Hypercapnic and Hypoxic Ventilatory Responses during Growth

Yoshiyuki HONDA, Yoshio OHYABU, Midori SATO, Hidenori MASUYAMA,
Yoshitake NISHIBAYASHI, Ryoko MARUYAMA, Yukio TANAKA,
Ikuo NAKAJO,* Hideharu SHIRASE,*
and Kazutaka HAYASHIDA*

*Department of Physiology, School of Medicine, Chiba University,
Chiba, 280 Japan and *School of Physical Education,
Tokai University, Hiratsuka, 254 Japan*

Abstract Cross-sectional studies on hypercapnic and hypoxic ventilatory chemosensitivities were performed in 71 children ranging in age from 7 to 18 yrs. The subjects were classified into 6 successive 2-year age groups. CO₂ ventilatory response was measured by rebreathing 5% CO₂ in O₂, a slight modification of the method originally proposed by Read. The results were evaluated when the CO₂-ventilation feedback control system was supposed to have attained the open-loop condition. Hypoxic ventilatory response was measured by the isocapnic progressive hypoxia test. To obtain good reproducibility in the ventilatory response, end-tidal P_{CO_2} was maintained at 5 mmHg higher than the resting condition throughout the test. Normalized ventilatory responses to CO₂ by body surface area (S/BSA) progressively decreased from the 7–8 through the 11–12 yr groups, and then tended to decrease further in a more gradual manner with increasing age. This trend was very similar to the normalized CO₂ output ($\dot{V}_{\text{CO}_2}/\text{BSA}$), but did not parallel so closely the normalized O₂ intake ($\dot{V}_{\text{O}_2}/\text{BSA}$). When ventilatory and metabolic parameters were normalized by body weight (BW), or the lean body mass (LBM), qualitatively similar relationships between CO₂ sensitivities and metabolic parameters were also obtained. Contrary to the hypercapnic response, hypoxic ventilatory chemosensitivities were not significantly different among the 6 different age groups. We concluded that normalized hypercapnic chemosensitivity decreased during growth and corresponded well with decreased CO₂ output per unit body mass.

Key words: hypercapnic ventilatory response, hypoxic ventilatory response, body weight, body surface area, lean body mass.

Several studies have reported that ventilatory responsiveness to CO₂ increases with gestational age and with postnatal age of about one month (FRANZ *et al.*, 1976; JANSEN and CHERNICK, 1983). However, once newborn infants are fully matured, their hypercapnic ventilatory sensitivity expressed in terms of ml/min per unit body weight was demonstrated to be of the same magnitude as in adults (AVERY *et al.*, 1963). Therefore, no further changes in CO₂ chemosensitivity during childhood seem to occur (AVERY *et al.*, 1963; JANSEN and CHERNICK, 1983). To our knowledge no definite trend in normalized ventilatory response by body size during human growth has been previously reported in the literature. Comparison of CO₂ sensitivity between normal infants and adults has been conducted by the method of rebreathing 100% O₂ (AVERY *et al.*, 1963). However, there is considerable difficulty in attaining equilibrium between ventilation and alveolar or arterial P_{CO_2} with this technique, as previously pointed out (CONFERENCE PERPORT, 1977; DEJOURS *et al.*, 1965).

Using the CO₂ rebreathing method of Read (READ, 1967; READ and LEIGH, 1967), which allows prompt equilibrium between alveolar and mixed venous P_{CO_2} so as to attain the open-loop ventilatory system, we studied CO₂ sensitivity in children. They were also examined for hypoxic chemosensitivity using the progressive hypoxia test (WEIL *et al.*, 1970).

METHODS

Subjects. Seventy-one subjects ranging in age from 7 to 18 yrs were studied. They were all healthy and participated in a few hours of judo training once or twice a week for physical fitness. The subjects had practiced judo for periods of from 0.5 to 7 yrs. No particularly elite athletes were included. They were classified into 2-yr age groups, so that six cross-sectional groups could be compared as to their physical characteristics as well as for ventilatory data (Table 1). The number of subjects in the 7–8, 9–10, 11–12, 13–14, 15–16 and 17–18 yr groups were 7, 16, 15, 3, 17 and 13, respectively. In 65 out of the total 71 subjects, skinfold thickness on the back and the arm was measured. Body fat in % body weight was estimated by using BROŽEK's equation (1963). Thus, the lean body mass (LBM) was calculated by subtracting body fat from body weight.

