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# Speed and Profile of the Arterial Peripheral Chemoreceptors as Measured by Ventilatory Changes in Preterm Infants

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**ABSTRACT. To measure the response time of the peripheral chemoreceptors, we studied 13 preterm infants [birth weight 1602 ± 230 g (mean ± SEM); gestational age 31 ± 1 wk; postnatal age 15 ± 1 d] during inhalation of 21% $O_2$ (15 ± 5 s) followed by 100% $O_2$ (1 min). We used a flow-through system to measure ventilation and gas analyzers to measure alveolar gases. Hypoventilation was observed at 3.6 ± 0.6 s and was maximal at 6.8 ± 1 s after $O_2$ began. This maximal response was always associated with an apnea (>3 s). Alveolar $P_{O_2}$ increased from 13.5 ± 0.1 kPa (101 ± 0.8 torr) (control) to 28.0 ± 1.2 kPa (210 ± 9 torr) (1st $O_2$ breath), to 42.0 ± 2.4 kPa (315 ± 18 torr) (1st hypoventilation), to 45.9 ± 4.1 kPa (344 ± 31 torr) (breath preceding maximal response), and to 53.6 ± 4.1 kPa (402 ± 31 torr) (at maximal response). Minute ventilation was 0.192 ± 0.011 (control), 0.188 ± 0.011 (1st $O_2$ breath), 0.088 ± 0.016 (1st hypoventilation; $p < 0.0001$), 0.122 ± 0.016 (breath preceding maximal response; $p < 0.0002$), and 0.044 ± 0.011 L/min/kg at maximal response ($p < 0.0001$). This decrease in ventilation was due to a decrease in frequency with no appreciable change in tidal volume. The initial period of hypoventilation (19 ± 4 s) was followed by a breathing interval (10 ± 2 s) and a second period of hypoventilation (14 ± 3 s) before continuous breathing resumed. These findings suggest that the peripheral chemoreceptors in these infants have a high baseline activity and a fast response time. (*Pediatr Res* 32: 226–229, 1992)**

Previous studies in preterm infants have shown that there is an immediate decrease followed by an increase in ventilation in response to inhalation of 100% $O_2$ (1–4). This immediate decrease in ventilation, usually associated with apnea, is traditionally attributed to the effect of $O_2$ on the peripheral chemoreceptors, producing what Julius Comroe (5) used to call the physiologic denervation of the peripheral chemoreceptors.

Because of the sharp breathing response to inhaled $O_2$ in these infants, we thought we could measure the response time of the peripheral chemoreceptors. Therefore, the purpose of our study was to test the hypothesis that the speed of the peripheral chemoreceptor response could be determined in "healthy" preterm infants by measuring the changes in ventilation induced by inhalation of 100% $O_2$.

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## MATERIALS AND METHODS

*Subjects.* We studied 13 healthy preterm infants with a birth weight of 1602 ± 230 g (mean ± SEM), a study weight of 1652 ± 260 g, a gestational age of 31 ± 1 wk, and a postnatal age of 15 ± 1 d. The study was approved by the faculty committee on the use of human subjects in research, University of Manitoba, and written parental consent was obtained from one of the parents.

*Methods.* We have previously described the system to measure ventilation (6, 7). Briefly, we used a nosepiece and a screen flowmeter to measure respiratory minute volume and alveolar gases. We used a constant background flow (3 L/min) to eliminate valves and to reduce dead space. The infant breathed through the nostril adapters and added to (expiration) or subtracted (inspiration) flow from the background flow. This background flow was electrically balanced to an artificial zero.

We monitored breath-to-breath alveolar $P_{O_2}$ and $P_{CO_2}$ using Beckman analyzers. The 95% rise times of the analyzers were 0.16 and 0.18 s for $CO_2$ and $O_2$, respectively. The EEG was monitored using a single channel with an electrode placed in the right frontal position and referenced to the left mastoid. The electrooculogram was recorded from eye electrodes referenced to the right ear. Oxygen saturations and ECG were used to monitor the infant's well-being but not as an end point of this study. Sleep state was monitored according to previous criteria (4). All variables were recorded on a polygraph (model 4221, Nihon Kohden, Tokyo, Japan).

