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Changes in Vasopressin, Atrial Natriuretic Factor, and Water Homeostasis in the Early Stage of Bronchopulmonary Dysplasia

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ABSTRACT. Arginine vasopressin (AVP), atrial natriuretic factor, and water balance were examined in the infants with or without bronchopulmonary dysplasia (BPD) during the first 4 wk of life. Fourteen premature infants, nine in the early stage of BPD secondary to respiratory distress syndrome (BPD infants) and five healthy low birthwt infants (LBW infants), were the subjects of this study. The water and sodium balance, renal function, and plasma AVP and atrial natriuretic factor concentrations were determined during the first 4 wk of life. Plasma AVP and atrial natriuretic factor levels of BPD infants at the 4th wk of life were higher than those of LBW infants at the corresponding age. Urine osmolality was higher and free water clearance was lower in BPD infants at the 4th wk of life when compared with each parameter in LBW infants, respectively. $Paco_2$ of BPD infants at the 4th wk of life was more elevated than that of LBW infants. These results suggest that elevated plasma AVP level may be related with pulmonary abnormalities and that atrial natriuretic factor may hence compensate the water retention resulted from the functionally activated AVP in the early stage of BPD. (*Pediatr Res* 27: 260–263, 1990)

Abbreviations

ANF, atrial natriuretic factor
AVP, arginine vasopressin
BPD, bronchopulmonary dysplasia
Ccr, creatinine clearance
CH_2O, free water clearance
FENa, fractional excretion of sodium
LBW, low birthwt
RDS, respiratory distress syndrome
SIADH, syndrome of inappropriate secretion of antidiuretic hormone

Infants with chronic BPD sometimes develop edema, oliguria, and hyponatremia (1–3). Some of these symptoms are similar to those seen in patients with SIADH (4, 5). Recently, Hazinski *et al.* (2) found that some infants with chronic BPD have elevated plasma AVP levels and they speculated the functional significance of these elevated values. However, all these articles are about water balance in the chronic stage of BPD. It has not been well established whether the changes of plasma AVP levels and water balance in the early stage of BPD are the same with those in chronic BPD.

On the other hand, ANF, found and isolated from the heart, has potent natriuretic and diuretic activities (6–8), even in the premature infants (9). Among a variety of physiological effects of ANF such as natriuresis, vasodilation, inhibition of aldosterone release (6, 10), it is suggested that ANF suppresses the AVP release (11, 12). We therefore investigated whether there are differences in plasma values of AVP, ANF, and water homeostasis during the 1st mo of life between infants in the early stage of BPD and healthy LBW infants.

MATERIALS AND METHODS

Study protocol. Fourteen premature infants (eight boys and six girls), nine in the early stage of BPD secondary to RDS (BPD infants) and five LBW infants, were the subjects of this study. Informed consent was obtained from each patient's parents. Our definition of BPD was based on three criteria: requirement of positive pressure ventilation as treatment for RDS in the 1st wk of life; clinical respiratory distress persisting after 1 mo of age; and presence of radiographic evidence of hyperexpansion with alternating atelectasis and focal emphysema. Gestational age, birthwt, and Apgar scores of these two groups were shown in Table 1. All of BPD infants were ventilated with the BP 2001 respirator. Duration of mechanical ventilation was 7.2 ± 6.0 (3 to 19) d. Three of LBW infants had low dose oxygen supplementation. All infants had i.v. infusion therapy, of which duration was 11.2 ± 2.3 (8 to 14) d in LBW infants and 9.3 ± 3.1 (6 to 14) d in BPD infants, respectively. The i.v. infusion fluid consisted of 10% glucose supplemented with calcium (100 mg/kg/d) within the first 3 d of life, after which sodium chloride (35 mEq/L) and potassium chloride (20 mEq/L) were added. Total water intake, i.v. infusion volume, and calorie intake were shown in Table 2. There was no difference in these parameters between the two groups. All infants were fed on their own mothers' breast milk. No infants were placed on aminoglycosides, indomethacin, diuretics during the study period. None of the infants had renal dysfunction or patent ductus arteriosus. Arterial blood pressure was monitored on the right arm using a Doppler ultrasound technique in all cases. The urinary sodium, potassium, osmolality, and creatinine were determined on the 7th d of life and at weekly intervals thereafter up to the 14th wk of life. Urine was fractionally collected in a collecting bag for a period of 6 h. Blood sampling was done at the midpoint of urine collection. Plasma AVP concentrations (n = 5, 4.9 ± 1.9 pg/mL) of five healthy full-term infants were determined at the 7th d of life when they were examined for plasma bilirubin level.

