Arterial Oxygen Studies in Premature Newborns with and without Mild Respiratory Disorders

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Arterial oxygen studies in full-term infants at various ages have been made by numerous authors (Stahlman, 1957; Weisbrot, James, Prince, Holaday, and Apgar, 1958; Graham, Koeff, Tsao, Sloan, and Wilson, 1959; Reardon, Baumann, and Hadded, 1960; Oliver, Demis, and Bates, 1961; Nelson, Prod'hom, Cherry, Lipsitz, and Smith, 1963). Few similar studies have been performed on premature infants (Graham, Reardon, Wilson, Tsao, and Baumann, 1950; Prod'hom, Levison, Cherry, Drorbaugh, Hubbell, and Smith, 1964). In 1965 Moss, Emmanouilides, Rettori, Higashimo, and Adams published data from premature infants in the first 72 hours of life, showing that 'normal' pretermatures had lower arterial oxygen tensions than adults, and that this difference was accentuated in pretermatures with 'mild respiratory distress': the criteria for classifying the babies as 'normal' were not explained in detail and the type and the severity of respiratory distress were not defined clearly. Furthermore, no studies were performed in infants of more than 72 hours.

The present paper provides data on arterial blood gases in normal premature infants from 3 hours to 40 days of age. The criteria for normality were based on clinical grounds and on chest *x*-ray findings. In addition, data from premature infants with tachypnoea and with transient mild respiratory distress, but without *x*-ray changes suggestive of pneumonia or hyaline membrane disease (Iannaccone, Bucci, and Savignoni, 1965), are also presented.

Material and Methods

The study includes 59 premature infants admitted between December 1964 and February 1966, and ranging in age from 3 hours to 40 days; the birthweight ranged between 1130 and 2480 g., and the gestational age from 28 to 40 weeks. All were admitted to the premature unit within 24 hours of birth. A physical examina-

tion and two antero-posterior chest *x*-ray films were taken on admission on each baby; Silverman's retraction score (Silverman and Andersen, 1956), the respiratory rate, skin colour, heart rate, and other physical findings were recorded every 3 hours during the first two days of life (or longer if abnormal) and less frequently thereafter. The chest *x*-ray films were evaluated separately by the radiologist and were graded according to previously published criteria (Iannaccone *et al.*, 1965). On the basis of the clinical and radiological findings the infants were divided into 3 groups (Table I).

The first group included 40 infants with birthweights between 1260 and 2480 g., who were both clinically and radiologically normal (i.e. Silverman's score ≤ 2 , respiratory rate ≤ 65 /min., skin colour normal, cardiac murmurs absent, and, on *x*-ray films, absence of vascular engorgement, atelectasis, emphysema, air bronchograms, or fine granularity).

The second group comprised 14 infants with birthweights between 1130 and 2260 g., who had respiratory rates above 65/min. for at least 24 hours and no other signs of respiratory or cardiac disorders (Silverman's score always ≤ 2). The chest *x*-ray films were normal in all except 2 babies in whom mild patchy atelectasis was present.

The third group comprised 5 infants with birthweights between 1790 and 2310 g., who had Silverman's scores of 3 in the first 24 hours of life and respiratory rates above 60/min. during the first 48 hours. The chest *x*-ray films showed mild patchy atelectasis in 2 babies and were normal in 3.

None of the infants studied had the radiological features of hyaline membrane disease (decreased translucency, reticulo-granular pattern, and air bronchogram) or pneumonia (coarse nodularity, severe patchy atelectasis, and emphysema), and all recovered and survived. Respiratory distress in infants of the second and third group was always mild, so that, on clinical grounds, it was judged safe to study them while breathing room air.

Thirteen normal adults were also studied and served as controls.