*Procedure.* Infants were studied on the Ohio Neonatal Intensive Care Unit (Ohio Medical Products, Madison, WI) in a neutral thermal environment with skin abdominal temperature at 36.5 ± 0.03°C. After appropriate placement of the various electrodes and the nosepiece, infants were allowed to sleep. Once they had been in quiet sleep breathing 21% $O_2$ for 2 min, 100% $O_2$ was given for 1 min. Minute ventilation, tidal volume, frequency, alveolar $P_{O_2}$, alveolar $P_{CO_2}$, inspiratory drive, and the "duty cycle" were measured breath by breath during 21% $O_2$ (15 ± 5 s) and during 100% $O_2$ (1 min).

*Data collection and analysis.* We analyzed the records by hand and transferred the data to a computer for appropriate treatment. Control values were taken from the last eight breaths preceding the administration of $O_2$. The speed of the response was measured from the initiation of inspiration immediately after the increase in fraction of inspired $O_2$. We used a paired $t$ test to assess the significance of the differences between control values and those obtained in response to 100% $O_2$. To find the 1st breath after 100% $O_2$ showing hypoventilation, we used a variation of the

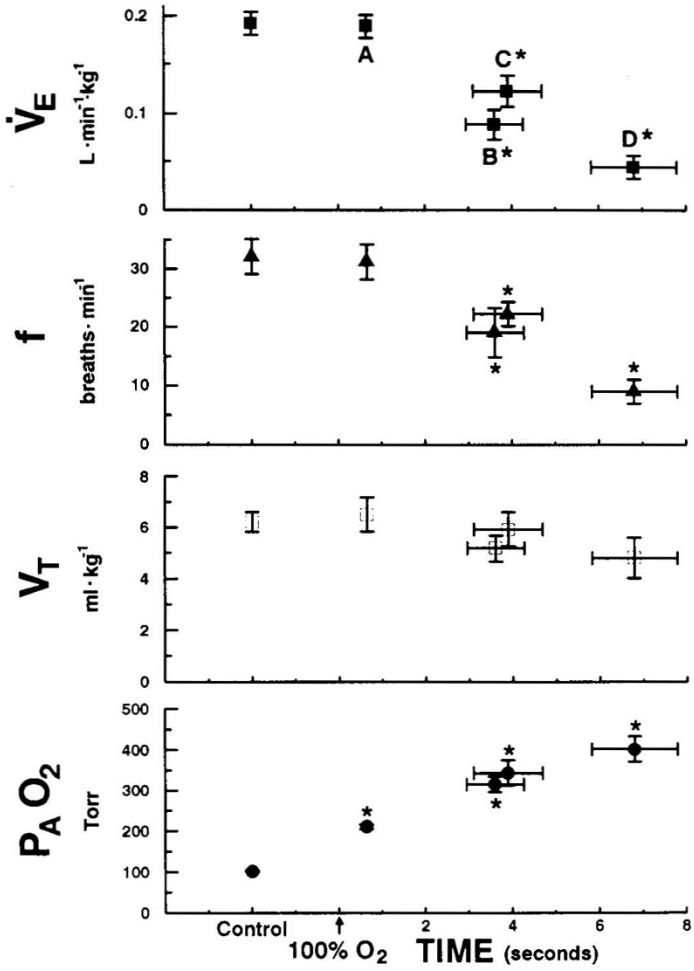


Fig. 1. Changes in ventilatory variables in response to 100% $O_2$. Hypoventilation occurred shortly after inhalation of 100% $O_2$ began (3.6 ± 0.6 s) and preceded the maximal response (apnea), which occurred at 6.8 ± 1 s. Values are mean ± SEM. *A*, 1st breath in 100% $O_2$; *B*, 1st breath with hypoventilation; *C*, breath preceding maximal response; *D*, maximal response (kPa = torr × 0.1333). $\dot{V}_E$, minute ventilation; f, frequency; $V_T$, tidal volume; and $P_AO_2$, alveolar $P_{O_2}$.

paired *t* test named "the comparison of a single value into the mean of the sample" (8). Analysis of variance and Fisher's least significant difference test were used to test the significance of the differences among values obtained during each cycle of hypoventilation and breathing observed in most babies after 100% $O_2$. Results are expressed as mean ± SEM. A probability value equal to or less than 0.05 was considered significant.

