

Renal Acid Excretion in Infants with the Respiratory Distress Syndrome

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Extract

Acid-base balance in blood and hydrogen ion, phosphorus concentrations, and acid-base excretion in urine were measured in 10 infants with respiratory distress syndrome (RDS), in 8 control full term infants, and in 7 control premature infants on days 1, 2, and 3 of life. Infants with RDS were acidemic in comparison with full term and premature control infants.

Hydrogen ion concentrations in urine were similar for premature control subjects and acidemic infants with RDS but lower in comparison with those of full term control infants. The inability of infants with RDS, in the face of acidemia, to create an appreciable urine to plasma hydrogen ion concentration gradient provided evidence for a renal tubular deficiency in hydrogen ion secretion.

Phosphate levels in urine and, as a result, titratable acid were usually low in the three groups of infants. Relative phosphaturia did occur in some infants with RDS, but, because of the deficiency in hydrogen ion secretion, urinary phosphate was often not utilized as titratable acid.

At high urinary concentrations of hydrogen ion (above 400 $\mu\text{mEq/liter}$), control premature infants and acidemic infants with RDS excreted urine having lower ammonium concentration than that found in control full term infants. The inability of infants with RDS with acidemia to excrete ammonium when hydrogen ion concentrations in urine were high was evidence of a renal tubular deficiency in ammonia production.

Infants with RDS differed from control premature infants by having high hydrogen ion and bicarbonate concentrations in blood in relation to higher blood PCO_2 values. In addition, at low hydrogen ion concentrations in urine, infants with RDS excreted urine that contained higher concentrations of bicarbonate than that found in control premature infants.

Because infants with RDS did not excrete ammonium, they could not compensate for the increased acid load and bicarbonate excretion associated with respiratory acidemia. In addition, they could not compensate for the low titratable acid, which resulted from decreased excretion of phosphate, characteristic of the newborn period.

Infants with RDS did not respond to acidemia by increasing net acid excretion in urine beyond that excreted by control infants. Indeed, some infants with RDS inappropriately excreted base, thereby aggravating their already existing acidemia.

Speculation

Low gestational and postnatal age is the likely etiologic factor responsible for the decreased capacity for urinary acid excretion seen in infants with RDS. The apparent

improvement in renal tubular hydrogen ion secretion with increasing gestational age may be associated with maturation of an enzyme system such as carbonic anhydrase. Likewise, the apparent improvement in renal tubular ammonia production with increasing gestational age may occur in relation to maturation of an enzyme system such as glutaminase.

Introduction

Respiratory distress syndrome of prematurity is commonly associated with combined respiratory and metabolic acidosis which often persists during week 1 of life [32]. The severity and duration of this acidosis has been shown to be inversely related to prognosis for survival [5, 32].

Renal excretion of acid is an important means for achieving acid-base homeostasis. Persistence of respiratory acidosis without an appreciable increase in extracellular bicarbonate concentration for 3 or more days [32] suggests that the renal capacity for acid excretion in these infants is impaired. Hatemi and McCance [12] have shown that normal full term infants at 1 week of age took longer than adults to excrete a comparable metabolic acid load. There is at present no information on the ability of premature infants to excrete acid in urine during week 1 of life. The present investigation was undertaken to compare acid excretion in urine in premature infants in response to acidosis associated with RDS with that in healthy, nonacidemic premature and full term infants.

Subjects

Ten infants with RDS, eight healthy full term control infants, and seven nondistressed premature control infants were studied during the first 3 days of life. The birth weight and gestational age of each infant are given in Table I. All full term control infants weighed 2960 g or more and all premature control infants weighed 1950 g or less. Two full term infants (*nos. 1 and 5*), whose gestational ages were unknown, had clinical criteria [34] for a gestational age of 40 weeks. Eight of the 10 infants with RDS weighed 2300 g or less. Two infants with RDS (*nos. 18 and 24*), both of whom were infants of diabetic mothers, weighed 3500 and 4710 g at gestational ages of 34.5 and 37.5 weeks, respectively. One infant with RDS (*no. 23*) whose gestational age was unknown had the clinical criteria [34] for a gestational age of 34 weeks.

Respiratory distress syndrome was diagnosed clinically when an infant had expiratory grunting, subcos-

tal retractions, and decreased breath sounds on auscultation persisting beyond the first 3 hr of life. All 10 infants with RDS had a clinical course which lasted 2–3 days. Two infants with RDS (*nos. 16 and 25*) had Apgar scores below 6 at 1 min of age. Three infants died, *no. 18* at 34 hr, *no. 24* at 33 hr, and *no. 25* at 13 hr of age, and at autopsy were found to have had hyaline membrane disease. One infant with RDS (*no. 16*) developed a right pneumothorax at 30 hr of age and survived.

The control infants did not have respiratory distress syndrome. The eight full term control infants had Apgar scores greater than 6. Two of the seven premature control infants (*nos. 9 and 12*) had Apgar scores below 6 at 1 min of age. All control infants were clinically well during the period of study and on discharge from the hospital.

Oral and parenteral fluid intake are tabulated for each infant in Table I. The volume and type of feeding given were determined by the clinical team responsible for the care of each infant. Other than insuring that bicarbonate was administered by slow constant intravenous infusion, no attempt was made to standardize intake. When infants regurgitated, the volume was estimated by the nursing staff and subtracted from the previous feeding. Three infants with RDS (*nos. 18, 24, and 25*) never received oral feedings because of the severity of the disease. Nine of the 10 infants with RDS and 2 (*nos. 12 and 13*) of the 7 premature control infants were treated intravenously with 10% glucose and bicarbonate according to a previously described regimen [33]. One infant with RDS (*no. 25*) who died at 13 hr of age and 2 premature control infants (*nos. 9 and 11*) were treated with 10% glucose and water without bicarbonate administered intravenously. Sodium bicarbonate, when given, was infused at rates of 0.13–0.41 mEq/kg/hr, and intravenous fluids at a rate of approximately 65 ml/kg/24 hr.

