Ventilatory Response to Carbon Dioxide in Newborn Infants

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Extract

In order to determine whether the mechanical characteristics of the lungs of newborn infants imposed limitations on their ventilatory response to carbon dioxide, 11 premature and 5 full term infants ranging in gestational ages from 28–40 weeks and in birth weights from 964 to 4,040 g were studied by a rebreathing technique. Sensitivity to carbon dioxide determined by this method revealed a good correlation with compliance ($r = 0.6$, $P < 0.001$), and an even stronger correlation with gestational age ($r = 0.84$, $P < 0.001$). Because compliance also improved with increasing postconceptional age, the current study does not permit one to differentiate between neurologic or pulmonary mechanical factors which may affect ventilatory response to carbon dioxide.

Speculation

Infants who respond to carbon dioxide with an increase in minute ventilation should also increase their rate of pulmonary work. Failure of this work rate to increase in response to elevated carbon dioxide tensions may indicate that nonresponsive infants are already working at their maximum level of pulmonary work, and would thus permit differentiation of infants who have mechanical limitations to increased performance as opposed to those who lack chemoreflexes.

Apneic spells of greater than 15–20 sec duration are a frequent occurrence in infants of low birth weight (9). During these spells, oxygen tension falls, pH drops, and carbon dioxide tension rises. The presence of apnea under these conditions suggests either an absence of the reflexes which are normally sensitive to these modalities, or an inability of the lungs and muscles of respiration to increase ventilation because of mechanical limitations. Previous studies from this and other laboratories (8, 12) have demonstrated the presence of chemoreceptors to oxygen in all infants, including those of very low birth weights. Newborn infants also are capable of forming a cerebrospinal fluid of appropriate pH in order to maintain a normal respiratory compensation (7). Term and premature infants are able to increase their ventilation ($\dot{V}_E$) in response to increased tensions of carbon dioxide (1, 2, 4). However, it is believed by some that their response to CO_2 is diminished compared with adults because of an inability to maintain a normal CO_2 during stimulation of respiration with CO_2 (13). The present study was undertaken to determine whether a limitation of ventilatory response to CO_2 exists in the premature infant, and whether mechanical factors could account for the changes in the ventilatory response to CO_2 observed during the neonatal period.

METHODS

Sixteen infants, all of appropriate birth weight for gestational age, were the subjects of this study. Eleven (cases 1–11) were premature and ranged in birth weight from 964–1,700 g and in gestational age from 28–36 weeks. Five (cases 12–16) were born at term (approximately 40 weeks), and ranged in birth weight from 2,480–4,040 g. None were ill. All were studied with the knowledge and consent of their parents.

The maturity of infants is described in three ways. Postnatal age refers only to age after birth. Gestational age refers to age from conception to the time of birth, and is used only in connection with infants under 1 week of age. Postconceptional age refers to total age after conception, and includes both intrauterine and extrauterine maturation.

Serial studies were carried out on all premature infants beginning during the first week of life when possible, and at approximately weekly intervals thereafter. All infants were studied within 60 min of feeding. Environmental temperatures were maintained at 34–36° by the use of heat lamp or, in the case of the smaller infants, by incubator.

Functional residual capacity (FRC) was measured by the helium dilution method of Krauss and Auld (6). Total pulmonary compliance was calculated from simultaneous tracings of intraesophageal pressure, obtained with a pressure

Fig. 1. Rebreathing and sampling apparatus used in the present study.

