Ventilation-Perfusion Abnormalities in the Premature Infant: Triple Gradient

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Extract

Serial studies of arterial and alveolar oxygen, carbon dioxide, and nitrogen tensions, arterial pH, and ratios of dead space: tidal volume were made in 24 nondistressed premature infants. By determining arterial-alveolar gradients, the sequence of development of ventilation/perfusion relations in the non-distressed premature infant can be determined. The presence of an arterial-alveolar carbon dioxide gradient and elevated V_D/V_T ratio indicate the presence of overventilated/underperfused areas. Alveolar-arterial oxygen gradients may be due to shunting, underventilation (low ventilation/perfusion ratio), or diffusion block. Although underventilation exists, as evidenced by the presence of a urinary-alveolar gradient for N_2 , it is not a major cause of arterial unsaturation. This evidence suggests that shunting of blood, either through intracardiac shunts or atelectatic lung, is a major cause of arterial unsaturation in the premature infant.

Speculation

Further extension of this work should make possible the construction of $\dot{V}_A/\dot{Q}$ curves for the individual patient and thus show in even greater detail the maturation of pulmonary ventilation and perfusion.

Introduction

The onset of respiration at birth requires adjustments in ventilation and perfusion of lungs. Inequalities in the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) will result in gradients between alveolar and arterial oxygen tension ($AaDO_2$), arterial-alveolar carbon dioxide tension ($aADCO_2$) and arterial-alveolar nitrogen tension ($aADN_2$). Assessment of these parameters, the so-called triple gradient, permits description of the nature of the abnormalities of ventilation and perfusion. This study investigated these gradients serially in a group of small nondistressed premature infants in order to determine the sequence of events in the adaptation of lungs to

extrauterine life. Serial measurements of anatomic and physiologic dead space and calculation of alveolar dead space were made, since these also are indications of the adequacy of ventilation-perfusion.

Materials and Methods

The subjects were twenty-four premature infants, all but one of whom had a birth weight less than 1800 g. With one exception, the infants were of appropriate weight for gestational age. Four infants recovering from hyaline membrane disease and two with roentgenographic findings of the Mikity-Wilson syndrome

were the only ones with symptoms of respiratory difficulty, although some of the smaller infants required an increased oxygen environment for several days after birth.

Alveolar-arterial oxygen gradients ($AaDO_2$) and arterial-alveolar carbon dioxide gradients ($aADCO_2$) were determined by methods previously reported [7]. The nitrogen gradient was measured as the urinary-alveolar nitrogen gradient ($uADN_2$) by the method of FARHI *et al.* [1]. Urine was collected in a polyethylene bag attached to the perineum of the infant. On voiding, the bag was immediately removed and a clamp was placed below the air-liquid interface. Urine was then anaerobically removed from the bag into a 5-ml syringe. Dead space of the syringe had been previously filled with distilled water and rinsed once with urine. Rectal temperature was recorded immediately with a thermometer [10]. PuN_2 was determined from measurement of dissolved nitrogen in an anaerobically collected specimen and the nitrogen content dissolved in an aliquot of the same sample which had been equilibrated with a gas of known P_{N_2} at the same temperature as that of the infant. The nitrogen content of the samples was determined using a Beckman GC-2A gas chromatograph [1]. A volume of 0.07 ml of urine was used for each determination and approximately 4 ml was needed for both anaerobic and equilibrated samples. A peak height of approximately 15 cm was obtained for each determination. Triplicate checks within 2.5 mm peak height were required and the mean value was used to calculate PuN_2 . The equilibrated sample was obtained by using a Twin tonometer for tonometering the urine with compressed air of known nitrogen content for 30 minutes at the exact rectal temperature of the infant. Urinary nitrogen was calculated from the mean peak height of the anaerobic sample, the mean peak height of the equilibrated sample, and the partial pressure of nitrogen in the equilibrated urine as follows:

$$PuN_2 = \frac{\text{peak height (anaerobic)}}{\text{peak height (equilibrated)}} \times P_{N_2} \text{ (equilibrated)}$$

The partial pressure of nitrogen in alveolar gas (PA_{N_2}) was determined from the alveolar air equation using the measured PA_{CO_2} and R equal to 0.7 in the first week of life, and R equal to 0.8 thereafter [2]. The $uADN_2$ was obtained by using the equation: $uADN_2 = PuN_2 - PA_{N_2}$.

