

## Air leaks and vasopressin release

N McIntosh, P Prakash, A Smith

### Abstract

Eleven very low birthweight babies being ventilated for respiratory problems during the first week of life developed air leaks on 22 occasions. On 16 out of 19 occasions the infants showed increases in urinary excretion of vasopressin after these events and on 10 occasions out of 13 there was a rise in the plasma arginine vasopressin concentration. The peripheral signs of the syndrome of inappropriate antidiuretic hormone release were seen on only one occasion in response to the sometimes high vasopressin concentrations.

Air leaks are common in infants who require ventilation for respiratory problems in the first week of life. In this unit the overall incidence has been 32%, and for infants weighing less than 1000 g at birth it has been 44%, during a six year period. Management of fluid balance is also difficult in these infants. The reports of release of the antidiuretic hormone, arginine vasopressin, together with the development of air leaks<sup>1-4</sup> might indicate that fluid intake should be reduced after such events as is done after birth asphyxia.<sup>5</sup> We have evaluated 11 very low birthweight infants who developed air leaks to determine the extent to which vasopressin release occurs and to identify features suggestive of consequent fluid retention.

### Patients and methods

Eleven very low birthweight infants (mean (SD) birth weight 1073 (298) g, mean (SD) gestation 27.6 (2.0) weeks) who had been included in a study to examine the control of water balance in the respiratory distress syndrome developed air leaks (pneumothorax either alone: n=7, or combined with pulmonary interstitial emphysema: n=3). A single infant developed pulmonary interstitial emphysema alone.

The infants were all nursed in air mode controlled incubators that were humidified if the infants weighed less than 1000 g (n=5). Fluid intake was standard with final adjustments on clinical grounds by the attending clinician depending on weight, electrolyte concentrations, and urine volumes. Urine was collected four hourly by the method of Liu and Anderson,<sup>6</sup> and the volume in the eight hours before the development of the air leak was compared with the volume passed in the following eight hours. In each four hour specimen the following were measured: osmolality (by freezing point depression), the sodium concentration

(by flame photometry), and the arginine vasopressin concentration, and the values before and after the air leak were compared (table 1). Samples of plasma were taken eight hourly for measurements of osmolality and creatinine, urea, electrolyte, and plasma vasopressin concentrations. All 11 infants had severe respiratory distress syndrome and were ventilated by Bourns BP200 ventilators using standard techniques. Continuous blood pressure monitoring and transcutaneous blood gas monitoring allowed one hourly values of systolic, diastolic, and mean blood pressures and transcutaneous oxygen and carbon dioxide tensions to be averaged for the eight hours before and after the development of the air leak. Intermittent sampling of arterial blood gases was carried out, usually at intervals of three to four hours. Acid base values eight hours before and after the air leak were similarly assessed. The babies were weighed daily (usually between 4 and 6 am) and plasma and urinary vasopressin concentrations were measured by specific radioimmunoassay.<sup>7</sup> The study was approved by the St George's Hospital medical ethics committee.

### Results

The results are shown in tables 1 and 2.

#### PLASMA CREATININE

The plasma creatinine values at the time of the development of the air leak are shown in table 1. The mean concentration (103  $\mu\text{mol/l}$ ) is within the normal newborn reference range but infants 3, 9, 10, and 11 have values above the upper limit of this range ( $>120 \mu\text{mol/l}$ ) indicating a degree of renal failure, though three of these infants later had values within the reference range.

#### PLASMA AND URINARY OSMOLALITIES

There was no significant difference (paired *t* test) between the plasma or urinary osmolalities before and after the air leaks. At both times the plasma osmolalities were high (mean (SD) before 299 (12) and after 306 (13)). The variable urine osmolalities are shown in table 1. There was no correlation between the change in the urinary or plasma osmolalities and the change in the arginine vasopressin excretion before and after the air leak.

#### PLASMA ARGININE VASOPRESSIN CONCENTRATION (FIG 1)

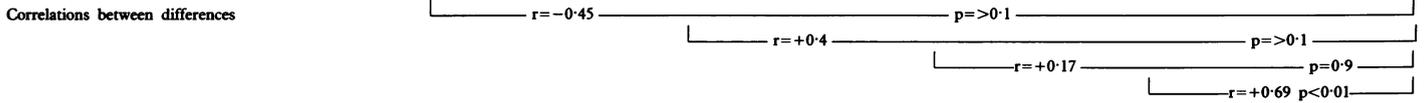
The plasma concentrations of arginine vasopressin increased after 10 of the 13 air leaks.