Using the techniques described in previous papers (Scalamandrè, Bucci, Orzalesi, Mendicini and Savignoni, 1966; Bucci, Scalamandrè, Savignoni, Orzalesi, and

TABLE I

Number of Subjects, Average Birthweight, Gestational Age, Average Silverman's Score, and Respiratory Rate at Different Ages, in the 3 Groups of Prematures Studied

Group	No.	Birthweight (kg.)	Gesta-tional Age (wk.)	1-6 Hours		7-24 Hours		25-48 Hours		49-72 Hours		73-96 Hours	
				Score	Respi-ratory Rate	Score	Respi-ratory Rate	Score	Respi-ratory Rate	Score	Respi-ratory Rate	Score	Respi-ratory Rate
Normal	40	1.76 (1.26-2.48)	34.5 (28-40)	0.8	56	0.6	52	0.5	51	0.2	48	0.2	46
Tachypnoea	14	1.72 (1.13-2.26)	33.6 (31-38)	1.2	71	1.4	69	1.1	66	0.6	58	0.4	54
Mild RDS	5	2.02 (1.79-2.31)	— (32-37)	—	—	3.0	67	2.4	64	1.0	57	0.8	55

Mendicini, 1966), 104 samples of arterial blood were taken from the radial artery, 22 from the temporal artery, and 8 from the umbilical artery. The infants breathed room air and remained generally quiet during the procedure.

All blood analyses were performed within 10 minutes of sampling. Arterial pH and base excess (BE) were measured at 37.5° C., using the Astrup apparatus* (Astrup, Jørgensen, Siggaard Andersen, and Engel, 1960) and carbon-dioxide tension (P_{aCO_2}) was derived from the Siggaard Andersen nomogram, after correcting for the amount of unsaturated haemoglobin (Siggaard Andersen, 1962). Arterial oxygen tension (P_{aO_2}) was measured at 37.5° C. with a Clark electrode*, and oxygen saturation (S_{aO_2}) was calculated from the P_{aO_2} and pH, using the foetal blood O_2 dissociation curves at various pHs, obtained by combining the data of Edwards and Ross (1959) and Nelson, Prod'hom, Cherry, and Smith (1964); S_{aO_2} in adults was derived from standard published curves (Rahn and Fenn, 1955). Haemoglobin concentration was measured with the cyanmethaemoglobin method.

Almost all determinations were carried out in duplicate, and all values of pH, P_{aCO_2} , and P_{aO_2} were corrected for the temperature of the babies using published correction factors (Bradley, Stupfel, and Severinghaus, 1956; Adamsons, Daniel, Gandy, and James, 1964).

Venous admixture (VA) in air was also calculated using the standard shunt equation (Comroe, Forster, Dubois, Briscoe, and Carlsen, 1962):

$$VA\% = \frac{O_2 \text{ content of pulm. capillary blood} - O_2 \text{ content of arterial blood}}{O_2 \text{ content of pulm. capillary blood} - O_2 \text{ content of mixed venous blood}}$$

Oxygen content of arterial and pulmonary capillary blood was calculated by multiplying the amount of saturated haemoglobin by 1.34. The amount of oxygen in mixed venous blood was assumed to be 4 vol. % lower than in arterial blood (Strang and Macleish, 1961). The S_{aO_2} of pulmonary capillary blood was derived from the foetal blood O_2 -dissociation curve,

assuming the pH and PO_2 of capillary blood to be equal to the arterial pH and alveolar PO_2 (P_{AO_2}) respectively*. The P_{AO_2} was calculated from the alveolar air equation (Comroe *et al.*, 1962):

$$P_{AO_2} = P_{IO_2} - P_{aCO_2} \times \left(F_{IO_2} + \frac{1 - F_{IO_2}}{R} \right).$$

P_{IO_2} and F_{IO_2} are the oxygen tension and concentration in the inspired air, and R is the respiratory quotient. The values of R published by Adams, Fujiwara, Spears, and Hodgman (1964) were used for premature infants and an R value of 0.85 was assumed for adults.

Results

The main clinical features of the infants studied are summarized in Table I. There were no appreciable differences in birthweight and gestational age between the first and the second group, while in the third group the average birthweight was slightly higher. The average respiratory rate in the second and third group, and the Silverman's score in the third group, were higher than normal in the first two days of life and decreased gradually thereafter.