In some infants, physiologic dead space (V_D), tidal volume (V_T), dead space tidal volume ratio (V_D/V_T), and alveolar ventilation ($\dot{V}_A$) were measured. For these studies, carbon dioxide production ($\dot{V}_{CO_2}$) was determined by using a Kipp and Zonen diaferometer, with the infant's environmental temperature at the neutral range. Tidal volume was measured by electron-

ically integrating the signal obtained from a pneumotachograph, the dead space of which was obliterated by a constant flow through of air [4]. Volumes were obtained from standard respiratory equations. The respiratory rate measured at the time of determination of $\dot{V}_{CO_2}$ was used for the calculations.

Evaluation of Nitrogen Gradient Data

The validity of the method of determination of the nitrogen gradient has been discussed previously [3]. In the present study, the smaller amount of urine used may have decreased the accuracy of the test. Thirteen determinations on a normal adult, however, showed a mean value of 4 mm Hg for $uADN_2$ with a range -9.3 to 12.3, and one determination on an adult with emphysema showed a value of 22 mm Hg. The assumption that body temperature at the time of urine formation was the same as at the time of collection may not be valid. Many of the infants were in isolettes, and there was some variation in body temperature. The relation $\dot{V}_A/\dot{Q}$ may possibly have changed between the time of urine formation and urine collection. The frequent sighs of premature infants may result in a constantly changing $\dot{V}_A/\dot{Q}$. These factors may explain some of the variations noted. There were several negative gradients that could not be explained, although such values have been noted by others.

Results

Data relating to serial studies appear in tables I and II and in figures 1 and 2. Initial values for $AaDO_2$ ranged from 25 to 60 mm Hg in nondistressed infants. The gradients decreased with age so that most infants had a value of 20 to 30 mm Hg by 60 days of age. Exceptions included two infants (Nos. 1 and 13) who developed the Mikity-Wilson syndrome (table I). These infants had values as high as 50 mm Hg as late as 104 days of age. Except for one infant (No. 24) who had respiratory distress (table I), the value for $aADCO_2$ on the first day of life was 0-12 mm Hg. This gradient tended to rise during the first week of life and then gradually fell, except in infants Nos. 1 and 13. Wide daily variations were found in values for $uADN_2$, but a general trend toward a low value with time was noted. Most infants were found initially to have a high ratio of V_D/V_T (fig. 3). There was a concomitant fall in the ratio of V_D/V_T and in $aADCO_2$. In most infants, this decrease was related to a rise in effective alveolar ventilation and a fall in alveolar dead space. Anatomic dead space generally increased as the infant grew in size. Some infants had over 25 percent nonperfused