## RESULTS

With inhaled $O_2$, alveolar $P_{O_2}$ increased from 13.5 ± 0.1 kPa (101 ± 0.8 torr) (control) to 28.0 ± 1.2 kPa (210 ± 9 torr) (1st $O_2$ breath), to 42.0 ± 2.4 kPa (315 ± 18 torr) (1st hypoventilation), to 45.9 ± 4.1 kPa (344 ± 31 torr) (breath preceding maximal response), and to 53.6 ± 4.1 kPa (402 ± 31 torr) (at maximal response) (Fig. 1, Table 1).

The inhalation of 100% $O_2$ was associated with an immediate decrease in ventilation at 3.6 ± 0.6 s (mean ± SEM) from 0.192 ± 0.011 (control) to 0.088 ± 0.016 L/min/kg (1st breath with hypoventilation, $p < 0.0001$). The maximal response was seen at 6.8 ± 1 s, with minute ventilation decreasing to 0.044 ± 0.011 L/min/kg ($p < 0.0001$) (Fig. 1, Table 1). This decrease in ventilation was due to a decrease in frequency from 32 ± 3 (control) to 19 ± 4 breath/min (1st breath with hypoventilation; $p < 0.0001$) and to 9 ± 2 breath/min at maximal response ($p < 0.0001$). There was no appreciable change in tidal volume (Fig. 1, Table 1). The maximal response was always associated with an apnea (> 3 s). This initial hypoventilation had a duration of 19 ± 4 s. It was followed by a breathing interval of 10 ± 2 s and a second apnea or hypoventilation of 14 ± 3 s before continuous breathing resumed (Figs. 2 and 3). The two periods of hypoventilation were significantly different from control and the two recovery periods ($p < 0.05$). This was due to a decrease in frequency with no change in tidal volume. The inspiratory drive did not change during the period leading to maximal hypoventilation and the duty cycle decreased as a consequence of an increase in expiratory time (Table 1). The increase in alveolar $P_{O_2}$ was fast, reaching levels of about 27 kPa (200 torr) during the first 2 s of 100% $O_2$ (Fig. 1).

## DISCUSSION

We found that the decrease in ventilation with 100% $O_2$ was very fast, occurring within the first three breaths after 100% $O_2$ began. This decrease in ventilation was related to a decrease in frequency with no appreciable change in tidal volume. The maximal response (maximal hypoventilation) was always associated with an apnea (> 3 s), which was followed by a breathing interval and a second period of hypoventilation or apnea before continuous breathing resumed. The sharp response to $O_2$ in these infants reflects a high baseline activity of the peripheral chemoreceptors, likely related to the relatively low arterial $P_{O_2}$ known to be present in these infants (7). This high baseline firing of the peripheral chemoreceptors is abolished when arterial $P_{O_2}$ increases after 100% $O_2$, eliminating the hypoxic drive from the chemoreceptors, with a consequent sharp decrease in ventilation (1, 2, 7).

Studies done in anesthetized cats, dogs, and rabbits measuring the ventilatory response to inhalation of 100% $O_2$ have shown an almost instantaneous reduction of the respiratory frequency and tidal volume after $O_2$ was given. Denervation of the sinus region abolished this response (9–11). Direct recording from a

Table 1. *Physiologic measurements in response to 100% $O_2$ (mean ± SEM)**

| Experimental conditions | $\dot{V}_E$ (L·min·kg$^{-1}$) | f (breaths·min$^{-1}$) | $V_T$ (mL·kg$^{-1}$) | $P_AO_2$ kPa | $P_AO_2$ torr | $V_T/T_i$ (mL·s$^{-1}$) | $T_i/T_{TOT}$ | % Δ $\dot{V}_E$ |
|---|---|---|---|---|---|---|---|---|
| Control | 0.192 ± 0.011 | 32 ± 3 | 6.2 ± 0.4 | 13.5 ± 0.1 | 101 ± 1 | 10.0 ± 0.7 | 0.345 ± 0.022 | |
| 1st breath in 100% $O_2$ | 0.188 ± 0.011 | 31 ± 3 | 6.5 ± 0.7 | 28.0 ± 1.2† | 210 ± 9† | 11.2 ± 1.1 | 0.310 ± 0.030 | −2 |
| 1st breath with hypoventilation | 0.088 ± 0.016† | 19 ± 4† | 5.2 ± 0.5 | 42.0 ± 2.4† | 315 ± 18† | 8.9 ± 1.0 | 0.172 ± 0.027† | −54† |
| Breath preceding maximal response | 0.122 ± 0.016† | 22 ± 2† | 5.9 ± 0.7 | 45.9 ± 4.1† | 344 ± 31† | 10.0 ± 1.1 | 0.214 ± 0.026† | −37† |
| Maximal response | 0.044 ± 0.011† | 9 ± 2† | 4.8 ± 0.8 | 53.6 ± 4.1† | 402 ± 31† | 38.7 ± 1.4 | 0.095 ± 0.022† | −77† |