Samples from the right and left radial and temporal arteries, and the umbilical artery, have been analysed together because Moss *et al.* (1965) have found no appreciable right-to-left ductal shunts in similar infants.

Normal infants. The results obtained in the 40 normal premature infants are shown in Table II and in Fig. 1, 2, and 3; the data from normal adults are included for comparison.

The pH, P_{aO_2} , and S_{aO_2} at 3-5 hours of age were lower than later, but this age-group included only 4 subjects and allows no conclusions.

After 5 hours of life there were no appreciable

* Astrup micro-equipment type AME 1 and oxygen monitor type PHA 928 and PO_2 electrode type E5044; Radiometer, Copenhagen, Denmark.

* When breathing air, the assumption that $P_{AO_2} = PO_2$ of pulmonary capillary blood may introduce an error in the calculation of VA; the latter may be overestimated and include the effect of a diffusion defect and/or of a ventilation/perfusion imbalance.

TABLE II
Arterial Blood Values in 'Normal' Premature Infants Studied at Different Ages (Means $\pm$ SD)

	3-5 Hr.	6-12 Hr.	13-24 Hr.	25-48 Hr.	3-4 Dy.	5-10 Dy.	11-40 Dy.	Adults
Number	4	9	12	22	13	12	8	13
Age (mean)	4 hr.	8 hr.	20 hr.	35 hr.	73 hr.	7.5 dy.	27.5 dy.	30 yr.
P _a O ₂ (mm. Hg) ..	59.5 $\pm$ 7.7	69.7 $\pm$ 11.8	67.0 $\pm$ 15.2	72.5 $\pm$ 20.9	77.8* $\pm$ 16.4	80.3* $\pm$ 12.0	77.8 $\pm$ 9.6	91.8 $\pm$ 12.4
S _a O ₂ (%)	91.3 $\pm$ 1.7	95.2 $\pm$ 1.2	95.3* $\pm$ 2.1	95.0 $\pm$ 2.0	95.7 $\pm$ 1.5	95.1 $\pm$ 1.3	96.0 $\pm$ 0.6	97.1 $\pm$ 1.1
VA (%)	19.5 $\pm$ 4.5	14.5 $\pm$ 4.8	16.3 $\pm$ 6.3	13.8 $\pm$ 8.7	9.8* $\pm$ 5.5	8.2 $\pm$ 4.5	8.4 $\pm$ 2.9	5.5 $\pm$ 5.1
pH	7.329* $\pm$ 0.038	7.425 $\pm$ 0.072	7.464 $\pm$ 0.064	7.434 $\pm$ 0.054	7.425 $\pm$ 0.044	7.378 $\pm$ 0.043	7.425 $\pm$ 0.033	7.443 $\pm$ 0.044
P _a CO ₂ (mm. Hg) ..	47.3* $\pm$ 8.5	28.2 $\pm$ 6.9	27.2 $\pm$ 8.4	31.3* $\pm$ 6.7	31.7* $\pm$ 6.7	36.4 $\pm$ 4.2	32.9 $\pm$ 4.0	37.9 $\pm$ 6.4
BE (mEq/l.)	-3.7 $\pm$ 1.5	-4.7 $\pm$ 3.1	-3.0 $\pm$ 3.3	-2.3 $\pm$ 3.0	-2.9 $\pm$ 2.3	-3.5 $\pm$ 2.3	-2.1 $\pm$ 2.2	+1.4 $\pm$ 1.5
Hb (g./100 ml.) ..	16.2 $\pm$ 1.7	16.1 $\pm$ 2.8	16.0 $\pm$ 2.3	15.7 $\pm$ 2.4	14.3 $\pm$ 4.8	13.3 $\pm$ 1.8	10.9 $\pm$ 3.0	13.0 $\pm$ 1.1

Values statistically different from adult controls: * = $p < 0.05$, † = $p < 0.01$, ‡ = $p < 0.001$.

changes in S_aO₂, except for a small increase at 11-40 days. The values at all ages were significantly lower than in adult controls (Table II).

