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Hyperoxia preterm infants
hypoxia ventilatory response

Immediate and Late Ventilatory Response to High and Low O_2 in Preterm Infants and Adult Subjects

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Summary

The differences in the immediate (30 sec or 1 min) and late (5 min) ventilatory response to high and low O_2 have not been quantitated in preterm infants and adult subjects using the same methods. It was thought that these differences might explain the paradoxical ventilatory response to CO_2 at various O_2 concentrations in preterm infants (12). Thus, 9 preterm infants and 10 adult subjects were given 21% O_2 to breathe and then 100 or 15% O_2 for 5 min each. Adults also breathed 15% O_2 before 100% O_2 or 12% O_2 in order to make their resting arterial PO_2 more comparable to those of infants breathing 21% O_2. The ventilatory response to 100% O_2 was the same in preterm infants and adult subjects, but the late response to 15% O_2 remained paradoxical, ventilation decreasing at 5 min by 18% in infants and increasing by 19% in adults. The authors conclude: 1) the traditional concept of the ventilatory response to 100% O_2 being different in infants and adult subjects is false; 2) the notion that the response to low O_2 is paradoxical in infants is correct; and 3) the data do not explain why the response to CO_2 under various background concentrations of O_2 in infants is the reverse of that in adult subjects, but the depressed ventilatory response to hypoxia in infants may justify, at least in part, their flatter response to CO_2 during low O_2 breathing.

Speculation

The findings suggest that the response of preterm infants to high and low O_2 per se is not the cause of the paradoxical response to CO_2 under various background concentrations of O_2. If it were, it would be expected that the response to low and high O_2 would differ in infants and adults. This was true for hypoxia only, the response to hyperoxia being the same in infants and adults. The speculation, therefore, is that differences in cerebral blood flow caused by CO_2 and O_2 interaction may be responsible for the paradoxical response to CO_2.

It has been shown that the ventilatory response to CO_2 in preterm infants at various background concentrations of O_2 is the reverse of that in adult subjects. In preterm infants, the higher the inspired O_2 concentration, the flatter is the response to CO_2 (12). Because the ventilatory response to CO_2 per unit of body is similar in preterm infants and adult subjects during normoxia (2, 7, 13), the difference in response may be related to the distinctive effects of inhalation of high and low O_2 on ventilation in small infants. Traditionally, these differences have been accepted (4, 5, 8, 10, 11), yet they have never been appropriately defined using the same methods. It was decided, therefore, to investigate the nature and amount of these differences by devising a breathing system for adults, similar to the one used for preterm infants (9). It was surprising to discover that contrary to conventional teaching, the response to hyperoxia was essentially the same in adult subjects and preterm infants, and the only difference was the response to hypoxia, which remained paradoxical in infants.

SUBJECTS AND METHODS

SUBJECTS

We compared the results obtained in nine "healthy" preterm infants studied during the first 8 days of life with those of 10 healthy adult subjects studied at a mean age (±SE) of 27 ± 3 yr. Infants had a mean gestational age (±SE) of 33.5 ± 0.5 weeks and mean birth weight of 1490 ± 80 g. Adult subjects had a mean weight of 65 ± 5 kg.

METHODS

The system to measure ventilation has been described previously (1, 9, 10). Briefly, in infants we used a nosepiece and screen flowmeter to measure respiratory minute volume and alveolar gases. We eliminated valves and reduced dead space by using a constant background flow which was electrically balanced to an artificial zero. The infant breathed through the nostril adapters and added to (expiration) or substracted from (inspiration) the background flow. The flow signal was electrically integrated to give volume.

Breath to breath PO_2 and PCO_2 was monitored as outlined elsewhere (12). In adults, a similar system was used with the following differences: 1) the background flow was 30 liter/min instead of 2.7 liter/min; 2) a Fleisch pneumotach no. 4 was used instead of the Monel screen flowmeter; and 3) a mouthpiece replaced the nostril adapters.

