodilation</td>
</tr>
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in children with unrepaired left-to-right shunts, 13.9 ± 17.3 pg/mL, as compared with controls, 3.5 ± 1.3 pg/mL, presumably secondary to the congestive heart failure and less than optimal end-organ perfusion often present in these patients. Several other studies have measured plasma AVP concentrations in children with congenital heart disease in their unrepaired state prior to surgical correction and at multiple time points post-operatively. These studies are organised in Table 2. Based on these data, it can be concluded that mean plasma AVP concentrations are elevated pre-operatively, increase further in the immediate post-operative period and return to baseline values or below by 24–48 hours.

For many infants and children recovering from cardiovascular surgery, the first 24–48 post-operative hours are the most critical, a dynamic state with minute-to-minute changes in circulating blood volume and hemodynamic stability. Post-operative low cardiac output, dysrhythmias, third-spacing, and in some cases, hemorrhage are all likely to contribute to the increases in endogenous plasma AVP concentrations noted above. Under these physiologic conditions, administration of additional AVP for therapeutic purposes is not intuitive. AVP is a potent systemic vasoconstrictor that, when provided in excess, could theoretically worsen cardiac output by adversely affecting loading conditions. Despite this apparent contradiction, many authors have reported successful use of exogenous AVP therapy to improve haemodynamic stability and end-organ perfusion in this patient population.

### Exogenous arginine vasopressin therapy

In 1999, Rosenzweig and colleagues were the first to report the use of AVP in children recovering from cardiac surgery. In their observational case series, 11 children received exogenous AVP for severe post-operative vasodilatory shock refractory to traditional catecholamines therapy. Since the predominant hemodynamic effect of AVP is vasoconstrictive, patients with vasodilatory shock should improve with AVP. Indeed, in all 11 patients, systolic blood pressure increased following the initiation of therapy and catecholamine dosages were reduced in 10 patients. The next report of AVP use in this patient population was not published until eight years later. In the paper by Lechner et al., a series of 17 neonates received exogenous AVP therapy for ‘vasopressor-resistant hypotension’ following cardiopulmonary bypass. Both systolic and diastolic pressure increased while exogenous catecholamine dosages decreased in all patients. In a small series published one year later, AVP was shown to increase blood pressure, decrease catecholamine requirements, and improve oxygenation in three infants with profound hypoxemia following surgery for complicated single cardiac ventricle anatomy. In this report, the authors utilized the vasoconstrictive action of AVP to increase systemic vascular resistance and encourage pulmonary blood flow in the setting of single ventricle physiology, somewhat analogous to the use of phenylephrine to manage a hypoxic patient with Tetralogy of Fallot. An example of one of these patients is provided in Figure 1. Moreover, AVP has been shown to decrease the ratio of pulmonary-to-systemic vascular resistance and may decrease pulmonary vascular resistance directly, offering clinicians faced with these patients a theoretical advantage over the more traditional adrenergic vasoconstrictors.

Following these initial encouraging studies, Jerath et al. described their experience with AVP in larger cohort of 85 children recovering from cardiac surgery. Mean catecholamine usage following AVP initiation significantly decreased in these children but, in contrast to the earlier reports, mean systolic blood pressure was not significantly different from baseline. It is probable that the early smaller observational studies focused solely on those patients in whom AVP use appeared beneficial, whereas this larger report was more inclusive with patients who experienced variable systolic blood pressure changes, likely increasing in some patients

### Table 2 Changes in plasma arginine vasopressin concentrations over time

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Results (mean plasma AVP concentrations)</th>
</tr>
</thead>
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| Antionu et al. CV Research, 1993 | 9                  | • Baseline: ~15 pg/mL  
• 15 minutes post-CPB: 137 pg/mL  
• 12 hours post-CPB: 153 pg/mL |
| Sun et al. JTCVS, 2005.       | 54                 | • Baseline: ~27 pg/mL  
• 24 hours post-CPB: ~48 pg/mL  
• 48 hours post-CPB: ~28 pg/mL |
| Morrison et al. Cardiol Young, 2008 | 39                | • Baseline: 18.6 pg/mL  
• During CPB: 87.1 pg/mL  
• Post-CPB: 88.1 pg/mL  
• 4 hours post-CPB: 44.9 pg/mL  
• 8 hours post-CPB: 54.9 pg/mL  
• 12 hours post-CPB: 43.6 pg/mL  
• 24 hours post-CPB: 17.8 pg/mL  
• 48 hours post-CPB: 7.3 pg/mL |