Experimental procedures. Ventilatory responses to hypercapnia and hypoxia were measured by the methods originally developed by READ (1967) and by WEIL *et al.* (1970), respectively. We made slight modifications of the original procedures as described below. In the hypercapnia test, the subjects rebreathed 5–7 l of about 5% CO₂ in the O₂ mixture. This initial 5% CO₂ mixture instead of the 7% used in the original method was decided upon in order to avoid subjecting such young children to great strain. Accordingly, for the purpose of calculating the ventilatory responses, this difference in inspired CO₂ had to be taken into account, and the end-tidal P_{CO_2} (P_{ETCO_2}) used was started from 7–8 mmHg higher than the resting P_{ETCO_2} . Such P_{ETCO_2} was assumed to have exceeded the mixed venous P_{CO_2} level.

Table 1. Physical characteristics and ventilatory chemosensitivity of subjects during growth.

Age	Yrs	7-8	9-10	11-12	13-14	15-16	17-18
<i>n</i>		7	16	15	3	17	13
Length of judo training	yr	2.2 ± 1.1	2.3 ± 1.4	4.2 ± 1.8	5.0 ± 2.2	1.0 ± 1.4	1.4 ± 1.7
Body weight (BW)	kg	26.3 ± 5.4	41.0 ± 15.1	44.5 ± 11.7	61.0 ± 12.8	63.2 ± 13.6	65.6 ± 10.5
Height	cm	124 ± 6	138 ± 6	148 ± 9	158 ± 8	168 ± 5	169 ± 5
Body surface area (BSA)	m ²	0.93 ± 0.11	1.15 ± 0.21	1.34 ± 0.20	1.61 ± 0.20	1.71 ± 0.15	1.75 ± 0.13
Lean body mass (LBM)	kg	21.0 ± 3.6	28.9 ± 5.3	33.8 ± 8.0	48.7 ± 7.1	50.9 ± 5.8	53.9 ± 6.0
			(<i>n</i> = 15)	(<i>n</i> = 12)	(<i>n</i> = 2)	(<i>n</i> = 16)	
Body fat	%BW	19.7 ± 4.3	26.6 ± 11.7	19.3 ± 3.2	25.7 ± 9.0	15.7 ± 5.4	17.3 ± 5.3
			(<i>n</i> = 15)	(<i>n</i> = 12)	(<i>n</i> = 2)	(<i>n</i> = 16)	
<i>P</i> _{ETCO₂}	mmHg	38.3 ± 1.3	38.8 ± 4.5	40.2 ± 3.8	38.3 ± 2.5	42.5 ± 3.2	43.5 ± 3.2
<i>f</i>	frequency · min ⁻¹	27.3 ± 7.6	25.1 ± 6.3	26.8 ± 8.2	16.5 ± 5.4	17.9 ± 5.9	17.1 ± 6.7
$\dot{V}_{O_2}$	ml · min ⁻¹	233 ± 38	303 ± 99	322 ± 45	375 ± 36	377 ± 87	384 ± 98
$\dot{V}_{CO_2}$	ml · min ⁻¹	221 ± 50	249 ± 59	272 ± 45	280 ± 36	312 ± 62	331 ± 74
Heart rate	pulse · min ⁻¹	81.9 ± 6.5	92.4 ± 11.4	86.3 ± 11.6	71.3 ± 15.2	85.8 ± 10.8	79.0 ± 9.3
Hypercapnic response:							
<i>S</i>	l · min ⁻¹ · mmHg ⁻¹	1.71 ± 0.64	1.33 ± 0.62	1.00 ± 0.31	0.87 ± 0.43	0.89 ± 0.34	0.81 ± 0.51
<i>B</i>	mmHg	39.1 ± 4.3	38.1 ± 6.8	33.1 ± 9.1	34.8 ± 2.8	39.3 ± 8.4	35.1 ± 14.3
Hypoxic response:							
<i>A</i>	l · min ⁻¹ · mmHg	278 ± 176	538 ± 469	520 ± 385	260 ± 73	874 ± 687	872 ± 496
$\dot{V}_O$	l · min ⁻¹	11.3 ± 3.2	11.2 ± 5.8	12.9 ± 4.8	11.3 ± 5.2	5.5 ± 8.0	5.0 ± 5.7
<i>C</i>	mmHg	28.3 ± 20.3	14.9 ± 15.3	17.9 ± 14.2	11.3 ± 15.5	15.6 ± 14.3	7.5 ± 10.9
$\Delta \dot{V}_{40}$	l · min ⁻¹	64.6 ± 60.9	27.4 ± 22.3	27.8 ± 17.6	17.9 ± 16.7	33.4 ± 13.6	29.4 ± 14.6

