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Birth weight
hyaline membrane disease
lung
newborn
respiratory distress syndrome

Serial Studies of Lung Volume and $\dot{V}A/\dot{Q}$ in Hyaline Membrane Disease

CARLOS A. TORI, ALFRED N. KRAUSS, AND PETER A. M. AULD[13]

Department of Pediatrics, Cornell University Medical College, New York City, USA

Extract

Twenty infants with a clinical and radiologic diagnosis of hyaline membrane disease were studied serially by measurement of functional residual capacity (FRC) and arterial and alveolar gradients for O_2, CO_2, and N_2. Nitrogen washouts were determined as well in nine infants.

The FRC, alveolar-arterial O_2 gradients (AaD_{O_2}) in 100% O_2, and true shunt ($\dot{Q}_s/\dot{Q}_t$), which are different ways of quantitating atelectasis and shunt in hyaline membrane disease, were shown to be statistically related. The FRC was below 1.0 ml/cm in all infants when sick and returned to the usual range for gestational age, generally around 15 days. Extensive cardiopulmonary shunting was recorded both at the height of illness and for a considerable time during recovery. However, during recovery, not all of the venous admixture was due to shunt. As maldistribution of ventilation was excluded, the possibility of a diffusion barrier was raised. Alveoli with a high $\dot{V}_A/\dot{Q}$ were identified by large arterial-alveolar CO_2 gradients (aAD_{CO_2}) both during illness and recovery. This indicates that maldistribution of pulmonary blood flow is an important physiologic abnormality in hyaline membrane disease.

Speculation

The FRC was shown to correlate inversely with AaD_{O_2} and $\dot{Q}_s/\dot{Q}_t$ ratios. As a low FRC is the only true unique characteristic of hyaline membrane disease, it is suggested that in the future the disease be defined in terms of the lung volume as well as in terms of the usual clinical and biochemical parameters which appear in other forms of respiratory distress in neonates. Constant positive airway pressure is an attempt to approach treatment from this point of view.

Introduction

Inequality of ventilation and perfusion and decreased functional residual capacity are major disturbances in the lungs of infants with hyaline membrane disease. Serial measurements of these parameters from onset of the disease until discharge from the nursery should characterize in more detail than previously the time course of development and resolution of these important abnormalities.

The degree of $\dot{V}_A/\dot{Q}$ imbalance can be assessed by measurement of alveolar and arterial gas gradients for O_2, CO_2, and N_2. Gradients for O_2 and N_2 reflect ventilatory disturbances and detect areas of low $\dot{V}_A/\dot{Q}$. A gradient for CO_2 identifies areas of increased $\dot{V}_A/\dot{Q}$. This study was undertaken to provide a more complete description of the pathophysiology of the disease.

Materials and Methods

The subjects were twenty infants with clinical and roentgenographic findings of hyaline membrane disease. The

infants ranged in birth weight from 1,200 to 3,940 g (an infant of a diabetic mother) and gestational age from 29 to 41 weeks. Attempts were made to study infants on the first day, although this was not possible in every instance. Further studies were performed at intervals until discharge from the hospital. Five were studied only after clinical recovery, defined here as the time when inspired oxygen concentration was 21 %. Although some infants were treated with assisted ventilation and buffering, all were breathing spontaneously at the time of the tests. The AaD_{O_2} and aAD_{CO_2} studies were performed when the infants were acutely ill. For these studies, blood was sampled from the temporal or right radial artery after 15 min 100% oxygen breathing. The FRC was determined by the helium rebreathing method of Krauss and Auld [3]. In the recovery period AaD_{O_2} in air and after 100% oxygen breathing aAD_{CO_2} and arterial alveolar nitrogen gradient (aAD_{N_2}) were determined. In nine infants nitrogen washouts were recorded as well. The methods used have been reported in detail elsewhere [4, 5]. The aAD_{N_2} determinations were performed using 0.1 ml of anaerobically collected blood; otherwise, the test was performed essentially as reported previously for urine [5].

Venous admixture ($\dot{V}_A/R_A$) and true shunt ($\dot{Q}_s/\dot{Q}_t$) were calculated using standard equations. For these calculations an arteriovenous oxygen saturation difference of 15% was assumed [9].

