Relationships between Hypoxic and Hypercapnic Ventilatory Responses in Man

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Abstract Ventilatory responses to hypoxia (A) and hypercapnia (S) were measured in 127 healthy men (105 males and 22 females) by a dual control system for regulating P_{aO_2} and P_{aCO_2} simultaneously and independently of each other. The subjects were classified into groups according to sex, age, family history, and genetics (twins). Mean values for A were $138 \pm SD 93$ liters/min $\cdot$ mmHg in group I (subjects without family history of chronic lung diseases) and 80 ± 56 liters/min $\cdot$ mmHg in group II (sons of patients with chronic obstructive pulmonary disease or silicosis). The difference was highly significant ($P < 0.001$).

Mean S were 1.11 ± 0.39 liters/min $\cdot$ mmHg $^{-1}$ in group I and 1.16 ± 0.48 liters/min $\cdot$ mmHg $^{-1}$ in group II. The difference was not significant. Mean values for A and S in the aged males (mean age = 71.3 years) did not differ from those in 15 adult males (mean age = 29.5 years) and 60 young twins (mean age = 16.4 years).

In every respect of age, sex, familial factors, and genetics, A and S were not interrelated. Mouth occlusion pressure ($P_{0.1}$) was measured during air breathing and it correlated neither with A nor S .

These results indicate 1) hypoxic and hypercapnic responses are not strongly related to each other, and 2) the aging process does not alter ventilatory responses to hypoxia and hypercapnia.

Hypoxic and hypercapnic ventilatory responses have been shown in man to be positively correlated: vigorous hypoxic responses were associated with vigorous hypercapnic responses (REBUCK *et al.*, 1973; HIRSHMAN *et al.*, 1975). The hypoxic response was obtained under either hypercapnic or normocapnic conditions and the hypercapnic response, under hyperoxic conditions, in their reports. Moreover, interactions of CO_2 and O_2 as chemical stimuli have experimentally been proved to occur at the peripheral chemoreceptors (CUNNINGHAM, 1974).

It might be worth reexamining the relationship between hypoxic and hypercapnic ventilatory responses with a more stable method and in a larger number

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of subjects, since clarification of the relationship, if any, would be of physiological and clinical importance. This communication was aimed at analyzing chemical control of breathing in man with a dual control system which maintains arterial blood gases (P_{aO_2} and P_{aCO_2}) at predetermined levels simultaneously and independently of each other.

MATERIALS AND METHODS

The subjects were 127 healthy men (105 males and 22 females). For the analyses of relationships between hypoxic and hypercapnic responses, the subjects were divided into two groups according to their family history. Group I consisted of 85 subjects (63 males and 22 females) in whom evidences of chronic lung diseases were not found, either in themselves or in their immediate relatives. There were 15 adult males, 10 aged males, 40 monozygotic twins, and 20 dizygotic twins. Group II subjects were 42 sons of patients with chronic obstructive pulmonary disease (COPD, $n=26$) and silicosis (pneumoconiosis due to silica deposition, $n=16$). All the subjects were healthy at the time of the study as estimated by chest roentgenograms, ECG, blood chemistry, and physical examinations. Pulmonary functions were evaluated in terms of spiograms, lung volume subdivisions, mechanics, single breath N_2 washout curves, flow-volume curves, and arterial blood gases and pH. Spiograms and flow-volume curves were obtained by a direct writing flow-volume recorder (Chestac STM 81). Airway resistance and functional residual capacity were measured with a constant volume body plethysmograph. Single breath N_2 washout curves were analyzed by relating expired N_2 concentration (Medical gas analyzer MGA-1100, Perkin-Elmer) to expired volume. These variables were normal in group I except for spiograms of aged males as shown in Table 1. Pulmonary functions were not necessarily normal in group II (Table 1).

Hypoxic and hypercapnic ventilatory responses were examined in the supine position after the subject took at least a 30 min rest on a bed. A dual control system was used to regulate P_{aO_2} and P_{aCO_2} simultaneously and independently of each gas. The detailed descriptions of the system have appeared elsewhere (KAWAKAMI *et al.*, 1981a). Briefly, the system utilized end-tidal gases (P_{AO_2} and P_{ACO_2}) as an indirect estimate of arterial blood gases. By assuming constant values for P_{aO_2}/P_{AO_2} and P_{aCO_2}/P_{ACO_2} during changes in inspiratory gas compositions, arterial blood gases could be controlled by regulating inspiratory gas compositions to obtain P_{aO_2} and P_{aCO_2} at predetermined levels. It took about 5 min to reach predetermined levels in end-tidal gases. Minute ventilation ($\dot{V}_E$) was monitored breath by breath by a hot wire respiratory flowmeter (Minato medical products, RF-H) through the electrical integration of air flow ($\dot{V}$). Effects of gas composition of flowmeter outputs were not corrected for since these were reported to be extremely small (YOSHIYA *et al.*, 1979). Respiratory gases were

Table 1. Anthropometric and pulmonary function data.

