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Evidence that maturation of the peripheral chemoreceptors is not complete in childhood

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Abstract. We examined the hypothesis that the peripheral chemoreceptors contribute a different degree of tone to respiration during exercise in normal young children as compared to adults. To improve resolution of the peripheral chemoreceptor contribution, the studies were conducted during controlled levels of exercise. Peripheral chemoreceptor function was assessed by the hyperoxic ($F_{I_{O_2}} = 0.80$) switch technique during steady-state, sub-anaerobic threshold exercise during air ($F_{I_{O_2}} = 0.21$) and mildly hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing in 9 healthy children (mean ± 1 SD age (years) = 8.2 ± 1.4) and 10 healthy adults (28.2 ± 6.5). Ventilation during exercise was significantly greater under hypoxic conditions in both children and adults. During air breathing exercise the mean ventilatory decrease in response to the hyperoxic switch was similar in the two groups ($27.9 \pm 10.7\%$ in children and $23.3 \pm 6.3\%$ in adults). In contrast, during hypoxic gas breathing exercise the children demonstrated a much greater decrease in ventilation following the hyperoxic switch ($57.9 \pm 3.6\%$) compared to adults ($38.9 \pm 5.5\%$) ($P < 0.0001$). Thus, the peripheral chemoreceptors have a greater role in the exercise hyperpnea during hypoxic exercise in young children as compared to adults, suggesting attenuation of peripheral chemoreceptor function during maturation.

Carotid body; Control of breathing; Exercise in children; Hyperoxic switch; Hypoxia

It is generally believed that the chemical control of respiration in humans is affected in large part by central (brainstem) and peripheral (carotid body) chemoreceptors (Kellogg, 1964). The central chemoreceptors are stimulated largely by pH (modulated by the P_{CO_2}) while the peripheral chemoreceptors are sensitive to changes in P_{O_2} as well. Thus, the level of ventilation is ultimately determined by the integrated output of these and other stimuli.

In human beings, the carotid bodies modulate the critically important ventilatory responses to hypoxia and are known to become active within one hour following birth in normal infants (Brady *et al.*, 1964). Much work has been done to understand the physiology of the peripheral chemoreceptors in infants (Brady *et al.*, 1964; Brady and

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Ceruti, 1966; Rigatto *et al.*, 1975); however, there is virtually no information concerning their function following the newborn period in normally active, growing children. A recent study of ventilatory responses to exercise suggests that respiratory control does, in fact, change in children during the growth period (Cooper *et al.*, 1987).

To evaluate the peripheral chemoreceptor contribution of the ventilatory drive, we abruptly and surreptitiously switched the inspired gas to 80% O₂ for 10 breaths while subjects performed steady-state exercise while breathing air or a hypoxic gas. Minute ventilation, tidal volume and breathing frequency were measured breath by breath. The maximum decrement in ventilation was taken as the carotid body contribution to ventilatory drive (Dejours *et al.*, 1957; Dejours, 1963). By performing these breath-by-breath measurements during exercise, random variation in minute ventilation relative to mean ventilation is reduced and therefore resolution of the magnitude of any abrupt change in carotid body tone by the hyperoxic switch could be improved. By selecting an exercise level below the subjects anaerobic threshold, the acid-base status of the arterial blood is the same as that of rest (Wasserman *et al.*, 1986). Thus, experiments were designed to measure peripheral chemoreceptor drive in children compared to adults during air and hypoxic gas breathing and to examine the hypothesis that the peripheral chemoreceptors have not yet matured in childhood.

Methods

Nine healthy children (5 boys and 4 girls, aged 6–10 yr, mean age 8.2 ± 1.4 yr, mean body weight 29.2 ± 9.1 kg) and 10 healthy adults (6 males and 4 females, aged 18–40 yr, mean age 28.2 ± 6.5 yr, mean body weight 63.9 ± 6.6 kg) comprised the study populations. All were volunteers and participated in normal physical activities, did not smoke or use medications. The study was approved by the Human Subjects Committee of Harbor-UCLA Medical Center. Informed consent was obtained from each subject and guardian.