Critique of Methods

Although the methods used have for the most part become standard for newborn infants, the reader should be aware of their limitations. The determination of AaD_{O_2}, nitrogen washouts, and FRC methods have been well validated. The respiratory exchange factor (R) is assumed for calculation of alveolar oxygen tension. The CO_2 gradients are probably the least accurate and suffer from the limitation that a true end-tidal point cannot always be defined. However the 90% response time of 0.2 sec indicates that a large error in end-tidal P_{CO_2} is unlikely. In this study, the value is reported only when a CO_2 plateau was recorded. The aAD_{N_2} data presented herein contain negative gradients, which, on theoretical grounds, should not occur. Most authors using the test have reported negative gradients and to date there has been no satisfactory explanation. Laboratory error appears unlikely, as the test was done and repeated with triplicate checks. Negative nitrogen gradients could be explained by the fact that the recovering infant is in an unsteady state and a high $\dot{V}_A/\dot{Q}$ is present. In this state it is theoretically possible that a negative nitrogen gradient could exist. Certainly, areas of high $\dot{V}_A/\dot{Q}$ exist in recovering patients as indicated by large aAD_{CO_2}. Because of these possible inadequacies of nitrogen gradients, nitrogen washouts were performed as well. This test will also identify areas of the lung in which there is maldistribution of ventilation.

The calculations of venous admixture and shunt have limitations because of the assumption of arteriovenous oxygen difference. However, during recovery, even with this assumption, they do allow a comparison of V_A/R_A and $\dot{Q}_s/\dot{Q}_t$ at virtually the same point in time.

Results

The clinical course of the infants in the study appear in Table I. Certain clinical parameters are presented to demonstrate the variation in severity of the infants studied. Fourteen infants were treated with assisted ventilation. Two infants died in the early neonatal period and one at 5 months of age with the Wilson-Mikity syndrome.

As FRC, AaD_{O_2} in 100% oxygen, and $\dot{Q}_s/\dot{Q}_t$ are really different ways of quantitating atelectasis and shunt in hyaline membrane disease, analysis was performed to determine whether a statistical relation could be demonstrated between these parameters.

FRC related to AaD_{O_2} measured in air with $r = 0.5$ ($P < 0.01$), FRC related to AaD_{O_2} in 100% oxygen with $r = 0.61$ ($P < 0.001$), and FRC related to $\dot{Q}_s/\dot{Q}_t$ with $r = 0.57$ ($P < 0.001$). Thus tests designed to measure shunt correlated well with FRC.

Previous work with normal premature infants showed an FRC over 1.0 ml/cm [3]. All infants in the study eventually showed an FRC below this value (Fig. 1). Two patterns of FRC change were noted in infants studied serially from the first day. One group had a normal FRC on the first day and a decrease on the following day (Fig. 2). The other group had an initially low FRC, which, in some cases, decreased further (Fig. 3). As shown in the figures, changes in FRC were paralleled by changes in gas gradients and shunt. Of the two patients who died, one had a very low FRC. The other had a normal FRC 24 hr prior to death, and at that time the infant was not severely ill clinically. A large intracranial hemorrhage noted at postmortem would appear to be the most probable cause of death.

Shunt and venous admixture are plotted against age in Fig. 4. The figure demonstrates the extensive cardiopulmonary shunting in both the initial period of illness as well as during recovery. Furthermore, during recovery, venous admixture is not entirely explained by shunting. Nitrogen gradients and nitrogen washouts were