	<i>n</i>	Age (yrs)	BSA (m ²)	VC (% pred)	FEV ₁ /FVC (%)	R_{aw} (cmH ₂ O/ liter·sec)	FRC (liters)	$\dot{V}_{50}$ (liters/sec)	$\dot{V}_{25}$ (liters/sec)	CV/VC (%)
Group I	85									
Adult male	15	29.5 ± 5.6	1.72 ± 0.12	105.5 ± 11.2	88.6 ± 4.8	1.15 ± 0.21	2.46 ± 0.53	5.23 ± 0.79	2.07 ± 0.50	12.5 ± 4.2
Aged male	10	71.3 ± 3.8	1.56 ± 0.13	103.5 ± 19.6 (10)	68.5 ± 8.5 (80)	1.57 ± 0.78	3.29 ± 0.54	2.14 ± 1.01	0.71 ± 0.25	28.5 ± 6.8
Twin										
Monozygotic	40	16.2 ± 1.1	1.59 ± 0.13	3.83 ± 0.78*	90.5 ± 7.3	1.74 ± 0.60	3.00 ± 0.71	4.34 ± 1.14	2.39 ± 0.71	10.8 ± 3.3
Dizygotic	20	16.7 ± 0.7	1.58 ± 0.16	3.85 ± 0.72*	90.7 ± 5.1	1.79 ± 0.64	2.81 ± 0.65	4.63 ± 0.65	2.39 ± 0.57	11.0 ± 4.5
Group II	42									
Sons of COPD patients	26	33.0 ± 9.5	1.71 ± 0.15	115.0 ± 20.3	82.6 ± 5.0 (27)	1.04 ± 0.33	2.79 ± 0.42	4.34 ± 0.42 (7)	1.71 ± 0.66 (16)	14.9 ± 5.8 (42)
Sons of silicosis patients	16	36.0 ± 13.8	1.65 ± 0.15	103.2 ± 30.2	87.1 ± 4.9 (19)	1.09 ± 0.11	3.32 ± 0.19	4.97 ± 1.06 (13)	2.19 ± 0.81 (6)	13.2 ± 5.2 (6)
Twin										
Male	MZ 24 DZ 14	16.1 ± 0.9	1.60 ± 0.08	4.13 ± 0.37*	90.0 ± 7.8	0.67 ± 0.17	3.14 ± 0.51	4.36 ± 1.15	2.42 ± 0.74	10.8 ± 2.6
Female	MZ 14 DZ 8	17.2 ± 0.9	1.47 ± 0.10	3.07 ± 0.30*	91.8 ± 6.6	0.59 ± 0.23	2.37 ± 0.48	3.97 ± 0.91	2.20 ± 0.71	12.3 ± 3.9

Abbreviations: BSA, body surface area; VC, vital capacity; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; R_{aw} , airway resistance; FRC, functional residual capacity; $\dot{V}_{50}$, forced expiratory flow at 50% of forced vital capacity; $\dot{V}_{25}$, forced expiratory flow at 25% forced vital capacity; and CV/VC, closing volume/vital capacity.

Values are mean ± SD.

Numbers in parentheses are occurrence of abnormal values in %.

* Units are liter (BTPS).

continuously monitored by the mass spectrometer. The electrical signals of end-tidal gases, $\dot{V}_E$, $\dot{V}$, heart rate, arterial oxygen saturation (Mochida-Luketron Oximet MET 1471), and mouth pressure were recorded on a polygraphic recorder (Sanei Sokki 142-8). Simultaneously, digital signals of $\dot{V}_E$, end-tidal gases and arterial saturation were recorded on a digital printer (Ricoh) fed by a signal processing computer (ATAC 450, Nihon Kohden).