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while remaining unchanged or even decreasing in others. This variable response has been since reported in other series\textsuperscript{14–18}. One of these studies closely examined this variable response in 34 patients with haemodynamic instability after cardiovascular surgery\textsuperscript{18}. In this series, patients were labelled as favourable responders to exogenous AVP therapy if systolic blood pressure increased and exogenous catecholamine requirements decreased after AVP initiation. Based on this definition, 17 of 34 patients responded favourably to exogenous AVP therapy. Changes in blood pressure and catecholamine requirements in these patients are illustrated in Figure 2. Interestingly, the patients who responded favourably were started on AVP therapy significantly later in the post-operative period, at a median post-operative time of 20 hours (Intra-quartile range (IQR): 16–27 hours), as compared to 6 hours (IQR: 5.5–21.5 hours) in those who did not respond, \(P = 0.032\). These findings are not surprising, considering endogenous plasma AVP concentrations would be expected to be higher 6 hours post-operatively as compared to 20 hours post-operatively. In other words, exogenous AVP administration would likely be less effective in patients who already have high endogenous plasma AVP concentrations. Further, haemodynamic compromise on the first post-operative night in children recovering from cardiac surgery is more often due to low cardiac output with elevated systemic vascular resistance rather than systemic vasodilatation/vasodilatory shock\textsuperscript{21}. Invasive bedside measurement of systemic vascular resistance following paediatric cardiac surgery is rare and physical exam as a means to determine systemic vascular resistance is unreliable\textsuperscript{22}. If AVP is administered in patients with low cardiac output and elevated systemic

![Figure 1](image1.png)

**Figure 1:** Change in pulmonary-to-systemic flow (Qp/Qs) and inotrope score in a patient with hypoxemia following stage I Norwood palliation for hypoplastic left heart disease. After arginine vasopressin initiation, Qp/Qs increases markedly and remains increased despite weaning the patient’s epinephrine infusion. Measured systemic venous saturation is provided at each time point, which is not adversely affected by AVP therapy. (From: Mastropietro CW et al. Pediatr Crit Care Med. 2008;9:506–10.)

![Figure 2](image2.png)

**Figure 2:** Mean hourly changes in (a) systolic blood pressure (SBP) and (b) catecholamine score after initiation of arginine vasopressin (AVP). In patients who responded favorably (dark circles), mean SBP steadily increased and mean catecholamine score steadily decreased after AVP was started (time 0) while mean SBP and catecholamine score in patients who did not respond or responded unfavourably (white circles) changed minimally. Error bars represent standard error of the mean. (From: Mastropietro CW et al. Cardiol Young. 2013;23:387–93.)
vascular resistance, it would likely be of little benefit and potentially harmful. Catecholamine requirements did increase in some of the patients who did not respond favourably to AVP, though it is not clear if this clinical worsening was related to AVP therapy.

**Relative deficiency of arginine vasopressin**

In the aforementioned first report of exogenous AVP therapy in children after paediatric cardiac surgery, Rosenzweig and colleagues measured plasma AVP concentrations in three of the 11 patients prior to AVP initiation. The measured AVP concentrations in these patients were 1.9, 4.4 and 52.4 pg/mL. The authors concluded that these patients, especially the two patients with AVP concentrations in the normal range, had low plasma AVP concentrations relative to what would have been expected given the degree of hypotension. From these data, they hypothesized the existence of relative AVP deficiency in some children following cardiopulmonary bypass. This hypothesis was proven correct in 2010, in a study that measured plasma AVP concentrations in 120 paediatric patients before cardiopulmonary bypass and at 4, 24 and 48 hours post-cardiopulmonary bypass. The authors a priori divided this cohort into two groups: patients with plasma AVP concentrations above the 25th percentile of all values obtained at this time point and patients with plasma AVP concentrations below the 25th percentile. The authors hypothesized that plasma AVP concentrations would not be increased in some patients at 4 hours post-cardiopulmonary bypass, and these patients would fall below the 25th percentile of all values measured at this time point. The results are provided in Figure 3.

