

Changes in Blood Gas Tensions Following Administration of Amine Buffer THAM to Infants with Respiratory Distress Syndrome

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A number of workers have shown that the prognosis in respiratory distress syndrome (RDS) is more closely related to the arterial oxygen tension than to acid-base disturbance, and depends to a large extent on the degree of shunting of venous blood past the gas-exchanging portions of lung, i.e. on the extent to which the arterial PO_2 responds to an increase in the concentration of oxygen breathed (Boston, Geller, and Smith, 1966; Gupta, 1966; Moss, Emmanouilides, Retorri, Higashino, and Adams, 1965). These findings are to some extent in conflict with claims that the prognosis is improved by correction of the secondary acid-base disturbance by infusion of glucose/bicarbonate solutions (Usher, 1959; Hutchison, Kerr, Douglas, Inall, and Crosbie, 1964). It occurred to us that these two points of view might be reconciled if it could be shown that correction of pH leads to improvement in oxygenation and diminution of shunting, a consequence that might be predicted in the newborn from the dependence of pulmonary perfusion on pH and blood gas tensions (Cassin, Dawes, Mott, Ross, and Strang, 1964) as well as on adequate cardiac function. THAM rather than bicarbonate was used because of its greater alkalinity and its ability to lower the P_aCO_2 (Nahas, 1959; Holmdahl, Nahas, Hassam, and Verosky, 1961) as well as to raise the pH . It was decided to measure PO_2 levels in arterial blood before and after administration of THAM and to see whether any improvement in P_aO_2 so achieved would be sustained. During the course of the study the work of Chu, Clements, Cotton, Klaus, Sweet, Thomas, and Tooley (1965) in Singapore became known to us, and reinforced our belief that pulmonary hypoperfusion might be a

major or reversible factor in the pathogenesis of RDS. The results reported below do, in our opinion, bear out this view.

Materials and Methods

The subjects of this investigation were newborn infants admitted to the neonatal ward of the Hammersmith Hospital. Most of the infants were born in the hospital but a few were admitted from the district or from other hospitals. The infants born at Hammersmith Hospital were assessed at one minute using a modification of the Apgar method (Tizard, 1964).

All infants were nursed in incubators. The incubator temperature varied between 32° and 35° C. but was kept constant for a given baby at a level as close as possible to the neutral temperature zone appropriate to its birth-weight (Scopes and Ahmed, 1966). At the time the study was made it was the rule to maintain the humidity at nearly 100%. The infants were kept under constant observation by trained nurses during the period of investigation. The observations consisted of 1/4-hourly respirations, 1/2-hourly apex beat, hourly rectal temperature, and general comments on the condition of the baby, i.e. skin colour, muscle tone, response to stimuli, irritability, and character of respiration. The first feed (usually at 6 hours) consisted of water. This was followed by full-strength expressed breast milk 20 ml./kg. divided into 8 feeds, with a daily increment of 20 ml./kg., so that at 8 days the infants were receiving 160 ml./kg. per day. This regimen was well tolerated.

A *clinical* diagnosis of RDS was made if two of the following three criteria were fulfilled on assessment at the age of 4 hours: (1) a respiratory rate of 60 or more on two successive observations, or a rise in respiratory rate of more than 20 breaths per minute from 1 to 4 hours of age; (2) intercostal or subcostal recession; and (3) grunting on expiration.

An x-ray film of the chest was obtained as early as possible and frequent clinical assessment was carried out to confirm the diagnosis and to distinguish RDS from other causes of dyspnoea, such as intrapartum pneumonia, requiring specific therapy. All babies who died had a necropsy.

Received January 3, 1967.

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† Supported by the Frank J. Duval Travelling Fellowship (Melbourne).

Arterial blood samples were collected from the iliac artery or the abdominal aorta by means of a polyvinyl catheter, size French 5 (Pharmaseal K32 premature infant feeding tube) inserted into an umbilical artery. The catheter was securely stitched to the umbilical stump and the open end was closed with a rubber bung. The cord stump and the surrounding skin were sprayed with 'polybactrin' solution and covered with a sterile dressing.

Umbilical arterial blood samples of 0.4-0.6 ml. were taken under anaerobic conditions with a 2 or 5 ml. paraffin-lubricated glass syringe, the dead space of which had been filled with heparin (1000 units/ml.). The syringe was then sealed with a metal cap. Most measurements of arterial oxygen tensions (P_{aO_2}) and pH were made immediately, the laboratory being adjacent to the neonatal ward. They were not routinely made in duplicate, as this would have involved taking unduly large samples. P_aCO_2 and standard bicarbonate were determined within 1 hour. It was aimed to take blood samples at 3-hourly intervals for the first 12 hours and 6-hourly intervals thereafter until the catheter was removed, but in practice it was found necessary to sample more frequently in severely ill babies and the above régime was not strictly adhered to for a number of practical reasons. After taking the blood sample the catheter was filled with heparinized saline solution (10 units/ml.) to prevent clotting.

Before collection of a blood sample the baby's rectal temperature was taken with a clinical thermometer (inserted 3-4 cm.) and the oxygen concentration in the incubator was measured with a Beckman D2 oxygen analyser. P_aO_2 measurements were carried out with a Beckman O_2 macro-electrode which was calibrated by using gas mixtures containing known concentrations of oxygen. Cord blood was equilibrated with the same gas mixtures in a tonometer and the PO_2 was measured after equilibration. The average difference in PO_2 between gas and blood equilibrated with the same gas was determined and a correction factor was applied (this was less than 3%). The gas mixtures were analysed by the Lloyd-Haldane technique. All the P_aO_2 values measured, except those above 200 mm. Hg were converted by using a nomogram (Bradley, Stupfel, and Severinghaus, 1956) to patient's rectal temperature. For P_aO_2 values above 200 mm. Hg the temperature corrections recommended by Hedley-Whyte and Laver (1964) have been used.