The P_aO₂ in infants up to 40 days of age was also significantly lower than in adults (Table II); there was, however, a significant rise in P_aO₂ from 6-24 hours to 3-10 days of life ($p < 0.05$).

Venous admixture in air (VA) during the first and second day of life was significantly greater than at 3-10 days ($p < 0.01$ and $p < 0.05$).

FIG. 1.—Mean ($\pm$ SD) arterial oxygen tension in 'normal' premature infants at different ages.

The base excess was always lower than in adults (Table II), but the pH was similar, because the infants were hyperventilating relative to adults, in so far as the P_aCO₂ at 6-24 and at 25-48 hours of life was significantly lower than in adults (Table II).

Infants with tachypnoea (Table III and Fig. 4 and 5). At 6-24 hours of life these babies had a significantly lower P_aO₂, S_aO₂, and pH, and a significantly higher P_aCO₂ than normal prematures of the same age (Table III). VA was higher than normal, but not significantly so.

As in the normal group, there was an increase in P_aO₂ and S_aO₂ and a decrease in VA from 6-24 hours to 3-10 days of age ($p < 0.01$).

Infants with mild respiratory distress (Table III and Fig. 4 and 5). The five prematures included in this group had a significantly lower than normal P_aO₂ and S_aO₂ and a higher VA at 6-24 hours of age. These abnormalities were still present on the second day of life, and disappeared thereafter. As in the other groups, the changes in P_aO₂, S_aO₂, and VA from 6-24 hours to 3-10 days of age were statistically significant ($p < 0.01$).

Discussion

The results of the present study are compared with data derived from previous publications in Table IV.

We have confirmed the presence of decreased arterial oxygenation in the newborn period in

FIG. 2.—Arterial oxygen saturation in 'normal' premature infants of different ages. Means $\pm$ SD are shown.

'normal' premature infants and have found that the decrease in P_{aO_2} and S_{aO_2} is not generally greater than in full-term infants. Our data show that oxygen unsaturation persists in premature infants until the end of the first month.

After the first 5 hours of life alveolar hypoventilation cannot account for the low P_{aO_2} and S_{aO_2} in 'normal' premature infants, since the P_{aCO_2}

remained below adult values. The presence of a large percentage of venous admixture in 'normal' premature infants implies the existence of one or more of three deficits of physiological function: a right-to-left shunt of blood, inequalities of ventilation to perfusion, or a diffusion defect. In the absence of studies during oxygen breathing it is impossible to be certain which of these deficits was

FIG. 3.—Venous admixture in air of arterial blood in 'normal' premature infants of different ages. Means $\pm$ SD are shown.

TABLE III

Arterial Blood Values in 3 Groups of Premature Infants Studied at Different Ages (Means $\pm$ SD)

