Arginine Vasopressin Levels Are Elevated and Correlate With Functional Status in Infants and Children With Congestive Heart Failure

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Background—Arginine vasopressin (AVP) is a vasoactive hormone that acts on the kidney to conserve solute-free water and produces a potent vasoconstrictive effect during hypovolemic states. AVP levels are elevated in adults with congestive heart failure (CHF), and early clinical trials using AVP antagonists are being conducted. The purpose of this study was to determine if AVP levels (1) are elevated in children with CHF attributable to left ventricular dysfunction or pulmonary overcirculation attributable to large left-to-right shunts and (2) can predict functional clinical status.

Methods and Results—AVP levels were measured in patients with dilated cardiomyopathy (DCM) and CHF and in patients with large-left-to-right intracardiac shunts. Each patient with DCM (ejection fraction percent <40%) was classified as NYHA functional class I through IV when the AVP level was drawn. Serum sodium was measured, serum osmolality was calculated, and echocardiograms and chest radiographs were performed on all study patients. AVP levels were also measured in age-matched controls. Mean AVP level in children with DCM (n=27) was 10.3 pg/mL (±12.8) versus 3.7 pg/mL (±2.4) in controls (n=15) (P<0.01). Mean AVP level in children with left-to-right shunts (n=14) was 13.9 pg/mL (±17.3) versus 3.5 pg/mL (±1.3) in controls (n=8) (P<0.04). In patients with DCM, AVP levels correlated directly with NYHA functional class (r²=0.73, P<0.001).

Conclusions—Arginine vasopressin levels are elevated in infants and children with CHF attributable to left ventricular dysfunction and in infants with large left-to-right intracardiac shunts. Furthermore, there is a direct relationship between AVP level and the severity of heart failure in patients with DCM. (Circulation. 2004;109:2550-2553.)

Key Words: pediatrics • heart failure • hormones

The antidiuretic hormone arginine vasopressin (AVP) exerts a profound vasoconstrictive effect during periods of hypovolemia and acts to conserve solute-free water when released in hyperosmolar conditions.1–2 Plasma levels of AVP are elevated in adults with chronic congestive heart failure attributable to ischemic cardiomyopathy, and it is thought that the release of AVP serves as a compensatory mechanism to preserve systemic perfusion in low-output states.3–7 Although possibly beneficial in the short term, chronic neurohormonal release causing an increase in systemic vascular resistance and free water retention may be deleterious to the patient with congestive heart failure (CHF). Pharmacological blockade of AVP receptors has therefore become an attractive method of improving symptomatology and functional class in adults with heart failure.5,11–13 To date, very limited data exist on secretion of AVP in infants and children with heart failure.14 The purpose of the present study was to determine whether AVP levels are elevated in children with CHF attributable to left ventricular dysfunction or symptomatic pulmonary overcirculation attributable to large left-to-right intracardiac shunts and to determine whether AVP levels correlate with functional clinical status in patients with ventricular dysfunction.

Methods

Patient Selection
We enrolled patients with biventricular hearts who had impaired left ventricular systolic function or large left-to-right intracardiac shunts. All subjects were enrolled from Texas Children’s Hospital inpatient and outpatient areas. Children age birth to 21 years of both sexes and all races, ethnicities, and backgrounds were eligible. Subjects were classified into 1 of the following 3 groups: (1) those with dilated cardiomyopathy (DCM) and ventricular systolic dysfunction (defined as an ejection fraction <40%), (2) those with pulmonary overcirculation (PO) attributable to large left-to-right intracardiac shunts, and (3) healthy controls. For the PO group, we required clear
evidence of overcirculation, including a respiratory rate ≥50 breaths per minute, subcostal retractions, nasal flaring, liver span ≥2 cm below the costal margin, the presence of a diastolic filling sound, weight below the tenth percentile for age, and evidence of increased pulmonary vascular markings and cardiomegaly on chest radiograph. Exclusion criteria for all enrollees included hypertension or hypotension, fever, renal failure, mechanical ventilation, clinical evidence of dehydration, and a history of malignancy or disease of the central nervous system.

**Protocol**

The Baylor College of Medicine Institutional Review Board approved the study, and procedures followed were in accordance with the board guidelines. A parent or guardian of each enrollee under 18 years of age gave informed consent.

Subjects in the DCM group were classified into New York Heart Association (NYHA) functional classes I through IV at the time phlebotomy was performed. Infants in that group were correlated to a NYHA class using a modification of a grading system for heart failure in infants previously described by Ross et al\(^\text{13}\) (Table 1).

