

## Basic and Clinical Studies on Mouth Occlusion Pressure in Healthy Subjects and Patients with Pulmonary and Muscular Diseases\*

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(Received September 25, 1982)

*Key words: Mouth occlusion pressure, Healthy subjects, Pulmonary diseases, Duchenne's muscular dystrophy*

### ABSTRACT

Mouth occlusion pressure was studied in 197 healthy subjects classed by age and sex group, and in patients with various diseases. Among the patients, there were 10 patients with fibrosing lung disease, 10 patients with pulmonary emphysema, 27 patients with chronic bronchitis, 48 patients with pneumoconiosis and 49 patients with Duchenne's muscular dystrophy. The following results were obtained.

1. There was no difference in the relationship of alveolar  $P_{CO_2}$  to  $P_{a,1}$  when re-breathing was performed using a 100%  $O_2$  or a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$  as the initial gas. In the study of 18 healthy subjects, two different types of relationship between alveolar  $P_{CO_2}$  and  $P_{a,1}$ , namely linear and exponential relationship were observed.

2. There was a significant decrease in functional residual capacity in the supine position in comparison with the sitting position in 15 healthy males studied, but there was no change in the values of  $P_{a,1}$  during room air breathing at rest between the two positions.

3. The mean values and standard deviations of  $P_{a,1}$  in healthy adults and healthy children were  $1.61 \pm 0.13$  cmH<sub>2</sub>O and  $2.87 \pm 0.38$  cmH<sub>2</sub>O respectively. No difference by sex could be observed.

4. In comparison with the healthy subjects, a significant increase of  $P_{a,1}$  ( $P < 0.001$ ) was observed in patients with fibrosing lung disease, pulmonary emphysema, chronic bronchitis and patients with pneumoconiosis.

5. In comparison with the healthy subjects, the  $P_{a,1}$  decreased significantly ( $P < 0.001$ ) in patients with Duchenne's muscular dystrophy for both adults' and children's groups.

6. The re-breathing is a valuable method for obtaining the ventilatory curve to  $CO_2$  and the  $P_{a,1}$  is a simple method which can be used clinically to evaluate the neural activity of the respiratory center.

### INTRODUCTION

Man takes in oxygen ( $O_2$ ) through breathing, which is necessary for the process of metabolism, consequently carbon dioxide ( $CO_2$ ) is produced as the results of tissue metabolism and is further transported in the blood and later exhaled from the lungs into the air.

In the brain stem, particularly the reticular formation of the medulla, respiratory movement is generated automatically. The group of these neurons is called the respiratory center as a whole. As inputs to this respiratory center, there is information from the peripheral and central chemoreceptors and also from the peripheral mechanoreceptor.

\* ファイナル・ニュース: 健常者, 肺疾患および筋肉疾患患者における  $P_{a,1}$  の基礎的, 臨床的研究

To move the respiratory muscles for respiration, the outputs from the respiratory center transmit activity to these muscles via the spinal nerves, particularly the phrenic nerves and the intercostal nerves from the thoracic nerves.

It has long been known that the function of this respiratory center is influenced by the disorders of the respiratory system, metabolism and cerebrovascular disease. However, no reliable method has yet been established to evaluate the function of this respiratory center.

To measure the function of the respiratory center, what has been done so far in the way of basic experimental studies is to insert electrodes into the medullary respiratory center to derive the activity of the respiratory neurons. Also any experiment has been done to derive the discharge of the phrenic nerves.

Further, in man, the  $O_2$  consumption of the respiratory muscles<sup>11)</sup>, the total respiratory muscles output<sup>6,10)</sup>, the inspiratory mechanical work<sup>12)</sup> and the change of ventilatory response to the loading of  $CO_2$ <sup>13)</sup> have been measured to evaluate the activity of the respiratory center.

Particularly in the measurement of ventilatory response to  $CO_2$  the steady state method, inhaling various concentration of  $CO_2$  and the rebreathing method, increasing the concentration of  $CO_2$  gradually in the bag, are often used. The steady state method is rather complicated since it is necessary to inhale various concentration of  $CO_2$  to obtain a curve of ventilatory response to  $CO_2$ . On the contrary, the rebreathing method is simple, faster to perform<sup>14)</sup> and is no less informative than the steady state method<sup>15,20)</sup>. But it is reported that the ventilatory response to  $CO_2$  may be influenced by temperature<sup>14,45)</sup>, age<sup>31)</sup>, sex<sup>28,41,50)</sup>, hereditary factors<sup>3,39,50)</sup> and the interval between measurements<sup>25,30)</sup>.

The necessity of special apparatus in the cases of respiratory failure with high arterial  $P_{CO_2}$ , may have disturbed this method to be used widely.

When a case clinically shows a decrease in ventilation, it is sometimes difficult to determine whether the primary cause lies in the respiratory center, respiratory muscles or lung-thoracic system. Hypoventilation occurs in such conditions, 1) the activity of the respiratory center is decreased due to disorders in the brain stem or drugs, with secondary decrease in the activity

of the respiratory muscles, 2) the activity of the respiratory muscles is decreased while the function of the respiratory center is normal, 3) respiratory resistance is increased, such as in chronic obstructive lung diseases, with normal function of the respiratory muscles.

As mentioned above, diseases causing hypoventilation are classified grossly into those of the respiratory center, muscles and lungs, and it is suggested to classify them correctly and give proper treatment. The functional disturbance of the lung has been evaluated so far fairly well, but there has been no method established of evaluating clinically the activity of the respiratory muscles or respiratory center.

In 1975 Whitelaw and Milic-Emili et al<sup>48,60)</sup> made a basic study, proposing the mouth pressure when the airway is occluded at the beginning of inspiration, the mouth occlusion pressure, as the index of activity of the respiratory center. During occluded inspiration, there is almost no air flow and no change in pulmonary air volume, therefore, the measurement is not influenced by the flow-resistance or compliance of the respiratory system, and by vagal lung volume-related reflexes<sup>61)</sup>.

Furthermore, it correlates well with the electrical activity in the phrenic nerves<sup>30)</sup>. Also, changes in occlusion pressure during hypercapnia correlate with changes in the electrical activity of the diaphragm and with ventilatory responses to  $CO_2$  in normal individuals<sup>1)</sup>.

If the curves of airway occlusion pressure are studied when airway occlusion is repeated, the pressures are reproducible up to about 0.2 sec from the beginning of inspiration, increasing linearly. The variation appears after this point, because of the subject being aware of an increase in the mouth pressure due to the airway occlusion through the intrapulmonary mechanoreceptors and gamma fiber system. Consequently, it is the airway occlusion pressure within 0.2 sec from the beginning of inspiration that reflects the activity of the respiratory center during ventilation at rest, and as the index the change of airway occlusion pressure initial 0.1 sec, namely  $P_{0.1}$  is used.

The author studied the following points which seemed to influence this  $P_{0.1}$ :

- 1) the relation between  $P_{0.1}$  and alveolar  $P_{CO_2}$  in the rebreathing method when the concentration of  $CO_2$  in the bag is 7% or

Table 1. Symbols and abbreviations

A-aDo <sub>2</sub>	alveolar-arterial oxygen pressure difference, (mmHg)
CB	chronic bronchitis.
D <sub>LCO</sub>	diffusing capacity of the lung by CO breath holding method, (ml/min/mmHg)
%D <sub>LCO</sub>	D <sub>LCO</sub> to predicted value ratio, (%)
f	respiratory frequency, (breaths/min)
FEV <sub>1.0</sub>	forced expiratory volume in 1.0 second, (liter)
FEV <sub>1.0</sub> %	FEV <sub>1.0</sub> to forced vital capacity ratio, (%)
FLD	fibrosing lung disease.
FRC	functional residual capacity, (liter)
%FRC	FRC to predicted value ratio, (%)
MVV	maximal voluntary ventilation, (liter/min)
%MVV	MVV to predicted value ratio, (%)
P <sub>ACO<sub>2</sub></sub>	alveolar carbon dioxide tension, (mmHg)
P <sub>ACO<sub>2</sub></sub>	arterial carbon dioxide tension, (mmHg)
P <sub>AO<sub>2</sub></sub>	arterial oxygen tension, (mmHg)
P <sub>s,1</sub>	mouth pressure during airway occlusion 100 msec after the onset of inspiration, (cmH <sub>2</sub> O)
RV	residual volume, (liter)
%RV	RV to predicted value ratio, (%)
RV/TLC	residual volume to total lung capacity ratio, (%)
T <sub>i</sub>	inspiratory time, (sec)
T <sub>i</sub> /T <sub>tot</sub>	the fraction of inspiratory time to total respiratory cycle duration.
TLC	total lung capacity, (liter)
%TLC	TLC to predicted value ratio, (%)
T <sub>tot</sub>	duration of the breathing cycle, (sec)
VC	vital capacity, (liter)
%VC	VC to predicted value ratio, (%)
V <sub>T</sub>	tidal volume, (liter)
Z <sub>RS</sub>	respiratory impedance, (cmH <sub>2</sub> O/liter/sec)

0% at the beginning of the test,

- the relation between P<sub>s,1</sub> and alveolar P<sub>CO<sub>2</sub></sub> when the rebreathing method is repeated successively,
- the relation between P<sub>s,1</sub> and alveolar P<sub>CO<sub>2</sub></sub> when rebreathing is started with 100% O<sub>2</sub> in the bag,
- the effects of changes in functional residual capacity on P<sub>s,1</sub>,
- P<sub>s,1</sub> in healthy subjects (children and adults), and
- P<sub>s,1</sub> in various diseases (fibrosing lung disease, pulmonary emphysema, chronic bronchitis, pneumoconiosis and Duchenne's muscular dystrophy).

The symbols and abbreviations used in the text are shown in Table 1.

### SUBJECTS

The subjects studied in this research included

197 normal healthy subjects and 144 patients with various diseases.

The normal healthy subjects consisting of 145 males and 52 females. The subjects were encountered during physical checkup sessions in companies or a school and appeared healthy—that is, those persons who had no history of respiratory disease and had no symptoms of respiratory disturbances such as cough and sputum, and no abnormal findings on physical examination or on chest roentgenogram. They are classed by age and sex group.

Among 144 patients, 10 patients with fibrosing lung disease, 10 patients with pulmonary emphysema, 27 patients with chronic bronchitis, 48 patients with pneumoconiosis and 49 patients with Duchenne's muscular dystrophy were also studied.

## METHODS

### A. General Pulmonary Function Tests

Routine pulmonary function tests were performed which included the determination of vital capacity (VC), VC to predicted value ratio (%VC), forced expiratory volume in 1.0 second ( $FEV_{1.0}$ ),  $FEV_{1.0}$  to forced vital capacity ratio ( $FEV_{1.0}\%$ ), maximal voluntary ventilation (MVV) and MVV to predicted value ratio (%MVV) with a dry spirometer (OST-80, Chest Co., Ltd., Tokyo, Japan).

The subdivisions of lung volume such as total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) were determined by the constant volume He-closed circuit method<sup>20</sup> and the pulmonary diffusing capacity was determined by the breath holding method<sup>19</sup>. For these determinations, the Box Spiro, CO Analyzer and the He Analyzer (P. K. Morgan Ltd., Chatham, Kent, England) were used. Predicted values for adults were obtained by using the prediction formulae developed at the Second Department of Internal Medicine, Hiroshima University<sup>46-50</sup> and for children by Ishida's prediction formulae<sup>50</sup>. Respiratory impedance ( $Z_{IN}$ ) was measured by the 3Hz oscillation method (Nihon Kohden Kogyo Co., Ltd., Tokyo, Japan). Blood samples taken from the brachial artery with the subject at rest and breathing room air were analyzed for  $O_2$  tension ( $P_{aO_2}$ ),  $CO_2$  tension ( $P_{aCO_2}$ ) and pH with appropriate electrodes (ABL3 Radiometer Co., Copenhagen, Denmark).