The 25th percentile was determined to be a plasma AVP concentration of 9.2 pg/dL. In patients with plasma AVP concentrations below this value, mean plasma AVP concentration was within the normal range at baseline (i.e. 1–7 pg/mL) and was not significantly increased from this baseline at 4, 24 or 48 hours after cardiopulmonary bypass. In contrast, mean plasma AVP in the rest of the patients was similar to that which was described previously, which is higher than the normal range at baseline, significantly increased from this baseline at 4 hours after cardiopulmonary bypass, and back to baseline by 24–48 hours. In fact, mean plasma AVP concentrations in the group of patients below the 25th percentile at 4 hours was significantly lower than the rest of the patients at all of time points, including baseline, suggesting that these patients may have an inherent inability to generate an appropriate AVP response. Established stimuli for endogenous AVP release such as changes in blood pressure, central venous pressure and serum sodium (i.e. osmolality) did not differ between groups at any time point. Catecholamine requirements, arterial blood gas measurements and volume resuscitation were also not statistically different between groups. In other words, patients with plasma AVP concentrations below the 25th percentile at 4 hours post-cardiopulmonary bypass were not considered to be ‘less sick’ than the rest of the patients. The authors concluded that these patients had ‘relative AVP deficiency’. Though arbitrary, the a priori decision by the authors to use the 25th percentile at 4 hours post-cardiopulmonary bypass was physiologically justified by the results.

It is important to note that many patients with relative AVP deficiency in this study were not haemodynamically unstable. Hence, relative AVP deficiency in and of itself did not cause hypotension. On the other hand, post-operative exogenous AVP infusions deemed necessary by the primary care team to manage hemodynamic instability were initiated in a small subset of patients in this study.
and pre-infusion plasma AVP measurements in these patients revealed the importance of identifying those with relative AVP deficiency. Three of these patients had clinical evidence of hemodynamic instability (e.g., high inotrope requirements) and concomitant low pre-infusion plasma AVP concentrations (<9.2 pg/mL). For these children, rapid hemodynamic improvement occurred following the initiation of low-dose exogenous AVP therapy. Within 6 hours, blood pressure increased and catecholamine requirements decreased. In contrast, two patients with similar degrees of hemodynamic instability had markedly elevated plasma AVP concentrations (175 and 181 pg/mL), and in these children, hemodynamic stability worsened with AVP therapy. Examples of two of these patients are provided in Figure 4. Therefore, though relative AVP deficiency in and of itself does not cause hypotension, patients with relative AVP deficiency are likely the best candidates for exogenous AVP therapy should hypotension arise. These data also provided evidence for the notion that hemodynamic response to AVP, at least in part, is dependent on pre-infusion endogenous AVP concentrations.

Unfortunately, relative AVP deficiency in this study\(^{14}\) could not be predicted on the basis of any demographic, anthropometric or clinical parameters including peripheral skin temperatures, which are used by some as a crude clinical marker of systemic vascular resistance. Moreover, direct measurement of plasma concentrations is too cumbersome and time-consuming (i.e. at least 48 hours to complete) to provide any value to bedside physicians caring for unstable cardiac patients. Consequently, we have no current means of practically identifying which of these infants and children have relative AVP deficiency. For this reason, indiscriminate use of exogenous AVP therapy (i.e. use in patients with elevated endogenous AVP concentrations and/or elevated systemic vascular resistance), at least for the time being, will likely continue to occur.