Phlebotomy was performed on each participant after at least 15 minutes of supine rest. Plasma arginine vasopressin levels, serum electrolytes, blood urea nitrogen, and creatinine were measured. Serum osmolality was calculated for each subject using the following equation: \[\text{[sodium]} + \frac{\text{blood urea nitrogen} \times 2.8 + \text{glucose} \times 18}{2}.\] All patients underwent echocardiography, and left ventricular ejection fraction was measured using Simpson’s biplane method in each subject in the DCM group at the time of enrollment. Chest radiographs were performed on each subject in the PO group as part of the criteria for inclusion in the study. Anticongestive medications were not discontinued during the study (Table 2). Volunteer subjects in the control group were examined by a board-certified pediatrician and deemed healthy before participation.

**Assay Technique**

Approximately 3 mL of blood was collected from each participant and added to a sterile test tube containing 10 mL of heparin. The samples were immediately chilled and then centrifuged and frozen at −70°C. Arginine vasopressin levels were measured using a highly sensitive and specific radioimmunoassay technique with an intra-assay coefficient of variation of 6.9% and an ability to detect changes in vasopressin as small as 1.5 pg/mL. Levels were sent to Nichols Institute Diagnostics in San Juan Capistrano, California, for testing.

**Statistical Analysis**

Mean AVP levels in study patients and healthy subjects were compared using the Student’s \(t\) test. Simple linear regression analysis (Pearson method) was used to determine the correlation between AVP (log scale) and NYHA functional classification. This relationship was also assessed using a nonparametric correlation method (Spearman). Because of lack of a normal (Gaussian) distribution in AVP values among the NYHA classes, a log transformation was applied before regression analysis. Values are expressed as mean±SD. \(P\leq0.05\) was considered statistically significant.

**Results**

**Patient Profile**

Twenty-seven patients with DCM were enrolled (mean age, 5.6±5.5 years). Etiologies for depressed systolic function included idiopathic (\(n=22\)) and myocarditis (\(n=5\)). The mean ejection fraction percent in the DCM group was 22% (±12). All patients in the DCM group had signs or symptoms of heart failure for at least 1 month. Fourteen patients met inclusion criteria for the PO group (mean age, 2.4±1.3 months). Anatomic defects included ventricular septal defect (\(n=1\)), complete atrioventricular septal defects (\(n=7\)), and complex atriopulmonary canal defect (\(n=6\)). All patients in the PO group had qualitatively good biventricular systolic function, and all had increased pulmonary vascular markings and cardiomegaly on chest radiograph (mean cardiothoracic ratio, 0.65±0.05). Six patients in the PO group had Down syndrome. Fifteen healthy control subjects were enrolled and age matched to the DCM group (mean age, 4.0±4.1 years), and 8 controls were age matched to the PO group (mean age, 3±0.5 months).

**Vasopressin and Electrolytes**

Mean plasma AVP levels were elevated in the DCM group compared with healthy controls (10.3±12.8 versus 3.7±2.4 pg/mL) \(P<0.01\) (Figure 1). Similarly, plasma AVP levels were elevated in the PO group compared with controls (13.9±17.3 versus 3.5±1.3 pg/mL) \(P<0.04\) (Figure 1). Mean serum sodium levels were normal in both study groups (DCM, 137±4.1 mEq/L; PO, 138±4.2 mEq/L). Mean serum osmolality was also normal in both groups (DCM, 286±6 mOsm/kg; PO, 287±6 mOsm/kg).

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**TABLE 1. CHF Classification for Infants With Left Ventricular Dysfunction**

<table>
<thead>
<tr>
<th>CHF Classification</th>
<th>Signs of CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>No signs</td>
</tr>
<tr>
<td>NYHA II (mild)</td>
<td>RR &gt;50, with or without hepatomegaly</td>
</tr>
<tr>
<td>NYHA III (moderate)</td>
<td>RR &gt;50, hepatomegaly, retractions</td>
</tr>
<tr>
<td>NYHA IV (severe)</td>
<td>RR &gt;60, hepatomegaly, retractions, HR &gt;160, with or without poor perfusion</td>
</tr>
</tbody>
</table>

RR indicates respiratory rate; HR, heart rate.

**TABLE 2. Patient Medications**

<table>
<thead>
<tr>
<th>Medication Profile, %</th>
<th>DCM Group (n=27)</th>
<th>PO Group (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasix</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Digoxin</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Dopamine</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Milrinone</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Mean AVP levels are elevated in the DCM and PO groups compared with controls (10.3 vs 3.7 pg/mL, \(P<0.01\); 13.9 vs 3.5 pg/mL, \(P<0.04\); respectively).
Among patients with DCM and ventricular dysfunction, there was a direct relationship of the AVP levels to functional classification between NYHA classes I through IV ($r^2=0.73$, $P<0.001$) (Figure 2). Similarly, a direct relationship was also revealed using a nonparametric correlation method (Spearman rank), $r=0.88$, $P<0.001$. Two patients in the DCM group who were classified as NYHA class IV had AVP levels much higher than the mean (44.8 and 56.4 pg/mL versus NYHA IV mean, 20.3 pg/mL). The clinical condition of both patients deteriorated rapidly, and they died within 1 week of the AVP levels being drawn.