### B. Determination of mouth occlusion pressure

The apparatus used for determining mouth occlusion pressure is shown in Fig. 1. The subjects abstained from food, drink and cigarettes for at least two hours before the study. The subject performed resting ventilation through a "J" valve. First the inspiratory side was opened to the ambient air. The subject breathed for a minimum of three minutes of quiet breathing in order to adjust to the apparatus. After it was ascertained that the subject was relaxed and his pattern of breathing was stable, resting mouth occlusion pressure was measured. Without informing the subject, the inspiratory side was periodically occluded during expiration, such that next inspiration was occluded completely from FRC level. When inspiration was begun after closing the inspiratory side, the respiratory muscles contracted isometrically and the mouth pressure became negative.

The negative pressure was measured by means of a pressure transducer (MFV 1100, Nihon Kohden Kogyo Co., Ltd., Tokyo, Japan), amplified by an amplifier (AP 620G, Nihon Kohden Kogyo Co., Ltd., Tokyo, Japan) and monitored by an oscilloscopic apparatus (Polygraph System, Nihon Kohden Kogyo Co., Ltd., Tokyo, Japan).

All tracings were recorded at a paper speed of 100 mm per sec on a heat-sensitive pen, highly responsive recorder (Linearcorder, Mark V Type WR3001, Watanabe Instruments Co., Tokyo, Japan). During the course of continu-

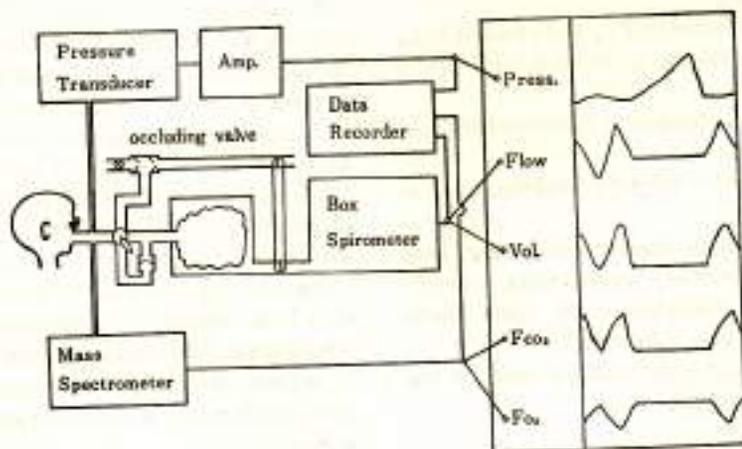


Fig. 1. Schematic outline of the method used to assess mouth occlusion pressure during room air breathing and during re-breathing.

ous records alveolar  $P_{CO_2}$  and  $P_{O_2}$  were measured by a mass spectrometer (MGA-1100, Perkin-Elmer Co., Pomona, California, USA) and recorded by a recorder (Shimadzu U-629, Nippon Denshi Kagaku Co., Ltd., Kyoto, Japan).

In Fig. 2 are shown representative curves for mouth pressure, flow, volume, alveolar  $P_{CO_2}$  and  $P_{O_2}$  from a healthy subject during rebreathing and at the time of airway occlusion. At the time of airway occlusion, a marked rise in mouth pressure was observed. However, the flow and volume of ventilation showed no change.

In Fig. 3 are shown 5 tracings of the  $P_{s,1}$  from the same healthy subject during resting ventilation. From these tracings it was obvious that at the same alveolar  $P_{CO_2}$  (mean value was  $36.4 \pm 0.7$  mmHg), mouth occlusion pressure showed excellent reproducibility.

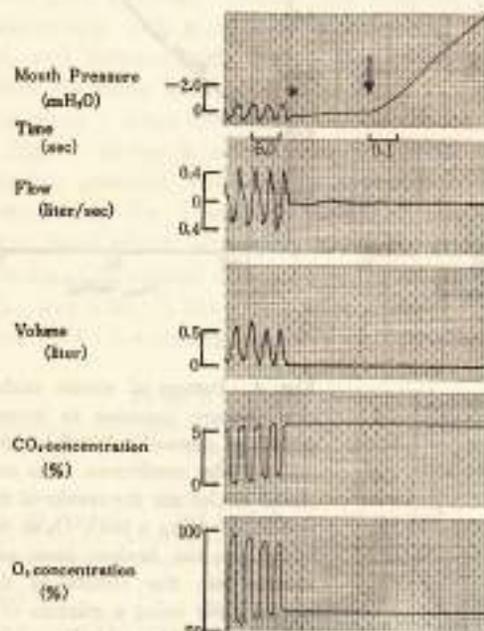


Fig. 2. Representative occlusions from a subject during rebreathing with a 100%  $O_2$ . The uppermost panel represents mouth pressure, the second represents flow, the third represents volume, the fourth represents  $CO_2$  concentration, and the lowest panel represents  $O_2$  concentration. The asterisk mark indicates the time when the inspiratory side was closed. The paper speed before the asterisk mark is 100 mm/min and after the mark is 100 mm/sec. The arrow indicates the beginning of mouth occlusion pressure.

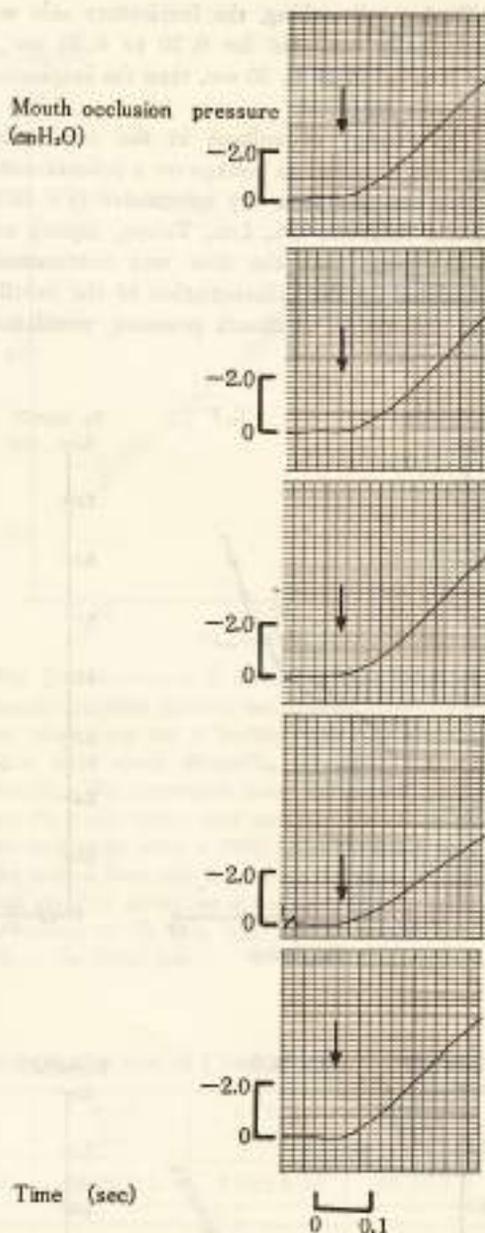


Fig. 3. Five mouth occlusion pressure tracings from a subject breathing air, shows an excellent reproducibility up to 300 msec. The arrow marks indicate the beginning of mouth occlusion pressure.

After recording the resting ventilation and measuring the resting mouth occlusion pressure, the inspiratory and expiratory side were connected to a 7 liter bag containing a 100%  $O_2$  or a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$ , and the subject started to rebreath.

During rebreathing, the inspiratory side was periodically occluded for 0.20 to 0.30 sec at the interval of 20 to 30 sec, then the inspiratory side was reopened.

The change of volume in the rebreathing bag was obtained as voltage on a potentiometer which attached to a dry spirometer (FV 5010, Tatebe Seishudo Co., Ltd., Tokyo, Japan), and at the same time the flow was continuously calculated by the differentiation of the ventilation volume. The mouth pressure, ventilation,

flow, alveolar  $P_{CO_2}$  and  $P_{O_2}$  were measured and recorded by using the same apparatus mentioned above. Values for tidal volume ( $V_T$ ), inspiratory time ( $T_i$ ), duration of the breathing cycle ( $T_{tot}$ ), respiratory frequency ( $f$ ) and minute volume ( $\dot{V}_E$ ) were calculated from the volume traces.

Most of healthy subjects were studied when they were sitting upright in a comfortable chair, but 15 of them were studied in both sitting and supine positions in order to induce a change

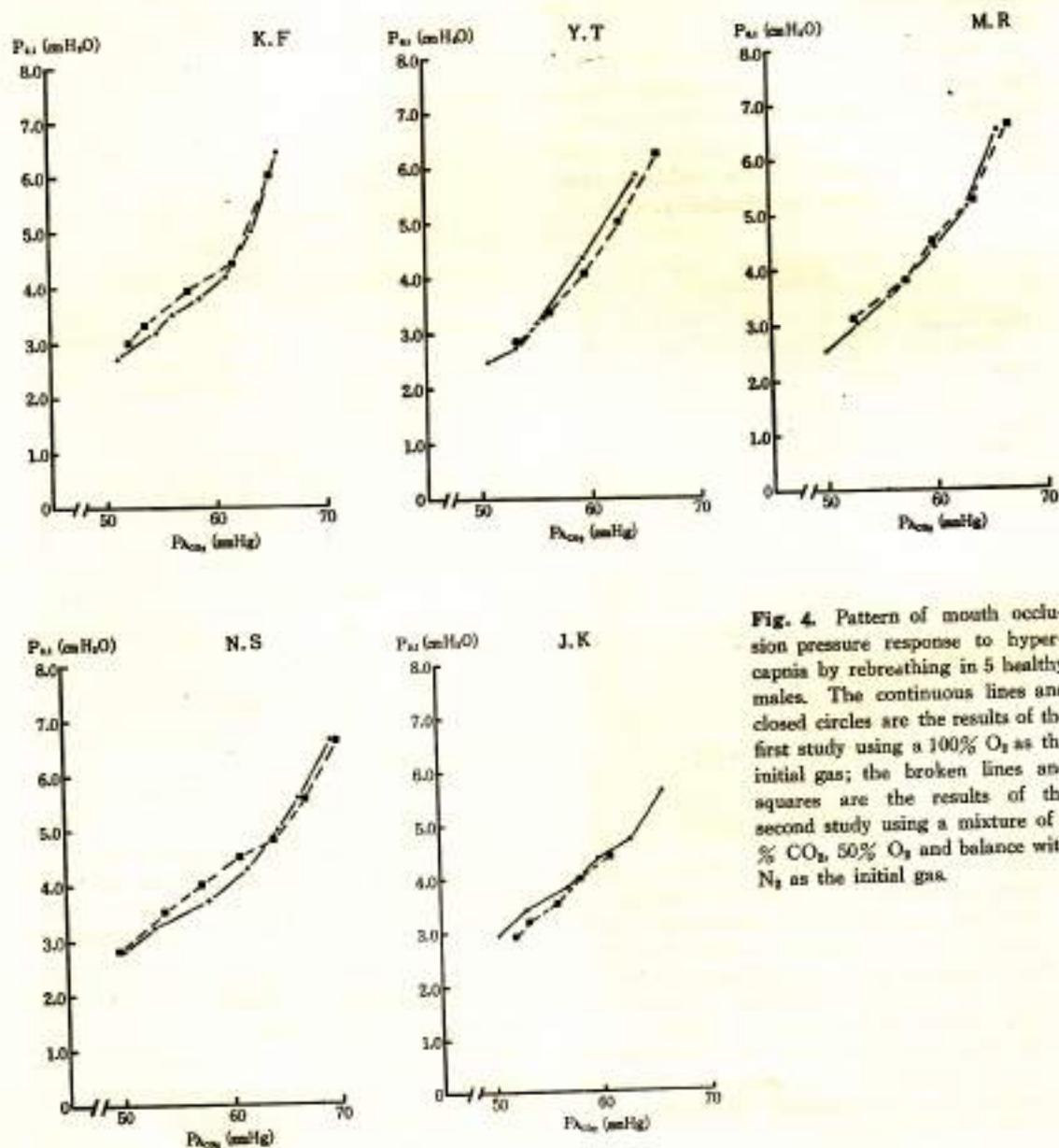


Fig. 4. Pattern of mouth occlusion pressure response to hypercapnia by rebreathing in 5 healthy males. The continuous lines and closed circles are the results of the first study using a 100%  $O_2$  as the initial gas; the broken lines and squares are the results of the second study using a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$  as the initial gas.

in the functional residual capacity. Patients with various diseases were studied in the sitting position.