Arterial blood pH was measured at 37° C. with a direct reading pH meter (Electronic Instruments Ltd.) correcting for temperature by adding or subtracting 0.0147 for each degree centigrade by which the body temperature differed from 37° C. (Rosenthal, 1948). By measuring the change in corrected pH after the sample had been equilibrated (using a home-made apparatus, Stevens and Lanning, 1964) with 3.5% and 6.5% CO_2 in oxygen, P_aCO_2 was derived by means of interpolation (Peters, 1923; Astrup, 1956). No significant difference was observed between the calculated P_aCO_2 values and direct simultaneous measurements made with a CO_2 electrode.

THAM was administered as a 3.6% solution (0.3M), the pH of which had been adjusted to approximately 8.8 at 37° C. by admixture with its hydrochloride. Dosage was empirical, the initial dose based on initial pH and birthweight amounting to approximately 1 ml./kg. for each pH unit below 7.4. Further doses were given according to the changes in P_aO_2 , pH, and PCO_2 achieved. The properties of THAM and the progressive nature of the illness are such that it was decided not to base the dosage on the apparent base deficit; however, THAM was not given unless arterial PCO_2 was above 40 mm., pH lower than 7.25, and P_aO_2 indicated a considerable shunt.

Early in the study THAM was given either by the umbilical artery or vein, but in the latter stages entirely by the umbilical vein because of apparently more beneficial results. The rate of injection was approximately 1 ml./min., and every dose was followed by a 'chaser' of saline to clear the dead space. Blood samples were taken immediately before giving THAM and again shortly afterwards, the average interval being 12 minutes (range 4-30 minutes). Careful histological examination in those babies who subsequently died failed to show any macro- or microscopic evidence of damage to vessel walls (whether artery or vein) or to the tissues supplied by them (such as the liver in the case of the umbilical vein, or the leg muscles in the case of the artery).

Surface activity of lung extracts was measured with a Wilhelmy balance, in two cases supplemented by static pressure volume curves.

Blood pressure measurements were made using the Minogograph 42B electromanometer. The transducer was connected to the catheter in the umbilical artery after previously being standardized with a mercury manometer.

Determination of arterial PO_2 at alveolar PO_2 660 mm. Hg (i.e. breathing 100% oxygen with alveolar PCO_2 40 mm. Hg). The shunt equation can be used to calculate the relation between alveolar PO_2 (P_{AO_2}) and arterial PO_2 (P_aO_2) (Nelson and Reynolds, 1964). Assuming the arteriovenous oxygen difference to be 4 ml./100 ml., and oxygen capacity of Hb to be 20 ml. O_2 per 100 ml. blood, isopleths (shunt lines) were constructed (Fig. 1) by calculating the P_{AO_2} for any given P_aO_2 at various degrees of shunting. If the calculations are made by assuming any other arteriovenous oxygen difference or any other oxygen capacity of the Hb or both, the isopleths retain the same shape but shift in position. It follows that if the P_aO_2 is measured at a known P_{AO_2} (assuming $P_{ACO_2} = 40$ mm.) one can derive from the isopleths (irrespective of the oxygen capacity of the blood or the arteriovenous oxygen difference) the expected P_aO_2 , were the infant to be breathing 100% oxygen (i.e. at P_{AO_2} 660 mm. Hg where P_{ACO_2} is assumed to be 40 mm. Hg). This provides a useful means for comparison in babies breathing different concentrations of oxygen, but it should be emphasized that the values so obtained usually differ from the actual P_aO_2 when breathing 100% oxygen and are, therefore, of purely illustrative value. This could be because increased oxygen concentrations in the alveoli may in themselves decrease

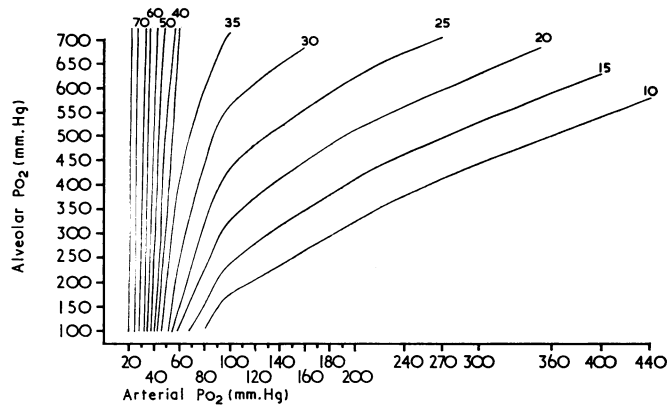


FIG. 1.—Isopleths (shunt lines) showing relation between alveolar and arterial oxygen tension (for derivation, see text). The numbers refer to percentage shunts.

shunting. The actual P_{aCO_2} was of course taken into account when placing a particular reading on the appropriate isopleth, and therefore the apparent diminution of shunting after THAM could not have been caused by the moderate fall in P_{aCO_2} produced by the drug. For comparative purposes P_{AO_2} values reported in this paper are derived values for P_{AO_2} 660 mm. Hg.

Results

We have grouped the infants into 'good prognosis cases' and 'bad prognosis cases' in line with the findings of Boston *et al.*, and Moss *et al.* (1965), who have noted that nearly all deaths due to RDS alone are in babies whose P_{aO_2} cannot be raised above 100 mm. Hg in 100% oxygen between 3 and 6 hours after

birth. From Table I it can be seen that the deaths in the group where this degree of oxygenation was achieved were not due directly to respiratory distress.

Infants with 'good prognosis' RDS. There were 33 infants in this group; 23 survived, 10 died.