Three types of exercise protocols with cycle ergometry were used in this study: (1) a ramp-type progressive exercise test during 15% O₂ breathing (Whipp *et al.*, 1981); (2) constant work rate exercise tests during air breathing; and (3) constant work rate exercise tests during 15% O₂ breathing. The level of cycle ergometer work used in the constant work rate protocols was determined from the progressive exercise protocol from which the anaerobic threshold (AT) at $FI_{O_2} = 0.15$ was estimated. It has been shown that the AT as we measure it (Wasserman *et al.*, 1973; Beaver *et al.*, 1986) corresponds to the O₂ uptake above which lactic acidosis occurs. The work rate used for the constant work rate tests was 75% of the hypoxic AT. This ensured that constant work rate tests performed during both air and hypoxic gas breathing would be below the subject's AT. Each subject performed at least 5 repetitions of the same constant work rate protocol, during which the decrement in ventilation, tidal volume, breathing frequency, and increase in PET_{CO_2} were measured breath-by-breath in response to the hyperoxic ($FI_{O_2} = 0.80$) switch. Since children and adults have widely different exercise

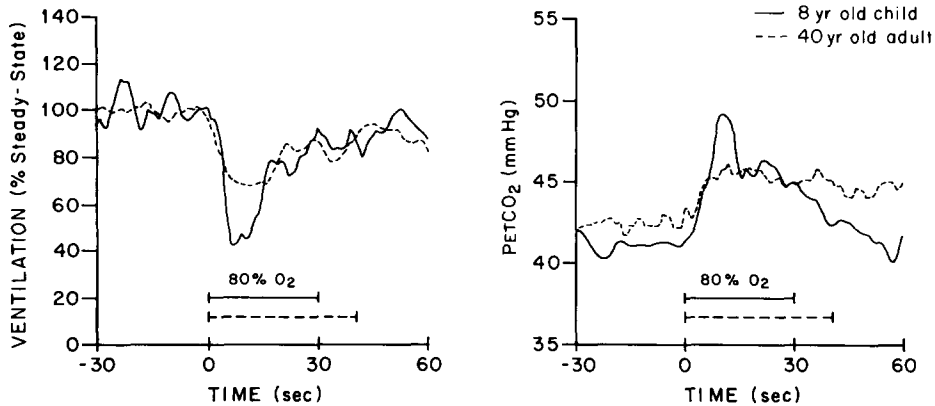


Fig. 1. Ventilatory (left panel) and CO_2 (right panel) responses to hyperoxic switch in an 8-yr-old child (solid line) and a 40-yr-old adult (dashed line). These studies were done during exercise under hypoxic conditions ($F_{\text{I}\text{O}_2} = 0.15$). The hyperoxic switch lasted 30 sec for the child and 40 sec for the adult. Ventilation was normalized to the steady-state exercise value which was 11.4 L/min in the child and 26.6 L/min in the adult.

Note the more marked reduction in \dot{V}_E and increase in PET_{CO_2} in the child compared to the adult.

capabilities, the work rate chosen was normalized in each subject to a specific physiologically based work intensity. By choosing work ranges below the AT, possible confounding effects of lactic acidosis on ventilation were avoided in both the adults and children. Steady-state exercise continued for 10 min, followed by a period of rest which was long enough (approximately 10 min) to allow ventilation (\dot{V}_E), O_2 uptake (\dot{V}_{O_2}), CO_2 output (\dot{V}_{CO_2}), and heart rate to return to the pre-exercise levels.