Values are mean ± S.D. Ventilatory response to CO₂ was analyzed by the equation $\dot{V} = S(P_{ETCO_2} - B)$. Ventilatory response to hypoxia was analyzed by the equation $\dot{V} = \dot{V}_O + A/(P_{ETO_2} - C)$. $\Delta \dot{V}_{40}$ is the increment in ventilation from $\dot{V}_O$ to that of P_{ETO_2} 40 mmHg.

The amount of rebreathing gas was reduced with smaller body size, and the rebreathing was maintained until P_{ETCO_2} had increased to at least 60 mmHg. More than half of the subjects tolerated the rebreathing until P_{ETCO_2} was elevated to between 65–75 mmHg. The number of subjects who discontinued CO_2 rebreathing at P_{ETCO_2} of less than 65 mmHg in 6 consecutive groups with increasing age as shown in Table 1 were 6, 14, 8, 2, 1 and 0, respectively. The P_{ETCO_2} -ventilation ($\dot{V}$) response was analyzed by the equation $\dot{V} = S((P_{ETCO_2} - B))$, where S and B are the slope and horizontal intercept of the response line, respectively.

In the hypoxia test, the subjects initially breathed room air, and then started rebreathing into a bag filled with 8–12 l of room air. Again, the amount of rebreathing air was changed according to body size. By adjusting the amount of O_2 inflow from an O_2 cylinder and of CO_2 absorbed by a CO_2 absorber in the by-pass circuit, end-tidal P_{O_2} (P_{ETO_2}) was set at 100 mmHg and P_{ETCO_2} was set 5 mmHg higher than the resting level. These P_{ETO_2} and P_{ETCO_2} values were maintained for at least 3 min in order to attain a steady-state condition. Then, while maintaining the P_{ETCO_2} constant, P_{ETO_2} was progressively lowered by turning off the O_2 supply. The rate of P_{ETO_2} reduction was approximately 10 mmHg per min. When the ventilatory response was so intense that the P_{ETO_2} reduction was suspended, it was necessary to introduce N_2 gas into the circuit. The rebreathing was terminated when P_{ETO_2} decreased to 45 mmHg.

The reason for examining hypoxic response with the P_{ETCO_2} 5 mmHg higher than the resting level was as follows. Generally, hypoxic stimulation is very weak until P_{ETO_2} decreases to about 60 mmHg. Therefore, if the ventilatory response is obtained at the resting P_{ETCO_2} level, its magnitude tends to be in a fluctuating state until P_{ETO_2} is about 60 mmHg. However, when P_{ETCO_2} is increased by several mmHg as in the present experiment, a stable ventilatory response can be assessed even at light and moderate hypoxia, and thus consistent hypoxic response curves are assured.