Department of  
Child Health,  
St George's Hospital  
Medical School,  
London  
N McIntosh  
P Prakash  
A Smith

Correspondence to:  
Professor N McIntosh,  
Department of Child Life  
and Health,  
17 Hatton Place,  
Edinburgh EH9 1UW.  
Accepted 10 May 1990

**Table 1 Biochemical values in 11 infants before and after developing 22 air leaks correlated with urinary arginine vasopressin**

Case No	Diagnosis	Plasma creatinine ( $\mu\text{mol/l}$ )			Plasma osmolality (mmol/l)			Urinary osmolality (mmol/l)			Urinary volume (ml)			Urinary sodium (mmol/l)			Urinary arginine vasopressin (pmol/mmol creatinine)			
		Before	After	Difference	Before	After	Difference	Before	After	Difference	Before	After	Difference	Before	After	Difference	Before	After	Difference	
1	PT	46	228	316	+28	146	155	+9	14	14	0	17	23	+6	1	1	0			
	PT	68	302	—	—	260	213	-47	5	7	+2	51	11	-40	1	5	4			
2	PT	98	—	306	—	84	175	+91	15	7	-8	21	26	+5	2.5	2.2	-1			
	PT	117	307	322	+15	405	387	-18	14	7 (ic)	—	70	64	-6	51	56	+4			
3	PT	117	307	322	+15	387	425	+38	8.5 (ic)	9.1	—	64	52	-8	—	—	—			
	PT	149	309	308	-1	338	398	+60	30	20	-10	126	137	+11	134	233	+99			
4	PT	95	309	308	-1	512	313	-200	14	9	-5	11	121	+10	127	610	+490			
	PT	103	290	310	+20	177	191	+14	40	21	-19	42	48	+6	1	1	0			
5	PT (urea 8.2)	292	302	+10	—	—	—	28	29	+1	44	58	+14	9	7	-2				
	PT (urea 7.2)	277	273	-4	—	—	—	35	16 (ic)	—	149	139	-10	40	440	+400				
6	PIE	111	304	303	-1	210	386	+176	7 (ic)	48	—	58	114	+56	136	324	+178			
	PT	111	303	—	—	386	340	-46	17	32	+15	114	125	+11	324	222	-102			
7	PIE	91	313	318	+5	392	413	+21	27	28	+1	114	119	+5	22	48	+26			
	PT	76	318	299	-19	182	—	—	38	30	-8	76	33	-43	24	99	+75			
8	PIE	110	278	—	—	178	246	+68	17	21	+4	40	61	+21	25	112	+87			
	PIE+PT	110	—	—	—	195	360	+165	21	27	+6	51	145	+96	112	2054	+1990			
9	PT	149	286	—	—	—	—	—	9 (ic)	(ic)	—	18	—	—	3	27	+24			
	PT	130	298	—	—	269	182	-97	32	17	-15	19	27	+8	5	4.8	-0.2			
10	PT	93	313	—	—	241	—	—	42	(ic)	—	42	—	—	6	9	+3			
	PT	130	298	288	-10	571	553	-18	11	12	+1	144	152	+8	191	397	+208			
11	PT	83	288	304	+16	384	250	-134	28	14	-14	88	35	-55	189	13	-176			
	PT	89	308	312	+4	416	450	+34	37	18	-19	157	169	+12	24	605	+577			
Mean (SD)		103 (26)	299 (12)	306 (13)		301 (132)	320 (116)		23 (11*)	19 (8*)		73 (45)	83 (52)							
Paired t test		$t = -1.55$ ( $p = 0.2$ )			$t = -0.33$ ( $p < 0.05$ )			$t = 1.82$ ( $p < 0.4$ )			$t = -0.74$			(Wilcoxon's signed pair test, $p < 0.02$ )						



\*Only calculated on complete collections: ic=incomplete collection. PT=pneumothorax; PIE=pulmonary interstitial emphysema.