(a) *Surviving infants of 'good prognosis' RDS group.* None of these was given any alkali or buffer (THAM or bicarbonate), despite the fact that in all but two infants the pH was less than 7.30 and in three infants was less than 7.20 when first measured. In all cases the pH rose spontaneously as the infant achieved a satisfactory arterial oxygen tension.

All these infants were given added oxygen, the concentration of which was adjusted according to

TABLE I
'Good Prognosis' Respiratory Distress

Infant No.	Gestational Age (wk.)	Birth-weight (g.)	Associated Conditions	Post-mortem Findings		Comment
				Immediate Cause of Death	State of Lungs	
24	25	820	—	Intraventricular haemorrhage	Atelectasis	Satisfactory blood gas tensions
25	29	1680	Hydrops (Rh.)	Respiratory failure; cardiac failure	Hyaline membranes	Twin pregnancy; twin I stillborn
26	30	1560	Apnoeic attacks	Massive pulmonary haemorrhage	Atelectasis	Satisfactory blood gas tensions until apnoeic attacks at 14 hr.
27	32	1240	Apnoeic attacks	Intraventricular haemorrhage	Atelectasis	Satisfactory blood gas tensions
28	32	1240	Apnoeic attacks	Intraventricular haemorrhage	Atelectasis	Satisfactory blood gas tensions
29	33	1840	Severe Rhesus incompatibility	Hypoglycaemia	Hyaline membranes	Satisfactory blood gas tensions
30	34	1460	—	Intraventricular haemorrhage	Hyaline membranes	Satisfactory blood gas tensions
31	36	2070	—	Intraventricular haemorrhage	Hyaline membranes	Satisfactory blood gas tensions
32	37	2380	Intrapartum asphyxia (cord round neck)	Cerebral birth injury	Atelectasis	Maintained with IPPR from age of 4 hours; repeated fits
33	37	2650	Maternal diabetes	Air embolism	Hyaline membranes	Satisfactory blood gas tensions; air embolism when umbilical venous catheter open

arterial oxygen tensions. The initial P_{aCO_2} values were (with one exception) above the mean for normal infants of birthweight less than 2500 g. (unpublished data).

(b) *Fatal case of 'good prognosis' RDS group.* The immediate cause of death and the lung findings at necropsy are shown in Table I. Nos. 25 and 32 were the only infants not to maintain satisfactory arterial oxygen tensions in the course of their illness. The remainder, who were recovering from respiratory distress, as judged by the ability to maintain satisfactory arterial oxygen tensions with decreasing ambient oxygen requirements, died as the result of secondary factors, as shown in the Table.

THAM was given to infants 24, 25, 26, and 32 in the terminal stages of their illness. There was a transient, but unsustained, rise in the P_{aO_2} and pH . Infant No. 29 was given THAM when his condition deteriorated following an exchange transfusion at the age of 1 hour; satisfactory P_{aO_2} was maintained from 8 to 22 hours when he suddenly collapsed and died. A blood sample taken at this time showed a glucose level of less than 10 mg./100 ml.

In 4 of those infants dying of intraventricular haemorrhage THAM was not given at any stage; in 1 it was given terminally (infant No. 24).

Infants with 'bad prognosis' RDS. There were 25 infants in this group; 10 survived, 15 died. Table II shows the relevant details. The age at which the initial data were obtained was not 3 hours in all cases, for as experience was gained in the use of THAM, infants were treated as early as possible in the illness; moreover, at the beginning of the study THAM was given only if the pH fell below 7.10, but later it was given when the P_{aO_2} was less than 100 mm. Hg in 100% oxygen, when the pH was less than 7.20, or when the P_{aCO_2} was greater than 45. The initial dose of THAM, the total of subsequent doses, and the gas tensions and pH before and after THAM are also shown.

In a high proportion of these infants there was a rapid and substantial rise in the P_{aO_2} following THAM. Fig. 2 shows this response. All values in this and subsequent figures show the calculated P_{aO_2} (derived from isopleths) for an alveolar oxygen tension of 660 mm. Hg. (It should be pointed out that as the arterial oxygen tensions rose following THAM the ambient oxygen was lowered.)

When THAM was given in the first 8 hours of the illness any rise in arterial oxygen tension that was obtained was usually sustained. This effect was much more obvious when THAM was given via the umbilical vein, and was associated with dramatic clinical improvement in infant No. 52 and with less

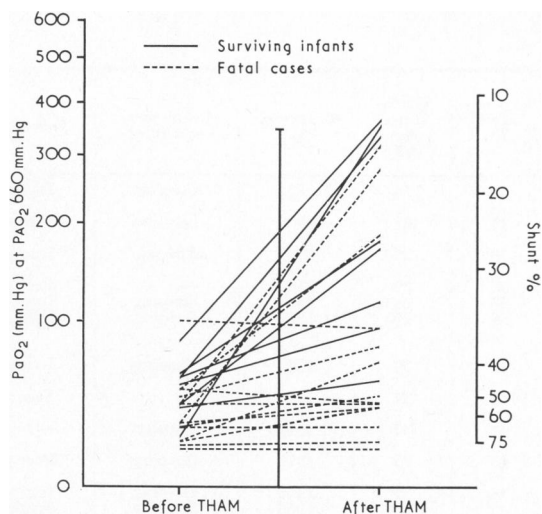


FIG. 2.—Severe RDS. Arterial oxygen tension before and after giving THAM in 22 cases. The percentage shunts are shown (see text).

dramatic but still substantial improvement in Nos. 37, 44, and 45.

There was no response to the initial dose of THAM in one infant (No. 45), but a substantial and sustained rise in the P_{aO_2} followed a second dose.

The pH in all these infants rose following THAM and again this rise was sustained in 8 out of the 10. In one of the other two (No. 44) bicarbonate (10 mEq) was given at the age of 6½ hours, with improvement in the pH . In the other infant who failed to respond to THAM or bicarbonate, it was apparent at 20 hours that there was a superimposed pneumonia.