REBUCK *et al.* (1973) also conducted a progressive hypoxia test with P_{ETCO_2} kept at a mixed venous P_{CO_2} level, which was probably about the same as the P_{ETCO_2} value used in the present study. The P_{ETO_2} – $\dot{V}$ response was analyzed by the hyperbola equation $\dot{V} = \dot{V}_O + A/(P_{ETO_2} - C)$, where $\dot{V}_O$ is the horizontal asymptote in ventilation for infinite P_{ETO_2} , A the slope constant of the hyperbola expressing hypoxic chemosensitivity of the subject, and C the vertical asymptote in P_{ETO_2} for infinite $\dot{V}$. The increment of ventilation at P_{ETO_2} 40 mmHg from hyperoxia was also calculated by the above hyperbola equation, and defined as $\Delta\dot{V}_{40}$.

A probe with a hot wire respiratory flowmeter (Minato Medical Sci. Co., Ltd., Tokyo) inserted between the rebreathing bag and the mouth piece was used to record tidal volume (V_T). P_{ETO_2} and P_{ETCO_2} were measured by an infrared CO_2 analyzer and a polarographic O_2 analyzer with rapid response (Sanei Expired Gas Monitor, 1H21, Tokyo). From the minute volume and O_2 and CO_2 concentrations of expired air collected in a smoothing bag, O_2 uptake ($\dot{V}_{O_2}$) and CO_2 output ($\dot{V}_{CO_2}$) were calculated. These were calculated before the ventilatory response test. At the

same time, ECG was recorded with a cardiac telemeter (Sanei Cardiosuper 2E31A, Tokyo). The average heart rate was recorded for every 8 R-R interval. All the details of these experimental procedures applied to adult subjects were reported in our previous communications (KIMURA *et al.*, 1984; OHYABU *et al.*, 1984).

RESULTS

Table 1 shows the physical characteristics and respiratory and heart rate data at rest as well as the ventilatory responses to CO₂ and hypoxia. The results were obtained from six different age groups from 7 to 18 yrs old. No obvious trend in changes with increasing age was seen in body fat in % BW, P_{ETCO_2} , heart rate, B values in CO₂ response, hypoxic chemosensitivity A , $\Delta \dot{V}_{40}$, and C values in the hypoxic response. On the other hand, age-dependent changes were found in BW, height, BSA, LBM, respiratory rate (f), $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, hypercapnic chemosensitivity S , and $\dot{V}_O$ values in the hypoxic response.

To compare the measured variables among the different age groups with different body size, hypercapnic ventilatory response S , $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$, and hypoxic ventilatory response A were all divided by BSA and are shown in Fig. 1. The average BW of the respective age groups is also shown here. S/BSA decreased progressively with increasing age in the first three groups, and then decreased gradually. The differences in S/BSA in the first three groups were significant. A similar tendency was observed in $\dot{V}_{CO_2}/BSA$ and $\dot{V}_{O_2}/BSA$, but was more marked in the former. As seen from this figure, no definite statistical trend was seen in $\dot{V}_{O_2}/BSA$. Contrary to the hypercapnic response, normalized hypoxic chemosensitivity, A/BSA , showed no consistent changes among the different age groups.

In accordance with the better correlation between S/BSA and $\dot{V}_{CO_2}/BSA$ than between S/BSA and $\dot{V}_{O_2}/BSA$ demonstrated in Fig. 1, the correlation coefficient in all the subjects between S/BSA and $\dot{V}_{O_2}/BSA$ was significant ($p < 0.01$), whereas between S/BSA it was not (Fig. 2).

S/BSA was inversely correlated with body weight as shown in Fig. 3 ($r = -0.56$, $p < 0.01$). A slightly better correlation was found when body weight was expressed in LBM as shown in Fig. 4 ($r = -0.65$, $p < 0.01$). However, the difference in correlation coefficients between Figs. 3 and 4 was not significant.

Hypercapnic chemosensitivity was also normalized by dividing BW or LBM. Thus the correlation coefficients between S/BW or S/LBM and other metabolic parameters, i.e., BW, $\dot{V}_{CO_2}/BW$ and $\dot{V}_{O_2}/BW$, were calculated and are shown in Table 2. The results were qualitatively similar to the relationships between S/BSA and the other metabolic parameters described above.