To assess the peripheral chemoreceptor activity during exercise for each constant work rate, each subject underwent hyperoxic switches during the steady-state phase of the constant work rate exercise (at least 5 under hypoxic conditions and 5 under air breathing conditions). The hyperoxic switches were performed by changing the inspired air to 80% oxygen, abruptly and without the subject's knowledge, for 10 breaths. Typical examples of the change in \dot{V}_E and PET_{CO_2} in response to the 80% O_2 switch during exercise while breathing 15% O_2 in a child and an adult are shown in fig. 1. The order of the air-breathing and hypoxic gas-breathing tests was randomized. It usually required three separate days to complete all protocols for each subject.

Ventilation and gas exchange were measured breath-by-breath. This allows a precise measurement of the kinetic responses of the ventilatory system. The subjects breathed through a mouthpiece connected to a turbine flowmeter for continuous measurement of inspired and expired volumes and a low resistance two-way valve. The apparatus dead space was 140 ml for the children and 170 ml for the adults. End-tidal P_{CO_2} (PET_{CO_2}) and P_{O_2} (PET_{O_2}) were measured by a mass spectrometer which sampled continuously from the mouthpiece at 1 ml/sec. Minute expired ventilation \dot{V}_E (BTPS), \dot{V}_{O_2} (STPD), \dot{V}_{CO_2} (STPD), PET_{O_2} and PET_{CO_2} were computed on-line, breath-by-breath, as previously described (Beaver *et al.*, 1981). For each subject, the results preceding and following each hyperoxic switch were time aligned and averaged to obtain

a second by second response. The maximum decrease in \dot{V}_E following the hyperoxic switch was expressed as percent of steady-state exercise ventilation and was used to quantify the peripheral chemoreceptor input to total ventilation.

The AT was measured noninvasively from the gas exchange data obtained during the progressive exercise. AT was defined as the \dot{V}_{O_2} at which the ventilatory equivalent for O_2 (\dot{V}_E/\dot{V}_{O_2}) and $P_{ET_{O_2}}$ increase without an increase in the ventilatory equivalent for CO_2 (\dot{V}_E/\dot{V}_{CO_2}) and $P_{ET_{CO_2}}$ (Whipp *et al.*, 1981; Cooper *et al.*, 1984).

Ventilatory responses within the groups (children or adults) to constant work rate exercise and to the hyperoxic switches during air and 15% O_2 breathing were compared using the paired *t*-test; comparison between the groups were done using the unpaired *t*-test. Differences were considered significant at $P < 0.05$. Values are expressed as mean \pm 1 SD.

Results

In children compared to adults, $P_{ET_{O_2}}$ was slightly but significantly higher while breathing both air ($F_{I_{O_2}} = 0.21$) and the hypoxic gas ($F_{I_{O_2}} = 0.15$) (air breathing: 110 ± 3 mm Hg in children and 106 ± 4 mm Hg in adults, $P < 0.05$; 15% O_2 breathing: 70 ± 3 mm Hg in children and 67 ± 3 mm Hg in adults, $P < 0.05$). Also $P_{ET_{CO_2}}$ during exercise was significantly lower in children compared to adults (air breathing: 41 ± 1 mm Hg and 44 ± 4 mm Hg, respectively, $P < 0.05$; 15% O_2 breathing:

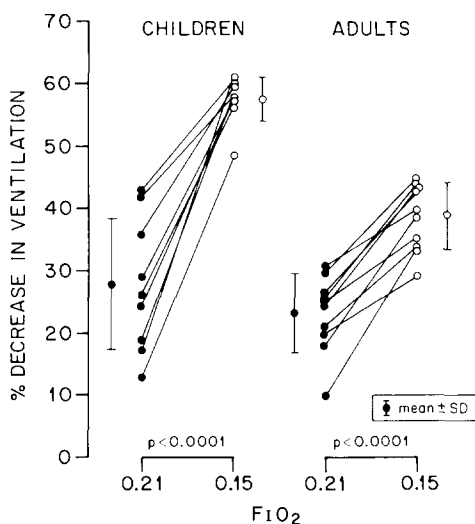


Fig. 2. Percent decrease in ventilation following the hyperoxic switch in children (left panel) and adults (right panel) during air ($F_{I_{O_2}} = 0.21$) and hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing exercise. Note that during air breathing, ventilatory responses were not significantly different between groups. However, in the hypoxic conditions children had a significantly greater decrement in \dot{V}_E in response to the hyperoxic switch ($P < 0.0001$).