During study periods all infants were nursed and fed in incubators [37] having a relative humidity of 90–100%. Body temperature was maintained within the normal range (36.5–37.5°).

Oxygen was administered to infants with RDS in amounts necessary to relieve cyanosis.

Table I. Birth weight, gestational age, and metabolic data

Subject no.	Birth wt, g	Gestational age, wk	Milk intake		Glucose water intake ²	NaHCO ₃ intake, mEq/kg/24 hr			Daily blood [H ⁺], μmEq/liter			Net acid excretion ³ , mEq/kg/24 hr		
			Type ¹	Vol, ml/kg/72 hr		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Full term control infants														
1	3575	Unknown	C20	366	22	0	0	0	44.0	43.6	(d)	+0.26	+0.61	(d)
2	3080	40.5	C20	534	95	0	0	0	43.7	45.3	(d)	+0.39	+1.45	(d)
3	3620	39	C20	277	21	0	0	0	(d)	41.5	39.2	(d)	+2.03	+1.58
4	3340	41.5	C20	385	17	0	0	0	48.2	43.4	41.3	+0.54	+1.72	+2.76
5	3090	Unknown	Human	362	16	0	0	0	40.5	42.0	42.2	-0.01	+0.59	+0.58
6	2960	40	HMS20	317	31	0	0	0	43.6	40.3	41.8	+0.35	+0.56	+1.39
7	3960	41	HMS30	277	17	0	0	0	44.8	(d)	41.0	+0.58	(d)	+0.52
8	3960	41	C20	331	19	0	0	0	45.1	43.0	43.7	+0.37	+1.19	+1.28
Mean	3448								44.3	42.7	41.5	+0.35	+1.16	+1.35
Premature control infants														
9	1220	28.5	Human	93	169	0	0	0	43.7	42.7	43.5	-0.11	0.00	+0.06
10	1950	35.5	C20	385	44	0	0	0	47.3	38.0	39.4	+0.15	+1.23	+1.42
11	1075	29	HMS30	172	225	0	0	0	49.1	46.3	43.9	0.00	+0.04	-0.04
12	1185	30	HMS30	187	154	9.5	0	0	42.3	36.9	38.7	-0.19	+0.05	-0.13
13	1590	30.5	Human	98	242	1.8	0	0	46.1	37.4	42.2	-0.41	-0.49	-0.13
14	1605	32.5	C20	425	66	0	0	0	40.8	(d)	44.8	+0.11	(d)	+1.45
15	1680	32.5	Human	321	46	0	0	0	43.4	(d)	39.4	+0.18	(d)	+0.68
Mean	1472								44.7	40.3	41.7	-0.04	+0.17	+0.47
Infants with RDS														
16	1805	30.5	C18	27	215	8.2	4.5	2.7	63.7	57.8	46.9	-0.31	-0.72	-1.94
17	2300	34	C18	145	102	1.7	2.4	0.1	49.8	44.1	42.4	+0.21	+0.14	+0.40
18	3500	34.5	NPO	0	(86) ^a	5.8	(3.2) ^a	(a)	64.8	71.2	(a)	+0.14	-0.98	(a)
19	1220	27	Human	110	247	0.8	0	0	45.2	44.0	50.8	-0.35	-0.41	-0.20
20	1290	29	Human	197	144	1.3	0	0	44.4	45.5	48.3	+0.03	-0.16	+0.05
21	1535	28	C23	157	68	5.3	0	0	62.1	43.7	45.7	+0.06	0.00	-0.20
22	1775	33.5	C20	223	82	2.1	0	0	48.3	41.8	45.1	+0.11	-0.38	+0.20
23	2150	Unknown	C20	331	70	1.3	0	0	51.7	45.8	45.3	+0.33	+1.01	+1.73
24	4710	37.5	NPO	0	(71) ^b	5.1	(3.6) ^b	(b)	53.2	55.0	(b)	+0.33	+0.65	(b)
25	1380	32	NPO	0	(41) ^c	0	(c)	(c)	87.8	(c)	(c)	-0.50	(c)	(c)
Mean	2167								57.1	49.9	46.4	-0.01	-0.09	+0.01

¹ Type of milk feeding: C18, $\frac{1}{2}$ diluted part skim evaporated cow's milk, 17.6 kcal/oz; C20, $\frac{2}{3}$ diluted whole evaporated cow's milk, 20 kcal/oz; C23, $\frac{1}{2}$ diluted whole evaporated cow's milk, 22.8 kcal/oz; HMS20, human milk substitute (Similac), 20 kcal/oz; HMS30, human milk substitute (Similac), 30 kcal/oz.

² Intravenous and *per os*.

³ +: Net acid excretion; -: net base excretion.

(a) Death at 34 hr.

(b) Death at 33 hr.

(c) Death at 12 hr.

(d) Urine collection grossly contaminated.

Methods

Using a Hepner-Lubchenco metabolic bed [14], urine was collected from each infant during the first 72 hr of life. Each voiding was collected separately in small polyethylene bottles, accurately timed by means of an electrical signalling device, immediately capped, and refrigerated at 4°. At 24, 48, and 72 hr of age, individual voidings were assembled into daily urine collections. Any individual voiding contaminated with stool was discarded, and its appropriate time period was subtracted from that of the daily urine collection. Each daily urine collection was mixed well and its volume was measured. It was then divided into aliquots of 5–30 ml and frozen in tightly capped polyethylene bottles at -30° until analyzed. Because of stool contamination, six daily urine collections from six con-

trol infants (no. 3 on day 1; nos. 7, 14, and 15 on day 2; nos. 1 and 2 on day 3) were not analyzed. Four daily urine collections from three infants with RDS (nos. 18, 24, and 25) were not obtained because the infants died before completion of the study.

