Nagoya J. Health, Physical Fitness, Sports Vol. 5, No. 1 (March 1982)

Ventilatory Response to Hypercapnia in the Monozygotic and Dizygotic Twins

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The present study was made to examine the importance of heredity of the ventilatory response to hypercapnia. The subjects were 17 monozygotic twin (MZ) pairs and 4 dizygotic twin (DZ) pairs, aged from 11 to 22 years. The ventilatory response to CO_2 was determined by the CO_2 rebreathing method for each subject. In this study, correlation ($r=0.82$, $p<0.01$) was found between hypercapnic ventilatory response ($\Delta\dot{V}_E/\Delta P_{ACO_2}$) for monozygotic twins and it was maintained when corrected for body size by dividing response by body surface area. The variability within twin pairs was smaller for monozygotic twins than dizygotic twins.
From these results, it was suggested that genetic factors are responsible for the variation of hypercapnic ventilatory response in normal young people.

The large variability in the ventilatory response to inhaled CO_2 have been known not only in the healthy subjects, but also in patients and athletes, while the reasons for this scatter are not fully understood. It may be related to various factors such as age (Kronenberg and Drage, 1973)[11], sex (Patrick and Howard, 1972[19]; Irsigler, 1976[5]; Miyamura *et al.* 1979[14]), temperature (Natsui, 1969[18], Natalino *et al.*, 1977[17]) and race (Beral and Read, 1971[2]; Patrick, 1976[20]). Recently it has been suggested that familial influences play an important role in the determination of ventilatory drives. However, the results reported so far are conflicting; Arkinstall *et al.* (1974)[1] have measured by hypercapnic ventilatory responses in identical and nonidentical twins and were unable to demonstrate a hereditary influence on the ventilatory response to hypercapnia, although they did find an effect on breathing frequency and tidal volume responses to hypercapnia. On the other hand, Saunders *et al.* (1976)[22] have shown a strong correlation between hypercapnic ventilatory responses seen in championship swimmers and their siblings. Therefore, to examine the importance of heredity, we studied the ventilatory response to hypercapnia in monozygotic twins (MZ) and dizygotic twins (DZ).

Methods

Twenty-one pairs of twins (17 MZ and 4 DZ) participated in the study. Both sexes were accepted in monozygotic twin pairs (10 male and 7 female), but same sex was only one female pairs in the dizygotic twins. Initial determination of zygosity was performed by obsterics doctors who were attend to birth of twins. Monozygotic twin pairs ranged in age from 11 to 22 yr and dizygotic twin pairs from 13 to 20 yr, respectively. No particular clinical examination was carried out but all subjects were healthy with no history of pulmonary disease. Physical data of the subjects are shown in Table 1.

The subjects were briefly informed about the

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Table 1. Physical characteristics and results of pulmonary test of the subjects.

	MZ		DZ	
	A	B	A	B
Age (yr)	16.4 ± 3.3		16.7 ± 2.5	
Height (cm)	159.4 ± 8.0	160.2 ± 8.2	161.7 ± 10.6	155.5 ± 5.0
Weight (kg)	49.5 ± 6.8	50.3 ± 6.6	53.3 ± 11.3	46.3 ± 0.7
BSA (m^2)	1.48 ± 0.13	1.50 ± 0.13	1.53 ± 0.20	1.42 ± 0.03
VC (l)	3.54 ± 0.85	3.62 ± 0.81	3.91 ± 1.03	2.66 ± 0.26
$FEV_{1.0}$ (l)	3.21 ± 0.83	3.28 ± 0.83	3.55 ± 0.80	2.44 ± 0.27
$FEV_{1.0}$/VC (%)	90.7 ± 5.1	90.1 ± 4.6	91.6 ± 4.4	91.9 ± 5.0

Values are mean ± SD. BSA; Body surface area, VC; Vital capacity, $FEV_{1.0}$; Forced expiratory volume in one second.

experimental procedure, but not about the results of any of the experiments until the study had been completed. All subjects gave their consent after the nature of the experiments had been explained. The subjects came to the laboratory twice. On the first day, each subject was only familiarized with the apparatus and testing procedure. The actual experiment was performed on the separate day about one week after the first day. The subjects were usually studied 2 hours or more after their last meal.

The ventilatory response line to hypercapnia was determined in the sitting position by the rebreathing method (Read, 1967)[21]. The experimental set-up was similar to that described previously (Miyamura, 1976)[13]. A rubber bag with a capacity of about 10 liters was placed in an air-tight plastic box which was connected at one end to a respirometer (Benedict Roth type, 13.5 liter, Fukuda, Japan) for recording ventilation. The opposite end of the rubber bag was connected to a three-way stopcock. The bag was filled with 5-6 liters of a gas mixture of about 7% CO_2 in O_2. After the subject rested on a comfortable chair for 30 min, rebreathing commenced at the end of a maximal expiration and continued for 4 min.