Table I. Clinical data on study patients

Case	Birth weight, g	Gestational age, weeks	Minimum pH	Maximum P_{CO_2}, mm Hg	Treatment				Outcome
					Maximum O_2, %	Duration O_2, days	Assisted ventilation	Buffers	
1	1,871	34	7.27	48	72	5	None	$NaHCO_3$	Survived
2	2,220	36	7.27	68	100	10	Yes	$NaHCO_3$	Died 5 months
3	2,030	36	7.16	68	100	2	Yes	$NaHCO_3$	Died 2 days
4	1,680	31	6.98	95	100	2.5	Yes	$NaHCO_3$ THAM	Died 2.5 days
5	1,780	32	7.10	70	100	6	Yes	$NaHCO_3$ THAM	Survived
6	1,220	33	7.18	72	92	4	None	$NaHCO_3$	Survived
7	2,660	39	7.34	40	64	2.5	None	None	Survived
8	2,140	36	7.23	66	68	5	Yes	$NaHCO_3$	Survived
9	2,180	35	7.30	83	100	8	Yes	$NaHCO_3$	Survived
10	1,840	34	7.34	71	100	8	Yes	$NaHCO_3$	Survived
11	1,780	33	7.25	83	100	60	Yes	$NaHCO_3$	Survived[1]
12	1,680	34	7.30	62	82	4	No	$NaHCO_3$	Survived
13	1,200	29	6.85	110	100	9	Yes	$NaHCO_3$ THAM	Survived
14	3,940	36	7.28	75	100	8	Yes	$NaHCO_3$	Survived
15	2,010	35	7.35	58	63	3.5	No	None	Survived
16	3,080	41	7.22	54	78	5	Yes	$NaHCO_3$	Survived
17	2,560	36	7.15	70	100	9	Yes	$NaHCO_3$	Survived
18	2,400	36	7.05	85	94	8	Yes	$NaHCO_3$	Survived
19	1,420	32	7.01	95	100	12	Yes	$NaHCO_3$	Survived
20	1,930	31	7.27	58	53	2.5	No	$NaHCO_3$	Survived

[1] Developed Wilson-Mikity syndrome.

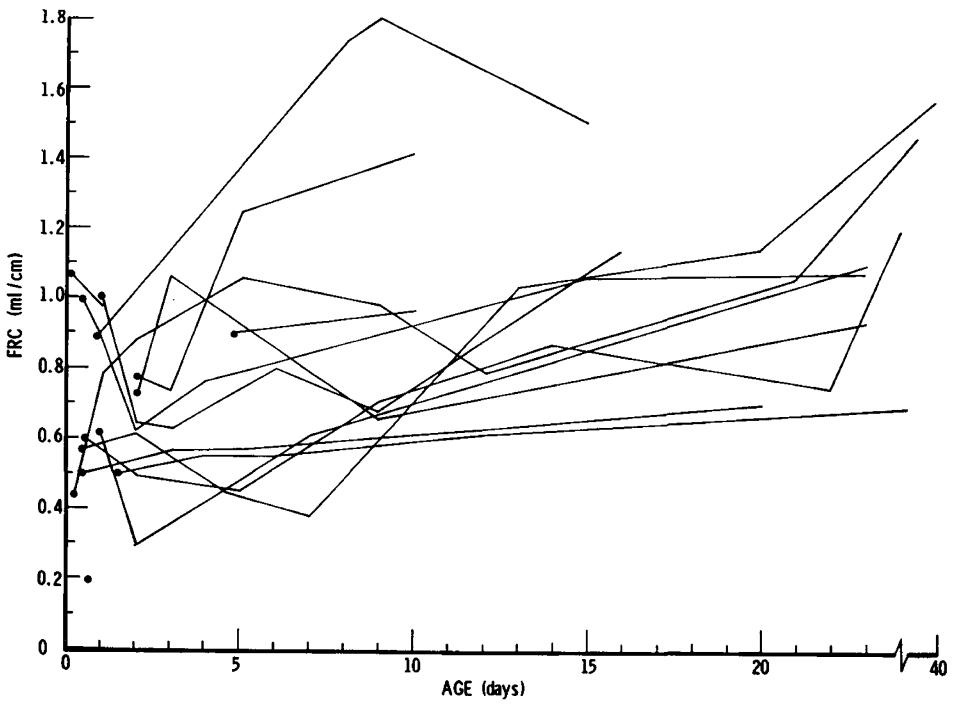

Fig. 1. Serial determinations of functional residual capacity (*FRC*) in milliliters per centimeter plotted against age from birth for infants with hyaline membrane disease.