Table I. Serial measurements of gradients for O₂, CO₂, and nitrogen¹

Case No.	Age days	Birth weight g	Weight ² g	Length cm	PAO ₂	PaO ₂	AaDO ₂	PaCO ₂	PA _{CO2}	aADCO ₂	uADN ₂	pH	Hct	Body temp. °C	Remarks
mm Hg															
1	1	822	820								16.8				
	34		1030	35	106.4	45.0	61.4	56.5	35.3	21.2	17.9	7.353	20	37.3	Mikity-Wilson
	35		1020								32.1				
	39										12.6				
	46		1210	36		40.7		55.5			33.6	7.370	25	37.3	
	53		1320		101.5	39.2	62.3	46.7	39.0	7.7		7.340	23	36.9	
	55										15.5				
	61		1540	40	105.5	49.9	55.6	56.4	35.4	21.0	10.5	7.453	26	36.8	
	69										6.8				
	76		1830	40	107.8	48.1	59.7	43.6	34.8	8.8	5.7	7.403	23	36.8	
	104		2560	46	111.6	42.9	68.7	42.1	29.5	12.6	2.5	7.445	23	36.8	
2	1	860	930		123.4	61.0	62.4	28.8	21.5	7.3	10.0	7.470	38	36.1	small for gestational age
	6		925	37	126.6	59.5	67.1	31.8	20.3	11.5	1.8	7.456	43	36.2	
	13		930		116.8	71.0	45.8	28.3	26.7	1.6	5.1	7.312	28	37.2	
	22		1160	38	107.4	76.4	31.0	34.2	32.2	2.0		7.410		37.2	
	40		1440	41	109.0	77.0	32.0	35.0	31.6	3.4		7.415	20	37.0	
	41										1.3				
3	2	1100	1130		104.6	61.9	42.7	44.2	38.4	5.8	4.3	7.354	30	36.5	died—8th day sepsis and enterocolitis
	3		1070		99.1	67.2	31.9	39.3	43.3			7.355	25	35.9	
	4		1070												
	6										-3.8				
4	3	1130	1050								9.7				
	9		990								14.7				
	10		990	38	106.9	52.0	54.9	40.0	36.4	3.6		7.315	26	36.4	
	24		1100	38	108.1	67.6	30.2	37.8	34.9	2.9	10.8	7.405	23	36.8	
	31										4.7				
	44		1420	41	118.2	89.4	26.8	34.2	28.1	5.1	5.8	7.315	24	37.1	
	52		1590	42	111.4	71.6	39.8	35.0	32.2	2.8	22.1	7.487	25	36.0	
	53		1600		111.9	66.7	45.2	38.4	35.0	3.4		7.410			
	54										3.1				
	67		2120	44	116.7	84.5	32.3	33.0	29.4	3.6	-2.0	7.443	22	36.2	

² Weight of time of study

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Table I. (Continued)

Case	Age	Birth	Weight ²	Length	PA _{O₂}	Pa _{O₂}	AaDO ₂	PaCO ₂	PA _{CO₂}	aAD _{CO₂}	uAD _{N₂}	pH	Hct	Body	Remarks
No.	days	weight	g	cm	mm Hg									temp.	
		g												°C	
5	5	1220	1120								9.7				
	9		1120								13.8				
	10		1160								9.6				
	14		1230								19.2				
	15		1280	42	98.2	57.5	40.7	57.0	42.4	14.6	2.5	7.34	30	37.1	
	16		1280								9.2				
	17		1315	42	102.0	61.4	40.6	34.6	39.8	-5.2		7.30	30	35.9	
6	1	1220	1220								22.5				
	2		1170			64.0		39.2			2.7			37.1	
	10		1180	40	107.2	68.6	38.6	47.5	35.6	11.9	-1.8	7.347	38	36.0	
	11										24.0				
	23		1440	41		83.0		39.6			-3.0	7.415	37	36.3	
	30		1660	42	112.6	82.3	30.3	33.1	32.6	0.5	1.1	7.390	27	36.0	
	36		1850								-2.3				
7	42		2080	45	116.6	76.6	40.0	33.8	27.0	6.8	9.9	7.425	20	36.6	
	1	1225	1225	37	115.4	58.4	57.0	39.6	29.0	10.6	7.4	7.440	44	36.8	
	6		1150	37		55.3		50.5				7.360	36		
	14		1220	39	116.0	60.5	55.5	59.2	28.4	30.8	6.2	7.360		37.5	
	20		1350	41	121.0	60.5	60.5	39.4	24.2	15.2	5.8	7.308		37.8	
	37		1820	41	101.9	57.8	43.1	42.1	40.1	2.0	-4.6	7.393	22	36.7	
	44		2080	43	97.7	41.5	56.2	41.4	41.3	0.1	-4.1	7.380	21	37.2	
8	1	1233	1175		117.7	56.1	61.6	28.0	26.2	1.8	15.0	7.470	41	36.1	
	6		1175	38	109.2	59.3	49.9	44.0	34.0	10.0	1.8	7.380	40	37.0	
	13		1220		101.6	66.1	35.5	36.8	32.8	4.0	8.2	7.327	35	36.3	
	22		1390	41	113.0	64.8	48.2	34.5	28.2	6.3		7.432	25	36.7	
	26		1470	41	104.8	54.3	50.5	39.1	36.3	2.8		7.415	28	36.8	
	40		1915	44	97.4	67.2	30.2	40.6	42.0	-1.4	-6.6	7.397		36.3	
9	2	1276	1170	37	104.9	88.4	16.5	39.1	36.1	3.0	-7.6	7.343	35	35.4	
	3		1190		107.7	65.9	41.8	49.0	35.9	13.1	7.5	7.455	27	36.5	
	7										-2.1				
	8		1120		108.7	51.5	57.2	43.3	34.9	8.4		7.355	22	35.5	² Weight at time
	9		1130	37	104.4	84.9	19.5	47.4	36.3	11.1	2.4	7.365	24	37.3	of study