## RESULTS

### A. Basic studies of various factors which seem to influence $P_{a,1}$

#### 1. Influences of inhaled gas with different composition on $P_{a,1}$

The subjects were 5 normal healthy males, their physical characteristics and pulmonary function tests are shown in Table 2. Rebreathing was started after the bag was filled with 5-6 liters of a 100%  $O_2$  or a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$ . Fig. 4 shows the pattern of  $P_{a,1}$  response to hypercapnia by rebreathing in the range of alveolar  $P_{CO_2}$  50-70 mmHg.

The continuous lines and closed circles represent the response by rebreathing with a 100%  $O_2$  as the initial gas, while the broken lines and squares represent the response by rebreathing with a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$  as the initial gas. With the same level of alveolar  $P_{CO_2}$ ,  $P_{a,1}$  did not show a large difference.

Fig. 5 shows a comparison of mouth occlusion pressure response to hypercapnia by rebreathing for 5 healthy males at alveolar  $P_{CO_2}$  level about 50 mmHg, 55 mmHg and 60 mmHg. At around alveolar  $P_{CO_2}$  of 50 mmHg,  $P_{a,1}$  was  $2.68 \pm 0.18$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was  $50.4 \pm 0.4$  mmHg for 100%  $O_2$  rebreathing,

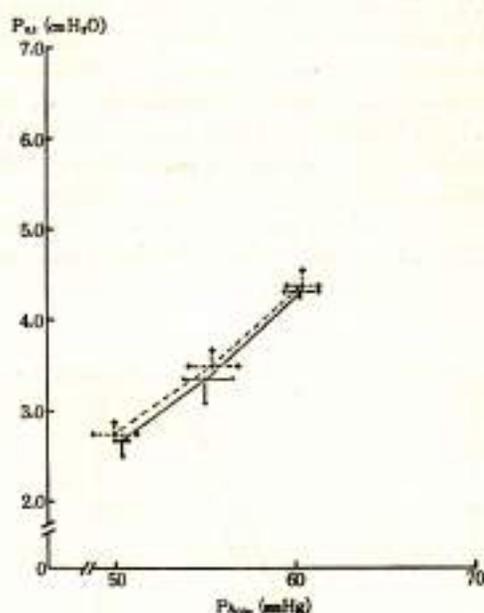


Fig. 5. Comparison of pattern of mean values of mouth occlusion pressure response to hypercapnia by rebreathing for 5 healthy males at alveolar  $P_{CO_2}$  level about 50 mmHg, 55 mmHg and 60 mmHg. The continuous lines and closed circles are the mean values and standard deviations of the first study using a 100%  $O_2$  as the initial gas; the broken lines and crosses are the mean values and standard deviations of the second study using a mixture of 7%  $CO_2$ , 50%  $O_2$  and balance with  $N_2$  as the initial gas.

Table 2. Physical characteristics and pulmonary function tests of 5 healthy males

Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1,0</sub> (liter)	FEV <sub>1,0</sub> % (%)
28.8±3.7	168.4±6.4	64.4±9.5	4.22±0.62	94.6±9.1	3.61±0.58	86.4±5.9
Z <sub>max</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)	TLC (liter)	%TLC (%)
2.6±0.2	1.44±0.16	101.8±9.0	2.85±0.32	93.2±9.7	5.46±0.64	95.2±8.1
RV/TLC (%)	D <sub>LCO</sub> (ml/min/mmHg)	%D <sub>LCO</sub> (%)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)
26.4±2.1	31.7±3.6	102.4±7.9	95.9±2.3	40.6±2.2	7.39±0.01	4.2±2.1
V <sub>T</sub> (liter)	f (breaths/min)	T <sub>i</sub> (sec)	T <sub>i</sub> /T <sub>tot</sub>	P <sub>a,1</sub> (cmH <sub>2</sub> O)		
0.60±0.12	16±2	1.6±0.4	0.36±0.06	1.64±0.03		

and  $2.74 \pm 0.11$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was  $50.0 \pm 1.2$  mmHg for 7% CO<sub>2</sub> rebreathing. This difference was statistically not significant. At around alveolar  $P_{CO_2}$  of 55 mmHg,  $P_{1.0}$  was  $3.38 \pm 0.27$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was  $55.1 \pm 1.5$  mmHg for 100% O<sub>2</sub>, and  $3.49 \pm 0.17$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was  $55.4 \pm 0.6$  mmHg, showing no significant difference. At around alveolar  $P_{CO_2}$  of 60 mmHg,  $P_{1.0}$  was  $4.32 \pm 0.08$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was

$60.3 \pm 1.0$  mmHg for 100% O<sub>2</sub> rebreathing, and  $4.37 \pm 0.16$  cmH<sub>2</sub>O when alveolar  $P_{CO_2}$  was  $60.5 \pm 1.0$  mmHg for 7% CO<sub>2</sub> rebreathing. This difference was statistically not significant. Thus, with the same alveolar  $P_{CO_2}$  level,  $P_{0.1}$  showed no significant difference for rebreathing with 100% O<sub>2</sub> and a mixture of 7% CO<sub>2</sub>, 50% O<sub>2</sub> and balance with N<sub>2</sub>.

2. Change of  $P_{1.0}$  when the rebreathing method was repeated successively

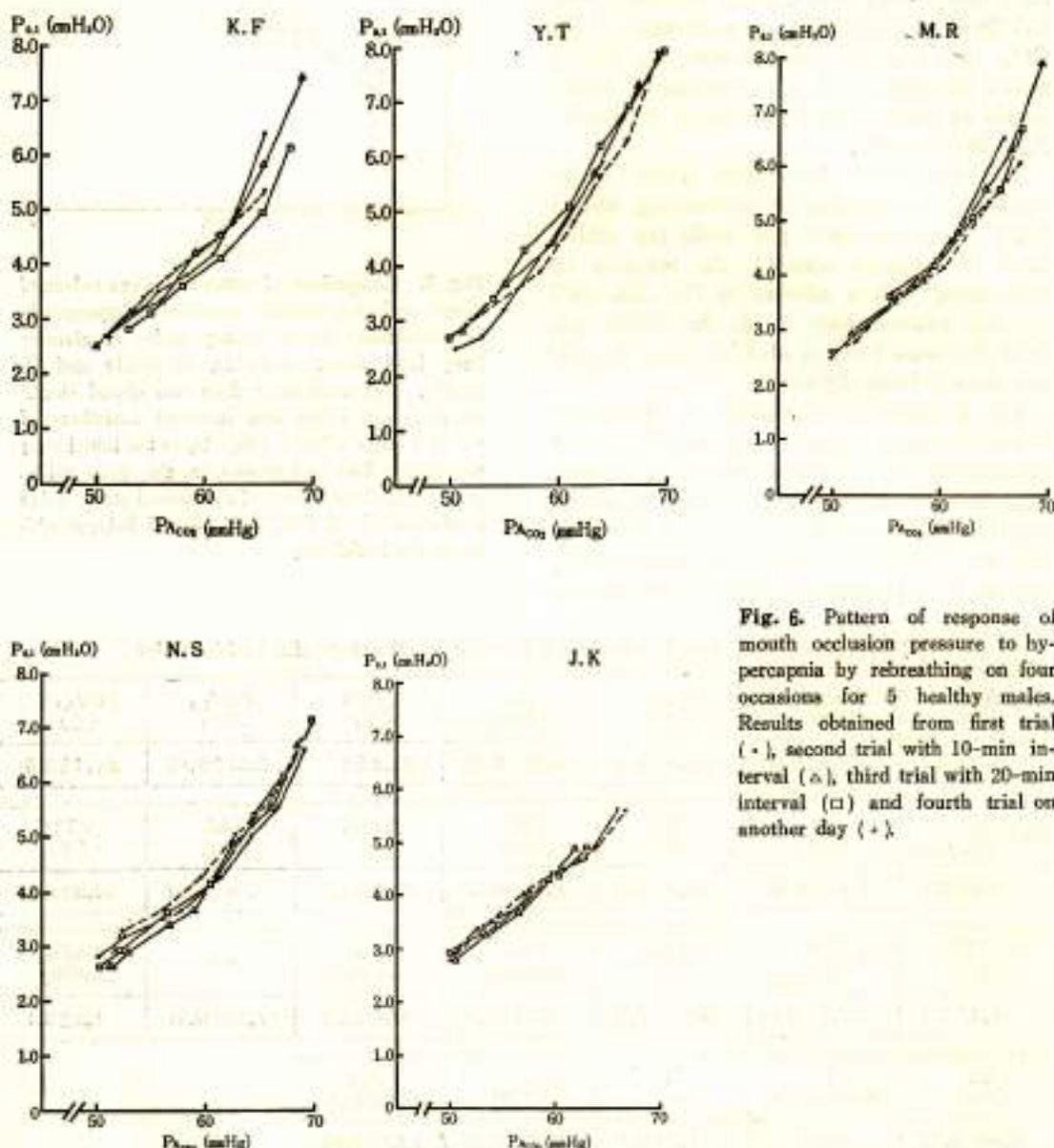


Fig. 6. Pattern of response of mouth occlusion pressure to hypercapnia by rebreathing on four occasions for 5 healthy males. Results obtained from first trial (·), second trial with 10-min interval (△), third trial with 20-min interval (□) and fourth trial on another day (×).

The subjects were the same as in the preceding item. The relation between alveolar  $P_{CO_2}$  and  $P_{a,1}$ , when rebreathing 100%  $O_2$  was studied on four occasions repeatedly. The first trial as control followed with 10-min, 20-min intervals and the fourth trial was studied on another day.

Fig. 6 shows the pattern of response of

mouth occlusion pressure to hypercapnia by rebreathing on four occasions. The relation between alveolar  $P_{CO_2}$  and  $P_{a,1}$  showed no trend of moving to the right or left with time.