Discussion

Endogenous AVP is a 9-amino-acid peptide with both pressor and antidiuretic properties. It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary for eventual release. Both osmotic and nonosmotic stimuli, such as hypovolemia and hyperosmolality, trigger the release of AVP. Once secreted, AVP activates V1 receptors on the surface of vascular smooth muscle cells, causing vasoconstriction, and V2 receptors on parietal cells in the collecting duct of the kidney, decreasing the rate of solute-free water clearance.16

Vasopressin and Heart Failure

Plasma levels of AVP are elevated in adults with CHF, and it has been postulated that nonosmotic release is attributable to arterial underfilling and stimulation of carotid baroreceptors. Because of its antidiuretic properties, AVP has been implicated in the renal water retention and dilutional hyponatremia of some adults with chronic heart failure.17 The coupled effects of free water retention and increased peripheral vascular tone of AVP may aggravate symptoms of heart failure and contribute to progressive ventricular dysfunction, which has led to the study of antagonists to the V1 and V2 AVP receptors. AVP antagonists have been studied in animals and adult humans with CHF with variable results. Some investigators have demonstrated a decrease in systemic vascular resistance with a concomitant rise in cardiac output, and others have shown a reduction in urine osmolality and increased solute-free water clearance in patients with advanced heart failure.8–12 Others have shown only minimal changes in vascular tone and perfusion in patients with very high plasma AVP levels.13

Pediatric Heart Failure

We have demonstrated that, like adults, plasma levels of AVP are elevated in infants and children with CHF. The levels of AVP are elevated in both forms of pediatric heart failure, left ventricular systolic dysfunction and pulmonary overcirculation. Furthermore, we have shown a direct relationship between the levels of plasma AVP and severity of heart failure in children with left ventricular dysfunction, with the highest AVP levels occurring in patients with NYHA IV functional classification. These levels are similar to AVP levels reported in adults with heart failure.9 Unlike some adults, there was no evidence of dilutional hyponatremia or inappropriately dilute serum osmolality in our cohort of infants and children.

Mechanisms of Release

The mechanism responsible for increased AVP levels in both types of CHF is not obvious. In fact, it is likely that multiple factors affect the release of AVP in these populations. We speculate that diminished systemic blood flow in these children may stimulate stretch receptors in the carotid bodies, thereby triggering the cardioregulatory center of the brain to increase AVP secretion as a compensatory mechanism. Systemic blood pressure would be preserved because of the increase in systemic vascular resistance afforded by higher circulating levels of AVP, similar to the action of other neurohormones, such as norepinephrine and renin. Impaired renal and hepatic clearance of AVP should also be considered as contributing to increased AVP levels, because the hormone is excreted by both renal and hepatic mechanisms.18 Two children in the DCM group had mildly elevated creatinine levels, but no patient had evidence of liver or kidney failure. The effects of diuretic and ACE inhibitor therapies cannot be excluded as a stimulus for AVP release, although normal serum sodium and osmolality argue against this possibility. Adults with CHF have elevated AVP levels even after their diuretic and ACE inhibitor therapies are held for at least 48 hours before measurements.5

These data confirm the notion that neurohormonal imbalances occur in infants and children with heart failure. By demonstrating that AVP levels are elevated in pediatric heart failure, this may allow for future studies using vasopressin receptor antagonists in this population. Larger, multicenter studies evaluating the role of AVP in pediatric heart failure should now be performed to further our understanding of the neurohormonal changes that occur in the heart failure syndrome and possibly for the inhibition of its pathophysiology and progression.

Study Limitations

Our conclusions should be tempered by acknowledging the relatively small number of patients enrolled. Also, although the control subjects were healthy, they were not drawn from the general population but rather from the outpatient depart-
ments of a large medical center in a major metropolitan area. In addition, study patients’ anticongestive medications were not discontinued from the study, and we cannot rule out an influence of these medications on the results of the study.

Conclusions
These data demonstrate that plasma levels of arginine vasopressin are elevated in infants and children with left ventricular systolic dysfunction and infants with pulmonary overcirculation attributable to large left-to-right intracardiac shunts. In addition, a direct relationship exists between vasopressin levels and symptomatic classification in patients with dilated cardiomyopathy and systolic ventricular dysfunction.

Acknowledgments
This study was supported in part by a grant from the J.S. Abercrombie Pediatric Cardiovascular Research Fund (to Dr Price). Dr Towbin is funded by grants from the National Institutes of Health; the National Heart, Lung and Blood Institute; the John Patrick Albright Foundation; the Muscular Dystrophy Association; the Abby Glaser Foundation; and the Texas Children’s Hospital Foundation Chair in Pediatric Cardiac Research.

References
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_Circulation_. 2004;109:2550-2553; originally published online May 17, 2004; doi: 10.1161/01.CIR.0000129764.84596.EB
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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