The P_{aCO_2} , which was high in 9 of the 10 cases, fell following THAM in 8 of them (in one after the second dose). Cases 52 and 44 illustrate these points.

Case 52. This infant was born by the breech following a spontaneous labour. The baby was apnoeic at 1 minute of age, with a heart rate of 96/min., and was limp and blue. He was intubated and given intermittent positive pressure respiration (IPPR) and began breathing shortly afterwards. At 2 hours of age he was still limp, was very cyanosed in 30% oxygen, and had a respiratory rate of 60/min., with marked expiratory grunting and severe costal recession. The air entry by auscultation was negligible. Chest x-ray film was compatible with RDS. The relevant gas tensions and pH changes are shown in Fig. 3. There was a sudden and dramatic improvement in the infant's condition during the intravenous injection of THAM: he became pink, cried, moved all his limbs, and lost his costal recession. This

Infant No.	Gestational Age (wk.)	Birthweight (g.)	Respiration at 1 min.	Resuscitation	Age at Initial Data (hr.)	Age at Initial Dose THAM (hr.)	Initial Dose of THAM (ml.)	Total Dose of THAM (ml.)	P _i O ₂ Before THAM (mm. Hg)	P _i O ₂ After THAM* (mm. Hg)
34	26	830	Gasping	Intubated	2½	4	5 I.V.	13	43	43 → 320†
35	27	950	Gasping	Intubated	2	2½	3 I.A.	6	47	42
36	28	1080	Apnoeic	Intubated	1½	2	5 I.V.	5	50	190
37	29	1100	—	Face mask O ₂	5	6	5 I.V.	10	84	365
38	29	1180	Gasping	Intubated	10	11½	5 I.V.	5	39	50
39	29	1220	Apnoeic	Intubated	2	2½	3 I.V.	9	32	75 → 280†
40	30	1360	Gasping	Intubated	3	7	3 I.V.	6	30	40
41	32	1640	—	Face mask O ₂	8	8½	5 I.V.	33	20	10-40
42	32	1640	Regular	Nil	5½	39	3 I.A.	3	29	28
43	33	1670	Gasping	Face mask O ₂	3	3½	5 I.V.	25	27	46
44	33	1760	Gasping	Intubated	2½	3	5 I.V.	5	60	340
45	33	1860	Apnoeic	Intubated	3	3½	5 I.A.	10	42	78 → 172†
46	33	1700	Gasping	Intubated	4	4½	5 I.A.	15	18	20
47	34	1640	—	Face mask O ₂	4	4½	5 I.V.	30	20	68
48	35	1960	Gasping	Intubated	11	—	—	—	59	—
49	35	3045	Gasping	Face mask O ₂	4	14	5 I.V.	5	44	77
50	35	2030	Gasping	Intubated	5	54	3 I.A.	11	16	17
51	35	2400	Gasping	Face mask O ₂	4½	12	5 I.V.	27	40	42
52	35	2300	Apnoeic	Intubated	2	2½	10 I.V.	10	23	46 → 350†
53	36	2000	Gasping	Face mask O ₂	4½	5	5 I.V.	20	57	50 → 115†
54	37	3520	Apnoeic	Intubated	8	8½	5 I.A.	10	53	93
55	37	2240	Regular; apnoeic	Intubated	4½	6	5 I.A.	15	100	93
56	38	3000	Apnoeic	Intubated	6	½	5 I.V.	5	32	—
57	40	3760	Apnoeic	Intubated	6	7½	5 I.V.	5	60	80 → 180
58	44	3420	Gasping	Intubated	8	—	—	—	65	—

* Average time after THAM = 12 minutes. † Response to further doses of THAM. IVH = intraventricular haemorrhage.

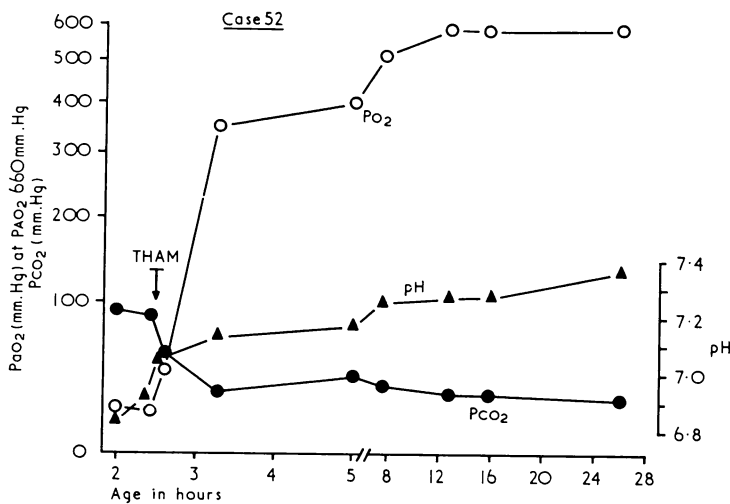


FIG. 3.—Case 52. Arterial oxygen tension, pH, and P_{CO}₂ before and after THAM (see text).