Plasma and urine assay. Blood samples were collected between

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0900 and 1200 h by puncture of the radial artery on the study day. Each specimen was collected in a syringe with EDTA as an anticoagulant. Samples were centrifuged at 2000 rpm for 10 min at 4°C. Plasma was decanted to determine AVP, ANF, creatinine, osmolality, and electrolytes.

Each 6-h urine sample was pooled for the determination of sodium, potassium, creatinine concentrations, and osmolality to calculate Ccr, FENa, and CH_2O, which were determined using standard formulas shown:

$$\text{Ccr (mL/min/kg)} = \frac{\text{Ucr} \times \text{V}}{\text{Pcr}}, \quad \text{FENa (\%)} = \frac{\text{UNa} \times \text{Pcr}}{\text{Ucr} \times \text{PNa}} \times 100$$

$$\text{CH}_2\text{O (mL/min)} = \text{V} - \frac{\text{Uosmol} \times \text{V}}{\text{Posmol}}$$

where PNa indicates plasma sodium concentration (mEq/L); V, urine flow (mL/min/kg); UNa, urinary sodium concentration (mg/dL); Pcr, plasma creatinine (mg/dL); Ucr, urinary creatinine (mg/dL); Uosm, urinary osmolality (mosmol/L); and Posm, plasma osmolality (mosmol/L). Creatinine and electrolytes in plasma and urine were determined using an autoanalyzer (Beckman Astra-8, Beckman Instruments, Inc., Fullerton, CA). Plasma and urine osmolality were determined using a Fiske osmometer.

ANF and AVP were measured by RIA method (13, 14). Plasma (1.0 mL) was extracted by ODS cartridges (Sep-Pak, Waters Associates, Milford, MN). RIA of ANF was performed by using an antibody generated in rabbits immunized with human α-ANF$^{1-28}$ (Peptide Institute, Osaka, Japan) coupled to bovine thyroglobulin by carbodiimide. The antibody crossreacted fully with α-human ANF$^{1-28}$, rat (γ) ANF$^{1-28}$ (40%), but less with α-human ANF$^{7-28}$ (2–5%), γ-ANF$^{5-28}$ (atriopeptin III), γ-ANF$^{5-27}$ (atriopeptin II) and γ-ANF$^{5-25}$ (atriopeptin I) and not at all with angiotensin II, arginine vasopressin, or bradykinin. The lowest concentration of human ANF yielding a binding significantly different from that found in the absence of standard α-human ANF at the 95% confidence interval was 2 pg/tube and the 50% intercept was 20 pg/tube. The interassay and intraassay coefficients of variations were less than 10%. The recovery of immune reactive human ANF applied to Sep-Sak cartridge was 50–60%.

Table 1. *Characteristics of low birth wt infants with BPD and without BPD (LBW)*

No. (M/F)	LBW $n = 5$ (3/2)	BPD $n = 9$ (5/4)
Gestational age (wk)	31.6 ± 2.7 (28–34)	32.9 ± 2.0 (29–35)
Birth wt (g)	1594 ± 359 (1080–2050)	1586 ± 312 (960–1980)
Apgar score		
1 min	7.6 ± 1.2 (6–9)	7.7 ± 1.3 (5–9)
5 min	9.6 ± 0.5 (9–10)	9.6 ± 0.7 (8–10)

RIA of AVP was performed by using an antibody generated in rabbits immunized with AVP coupled to BSA with glutaraldehyde. The cross-reactivity of the antiserum with 8-lysine VP was 0.04%; it was 0.19% with 1-deamino-8-D-arginine vasopressin and less than 0.01% with oxytocin and 8-arginine vasopressin. The sensitivity of the assay was 0.06 pg/tube. The interassay and intraassay coefficients of variations were 7.4 and 7.8%, respectively. All values were corrected for the recovery during the extraction procedure.

Statistical analysis was performed by the two-way analysis variance. Data was presented as mean ± SD.