**Table 2 Plasma and urinary arginine vasopressin, body weight, plasma sodium, blood gases, and blood pressures in 11 infants before and after developing 22 air leaks**

Case No	Diagnosis	Urinary arginine vasopressin (pmol/l)		Plasma arginine vasopressin (pmol/l)		Weight (g)		Plasma sodium (mmol/l)		Blood gases				Blood pressure			Acute hypoxia									
		Before	After	Before	After	Before	After	Before	After	FiO <sub>2</sub> (%)	PaO <sub>2</sub> (kPa)	PaCO <sub>2</sub> (kPa)	pH	Systolic	Diastolic	Mean										
1	PT	1	1	1	4	980	1020	140	151	66	71	7.4	7.7	8.0	7.6	7.0	7.2	46	59	22	29	28	39	++		
	PT	1	8	1	60	0.7	1.8	1060	980	139	139	50	40	8.9	8.8	10.3	7.3	7.12	7.24	61	55	30	33	40	0	
2	PT	1	4	5	12	1	1	1800	1820	137	153	62	51	8.7	8.1	9.2	6.9	7.27	7.27	42	41	23	25	32	36	0
	PT	92	84	506	714	13.3	10	975	940	142	145	41	75	7.6	6.9	4.9	7.9	7.21	7.14	50	41	29	18	34	25	+
3	PT	67	163	257	1630	13.8	46	1010	880	146	145	59	76	7.6	7.4	7.9	10.6	7.14	7.01	45	44	22	20	29	28	0
	PT	228	244	1368	610	—	—	880	875	146	142	29	27	8	8.8	8.45	4.9	7.14	7.27	55	61	37	35	47	45	0
4	PT	1	1	15	7	1	4	1160	1820	140	147	72	77	7.7	7.9	6.78	5.77	7.23	7.24	38	48	19	20	28	30	+
	PT	3	5	41	44	1.4	3	840	780	132	136	60	45	8.2	9	7.01	6.11	7.25	7.28	40	39	28	30	32	35	0
5	PT	28	264	—	3168	1	2.7	780	830	136	129	?	?	9	9	7.2	11.2	7.27	7.03	44	41	34	29	39	36	++
	PIE	122	162	329	2673	—	—	740	860	136	142	75	95	8	7.9	8.7	7.8	6.9	7.15	40	39	28	34	34	35	0
6	PT	89	160	2803	—	1	100	740	860	136	142	94	81	8	8.3	6.8	5.6	7.22	7.28	39	41	34	36	35.5	38	0
	PIE	20	57	280	712	5	10	1100	1095	146	146	66	90	7.1	7.6	5.1	6.3	7.3	7.2	48	50	31	35	36.5	43	0
7	PT	52	80	197	2160	4.6	3.2	1095	1070	138	144	69	71	7.6	8	5.0	6.1	7.45	7.39	45	43	34	28	42	34	+
	PIE	15	67	112	835	—	—	1140	Not weighed	135	137	68	97	6.6	7.0	6.1	7.4	7.25	7.19	40	49	21	28	29	37	++
8	PT	67	1027	837	1691	7	42	Not weighed	137	140	98	97	6.8	8.2	7.4	6.9	7.14	7.24	48	46	27	31	36	37	++	
	PT	2	19	9	25	—	—	740	790	142	141	77	98	7.1	7.4	7.1	6.9	7.27	7.27	46	37	24	15	29	23	++
9	PT	15	8	152	80	—	—	1200	1130	140	139	67	79	8.5	7.5	5.19	5.16	7.3	7.3	37	47	28	36	33	40	++
	PT	5	13	90	312	110	160	1130	139	139	88	100	7.5	3.7	6.3	5.5	7.17	6.97	42	37	23	20	31	28	++	
10	PT	446	873	2810	4365	2	9	1185	1185	140	140	46	43	7.4	7.8	7.1	7.0	7.26	7.26	Not measured	—	—	—	—	54	0
	PT	246	13	1968	260	2	9	1185	1185	140	137	33	23	8.1	9.2	6.3	3.4	7.38	7.36	64	75	33	36	46	50	0
11	PT	17	484	408	5808	—	—	1030	985	149	148	21	21	11.7	11.3	7	6	6.95	7.36	45	47	26	26	32	34	++

PT=pneumothorax; PIE=pulmonary interstitial emphysema.

The median increase of 7 pmol/l after the 21 air leaks. The maximum fall was 7 mmol/l (from 136 to 129 mmol/l). This baby gained 50 g in weight, and this was the only occasion on which a possible effect of the secretion of arginine vasopressin was seen. The plasma arginine vasopressin concentration rose from 1 to 2.7 pmol/l, but the urinary excretion rose from 40 to 440 pmol/mmol creatinine. The baby who had a fall in plasma sodium concentration of 1 mmol/l had an increase in urinary excretion from 3 to 27 pmol/mmol creatinine, but plasma arginine vasopressin measurements were not available.