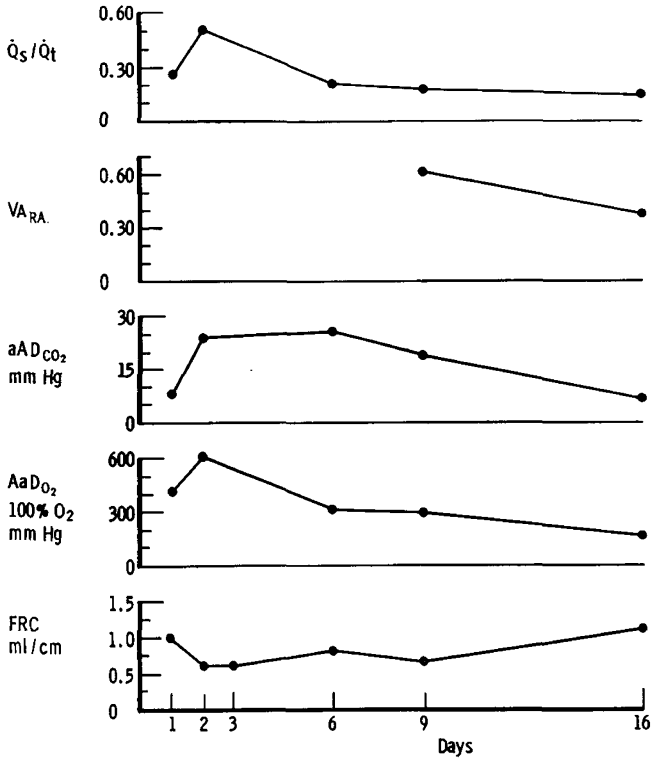

Fig. 2. Serial values for *patient 9* showing normal functional residual capacity (*FRC*) on day 1 and subsequent value. Also shown are worsening gradients. $\dot{Q}_s/\dot{Q}_t$: True shunt. VA_{RA}: Venous admixture. aAD_{CO_2}: Arterial-alveolar CO_2 gradients. AaD_{O_2}: Alveolar-arterial O_2 gradients.

performed to determine whether some of the venous admixture was due to maldistribution of ventilation. Nitrogen gradients were nearly always normal (Fig. 5). Analysis of nitrogen washout shows only a very small fast space and a large normally ventilated space consistent with normal distribution of ventilation (Table II).

The presence of aAD_{CO_2} indicates alveoli with a high $\dot{V}_A/\dot{Q}$ (either overventilation or underperfusion). In this study, large aAD_{CO_2} were measured, the gradients generally increasing as FRC decreased. Large gradients persisted into the recovery period (Fig. 6).

Discussion

The results presented here describe serial changes in FRC and $\dot{V}_A/\dot{Q}$ in hyaline membrane disease from onset through recovery to discharge from the hospital. The pattern of disease is not uniform clinically nor is it uniform when assessed by these physiologic parameters. As the principal pathologic lesion is atelectasis, measurements of FRC should be an excellent reflection of its severity in the living patient. All infants with hyaline membrane disease eventually had a reduced FRC. Two separate patterns of FRC change were noted. In some infants FRC was in normal range on the first day with a fall to an abnormal level on the second or third day. This was the case even though clinically the infant was distressed from birth. A clinical parallel occurs when the chest roentgenogram fails to show the "typical" pattern until 24 hr. More common, however, was the instance in which FRC was abnormally low at the initial evaluation. The data obtained in this study shows that FRC is inversely correlated with AaD_{O_2} and $\dot{Q}_s/\dot{Q}_t$ or shunt. Therefore, it is suggested that the severity of hyaline membrane disease be defined specifically in terms of reduced FRC rather than the usual clinical parameters (grunting, retractions, etc.) or biochemical parameters (hypercapnia and acidosis), all of which can appear in other clinical syndromes and are nonspecific.

The studies of AaD_{O_2} and aAD_{CO_2} confirm the presence of cardiopulmonary shunting and of alveoli with the high $\dot{V}_A/\dot{Q}$ relation [7, 8]. Development of these