3. Relation between alveolar  $P_{CO_2}$  and  $P_{a,1}$   
The subjects were 17 males and 1 female, 18 normal healthy subjects in total. The physical characteristics and pulmonary function tests

Table 3. Physical characteristics and pulmonary function tests of 18 normal healthy subjects

Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.0</sub> (liter)	FEV <sub>1.0</sub> % (%)
38.7±13.8	166.0±5.1	58.8±8.8	3.92±0.69	95.1±10.0	3.36±0.69	84.8±5.3
MVV (liter/min)	%MVV (%)	Z <sub>SH</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)
132.6±19.6	102.1±17.0	3.2±0.7	1.49±0.28	97.4±15.7	5.33±0.66	94.7±9.1
TLC (liter)	%TLC (%)	RV/TLC (%)	D <sub>LCO</sub> (ml/min/mmHg)	%D <sub>LCO</sub> (%)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)
5.33±0.66	95.9±9.1	27.9±4.3	28.0±4.7	97.8±9.8	94.1±7.5	41.5±2.6
pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)	V <sub>T</sub> (liter)	f (breaths/min)	T <sub>i</sub> (sec)	T <sub>i</sub> /T <sub>100</sub>	P <sub>a,1</sub> (cmH <sub>2</sub> O)
7.39±0.01	5.9±4.9	0.56±0.19	17±2	1.3±0.3	0.41±0.06	1.65±0.06

Table 4. Correlation between  $P_{a,1}$  and alveolar  $P_{CO_2}$  in terms of linear regression lines or exponential regression curves in 18 healthy subjects

No.	Subject	a	b	c	d	Correlation Coef. (r)	Regression Line
1.	Y. A.	0.213	-8.126	—	—	0.993	L
2.	S. M.	0.235	-9.543	—	—	0.991	L
3.	K. S.	0.302	-12.099	—	—	0.976	L
4.	M. K.	0.258	-9.137	—	—	0.996	L
5.	M. I.	0.242	-9.823	—	—	0.980	L
6.	H. T.	0.229	-8.478	—	—	0.985	L
7.	K. S.	0.218	-3.223	—	—	0.996	L
8.	Y. T.	0.261	-10.989	—	—	0.988	L
9.	M. R.	0.232	-9.215	—	—	0.969	L
10.	J. K.	0.170	-5.780	—	—	0.974	L
11.	K. T.	—	—	0.242	0.047	0.998	E
12.	Y. S.	—	—	0.373	0.042	0.982	E
13.	K. M.	—	—	0.218	0.053	0.980	E
14.	S. H.	—	—	0.254	0.048	0.992	E
15.	M. S.	—	—	0.103	0.061	0.995	E
16.	Y. U.	—	—	0.116	0.059	0.989	E
17.	K. F.	—	—	0.154	0.056	0.981	E
18.	N. S.	—	—	0.346	0.042	0.992	E

L = Linear Regression Line :  $y = ax + b$

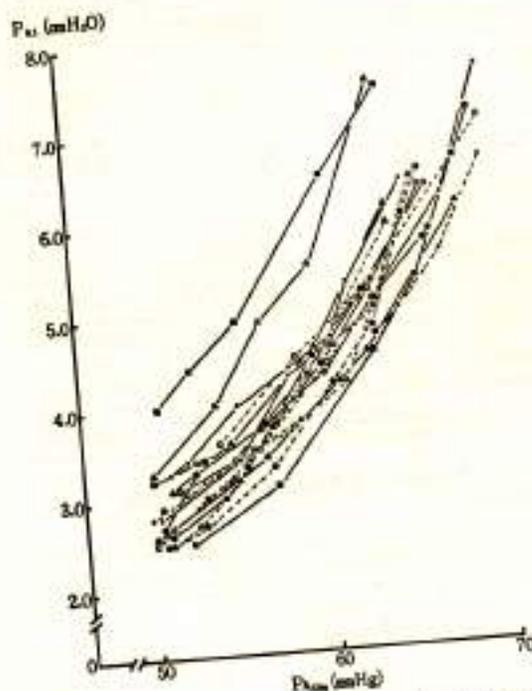
E = Exponential Regression Curve :  $y = ce^{dx}$

**Table 5-a.** Physical characteristics and pulmonary function tests of 15 normal healthy males

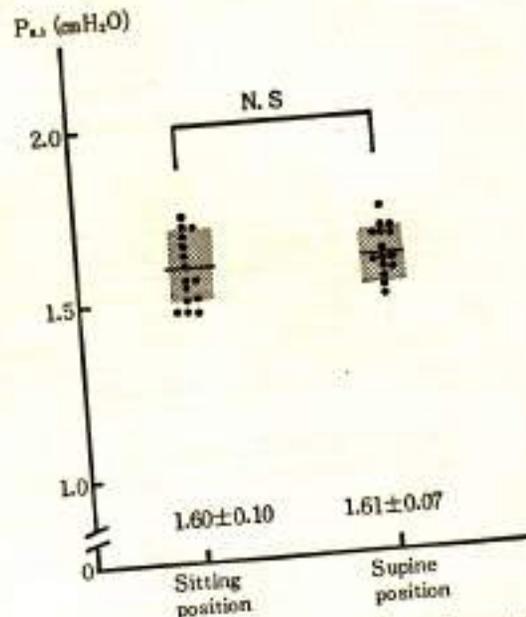
Age (yr)	Height (cm)	Weight (kg)
44.3±10.6	164.5±7.7	61.3±7.4

**Table 5-b.**

Position	VC (liter)	RV (liter)	FRC (liter)	TLC (liter)	D <sub>100</sub> (ml/min/mmHg)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	P <sub>100</sub> (cmH <sub>2</sub> O)
Sitting	3.99±0.49	1.66±0.25	3.60±0.65	5.92±0.47	25.1±2.8	90.5±6.3	38.6±2.2	7.40±0.03	1.60±0.10
Supine	3.87±0.53	1.61±0.21	2.76±0.73	5.94±0.89	27.0±3.9	84.4±5.3	39.2±2.9	7.40±0.03	1.61±0.07



**Fig. 7.** Pattern of response of mouth occlusion pressure to hypercapnia by rebreathing in 18 healthy subjects



**Fig. 8.** Comparison of values for resting mouth occlusion pressure for 15 healthy males in the sitting position and in the supine position.

**Table 6** Physical characteristics and pulmonary function tests of healthy children

Subject	N	Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.0</sub> (liter)	FEV <sub>1.0</sub> % (%)
Male	22	9.5±0.5	136.4±6.9	33.1±6.7	2.53±0.30	118.5±14.3	2.08±0.33	84.0±5.7
Female	17	9.8±0.4	136.8±5.1	32.4±5.8	2.41±0.32	117.9±16.1	2.00±0.29	83.0±7.1
Total	39	9.6±0.5	136.5±6.1	32.8±6.3	2.45±0.31	118.2±14.9	2.04±0.32	83.6±6.3

Subject	N	Z <sub>100</sub> (cmH <sub>2</sub> O/liter/sec)	V <sub>T</sub> (liter)	f (breaths/min)	T <sub>I</sub> (sec)	T <sub>I</sub> /T <sub>I+1</sub>	P <sub>0.1</sub> (cmH <sub>2</sub> O)
Male	22	5.3±0.9	0.49±0.03	23±2	1.2±0.4	0.49±0.06	2.88±0.38
Female	17	5.4±0.6	0.49±0.06	20±4	1.0±0.3	0.45±0.03	2.85±0.40
Total	39	5.4±0.8	0.49±0.05	22±4	1.1±0.4	0.47±0.05	2.87±0.38

of the subjects are shown in Table 3. Fig. 7 shows pattern of response of mouth occlusion pressure to hypercapnia by rebreathing. Table 4 shows the study of regression formula of the correlation between  $P_{s,1}$  and alveolar  $P_{CO_2}$ . From the coefficient regression, it was found

that in 10 subjects the relation was linear regression, while in 8 subjects the relation was exponential regression.

4. The effect of change of functional residual capacity on  $P_{s,1}$ . Changes of functional residual capacity of

Table 7. Physical characteristics and pulmonary function tests of normal healthy subjects

Subject	Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1,0</sub> (liter)	FEV <sub>1,0</sub> % (%)	
20-29	Male	24.9±2.9 (n=26)	168.0±6.1 (n=26)	60.2±6.3 (n=26)	4.29±0.47 (n=26)	95.1±8.9 (n=26)	3.75±0.49 (n=26)	87.7±7.0 (n=26)
	Female	21.4±2.5 (n=12)	156.3±4.9 (n=12)	51.5±4.9 (n=12)	2.99±0.22 (n=12)	90.6±6.4 (n=12)	2.67±0.30 (n=12)	89.4±5.9 (n=12)
30-39	Male	35.5±2.5 (n=36)	164.7±6.5 (n=36)	62.0±6.6 (n=36)	3.93±0.50 (n=36)	94.6±10.6 (n=36)	3.43±0.55 (n=36)	86.8±8.0 (n=36)
	Female	34.1±3.1 (n=7)	156.9±2.0 (n=7)	51.0±5.4 (n=7)	2.91±0.44 (n=7)	91.7±8.8 (n=7)	2.35±0.56 (n=7)	80.0±8.9 (n=7)
40-49	Male	44.2±3.1 (n=29)	164.3±5.5 (n=29)	63.4±8.1 (n=29)	3.68±0.41 (n=29)	94.1±9.9 (n=29)	3.12±0.40 (n=29)	85.3±7.5 (n=29)
	Female	42.8±2.2 (n=4)	154.5±3.9 (n=4)	56.8±7.2 (n=4)	3.07±1.00 (n=4)	101.5±22.6 (n=4)	2.50±0.75 (n=4)	75.0±3.6 (n=4)
50-59	Male	54.6±3.4 (n=21)	160.4±7.8 (n=21)	58.7±8.3 (n=21)	3.62±0.39 (n=21)	102.4±10.2 (n=21)	3.02±0.34 (n=21)	83.6±5.4 (n=21)
	Female	53.8±2.3 (n=8)	153.0±5.5 (n=8)	55.8±8.6 (n=8)	2.75±0.38 (n=8)	105.6±12.6 (n=8)	2.15±0.30 (n=8)	78.4±4.7 (n=8)
60-	Male	64.5±4.6 (n=11)	160.5±6.2 (n=11)	54.7±5.3 (n=11)	3.36±0.68 (n=11)	100.2±18.5 (n=11)	2.63±0.50 (n=11)	79.0±6.3 (n=11)
	Female	66.3±2.2 (n=4)	150.5±4.8 (n=4)	52.3±5.6 (n=4)	2.26±0.20 (n=4)	97.3±6.6 (n=4)	1.76±0.14 (n=4)	78.3±5.6 (n=4)

Subject	MVV (liter/min)	%MVV (%)	Z <sub>max</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)	
20-29	Male	137.5±21.9 (n=2)	90.0±14.1 (n=2)	3.5±1.0 (n=26)	1.51±0.33 (n=4)	107.0±21.0 (n=4)	2.93±0.18 (n=4)	111.0±10.0 (n=4)
	Female	107.5±23.3 (n=2)	126.5±20.5 (n=2)	3.2±0.6 (n=12)	1.05±0.15 (n=2)	113.0±12.7 (n=2)	2.19±0.15 (n=2)	106.5±3.5 (n=2)
30-39	Male	127.0±15.6 (n=5)	90.0±9.9 (n=5)	3.3±0.9 (n=36)	1.46±0.32 (n=9)	85.8±16.2 (n=9)	2.94±0.59 (n=9)	95.5±17.8 (n=9)
	Female	—	—	3.5±0.6 (n=7)	—	—	—	—
40-49	Male	121.4±25.9 (n=7)	97.0±20.1 (n=7)	3.5±0.8 (n=29)	1.75±0.32 (n=9)	106.7±19.5 (n=9)	3.02±0.54 (n=9)	96.9±16.8 (n=9)
	Female	—	—	4.2±0.5 (n=4)	—	—	—	—
50-59	Male	98.6±21.7 (n=5)	90.8±17.9 (n=5)	3.6±0.8 (n=21)	1.81±0.34 (n=12)	106.1±17.9 (n=12)	2.95±0.51 (n=12)	95.9±13.8 (n=12)
	Female	—	—	4.2±1.0 (n=8)	—	—	—	—
60-	Male	97.3±33.1 (n=4)	85.8±7.3 (n=4)	4.0±0.8 (n=11)	1.92±0.28 (n=4)	104.3±16.0 (n=4)	3.24±0.37 (n=4)	100.5±11.0 (n=4)
	Female	—	—	3.7±0.7 (n=4)	—	—	—	—

the subjects achieved by changing from the supine to the sitting position. Subjects were 15 healthy males, their physical characteristics and the results of their pulmonary function tests at both positions are shown in Tables 5-a and 5-b. FRC was  $3.60 \pm 0.65$  liters in the sitting position and  $2.76 \pm 0.73$  liters in the

supine position, showing a significant difference ( $P < 0.001$ ). Arterial  $P_{CO_2}$  was  $38.6 \pm 2.2$  mmHg in the sitting position and  $39.2 \pm 2.5$  mmHg in the supine position, showing no significant difference. Further, there were no significant change in VC, TLC and  $D_{LCO}$  between the sitting and supine position. As