Minute ventilation ($\dot{V}_E$) was calculated for successive 30 second intervals from a spirographic recording, and gas volume was corrected to BTPS conditions. Alveolar P_{CO_2} (P_{ACO_2}) during rebreathing was continuously recorded with an infrared CO_2 analyzer (capnograph, Godart, Holland) into which gas samples were continuously drawn from the subject's mouth-piece. After passing through the analyzer, the gas sample was returned to the rebreathing bag. The slope of the ventilatory response line to CO_2, S (l/min/mmHg) and their intercept on the P_{CO_2} axis, B (mmHg) were calculated by the least square regression as follows: $\dot{V}_E = S\ (P_{ACO_2} - B)$.

To estimate aerobic work capacity, maximal oxygen uptake was determined using motor driven treadmill after one hour of hypercapnic drive test; the subjects warmed up for 3 min by running on the treadmill at speed of 80 − 120 m/min constant grade of 8.6%. This was followed by a 2 or 3 min rest and thereafter maximal exhaustive exercise was carried out with a stepwise incremental loading technique in which the speed of treadmill was increased by 10 m/min every minute until the subject became exhaustion within 6 to 10 min. Expired gas during exercise was collected by the Douglas bag every minute. The collected gas was measured with a wet-gasometer (Shinagawa, Japan), and gas analysis was performed with an oxygen analyzer (S-3A type, Morgan, England) and an infrared CO_2 analyzer (capnograph, Godart, Holland). These analyzers was calibrated with two known calibration gases that had been analyzed by the Scholander gas analyzer. Heart rate during exercise was continuously monitered from a bipolar chest lead equipped with digital display of minute heart rate.

Results

The partners of a twin pair were allocated as A or B by random numbers. If values of twin pairs are plotted on a X−Y system of coordinates, the degree to which a twin pair departs from the line of identity will indicate the discordance between the two partners.

It was found that maximum pulmonary ventilation ($\dot{V}_{E\,max}$) and maximum oxygen uptake per kilogram of body weight ($\dot{V}O_{2\,max}/W$) for members of monozygotic twin pairs are significantly correlated ($r=0.86$, $p<0.01$, and $r=0.90$, $p<0.01$) as shown in Fig. 1. In contrast no significant correlation was found between members of dizygotic twin pairs. Fig. 2 shows the results of the slope of the ventilatory response line to hypercapnia obtained in the monozygotic and dizygotic twins. Correlation ($r=0.82$, $p<0.01$) was found between hypercapnic ventilatory response ($S=\Delta\dot{V}_E/\Delta P_{ACO_2}$) for monozygotic twins (left panel) and it was maintained when corrected for body size by dividing response by body surface area (right panel). The variability within twin pairs was smaller for monozygotic twins than dizygotic twin.

Although respiratory frequency increased gradually during rebreathing in all subject, there was a strong correlation ($r=0.90$, $p<0.01$) between respiratory frequency which was measured from 3 to 3.5 min during rebreathing in the monozygotic

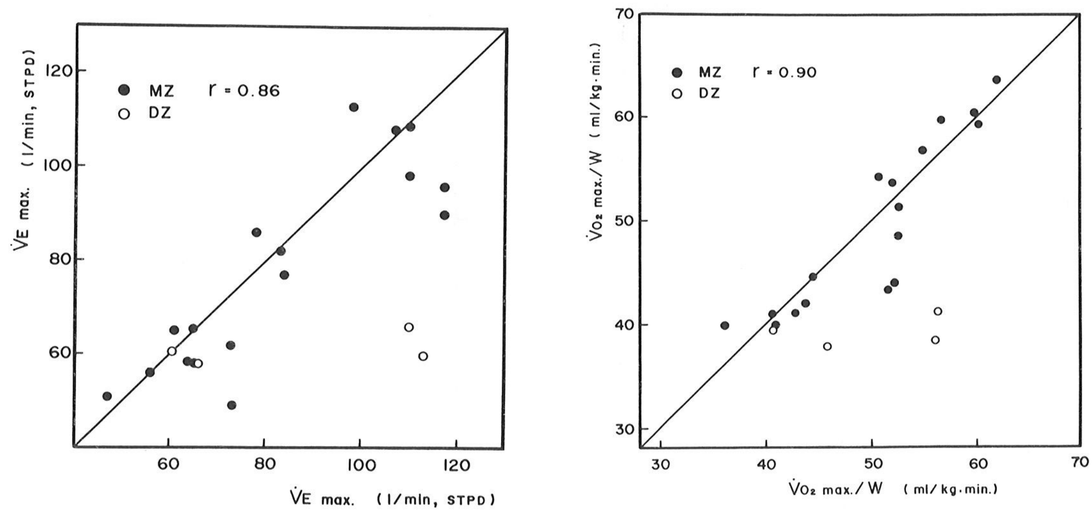
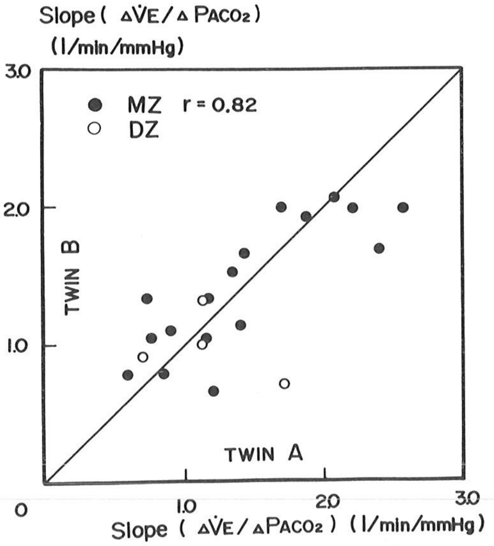


Figure 1. Intrapair comparison of maximum pulmonary ventilation ($\dot{V}_{E\,max}$) and maximum oxygen uptake per kilogram of body weight ($\dot{V}_{O_2 max}/W$) in the monozygotic (MZ) and dizygotic (DZ) twins.