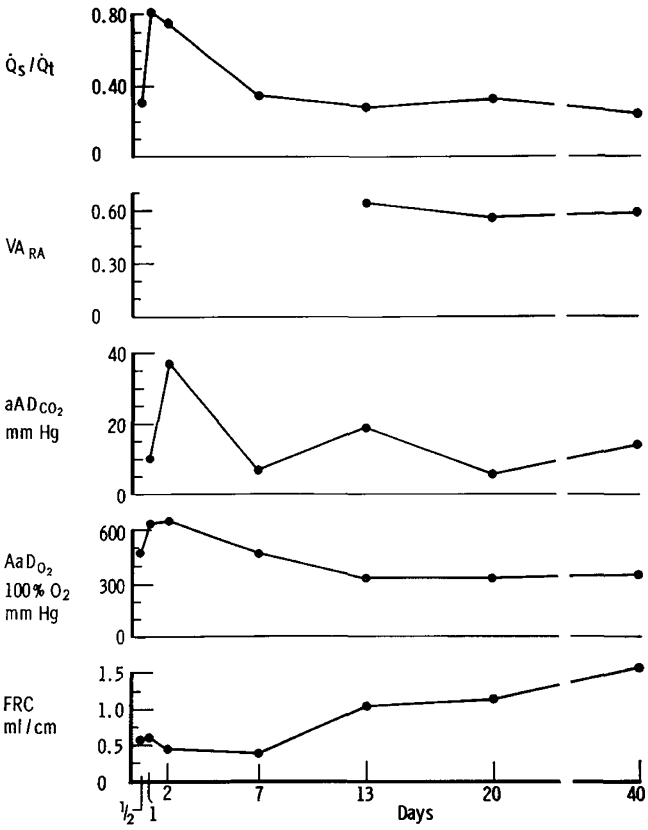

Fig. 3. Serial studies on *patient 2* who presented with an initially low functional residual capacity (*FRC*). For description of terms appearing on figure, see legend to Figure 2.

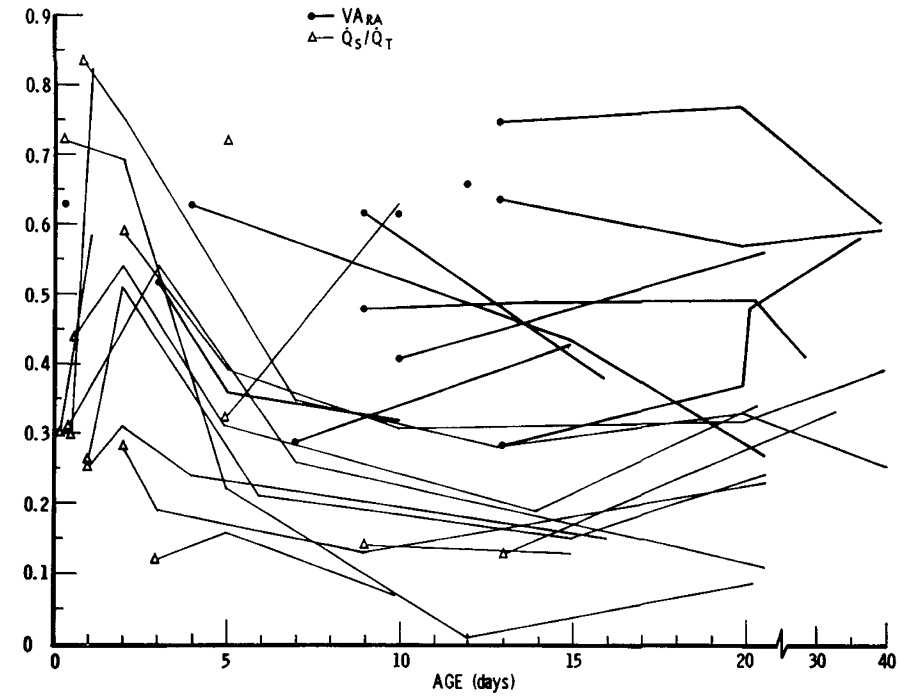

Fig. 4. Shunt and venous admixture plotted against age. Note that shunt does not represent total venous admixture. VA_{RA} : Venous admixture. $\dot{Q}_s/\dot{Q}_t$: True shunt.