**URINARY ARGININE VASOPRESSIN CONCENTRATION (FIG 2)**

In 17 of the 21 air leaks there was an increase in the excretion of arginine vasopressin in the four hours after the leaks. The median increase of 32 pmol/mmol creatinine was significant ( $p < 0.02$ , Wilcoxon's signed pair test).

**PLASMA SODIUM CONCENTRATION**

The median change in the plasma sodium was 0

Arch Dis Child: first published as 10.1136/adc.65.11.1259 on 1 November 1990. Downloaded from http://adc.bmj.com/ on 22 July 2019 by guest. Protected by copyright.

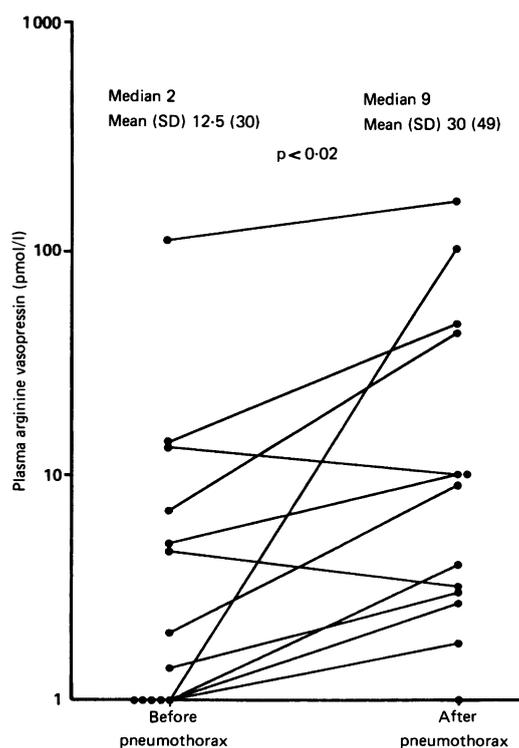


Figure 1 Plasma arginine vasopressin concentrations before and after 13 pneumothoraces or air leaks.

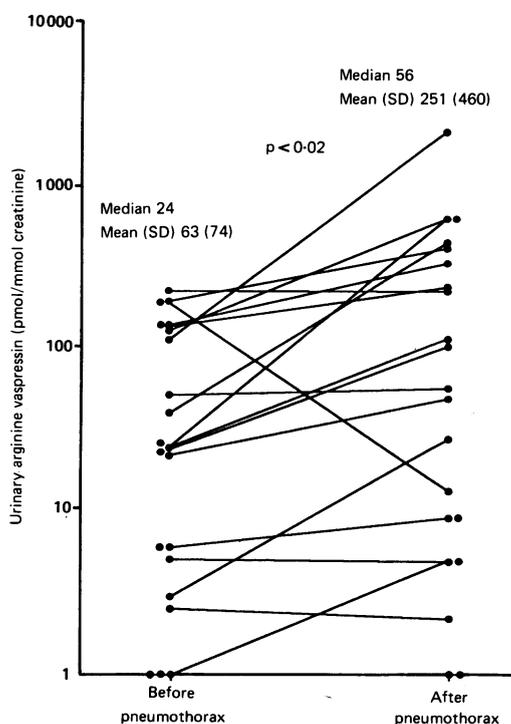


Figure 2 Urinary arginine vasopressin concentrations before and after 21 pneumothoraces or air leaks.

#### URINARY SODIUM CONCENTRATION

There was no significant change in the urinary sodium concentration when an air leak developed (table 1), though there was a highly significant correlation ( $p < 0.01$ ) between the change in urinary arginine vasopressin excretion and the change in urinary sodium concentration.

#### URINE VOLUMES

The development of an air leak was accompanied by a significant reduction in the urine volume (23 (11) ml during the eight hours before, compared with 19 (8) ml during the eight hours after,  $p < 0.05$ ) though the change in urine volume did not correlate with the change in urinary arginine vasopressin excretion.

#### WEIGHT

There was a median weight loss of 15 g (ranging from a loss of 130 g to a gain of 120 g). Three babies gained 120 g but all also had rises in plasma sodium concentrations. In only two babies was a gain in weight accompanied by a decrease in plasma sodium concentration, though in one case this was only by 1 mmol/l, which is within the range of error of the measurement.