Hypoxic ventilatory responses were assessed by the equation (WEIL *et al.*, 1970):

$$\dot{V}_E = \dot{V}_{E0} + A/(P_{AO_2} - 32),$$

where $\dot{V}_E$, minute ventilation in liters/min; $\dot{V}_{E0}$, horizontal asymptote for ventilation obtained by extrapolation; A , slope factor which determines the shape of the response curve such that a high value for A designates a vigorous ventilatory response to hypoxia and a low value, a blunted response. P_{aCO_2} was kept at 40 mmHg during the hypoxic response while P_{aO_2} was progressively lowered to 40 mmHg. After P_{aO_2} and P_{aCO_2} attained the predetermined levels, 3 min were allowed to stabilize $\dot{V}_E$.

Hypercapnic ventilatory responses were analyzed by the equation:

$$\dot{V}_E = S \times (P_{ACO_2} - B),$$

where S , slope of the P_{ACO_2} -ventilation line in liters/min $\cdot$ mmHg⁻¹; P_{ACO_2} , end-tidal P_{CO_2} in mmHg; and B , intercept on the abscissa (P_{ACO_2}) in mmHg. P_{aO_2} was kept at 95 mmHg while P_{aCO_2} was progressively raised up to 50 mmHg.

After each measurement of hypoxic and hypercapnic ventilatory responses, $\dot{V}_E$ and end-tidal gases obtained every 15 sec interval were displayed on an X-Y plotter (Hewlett Packard) or on a CRT of the computer to examine the shape of the response curves. A linear part of the P_{ACO_2} -ventilation relationship was used for the computation of S ; curvilinear parts of the slope were often seen in some subjects a few mmHg above P_{ACO_2} on air and these parts were discarded from the computation. The variable A was computed by a least square method relating $\dot{V}_E$ to P_{AO_2} every 15 sec period. The variable S was obtained by directly relating $\dot{V}_E$ to P_{ACO_2} every 15 sec. The BASIC program for this computation and display can be offered on request.

While the subject was breathing room air, arterial blood was drawn from the brachial artery, and arterial blood gases and pH were analyzed immediately after sampling by a blood gas analyzer (Instrumentation Labs type 813). The analyzer was calibrated prior to the experiment with gas mixtures whose concentrations had been checked by a Scholander apparatus. Plasma $[HCO_3^-]$ was determined by P_{aCO_2} and pH with the Siggaard-Andersen alignment nomogram.

Mouth occlusion pressure ($P_{0.1}$) was measured in triplicate by manually closing a three way valve momentarily without the subject's notice during inspiration while breathing room air (WHITELAW *et al.*, 1975). Average $P_{0.1}$ from triplicate measurements was used for the statistical analyses.

Table 2. Arterial blood gases and ventilatory responses.

	P_{aO_2} (mmHg)	P_{aCO_2} (mmHg)	pH	$[HCO_3^-]$ (mEq/liter)	$\dot{A}$ (liters/min· mmHg)	$\dot{A}/BSA$ (liters/min· mmHg·m ⁻²)	$\dot{S}$ (liters/min· mmHg ⁻¹)	$\dot{S}/BSA$ (liters/min· mmHg ⁻¹ ·m ⁻²)	$P_{0.1}$ (cmH ₂ O)
Group I									
Adult male	90.1±9.0	40.2±2.8	7.375±0.019	22.9±1.5	101±82	58.7±32.8	1.18±0.40	0.69±0.23	1.1±0.6
Aged male	79.9±8.3	37.2±2.2	7.406±0.019	22.9±1.2	133±47	90.4±22.1	1.40±0.48	0.90±0.32	1.1±0.4
Twin					138±93*	85.9±55.7	1.11±0.39**	0.69±0.24	1.1±0.6
Monozygotic	94.9±6.4	37.9±2.6	7.398±0.020	22.9±1.5	158±108	97.1±64.3	1.04±0.32	0.65±0.19	1.2±0.6
Dizygotic	95.3±5.9	38.7±3.2	7.386±0.015	22.7±1.7	131±96	80.9±55.9	1.06±0.42	0.66±0.26	1.0±0.5
Group II									
Sons of COPD patients	84.5±9.5 (23)	40.7±2.9 (8)	7.377±0.03 (18)	23.4±1.7	80±56	48.7±34.6	1.16±0.48	0.69±0.27	1.1±0.5
Sons of silicosis patients	91.5±7.9	38.2±2.6	7.397±0.02	23.0±1.5	89±64	52.1±36.2	1.17±0.46	0.69±0.28	1.2±0.5
Twin					68±49	42.7±31.7	1.15±0.52	0.69±0.27	1.1±0.6
Male	94.5±6.1	38.6±2.5	7.394±0.016	23.1±1.3	168±110	104.4±63.7	1.08±0.29	0.68±0.18	1.7±0.6
Female	96.1±6.4	36.5±2.7	7.398±0.023	20.1±1.8	102±104	67.0±63.0	0.85±0.10	0.58±0.07	2.1±0.6

Values are mean±SD.