DISCUSSION

Our results demonstrated that normalized ventilatory chemosensitivity to CO₂, S/BSA , S/BW , or S/LBM decreased progressively from 7 to 12 yrs old, then further

Fig. 1. Normalized ventilatory and metabolic parameters by body surface area (BSA) and body weight (BW) were plotted against 6 different age intervals. Values are mean $\pm$ S.D. Normalized hypercapnic response (S/BSA) decreased progressively from the 7-8 to 11-12-yr group, then gradually decreased with increasing age. A similar trend was seen in $\dot{V}_{CO_2}/BSA$ and to a lesser degree in $\dot{V}_{O_2}/BSA$. BW increased progressively with increasing age. Contrary to hypercapnic response, normalized hypoxic ventilatory chemosensitivity (A/BSA) showed no definite tendency during growth.

decreased more gradually up to 18 yrs. This tendency was found to be well correlated with metabolic CO_2 production expressed per unit body mass. As shown in Table 1, resting P_{ETCO_2} was approximately the same among all the different age groups. Therefore, a dominant role in determining alveolar and arterial P_{CO_2} can

Fig. 2. Normalized hypercapnic ventilatory chemosensitivities (S/BSA) were plotted against normalized CO₂ output (left) and normalized O₂ intake (right). A significant correlation was found in the former ($p < 0.01$), but not in the latter.

Fig. 3. Normalized hypercapnic ventilatory chemosensitivities (S/BSA) were plotted against body weight (BW). A significant inverse relationship was observed ($p < 0.01$).

Fig. 4. Normalized hypercapnic ventilatory chemosensitivities (S/BSA) were plotted against lean body mass (LBM). A better correlation than in Fig. 3 was found, but the difference in correlation coefficient in Fig. 3 and Fig. 4 was not significant.

Table 2. Correlation coefficient between CO_2 chemosensitivities normalized by body weight (BW) or lean body mass (LBM) and other metabolic parameters.

I ($n=71$)		II ($n=65$)	
	S/BW		S/LBM
BW	-0.66	LBM	-0.70
$\dot{V}_{\text{CO}_2}/BW$	0.60	$\dot{V}_{\text{CO}_2}/LBM$	0.62
$\dot{V}_{\text{O}_2}/BW$	0.48	$\dot{V}_{\text{O}_2}/LBM$	0.48

Correlation coefficients in the 2nd and 3rd rows in series I and II were not significantly different.

probably be attributed to hypercapnic chemosensitivity in these age groups.

Contrary to the hypercapnic response, normalized ventilatory chemosensitivity to hypoxia showed no consistent trend among the different age groups. This seems to have confirmed the fact that resting ventilation in human beings is not critically determined by oxygen tension during air breathing (DEJOURS, 1981).

We found no cross-sectional age studies comparing normalized ventilatory chemosensitivities in the literature. However, data to calculate these parameters were obtained from two papers. Using Read's rebreathing method, COSGROVE *et al.* (1975) studied CO_2 chemosensitivity of 43 subjects ranging in age from 6.5 to 50 yrs.

S/BSA and S/BW of 28 subjects between 6.5 and 18 yrs old could be calculated from their data. Both S/BW and S/BSA progressively decreased from 6.5 to about 11 yrs, and then gradually decreased with increasing age. The correlation coefficients between S/BW or S/BSA and age were both -0.49 ($p < 0.01$). Using almost identical methods to those used in the present study, COLLINS *et al.* (1978) studied hypercapnic and hypoxic chemosensitivities in 24 pairs of twins. Twenty pairs of their subjects were 10–18 yrs old. Our calculation on data from these pairs revealed that there was a significant negative correlation between S/BSA and age ($r = -0.35$, $p < 0.05$), but not between A/BSA and age ($r = -0.24$, n.s.). Therefore, the results of the calculations of these two investigations seemed to confirm our data.