#### BLOOD PRESSURE AND BLOOD GAS TENSIONS

There were no significant changes in systolic, diastolic, or mean blood pressures, or pH arterial carbon dioxide ( $\text{PaCO}_2$ ) or oxygen ( $\text{PaO}_2$ ) tensions. In 11 cases there was appreciable acute 'hypoxia' (described in the hospital notes) at the time of the development of air leak, which was rapidly corrected. These babies did not show any significant changes in blood pressure as a consequence and showed no greater increase in plasma vasopressin concentrations ('hypoxia', median increase = 2.0 pmol/l, compared with 'no appreciable hypoxia', 5 pmol/l) or in the urine excretion ('hypoxia', median increase = 24 pmol/mmol creatinine compared with 'no appreciable hypoxia', 11 pmol/mmol creatinine).

#### Discussion

In 1977 Paxson *et al* reported the syndrome of inappropriate antidiuretic hormone release after air leaks in ventilated newborns.<sup>1</sup> The diagnosis was made because of the development of hyposmolar serum in the presence of concentrated urine. Neither plasma concentrations nor urine vasopressin excretion were measured. Analysis of these patients indicated no association with hypoxaemia and there was no apparent difference in the clinical features of babies who had pneumothorax and inappropriate antidiuretic hormone release (14%) and those who did not (86%). Stern *et al* described 10 ventilated patients with acute and symptomatic pneumothorax; all had significant deterioration in  $\text{PaO}_2$  and acid base, but none was recorded as being hypotensive.<sup>2</sup> Vasopressin excretion rose significantly but with successful treatment returned to normal within 8–16 hours. Only two of the infants became hyponatraemic and fulfilled the criteria for inappropriate antidiuretic hormone release. Three babies who had high and prolonged arginine vasopressin excretion did not develop hyponatraemia. Rees *et al* (1984) described one baby who had a large increase in arginine vasopressin excretion after a bilateral tension pneumothorax and the urine became concentrated. The baby was also acidotic and hypoxaemic.<sup>3</sup> Wiriathian *et al*, investigating serial arginine vasopressin excretion, described four infants in whom significant increases in arginine vasopressin excretion followed a pneumothorax but no plasma concentrations were mentioned and there is no indication that these infants developed inappropriate antidiuretic hormone release.<sup>4</sup>

Our data are the first to examine changes in plasma vasopressin concentrations at the same time as urinary vasopressin excretion in the presence of air leaks in newborn infants. We agree that there is often a sustained excretion of vasopressin in response to the development of an air leak, but this is certainly not invariable and happened in only 15 of 21 episodes (71%). In addition, the high urinary excretion is also not always accompanied by high plasma concentrations. It is difficult to explain this unless concurrent renal damage is leading to a vasopressin leak without accumulation in the plasma, or unless the release of vasopressin has been short lived. Although four of our infants had raised plasma creatinine values, in three it was for only a short time and we believe that the release of arginine vasopressin is sometimes short lived after an air leak. In contrast, on two occasions a pronounced rise in plasma vasopressin concentration was not associated with an increase in urinary vasopressin excretion, and the correlation—considering all infants—between plasma concentration and the preceding four hourly excretion was not significant ( $r=0.18$ ,  $p=0.55$ ). The babies reported in these studies all had respiratory problems and were also being ventilated, both of which factors have been associated with inappropriate antidiuretic hormone release.<sup>8,9</sup>

Analysing the mechanism stimulating secretion is difficult. Paxson *et al* could not show any association with hypoxaemia and we agree.<sup>1</sup> Although hypoxia is a powerful stimulant of vasopressin release,<sup>12</sup> we are not aware of work showing that the release occurs at a particular  $\text{PaO}_2$ , either immediately or after a finite period, or whether there is an inverse linear relationship of vasopressin excretion with  $\text{PaO}_2$  (other stimuli not contributing). None of the 11 infants recorded as being 'acutely hypoxic' in the case notes had a chronic reduction of  $\text{PaO}_2$  before or after the events when average hourly data were examined, but the urgency with which air leaks are rectified by thoracocentesis usually means that hypoxia is short lived. This may account for the lack of difference in 'hypoxic' compared with 'non-hypoxic' infants. There was no significant change in our babies in blood gas or acid base state, and no change in mean blood pressure.