	6-24 Hr.			25-48 Hr.			3-10 Dy.		
	Normal	Tachypnoea	RDS	Normal	Tachypnoea	RDS	Normal	Tachypnoea	RDS
Number	21	11	4	22	6	3	25	9	5
Age (mean) ..	15 hr.	12.5 hr.	15 hr.	35 hr.	34.5 hr.	41 hr.	5.5 dy.	5.4 dy.	5.5 dy.
P _a O ₂ (mm. Hg) ..	68.2 $\pm$ 13.4	58.7* $\pm$ 10.2	52.5* $\pm$ 12.4	72.5 $\pm$ 20.9	59.7 $\pm$ 15.0	57.3 $\pm$ 13.8	79.0 $\pm$ 9.9	76.8 $\pm$ 12.7	71.1 $\pm$ 5.3
S _a O ₂ (%)	95.2 $\pm$ 1.7	92.0† $\pm$ 2.5	90.2‡ $\pm$ 2.0	95.0 $\pm$ 2.0	93.7 $\pm$ 2.3	93.1* $\pm$ 1.0	95.4 $\pm$ 1.5	94.8 $\pm$ 1.6	94.8 $\pm$ 1.4
VA (%)	15.6 $\pm$ 5.7	21.4 $\pm$ 9.3	28.7† $\pm$ 8.3	13.8 $\pm$ 8.7	18.9 $\pm$ 7.5	17.5 $\pm$ 5.4	9.0 $\pm$ 5.0	10.0 $\pm$ 6.3	9.7 $\pm$ 3.1
pH	7.448 $\pm$ 0.069	7.380‡ $\pm$ 0.022	7.381 $\pm$ 0.062	7.434 $\pm$ 0.054	7.420 $\pm$ 0.023	7.395 $\pm$ 0.022	7.402 $\pm$ 0.049	7.378 $\pm$ 0.038	7.398 $\pm$ 0.044
P _a CO ₂ (mm. Hg) ..	27.5 $\pm$ 7.8	36.9† $\pm$ 7.1	33.2 $\pm$ 7.3	31.3 $\pm$ 6.7	30.9 $\pm$ 3.7	34.4 $\pm$ 10.9	33.9 $\pm$ 5.9	35.7 $\pm$ 4.8	40.6 $\pm$ 7.3
BE (mEq/l.) ..	-3.7 $\pm$ 3.3	-3.7 $\pm$ 2.1	-5.3 $\pm$ 2.8	-2.3 $\pm$ 3.0	-3.5 $\pm$ 2.2	-3.7 $\pm$ 2.6	-3.2 $\pm$ 2.2	-3.9 $\pm$ 2.5	-1.9 $\pm$ 3.4
Hb (g./100 ml.) ..	16.0 $\pm$ 2.5	15.5 $\pm$ 2.3	16.2 $\pm$ 0.2	15.7 $\pm$ 2.4	14.3 $\pm$ 1.0	14.1 $\pm$ 1.4	13.8 $\pm$ 3.6	14.3 $\pm$ 1.8	14.4 $\pm$ 1.2

Values significantly different from 'normal' of the same age: * = $p < 0.05$; † = $p < 0.01$; ‡ = $p < 0.001$.

present in the babies studied. Nelson and co-workers (1963) and Prod'hom and co-workers (1964) have demonstrated, in newborn infants with a higher birthweight, a large right-to-left shunt. On the other hand, from the data of Moss and co-workers (1965), it can be calculated that a true right-to-left shunt cannot account completely for the low P_aO₂ and S_aO₂ in premature infants breathing room air; this implies that a ventilation-perfusion imbalance (or possibly a diffusion defect) is also present.

The infants with tachypnoea were hypoventilating when compared with the normal prematures (the P_aCO₂ was higher), and in addition their venous admixture was greater. These two changes account for the lower oxygen tension and saturation in these infants.

In the prematures with mild respiratory distress the venous admixture was greater than in either of the other groups, a finding that probably reflects a larger right-to-left shunt and also inequalities of ventilation and perfusion. As the arterial PCO₂ was

FIG. 4.—Arterial oxygen saturation at different ages in the 3 groups of premature infants studied. Means $\pm$ SE are shown.

FIG. 5.—Venous admixture in air of arterial blood, at different ages, in the 3 groups of premature infants studied. Means $\pm$ SE are shown.

TABLE IV

Comparison of Present Data with Those Found by Other Authors in Normal Full-term and Premature Newborn Infants