* Significantly different from A in group II ($p<0.001$).

** Not different from S in group II.

The relations between two variables were examined by a linear correlation coefficient (r). When the t values were less than 0.05, the relation was assumed to be significant.

RESULTS

Mean values for A were 138 ± 93 liters/min $\cdot$ mmHg in group I and 80 ± 56 liters/min $\cdot$ mmHg in group II (Table 2). Mean values for arterial blood gases, acid-base status, and ventilatory responses in subgroups of group I are listed in Table 2. There were no significant differences in A and S between four subgroups of group I. Mean A of group II was significantly lower than that in group I.

Mean values for S were 1.11 ± 0.39 liters/min $\cdot$ mmHg $^{-1}$ in group I and 1.16 ± 0.48 liters/min $\cdot$ mmHg $^{-1}$ in group II as shown in Table 2. There were no differences in S between groups I and II.

Correlations between A and S in groups I and II are tabulated in Table 3. No significant correlations were seen between A and S in any 6 subgroups. There were no correlations found between A and S when overall relationships in groups I and II were examined (Figs. 1 and 2).

Mean values for $P_{0.1}$ during air breathing did not differ between any of the groups and subgroups. $P_{0.1}$ correlated neither with A nor S in groups and subgroups, as shown in Table 3.

Fig. 1. Relationships between hypoxic (A) and hypercapnic (S) ventilatory responses in group I.

Fig. 2. Relationships between A and S in group II.

Table 3. Correlation coefficients between A and S .

	A vs. S	$P_{0.1}$ vs. A	$P_{0.1}$ vs. S
Adult male	0.068	-0.110	-0.243
Aged male	-0.402	-0.106	-0.107
Monozygotic twin	0.299	-0.129	0.133
Dizygotic twin	0.360	0.141	-0.154
Son of COPD patient	0.219	0.368	0.063
Son of silicosis patient	-0.220	0.416	-0.077
Male twin	0.255	-0.024	-0.126
Female twin	0.343	-0.058	0.269

All the coefficients were not significant.

DISCUSSION

Our study indicates that hypoxic and hypercapnic ventilatory responses remain at normal values in normal subjects whose age ranges from 14 to 79 years and that chemical control systems of hypoxia and hypercapnia seem not directly related with every respect of age, sex, family history, and genetics. Mouth occlusion pressure ($P_{0.1}$) during air breathing is not directly related to hypoxic and hypercapnic ventilatory responses.

A dual control system used in the present study was able to regulate P_{aO_2} and P_{aCO_2} simultaneously and independently of each other. The accuracy as estimated by the coefficients of variation was relatively high: for P_{aO_2} 7.1% during normoxic normocapnia, 9.7% during normocapnic hypoxia, and 11.7% during normoxic hypercapnia. For P_{aCO_2} the values were 7.8%, 6.4%, and 6.4%, respectively (KAWAKAMI *et al.*, 1981b). Manual control of inspiratory gas composition has often been difficult for maintaining isocapnic and isoxic conditions, whereas automatic servo-control, although more sophisticated and expensive, enables an accurate control of arterial blood gases at predetermined levels. Additionally, a computerized system for X-Y display and calculations of A , S , $\dot{V}_{E0}$, and B saves time on tedious calculations.

Present values for A and S seem to be in accordance with the previous values reported with the rebreathing method by HIRSHMAN *et al.* (1975). Physical characteristics as estimated by weight, height, and body surface area are known to affect the values for A and S (HIRSHMAN *et al.*, 1975). When the differences in body surface area are taken into consideration, the mean value for A/BSA in group I is very close to the value reported by HIRSHMAN *et al.* (1975). However, the mean values for S/BSA in groups I and II are significantly lower in the present study than those in the previous reports (REBUCK *et al.*, 1973; HIRSHMAN *et al.*, 1975). Although the exact reason is not known, one of the possible causes is a different procedure for analyzing ventilatory responses between our own (dual control) and previous rebreathing methods. Another possible cause might be racial difference. However, for Japanese young males, HONDA *et al.* (1971) and

OHKUWA *et al.* (1980) reported the values of $1.26 \pm \text{SD } 0.52$ and 1.19 ± 0.81 liters/min $\cdot$ mmHg⁻¹ $\cdot$ m⁻², respectively, which are still higher than ours. On the contrary, the value (0.70 ± 0.26 liters/min $\cdot$ mmHg⁻¹ $\cdot$ m⁻²) reported by NISHINO *et al.* (1977) is in close agreement with ours.