Since urine was collected under conditions allowing exposure to air, the anerobic urine pH was derived from the mean capillary blood carbon dioxide tension (PCO₂) and the pH/log PCO₂ buffer line for each daily urine collection. The pH was measured potentiometrically at 38° after equilibration of urine samples with two known CO₂ mixtures. The pH/log PCO₂ buffer line was plotted from these two paired pH and PCO₂ values. The pH on the buffer line corresponding to the mean arterialized capillary blood PCO₂ is the derived anerobic pH. Figure 1 demon-

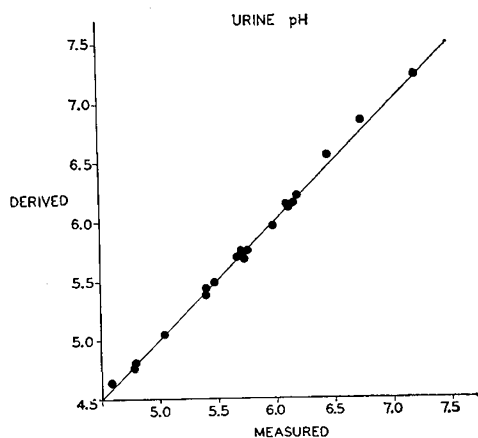


Fig. 1. Correlation between the pH measured on anaerobically collected urine and the derived "anaerobic" pH determined on anaerobically collected urine using the method described in the text.

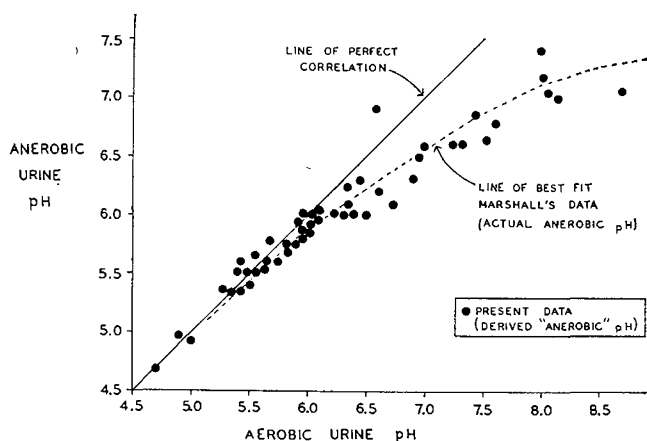


Fig. 2. Relation between the derived "anaerobic" pH and the pH of aerobic urine in 51 24-hr urine specimens from 12 newborn infants. The dotted line is that which best fits Marshall's data [20] from single voidings in adults comparing the pH of anaerobically collected urine with that which was subsequently exposed to air.

strates that the derived pH of single voidings from 19 infants having capillary blood PCO_2 values ranging from 20 to 61 mm Hg closely approximates the pH of an anaerobically collected sample from the same voiding. Anaerobic samples were collected in 100- μ l capillary tubes that were filled directly from the urinary stream and immediately sealed with plasticine. The pH of the anaerobic samples was measured potentiometrically at 38° within 15 min of collection. Figure 2 illustrates the alkaline shift from the derived anaerobic pH that occurred when the carbon dioxide tension of 51 24-hr urine collections from 12 infants was equilibrated with that of air. Also illustrated is the line of

best fit for the alkaline shift found by Marshall [19] in single voidings collected anaerobically from adults (Fig. 2). The close correlation observed between these data from newborn 24-hr urine collections and Marshall's data from adult single voidings is evidence that the pH derived on 24-hr collections by the above technique closely approximates that pH which would have been measured if the urine had not been exposed to air. This technique, established for single voidings, was therefore applied to 24-hr urine collections; the derived anaerobic pH was calculated from the urine pH/log PCO_2 buffer plot and the mean capillary blood PCO_2 . Acid and base concentrations were measured on each daily urine collection. "Titratable acid minus bicarbonate" concentration, which remains unchanged when urine is exposed to air, was measured titrimetrically at room temperature as the excess alkali required, after removal of bicarbonate by acidification, to reach an end point pH of 7.4 [1]. Urinary bicarbonate and titratable acid concentrations were measured titrimetrically at room temperature. The derived anaerobic urine pH and pH 7.4 were used as end points for titration of bicarbonate and titratable acid, respectively. Results of the titrimetric procedures were not corrected for variations in urinary ionic strength [26] and are subject to error resulting from the differences between body temperature and the temperature at which the titration was performed [36]. Since the phosphate concentration of newborn urine is low, the maximum theoretical cumulative error in "titratable acid minus bicarbonate" concentration due to urinary ionic strength and to temperature may be as great as 1.5 mEq/liter [26, 36]. Urinary titratable acid and bicarbonate measurements are, in addition, subject to that error due to differences between the derived and the true anaerobic pH.

Urinary ammonium concentration was measured by the microdiffusion method of Seligson and Seligson [29]. Net acid concentration, which is not altered by exposure of urine to air, was calculated as the sum of "titratable acid minus bicarbonate" and ammonium concentrations.

Mean daily body weight was determined from body weights measured twice daily. Urine flow was proportionately converted to volume per 24 hr. Using mean daily body weights, urine flow was expressed as milliliters per kilogram body weight per 24 hr and served as a basis for calculation of excretion rates.