39 ± 2 mm Hg and 42 ± 3 mm Hg respectively, $P < 0.05$). The increase in ventilation during steady-state exercise was small but significantly greater during hypoxia as compared to air breathing in both children and adults. Although the children had a greater relative increase in ventilation than the adults this difference was not significant ($9.2 \pm 7.8\%$ compared to $4.6 \pm 5.4\%$, respectively).

In both children and adults, the hyperoxic switch during air and hypoxic breathing conditions resulted in a transient reduction in \dot{V}_E . During air breathing exercise, the mean reduction in ventilation following the hyperoxic switch was not significantly different in the two groups ($27.9 \pm 10.7\%$ in the children and $23.3 \pm 6.3\%$ in the adults). But during hypoxic exercise, the children demonstrated a significantly greater decrease in ventilation following the hyperoxic switch than did the adults. The mean decrease in \dot{V}_E during 15% O_2 breathing in response to the hyperoxic switch was $57.6 \pm 3.6\%$ in the children and $38.9 \pm 5.5\%$ in the adults, $P < 0.0001$ (fig. 2).

The decrease in ventilation following the hyperoxic switch was due to changes in breathing frequency (fig. 3) and tidal volume (fig. 4), both in children and adults. These changes were significantly greater during the hypoxic studies as compared to the air breathing studies. The percent decrease in breathing frequency was significantly greater in children, both during the air breathing studies (children: $19.6 \pm 13.4\%$; adults: $8.0 \pm 7.8\%$, $P < 0.05$) and the hypoxic studies (children: $38.6 \pm 13.4\%$; adults:

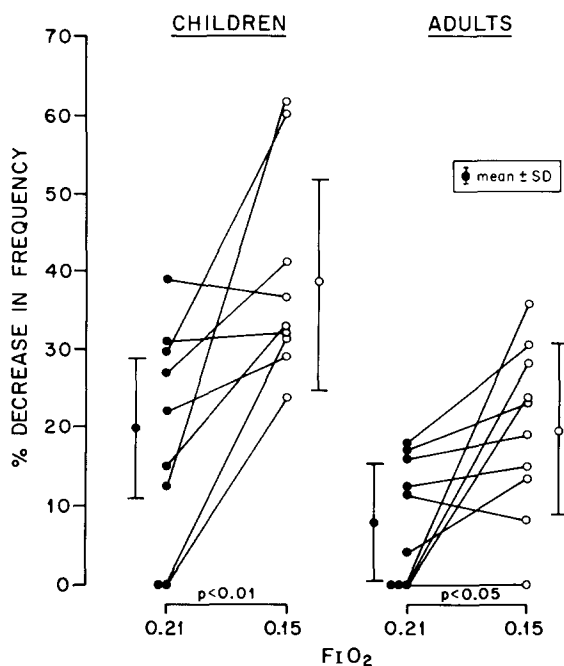


Fig. 3. Percent decrease in breathing frequency following the hyperoxic switch in children (left panel) and adults (right panel) during air ($F_{I O_2} = 0.21$) and hypoxic gas ($F_{I O_2} = 0.15$) breathing exercise. Note that breathing frequency decreased significantly more in children compared to adults both during air breathing ($P < 0.05$) and hypoxic gas breathing exercise ($P < 0.005$).