Infants were studied on the Ohio Neonatal Intensive Care Unit shortly after a feed. Abdominal skin temperature was kept at 36.5 ± 0.03°C. Xylocaine ointment was used to anesthetize the skin around the nostrils and to provide an airtight seal around the nostril adapters. After breathing 21% O_2, they were given 100% O_2 for 5 min each. Breathing was allowed to return to control levels on 21% O_2, and then 15% O_2 was given for 5 min.

Adult subjects were studied after a light meal, sitting comfortably, breathing through the mouthpiece and having the nostrils closed with a nose clip. Similarly to infants, they breathed 21% O_2, then 100% O_2 for 5 min each. When breathing returned to control levels on 21% O_2, 15% O_2 was given for 5 min. In addition, adults also breathed 15% O_2 as the control mixture before 100 or 12% O_2, in order to make their resting arterial PO_2 more comparable to those of preterm infants breathing 21% O_2. That this was achieved, was shown by measurements of arterial PO_2 in radial samples taken from two adult subjects. The order of administration of the various O_2 mixtures was randomized without prior knowledge of the subjects. Alveolar PCO_2 was kept within ± 3 mm Hg of control values. A presentative tracing is shown in Figure 1.

We used the paired *t* test to characterize the significance of the differences in minute ventilation during control and during high and low O_2 breathing. The unpaired *t* test was used to define the significance of the differences between the responses of infants and adult subjects.

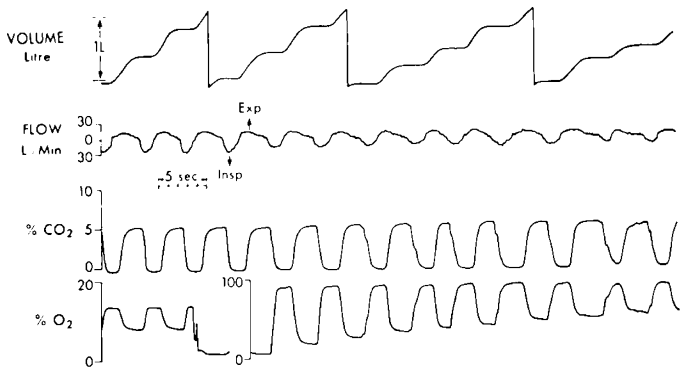

Fig. 1. Representative tracing in adult subject when 100% O_2 was abruptly substituted for 21% O_2. Note the immmediate decrease in ventilation with 100% O_2.

RESULTS

Results are summarized in Table 1. In infants, with 21% O_2 as the control gas mixture, the immediate response to 100% O_2 was a 26% decrease in $\dot{V}_E$ ($P < 0.05$) (Fig. 2); the immediate response to 15% O_2 was a 15% increase in $\dot{V}_E$ ($P < 0.05$) (Fig. 3). Adults showed a similar response, but the immediate decrease in ventilation with 100% O_2 was only 10% ($P < 0.05$). When adults breathed 15% O_2 before 100% O_2, the immediate decrease in ventilation was 24%, practically the same as that in infants (Fig. 4).

The late response (5 min) to 100% O_2 was essentially the same in infants and adult subjects, no matter what the control O_2 concentration was. The late response to hypoxia, however, showed a sustained hyperventilation in adult subjects. This was more pronounced (41 *vs.* 4%) when the control O_2 concentration was 15% instead of 21% O_2 (Figs. 3 and 5). Infants invariably depressed their respiratory minute volume with 15% O_2, the average being 18% ($P < 0.05$).

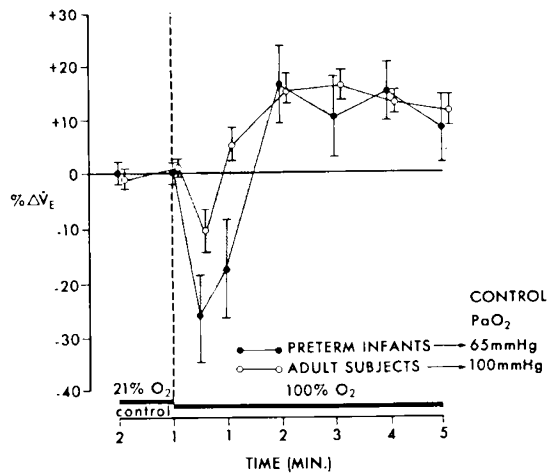

Fig. 2. Percent change in ventilation when 100% O_2 was substituted for 21% O_2 in preterm infants (*closed circles*) and adult subjects (*open circles*). Note that the biphasic response was similar except for the more pronounced decrease in ventilation in preterm infants immediately after change in inspired gas.