II
 Respiratory Distress

pH Before THAM	pH After THAM	P _A CO ₂ Before THAM (mm. Hg)	P _A CO ₂ After THAM (mm. Hg)	Outcome	Findings at Necropsy		Comment
					Immediate Cause of Death	State of Lungs	
7.03	7.12	—	—	Death 46 hr.	IVH	Normal; surfactant present	
6.90	7.04	95	64	Death 6 hr.	RDS	HMD	Repeated apnoeic attacks IPPR from 4 hr.
7.03	7.13	30	30	Death 41 hr.	IVH	Normal; surfactant present	
7.00	7.09	105	73	Survived			
7.17	7.21	54	64	Survived			
6.88	6.92	43	39	Death 18 hr.	IVH		Repeated apnoeic attacks Good response to 2nd dose THAM; repeated apnoeic attacks
7.04	7.29	42	32	Death 19 hr.	IVH	Small pneumothorax; HMD	Repeated apnoeic attacks
6.83	7.02	100	66	Death 74 hr.	RDS	HMD; no surfactant	IPPR from onset
7.21	7.25	29	35	Death 46 hr.	RDS	Pneumonia; HMD	
6.94	6.95	65	51	Death 16 hr.	RDS	HMD; no surfactant	
7.01	7.12	60	39	Survived			
6.99	7.00	160	127	Survived			
	7.13	127	72				
7.04	7.12	59	41	Death 10 hr.	RDS; aspir. maternal blood	HMD	Good response to 2nd dose of THAM
6.82	6.97	120	68	Death 9 hr.	RDS	HMD	Massive antepartum haemorrhage Hypothermia; IPPR from 4½ hr.
7.29	—	30	—	Survived			
6.93	7.04	65	38	Death 14 hr.	Subdural haemorrhage	HMD	Repeated apnoeic attacks
7.20	7.19	38	31	Death 66 hr.	IVH	Bronchopneumonia HMD	Placenta praevia APH
7.06	7.09	38	26	Death 23 hr.	RDS	Atelectasis; pulm. haem.	Repeated apnoeic attacks
6.89	7.06	87	58	Survived			
7.06	7.10	50	62‡	Survived			
		62	37				
7.14	7.32	69	38	Survived			
7.12	7.17	52	38	Death 41 hr.	Tension pneumothorax	HMD	
7.18	—	25	—	Death 69 hr.	Pneumonia	Pulm. haem.; HMD	Severe intrapartum asphyxia
7.26	7.26	52	45	Survived			Intrapartum asphyxia
7.33	—	24	—	Survived			Intrapartum asphyxia

RDS = respiratory distress syndrome. HMD = atelectasis and hyaline membrane. ‡ P_ACO₂ rise caused by brief apnoeic episode after infection.

clinical improvement corresponded with a sudden rise in P_aO₂ which was sustained, and the infant subsequently recovered.

Case 44. This infant was a vertex delivery following a spontaneous premature labour. At 1 minute he was gasping with a heart rate of 180/min. He subsequently deteriorated and required intubation but breathed spontaneously at 5 minutes. At 2 hours he had marked costal recession, grunting respiration, and a respiratory rate of 80/min. Air entry was poor. Chest x-ray film was compatible with RDS. Fig. 4 shows the blood gas and pH values before and after THAM. There was a marked improvement during the time THAM was being given. The costal recession became less; the grunting respirations eased; and the infant showed more activity. At this time the right radial artery was catheterized and thereafter simultaneous arterial samples were taken from the radial artery and the lower aorta (i.e. above and below the ductus). It can be seen that P_aO₂ values from each site were identical. A single dose of 5 mEq sodium

bicarbonate was given at the age of 6½ hours as the pH had not risen as expected. This caused a rise in pH but a fall in P_aO₂. The infant made an uneventful recovery.

Fatal cases of 'bad prognosis' group. The associated illness, the immediate cause of death and relevant post-mortem lung findings are shown in Table II. Fig. 2 shows the P_aO₂ values (derived from isopleths) at a P_AO₂ of 660 mm. Hg before and after THAM.

Three of these infants (Nos. 34, 36, and 39) had substantial and sustained increases in the P_aO₂ following THAM. They were recovering from RDS and had normal gas tensions, when they suddenly deteriorated and died at the age of 46, 41, and 18 hours, respectively. It will be noted that Nos. 34 and 36 had stable lungs at necropsy.

Infants Nos. 35, 38, 39, 40, 49, and 51 had repeated apnoeic attacks requiring intubation and

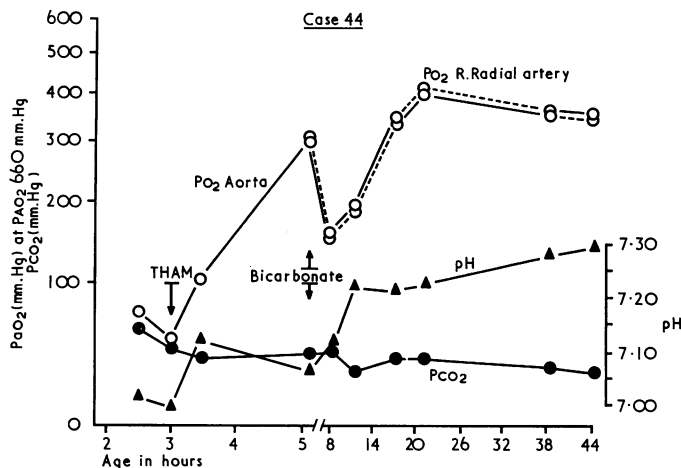


FIG. 4.—Case 44. Arterial oxygen tension, pH, and P_{co}₂ before and after THAM (see text).

IPPR at times during their illness. Only one (No. 38) of this group survived: in the remainder there was little response to THAM and, where a rise in the P_aO₂ was obtained, it was not sustained.

It can be seen that of these 15 infants only 7 died from RDS alone. Among these 7 infants, Cases 42 and 55 showed satisfactory P_aO₂ values initially but subsequently deteriorated, while infant No. 41 was treated late in the disease, requiring IPPR from the outset. The P_aO₂ did not rise with THAM in these cases.

The pH which was below 7.20 at the outset in all cases rose following THAM in all but one; this rise, however, was not sustained.

The P_aCO₂ was raised initially in all cases except one. Again there was a consistent fall following THAM, but subsequently the levels once again rose. Infant No. 41 had the right radial artery catheterized and simultaneous measurements of P_aO₂ were made from this site and from the lower aorta. The values obtained were identical in each instance, indicating there was no net right-to-left shunt through the ductus. Cases 36 and 43 illustrate these points.