Subject		TLC (liter)	%TLC (%)	RV/TLC (%)	$D_{LCO}$ (ml/min /mmHg)	% $D_{LCO}$ (%)	$P_{aO_2}$ (mmHg)	$P_{aCO_2}$ (mmHg)
20-29	Male	$5.93 \pm 0.29$ (n = 4)	$115.5 \pm 9.9$ (n = 4)	$25.5 \pm 4.1$ (n = 4)	$34.4 \pm 1.1$ (n = 2)	$109.0 \pm 4.2$ (n = 2)	$95.2 \pm 2.0$ (n = 4)	$41.0 \pm 3.5$ (n = 4)
	Female	$4.04 \pm 0.25$ (n = 2)	$104.5 \pm 3.5$ (n = 2)	$25.5 \pm 2.1$ (n = 2)	$22.3 \pm 4.3$ (n = 2)	$96.0 \pm 15.6$ (n = 2)	$108.1 \pm 2.8$ (n = 2)	$38.3 \pm 0.3$ (n = 2)
30-39	Male	$4.89 \pm 0.62$ (n = 9)	$90.2 \pm 15.3$ (n = 9)	$29.8 \pm 5.5$ (n = 9)	$26.5 \pm 1.6$ (n = 5)	$89.5 \pm 6.4$ (n = 5)	$96.3 \pm 2.2$ (n = 9)	$39.0 \pm 3.0$ (n = 9)
	Female	—	—	—	—	—	—	—
40-49	Male	$5.72 \pm 0.62$ (n = 9)	$104.2 \pm 12.4$ (n = 9)	$31.6 \pm 3.8$ (n = 9)	$27.0 \pm 3.3$ (n = 7)	$99.1 \pm 12.8$ (n = 7)	$94.8 \pm 3.2$ (n = 9)	$41.5 \pm 3.5$ (n = 9)
	Female	—	—	—	—	—	—	—
50-59	Male	$5.14 \pm 0.64$ (n = 12)	$95.1 \pm 10.3$ (n = 12)	$35.0 \pm 4.3$ (n = 12)	$21.1 \pm 3.4$ (n = 5)	$83.0 \pm 8.0$ (n = 5)	$96.1 \pm 2.2$ (n = 12)	$38.7 \pm 2.1$ (n = 12)
	Female	—	—	—	—	—	—	—
60-	Male	$5.45 \pm 0.70$ (n = 4)	$100.3 \pm 12.2$ (n = 4)	$35.3 \pm 3.1$ (n = 4)	$20.0 \pm 2.3$ (n = 4)	$82.3 \pm 9.2$ (n = 4)	$87.5 \pm 1.9$ (n = 4)	$41.4 \pm 3.3$ (n = 4)
	Female	—	—	—	—	—	—	—

Subject		pH	A-a $D_{O_2}$ (mmHg)	$V_T$ (liter)	f (breaths /min)	$T_i$ (sec)	$T_i/T_{tot}$	$P_{aO_2}$ (cmH <sub>2</sub> O)
20-29	Male	$7.41 \pm 0.03$ (n = 4)	$7.1 \pm 3.8$ (n = 4)	$0.63 \pm 0.18$ (n = 26)	$16 \pm 2$ (n = 26)	$1.4 \pm 0.3$ (n = 26)	$0.43 \pm 0.03$ (n = 26)	$1.62 \pm 0.13$ (n = 26)
	Female	$7.39 \pm 0.04$ (n = 2)	$4.1 \pm 2.1$ (n = 2)	$0.45 \pm 0.01$ (n = 12)	$18 \pm 4$ (n = 12)	$1.5 \pm 0.5$ (n = 12)	$0.41 \pm 0.05$ (n = 12)	$1.66 \pm 0.13$ (n = 12)
30-39	Male	$7.39 \pm 0.02$ (n = 9)	$6.7 \pm 2.6$ (n = 9)	$0.54 \pm 0.14$ (n = 36)	$18 \pm 2$ (n = 36)	$1.4 \pm 0.2$ (n = 36)	$0.42 \pm 0.04$ (n = 36)	$1.63 \pm 0.15$ (n = 36)
	Female	—	—	$0.53 \pm 0.13$ (n = 7)	$21 \pm 3$ (n = 7)	$1.1 \pm 0.1$ (n = 7)	$0.40 \pm 0.05$ (n = 7)	$1.69 \pm 0.13$ (n = 7)
40-49	Male	$7.39 \pm 0.03$ (n = 9)	$5.5 \pm 2.5$ (n = 9)	$0.56 \pm 0.12$ (n = 29)	$16 \pm 3$ (n = 29)	$1.4 \pm 0.3$ (n = 29)	$0.42 \pm 0.03$ (n = 29)	$1.60 \pm 0.13$ (n = 29)
	Female	—	—	$0.52 \pm 0.19$ (n = 4)	$16 \pm 4$ (n = 4)	$1.7 \pm 0.7$ (n = 4)	$0.43 \pm 0.06$ (n = 4)	$1.59 \pm 0.08$ (n = 4)
50-59	Male	$7.40 \pm 0.03$ (n = 12)	$6.3 \pm 3.3$ (n = 12)	$0.68 \pm 0.18$ (n = 21)	$18 \pm 5$ (n = 21)	$1.6 \pm 0.4$ (n = 21)	$0.46 \pm 0.03$ (n = 21)	$1.67 \pm 0.12$ (n = 21)
	Female	—	—	$0.54 \pm 0.15$ (n = 8)	$20 \pm 4$ (n = 8)	$1.2 \pm 0.2$ (n = 8)	$0.38 \pm 0.04$ (n = 8)	$1.61 \pm 0.10$ (n = 8)
60-	Male	$7.39 \pm 0.01$ (n = 4)	$7.9 \pm 1.7$ (n = 4)	$0.57 \pm 0.13$ (n = 11)	$18 \pm 4$ (n = 11)	$1.3 \pm 0.3$ (n = 11)	$0.44 \pm 0.04$ (n = 11)	$1.59 \pm 0.11$ (n = 11)
	Female	—	—	$0.62 \pm 0.18$ (n = 4)	$17 \pm 2$ (n = 4)	$1.5 \pm 0.2$ (n = 4)	$0.42 \pm 0.04$ (n = 4)	$1.64 \pm 0.03$ (n = 4)

shown in Table 5-b and Fig. 8,  $P_{0.1}$  was  $1.60 \pm 0.10$  cmH<sub>2</sub>O in the sitting position and  $1.61 \pm 0.07$  cmH<sub>2</sub>O in the supine position. This difference was not statistically significant. Thus,  $P_{0.1}$  was not influenced by the change in FRC due to the change of postures in the healthy subjects.

## B. Clinical study of $P_{0.1}$

### 1. Study of $P_{0.1}$ in healthy subjects

#### a) Study in children

The children were only between the age of 9 and 10 years, their physical characteristics and the results of their pulmonary function tests are shown in Table 6. The mean values and standard deviations of %VC for boys and girls were  $118.5 \pm 14.3\%$  and  $117.9 \pm 16.1\%$  respectively, FEV<sub>1.0</sub>% were  $84.0 \pm 5.7\%$  and  $83.0 \pm 7.1\%$ . Thus, the spirometry showed no abnormality in both boys and girls. The mean value of respiratory impedance was greater than 5 cmH<sub>2</sub>O/liter/sec for both sexes, showing a higher value than those of healthy adults. There were no significant differences in various parameters of ventilation at rest between boys and girls.  $P_{0.1}$  was  $2.88 \pm 0.38$  cmH<sub>2</sub>O in boys and  $2.85 \pm 0.40$  cmH<sub>2</sub>O in girls, this difference was not statistically significant.

#### b) Study in adults

The subjects were 158 males and females, classed by the age and sex group. Their physical

characteristics and the results of their pulmonary function tests are shown in Table 7. The values of their pulmonary function tests were 90-105% for %VC and greater than 80% for FEV<sub>1.0</sub>% in young subjects.  $Z_{1R}$  was between 3.2 and 4.2 cmH<sub>2</sub>O/liter/sec, lower than those of children. Tidal volume at rest was 0.45-0.68 liters, respiratory frequency (*f*) was 16-21 breaths/min,  $T_i$  was 1.1-1.7 sec,  $T_i/T_{i+1}$  was 0.38-0.46. The mean values and standard deviations of  $P_{0.1}$  for male and female adults were  $1.62 \pm 0.13$  cmH<sub>2</sub>O and  $1.66 \pm 0.13$  cmH<sub>2</sub>O in the 20's,  $1.63 \pm 0.15$  cmH<sub>2</sub>O and  $1.69 \pm 0.13$  cmH<sub>2</sub>O in the 30's,  $1.60 \pm 0.13$  cmH<sub>2</sub>O and  $1.59 \pm 0.08$  cmH<sub>2</sub>O in the 40's,  $1.57 \pm 0.12$  cmH<sub>2</sub>O and  $1.61 \pm 0.10$  cmH<sub>2</sub>O in the 50's,  $1.59 \pm 0.11$  cmH<sub>2</sub>O and  $1.64 \pm 0.03$  cmH<sub>2</sub>O in the over 60 years of age respectively. These differences among each age group and between male and female were statistically not significant.

Fig. 9 shows values of  $P_{0.1}$  for all healthy subjects studied. The mean values and standard deviations of  $P_{0.1}$  for children and adults were  $2.87 \pm 0.38$  cmH<sub>2</sub>O and  $1.61 \pm 0.13$  cmH<sub>2</sub>O respectively, tending to be significantly higher in the children group ( $P < 0.001$ ).

### 2. Study of $P_{0.1}$ in various diseases

#### a) Fibrosing lung disease

Table 8 shows the physical characteristics

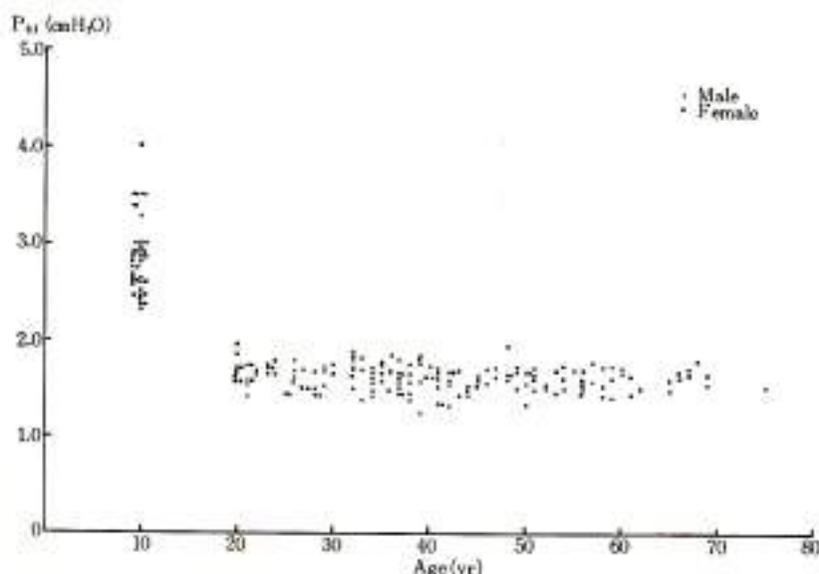


Fig. 9. Relation of  $P_{0.1}$  (cmH<sub>2</sub>O) and age (yr) in 39 healthy children and in 158 healthy adults. Boys and male adults are indicated by closed circles; girls and female adults by crosses.

