Intravenous Arginine-Vasopressin in Children With Vasodilatory Shock After Cardiac Surgery

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Background—Recent investigations at our institution have studied a variety of vasodilatory shock states that are characterized by vasopressin deficiency and pressor hypersensitivity to the exogenous hormone. Our experience in adults prompted the use of arginine-vasopressin (AVP) in a similar group of critically ill children.

Methods and Results—This report describes our early experience (from February 1997 through April 1998) in 11 profoundly ill infants and children (5 male, 6 female) ages 3 days to 15 years (median, 35 days) treated with AVP for hypotension after cardiac surgery which was refractory to standard cardiopressors. Although underlying heart disease was present (congenital heart defects in 10 and dilated cardiomyopathy in 1), only 2 patients had severely depressed cardiac function as demonstrated by 2D echocardiogram before administration of AVP. All patients were intubated and receiving multiple catecholamine pressors and inotropes, including dobutamine (n = 10), epinephrine (n = 8), milrinone (n = 7), and dopamine (n = 4) before receiving AVP. Five patients received AVP intraoperatively immediately after cardiopulmonary bypass, 5 in the intensive care unit within 12 hours of surgery, and 1 on postoperative day 2 for hypotension associated with sepsis. The dose of AVP was adjusted for patient size and ranged from 0.0003 to 0.002 U · kg⁻¹ · min⁻¹. During the first hour of treatment with AVP, systolic blood pressure rose from 65 ± 14 to 87 ± 17 mm Hg (P < 0.0001; n = 11), and epinephrine administration was decreased in 5 of 8 patients and increased in 1. Plasma AVP levels before treatment were available in 3 patients and demonstrated AVP depletion (median, 4.4 pg/mL; n = 3). All 9 children with vasodilatory shock survived their intensive care unit stay. The 2 patients who received AVP in the setting of poor cardiac function died, despite transient improvement in blood pressure.

Conclusions—Infants and children with low blood pressure and adequate cardiac function after cardiac surgery respond to the pressor action of exogenous AVP. AVP deficiency may contribute to this hypotensive condition. (Circulation. 1999;100[suppl II]:II-182–II-186.)

Key Words: vasodilation ■ shock ■ pediatrics ■ vasopressin

Recent investigations at our institution have studied a variety of vasodilatory shock states that are characterized by deficiency of endogenous vasopressin and hypersensitivity to the administration of exogenous hormone. Landry and colleagues first reported a beneficial use of arginine-vasopressin (AVP) in critically ill adult patients with septic shock in whom inotropic and maximal pressor therapy had failed to maintain adequate blood pressure. These patients also demonstrated a deficiency of vasopressin that was probably secondary to a defect in baroreflex-mediated release of the hormone. When AVP was administered at very small doses by continuous intravenous infusion, marked improvement occurred in blood pressure and exogenous catecholamine vasopressor requirement decreased. Furthermore, systemic vascular resistance increased without significant changes to cardiac output.

A syndrome of vasodilatory shock after cardiopulmonary bypass associated with relative deficiency of vasopressin and hypersensitivity to the exogenous hormone has also been described. Recently, a randomized trial of vasopressin in patients undergoing left ventricular assist device (LVAD) placement demonstrated a marked pressor response and a significant reduction in need for exogenous catecholamine pressors in patients with vasodilatory shock. These findings in adults prompted the use of AVP in a similar group of critically ill children. This report describes our initial experience in 11 moribund children treated with AVP for hypotension that was refractory to standard cardiopressors after cardiac surgery.

Methods

We reviewed the hospital records of all critically ill infants and children treated with AVP for severe hypotension after cardiac surgery.
surgery between February 1997 and April 1998 (n = 11). The patients were treated within 48 hours of cardiac surgery in the operating room (n = 5) or intensive care unit (n = 6) under close monitoring. All were treated within 48 hours of cardiac surgery in the operating room or intensive care unit during AVP infusion.

The dose of AVP was based on patient weight and started as a continuous intravenous infusion. Once AVP was started, it was adjusted for effect (ie, increase in systemic blood pressure without concurrent side effects). All patients were monitored in the operating room or intensive care unit during AVP infusion.

Systemic blood pressure was measured by use of an indwelling arterial catheter before and after initiation of AVP (Pitressin, Parke Davis). We calculated the average blood pressure over 8 hours or during time off bypass if this time was <8 hours before initiation of AVP. This result was compared with the mean blood pressure after 1 hour of AVP treatment. Heart rate before and after AVP and right atrial pressure (in mm Hg) were recorded in patients who had right atrial pressure transducers postoperatively. To describe the severity of the patient’s condition and the level of medical support, we used a modification of an inotropic score previously described by Wernovsky et al. The modified inotropic score was calculated as follows: dosages of dopamine + dobutamine + epinephrine × 100 + milrinone × 10. All dosages were calculated in micrograms per kilogram per minute. The score was based on the dose and type of inotropic and cardiopressor medications just before the initiation of AVP and 1 hour after the initiation of AVP.