	14		1220	40	118.7	86.5	32.2	45.0	24.6	20.4		7.430	23	36.9	
	21		1380	41	119.2	70.7	48.5	38.0	25.4	12.6	-5.0	7.353	36	37.0	
	30		1620	42	105.9	81.0	24.9	38.6	36.0	2.6	5.8		24	36.8	
	45		2030	45	118.2	96.6	21.6	35.2	25.8	10.4	20.8	7.413	20	37.1	
	46		2040	45	111.1	85.8	25.3	32.4	31.2	1.2	11.2	7.420	21	36.5	
10	2	1304	1230		110.5	79.0	31.3	42.0	32.5	9.5	11.4	7.423	37	37.0	
	5		1230	38	109.1	85.8	23.3	32.4	32.8	-0.4	-12.0	7.467	37	36.6	
	13		1300	39	113.3	85.6	27.7	39.6	30.5	9.1	16.0	7.415	35	36.8	
	26		1620	41	109.9	75.4	34.5	35.1	32.0	3.1		7.397	32	36.8	
	27			41							14.3				
11	6	1304	1200		85.6	53.8	31.8		54.3		-13.4	7.27	32	36.5	
	14		1310	41	73.7	38.7	35.0	71.8	64.4	7.4	-0.2	7.320	25	36.3	
	20		1460	42	91.1	49.9	41.2	73.3	66.8	6.5	3.8	7.370	17	36.8	
	31										5.3				
	34		1780			51.0		56.6				7.443	15	37.3	
	51		2240	44	108.5	85.6	22.9	45.5	34.5	11.0	-2.2	7.385	18	36.8	
12	1	1340	1300	37	99.8	37.3	62.5	51.7	47.9	3.6		7.380	52	35.6	
	2		1240	37		38.0		40.5			11.4	7.430		36.4	
	10		1180	39	106.8	73.2	33.6	40.9	36.1	4.8	2.4	7.350	43	35.2	
	24		1350	41	109.2	93.8	15.4	37.9	35.6	2.3	-7.2	7.475	26	37.2	
	32			42	113.0	93.8	19.2	34.1	30.9	3.2	26.0	7.475	29	36.0	
	33			42	117.3	84.4	32.9	34.3	24.7	9.6	11.1	7.430	26	36.9	
	45		1870	43	123.4	85.0	38.4	31.4	23.4	8.0		7.447		36.5	
	46			43							11.6				
13	1	1361	1360	41	111.6	51.8	59.8	31.5	32.4	-0.9	-4.3	7.40		35.5	Mikity-Wilson
	2		1295	41	107.2	65.6	41.6	41.3	35.2	6.1	-6.0	7.40		37.0	
	8		1340		102.4	62.3	40.1	38.2	34.4	3.8	4.2	7.39	32	36.5	
	15										14.1				
	17		1540		104.1	60.4	43.7		35.7		9.0	7.45	26	36.7	
	23		1680	42	89.1	50.4	38.7	55.4	51.7	3.7	3.3	7.369	18	36.8	
	28		1805		93.3	45.6	47.7	54.5	47.8	6.7		7.418	24	37.2	
	29		1820	42		40.8		49.5			39.1	7.406		36.8	
	33										32.6				
	42		2180	46	104.5	55.6	48.9	56.7	36.6	20.1	5.6	7.318	25	36.9	
14	1	1430	1440		111.1	75.0	36.1	41.0	30.0	11.0		7.425	38	37.7	
	3		1375		113.0	83.6	29.4	41.6	29.5	12.1		7.437	38	36.7	
	6		1360		105.0	90.5	14.5	39.0	38.5	0.5		7.370	32	36.4	