**Table 8.** Physical characteristics and pulmonary function tests of 10 patients with fibrosing lung disease

Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.5</sub> (liter)	FEV <sub>1.5</sub> % (%)
58.0±12.3	157.5±6.5	54.6±7.4	2.65±0.57	81.3±11.2	2.16±0.43	83.1±8.2
Zs <sub>1.5</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)	TLC (liter)	%TLC (%)
4.2±1.4	1.12±0.60	65.0±25.9	2.05±0.59	70.6±16.5	3.80±0.95	77.2±15.0
RV/TLC (%)	D <sub>LCO</sub> (ml/min/mmHg)	%D <sub>LCO</sub> (%)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)
28.7±8.9	12.2±5.0	53.2±20.3	82.5±13.4	38.6±2.7	7.42±0.01	20.0±10.0
V <sub>T</sub> (liter)	f (breaths/min)	T <sub>i</sub> (sec)	T <sub>i</sub> /T <sub>tot</sub>	P <sub>6.1</sub> (cmH <sub>2</sub> O)		
0.61±0.15	14±2	1.3±0.3	0.40±0.03	2.09±0.30		

**Table 9.** Physical characteristics and pulmonary function tests of 10 patients with pulmonary emphysema

Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.5</sub> (liter)	FEV <sub>1.5</sub> % (%)
63.5±6.5	162.1±5.5	56.2±10.6	2.40±0.91	70.8±26.5	0.91±0.41	45.5±8.7
Zs <sub>1.5</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)	TLC (liter)	%TLC (%)
6.1±1.1	2.99±0.57	150.2±32.3	3.83±0.56	117.5±17.4	5.73±0.73	103.9±11.6
RV/TLC (%)	D <sub>LCO</sub> (ml/min/mmHg)	%D <sub>LCO</sub> (%)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)
52.6±9.7	15.4±4.3	63.2±17.1	80.3±13.6	41.0±3.9	7.39±0.02	18.7±14.4
V <sub>T</sub> (liter)	f (breaths/min)	T <sub>i</sub> (sec)	T <sub>i</sub> /T <sub>tot</sub>	P <sub>6.1</sub> (cmH <sub>2</sub> O)		
0.65±0.25	18±8	1.4±0.8	0.38±0.05	2.84±0.54		

and the results of pulmonary function tests of 10 patients with fibrosing lung disease. The mean and standard deviation of age was 58.0±12.3 years, %VC was 81.3±11.2%, lower limit of normal value, FEV<sub>1.5</sub>% was 83.1±8.2%, relatively good value for the age. In the subdivisions of lung volume, %FRC was 70.6±16.5% and %TLC was 77.2±15.0%, they were slightly lower values. The %D<sub>LCO</sub> was 53.2±20.3%, showing a marked decrease. At the arterial blood gas analysis, arterial P<sub>O<sub>2</sub></sub> was 82.5±13.4 mmHg, lower than the normal value

for the same age, but arterial P<sub>CO<sub>2</sub></sub> was 38.6±2.7 mmHg, nearly the same as the normal value for the same age. Tidal volume at rest was 0.61±0.15 liters, showing no decrease, and respiratory frequency was 14±2 breaths/min, showing no increase. T<sub>i</sub> was 1.3±0.3 sec, and T<sub>i</sub>/T<sub>tot</sub> was 0.40±0.03, slightly smaller than those of healthy subjects. P<sub>6.1</sub> was 2.09±0.30 cmH<sub>2</sub>O, higher (P<0.001) than the values found in normal subjects of 50 years of age.

#### b) Pulmonary Emphysema

In Table 9 are shown the physical charac-

istics and the results of pulmonary function tests for 10 patients with pulmonary emphysema. The mean age of this group was  $63.5 \pm 6.5$  years. Spirometry showed that there was a slight decrease in %VC which was found to be  $70.8 \pm 26.5\%$ , a marked decrease in  $FEV_{1.0}\%$  which was  $45.5 \pm 8.7\%$  indicating the presence of a mixed ventilatory disturbance. The respiratory impedance was  $6.1 \pm 1.1$  cmH<sub>2</sub>O/liter/sec which was higher than normal for the healthy subjects in their 60's. In the subdivisions of lung volume, %FRC showed a high value at  $117.5 \pm 17.4\%$  but almost no increase in the %TLC was observed which was measured at  $103.9 \pm 11.6\%$ . However, RV/TLC was observed to undergo a marked rise of  $52.6 \pm 9.7\%$ . The %D<sub>LCO</sub> was measured at  $63.2 \pm 17.1\%$  showing a moderate decrease.

The arterial P<sub>O<sub>2</sub></sub> was  $80.3 \pm 13.6$  mmHg, showed a slight decrease and the arterial P<sub>CO<sub>2</sub></sub> was  $41.0 \pm 3.9$  mmHg, nearly the same as the normal value for the same age.

The tidal volume during resting ventilation was  $0.65 \pm 0.25$  liters and respiratory frequency was  $18 \pm 8$  breaths/min which showed no significant difference in comparison with the healthy subjects in their 60's. The T<sub>i</sub> value was  $1.4 \pm 0.8$  sec and the T<sub>i</sub>/T<sub>1.01</sub> was  $0.38 \pm 0.05$ . P<sub>e,1</sub>  $2.84 \pm 0.54$  cmH<sub>2</sub>O, markedly higher ( $P < 0.001$ ) than the values found in normal subjects in their 60's.

#### c) Chronic Bronchitis

The patients with chronic bronchitis were

divided into two groups based on Nishimoto's classification<sup>24</sup>, namely the group without obstructive disturbance (Type I and II of Nishimoto's classification) consisting of 24 patients and the group with obstructive disturbance (Type III and IV of Nishimoto's classification) consisting of 3 patients.

The physical characteristics and the results of lung function tests for each group are presented in Table 10. There was a decrease in both the %VC and the  $FEV_{1.0}\%$  in the group with obstructive ventilatory disturbance and the respiratory impedance tended to rise. However, no difference was observed in either arterial P<sub>CO<sub>2</sub></sub> or arterial P<sub>O<sub>2</sub></sub> between the two groups.

Concerning the tidal volume during resting ventilation, respiratory frequency, T<sub>i</sub> and T<sub>i</sub>/T<sub>1.01</sub>, no significant differences were observed between the two groups.

P<sub>e,1</sub> was  $1.92 \pm 0.21$  cmH<sub>2</sub>O in the group without obstructive disturbance and  $2.01 \pm 0.32$  cmH<sub>2</sub>O in the group with obstructive disturbance. This difference was statistically not significant.

#### d) Pneumoconiosis

The subjects consisting of 48 patients with pneumoconiosis were divided into two groups based on chest X-ray examinations<sup>19,20</sup>. In the first group patients showed a few small opacities distributed in the both lungs (mild pneumoconiosis) and in the second group patients showed a widespread distribution with high

Table 10. Physical characteristics and pulmonary function tests of 27 patients with chronic bronchitis

Subject	N	Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.0</sub> (liter)
CB I, CB II	24	57.2±6.1	159.6±8.5	55.9±7.6	3.06±0.81	85.8±18.4	2.49±0.65
CB III, CB IV	3	59.7±4.6	156.7±3.5	50.3±1.5	2.44±0.35	70.7±11.0	1.45±0.44
Subject	N	FEV <sub>1.0</sub> % (%)	Z <sub>1000</sub> (cmH <sub>2</sub> O/liter/sec)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)
CB I, CB II	24	84.5±6.9	3.9±1.0	88.9±12.0	38.2±2.7	7.41±0.02	14.7±9.5
CB III, CB IV	3	58.3±10.0	4.7±3.0	90.2±12.1	38.3±2.8	7.41±0.03	12.7±10.4
Subject	N	V <sub>T</sub> (liter)	f (breaths/min)	T <sub>i</sub> (sec)	T <sub>i</sub> /T <sub>1.01</sub>	P <sub>e,1</sub> (cmH <sub>2</sub> O)	
CB I, CB II	24	0.59±0.09	16±2	1.3±0.4	0.42±0.06	1.92±0.21	
CB III, CB IV	3	0.64±0.27	18±4	1.2±0.2	0.40±0.05	2.01±0.32	

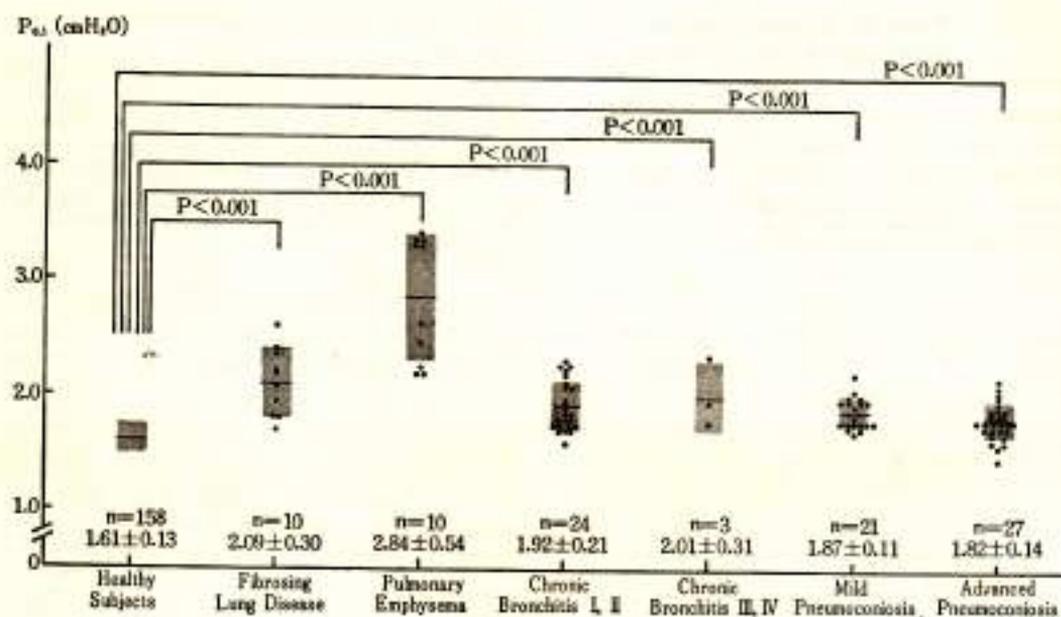


Fig. 10. Values for resting mouth occlusion pressure ( $P_{0.1}$ ) are shown for subjects studied, grouped according to diagnosis.