Carbon dioxide tension (PCO_2), hydrogen ion, and actual bicarbonate concentrations were measured by the micro-Astrup technique [3] on blood obtained by heel prick after the foot had been immersed for 5 min

in a water bath at 42° [10]. Measurements were made at 38° and were not corrected for actual body temperature. The PCO₂ values in blood and bicarbonate concentrations were not corrected for hemoglobin desaturation. Acid-base values in blood were measured at the beginning and end of each daily urine collection in all infants and more frequently in infants who were acidotic. A daily value represents the weighted mean of the individual determinations obtained during the corresponding urine collection period; *i.e.*, weighted for the time period represented by the individual values: for example, the weighted mean for values A, B, and C obtained at 0, 8, and 24 hr, respectively, in a 24-hr study is calculated as:

$$\frac{[8 \text{ hr} \times (A + B)/2] + [16 \text{ hr} \times (B + C)/2]}{24 \text{ hr}}$$

Because of small numbers of infants in each group, statistical analyses were not applied to these data.

Results

Acid-Base Balance in Blood

Daily acid-base values in blood during the first 3 days of life are presented on a nomogram in Figure 3. Each value corresponds to a day on which a urine collection was obtained. Isobars for PCO₂ were calcu-

lated from the Henderson equation [13]. In addition, hydrogen ion concentrations in blood for each day studied are presented in Table I.

Full term and premature control infants had a mild metabolic acidemia which was compensated by mild hypocapnia so that daily hydrogen ion concentrations in blood were not greater than 49.1 μmEq/liter (pH < 7.31). Infants with RDS had higher levels of PCO₂ in blood resulting in higher hydrogen ion and bicarbonate concentrations than those found in control infants. Among infants with RDS, high bicarbonate concentrations were associated with high hydrogen ion concentrations in blood. Bicarbonate concentration was greater than 24 mEq/liter in 10 of the 26 observations on infants with RDS; 6 were associated with hydrogen ion concentrations greater than 50 μmEq/liter (pH < 7.30). Nine of 10 infants with RDS who received intravenous sodium bicarbonate remained acidemic in relation to control infants. No infant with RDS ever became alkalemic, the single lowest measured concentration of hydrogen ion in blood being 37.2 μmEq/liter (pH = 7.43).

Urine Hydrogen Ion Concentration

The hydrogen ion concentration and pH in urine during days 1, 2, and 3 of life are presented in Figure

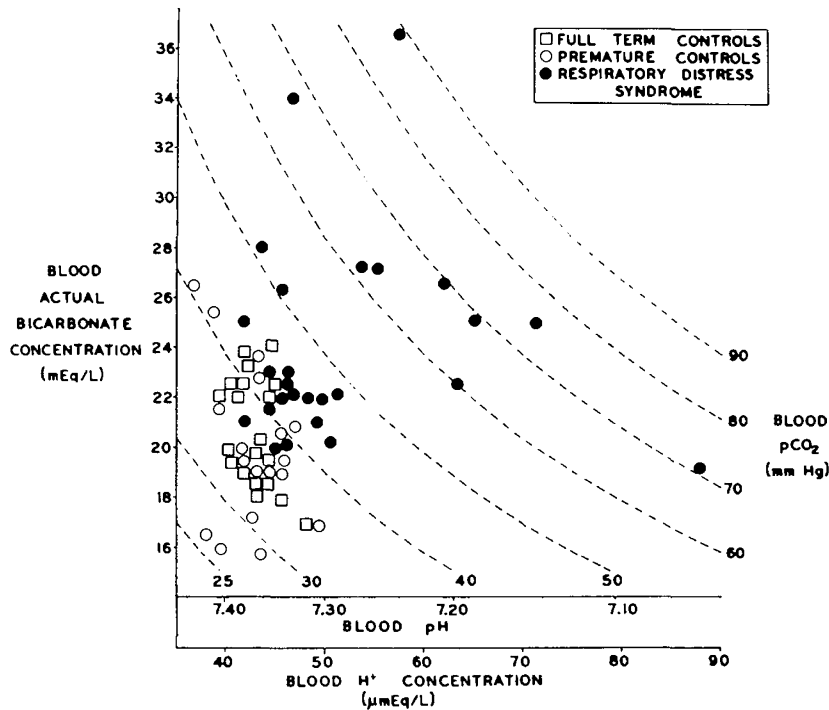


Fig. 3. Daily hydrogen ion, bicarbonate, and PCO₂ values in blood in full term control infants (□), premature control infants (○), and infants with RDS (●) during the first 3 days of life. Each value corresponds to a day on which a urine collection was obtained.

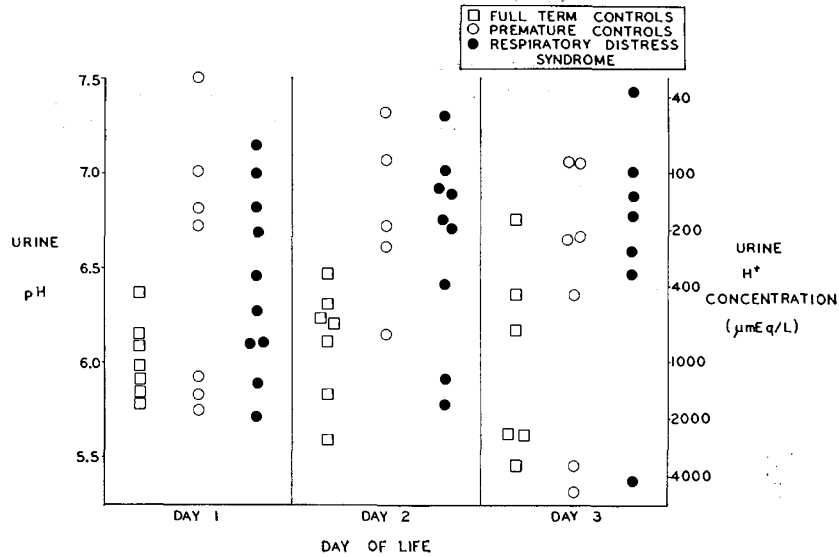


Fig. 4. Hydrogen ion concentration (plotted on a log scale) of daily urine collections obtained on each of the first 3 days of life.