Table I. (Continued)

Case	Age	Birth	Weight ²	Length	PA _O ₂	Pa _O ₂	AaD _O ₂	Pa _{CO} ₂	PA _{CO} ₂	aAD _{CO} ₂	uAD _N ₂	pH	Hct	Body	Remarks
No.	days	weight g	g	cm	mm Hg									temp. °C	
	11		1480	40	113.8	86.4	27.4	34.3	29.7	4.6	24.6	7.300	32	37.3	
	26			40							10.2				
	28		1820	42	105.0	103.0	2.0	33.5	37.5	4.0		7.405	30	36.4	
15	5	1474	1380	40		65.2		41.7			16.1	7.368		37.1	
	13		1460	40	105.5	91.5	16.5	44.5	34.6	9.9	-8.0	7.423	33	37.0	
	19		1680	41	111.1	97.9	13.2	34.2	33.7	0.5		7.433	32	36.5	
	20		1710	41	112.4	104.2	8.2	33.0	32.2	0.8	-2.5	7.530	30	35.9	
	21										6.2				
16	1	1474	1390		108.6	85.2	23.4	40.0	34.7	5.3	-9.9	7.39	38	35.3	
	2		1390	39	104.3	76.1	28.1	39.9	38.4	1.5	-7.8	7.37	37	35.7	
	16		1450		97.4	69.7	27.7	43.2	43.2	0.0	14.0	7.380	20	36.1	
	17										7.4				
	32		1810			88.8		38.4			8.2	7.370	23	36.6	
	34		1950		108.6	89.0	19.6	48.0	33.6	14.4		7.385	20	35.8	
	34		1950		102.6	83.0	19.6	42.0	38.3	3.7	22.5	7.358	20	36.4	
	38										1.6				
	41		2200	43											
17	8	1500	1420		113.9	51.0	62.9	42.9	29.4	13.5	10.1	7.455	35	36.4	post-respiratory
	10		1400	42	114.7	62.0	52.7	38.2	30.2	8.0	28.3	7.362		37.1	distress syndrome
	13										9.8				
	22		1500	42	112.8	55.4	57.4	34.4	32.1	2.3	-5.4	7.386	40	36.3	
	37		2010	44	114.2	83.6	30.6	31.7	30.8	0.9	13.9	7.405	18	36.8	
18	1	1520	1520								1.4				
	2										12.3				
	9		1500	40	96.8	92.7	4.1	39.1	45.0	-5.9	12.8	7.348	26	36.8	
	20		1880	44	102.2	82.0	20.2	44.0	39.8	4.2	-0.8	7.470	26	36.6	
	28		2130	45	110.1	105.0	5.1	43.6	33.5	10.1	-7.4	7.367	28	36.8	
19	1	1600	1600	43	115.0	55.0	60.0	36.0	26.1	9.9	-3.0	7.410	45	36.5	² Weight at time
	5		1460	43	112.8	53.0	59.8	44.6	30.4	14.2	13.1	7.363	42	36.5	of study