RESULTS

Blood pH, $Paco_2$, arterial blood pressure, and pulse rate during the first 4 wk of life are shown in Table 3. $Paco_2$ of BPD infants at the 4th wk of life were more elevated when compared with those of LBW infants. Changes of body wt, water intake/output ratio, and plasma ANF concentrations during the study period are shown in Table 4. Plasma ANF concentrations of BPD infants at the 4th wk of life were more elevated than those of LBW infants (Fig. 2).

Plasma and urine osmolality, plasma/urine osmolality ratio, Ccr, FENa, and CH_2O are shown in Table 4. Urine osmolality of BPD infants was elevated when compared with that of LBW infants at the 4th wk of life, although there was no difference in plasma osmolality between the two groups. Plasma/urine osmolality ratio was decreased in BPD infants when compared with that in LBW infants at the 4th wk of life. Free water clearance of BPD infants was decreased when compared with that of LBW infants at the 4th wk of life. Plasma AVP levels of the two groups during the first 4 wk of life are shown in Figure 1. Plasma AVP level of BPD infants at the 4th wk of life was significantly elevated when compared with that of LBW infants (43.3 ± 31.5 *versus* 6.3 ± 4.3, $p < 0.05$). Plasma AVP levels of these two groups at the 1st wk of life were significantly elevated than those of healthy fullterm infants (BPD infants *versus* term infants, $p < 0.05$; LBW infants *versus* term infants, $p < 0.01$) (Fig. 2).

DISCUSSION

We found that plasma AVP levels in BPD infants were significantly elevated at the 4th wk of life. Usually, the typical roentgenographical characteristics of BPD are completed at 1 mo of life as described by Northway *et al.* (15). In this study, high plasma AVP levels in BPD infants at the 4th wk of life were combined with elevation of $Paco_2$, although the plasma AVP levels were not correlated with $Paco_2$. In addition to above observations, plasma AVP levels of premature infants with or without BPD were significantly more elevated than those of healthy full-term infants at 1 wk.

Krauss and Auld (16, 17) found that gas trapping is present from birth and persists for a variable period of time in premature infants and that the lung of a premature infant is not a physiologically homogeneous organ with respect to ventilation and perfusion. These results suggest that hypersecretion of AVP may

Table 2. *Total water intake, i.v. infusion volume, and calorie intake in BPD and LBW infants during the first 4 wk of life**

		D of life		Wk of life			
	Group	1st	4th	1	2	3	4
Total water intake (mL/kg/d)	LBW	65 ± 10	86 ± 17	142 ± 25	152 ± 19	162 ± 18	163 ± 17
	BPD	57 ± 15	91 ± 12	126 ± 26	148 ± 17	173 ± 11	176 ± 11
Intravenous infusion volume	LBW	60 ± 12	49 ± 22	45 ± 28	15 ± 13	0	0
(mL/kg/d)	BPD	54 ± 12	44 ± 11	27 ± 26	13 ± 23	0	0
Calorie intake (cal/kg/d)	LBW	28 ± 5	54 ± 18	80 ± 16	97 ± 13	106 ± 10	106 ± 11
	BPD	26 ± 6	53 ± 8	75 ± 18	92 ± 16	109 ± 5	116 ± 8

* Data were presented as mean ± SD.

Table 3. *Blood pH, $Paco_2$, mean arterial blood pressure, and pulse rate in BPD and LBW infants during the first 4 wk of life**

	Group	1st d	1 wk	2 wk	3 wk	4 wk
Blood gas pH	LBW	7.29 ± 0.04	7.39 ± 0.08	7.36 ± 0.02	7.40 ± 0.04	7.37 ± 0.03
	BPD	7.26 ± 0.09	7.39 ± 0.06	7.42 ± 0.05	7.34 ± 0.03	7.35 ± 0.01
$Paco_2$ (mm Hg)	LBW	38.3 ± 7.0	36.9 ± 10.0	47.9 ± 5.1	35.8 ± 6.0	37.6 ± 4.3
						$p < 0.02$
	BPD	47.1 ± 12	41.9 ± 12	42.2 ± 5.4	48.4 ± 6.3	50.2 ± 5.5
Mean arterial blood pressure (mm Hg)	LBW	42.7 ± 3.3	48.5 ± 2.8	48.8 ± 7.8	52.8 ± 3.9	52.7 ± 4.4
	BPD	44.4 ± 3.6	46.3 ± 4.2	46.7 ± 4.3	51.5 ± 4.3	50.1 ± 5.7
Pulse rate (/min)	LBW	144.7 ± 2.1	139.0 ± 4.3	145.3 ± 4.9	143.0 ± 3.8	142.0 ± 4.0
	BPD	145.2 ± 3.7	145.4 ± 3.9	147.0 ± 2.5	146.0 ± 3.2	147.0 ± 3.1

* Data were presented as mean ± SD.