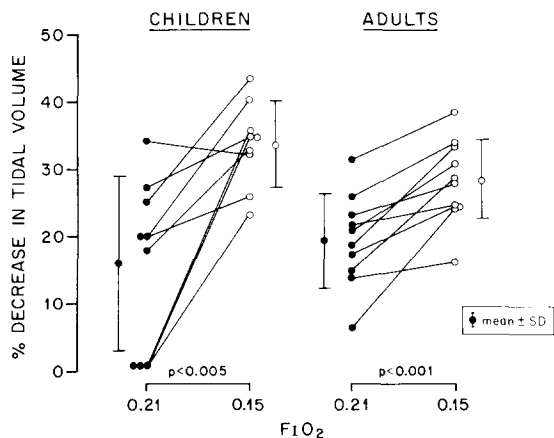


Fig. 4. Percent decrease in tidal volume following the hyperoxic switch in children (left panel) and adults (right panel) during air ($F_{I_{O_2}} = 0.21$) and hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing exercise. Note that the percent decrease in tidal volume was not significantly different in children compared to adults either during air breathing or hypoxic exercise.

$19.9 \pm 11.0\%$, $P < 0.0005$). However, tidal volume decreased similarly in children and adults during air breathing (children: $16.1 \pm 13.0\%$; adults: $18.9 \pm 9.7\%$, NS) and the hypoxic studies (children: $33.5 \pm 6.4\%$; adults: $27.9 \pm 6.4\%$, NS). But note that the decrement in \dot{V}_E in response to the hyperoxic switch was more uniform than breathing frequency or tidal volume.

The change in $P_{ET_{CO_2}}$ in response to the hyperoxic switch is shown in fig. 5. During air breathing exercise, the mean increase in $P_{ET_{CO_2}}$ was 2.3 ± 0.8 mm Hg in the children and 1.5 ± 0.6 mm Hg in the adults ($P < 0.05$). During the hypoxic studies, the children

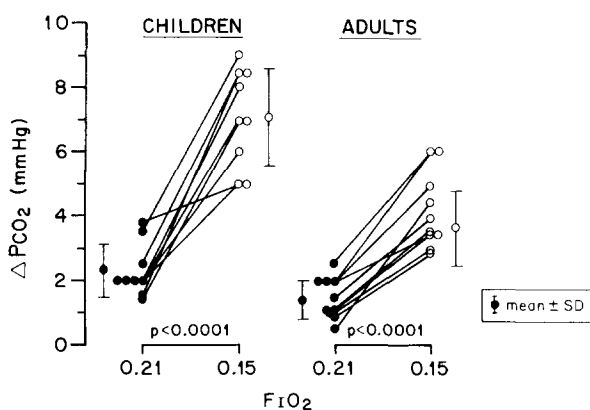


Fig. 5. Increase in $P_{ET_{CO_2}}$ following the hyperoxic switch ($P_{ET_{CO_2}}$) in children (left panel) and adults (right panel) during air ($F_{I_{O_2}} = 0.21$) and hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing exercise. Note that children had a significantly greater increase in $P_{ET_{CO_2}}$ both during air breathing ($P < 0.05$) and hypoxic breathing studies ($P < 0.0005$).

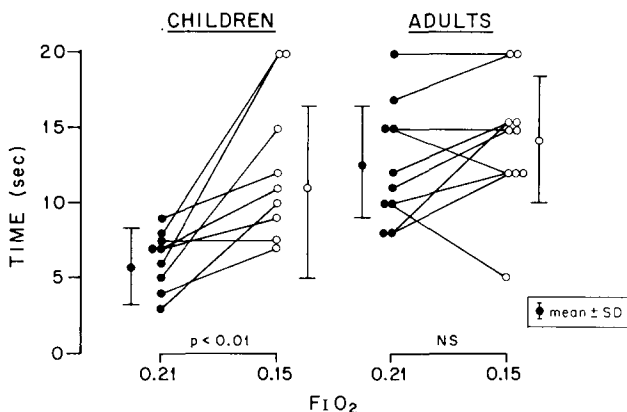


Fig. 6. The time to nadir of ventilation following the hyperoxic switch in children (left panel) and adults (right panel) during air ($F_{I_{O_2}} = 0.21$) and hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing exercise. Note that the time to the nadir ventilation was significantly shorter in children during the air breathing exercise ($P < 0.0005$).