	13		1610	45	106.9	56.2	50.7	47.0	36.1	10.9	16.6	7.368	33	37.0	
	21		1920		117.9	57.6	60.0	39.4	35.3	4.1			37	36.6	
20	6	1640	1620		103.0	68.7	34.3	44.3	40.8	3.5	-10.5	7.495	35	37.4	post-respiratory distress syndrome
	12		1660	41	97.5	59.1	38.4	43.6	40.0	3.6	2.5	7.500	38	36.8	
	15		1820	41	98.2	76.9	21.3	44.5	44.0	0.5	7.4	7.415		36.7	
21	2	1758									-7.2				
	4		1670	42	100.8	79.7	21.6	40.4	40.0	0.4	-3.1	7.35	47	36.5	
22	7	1760									-5.1				
	8		1650	42	104.5	48.7	55.8	46.0	36.2	9.8	-4.6	7.302	30	36.7	post-respiratory distress syndrome
	14		1680	43	113.2	54.7	58.5	46.6	30.3	16.3	-3.0	7.375	21	36.1	
	20		1860	43	114.1	73.9	40.2	36.2	29.3	6.9	-1.9	7.395	19	36.5	
	22		1860	43	116.8	66.0	50.8	43.1	29.4	13.7	-6.0	7.320	19	36.5	
23	2	1770	1800		107.6	92.0	15.6	39.0	35.4	3.6	10.2	7.475	26	36.4	
	3		1800	43	109.3	74.7	34.6	35.9	32.4	3.5	-5.0	7.420	29	36.2	
	9		1640	44	116.0	70.8	45.2	48.2	27.9	20.3	9.5	7.453	26	36.2	
	18		1800	45	104.8	68.6	36.2	44.6	37.3	7.3	5.8	7.443	38	36.8	
	24		2110		108.0	96.5	11.5	40.2	34.2	6.0	3.7		22	37.1	
24	1	2610	2610	46	110.5	25.4	85.1	55.5	31.6	22.9	-3.0	7.267	33	36.7	respiratory distress syndrome
	2		2500			30.8		50.0				7.392	28	38.3	
	3		2420			43.1		38.8				7.445	37	36.9	
	5		2350		121.0	65.2	55.8	44.0	33.4	10.6	11.5			36.8	
	8		2360		109.2	85.0	24.2	37.6	33.5	4.1	-5.6		37	37.3	

¹ Symbols for tables I and II.

PA_{O_2} : Alveolar oxygen tension.
 Pa_{O_2} : Arterial oxygen tension.
 $AaDO_2$: Alveolar-arterial oxygen gradient.
 Pa_{CO_2} : Arterial carbon dioxide tension.
 PA_{CO_2} : Alveolar carbon dioxide tension.
 $aADCO_2$: Arterial-alveolar carbon dioxide gradient.
 $uADN_2$: Urinary-alveolar nitrogen gradient.
Hct: Hematocrit.
f: Breaths/min.
 $\dot{V}_{CO_2}$: CO_2 production, ml/min STPD.
 $\dot{V}_{O_2}$: O_2 consumption, ml/min STPD.

R: Respiratory exchange ratio.
 V_{DP} : Physiologic dead space.
 V_T : Tidal volume.
 V_D/V_T : Physiologic dead space/tidal volume ratio.
 $\dot{V}_E$: Minute ventilation.
 $\dot{V}_A$: Alveolar ventilation, ml/min BTPS.
 $\dot{V}_{DP}$: Physiologic dead space ventilation.
 $V_{Danat.}$: Anatomic dead space.
 $\dot{V}_{Danat.}$: Anatomic dead space ventilation.
 $V_{Dalv.}$: Alveolar dead space ($V_{DP} - V_{Danat.}$).
 $\dot{V}_A/\dot{V}_{O_2}$: Alveolar ventilation/oxygen consumption.