Table 4. *Body wt, water intake/output ratio, plasma ANF and AVP concentrations, plasma and urine osmolality, creatinine clearance, FENa and CH_2O in LBW, and BPD infants during the first 4 wk of life**

		Wk of life			
	Group	1	2	3	4
Body wt (g)	LBW	1.483 ± 394	1.603 ± 368	1.764 ± 454	1.929 ± 472
	BPD	1.515 ± 328	1.619 ± 303	1.792 ± 350	1.952 ± 438
Water intake/output ratio	LBW	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.1
	BPD	1.6 ± 0.6	1.5 ± 0.1	2.0 ± 1.0	1.9 ± 0.8
Plasma ANF (pg/mL)	LBW	63.5 ± 23.5	61.5 ± 28.5	90 ± 17	64.5 ± 48.5
					$p < 0.05$
	BPD	68.8 ± 37.3	69.5 ± 51.5	89 ± 34.3	130 ± 52.5
Plasma AVP (pg/mL)	LBW	17.5 ± 2.0	8.8 ± 5.9	14.9 ± 8.4	6.3 ± 4.3
				$p < 0.05$	$p < 0.01$
	BPD	22.6 ± 12.5	14.9 ± 7.5	37.1 ± 22.2	43.8 ± 28
Plasma osmolality (mosm of/L)	LBW	282.2 ± 9.1	279.0 ± 8.2	282.0 ± 3.1	277.3 ± 7.8
	BPD	285.0 ± 4.7	282.0 ± 4.0	282.0 ± 4.2	277.3 ± 2.3
Urine osmolality (mosm of/L)	LBW	90 ± 62	88 ± 58	103 ± 51	62 ± 19
					$p < 0.05$
	BPD	193 ± 121	111 ± 67	108 ± 53	105 ± 29
Plasma/urine osmolality	LBW	4.0 ± 2.1	4.4 ± 3.2	3.2 ± 1.3	4.7 ± 1.0
		$p < 0.05$			$p < 0.02$
	BPD	2.0 ± 1.1	3.8 ± 1.6	3.1 ± 1.3	2.8 ± 0.8
Creatinine clearance (mL/kg/min)	LBW	0.58 ± 0.52	0.80 ± 0.1	1.30 ± 0.24	1.28 ± 0.32
	BPD	0.80 ± 0.40	0.92 ± 0.46	1.46 ± 0.51	1.80 ± 0.50
FENa (%)	LBW	1.50 ± 1.10	0.43 ± 0.27	0.16 ± 0.13	0.16 ± 0.10
	BPD	1.40 ± 0.65	0.95 ± 1.90	0.25 ± 0.15	0.28 ± 0.30
CH_2O (mL/min)	LBW	0.054 ± 0.030	0.053 ± 0.032	0.059 ± 0.001	0.063 ± 0.001
					$p < 0.05$
	BPD	0.027 ± 0.019	0.038 ± 0.017	0.048 ± 0.017	0.050 ± 0.012

* Data were presented as mean ± SD.

be related with pulmonary abnormalities visible on a chest radiograph. Although hypersecretion of AVP usually occurs on stimulation of hypothalamus such as head decompression or elevation of plasma osmolality (18), it is reflected by the hyperinflation of the lungs, decreased intrathoracic blood volume, the resultant effects on the baroreceptors (4, 5). Rao *et al.* (3) demonstrated elevated AVP levels in 12 infants with BPD, suggesting that the mechanism for elevated AVP levels was air-trapping in the chest, which causes pulmonary hypovolemia, decreased left atrial filling, and decreased transmural pressure of the left atrium.