* $\dot{V}_E$, minute ventilation; f, frequency; $V_T$, tidal volume; $P_AO_2$, alveolar $P_{O_2}$; $V_T/T_i$, inspiratory drive; $T_i/T_{TOT}$, duty cycle; and % Δ $\dot{V}_E$, % change in minute ventilation.

† $p \leq 0.0005$ in relation to control values.

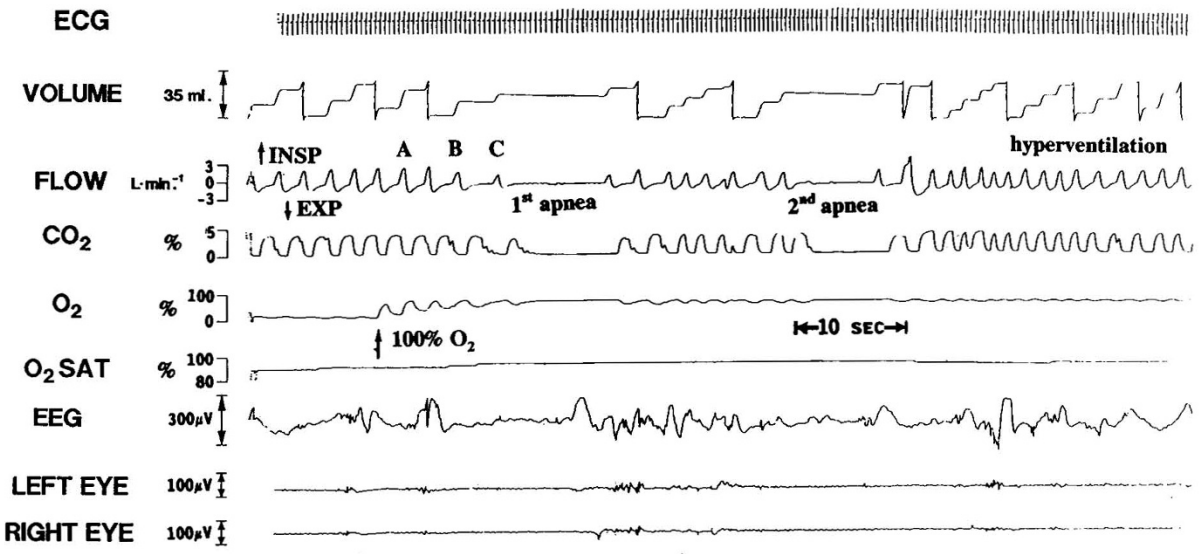


Fig. 2. Representative tracing during quiet sleep. Note the progressive decrease in respiratory frequency with 100% $O_2$ leading to the first apnea, which was followed by a breathing interval and a second apnea before regular breathing resumed. *A*, First breath in 100% $O_2$; *B*, first breath with hypoventilation and breath preceding maximal response; and *C*, maximal response. $O_2$ SAT, $O_2$ saturation.