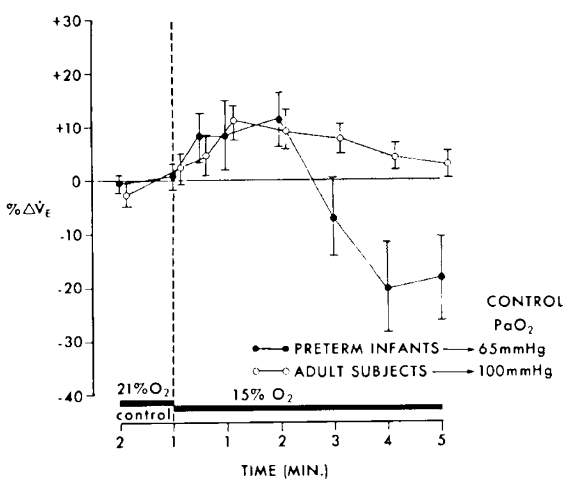

Fig. 3. Percent change in ventilation when 15% O_2 was substituted for 21% O_2 in preterm infants (*closed circles*) and adult subjects (*open circles*). Note that the immediate response was the same in both groups. Preterm infants, however, did not sustain hyperventilation and ventilation decreased towards the end of 5 min on 15% O_2.

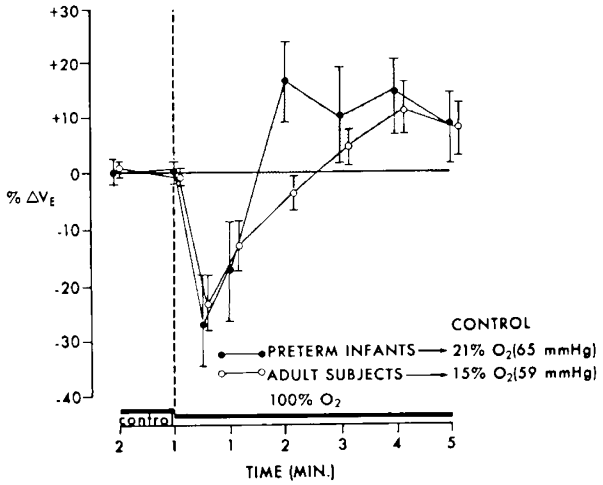

Fig. 4. Percent change in ventilation when 100% O_2 was substituted for 21% O_2 in preterm infants (*closed circles*) and 15% O_2 in adult subjects (*open circles*). Note that when the control resting PaO_2 were matched, the immediate response to 100% O_2 was essentially the same in infants and adult subjects.

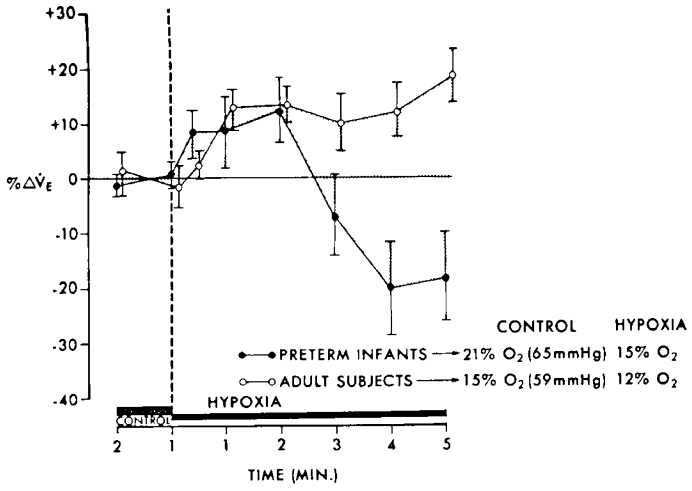

Fig. 5. Percent change in ventilation when 15% O_2 was substituted for 21% O_2 in preterm infants (*closed circles*) and 12% O_2 substituted for 15% O_2 in adult subjects (*open circles*). Hyperventilation is more sustained in adults and the paradoxical response to hypoxia remained in preterm infants.