Baseline 2D echocardiograms were available on all patients just before the initiation of AVP infusion (echocardiogram machine model Hewlett Packard 1500) and were reviewed retrospectively by 2 investigators to assess the effect of cardiac function on the efficacy of AVP. Left ventricular function was graded qualitatively as normal, mildly, moderately, or severely depressed. Parameters of organ perfusion were evaluated at baseline (ie, just before initiation of AVP and after 8 to 24 hours of AVP infusion) because of a concern that an acute increase in peripheral vascular resistance might be associated with further compromise of end organ perfusion. These included urine output, serum bicarbonate score, and serum sodium concentration. The average urine output in cubic centimeters per kilogram per hour was calculated and compared for the 8 hours before AVP infusion and the first 24 hours of AVP infusion in the 6 patients in whom these data were available. The serum bicarbonate score was calculated as the average serum bicarbonate during the 8 hours before initiation of AVP (derived from arterial blood gas, measured in mEq/L) minus (NaHCO3 given during 8 hours before AVP initiation, in mEq/L, divided by patient weight in kg times 4). Plasma vasopressin levels were measured by radioimmunoassay (SmithKline Beecham) before the initiation of AVP.

Data are reported as mean ± SD. Paired variables were analyzed by the Student paired t test or the paired sign test when appropriate.

### Results

Eleven infants and children with hypotension and shock received AVP for a mean of 71 ± 46 hours (range, 6 to 144 hours). The study group included 5 males and 6 females, with a median age of 35 days (range, 3 days to 15 years) (Table). The dose of AVP was adjusted for patient weight and ranged from 0.0003 to 0.002 U · kg⁻¹ · min⁻¹. Ten patients had congenital heart defects of various types and 1 had dilated cardiomyopathy (Table). Three of the 11 patients had single-ventricle anatomy, and the rest had undergone anatomical repairs. Five patients received AVP intraoperatively immediately after cardiopulmonary bypass, 5 received AVP in the intensive care unit within 12 hours of surgery, and 1 received...
AVP on the second postoperative day for hypotension associated with sepsis. All children were intubated and received multiple catecholamine pressors and inotropes, including dobutamine (n = 10), epinephrine (n = 8), milrinone (n = 7), and dopamine (n = 4), before being given AVP. Additional support in 5 of the children included a temporary pacemaker for junctional tachycardia (patient 11), temporary chest closure (patient 5), nitroglycerin drip for ST-segment changes before AVP (patient 1), and recent discontinuation of an LVAD (patients 7 and 9).

At baseline, the systolic blood pressure (SBP) was low and rose 34% with administration of AVP from 65±14 to 87±17 mm Hg (P<0.0001; n = 11) (Figure). Before initiation of AVP, the SBP was <2 SD below the mean for age and sex in 6 patients and <1 SD below the mean in 2 others. At follow-up on AVP, only 1 patient had SBP <2 SD below the mean and 2 had a SBP <1 SD below the mean. Four patients had SBP >1 SD above the mean on AVP. Diastolic blood pressure (DBP) increased 31%, from 35±11 to 46±13 mm Hg (P<0.005; n = 11), and mean arterial pressure increased 31%, from 45±11 to 59±11 mm Hg (P<0.0005; n = 11).

Right atrial pressure was elevated at baseline and unchanged after 1 hour of AVP administration (11±6 versus 11±6 mm Hg; n = 7; P=NS). The mean heart rate at baseline and after 1 hour of AVP infusion was essentially unchanged (154±41 versus 157±33 bpm; n = 10; P=NS).

Pressor requirement as assessed by the inotrope score improved in 9 patients and was unchanged in 2 patients (Table). The total inotrope score decreased from a mean of 43 to 23 (paired sign test; P<0.005; n = 11). The mean doses of pressors at baseline and follow-up were dobutamine 10±3 versus 8±5 μg·kg⁻¹·min⁻¹ (n = 10), epinephrine 0.36±0.49 versus 0.14±0.18 μg·kg⁻¹·min⁻¹ (n = 9), dopamine 7.0±2.9 versus 6.0±3.1 μg·kg⁻¹·min⁻¹ (n = 4), and milrinone 0.5±0.1 versus 0.4±0.2 μg·kg⁻¹·min⁻¹ (n = 7). A trend was noted toward a significant decrease in the dose of epinephrine on AVP compared with baseline (P<0.1). The dosages of catecholamine pressors (ie, epinephrine [n = 8] and high-dose dopamine [n = 3]) decreased in 6 patients, were unchanged in 1, and slightly increased in 1.