Table II. Serial studies on premature infants of dead space and related parameters¹

Case No.	Age ^a days	f min	$\dot{V}_{CO_2}$ ml/min	$\dot{V}_{O_2}$ ml/min	R	V_{DP} ml	V_T ml	V_D/V_T	$\dot{V}_E$ ml/min	$\dot{V}_A$ ml/min	$\dot{V}_{Danat.}$ ml/min	V_{DP} ml	$V_{Danat.}$ ml	$V_{Dalv.}$ ml	$\dot{V}_A/\dot{V}_{O_2}$	% alveoli	
																Not per-fused	Not venti-lated
2	6	80	4.2	7.2	0.58	1.9	3.1	0.61	248	114	96	150	1.2	0.7	15.8	50	30
	40	65	9.9	12.8	0.81	4.7	7.8	0.61	507	244	286	306	4.4	0.3	19.1	5	15
4	10	41	6.3	7.2	0.88	4.3	6.9	0.62	283	135	164	172	4.0	0.3	18.8	5	40
	44	31	9.5	10.7	0.89	5.4	12.1	0.45	376	240	136	168	4.4	1.0	22.1	5	10
6	2	55	4.1	8.0	0.51	8.2	9.5	0.86	522	91		450			11.4		
	24	47	9.4	9.6	0.98	7.6	11.3	0.68	530	205		358			21.4		
	30	65	13.3	17.5	0.76	5.0	10.4	0.48	676	344	318	325	4.9	0.1	19.7	0	15
8	6	49	6.1	5.9	1.05	5.1	7.1	0.71	348	120	219	250	4.5	0.6	20.4	20	25
	26	44	9.4	11.2	0.84	8.5	12.4	0.69	548	208	361	374	8.2	0.3	18.6	0	30
	40	44	12.4	14.2	0.87	8.4	13.3	0.63	585	263	370	370	8.4	0.0	18.5	0	15
10	2	52	4.5	7.9	0.57	4.4	5.9	0.75	306	93	208	230	4.0	0.4	11.7	20	15
	5	44	5.7	8.1	0.70	5.4	8.2	0.66	361	152	236	236	5.4	0.0	18.8	0	10
	26	47	10.0	12.6	0.79	5.0	13.1	0.38	615	246	197	235	4.2	0.8	19.5	5	15
12	1	55	6.9	10.7	0.65	7.0	8.8	0.80	485	150	380	387	6.9	0.1	14.0	0	>50
	10	57	6.5	7.3	0.89	5.5	9.8	0.73	428	138	296	313	5.2	0.3	18.9	5	15
	24	44	8.9	10.6	0.84	7.0	12.1	0.58	410	202	295	308	6.7	0.3	19.0	5	5
15	13	59	7.9	8.9	0.89	9.5	11.6	0.82	684	153	523	560	8.9	0.6	17.2	10	7
	19	45	10.6	16.6	0.64	6.2	11.2	0.55	502	267	274	277	6.1	0.05	16.1	0	5
20	6	35	7.1	9.6	0.74	9.1	12.4	0.73	434	139	307	317	8.8	0.3	14.5	5	15
	15	30	11.1	15.9	0.70	2.8	2.8	0.32	265	215	84	84	2.8	0.0	13.5	0	10
22	8	68	8.7	13.0	0.67	6.5	8.5	0.77	580	163	374	442	5.5	1.0	12.5	20	50
	22	73	15.0	17.0	0.88	11.6	15.2	0.76	1110	298	725	850	9.9	1.7	17.4	30	25
24	1	72	11.2	22.9	0.49	10.5	12.5	0.84	906	179	550	706	7.6	2.7	16.0	>25	>50
	2	81	12.7	22.7	0.56	10.3	12.5	0.82	1012	219		830			17.2		
	3	45	14.4	23.7	0.61	6.4											
	5	46	12.1	19.3	0.63	9.8	14.5	0.68	620	236	268	455	5.8	3.0	19.5	25	30
	8	35	14.5	22.7	0.64	6.0	13.9	0.43	486	332	128	210	5.1	0.9	22.9	10	10

¹ See footnote 1 in table I for symbols.² At time of studies.