Pressure changes in the mediastinum may be transmitted to the intrathoracic baroreceptors and might be considerable when a pneumothorax develops. It might explain the high circulating concentrations of antidiuretic hormone in babies that are ventilated with positive pressure ventilation.<sup>9,10</sup> Only one of our infants (case 5) showed any suggestion of inappropriate antidiuretic hormone release with a rise in body weight and a fall in plasma sodium and osmolality. The urinary sodium remained high throughout, and the episode required no treatment. It is surprising that the syndrome was not seen more often as in many cases both the plasma concentrations and the urinary excretions of vasopressin were massive. Both Wiriyathian *et al*,<sup>4</sup> and Rees *et al*,<sup>3</sup> have suggested a relative refractoriness of the neonatal kidney to the antidiuretic effects of arginine vasopressin—possibly as a result of the presence of circulating antagonists such as prostaglandin  $\text{E}_2$ .<sup>11</sup> This might account for our results, but no measurements were made.

A further confounding variable might be the development of intraventricular haemorrhage. Such haemorrhages are common in preterm infants with respiratory problems and air leaks and may also be associated with vasopressin secretion.<sup>3</sup> During the time of this study we were not carrying out repeated ultrasound scans so have no data about whether some of the high plasma concentrations and urinary excretions were associated with this problem.

The weight loss in these infants is no more than one would expect in newborn infants over the first days of life and although the plasma osmolalities were high we do not think that this was the result of dehydration because of the appropriate release of arginine vasopressin. The rise in seven osmolar points is far from significant, and there is no correlation between the osmolalities or the change in osmolality with the vasopressin release.

Overall we believe that the rises in both plasma concentration and urinary excretion of vasopressin is related to the development of the air leak, though the mechanism remains unclear and could be related to disturbed mediastinal pressure.

Of practical importance is whether fluid should be restricted after the development of an air leak in the same way as after birth asphyxia.<sup>6</sup> Our results suggest that such restriction should certainly not be routine. In five of the infants the increase in vasopressin with the event was  $<2$  pmol/l, and in two of these the concentrations fell. We believe that because of the previous reports,<sup>1-4</sup> the urinary and plasma osmolality and the plasma sodium concentration should be monitored, but that fluid restriction should not usually be necessary.

We thank doctors and nurses in the South West Thames Regional Neonatal Intensive Care Unit for their care and cooperation, Miss Elaine Forbes for secretarial assistance, and Birthright for support of AS.

- 1 Paxson CL, Stoerner JW, Denson Se, Adcock EW, Morriss FH. Syndrome of inappropriate antidiuretic hormone secretion in neonates with pneumothorax or atelectasis. *Pediatrics* 1977;91:459-63.
- 2 Stern P, La Rochelle FT, Little GA. Vasopressin and pneumothorax in the neonate. *Pediatrics* 1981;68:499-503.
- 3 Rees L, Brook CGD, Shaw JCL, Forsling ML. Hyponatraemia in the first week of life in preterm infants. Part 1: arginine vasopressin secretion. *Arch Dis Child* 1984;59:414-22.
- 4 Wiriyathian S, Rosenfeld CR, Arant BS, Porter JC, Faucher DJ, Engle WD. Urinary arginine vasopressin: pattern of excretion in the neonatal period. *Pediatr Res* 1986;20:103-8.
- 5 Hill D, Volpe JF. Hypoxic ischaemic encephalopathy. In: Robertson NRC, ed. *Textbook of neonatology*. Edinburgh: Churchill Livingstone, 1986:546-58.
- 6 Liu H-Y, Anderson GJ. A method for long-term quantitative and fractional urine collection. *Pediatrics* 1967;70:276-9.
- 7 Smith A, McIntosh N. A radioimmunoassay for arginine vasopressin in unextracted human urine. *Biochem Soc Trans* 1986;14:782-3.
- 8 Weinberg JA, Weitzman RE, Zakaudinn S, Leake RD. Inappropriate secretion of antidiuretic hormone in a premature infant. *Pediatrics* 1977;90:111-4.
- 9 Hemmer M, Viquerat CE, Suter PM, Vallotton MB. Urinary antidiuretic hormone excretion during mechanical ventilation and weaning in man. *Anesthesiology* 1980;52:395-400.
- 10 Kumar A, Pontoppidan H, Baratz RA, Laver MB. Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. *Anesthesiology* 1974;40:215-21.
- 11 Joppich R, Haberle DA, Weber PC. Studies in the immaturity of the ADH dependent cAMP system in conscious newborn piglets—possible impairing effects of renal prostaglandins. *Pediatr Res* 1981;15:278-81.
- 12 Daniel SS, Stark RI, Zubrow AB, Fox HE, Husain MK, James SL. Factors in the release of vasopressin by the hypoxic fetus. *Endocrinology* 1983;113:1623.