4. Premature control infants and infants with RDS excreted urine having similar concentrations of hydrogen ion, but alkaline in comparison with that excreted by full term control infants.

Urinary Acid-Base Concentrations

Urinary titratable acid, ammonium, bicarbonate, and net acid concentrations are presented in relation

to hydrogen ion concentrations in urine (Figs. 5 and 6). Titratable acid and ammonium concentrations varied directly, and bicarbonate concentration inversely, with hydrogen ion concentration in urine. Net acid (titratable acid + ammonium - bicarbonate) concentration, therefore, varied directly with hydrogen ion concentration. Urine having hydrogen ion concentrations greater than 450 μmEq/liter (pH < 6.35) always contained net acid while urine having concentrations

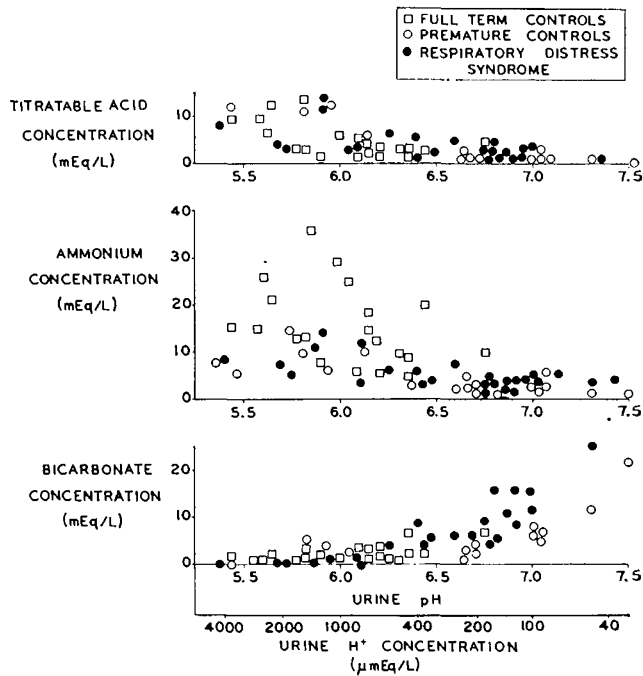


Fig. 5. Relation between hydrogen ion concentration in urine and concentration of titratable acid, ammonium, and bicarbonate in urine during the first 3 days of life.

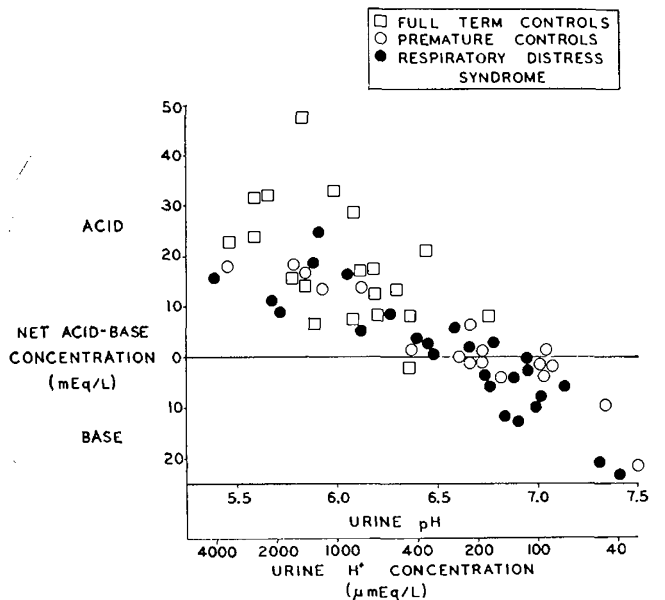


Fig. 6. Relation between hydrogen ion concentration in urine and concentration of net acid-base in urine during the first 3 days of life.

less than 85 $\mu\text{mEq/liter}$ ($\text{pH} > 7.07$) always contained net base.

Correlations between titratable acid and hydrogen ion concentrations in urine were similar for all three groups of infants. When hydrogen ion concentration was greater than 400 $\mu\text{mEq/liter}$ ($\text{pH} < 6.40$), ammonium concentrations were appreciably greater in full term control infants than in either premature control infants or infants with RDS. When the hydrogen ion concentration in urine was less than 400 $\mu\text{mEq/liter}$ ($\text{pH} > 6.40$), bicarbonate concentration was higher in infants with RDS than in urine of premature control infants. Because of these differences, at high hydrogen ion concentrations, full term control infants excreted urine having higher net acid concentration than did premature control infants and infants with RDS. At low hydrogen ion concentrations, infants with RDS excreted urine having higher net base concentration than did premature control infants.

Contribution of Urine Phosphorus to Urine Titratable Acid Concentration

Figure 7 presents the relation between urine phosphorus and titratable acid concentrations. The dotted line extending from the origin is the expected titratable acid concentration if all urine phosphorus and only urine phosphorus were utilized as titratable acid; *i.e.*, $[\text{HPO}_4^-]/[\text{H}_2\text{PO}_4^-] = 4/1$, present at normal plasma hydrogen ion concentration, changed to $[\text{HPO}_4^-]/[\text{H}_2\text{PO}_4^-] = 1/99$, present in acidified urine ($\text{pH} 4.8$) (calculated as: $\text{mg}/100 \text{ ml P} \times \text{mole fraction of P acidified/atomic wt P} = [(\text{mg}/100 \text{ ml P} \times 0.79)/31] \times 10 \text{ mM/liter}$). During the first 3 days of life, there was no correlation between urine phosphorus and titratable acid concentrations. High concentrations of titratable acid occurred in relation to low concentrations of phosphorus. Conversely, high concentrations of phosphorus occurred in relation to low concentrations of titratable acid.