Table 1. *Ventilatory response of preterm infants and adult subjects to high and low O_2 concentrations*

Preterm infants									Adult subjects																	
	$\dot{V}_E$ (liter/min/kg)									$\dot{V}_E$ (liter/min/kg)									$\dot{V}_E$ (liter/min/kg)							
	100% O_2				15% O_2					100% O_2				15% O_2					100% O_2				12% O_2			
Infants	Control[1]	30 sec	1 min	5 min	Control[1]	30	1	5	Adults	Control[1]	30	1	5	Control[1]	30	1	5	Control[2]	30	1	5	Control[2]	30	1	5
1.	0.248	0.201	0.219	0.211	0.232	0.243	0.221	0.240	1.	0.101	0.080	0.098	0.106	0.086	0.100	0.108	0.090	0.090	0.058	0.059	0.114	0.092	0.090	0.110	0.119
2.	0.395	0.406	0.407	0.354	0.215	0.262	0.216	0.241	2.	0.138	0.153	0.150	0.180	0.149	0.141	0.156	0.142	0.143	0.114	0.141	0.168	0.144	0.142	0.164	0.158
3.	0.228	0.157	0.190	0.222	0.191	0.187	0.186	0.175	3.	0.101	0.075	0.099	0.116	0.098	0.118	0.105	0.103	0.102	0.085	0.086	0.116	0.140	0.134	0.148	0.156
4.	0.278	0.078	0.120	0.255	0.170	0.221	0.209	0.091	4.	0.115	0.120	0.130	0.121	0.126	0.120	0.132	0.121	0.132	0.098	0.115	0.132	0.138	0.151	0.149	0.151
5.	0.284	0.210	0.298	0.359	0.205	0.221	0.213	0.155	5.	0.095	0.085	0.094	0.111	0.113	0.119	0.127	0.114	0.109	0.088	0.106	0.098	0.142	0.148	0.164	0.184
6.	0.293	0.218	0.296	0.290	0.189	0.162	0.215	0.178	6.	0.097	0.097	0.119	0.112	0.089	0.091	0.090	0.092	0.088	0.099	0.095	0.118	0.152	0.168	0.179	0.169
7.	0.326	0.258	0.201	0.457	0.120	0.137	0.175	0.097	7.	0.102	0.085	0.107	0.102	0.128	0.135	0.132	0.113	0.116	0.073	0.094	0.115	0.147	0.153	0.159	0.169
8.	0.268	0.288	0.308	0.313	0.368	0.405	0.405	0.168	8.	0.134	0.111	0.121	0.136	0.131	0.106	0.134	0.150	0.133	0.105	0.130	0.121	0.126	0.115	0.139	0.143
9.	0.305	0.145	0.131	0.380	0.228	0.245	0.216	0.177	9.	0.112	0.105	0.122	0.121	0.119	0.142	0.150	0.134	0.138	0.074	0.093	0.135	0.122	0.111	0.127	0.165
									10.	0.106	0.083	0.112	0.124	0.096	0.103	0.117	0.102	0.109	0.088	0.094	0.117	0.170	0.194	0.206	0.194
Mean	0.292	0.218	0.241	0.316	0.213	0.230	0.228	0.169		0.110	0.099	0.115	0.123	0.114	0.118	0.125	0.116	0.116	0.088	0.101	0.123	0.137	0.141	0.155	0.161
±SE	±0.016	±0.031	±0.031	±0.027	±0.022	±0.026	±0.023	±0.017		±0.005	±0.008	±0.005	±0.007	±0.007	±0.006	±0.007	0.007	±0.006	±0.005	±0.007	±0.006	±0.007	±0.010	±0.009	±0.007
P		<0.01	0.05	N.S.		<0.05	0.05	0.05			<0.025	N.S.	0.005		N.S.	<0.005	N.S.		<0.01	<0.01	N.S.		N.S.	<0.001	<0.001

[1] Control = 21% O_2.
[2] Control = 15% O_2.