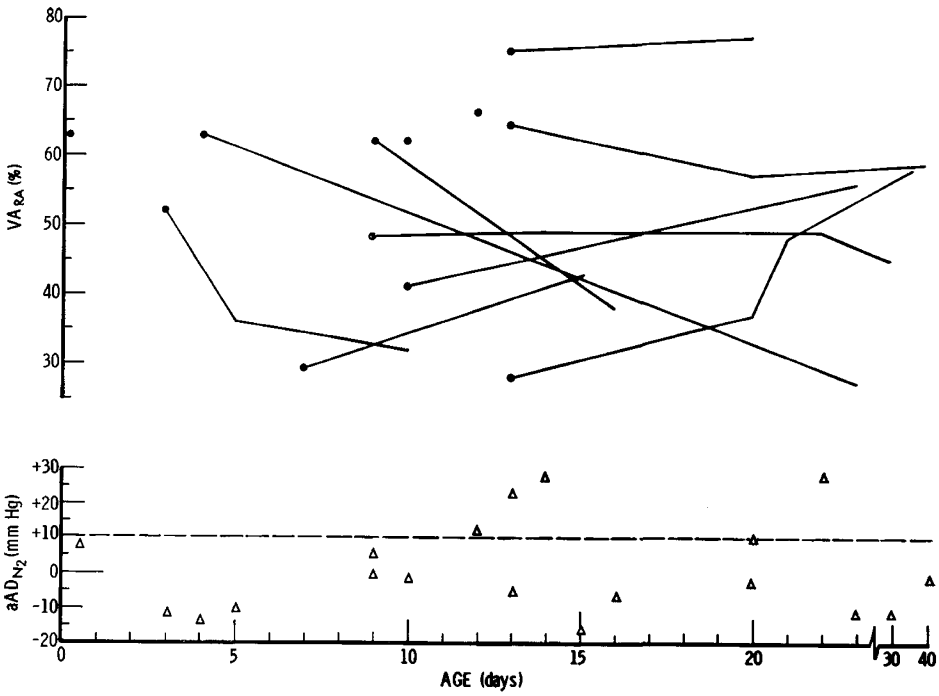

Fig. 5. Venous admixture (VA_{RA}) and nitrogen gradients (aAD_{N_2}). Gradients rarely greater than 10 mm Hg.

Table II. Summary of data on nitrogen washout[1]

Case	f_1	f_2	f_3	PCD_{N_2}, %	$\dot{V}_A/L_1$	$\dot{V}_A/L_2$	$\dot{V}_A/L_3$	$\dot{V}_{A_1}/V_T$	$\dot{V}_{A_2}/V_T$	$\dot{V}_{A_3}/V_T$	L_1/L_T	L_2/L_T	L_3/L_T
12	0.01	0.99		0	40	2.45		0.25	0.75		0.16	0.84	
13	0.12	0.88		51	25	2.80		0.52	0.48		0.11	0.89	
	0.18	0.82		32	46	4.20		0.54	0.46		0.13	0.87	
14	1.0			0	6.2			1.0			1.0		
	0.10	0.90		21	46	5.10		0.27	0.73		0.30	0.70	
15	0.31	0.69		26	32.1	2.51		0.49	0.51		0.13	0.87	
16	0.15	0.85		88	16.2	2.34		0.44	0.56		0.08	0.91	
	1.0			0	6.9			1.0			1.0		
17	1.0	0	0	0	2.4			1.0			1.0		
18	0.25	0.75		127	25.1	2.76		0.72	0.28		0.07	0.93	
19	0.06	0.06	0.88	55	55.3	27.6	4.38	0.07	0.22	0.71	<0.01	0.015	0.984
20	0.07	0.93		85	34.5	2.38		0.60	0.40		0.13	0.87	

[1] f: Fraction of lung volume. PCD_{N_2}: Percentage of pulmonary clearance delay of N_2. $\dot{V}_A/L$: Alveolar ventilation per liter of lung volume (liters per minute per liter of lung). $\dot{V}_A/V_T$: Fraction of alveolar ventilation. L_1/L_T: Fraction of total lung volume.