The present subjects took up a supine position, whereas an upright or semi-recumbent position was usual in the literature. In the report of RIGG *et al.* (1974), the posture did not affect the ventilatory response to CO₂. Although either the sitting or supine position is recommended by the workshop of the American Thoracic Society, whether the postures significantly affect the values for hypoxic ventilatory response is not known, to our knowledge.

Our results indicate that chemical control of breathing is not depressed in the aged. According to KRONENBERG and DRAGE (1973), ventilatory and heart rate responses were attenuated with increasing age. Ventilatory responses to isocapnic hypoxia in the aged (mean age=70 years) were 51% of those in young subjects (mean age=26 years). Hypercapnic ventilatory responses were 41%. Mechanisms of the diminished responses were not known and other factors unrelated to chemoreceptor function could not be excluded in their report. Although body sizes were larger in their subjects than our aged males, mean ages were equivalent. Arterial blood gases and acid-base status were not shown in their report, which makes a comparison difficult. There have been numerous factors reported as influencing *A* and *S*: genetics, sex, body characteristics, nutrition, sports, high altitude, and cardiopulmonary disorders, to quote a few. Since the cause(s) of discrepant results with respect to age is not known in the present study, this merits further investigation. Among many physiological factors modifying normal values for *A* and *S*, genetics seems to be important. The twin studies by COLLINS *et al.* (1978) and Kawakami *et al.* (unpublished data) have clarified that chemical control of breathing is strongly influenced by hereditary factors. Although only *A* was presumably controlled by genetics in Collins *et al.*'s study, both *A* and *S* seemed to be influenced by genetic factors in our study (Kawakami *et al.*, unpublished data). It is quite possible that discrepant results between Kronenberg and Drage's report and the present data was due to genetics. Genetic factors are unique in that they cannot be corrected for by a numerical standardization such as body surface area.

Body size influences the levels of ventilatory responses (HIRSHMAN *et al.*, 1975). This seems especially true for *A*, since adult males and sons of COPD patients showed a larger body surface area than the other subgroups and their *A* was significantly lower than those seen in aged males and twins. Both *A* and *S* increase as weight and height increase (HIRSHMAN *et al.*, 1975). The lower values for *A* and *A*/BSA in our adult males and sons of COPD patients would probably be due to obesity. In contrast, the lower value for *A* and *A*/BSA in sons of silicosis patients does not seem to be due to body characteristics. Familial factors of silicosis patients are the possible cause.

Abnormal pulmonary function was frequently seen in sons of patients with COPD. This fact seems to indicate that early pulmonary abnormalities are already present in the apparently healthy sons of COPD patients. Group II subjects did not show significant correlations between A and S in the present study. Mean values for A and A/BSA were significantly lower in group II than those in group I (Table 2). Although it can be hypothesized that early pulmonary disorders affect chemical control of breathing, A and S are not related to each other in the subjects with slight deteriorations in pulmonary function.

The rebreathing method for measuring ventilatory responses is widely accepted for physiological and clinical studies because of the simplicity and the theoretical validity (READ, 1967). However, hyperoxic conditions associated with the method may influence the hypercapnic ventilatory response by two possible mechanisms. One is the variable response to hypoxia among subjects. The degree of released hypoxic ventilatory drive is apparently dependent on how far the carotid bodies are chemically denervated by hyperoxia. It is not likely that $P_{a\ O_2}$ levels of the present study (95 mmHg) influenced the hypercapnic ventilatory response, although chemical denervation of carotid bodies seems incomplete with these levels of arterial oxygenation. If complete denervation was not accomplished in the present study, S would have been higher than the reported values obtained with the rebreathing method. The other possible mechanism is interstitial acidosis due to accumulation of CO_2 in the brain under hyperoxic conditions. Hyperoxia causes a rapid reduction in cerebral blood flow which further causes elevation in jugular venous P_{CO_2} , indicating interstitial and cerebrospinal fluid accumulation of CO_2 (GIBBS *et al.*, 1935; LAMBERTSEN *et al.*, 1953). Although the rapidity of CO_2 accumulation in the cerebral tissue is not known, it is possible, but unproven, that the augmentation of ventilatory responses to hypercapnia by interstitial acidosis in the central chemoreceptor region forms a basis for higher values for S/BSA in the previous literature.