Case 36. This infant was born following a spontaneous premature labour by vertex delivery. He was apnoeic at 1 minute of age, heart rate 40/min., cyanosed, and limp. He was intubated and given IPPR. The colour improved and spontaneous respiration started at 4 minutes, but he remained unresponsive for 15 minutes. He developed respiratory distress and at the age of 1 hour the P_aO₂ was 51 mm. Hg, and the pH 7.03 (Fig. 5). Ten minutes after THAM the P_aO₂ rose to 190 mm. Hg and the pH to 7.13; the P_aCO₂ remained at 30 mm. Hg. His clinical condition also improved in that grunting

became less and costal recession eased. The gas tension and pH remained satisfactory until the age of 37 hours when he suddenly became pale and limp. Shortly afterwards he had the first of three apnoeic attacks and despite IPPR he died at the age 41 hours.

Necropsy showed a massive intraventricular haemorrhage and well-expanded lungs. Pressure-volume curves were normal and surfactant was detected in the lungs.

Case 43. This infant was born following a spontaneous premature labour at 33 weeks by a vertex delivery. At 1 minute the infant was gasping, heart rate 110/min., and was blue. The colour improved with face-mask oxygen, but he then developed respiratory distress. Fig. 6 shows the blood gas tension and pH. At 3 hours of age the P_aO₂ was 27 mm. Hg, pH 6.94, and P_aCO₂ 65 mm. Hg. Following THAM the P_aO₂ rose slightly, the P_aCO₂ fell, and the pH remained the same. Subsequently doses of THAM produced little response and terminally the P_aCO₂ rose and pH fell. (P_aO₂ measurements were not obtained in the latter stages due to a fault in the apparatus.)

Necropsy showed the lungs to be collapsed; histology revealed hyaline membrane; and no surfactant was detected after 24 hours cycling. Owing to a technical breakdown this infant was not treated adequately in the early stages of the disease.

Effect of THAM on arterial blood pressure. The arterial blood pressure was recorded directly by a pressure transducer in 5 infants while THAM was being administered via the umbilical vein. There was no change in the blood pressure during this time and for periods of up to 20 minutes afterwards.

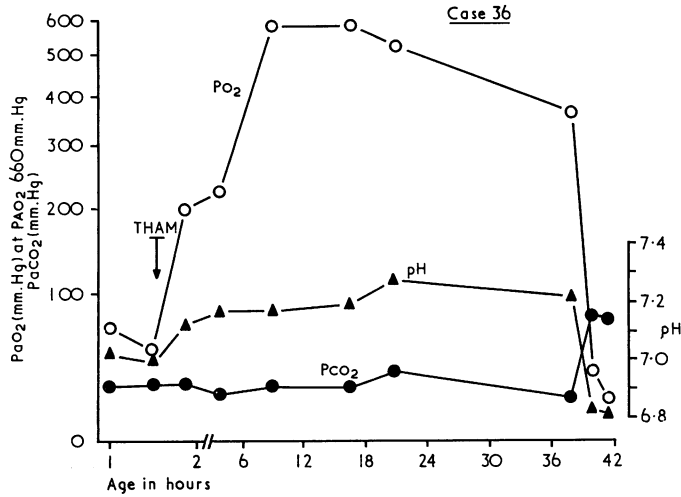


FIG. 5.—Case 36. Arterial oxygen tension, pH, and Pco₂ before and after giving THAM (see text).

Side effects. THAM has been shown to cause hypoglycaemia and hyperkalaemia (Bennett and Tarail, 1961) in animal experiments but no such effects were seen in this series of human infants. Respiratory depression (Nahas, Fink, Ploski, and Teneick, 1963) was observed on occasions, but only in the terminal stages of the illness and never with the initial dose. On one occasion a fall rather than a rise in P_aO₂ was seen after an injection of THAM which was given into the umbilical artery. This was not associated with a fall in P_aCO₂ or rise in pH. It will be noted that this patient had a tension pneumothorax. We do not recommend the use of THAM in cases of predominantly metabolic acidemia when the P_aCO₂ level is within the normal range for newborn infants, since in these circumstances it may cause respiratory depression.

Management. The use of THAM in respiratory distress necessitates the presence of indwelling umbilical arterial and venous catheters over the course of the illness both for injection (which causes tissue necrosis when given through smaller vessels) and for monitoring blood gas tensions and pH. A measure of the dramatic effect of treatment in some cases is the need to watch for excessively high oxygen tensions after THAM in treated infants nursed in high ambient oxygen concentrations. The presence of indwelling catheters makes it imperative to avoid umbilical sepsis, and this can be achieved by spraying the cord stump at birth and daily thereafter with 'polybactrin' and by painting it with iodine before manipulation. The use of heparin to keep the catheters open involves partial heparinization of the infant, and this may need to be

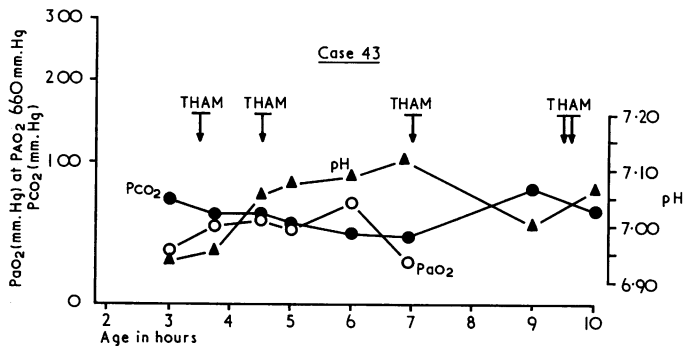


FIG. 6.—Case 43. Arterial oxygen tension, pH, and Pco₂ before and after giving THAM (see text).

countered with appropriate quantities of protamine when the infant is tiny and frequent sampling is needed.