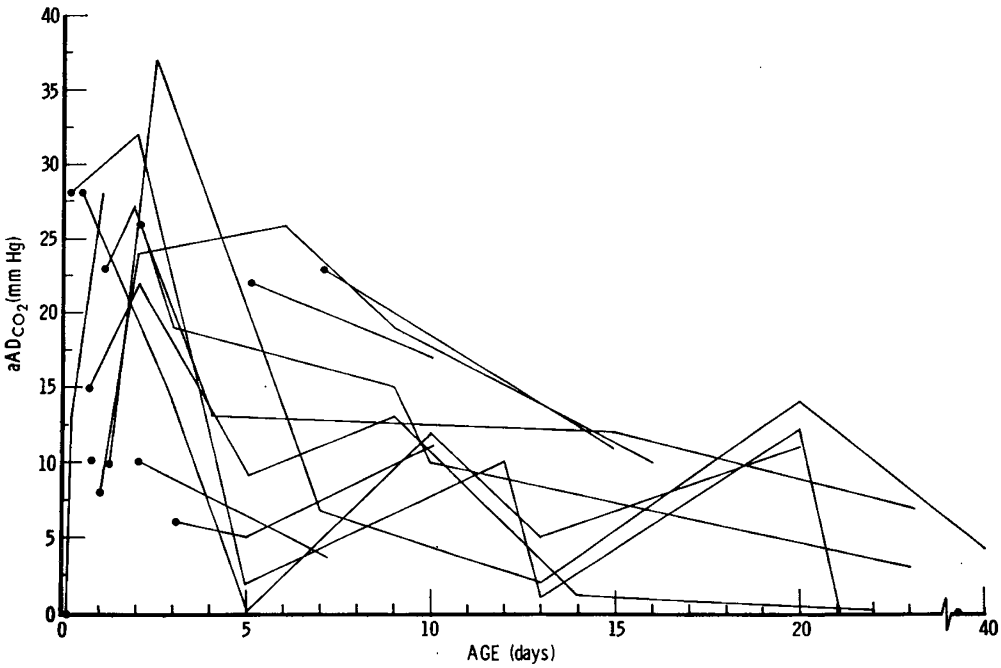

Fig. 6. Serial studies of arterial-alveolar CO_2 gradient (aAD_{CO_2}) plotted against age.

gradients show the same patterns noted with FRC, *i.e.*, some are very large from the onset and others increase progressively. They indicate that at least three groups of alveoli are present in infants with hyaline membrane disease: those that are normally ventilated and perfused, those that are nonventilated and perfused (shunt), and a group that are either overventilated or underperfused (high $\dot{V}_A/\dot{Q}$). The fact that O_2 and CO_2 gradients worsen as the disease progresses, at least in some infants, indicates that alveoli with normal $\dot{V}_A/\dot{Q}$ are developing one of the two pathologic configurations. Although most theories of etiology of hyaline membrane disease imply that the insult that produces the disease occurs prior to birth, the fact that, in some infants, FRC decreases and gradients increase with time indicates that the stimulus producing disease may be acting after birth as well. Alternatively, these cases may represent instances in which the infant is born with a decreased amount of surfactant, which is utilized and not replaced.

During the recovery process the two populations of alveoli with abnormal $\dot{V}_A/\dot{Q}$ relationships are present for prolonged periods of time. However, the usually

normal nitrogen gradients with normal nitrogen washouts indicate that, with recovery, the alveoli pop open and ventilate normally rather than proceeding through an intervening stage in which ventilation is poorly distributed. This process appears to be similar to that noted in nondistressed premature infants who qualitatively have the same $\dot{V}_A/\dot{Q}$ abnormalities and who develop a normal $\dot{V}_A/\dot{Q}$ by the same process [6]. Thus, the persistence of $\dot{V}_A/\dot{Q}$ abnormalities long after clinical recovery and after FRC has returned to the usual range for gestational age merely reflects that the lungs have returned to the physiologic state they would have been in if no hyaline membrane disease had occurred. During the recovery period the combination of good distribution of ventilation and absence of areas of low $\dot{V}_A/\dot{Q}$ as determined by aAD_{N_2} indicates that the increased $\dot{V}_A/\dot{Q}$ at this time is related to maldistribution of pulmonary blood flow rather than overventilation. A similar conclusion was reached by Nelson *et al.* [8].

The study confirms the fact that venous admixture continues long after clinical recovery [1]. Maldistribution of ventilation and shunting are not full explanations, but the results suggest that a diffusion barrier may be present at this time. If such a defect is present, it may be part of the disease process itself or could be related to the direct effects of oxygen on the lung. Work in monkeys has shown that oxygen toxicity produces a diffusion barrier [2].

Summary

Serial studies of FRC, AaD_{O_2}, and aAD_{N_2} have been performed on a group of infants with hyaline membrane disease during the acute disease and during recovery. In addition, nitrogen washouts were performed and venous admixture and shunts calculated. The data confirms that FRC is reduced and cardiopulmonary shunting is present and persists for prolonged periods in the recovering infant. Alveoli with high $\dot{V}_A/\dot{Q}$ ratios were present and persisted into the recovery period. Although venous admixture persists in the recovery period, it is not due only to shunting or maldistribution of ventilation. Maldistribution of pulmonary blood flow, at least during the recovery period, is an important abnormality of lung function in infants with hyaline membrane disease.

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13. Requests for reprints should be addressed to: PETER A. M. AULD, M.D., 525 East 68th Street, New York, N. Y. 10021 (USA).
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