Table 1. Clinical data on study patients¹

Case	Gesta- tional age, wk	Study age, days	Birth wt, g	Study wt, g	Study length, cm	Body surface area, m ²	FRC, cc	FRC, cc/cm	Compliance, ml/cm H ₂ O	Compli- ance/FRC, ml/cm H ₂ O/cc	Total pulmonary resistance	Baseline V _E ml/min	ΔV_E P _{CO₂} , ml/mm Hg	$\Delta \dot{V}_E$ /FRC/ P _{CO₂} , ml/cc/mm Hg	Frequency in room air	$\Delta f/\Delta P_{CO_2}$	V _T in room air, cc	ΔV_T / ΔP_{CO_2} , ml/mm Hg
1	28	53	964	1,790	46	0.205	66	1.43	1.26	0.019	112	1,376	57	1	74	-0.6	18.6	1.1
		60		2,080	46	0.273	65	1.41	2.36	0.036	84	1,393	118	2	86	-1.2	16.2	1.8
2	30	1	1,300	1,300	38	0.169	33	0.87	1.77	0.054	52	864	8	0.2	96	.9	9.0	0
		10		1,250	39	0.167	41	1.03	1.59	0.039	108	1,210	246	6	72	3.8	16.8	2.4
		17		1,380	40	0.183	44	1.09	1.02	0.023	97	1,057	59	1	85	-2.1	12.4	1.2
		34		1,710	43	0.225	41	0.95	1.50	0.037	65	1,601	354	9	88	4.5	18.2	2.5
3	30	1	1,300	1,300	40	0.175	41	1.03	1.98	0.048	155	620	-21	-0.4	56	-8.8	11.0	1.6
		9		1,230	41	0.171	69	1.68	1.58	0.023	107	1,006	-65	-1	85	-8.9	11.8	1.8
		37		1,650	41	0.212	69	1.68	1.57	0.023	98	1,719	496	7	90	2.3	19.0	4.7
		50		2,130	45	0.273	75	1.67	6.42	0.086		2,290	753	10	68	5.0	33.9	6.4
4	28	10	1,006	1,100	39	0.152	26	0.67	0.74	0.028	121	582	33	1	87	-3.5	6.7	0.5
		20		1,130	40	0.158	62	1.55	0.88	0.014	159	994	6	0.1	78	-4.0	12.6	1.3
		35		1,430	40	0.188	33	0.83	1.54	0.047	98	1,783	80	2	123	-5.0	14.3	3.3
		50		2,050	45	0.266	45	1.00	0.74	0.016	236	1,189	182	4	55	-3.8	21.5	3.5
5	29	2	1,180	1,190	35	0.149	11	0.31	1.36	0.124	219	748	-10	-1	87	-0.5	8.6	-0.1
		11		1,070	36	0.141	21	0.58	0.46	0.220	297	703	55	3	58	-0.5	11.8	0.7
6	28	1	1,020	1,049	38	0.145	56	1.47	2.13	0.038	190	428	28	0.7	41	0	10.8	0.8
		15		990	39	0.141	26	0.67	1.10	0.042	116	387	79	3	51	0	7.4	1.7
		49		1,230	41	0.171	51	1.24	1.70	0.033	177	1,157	349	7	60	3.4	19.3	4.3
7	34	1	1,920	1,920	44	0.249	42	0.95	2.22	0.053	59	1,061	149	4	87	-0.4	12.2	1.5
		9		1,860	44	0.243	56	1.27	1.82	0.033	47	988	102	2	68	-2.3	14.5	2.0
8	34	5	1,700	1,560	43	0.211	41	0.95	2.16	0.053	106	995	155	3	60	3.7	16.6	0.6
		12		1,620	44	0.220	59	1.34	2.29	0.039	112	765	140	2	42	0.9	18.0	1.8
		26		1,900	45	0.251	67	1.49	1.28	0.019	98	1,522	231	4	67	4.3	22.7	1.2
9	36	1	1,580	1,580	43	0.213	37	0.84	4.35	0.118	23	378	108	3		0.5		1.3
		10		1,600	44	0.218	42	0.95	1.57	0.038	144	752	55	1	62	-0.4	12.0	1.2
		18		1,890	45	0.250	58	1.29	2.63	0.045		938	49	0.8	61	-1.0	15.3	1.0
10	35	2	1,580	1,615	41	0.209	54	1.32	1.66	0.031	99	983	21	0.3	68	1.9	14.5	-0.1
		10		1,600	42	0.211	56	1.33	2.10	0.038	81	950	109	2	50	-0.2	18.7	2.1
		21		1,960	44	0.253	78	1.77	2.02	0.026	63	1,204	209	3	56	2.1	21.5	2.3
11	36	1	1,660	1,660	42	0.217	55	1.31	1.53	0.028	40	654	123	2	83	1.7	7.9	1.4
		9		1,580	44	0.216	53	1.20	2.14	0.040	75	785	171	3	41	-0.2	19.1	3.3
		29		2,200	47	0.288	66	1.40	2.85	0.043		1,597	415	6	50	-1.3	32.3	6.8
12	40	4	2,520	2,450	45	0.302	112	2.49	7.12	0.064	32	1,669	469	4	78	2.4	21.4	5.0
13	40	2	3,200	3,020	51	0.385	71	1.39	3.46	0.049	74	1,306	479	7	52	6.1	25.4	5.5
14	40	10	2,750	2,480	48	0.319	42	0.88	2.73	0.065	54	992	268	6	47	1.5	20.6	4.4
15	40	3	4,180	4,040	51	0.476	95	1.86	5.59	0.059	125	1,432	187	4	70	2.0	20.8	2.5
16	40	1	3,250	3,150	46	0.188	87	1.89	3.87	0.044	52	1,854	400	2	71	4.0	26.0	4.6