DISCUSSION

It was found that the immediate and late ventilatory response to 100% O_2 was essentially the same in preterm infants and adult subjects. This was more obvious when adults breathed 15% O_2 as the control gas mixture. On the other hand, the late ventilatory response to hypoxia differed substantially in both groups, infants hypoventilating and adults sustaining their initial hyperventilation. These findings suggest 1) the traditional concept that the ventilatory response to 100% O_2 differs in infants and adults is false; 2) the notion that the response to low O_2 is paradoxical in infants is correct; 3) the data do not explain why the response to CO_2 in 100% O_2 in infants should be the opposite of that in adult subjects; and finally, 4) the depressed response to hypoxia may explain, at least in part, the flat response to CO_2 in infants as compared to adult subjects.

The surprising finding of this study was the similarity of the ventilatory response to 100% O_2 in infants and adult subjects. Why should this be the case, when so many have postulated that this response is different in infants and adults (4, 5, 8, 11)? The answer seems to lie in the fact that no one has ever looked at the response under similar experimental conditions. Moreover, most of the studies concerning the ventilatory response to 100% O_2 are old and deal with the overall response rather than min by min changes (6–8). In studies done by Lambertsen (7) and coworkers, the biphasic response, *i.e.*, a depression followed by a slight hyperventilation, was present in most of their adult subjects. Dripps and Comroe (6) did not analyze in detail the immediate response, but the response in their adult subjects showed that late hyperventilation was present. Purves (8) showed that some newborn lambs did hyperventilate, some did not. So, it seems that the "traditional" differences, never remarkable, were quantitative rather than qualitative. This study, using similar methods, suggests that such differences do not exist.

Similarity of the immediate response to 100 and 15% O_2 in infants and adult subjects suggests that both have well developed peripheral chemoreceptors. This has been traditionally accepted (4, 5, 11). The unanswered question so far is why preterm infants depress ventilation with hypoxia while adults show sustained hyperventilation. This is unknown. The authors and others have suggested that, in infants, the central effects of hypoxia overrule the peripheral stimulant effects (3, 5, 11). But why did this not occur in adults, even when resting control PaO_2 (65 mm Hg in infants and 57 mm Hg in adults) were similar and the hypoxic challenge of the same magnitude? It is unlikely that minor differences in O_2 delivery to the tissues related to the slight decrease in P_{50} due to the presence of fetal hemoglobin in the immediate neonatal period could account for the paradoxical response to hypoxia (14). Information regarding the mechanisms of action of O_2 on the central respiratory neurones may help to unravel the reason for this paradoxical response.

These findings were not gratifying in terms of explaining why in preterm infants the CO_2 response curve under various background concentrations of O_2 in preterm infants is the opposite of that in adult subjects (12). The response to 100% O_2 being similar, some other factor, maybe dependent on the interaction of CO_2 and O_2, should be responsible for the differences observed. The depressed response to O_2 may, in part, explain the flatter response to CO_2 under hypoxia in infants as compared to adults.

CONCLUSION

The ventilatory response to high and low O_2 in preterm infants and adult subjects was measured. The authors found that the response to hyperoxia was the same in infants and adults. The response to hypoxia, however, remained paradoxical in infants. It is suggested that: 1) the traditional concept of the response to hyperoxia being different in preterm infants and adult subjects is false; and 2) the response to high O_2 cannot explain the reversed response to Co_2, but the paradoxical response to O_2 may be partially responsible for the depressed response to Co_2 during hypoxia.

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