However, there was no difference in the response time during the hypoxic gas breathing exercise.

has a much greater increase in $P_{ET_{CO_2}}$ (7.1 ± 1.5 mm Hg) compared to the adults (4.2 ± 1.1 mm Hg) ($P < 0.005$).

The time to the nadir in \dot{V}_E in response to the hyperoxic switch is shown in fig. 6. During air breathing, children had a significantly shorter time to the nadir as compared to adults (children: 5.7 ± 2.7 sec; adults: 12.6 ± 4.0 sec; $P < 0.005$). During the hypoxic studies, the time to the nadir in ventilation increased significantly in children to 11.2 ± 6.1 sec ($P < 0.01$). However, in the adults, hypoxia resulted in only a small and insignificant change.

Discussion

Our data show that the peripheral chemoreceptor contribution to ventilatory drive during air breathing was not significantly different in children when compared to adults; however, if the increase in $P_{ET_{CO_2}}$ is used to assess the effect of the hyperoxic switch on alveolar ventilation, there is a small but significantly greater attenuation of respiratory drive in the children. This was possibly due to the greater decrease in breathing frequency in the children (fig. 3). In contrast, during hypoxic breathing, the peripheral chemoreceptor input was significantly greater in the children than in the adults whether assessed by the decrease in \dot{V}_E or increase in $P_{ET_{CO_2}}$. We considered the possibility that increases in dead space/tidal volume ratio (V_D/V_T) in children during the hypoxic gas breathing caused by pulmonary vasoconstriction, subsequently relieved by the 10 breaths of O_2 breathing, could account for the large decrement in \dot{V}_E . For example, a hypoxia-induced increase in V_D/V_T in children could result in an increase in \dot{V}_E without a concomitant decrease in P_{CO_2} . But in fact we found that the increase in ventilation under hypoxic conditions was small and accompanied by a decrease in $P_{ET_{CO_2}}$, and

the decrease in ventilation following the hyperoxic switch was accompanied by an increase in $P_{ET_{CO_2}}$ both in adults and children (fig. 5).

Studies in infants have demonstrated that the peripheral chemoreceptors' contribution to ventilation in air breathing conditions (estimated by the hyperoxic switch) is 20–40% (Brady *et al.*, 1964). This was similar to our findings in both the children and the adults. But there is no information regarding sensitivity of the peripheral chemoreceptors in the neonate studied by the hyperoxic switch under hypoxic conditions. Studies in the opossum (Farber *et al.*, 1972) have shown that the ventilatory response to hypoxia is maximal in early life and decreases with age reaching its lowest level in the adult. This suggests that hypoxic chemoreflex ventilatory drive decreases during the growth process in this species.

The hyperoxic switch allows partitioning of the sources of ventilatory drive into peripheral chemoreceptor and non-peripheral chemoreceptor drive (fig. 7). The ventilatory drive attributable to stimuli other than those from the peripheral chemoreceptors (*i.e.*, the residual ventilation following the hyperoxic switch) was actually lower during hypoxia compared to breathing air. Non-peripheral chemoreceptor drive appeared to account for 42% of the total ventilation during hypoxia in children compared to 61% under similar conditions in the adults ($P < 0.0001$).