In none of these cases was there any clinical or post-mortem evidence of arterial thrombosis. In 3 (very small) babies one leg became pale and pulseless, but the circulation was restored immediately on removal of the catheter.

Finally, careful precautions have to be taken against bleeding from the cord stump when the catheters are removed, and, indeed, from the catheters themselves. In cases in which very frequent sampling is in the infant's interest, we do not hesitate to replace the blood that is removed by a small transfusion, if this exceeds 10% of the calculated blood volume.

Discussion

The results presented re-emphasize the need for a clear distinction between *good prognosis* and *bad prognosis* RDS in the evaluation of treatment, the former having a good prognosis as regards respiratory sufficiency even without specific treatment for acidaemia, the latter doing badly if such therapy is withheld. Initial P_{aO_2} levels in 100% ambient oxygen concentrations have been shown by a number of workers (Boston *et al.*, 1966; Moss *et al.*, 1965) to be a more reliable guide to prognosis than changes in pH , standard bicarbonate, or P_{aCO_2} levels; and on this basis it is possible to single out a group of badly affected infants whose mortality conventionally treated is of the order of 80%. Improvement in the outlook of this category is in our opinion likely to be a better guide to the efficiency of treatment than comparison of death rates in consecutive series, or even in alternate but unselected cases, in a disease where the prognosis is affected by so many variables. For instance, in our experience two-thirds of infants who die of massive intraventricular haemorrhage (IVH) have no clinical or pathological evidence of RDS, and in one-third of all cases dying of RDS there is an associated IVH, though in some of these the haemorrhage occurred when the infant no longer showed signs of respiratory failure. The undoubted association of RDS and IVH may be coincidental on the basis of low gestational age.

Treatment of the secondary metabolic effects of respiratory failure in RDS with mixtures of water, sodium, glucose, and bicarbonate, has been in vogue since its introduction by Usher (1959). From some centres (Hutchison *et al.*, 1964) it is claimed that the prognosis can be greatly improved thereby, though Usher himself has pointed out (1963) that glucose/

bicarbonate therapy does not seem to improve the prognosis in babies of under 1500 g. birthweight, a category that includes many of the severe cases; and the results of a reasonably well-controlled trial in a large series of cases in Singapore have demonstrated no significant advantages to the treated infants (Teck, 1965).

In our view, death in RDS is primarily due to hypoxia and therefore, in a disease that lasts for upwards of 48 hours, any attempt to neutralize the acidaemia resulting from inadequate pulmonary CO_2 elimination by infusion of buffer or alkali is unlikely to succeed in just those cases where respiratory failure is of a degree to threaten life. The demonstration that in certain circumstances the administration of alkali actually appears to improve oxygenation, as well as correcting pH , etc., and that this improvement may be sustained, is therefore of considerable importance both in theory and practice. That it is seen alike in ultimately fatal cases, in babies on IPPR, and in bad risk infants who recover, makes it unlikely that the effect is due to spontaneous improvement, to changes in respiration, or to random fluctuation in P_{aO_2} . As suggested by Gupta (1965) and independently by Chu *et al.* (1965), it also implies that part of the respiratory failure in RDS is the result of the inadequate pulmonary perfusion; indeed, the very rapid response to treatment suggests that this may be the primary cause of the disease and that other changes, such as loss of surfactant, demonstrable at necropsy, may be in some measure secondary. Inadequate pulmonary perfusion is presumably the result of either a low cardiac output or of the shunting of blood past functional lung tissue, i.e. through the foramen ovale, through the ductus arteriosus, or through non-ventilated lung. This involves an alteration in normal pressure relationship (Rudolph, Drorbaugh, Auld, Rudolph, Nadas, Smith, and Hubbell, 1961; Moss, Emmanouilides, and Duffie, 1963) such that (1) in the case of the foramen ovale, right atrial pressure must exceed left atrial pressure, (2) in the case of the ductus, pulmonary arterial must exceed systemic arterial pressure, and (3) where there is perfusion of unventilated lung, the vascular resistance in the unventilated segments must not increase. We have not measured cardiac output, nor pressure in the atria, ventricles, or great vessels, but in 5 cases in which the arterial pressure was measured before and after THAM, no change was noted. In 4 further cases in which P_{aO_2} levels were measured simultaneously in the aorta (via the umbilical artery) and in the right radial artery, there was no difference between P_{aO_2} levels above and below the opening of the ductus arteriosus into the aorta. It is, therefore,

unlikely that changes in cardiac output or in ductal shunting were responsible for the P_{aO_2} changes observed following THAM in these cases. Since the closure of the foramen ovale is dependent on a change in atrial pressure relationships caused by the increase in pulmonary perfusion that takes place at birth, and since this increase in pulmonary perfusion probably results from a fall in pulmonary vascular resistance, it seems likely that in RDS there may be a major shunting through the foramen ovale and that this is in part due to a rise in pulmonary vascular resistance producing a fall in pulmonary blood flow. Pulmonary vascular resistance is known to be dependent on pulmonary gas tensions and pulmonary distension (Cassin *et al.*, 1964; Rokseth, 1966), both of which are likely to be altered in an adverse way in the course of RDS, and it, therefore, seems possible that the timely administration of alkali may, by lowering pulmonary vascular resistance, promote adequate pulmonary perfusion, reduce shunting, improve blood and alveolar gas tensions, and prevent irreversible pulmonary damage. It appears likely that the changes in P_{aO_2} described are due to a direct effect of THAM in the lung or on the heart rather than to changes in total body acid-base balance, the doses used probably being too small to achieve the results observed except through a concomitant improvement in respiratory function. It may be that in some cases lack of response to alkali was due to a failure of the drug to reach the lung or heart, either because of extreme shunting, lodgement of the venous catheter in the liver, or injection into the umbilical artery instead of vein, whereas in others it was because the drug was given too late when irreversible pulmonary damage had occurred. This effect could be on the pulmonary arteries (pulmonary artery pressure is known to be high except in the terminal stages of the illness (Rudolph *et al.*, 1961; Moss *et al.*, 1965)), but since the apparent pulmonary hypoperfusion is accompanied by congestion of the lung at necropsy, an effect on the pulmonary veins seems more likely. A. J. Hauck (1963, personal communication) has in fact observed a raised pulmonary venous pressure in RDS in the presence of a normal left atrial pressure. That hypoperfusion is the initiating disturbance would, for instance, explain the normal quantities of surfactant found at necropsy in the two cases described in this report, which recovered from severe RDS and subsequently died with IVH after a period when there appeared to be no clinical signs of respiratory embarrassment. The evidence herein adduced, and the argument based thereon, suggests that RDS in its early stages may be aborted rather than ameliorated by the