¹ FRC: functional residual capacity; FRC, cc/cm = cubic centimeters of FRC per centimeter of body length; $\dot{V}_E$ = minute volume; $\Delta V_E/\Delta P_{CO_2}$ = change in minute volume per mm Hg P_{CO₂}; frequency in room air = breaths per minute; $\Delta f/\Delta P_{CO_2}$ = change in frequency/mm Hg P_{CO₂}; V_T = tidal volume in cubic centimeters; $\Delta V_T/\Delta P_{CO_2}$ = change in tidal volume per mm Hg P_{CO₂}.

transducer attached to a water-filled, open-ended polyethylene feeding tube, and tidal volume, obtained with a pediatric wedge spirometer. Total pulmonary resistance was calculated from simultaneous tracings of intraesophageal pressure and respiratory flow using the same apparatus. The infant breathed into the spirometer through a rubber-rimmed face mask covering both nose and mouth. The mask was attached to the spirometer with stiff polyethylene tubing with no measurable resistance. Recordings were made on a 4-channel polygraph (14). Calculations of resistance and compliance were made from tracings of 6–10 breaths during quiet spontaneous respiration according to the method of Cook and colleagues (3). Volume was calibrated using a syringe of known volume. Pressure was calibrated with a water-filled manometer. Flow was calibrated electronically.

Ventilatory response was determined by the method of Read (11), allowing the patient to rebreathe 40% oxygen and 5% carbon dioxide in a bag with a volume approximately equal to that of the patient's FRC. Tidal volume was measured with a pneumotachygraph mask with a resistance of 1.0 cm H₂O/liter/sec (Fig. 1). Flow through this mask was electronically integrated to give volume. Gas was sampled from the mask at the infant's nose and recirculated via an infrared CO₂ meter (15). The polygraph was used to obtain a simultaneous tracing of tidal volume and end-tidal carbon dioxide. The carbon dioxide built up at a rate of 1–1.5%/min. Leaks were manifest as an acute fall in the continuous CO₂ tracing; when this occurred the run was abandoned. Using the method of least squares tidal volume, respiratory frequency (*f*), and minute volume ($\dot{V}_E$) were plotted against end-tidal CO₂. Four or five points obtained at 30-sec intervals were obtained for the construction of each plot. The slope of the plot, $\Delta\dot{V}_E/P_{CO_2}$, represents the CO₂ sensitivity. All data are presented in Table 1. In addition, the data was analyzed in respect to body weight (in kilograms) and FRC to determine the effect of infant size.

RESULTS

A significant correlation between CO₂ sensitivity and compliance ($r = 0.60$, $P < 0.001$) was found when all data were pooled. No correlations between specific compliance ($r = 0.005$) and total pulmonary resistance ($r = 0.37$) and CO₂ sensitivity were found.

When data from individual infants were examined, the correlations between CO₂ sensitivity and compliance were less apparent. Some infants showed increases in CO₂ sensitivity despite little or no change in the mechanical characteristics of their lungs (cases 2, 4, 6, 8, and 10). This led to an examination of the relation between CO₂ sensitivity and age. In general, increased CO₂ sensitivity was seen with both increasing postnatal age (Fig. 2) and postconceptional age (Fig. 3). Infants studied after 37 weeks' postconceptional age had 6 times the CO₂ sensitivity of infants studied at less than 33 weeks' postconceptional age (262 cc/min/mm Hg versus 38 cc/min/mm Hg, $P < 0.005$). These differences are listed in Table 2, along with data sized by body weight and FRC.

In order to separate the effects of extrauterine development from intrauterine maturation, all infants studied at under 1 week of postnatal age were compared after being separated into groups by gestational age. CO₂ sensitivity showed a highly significant correlation with gestational age ($r = 0.84$, $P < 0.001$). These data are presented in Figure 4.

When change in minute volume per kilogram of body weight or per cubic centimeter of FRC was plotted against P_{CO_2} , less mature infants continued to show a significantly diminished response to CO₂ than more mature infants (Figs. 5–7). Correlations with various physical and maturational variables are listed in Table 3.

Fig. 2. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) versus postnatal age in days in infants of differing maturity.

Fig. 3. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) versus postconceptional age in weeks in infants of differing maturity.

Thirteen of the 16 infants studied had determinations of blood gases; all were within normal limits at the time of study.