Suppression of output from non-peripheral chemoreceptor stimuli can be explained by several possible mechanisms. First, during hypoxic gas breathing, central chemoreceptors may be inhibited (Lee and Milhorn, 1975); second, the increase in cerebral blood flow during hypoxia (Edelman *et al.*, 1984) causing a decreased P_{CO_2} in the brain tissue will attenuate the stimulation of the central chemoreceptors. Since respiratory

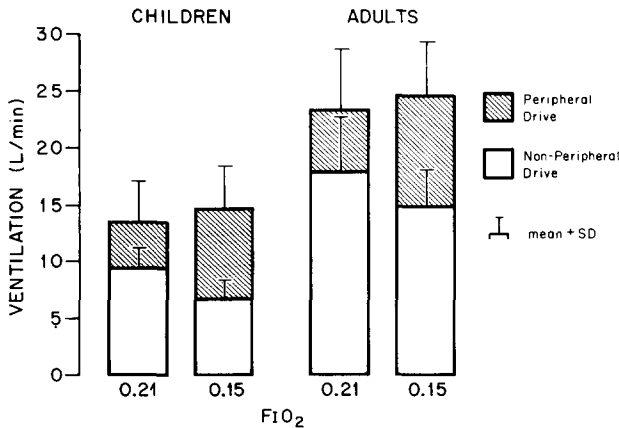


Fig. 7. Ventilation during air ($F_{I_{O_2}} = 0.21$) and hypoxic gas ($F_{I_{O_2}} = 0.15$) breathing exercise in children (left panel) and adults (right panel). The ventilatory responses were divided into the peripheral chemoreceptor (hatched bars) and the non-peripheral chemoreceptor (clear bars) contribution to the ventilatory drive. The results are presented as mean \pm SD. Note that hypoxic gas breathing resulted in an increase in the peripheral chemoreceptor and a decrease in the non-peripheral chemoreceptor contribution to ventilation in both children and adults as compared to air breathing but the relative changes were greater in the children.

control is an integrated response of several inputs (*e.g.*, peripheral chemoreceptors, exercising limbs, stretch receptors in the lungs, central chemoreceptors, *etc.*), the increase in peripheral chemoreceptor gain induced by hypoxia may concomitantly suppress non-peripheral chemoreceptor inputs to prevent excessive hyperventilation and important respiratory alkalosis which might otherwise develop.

The hyperoxic switch technique to determine peripheral chemoreceptor contribution to ventilation has a number of advantages and a single disadvantage. The advantages are (1) it is rapid, (2) it can do no harm to the patient and (3) it can be used in patients who have ventilatory restriction. Its major disadvantage is that a numerical grading of sensitivity cannot be applied. Rather, quantification is that of the total response.

The rapidity of the ventilatory depression following the hyperoxic switch is excellent evidence that the inhibition of ventilation by the hyperoxic switch is due to the removal of peripheral chemoreceptor tone. A breath-by-breath analysis is needed in order to accurately quantify the peripheral chemoreceptor input. Conceivably, the carotid body contribution to ventilation by this technique is underestimated because of the increase in Pa_{CO_2} evidenced by the increase in PET_{CO_2} (fig. 1).

Is there an advantage to increased peripheral chemoreceptor response to hypoxia in children compared to adults? In the newborn period, peripheral chemoreceptors highly sensitive to hypoxia are important, since hypoxic episodes are likely to occur due to the erratic pattern of breathing (Roffwarg *et al.*, 1966). After infancy, if increased peripheral chemoreceptor sensitivity is no longer needed, one might expect this attribute of respiratory control to fade. A continually decreasing chemoreceptor sensitivity to hypoxia has, in fact, been noted throughout life in the opossum (Farber *et al.*, 1972); but no studies exist in humans. Perhaps the persisting high hypoxic sensitivity of the peripheral chemoreceptors in children compared to adults may result from increased exposure to hypoxia. This exposure may occur during sleep since sleep is associated with hypoventilation and hypoxia (Shepard, 1985), and children spend more time sleeping than do adults (Roffwarg *et al.*, 1966). It is therefore possible that children, in fact, need a more sensitive defense mechanism against hypoxia than do adults. Thus maturation of respiratory control does not occur until later in life, presumably in early adulthood.

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