**Copeptin**

Copeptin is a byproduct of the AVP precursor pro-vasopressin with an undefined biological function. It is released with AVP in an equimolar ratio, is more stable and much easier to measure\(^{23}\). Plasma copeptin concentrations have been shown to positively correlate with plasma AVP concentrations in adult patients in a variety of clinical scenarios\(^{24-29}\) including post-cardiac surgery. More recently, a significant positive association was demonstrated between plasma AVP and copeptin concentrations in children undergoing paediatric cardiac surgery\(^{18}\). In this study, plasma AVP and copeptin concentrations were measured at baseline, 4 and 24 hours.

**Figure 4:** Changes in systolic blood pressure (SBP, circles) and inotrope requirements (squares) of two representative patients after administration of exogenous arginine vasopressin (AVP) on post-operative day 1. (A) Immediately prior to AVP administration, plasma AVP was only 9.1 pg/mL despite inotrope score of 19 and SBP of 64 mmHg. Upon administration, SBP increased to 84 mmHg and remained increased while decreasing catecholamine dosage by >50%. (B) Plasma AVP was 185.1 pg/mL prior to AVP administration in this patient. Not surprisingly, SBP did not increase with exogenous AVP; rather, further inotropic escalation was required. (From: Mastropietro CW et al. Crit Care Med. 2010;38:2052–8.)
following cardiopulmonary bypass in 41 children. The relationship between the values obtained for the 4-hour time point is illustrated in Figure 5. Plasma copeptin concentration less than 1.12 ng/ml at 4 hours post-cardiopulmonary bypass had a sensitivity of 92% (95% confidence intervals: 62–100%) and specificity of 71% (95% confidence intervals: 51–86%) for relative AVP deficiency (<9.2 pg/mL), as defined in the previous study discussed above\(^1\), with a negative predictive value of 95% (95% confidence intervals: 74–100%). Using all values obtained from all patients at all three time points, a 1% increase in AVP was associated with a 0.19% increase in copeptin.

Copeptin clearly has potential to be a more easily measured marker of plasma AVP activity and hopefully help identify patients with relative AVP deficiency. The copeptin assay used in the aforementioned study however requires approximately 6 hours to complete and did not appear to be sensitive enough to accurately measure very low copeptin concentrations. A different assay, the assay that has been used in most of the previously adult published studies of copeptin\(^2\)\(^–\)\(^29\), has a lower level of detection and is much faster, delivering the results in less than 45 minutes (Nils Morgenthaler, Institute for Experimental Endocrinology, Berlin, Germany, written communication 26 March 2012). A larger study including a greater number of patients using this assay should lead to a more precise copeptin definition of relative AVP deficiency. If AVP and copeptin concentrations can be obtained in some of these patients prior to initiation of an exogenous AVP infusion, a copeptin threshold above which further exogenous AVP therapy is not helpful could be identified.

**Conclusion**

For the majority of infants and children recovering cardiovascular surgery, endogenous AVP concentrations will be elevated, especially in the immediate post-operative period, and thus, further AVP provided exogenously will likely be of little benefit and theoretically detrimental. Judicious use of AVP therapy is therefore warranted. Based on what we know of AVP pharmacology and the experiences with exogenous AVP in this patient population, children with clinical evidence of systemic vasodilation after the first post-operative night or systemic hypotension in the setting of pulmonary hypertension represent reasonable candidates for AVP therapy. When initiated, hemodynamic response following AVP initiation should be closely monitored and clinicians should consider discontinuing AVP if clinical improvement does not occur. Future research focusing on identification of those patients with relative AVP deficiency will hopefully provide a better means of identifying optimal candidates for AVP therapy.

**References**

4. McIntosh N, Smith A. Serial measurement of plasma arginine vasopressin

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**Figure 5:** Plasma arginine vasopressin (AVP) and copeptin measurements obtained at 4 hours post-cardiopulmonary bypass. Both axes were log transformed due to the wide range of plasma AVP concentrations. Patients with relative AVP deficiency are represented by open circles. Dotted Y-axis reference line corresponds to plasma copeptin concentration = 1.12 ng/ml. (From: Mastropietro CW et al. Intensive Care Med. 2012;38(12):2047–54.)