Patients with COPD are often representative of hypoxemia with hypercapnia. REBUCK *et al.* (1973) thought that this fact supported their findings that A and S were highly correlated in the normal subjects. There have been numerous reports that arterial blood gases and pH are related to the degree of blunted ventilatory responses to either hypoxia or hypercapnia. However, a considerable number of patients with COPD reveal hypoxemia alone except in the advanced stages. Furthermore, ventilatory responses to chemical stimuli in these patients are extremely variable: patients with combined hypoxemia and hypercapnia do not always show more pronounced reduction in ventilatory responses than patients with hypoxemia alone (FLENLEY *et al.*, 1970). This fact may raise the possibility that positive correlation between A and S holds good only in certain subjects such as athletes (BYRNE-QUINN *et al.*, 1971). Clinical experiences of many physicians would agree with the report of FLENLEY *et al.* (1970) in that predictions of chemosensitivity are extremely difficult on the basis of arterial blood gases, pH,

and $[\text{HCO}_3^-]$. We share this experience with some doubt on the reports that arterial blood gases are correlated with the chemical control of breathing as estimated by ventilatory responses.

Why are A and S not correlated among normal and subnormal subjects? Among many possibilities, the difference in control mechanisms between hypoxic and hypercapnic responses should be considered. Hypoxic ventilatory responses are sensed primarily by the carotid bodies from which signals are transmitted to the medulla. On the other hand, mechanisms of hypercapnic ventilatory responses seem more complicated: chemical stimuli are sensed by the carotid bodies to a smaller extent and, to a larger extent, by central chemoreceptors. Our present method seems far from steady in respect of acid-base balance. It is quite possible that the intensity of chemical stimuli was ever-changing throughout the experiment and that they were quite different regarding time sequence between carotid bodies and central chemoreceptors. Even if a complete steady state is attained during the measurement, signals originating from two receptors would differ greatly in their intensity. Whatever the mechanisms, a functional feedback loop between peripheral chemoreceptors which respond to hypoxic and hypercapnic stimuli and central chemoreceptors which respond to hypercapnic stimuli is, if it exists, not strong enough to be reflected in the correlation between A and S . However, this does not necessarily exclude the possibility of compensatory mechanism(s) between two responses in patients and normal subjects under special circumstances.

Our findings seem interesting in the teleological sense. If A and S are not related, it would be rather advantageous when the insults affect the body. Even if one of the ventilatory responses is blunted as a result of the insults, the other response will operate to regulate ventilation, and deteriorations in acid-base status will be greatly alleviated. Conversely, if there is a positive correlation between A and S , the subject with blunted ventilatory responses is vulnerable to acid-base imbalance. In facts, our previous report (KAWAKAMI *et al.*, 1979a) of familial factors of ventilatory responses and pulmonary function disclosed that sons of patients with type B COPD (combined hypoxemia and hypercapnia) showed blunted hypoxic response and normal hypercapnic response. Our family study (KAWAKAMI *et al.*, 1980) also indicated that A and S were *inversely* correlated in 5 family members of a patient with CO₂ retention. All the members showed the blunted ventilatory responses either to hypoxia or hypercapnia. KRONENBERG *et al.* (1977) reported on a 64-year-old woman with marked obesity. She had experienced acute respiratory failure without marked abnormalities in pulmonary function. Her hypoxic ventilatory response remained absent but the hypercapnic response was restored to normal as she lost weight. These facts would be another indication for the discrepant relationships between A and S .

Our findings that $P_{0.1}$ during air breathing was not correlated with A and S support the report of SORLI *et al.* (1978) indicating that $P_{0.1}$ at rest was not significantly different between hypercapnic and non-hypercapnic patients. These facts

support that $P_{0.1}$ includes signals of chemical as well as of neural control systems. The measurements of $P_{0.1}$ seem especially suited for patients with mechanical limitations to breathing, since ventilatory responses as estimated by ventilation will be largely influenced by such limitations. For the purpose of reliable evaluation of respiratory center output in patients, $P_{0.1}$ must be measured breath by breath throughout the analyses of A and S . For this, however, sophisticated electrical circuits are necessary.

In conclusion, hypoxic and hypercapnic ventilatory responses are not strongly interrelated in normal and subnormal subjects. Although this is teleologically advantageous for most of the normal subjects, it is not necessarily so for athletes or long-distance swimmers. The aging process does not seem to markedly blunt chemical control of breathing.

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