Urinary Net Acid-Base Excretion

The values for excretion of net acid or net base for each infant on days 1, 2, and 3 of life are presented in Table I and Figure 8. The mean net acid-base excretion in urine for each group of infants on each day of life is presented in Table I. On each day, seven of the eight full term control infants always excreted 0.26 $\text{mEq/kg}/24 \text{ hr}$ or more of net acid in urine. None of the premature control infants excreted this amount on day 1 and only three of five premature control infants who did not receive bicarbonate achieved this level on day 3. In both control groups mean net acid excretion

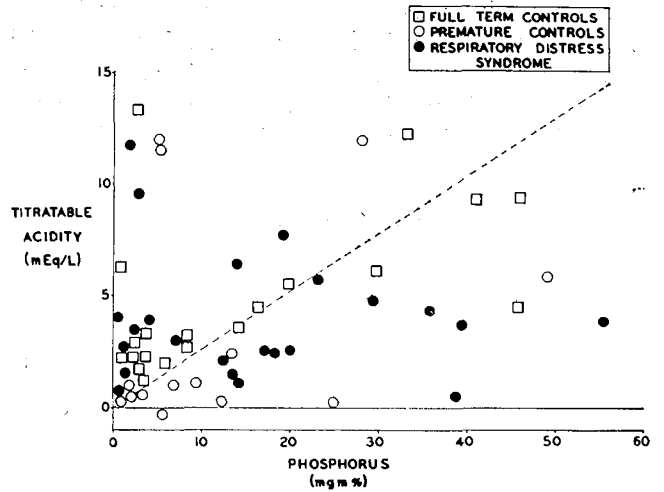


Fig. 7. Relation between phosphorus concentration and titratable acid concentration in urine during the first 3 days of life. The dotted line represents the expected titratable acid concentration if all phosphorus and only phosphorus in urine were titrated.

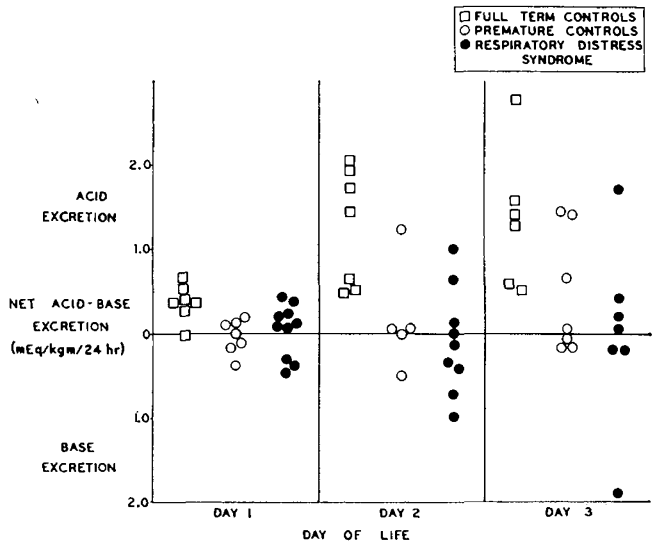


Fig. 8. Net acid-base excretion in urine on each of the first 3 days of life.

in urine increased with each day of advancing postnatal age. On each day, mean net acid excretion was greater in full term control infants than in either premature control infants or infants with RDS.

Infants with RDS were similar to premature control infants in excreting net acid in 14 of the 26 daily urine collections. In contrast with premature control infants, however, there was no apparent tendency for net acid excretion in urine to increase with advancing postnatal age in infants with RDS.

During days 2 and 3 of life, all nonacidemic full

term control infants excreted more than 0.50 mEq/kg/24 hr of net acid in urine. In contrast, only three of the seven nonacidemic premature control infants and two of the nine infants with RDS, even though acidemic, attained this level of urinary acid excretion.

Relation between Acid-Base Balance in Blood and Net Acid-Base Excretion in Urine

Figure 9 presents the relation between the degree of acidemia and net acid excretion in urine during the

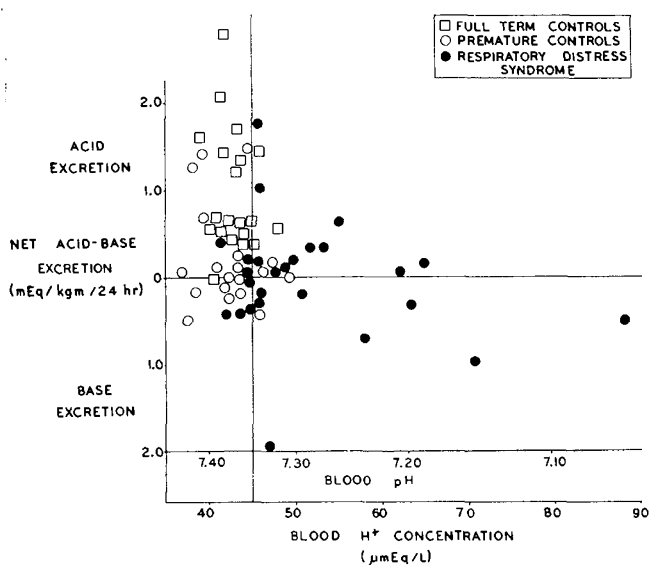


Fig. 9. Relation between hydrogen ion concentration in blood and net acid-base excretion in urine during the first 3 days of life.