Table 12. Physical characteristics and pulmonary function tests of 49 patients with Duchenne's muscular dystrophy

Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1.0</sub> (liter)	FEV <sub>1.0</sub> % (%)	MVV (liter/min)
15.6±4.5 (n=49)	142.6±12.6 (n=49)	35.0±11.2 (n=49)	1.25±0.53 (n=49)	44.0±25.2 (n=49)	1.04±0.48 (n=49)	85.9±14.4 (n=49)	39.8±16.6 (n=49)
%MVV (%)	Z <sub>1n<sub>s</sub></sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)	FRC (liter)	%FRC (%)	TLC (liter)	%TLC (%)
41.0±15.9 (n=49)	4.4±2.0 (n=49)	1.45±0.52 (n=40)	172.3±48.9 (n=40)	1.78±0.59 (n=40)	100.2±37.0 (n=40)	2.56±0.73 (n=40)	69.7±23.8 (n=40)
RV/TLC (%)	P <sub>aO<sub>2</sub></sub> (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)	V <sub>T</sub> (liter)	f (breaths/min)	P <sub>0.1</sub> (cmH <sub>2</sub> O)
56.4±13.9 (n=40)	89.1±8.6 (n=43)	42.3±4.9 (n=43)	7.38±0.02 (n=43)	8.6±5.8 (n=43)	0.38±0.15 (n=49)	24±7 (n=49)	1.85±0.69 (n=49)

the physical characteristics and the results of pulmonary function tests for all these patients are presented. The mean age for the entire group was 15.6±4.5 years old. The %VC showed a marked decrease being 44.0±25.2% but the FEV<sub>1.0</sub>% was 85.9±14.4% showed no decrease. Therefore, the spirometry showed the presence of restrictive changes. In the subdivisions of lung volume, %FRC was 100.2±37.0% within normal limits but %TLC

decreased with a mean value of 69.7±23.8%. The arterial P<sub>O<sub>2</sub></sub> was 89.1±8.6 mmHg and the arterial P<sub>CO<sub>2</sub></sub> was 42.3±4.9 mmHg. The value of P<sub>0.1</sub> was 1.85±0.69 cmH<sub>2</sub>O.

In order to compare the value of P<sub>0.1</sub> with those of healthy subjects, the patients were divided into two groups based on age, the children's group including 7 patients ranging in age from 8 to 11 years old and the adults' group consisting of 7 patients older than 20.

**Table 13.** Physical characteristics and pulmonary function tests of children's and adults' patients with Duchenne's muscular dystrophy

Subject	N	Age (yr)	Height (cm)	Weight (kg)	VC (liter)	%VC (%)	FEV <sub>1,0</sub> (liter)
Children	7	9.3±1.3	119.6±7.7	24.9±6.0	1.26±0.25	81.6±17.5	0.97±0.29
Adults	7	21.9±1.8	150.3±5.5	38.7±5.4	1.11±0.45	26.4±11.3	1.03±0.45

Subject	N	FEV <sub>1,0</sub> % (%)	MVV (liter/min)	%MVV (%)	Z <sub>max</sub> (cmH <sub>2</sub> O/liter/sec)	RV (liter)	%RV (%)
Children	7	75.7±16.3	38.0±6.4	43.0±12.5	8.1±3.4	0.87±0.30	191.3±27.9
Adults	7	97.9±2.3	38.5±14.9	39.3±15.3	3.9±0.5	2.04±0.20	176.7±14.7

Subject	N	FRC (liter)	%FRC (%)	TLC (liter)	%TLC (%)	RV/TLC (%)	P <sub>aO<sub>2</sub></sub> (mmHg)
Children	7	1.16±0.29	139.3±24.7	1.96±0.36	99.7±12.9	43.7±9.8	94.1±6.7
Adults	7	2.32±0.17	86.7±4.0	3.06±0.34	60.1±6.9	67.4±10.2	83.0±13.3

Subject	N	P <sub>aCO<sub>2</sub></sub> (mmHg)	pH	A-aD <sub>O<sub>2</sub></sub> (mmHg)	V <sub>T</sub> (liter)	f (breaths/min)	P <sub>AJ</sub> (cmH <sub>2</sub> O)
Children	7	38.8±3.1	7.39±0.02	8.4±4.8	0.43±0.23	24±6	2.30±0.83
Adults	7	48.1±7.5	7.36±0.02	7.3±5.5	0.43±0.15	20±7	1.29±0.36

In table 13, the physical characteristics and the results of pulmonary function tests for both the adults' and children's groups are presented.

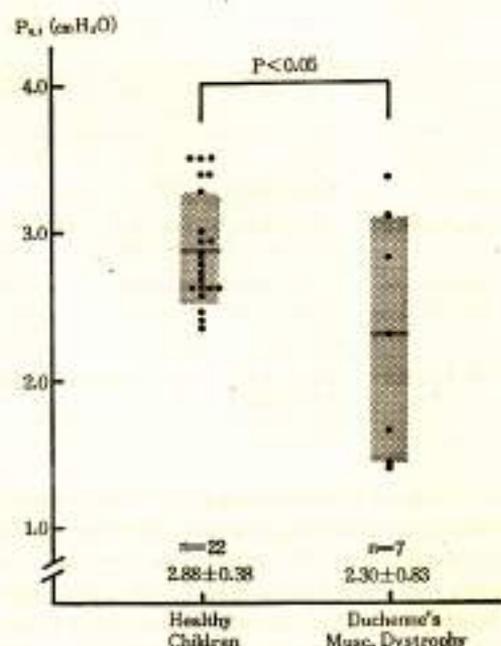
The mean age of the children's group was 9.3±1.3 years old and of the adults' group 21.9±1.8 years old.

The %VC was 81.6±17.5% in the children's group and 26.4±11.3% in the adults' group, thus the %VC showed a marked decrease in the adults' group compared to the children's group. The FEV<sub>1,0</sub>% tended to be higher in the adults' group, it appears that restrictive changes become more severe with the progress of muscular dystrophy.

In the subdivisions of lung volume, %FRC and %TLC tended to decrease in adults' group. Arterial P<sub>aO<sub>2</sub></sub> was 94.1±6.7 mmHg in the children's group and 83.0±13.3 mmHg in the adults' group. The arterial P<sub>aCO<sub>2</sub></sub> was 38.8±3.1 mmHg in the children's group, an increase in the arterial P<sub>aCO<sub>2</sub></sub> was observed in the adults' group.

The tidal volume during resting ventilation was about 0.4 liter and the respiratory frequency was about 20 to 24 breaths/min.

As shown in Fig. 11, 7 children with Duchenne's muscular dystrophy with a mean age of 9.3±1.3 years old were compared to a group



**Fig. 11.** Comparison of values for resting mouth occlusion pressure in healthy children and children with Duchenne's muscular dystrophy.

of 22 healthy boys with a mean age of  $9.5 \pm 0.5$  years old. The  $P_{0.1}$  among the healthy boys was  $2.88 \pm 0.38$  cmH<sub>2</sub>O and among children with Duchenne's muscular dystrophy  $2.30 \pm 0.83$  cmH<sub>2</sub>O, the Duchenne group showed a decrease ( $P < 0.05$ ).

As shown in Fig. 12, 7 adult patients with

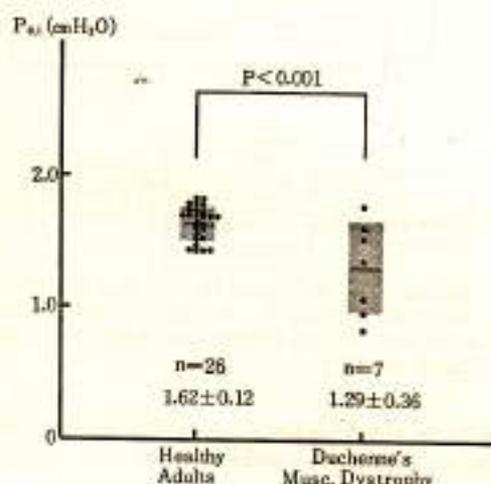


Fig. 12. Comparison of values for resting mouth occlusion pressure in healthy adults and adult patients with Duchenne's muscular dystrophy.

Duchenne's muscular dystrophy with a mean age of  $21.9 \pm 1.8$  years old were compared to a group of 26 normal healthy adult males with a mean age of  $24.9 \pm 2.9$  years old. The  $P_{0.1}$  among the healthy adults was  $1.62 \pm 0.12$  cmH<sub>2</sub>O and among the adult patients with Duchenne's muscular dystrophy  $1.29 \pm 0.36$  cmH<sub>2</sub>O, the Duchenne's muscular dystrophy group showed a marked decrease ( $P < 0.001$ ).

### DISCUSSION

For the study of activity of the respiratory center, experiments have been conducted in the past using the increase in ventilation induced by the breathing of CO<sub>2</sub> containing gas as an index. One of the tests that has been employed is the steady state method. By this method the changes in ventilation due to changes in arterial  $P_{CO_2}$  through breathing several types of gas mixture having various concentration of CO<sub>2</sub> for more than ten minutes were measured.

However, it cannot be said that this steady

state method is an appropriate procedure to be employed clinically inasmuch as a long period of time is required in the test. In contrast to this method, in the rebreathing method developed by Read<sup>50</sup>, alveolar CO<sub>2</sub> concentration is continuously elevated by rebreathing in a small bag and the changes in ventilation are examined by the elevation of CO<sub>2</sub> concentration. This method has such advantages as short time requirement for obtaining a curve of ventilatory response to CO<sub>2</sub>, excellent reproducibility and the relationship between ventilation and end tidal CO<sub>2</sub> tension being linear.

In this method the changes in ventilation in relation to CO<sub>2</sub> tension are used as index of the activity of the respiratory center. As the ventilation is markedly influenced by the changes in resistance and compliance of the respiratory system, it is said that this method is influenced not only by the activity of the respiratory system but also by receptor<sup>51</sup>.

For the study of the activity of the respiratory center, in addition to the foregoing indices, inspiratory mechanical work<sup>5,40</sup>, O<sub>2</sub> consumption of breathing<sup>11</sup>, and diaphragmatic electromyography<sup>40</sup> have been employed as parameters. This latter method, put the patient to great discomfort inasmuch as a balloon is inserted into the esophagus for measuring the esophageal pressure, and electrodes must be inserted into the body for recording the electromyogram.

Recently a new method of examining the activity of the respiratory center has been reported to replace the foregoing methods<sup>9,28,30,43,51</sup>. In this method, the mouth occlusion pressure produced by the inspiratory muscles when the airway occluded at the FRC level is measured. As the reproducibility of the changes in mouth occlusion pressure is extremely good for 200 msec after airway occlusion, the mouth occlusion pressure from onset of increase to 100 msec referred to as  $P_{0.1}$  is employed to study the activity of the respiratory center<sup>51</sup>.

In this method the examination is made at the FRC level when there is no elasticity of the respiratory system, thus all the forces produced by the contraction of the respiratory muscles are reflected as changes of mouth occlusion pressure.

It is further said that as the gas within the

airway during occlusion of the airway does not move, the changes in lung volume can be ignored and the value of  $P_{i,s}$  is not affected by resistance or compliance of the airway system<sup>49,51</sup>. Since the respiratory muscles can be expected to shorten much less during the occlusion than during unobstructed breathing, their force-velocity relations have a relatively small influence on the  $P_{e,s}$ <sup>49</sup>.

Furthermore, as the change in lung volume during measurement of  $P_{o,s}$  is almost insignificant, there is no effect on the intrapulmonary mechanoreceptor via the vagal nerve.

As described above, in this method the various mechanical factors considered to influence the activity of the respiratory center could be eliminated.

The author conducted basic and clinical studies on

- 1) How  $P_{e,s}$  changes with changes in  $CO_2$  tension,
- 2) Whether  $P_{e,s}$  changes when FRC level changes,
- 3)  $P_{e,s}$  of healthy subjects and
- 4)  $P_{e,s}$  of various types of diseases.