Author	Birthweight (kg.)	Gestation (wk.)	No.	Age (hr.-dy.)	P _a O ₂ (mm. Hg)	S _a O ₂ (%)	pH	P _a CO ₂ (mm. Hg)	VA (%)
Stahlman (1947) (Femoral artery)	3.23 (2.50-4.08)	Full-term	8	16.5 hr. (9-22)	—	93.0	7.434	30.9	—
			15	34 hr. (29-48)	—	94.6	7.424	31.3	—
			11	58 hr. (50-72)	—	94.6	7.429	30.5	—
			6	82 hr. (75-96)	—	92.9	7.465	29.2	—
Weissbrodt <i>et al.</i> (1958) (Left atrium)	2.50	Full-term	7	3 hr.	—	94.7	7.341	38.3	—
			14	24 hr.	—	93.2	7.408	33.6	—
Reardon <i>et al.</i> (1960) (Temporal artery)	3.15 (2.30-3.90)	Full-term	17	2.6 hr. (1-4)	—	94.9	7.306	38.3	—
			6	7.0 hr. (4-10)	85.3	—	—	—	—
			27	11 hr. (6-24)	—	94.1	7.368	34.4	—
			6	38 hr. (30-45)	78.8	—	—	—	—
			20	45 hr. (30-48)	—	94.4	7.386	33.9	—
			7	97 hr. (76-112)	87.0	—	—	—	—
			36	86 hr. (72-96)	—	94.5	7.379	36.3	—
			6	5 dy.	—	94.9	7.390	35.2	—
Prod'homme <i>et al.</i> (1964) (Umbilical artery)	3.18 (2.27-4.31)	36.5 (35-39)	20	1 hr.	61.0	—	7.310	46.0	31
			19	4 hr.	72.0	—	7.370	40.0	20
			14	24 hr.	71.0	—	7.430	36.0	20
Moss <i>et al.</i> (1965) (Ascending aorta)	2.02 (1.36-2.33)	?	6	9 hr. (2-12)	68.5	94.0	7.376	32.7	17
			15	18 hr. (13-24)	61.3	93.5	7.391	29.8	16
			20	34 hr. (25-48)	75.9	94.7	7.394	29.3	15
			7	67 hr. (49-120)	77.7	94.3	7.356	31.9	11
Present data (Umbilical, temporal, and radial artery)	1.76 (1.26-2.48)	34.5 (28-40)	4	4 hr. (3-5)	59.5	91.3	7.329	47.3	20
			21	15 hr. (6-24)	68.2	95.2	7.448	27.5	16
			22	35 hr. (25-48)	72.5	95.0	7.434	31.3	14
			25	5.5 dy. (3-10)	79.0	95.4	7.402	33.9	9
			8	27.5 dy. (11-40)	77.8	96.0	7.425	32.9	8

normal (or even low) in these infants, hypoventilation was not a factor in the production of arterial oxygen unsaturation.

The results of this study are consistent with the view that right-to-left shunting of blood and maldistribution of gas with respect to blood flow are common in premature infants, and may persist throughout the first month of life. When the infants are asymptomatic these abnormalities do not seem greater than in full-term infants, but in the presence of clinically apparent symptoms (tachypnoea or mild respiratory distress, even with normal chest x-ray films) more severe derangements of function are present.

Summary

Arterial oxygen and carbon-dioxide tension (P_aO₂ and P_aCO₂), pH, base excess, and Hb concentration were measured in 59 premature infants from 3 hours to 40 days of age and in 13 normal adults; oxygen saturation (S_aO₂) and venous admixture in air (VA) were also calculated. The babies were divided into 3 groups.

In a group of 40 'normal' prematures S_aO₂ did not change appreciably after 5 hours of age, whereas there was a significant rise in P_aO₂ and a fall in VA from 6-24 hours to 3-10 days of life. P_aO₂ and S_aO₂ at all ages were significantly lower than in normal adults.

A group of 14 prematures with tachypnoea had significantly lower P_{aO_2} and S_{aO_2} and higher P_{aCO_2} at 6-24 hours of life when compared to normal prematures of the same age.

A third group of 5 prematures who showed mild transient respiratory distress had lower than normal P_{aO_2} and S_{aO_2} and higher VA at 6-24 hours of age. These abnormalities were still present on the second day of life.

The significance and the implications of these findings have been discussed.

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Addendum

After this paper was accepted Thibeault, Clutario, and Auld (1966) found similar results to ours.

REFERENCE

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