Other papers have reported on ventilatory chemosensitivity in children. SAUNDERS *et al.* (1976) studied the hypercapnic response in young athletes by Read's method. The forty-two children in their study were 10–17 yrs old, but the calculation of normalized CO₂ sensitivity was not possible from their data. Using the method of rebreathing 100% O₂, LWIN and GIAMMONA (1972) studied the CO₂ response in 8 normal children aged from 7 to 18 yrs. No definite trend in normalized hypercapnic chemosensitivity, S/BW , was found by calculation from their data. This was probably because the number of subjects was few and the method was different from that used in the present study.

It must be noted here that the magnitudes of hypercapnic sensitivity, S , obtained in the present study were between 0.81 and $1.71 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ on the mean, as shown in Table 1. These values are relatively low when compared with the magnitudes reported in the literature (HIRSHMAN *et al.*, 1975; RIGG *et al.*, 1974; WEISSMAN *et al.*, 1982). However, S values reported by KAWAKAMI *et al.*, (1982) in 20 pairs of identical twins of 16.2 ± 1.1 yrs and in 11 pairs of non-identical twins of 16.7 ± 0.7 yrs were 0.653 ± 0.193 and $0.663 \pm 0.256 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, respectively. These data are comparable with our hypercapnic response because the S value of 17 subjects in the 15–16-yr age group was $0.89 \pm 0.34 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, as indicated in Table 1. In general, it seems possible to conclude that the S value in Japanese is lower than the magnitude reported in Caucasians (HIRSHMAN *et al.*, 1975; RIGG *et al.*, 1974; WEISSMAN *et al.*, 1982).

There seem to be no studies on ventilatory chemosensitivities in children younger than the subjects in the present study. It is difficult in such young children to apply the method of rebreathing high CO₂ or hypoxic air. However, because good correlations between normalized S and CO₂ output were seen in our study, still higher hypercapnic chemosensitivities could be expected.

Applying the method of rebreathing 100% O₂, AVERY *et al.* (1963) claimed that the hypercapnic CO₂ response in normal newborn infants and adults is the same. However, linearity in the rate of increase of P_{CO_2} rise and the attainment of the open-loop condition in the CO₂ ventilation control system is doubtful in such experimental conditions (CONFERENCE REPORT, 1977; DEJOURS *et al.*, 1965). Using the steady-state method with 2 and 4% CO₂ inhalation, FRANZ *et al.* (1976) observed the maturational effects on CO₂ responsiveness in premature infants. The

S values of infants at 29–32 and 33–36 wks of gestation were 10.8 ± 5.6 and 53.5 ± 10.8 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{mmHg}^{-1}$, respectively at 3–4 postnatal days, and 21.6 ± 6.6 and 58.4 ± 10.6 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{mmHg}^{-1}$, respectively at 7–10 postnatal days. The last S value is approximately the same as the value we obtained in the 7–8-yr age group (64.1 ± 17.7 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{mmHg}^{-1}$). Whether or not there is further maturation in the hypercapnic chemosensitivities in newborn and very young children remains to be explored.