administration of THAM, and that this effect is more likely to be a primary one on the walls of the pulmonary vessels than secondary to changes in total body acid base balance. Direct measurements of the quantities involved (oxygen consumption, pulmonary arterial and atrial pressures), and the calculation of pulmonary blood flow before and after treatment, would go far to disprove or substantiate this hypothesis.

Summary

Babies with respiratory distress syndrome can be divided into two groups with a *good* and *bad prognosis* on the basis of an initial arterial oxygen tension measurement taken when breathing 100% oxygen, providing a measure of the extent of V-A shunting. Following intravenous THAM given early in the course of the illness, there is a considerable and often sustained rise in arterial oxygen tension in the *bad prognosis* group which can best be accounted for by a diminution in such shunting. The alteration in calculated shunt induced by THAM injection suggests that reversible hypoperfusion is a factor in the aetiology of the pulmonary changes seen in the respiratory distress syndrome.

The authors wish to acknowledge the help of Mrs. Lee, departmental secretary, Mr. J. F. Stevens, senior technician, colleagues at the Royal Postgraduate Medical School, and Professor J. P. M. Tizard in the preparation of this paper. The work reported was stimulated by observations on the effect of THAM in respiratory distress made in the department of Paediatrics, University of Groningen (Professor J. Jonxis, Dr. H. Visser, and Dr. J. Troelstra). Dr. Colin Normand of University College Hospital kindly carried out the determinations of surface tension-reducing activity and Dr. J. S. Wigglesworth the pressure volume curves. The laboratory work was carried out in the Sir William Coxen Laboratories of the Nuffield Neonatal Research Unit using instruments paid for by the Variety Club of Great Britain.

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- to hypoventilation will be very small, and greater accuracy can therefore be expected in calculating the right-to-left shunt if the subject breathes a high concentration of oxygen rather than air (Perkins, Adams, Flores, Harper, and Landahl, 1958).
- Large right-to-left shunts (over 70%) cause arterial PCO₂ appreciably to exceed alveolar values (Strang and MacLeish, 1961), and this will give a falsely low value for alveolar Po₂ by the alveolar air equation. As the error is small no correction for it has been made.
- For the calculation of alveolar Po₂ the respiratory quotient has been assumed to be 0.8. In the newborn infant RQ varies from 0.7 to 1.0 (Cross, Tizard, and Trythall, 1957) and this could result in a maximum error of 40 mm. Hg in the calculated P_AO₂ in a severely ill infant. Such infants, however, will be breathing very high concentrations of oxygen and as such the error in the calculated shunt will be small.
- As explained in the text, mixed venous samples are difficult to obtain in newborn babies. Strang and MacLeish (1961) observed that the arteriovenous oxygen differences in all their cases were between 2 and 6 ml./100 ml., and they showed that the calculated shunt value at 4 did not differ from those at 2 and 6 ml./100 ml. by more than 12%; hence, with an assumption of an arteriovenous difference of 4 ml./100 ml. an error of ± 12% may occur.
- Oxygen capacity has been assumed to be 20 ml./100 ml., which is equivalent to 15.8 g. Hb/100 ml. This is, of course, not correct for all infants since their Hb concentrations may differ. Moreover, because of the changes in haematocrit that occur in the first few days of life (Gairdner, Marks, Roscoe, and Brettell, 1958) the value in a particular infant will also vary. To determine the magnitude of the error, shunts were calculated by assuming oxygen capacities of 18.2 and 23.4 ml./100 ml. (i.e. Hb concentrations of 14 and 18 g./100 ml.). The maximum difference was ± 10% from those calculated by assuming a value of 20 ml./100 ml.
- A further uncertainty is introduced by the fact that the proportion of foetal Hb may vary in the infants studied; whereas the standard oxygen dissociation curve for foetal Hb at 37° C. at pH 7.40 was used to determine the oxygen content in all cases.
- Another possible source of error is that the results are expressed as percentage of cardiac output, which of course may vary from time to time in a particular infant. No correction has been applied to the oxygen dissociation curve for differences in temperature and pH, as recommended by Bradley, Stupfel, and Severinghaus (1956), since the error introduced by this omission is insignificant in relation to other possible errors as a result of the assumptions made.
- Because of all these possible sources of error the changes in shunting demonstrated must be considered as only semi-quantitative, but this does not affect the argument of the paper, which remains valid.

Appendix

Sources of Errors Due to Assumptions Made in Calculating Shunt

End pulmonary capillary oxygen content (CCO₂) has been derived from alveolar oxygen tension (P_AO₂) using the alveolar air equation. While entirely valid for subjects who are breathing normally, the assumption does not hold when there is any degree of respiratory depression, for this causes a fall in P_AO₂, as a result of which the calculated value for CCO₂ will be higher than the actual one; so giving a falsely high shunt value. However, if the alveolar Po₂ is high, the fall in CCO₂ due

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