High plasma AVP level was combined with high plasma ANF levels at the 4th wk of life in BPD infants. It has been reported that ANF is released in response to volume distention of the extracellular space (19). ANF acts on the glomerular membranes to oppose angiotensin II, to directly increase permeability resulting in the glomerulotubular balance toward natriuresis, or to modulate the prevailing levels of renal perfusion pressure and renal vascular resistance (10, 20, 21). Recently, Manning *et al.* (11) demonstrated the existence of a negative feedback endocrine loop; AVP stimulates ANF release, which in turn suppresses AVP release. It seems likely that a high ANF level observed in BPD infants may be reflected from the stimulation of high AVP itself, or volume overload of the extracellular space resulting from functionally activated AVP. However, we could not clearly demonstrate the changes in plasma osmolality and water intake/output ratio resulting from a high plasma AVP level. The inability to demonstrate changes in plasma osmolality and water

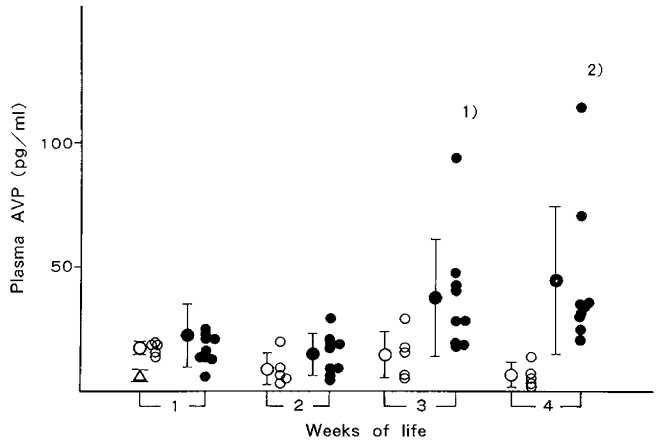

Fig. 1. Sequential changes of plasma AVP concentrations during the first 4 wk of life. *Open circles* indicate plasma AVP of LBW and *closed circles* indicate plasma AVP of BPD; *bars* show standard deviation. *Open triangles* indicate mean plasma AVP in the healthy fullterm infants at the 1st wk of life ($n = 5$). (*1*) $p < 0.05$; LBW *versus* BPD at 4th wk of life; BPD *versus* healthy fullterm infants at the 1st wk of life. (*2*) $p < 0.01$; LBW *versus* healthy fullterm infants at the 1st wk of life.

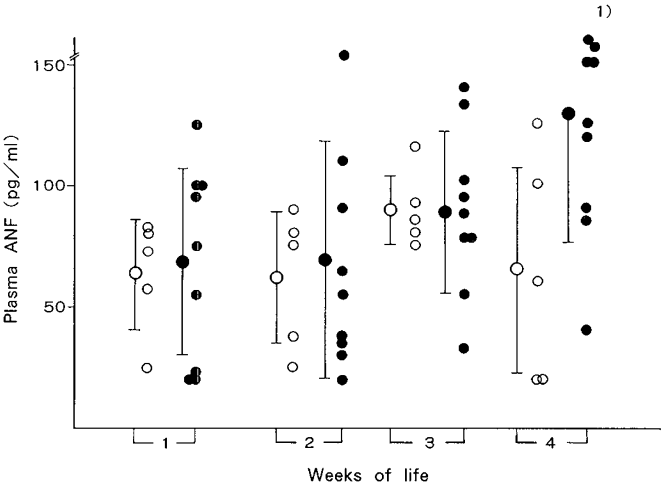

Fig. 2. Sequential changes of plasma ANF concentrations during the first 4 wk of life. *Open circles* indicate plasma ANF of LBW and *closed circles* indicate plasma ANF of BPD; *bars* show SD. (*1*) $p < 0.05$; LBW *versus* BPD at 4th wk of life.

intake/output ratio despite high plasma AVP levels may be related to the immaturity of AVP receptor responses during the newborn period (22). Recently, Sulyok (23) demonstrated that the neonatal pituitary is capable of responding with arginine vasopressin release to physiologic stimulation and pathologic events commonly seen in the perinatal period.

From these observations, we speculate that mild water retention established in response to the hypersecretion of AVP may stimulate the secretion of ANF and that ANF may hence compensate the effect of AVP in the early stage of BPD. Further studies should be considered to clarify the mechanism of water homeostasis in BPD infants.

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