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REFERENCES

- AVERY, M. E., CHERNICK, V., DUTTON, R. E., and PERMUTT, S. (1963) Ventilatory response to inspired carbon dioxide in infants and adults. *J. Appl. Physiol.*, **18**: 895–903.
- BROŽEK, J., GRANDE, F., ANDERSON, J. T., and KEYS, A. (1963) Densitometric analysis of body composition. Revision of some quantitative assumptions. *Ann. N.Y. Acad. Sci.*, **110**: 113–140.
- COLLINS, D. D., SCOGGIN, C. H., ZWILLICH, C. W., and WEIL, J. V. (1978) Hereditary aspects of decreased hypoxic response. *J. Clin. Invest.*, **62**: 105–110.
- CONFERENCE REPORT (1977) Workshop on assessment of respiratory control in humans. I. Methods of measurement of ventilatory responses to hypoxia and hypercapnia. *Am. Rev. Respir. Dis.*, **115**: 177–181.
- COSGROVE, J. F., NEUNBURGER, N., BRYAN, M. H., BRYAN, A. C., and LEVISON, H. (1975) A new method of evaluating the chemosensitivity of the respiratory center in children. *Pediatrics*, **56**: 972–980.
- DEJOURS, P., PUCCINELLI, R., ARMAND, J., and DICHARRY, M. (1965) Concept and measurement of ventilatory sensitivity to carbon dioxide. *J. Appl. Physiol.*, **20**: 890–897.
- DEJOURS, P. (1981) Control of respiration. In: *Principle of Comparative Respiratory Physiology*, 2nd revised ed., Elsevier, Amsterdam, pp. 185–220.
- FRANZ, I. D. III, ADLER, S. M., THACH, B. T., and TAEUSCH, H. W. JR. (1976) Maturation effects on respiratory responses to carbon dioxide in premature infants. *J. Appl. Physiol.*, **41**: 41–45.
- HIRSHMAN, C. A., MCCULLOUGH, R. E., and WEIL, J. V. (1975) Normal values for hypoxic and hypercapnic ventilatory drive in man. *J. Appl. Physiol.*, **38**: 1095–1098.
- JANSEN, A. H. and CHERNICK, V. (1983) Development of respiratory control. *Physiol. Rev.*, **63**: 437–483.
- KAWAKAMI, Y., YOSHIKAWA, T., SHIDA, A., ASANUMA, Y., and MURAO, M. (1982) Control of breathing in young twins. *J. Appl. Physiol.: Respir. Environ. Exercise Physiol.*, **52**: 537–542.
- KIMURA, H., HAYASHI, F., YOSHIDA, A., WATANABE, S., HASHIZUME, I., and HONDA, Y. (1984) Augmentation of CO_2 drives by chlormadinone acetate, a synthetic progesterone. *J. Appl. Physiol.: Respir. Environ. Exercise Physiol.*, **56**: 1627–1632.
- LWIN, N. and GIAMMONA, S. T. (1972) Ventilatory responses to inspired CO_2 in patients with cystic fibrosis. *Chest*, **61**: 206–212.
- OHYABU, Y., YOSHIDA, A., HAYASHI, F., NISHIBAYASHI, Y., SAKAKIBARA, Y., SATO, N., and

- HONDA, Y. (1984) Ventilatory and heart rate responses to hypoxia in well-trained judo athletes. *Eur. J. Appl. Physiol.*, **52**: 451–456.
- READ, D. J. C. (1967) A clinical method for assessing the ventilatory response to carbon dioxide. *Australas. Ann. Med.*, **16**: 20–32.
- READ, D. J. C. and LEIGH, J. (1967) Blood-brain tissue P_{CO_2} relationships and ventilation during rebreathing. *J. Appl. Physiol.*, **23**: 53–70.
- REBUCK, A. S., KAMAGALEE, M., PENGELLY, L. D., and CAMPBELL, E. J. M. (1973) Correlation of ventilatory responses to hypoxia and hypercapnia. *J. Appl. Physiol.*, **35**: 173–177.
- RIGG, J. R. A., REBUCK, A. S., and CAMPBELL, E. J. M. (1974) Effect of posture on the ventilatory response to CO₂. *J. Appl. Physiol.*, **37**: 487–490.
- SAUNDERS, N. A., LEEDER, S. R., and REBUCK, A. S. (1976) Ventilatory responses to carbon dioxide in young athletes: A family study. *Am. Rev. Respir. Dis.*, **113**: 497–502.
- WEIL, J. V., BYRNE-QUINN, E., SODAL, I. E., FRIESEN, W. O., UNDERHILL, B., FILLEY, G. J., and GROVER, R. F. (1970) Hypoxic ventilatory drive in normal man. *J. Clin. Invest.*, **49**: 1061–1072.
- WEISSMAN, C., ABRAHAM, B., ASKANAZI, J., MILIC-EMILI, J., HYMAN, A. I., and KINNEY, J. M. (1982) Effect of posture on the ventilatory response to CO₂. *J. Appl. Physiol.: Respir. Environ. Exercise Physiol.*, **53**: 761–765.