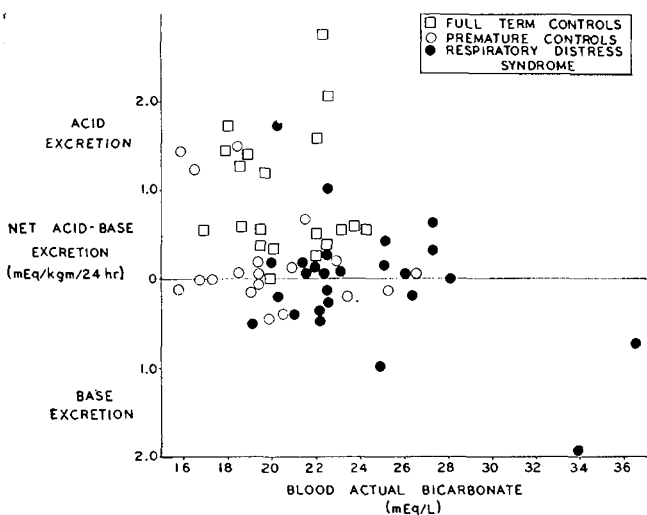


Fig. 10. Relation between bicarbonate concentration in blood and net acid-base excretion in urine during the first 3 days of life.

first 3 days of life. Only one full term control infant excreted net base; his hydrogen ion concentration in blood was 40.5 μmEq/liter (pH = 7.39). Premature control infants excreted either net acid or net base in association with normal hydrogen ion concentrations in blood. Infants with RDS did not excrete net acid when they were severely acidemic.

Net acid-base excretion in urine is presented in relation to bicarbonate concentration in blood in Figure 10 and to PCO₂ values in blood in Figure 11. In full-term and premature control infants no correlation was observed between net acid excretion in urine and bicarbonate concentration or PCO₂ values in blood. Some acidemic infants with RDS, however, excreted large amounts of net base in relation to both high bicarbonate concentrations and high PCO₂ levels in blood.

Discussion

During the first 3 days of life, the range of hydrogen ion concentrations in urine in normal full term infants has been found to be similar to that in adults [20, 21, 30]. Despite adequate hydrogen ion concentrations in urine, however, McCance and Widdowson [21] showed that full term infants, during the first 2 days of life, excreted less acid per unit body weight in urine than adults. This apparent deficiency in acid excretion was related to decreased excretion of phosphate which is utilized as buffer for titratable acid [21]. Because of this decreased titratable acid excretion, when compared with adult values, a greater proportion of total acid was excreted as ammonium by infants than that excreted by adults [21].

On day 7 of life, Hatemi and McCance [12] demonstrated that in response to an acute acid load, acid

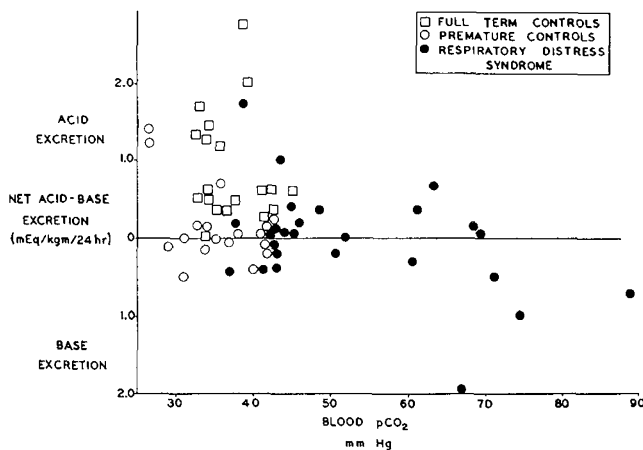


Fig. 11. Relation between PCO₂ in blood and net acid-base excretion in urine during the first 3 days of life.

excretion in urine per unit of body surface area in full term infants was decreased compared with that in adults. This decreased capacity for acid excretion in newborn infants was associated with decreased hydrogen ion concentration and decreased titratable acid excretion in urine, in comparison with that in adults. The decrease in titratable acid excretion was again related to low phosphate excretion in urine and was improved by prior phosphate loading [12].

Edelmann *et al.* [6] have demonstrated a lowered renal bicarbonate threshold in infants 1.5–12 months of age in comparison with that in normal adults and suggested that this was due to functional heterogeneity of nephrons.

Acid excretion in urine has not previously been evaluated in premature or low birth weight infants during week 1 of life. The acute renal response to an acid load in low birth weight infants between 26 and 49 days of age was shown by Ruben *et al.* [24] to be similar to that in adults. Three low birth weight infants, 11–45 days of age, were found by Gordon *et al.* [11] to excrete less urinary ammonium than 3 full term infants, 51–122 days of age. Rubin *et al.* [25] found that 4 smaller low birth weight infants, 9 days of age, excreted less urinary ammonium than 3 larger low birth weight infants, 11–14 days of age. Tudvad *et al.* [31] showed that the maximum tubular reabsorption rate of bicarbonate in 12 low birth weight infants, 8–37 days of age, was 25–26 mEq/liter and concluded that acidosis associated with prematurity was not due to defective bicarbonate reabsorption, although the renal threshold for bicarbonate excretion was not evaluated.

Dietary acid load varies with the amount and type of milk formula [9, 15–17]. The effect of diet on acid-base balance and on acid excretion was assumed to be minimal during the first 3 days of life and small in comparison with the changes associated with RDS.

The present investigation demonstrated that some infants with RDS not only failed to respond to acidemia by increasing acid excretion in urine but often excreted net base, thereby exacerbating the existing acidemia (Figs. 8 and 9).