Indexes of organ perfusion, including urine output and sodium bicarbonate scores, were not significantly changed during the first 24 and 8 hours, respectively, on AVP infusion, suggesting no adverse effect on renal perfusion. Urine output remained the same at baseline and with AVP treatment (3.9±3.0 versus 4.3±3.1 cm³·kg⁻¹·h⁻¹; n = 6; P=NS). The serum bicarbonate score at baseline and on AVP (24±3 versus 23±2 mEq/L; n = 10; P=NS) was similar. After 24 hours of AVP infusion, the serum bicarbonate levels were normal without the administration of exogenous sodium bicarbonate in all 9 patients with vasodilatory shock. In contrast, in the 2 patients who had cardiogenic shock and ultimately died, additional sodium bicarbonate boluses were still required while on AVP. Serum sodium concentration was unchanged during the first 24 hours on AVP (baseline, 141±7 versus 138±7 mmol/L; P=NS; n = 10). One child (patient 8) had mixed venous oxygen saturation levels measured at baseline and on AVP that demonstrated an increase from 48% to 64% within 1 hour of AVP infusion.

Vasopressin levels in 3 patients demonstrated an absolute depletion in 2 patients (vasopressin levels, 1.9 and 4.4 pg/mL) and a relative vasopressin depletion in 1, (vasopressin level, 52.4 pg/mL) within 24 hours after cardiopulmonary bypass. Previous reports by Ationu et al⁷ have demonstrated a 10-fold increase in plasma AVP levels in children even 24 hours after cardiopulmonary bypass (ie, mean levels in the range of 100 pg/mL). Two of the 11 patients had poor left ventricular function before initiation of AVP but were started on therapy because of failure of all other conventional medical treatments. Cardiac function was normal or slightly depressed in 9 of the 11 patients.

Complications
There were no episodes of peripheral vasoconstriction or cyanosis that required discontinuation of AVP.

Early Outcome
Early outcome (24 hours) was favorable in the 9 critically ill patients. Of the 9 patients with vasodilatory shock, 1 was taken off LVAD and subsequently underwent successful heart transplantation (patient 7), 1 avoided LVAD placement.
as a bridge to heart transplantation (patient 8), and 5 were successfully weaned from cardiopulmonary bypass. The 2 patients with cardiogenic shock (poor left ventricular function by echocardiogram before initiation of AVP) died at 6 hours (patient 10) and 6 days (patient 11) after initiation of continuous AVP, despite transient improvements in systemic arterial blood pressure.

Long-Term Outcome
Eight of the 9 early survivors were discharged from the hospital. One patient remains hospitalized for chronic lung disease. Three patients died within 14 days to 6 months after AVP administration of causes not related to the initial event: patient 1 died 14 days after administration of vasopressin during an interventional cardiac catheterization procedure; patient 8 died during subsequent heart transplantation secondary to hemorrhage; and patient 9 died 6 months after heart transplantation, presumably from acute rejection.

Discussion
Children with severe vasodilatory hypotension refractory to standard pressor regimens after cardiac surgery can be extremely challenging to manage. Routine therapy includes administration of volume and high doses of catecholamine pressors to maintain adequate systemic arterial blood pressure. Severe hypotension with end-organ failure, significant volume overload, and death are potential adverse outcomes if medical management fails. To avoid the complications of severe hypotension, AVP was administered to 11 critically ill children after cardiac surgery. And, as in adult patients with other forms of vasodilatory shock (ie, septic shock or after cardiopulmonary bypass), hypotension improved with intravenous AVP administration. Stabilization of blood pressure enabled 5 patients to leave the operating room; permitted discontinuation of LVAD in 1; and, in an additional patient who was being considered for LVAD, AVP eliminated the need for LVAD as a bridge to transplantation. Furthermore, by decreasing the pressor requirements, the potential for adverse effects related to the pressors was decreased.