Infants 2–5 and 10 were found to have essentially no increase in minute volume in response to increased CO₂ during the first week of life, as indicated by a reduced slope ($\Delta\dot{V}_E/P_{CO_2}$). In three of these cases (2, 4, and 5), tidal volume did not increase in response to increased CO₂. Tidal volume fell in cases 5 and 10. Case 3 showed a fall in respiratory rate, which is reflected in a reduced $\dot{V}_E$.

Table 2. CO₂ sensitivity versus postconceptional age in weeks¹

Postconceptional age, wk	Unsize				Sized by body wt, kg				Sized by FRC, cc			
	Mean $\Delta\dot{V}_E/P_{CO_2}$, ml/min/mm Hg	SD	SE	P	Mean $\Delta\dot{V}_E/kg/P_{CO_2}$, [(ml/min)/kg]/mm Hg	SD	SE	P	Mean $\Delta\dot{V}_E/FRC/P_{CO_2}$, [(ml/min)/cc]/mm Hg	SD	SE	P
< 33 wks n = 13	44	79	22	< 0.01	22	40	12	< 0.01	1.3	2.0	0.6	< 0.05
33–36 wks n = 13	174	138	38		106	96	27		3.4	2.6	0.7	
37–40 wks n = 13	292	201	55		127	90	25		4.0	2.6	0.7	

¹ FRC: functional residual capacity. Fig. 4. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) measured during the first week after birth in infants of 28–32 weeks, 34–36 weeks, and 40 weeks of gestational age.

DISCUSSION

The present study demonstrates that premature infants of less than 33 weeks' gestational age have reduced ventilatory response to inspired carbon dioxide. Sensitivity to inspired CO₂ appears to increase as 40 weeks' postconceptional age is approached. This effect appears to be strongly related to postconceptional age, since more mature infants have a higher CO₂ response even during the first week of life.

Less mature infants tend to have smaller lung volumes and lower body weights than more mature infants. When changes in minute volume per millimeter of CO₂ are expressed in terms of body size (length, weight, or lung volume), less mature infants still exhibit a diminished response to carbon dioxide when compared with term infants. Therefore, data from this study indicate a maturational effect independent of body size alone.

Although CO₂ sensitivity correlates well with pulmonary compliance ($r = 0.6$), the effects of increased pulmonary compliance on CO₂ response cannot be separated from those of age alone. Pulmonary compliance increases with postconceptional and postnatal ages. Thus, the roles of pulmonary and neurologic maturity cannot be separated in this study.

A significant finding was the failure of some infants to

increase either tidal volume or respiratory rate during CO₂ rebreathing. It has been suggested that the CO₂ response of an individual is related to the ability to perform increased pulmonary work (5, 10). The data obtained in this study of premature infants suggest that the infants who appear to be unresponsive to CO₂ are either (1) performing respiratory work at the maximum rate possible or (2) truly lack reflexes for CO₂ sensitivity. Since chemoreceptors for oxygen appear

Fig. 5. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) per kilogram of body weight versus postnatal age in days. Fig. 6. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) per kilogram of body weight versus postconceptional age in weeks.

Fig. 7. Ventilatory response to carbon dioxide ($\Delta\dot{V}_E/P_{CO_2}$) per kilogram of body weight during the first week of life in infants of 28–32 weeks, 34–36 weeks, and 40 weeks of gestational age.

Table 3. Response to CO_2 ¹

$\Delta\dot{V}_E/\Delta P_{CO_2}$ with	r	P
Gestational age	0.84	<0.001
Compliance	0.6	<0.001
Postconceptional age	0.55	<0.001
FRC (total)	0.5	<0.005
Body weight (kg)	0.5	<0.005
Body length (cm)	0.47	<0.01
Postnatal age	0.37	<0.05
Total pulmonary resistance	0.37	<0.05
Specific compliance	0.005	

¹ FRC: functional residual capacity.

to be present in the most immature infants (8, 12), one might reason that nonresponsive infants lack the ability to increase their pulmonary work. This matter awaits further investigation.

SUMMARY

Premature infants were found to have a reduced sensitivity to carbon dioxide when compared with term infants.

Sensitivity increased with postnatal age, body size, lung volume, and pulmonary compliance. Reduced sensitivity remained when all infants were compared on a weight or lung volume basis. This suggests a maturational effect unrelated to body size.

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16. Dr. A. N. Krauss is recipient of a fellowship from the Tuberculosis and Respiratory Disease Association of New York and a travelling fellowship, Royal Society of Medicine Foundation.
17. Dr. P. A. M. Auld was supported by United States Public Health Service Research Grant no. HD-02644.
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19. Accepted for publication July 31, 1974.