- 1) The relationship between  $P_{s,s}$  and alveolar  $P_{CO_2}$

In the study of Read<sup>54</sup> on ventilatory response to  $P_{CO_2}$  by the rebreathing method and in the study of Whitelaw et al<sup>61</sup> on mouth occlusion pressure, a mixture of 7%  $CO_2$  has been used. By making  $P_{CO_2}$  of the inspired gas identical to  $P_{CO_2}$  of the mixed venous blood from the commencement of rebreathing, it is possible to make the closed loop in the block diagram of the chemical regulatory system of respiration shown in Fig. 13 become an open loop sooner, because the arterial  $P_{CO_2}$  can be suddenly elevated<sup>54</sup>. This elevation of  $P_{CO_2}$  is detected by the central and peripheral chemoreceptors and is transmitted as information to the respiratory center, but it is said that the change of  $HCO_3^-$  is somewhat later than the change of  $P_{CO_2}$  in the cerebrospinal fluid due to the blood brain barrier. Irsigler<sup>59</sup>, Shan et al<sup>55</sup> and Hulsbosch et al<sup>57</sup> have measured the ventilatory response to  $CO_2$  by rebreathing repeatedly and have reported that there was no systematic difference in the slopes between the curves. However, Miyamura et al<sup>60</sup> have reported observing some cases in which the

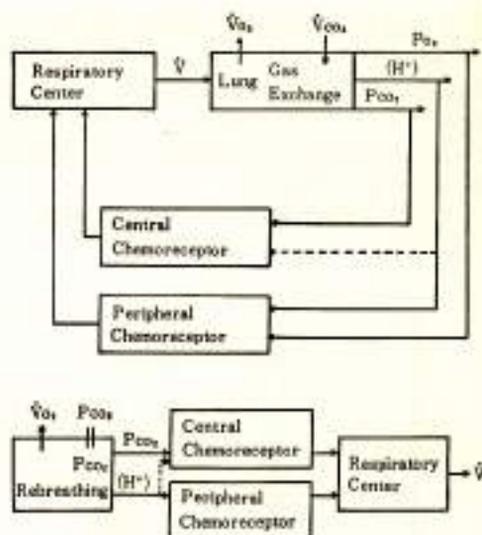


Fig. 13. The diagram of the chemical regulatory system of respiration. The upper panel is the closed loop and the lower panel is the open loop. (Honda et al.<sup>56</sup>)

slope of the  $CO_2$  response curves became lower by repeating rebreathing over an extended period.

The author made a study on how  $P_{e,s}$  changed when  $CO_2$  concentration in the rebreathing bag was 0 and when it was 7% and when rebreathing was made at a given interval. As can be seen in Fig. 4 and Fig. 5, the relationship between  $P_{e,s}$  and alveolar  $P_{CO_2}$  was hardly affected when the  $CO_2$  concentration in the bag was either 0% or 7% at the time of commencement of rebreathing. As shown in Fig. 6 there was no change in the relationship of alveolar  $P_{CO_2}$  to  $P_{e,s}$  following repetitive rebreathing over an extended period.

Through this study it was ascertained that the gas used in this method does not have to contain  $CO_2$  in particular and that the test may be repeatedly conducted.

Furthermore, a study was made to determine whether the relationship between alveolar  $P_{CO_2}$  and  $P_{i,s}$  is linear or exponential. Using 18 healthy individuals as subjects, the alveolar  $P_{CO_2}$  level was slowly increased by rebreathing and airway occlusion was made at each of several breaths. As shown in Fig. 7 and Table 4, with the elevation of alveolar  $P_{CO_2}$ ,  $P_{i,s}$  increased linearly in 10 cases and exponentially in 8 cases. During the course, as the activity of the respiratory center increased, there was

remarkably differs from that of an adult group. As shown in Fig. 9 and Table 6, in a group of 39 children of both sexes aged 9-10,  $P_{a,1}$  showed a high value of  $2.87 \pm 0.38 \text{ cmH}_2\text{O}$ . according to the report of Gaultier et al,  $P_{a,1}$  value of children age 9-10 showed a value of  $2.1 \text{ cmH}_2\text{O}$  which is much higher than that of normal subjects who were older than 18 years, but in a group of children no difference by sex could be observed.

The possible reason for this higher  $P_{a,1}$  value in children than in adults are that 1) FRC is smaller and 2) lung compliance is smaller.

4)  $P_{a,1}$  of various types of diseases

i) In fibrosing lung disease hardly and elevation of airway resistance is observed and the elastic recoil is remarkably increased.

No report has been published on  $P_{a,1}$  in fibrosing lung disease. According to the results of present study,  $P_{a,1}$  in fibrosing lung disease was  $2.09 \pm 0.30 \text{ cmH}_2\text{O}$  and in comparison with  $1.61 \pm 0.13 \text{ cmH}_2\text{O}$  in the healthy adults it was significantly elevated ( $P < 0.001$ ).

As for the cause of this elevation, it is considered that 1) decrease in FRC and 2) decrease in lung compliance affect the activity of the external intercostal muscles or the inspiratory muscles by acceleration the activity of the gamma-fiber system.

The value of %FRC is low, almost about 70%, suggesting the possibility that the mechanism is similar to the high  $P_{a,1}$  in normal children having a small FRC. Also, due to the effect of the gamma-fiber system, the activity of the respiratory system is accelerated and as a result a rapid transition is made from inspiration to expiration. It is considered that due to these changes in FRC and intervention neural reflex,  $P_{a,1}$  elevates in fibrosing lung disease.

ii) Several studies<sup>9,11,12,49,50</sup> have reported on  $P_{a,1}$  in chronic obstructive lung disease. It has been reported that in chronic obstructive lung disease with no elevation of arterial  $P_{\text{CO}_2}$  demonstrable by arterial blood gas analysis, and at alveolar  $P_{\text{CO}_2}$  60 mmHg,  $P_{a,1}$  is more elevated than in healthy subjects<sup>11</sup>. According to the results of this present study, elevated alveolar  $P_{\text{CO}_2}$  was observed in one case out of 10 cases of pulmonary emphysema. The  $P_{a,1}$  value of these 10 patients was  $2.84 \pm 0.54 \text{ cmH}_2\text{O}$ , which remarkably higher than that of

healthy subjects. In cases of chronic bronchitis,  $P_{a,1}$  value in Type I and Type II of Nishimoto's classification not having obstructive ventilatory disturbance was  $1.92 \pm 0.21 \text{ cmH}_2\text{O}$  and that in Type III and Type IV having obstructive ventilatory disturbance  $P_{a,1}$  showed a slightly stronger tendency to increase compared to that of Type I and Type II not having this disturbance, but no significant difference could be demonstrated.

As for the mechanism involved in the elevation of  $P_{a,1}$  in cases of chronic obstructive lung disease, it is considered to be due to the response of the respiratory center as observed in loading of viscous resistance in healthy subjects. When ventilation is made in healthy subjects and animals through a viscous resistance tube having a small inner diameter, a minute volume decreases whereas  $P_{a,1}$  elevates. It is considered that non-chemical response via the vagal nerve is implicated. Thus, it is considered that in Patients with chronic obstructive lung disease the activity of the respiratory center cannot be adequately evaluated by minute volume or by arterial  $P_{\text{CO}_2}$ .

iii)  $P_{a,1}$  in pneumoconiosis was studied by classifying the cases into a mild group and an advanced group according to the finding on the chest X-ray films<sup>19,60</sup>.

In both groups only a few cases showed ventilatory disturbance by spirometry, the degree being of the same level in both groups.  $P_{a,1}$  was  $1.87 \pm 0.11 \text{ cmH}_2\text{O}$  in the mild group and  $1.82 \pm 0.14 \text{ cmH}_2\text{O}$  in the advanced group with no significant difference between the two groups. However, when compared with the healthy group, the values were significantly higher ( $P < 0.001$ ).

The pathological changes of pneumoconiosis was basically fibrosis. Thus, it is considered that  $P_{a,1}$  in pneumoconiosis is more elevated than that of the normal group by a mechanism similar to that of the fibrosing lung disease group. However, as the degree of pulmonary fibrosis in the pneumoconiosis group is milder than that in the fibrosing lung disease group, it is assumed that  $P_{a,1}$  did not elevate very much.

iv) Hardly any study has been made on the activity of the respiratory center in Duchenne's muscular dystrophy. The only reported study made on  $P_{a,1}$  in Duchenne's muscular

dystrophy in particular is that in the report of Bégin et al<sup>7</sup>. Bégin et al determined  $P_{0.1}$  value in 9 patients having Duchenne's muscular dystrophy and reported that the value was slightly lower than the mean of normal subjects with no significant difference between them. This present study determined  $P_{0.1}$  values of Duchenne's muscular dystrophy patients by classifying the patients into a group of children and an adults' group. The value in the children's group was found to be significantly decreased when compared to the healthy group. Even in the adults' group the  $P_{0.1}$  value was markedly decreased when compared to the healthy group, the difference being significant ( $P < 0.001$ ).

It has been reported that the  $P_{0.1}$  value is elevated under slightly decreased respiratory muscle power, for example in loading of elastic resistance in healthy subjects<sup>15,16</sup>, and in patients with milder neuromuscular disease<sup>10</sup>. This is probably due to accelerated activity of the respiratory center which strengthens the contraction power of the respiratory muscles. However, under decreased respiratory muscle power of a moderate to severe degree, increased respiratory center stimulation is not reflected as contraction of the respiratory muscles and thus it is considered that  $P_{0.1}$  shows a low value. The pulmonary function of Duchenne's muscular dystrophy studied by this present study is a restrictive ventilatory disturbance which progresses with age and is considered to originate from reduction in respiratory muscle power. In the children's group there is a reduction of respiratory muscle power of a moderate level, while in the adults' group the reduction of respiratory muscle power is greater.

Therefore, despite the accelerated activity of the respiratory center happened, the contraction of the respiratory muscle is weak and causing the reduction of  $P_{0.1}$ . In the present study, the reduction of  $P_{0.1}$  in the adults' group is greater than in the children's group because the disturbance in the adults' group is more severe than in the children's group.

$P_{0.1}$  can be used to evaluate the neural activity of the respiratory center and the efficiency of the respiratory muscles, and it can be easily utilized in the clinic as the apparatus involved is simple.

## ACKNOWLEDGMENTS

The author is greatly indebted to Professor Yukio NISHIMOTO, chairman of the Second Department of Internal Medicine, for his kindness, advice and invaluable support during the four years of study in his department.

The author wishes to express his deep gratitude to Dr. Osami NISHIDA and Dr. Takehiko HIRAMOTO who suggested making this study, for their direct guidance, support and advice during the course of this study.

He is also grateful to Dr. Ken-ichi ARITA for his skillful technical guidance, professional support and helpful suggestion, to all members of the Pulmonary Function group especially to Dr. Kenta FUJIWARA, Dr. Teruomi MIYAZAWA, Dr. Hiroyuki ARITA, Dr. Shigekiyo NAKANISHI, Dr. Mitsuhide HIRAMOTO, Dr. Hirofumi FUKUHARA and Dr. Yoko KAGAWA for their wholehearted cooperation.

Last but not least, his heartfelt thanks are also extended to all members of the Second Department of Internal Medicine, every member of the university and to officers and members of the Hiroshima University Foreign Student Association especially to Ir. A. Rasyidi FACHRY and Drg. Ismet Danial NASUTION for making his four years most enjoyable and meaningful.

This study was performed under a postgraduate fellowship program of the Japanese Ministry of Education in the Second Department of Internal Medicine, Hiroshima University School of Medicine.

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