Fig. 1. Serial determination of uADN₂ in infants with birth weights under 1200 g. M.W. was an infant with Mikity-Wilson disease.

Fig. 2. Serial studies of uADN₂ in infants with birth weights over 1200 g. RDS infants had hyaline membranes disease. M.W. had Mikity-Wilson disease.

alveoli, with a similar number nonventilated, utilizing the method of SEVERINGHAUS and STUPPEL [6]. It should be emphasized that the sequence of relations is the result of several factors: increasing physical size of the lungs, changing $\dot{V}_A/\dot{Q}$ and metabolic rates, and respiratory rates.

Discussion

The data confirm the conclusions of previous studies [1] from this laboratory in which high values for AaDO₂ and aADCO₂ were exhibited in the smaller premature infants. The higher values for aADCO₂ reflected areas of increased ventilation-perfusion ratio, and the AaDO₂ values during air breathing indicated abnormalities in oxygenation as a result of shunting, diffusion, or alveoli with a low ventilation-perfusion ratio. An increased uADN₂ develops in alveoli with a low $\dot{V}_A/\dot{Q}$, and this test may thus be used to separate some of the compo-

Fig. 3. Serial studies of V_D/V_T in infants with and without hyaline membrane disease.

Fig. 4. Urinary-alveolar nitrogen gradient plotted with respect to alveolar-arterial oxygen gradient. Guide-lines indicate uADN₂ as a percent of simultaneously determined AaDO₂.

nents of AaDO₂. Large daily variations in uADN₂ were noted with a tendency toward lessening as the infant aged. The present data, together with the studies of THIBEAULT *et al.* [8], in which considerable prolonged

intrapulmonary shunting was demonstrated, indicate that there are at least two reasons for the high AaD_{O_2} in the premature infant: shunting and $\dot{V}_A/\dot{Q}$ unevenness. Analysis of the data shown in figure 4 indicates that a major component of the oxygen gradient is not due to $\dot{V}_A/\dot{Q}$ unevenness. The results are consistent with the concept that the infant has atelectasis or non-ventilated alveoli that gradually return to normal. These conclusions are in contradistinction to the opinion of LEDBETTER *et al.* [3] that in the full-term infant, the major component of AaD_{O_2} is $\dot{V}_A/\dot{Q}$ unevenness, although the studies of NELSON *et al.* [5] favor shunting to be the major abnormality. The possibility that part of the shunting is intracardiac (foramen ovale) cannot be excluded.

The expansion of the premature infant's lung from its initial fluid-filled state does not proceed in a smooth, orderly fashion. A pattern of extrauterine adaptation of the lungs, based on physiologic observation, is emerging. Initially, these infants have a large thoracic gas volume that decreases in the first week of life [9] and is associated with gas trapping [7], shunting [8], and ventilation-perfusion unevenness. As the lungs increase in size with the growth of the infant, atelectasis and shunting persist and pulmonary development progresses with evidence of areas of both high and low values for $\dot{V}_A/\dot{Q}$. Thus, the tendency of these small premature infants to develop respiratory difficulty from relatively minor stresses such as distended stomach and feeding is readily explicable on the basis of altered pulmonary physiology. Data on infants with hyaline membrane disease suggest, qualitatively at least, that they have many of the same defects.

Summary

The lung of the premature infant is not a physiologically homogenous organ with respect to ventilation and perfusion. Areas of high and low $\dot{V}_A/\dot{Q}$ contributing to aAD_{CO_2} and uAD_{N_2} , and atelectasis reflected in AaD_{O_2} , exist simultaneously. Overperfusion of poorly ventilated alveoli occurs as atelectasis resolves, but does not appear to be a major reason for the persistent AaD_{O_2} .

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