Slow, constant infusion intravenous bicarbonate therapy in 9 of the 10 infants with RDS may have caused the increased excretion of net base observed in these infants. Four of the 10 infants remained acidemic throughout the study; however, none ever became alkalemic or hyperbicarbonatemic in relation to the steady state adjustment of blood bicarbonate concentration to graded degrees of chronic hypercapnia

defined in dogs by Schwartz *et al.* [27], in man by van Ypersele de Strihou *et al.* [35], and in children with cystic fibrosis of the pancreas by Engel *et al.* [8]. Moreover, 1 infant with RDS (*no.* 25) did not receive bicarbonate therapy. This infant became severely acidemic (blood $[H^+] = 87.8 \mu\text{mEq/liter}$) and excreted net base (0.50 mEq/kg/24 hr) comparable to the amounts excreted by infants with RDS who received slow infusions of bicarbonate. Expansion of the extracellular fluid space due to intravenous therapy may have decreased the tubular reabsorption of sodium and therefore bicarbonate; however, total oral and parenteral fluid intake differed very little in the three groups (Table I). It seems unlikely, therefore, that the slow constant intravenous infusion of bicarbonate solution accounted for the net base excretion observed in acidemic infants with RDS.

Nonacidemic full term control infants excreted more acid on each day of life than nonacidemic premature control infants and acidemic infants with RDS (Fig. 8). In addition, both full term and premature control infants increased acid excretion with each day of advancing postnatal age (Fig. 8). Since RDS is a disease associated with low gestational age and occurs during the first 3 days of postnatal life, the apparently decreased capacity for acid excretion seen in these infants could well have been related to age rather than to the disease process itself. Data relating gestational and postnatal age to the renal capacity for acid excretion will be published [2].

Hydrogen ion concentrations in urine of infants with RDS were similar to those found in premature control infants (Fig. 4); however, infants with RDS differed from premature control infants in the following ways: (1) by having higher blood PCO_2 , hydrogen ion, and bicarbonate concentrations (Fig. 3); (2) by excreting higher bicarbonate concentrations in urine (Fig. 5) and, therefore, higher net base concentrations at low urine hydrogen ion concentration (Fig. 6); and (3) by failing to increase net acid excretion with advancing postnatal age (Fig. 8). Infants with RDS, therefore, did not respond appropriately to acidemia by excreting more net acid than nonacidemic premature control infants (Figs. 8 and 9).

Premature control infants and infants with RDS excreted urine having lower hydrogen ion concentrations than full term control infants (Fig. 4). The failure of acidemic infants with RDS to create a high urine/plasma hydrogen ion concentration gradient suggests a deficiency in the renal tubular secretion of hydrogen ion [4, 7, 22]. Improvement of this function with gesta-

tional age in control infants suggests the maturation of a partially deficient enzyme system such as carbonic anhydrase [4, 28].

Compared with the excretory capabilities of adults, and in agreement with results found in infants studied by McCance *et al.* [12, 21], the infants presented here were limited in their ability to excrete urine titratable acid by low phosphate excretion (Fig. 7). Infants with severe RDS, however, who had relatively higher phosphate concentrations in urine due to catabolism, did not acidify this urinary buffer to form titratable acid (Fig. 7). The apparent deficiency in tubular secretion of hydrogen ion, therefore, superseded the apparent deficiency in phosphate excretion.

When hydrogen ion concentrations in urine were greater than 400 $\mu\text{mEq/liter}$ ($\text{pH} < 6.40$), acidemic infants with RDS and nonacidemic premature control infants excreted urine having a lower ammonium concentration than nonacidemic full term control infants (Fig. 5). Ammonium concentration in urine is determined by renal tubular ammonia production and by "diffusion trapping" of ammonia in tubular urine having a high hydrogen ion concentration [18, 22]. At higher hydrogen ion concentrations, therefore, ammonium concentration reflects renal tubular ammonia production [18]. The failure of infants of low gestational age to excrete ammonium at high hydrogen ion concentrations suggests a deficiency in renal tubular ammonia production. The apparent increase with greater gestational age suggests the maturation of a partially deficient renal ammonia-producing enzyme system, such as glutaminase I [18].

Higher bicarbonate concentration in blood due to CO_2 retention results in the delivery of a greater filtered load of bicarbonate to the renal tubule for reabsorption [7, 22]. In examining the response of mongrel dogs to atmospheres containing 11–13% CO_2 , Polak *et al.* [23] found a fall in hydrogen ion concentration in urine, a small increase in titratable acid excretion on day 1 followed by a decrease, and an increase in bicarbonate excretion. The generation of bicarbonate in compensation for respiratory acidemia was achieved in these dogs by large increases in ammonium excretion, which exceeded the decrease in titratable acid and increase in bicarbonate excretion. Infants with RDS did not respond to respiratory acidemia and to consequent higher concentration of filtered bicarbonate by change in hydrogen ion concentration and titratable acid excretion in urine (Figs. 4 and 5). Assuming similar glomerular filtration rates, a greater filtered load of bicarbonate would have been reabsorbed and therefore

more hydrogen ions secreted by infants with RDS in comparison with that secreted by premature control infants. Infants with RDS, however, did not increase urine/plasma hydrogen ion concentration gradient beyond that produced by nonacidemic premature infants and, therefore, at higher PCO_2 values formed urine containing higher bicarbonate concentration. This resulted in greater bicarbonate excretion and was similar to the response seen in dogs exposed to CO_2 [23].

Infants with RDS, because they were prematurely born, did not show the physiologic increase in ammonium excretion that was found in dogs exposed to CO_2 [23] and therefore compensated neither for the increased bicarbonate excretion nor for the accumulation of hydrogen ion due to respiratory acidemia. The deficiency of ammonium excretion, therefore, resulted in the failure of bicarbonate generation needed to restore the body buffer ratios and in some acidemic infants resulted in net bicarbonate excretion that worsened the existing acidemia.

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