In our patients, plasma vasopressin levels before initiation of AVP demonstrated absolute AVP depletion in 2 patients and relative AVP depletion in 1. Previous studies have demonstrated that adults with septic shock have both an absolute vasopressin deficiency due to baroreflex-mediated stimuli and relative hypersensitivity to exogenously administered hormone. However, patients who started AVP associated with LVAD placement showed a bimodal distribution of AVP, with 1 group absolutely deficient and a second with moderately elevated plasma levels that were nonetheless lower than those of control patients on cardiopulmonary bypass. Further, Argenziano et al found that even though the group of patients who had higher levels of AVP had a lesser response to exogenous hormone, they still had significant improvement. A study by Tarpey et al demonstrated similar responses to exogenous AVP in both Long-Evans and Brattleboro (vasopressin-depleted) rats infused with lipopolysaccharide. The important message is that regardless of whether vasopressin was depleted, the children with vasodilatory shock responded to exogenous hormone with improvements in systemic arterial blood pressure and ability to wean catecholamine pressors. Of note, the dose of AVP used is without significant pressor action in normal adult subjects. The mechanism of AVP pressor hypersensitivity remains to be determined.

Urinary output and serum sodium concentration were analyzed because of a concern about the side effect syndrome of inappropriate antidiuretic hormone with administration of AVP. Additionally, a concern existed that an acute increase in peripheral vascular resistance might be associated with further compromise of end-organ perfusion, but this was not observed. We found no significant changes in urine output, serum bicarbonate levels, or serum sodium concentration after 24 hours of AVP infusion in this group of patients who received AVP short term. Furthermore, in all 9 children who survived, additional sodium bicarbonate boluses were not needed within 24 hours of AVP infusion.

Nine of 11 patients demonstrated good or only mildly depressed left ventricular function at the time of initiation of AVP, and 2 patients demonstrated very poor left ventricular function (Table). Although AVP has previously been beneficial in patients with vasodilatory shock, its use in cardiogenic shock is highly speculative. A recent case report by Overland and Teply described a patient who developed increases in both systemic vascular resistance and cardiac index with AVP infusion. The increase in cardiac index was hypothesized to occur from either an increase in inotropy or an increase in coronary perfusion pressure. Additionally, isolated case reports of AVP use in patients with refractory cardiac arrest have been described after initial investigations in a pig model; however, the mechanism of action of AVP is still not completely understood. In contrast, a previous animal model study by Gardiner et al showed a decrease in cardiac output with AVP administration. Our previous experience in adult patients indicated that vasopressin is most useful in vasodilatory shock. Of note, 2 of our patients who received AVP, (patients 10 and 11) were hypotensive and in cardiogenic shock but received AVP anyway because they were failing on catecholamine pressors. Although AVP transiently increased the blood pressure in both of these patients, they both died with severely depressed cardiac function. Given the findings that the 2 patients who died during AVP infusion had poor ventricular function and our experience in adult patients that AVP frequently further depresses cardiac output in the setting of cardiogenic shock, we would not recommend AVP for cardiogenic shock in pediatric patients.

Study Limitations
Due to the small number of plasma AVP samples obtained, AVP levels could not be analyzed critically. In future studies, measurement of AVP levels before and during AVP treatment will be important. In addition, unlike the adult patients, infants and children undergoing cardiac surgery in our institution do not routinely have a Swan-Ganz catheter placed; thus, we did not have the benefit of measuring simultaneous cardiac output and systemic vascular resistance with our blood pressure measurements. It is of great importance to demonstrate any changes in cardiac output that might occur with AVP infusion so that future use could be tailored accordingly.
The heterogeneity of the group in terms of the types of cardiac defects and the type of surgery performed might be seen as a limitation. Three patients had single-ventricle anatomy, and the rest had undergone complete surgical repairs. One would expect the physiology and response to AVP to be similar in the patients with complete repairs (n=7) and cardiomyopathy (n=1). No obvious differences were seen between children with single-ventricle anatomy and those after complete repair. Nonetheless, the 2 groups were too small for a meaningful comparison in this study.

Although AVP was associated with improved blood pressure in our study (with each patient as his or her own control), one may not conclude that use of AVP and catecholamines is generally superior to use of catecholamines alone in terms of clinical outcome. Future randomized double-blinded studies with a control group for comparison are needed. Our findings in these critically ill patients near extremis so contrasts with the clinical expectations for this group that they support its limited use in this narrowly defined subgroup of infants and children with vasodilatory shock after cardiopulmonary bypass, pending a controlled trial.

Conclusions
In summary, AVP infusion may be a viable treatment option for pediatric patients in a refractory vasodilatory state after cardiac surgery, to improve systemic arterial blood pressure when conventional therapies fail. Further studies are required before AVP can be recommended for the routine postoperative management of infants and children with congenital cardiac defects. However, AVP should be a consideration for patients with intractable symptomatic vasodilation. These data suggest that, as in adults, AVP should not be used in pediatric patients with severe left ventricular dysfunction until more is known about the effect of this agent on myocardial function.

References
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