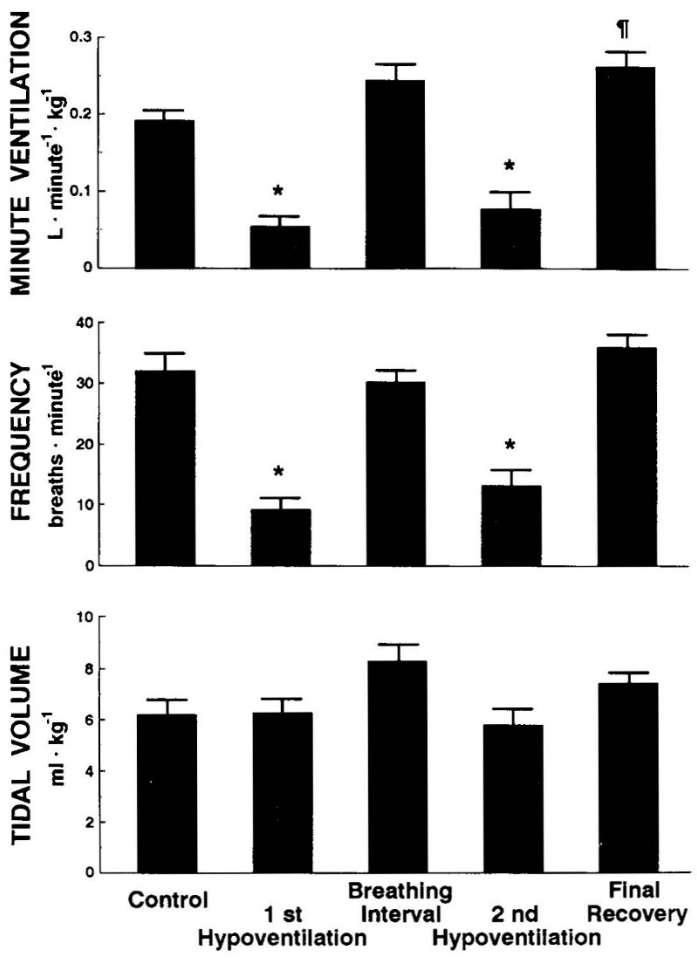


Fig. 3. The first decrease in ventilation was followed by a short recovery and a second decrease in ventilation (2nd hypoventilation) before regular breathing resumed. Values are mean ± SEM for each event. *, $p < 0.05$ compared with control and the two breathing intervals; ¶, $p < 0.05$ compared with control.

single chemoreceptor fiber also showed an immediate (after a few seconds) decrease in the number of nerve impulses per unit of time when the animal was made hyperoxic by breathing pure $O_2$ (12–14). In the present study, the speed of the response (3.6 ± 0.6 and 6.8 ± 1 s for the 1st breath with hypoventilation and maximal response, respectively) was similar to that found by Girard *et al.* (15) and by Brady *et al.* (1) in term infants. Brady *et al.* (1) found the response time in term infants difficult to measure accurately because of lack of abrupt change in ventilation. This was not a problem in preterm infants because the breathing responses were quite abrupt.

The decrease in ventilation with inhaled $O_2$ is related to a primary decrease in frequency in preterm infants (2–4, 16). The decrease in frequency is related to apnea, which commonly occurs with 100% $O_2$. Term infants and adult subjects do not become apneic with high inhaled $O_2$ mixtures, but they change ventilation by primarily decreasing tidal volume (1, 11, 17–20). This distinct response observed in small babies, although not entirely understood, is likely related to the relatively low arterial $P_{O_2}$ and high chemoreceptor firing in these infants (1, 2, 7).

The administration of 100% $O_2$ initiated a characteristic pattern of breathing with alternating apneas and breathing intervals. This was observed in most infants (nine of 13) and mimicked what Haldane called "the hunting of the respiratory centers" (21). The inhaled $O_2$ induces the first apnea. During apnea, arterial $P_{CO_2}$ rises, triggering the resumption of breathing until arterial $P_{CO_2}$ decreases again and the hypoventilation or apnea reappears. This sequence goes on, with apneas successively shorter until continuous or regular breathing resumes. The imbalance of ventilation in this situation appears to be due in great part to the action of $O_2$ at the peripheral chemoreceptors. Oxygen appeared not to affect the inspiratory drive, but it decreased the duty cycle because of a prolonged expiratory time.

In summary, we gave 100% $O_2$ to preterm infants to breathe to measure the speed and profile of the peripheral chemoreceptor response. With inhaled $O_2$, there was an immediate and sharp decrease in ventilation that is conventionally attributed to a decrease in peripheral chemoreceptor drive. Breathing remained unbalanced for a short period before regular breathing resumed. The response time of the peripheral chemoreceptors was 3.6 ± 0.6 s.

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