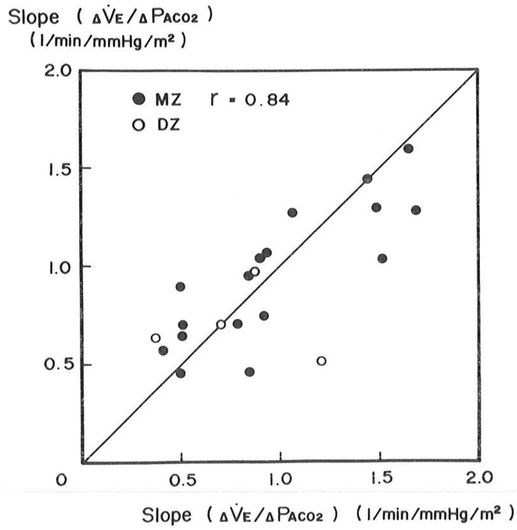


Figure 2. Intrapair comparison of slope ($\Delta\dot{V}_E/\Delta P_{ACO_2}$) of the ventilatory response line to hypercapnia at rest in the MZ and DZ twins.

twins (Fig. 3). Furthermore, correlation ($r=0.84$, $p<0.01$) was found for ventilatory response to CO_2 expressed as $\Delta f/\Delta P_{ACO_2}$ in monozygotic twins as shown in Fig. 4.

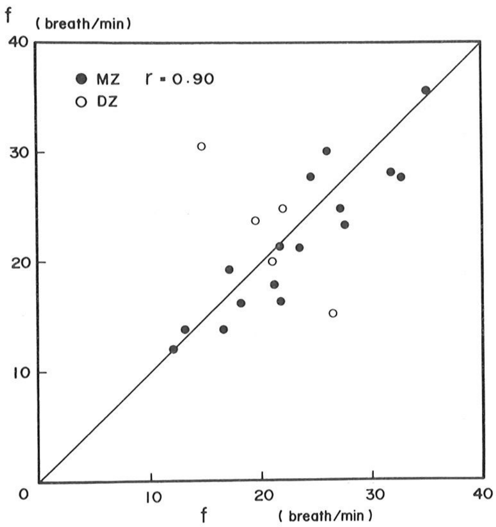


Figure 3. Intrapair comparison of respiratory frequncy (f) for 3 — 3.5 min during rebreathing for 4 min.

Discussion

Several authors (Klissouras, 1971[7]; Klissouras

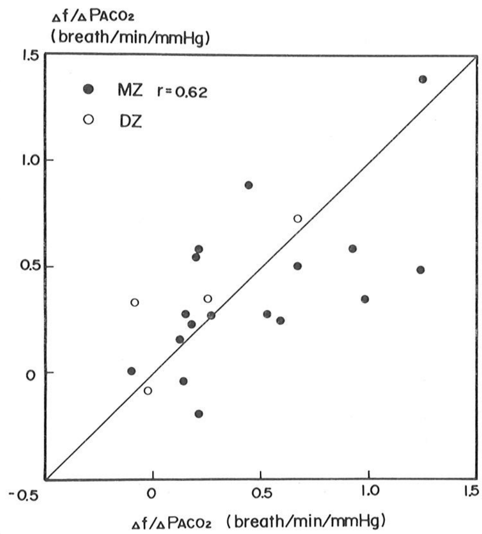


Figure 4. Intrapair comparison of ventilatory response to hypercapnia expressed as $\Delta f/\Delta P_{ACO_2}$

et al., 1973[8], Arkinstall *et al.*, 1974[1]; Komi *et al.*, 1977[10]) have calculated intrapair variance either in monozygotic and dizygotic twins to estimate the heritability (Hest). This heritability index signifies the propotion of the total variance attributable to genetic variability. Since dizygotic twins in this study were only 4 pairs, however, we used a correlation technique to examine the effects of genetic factors on ventilatory response in the twin pairs.

As shown in Fig. 1, maximum oxygen uptake for the members of monozygotic twins are significantly correlated and no significant correlation was found between members of dizygotic twin pairs, indicating that monozygotic twins are more homogeneous with respect to aerobic work capacity than dizygotic twins. These results agree well with those reported by Klissouras (1971)[7] and Komi *et al.* (1976)[9].

Arkinstall *et al.* (1974)[1], who determined the ventilatory response to CO_2 in 17 sets of monozygotic and 13 sets of dizygotic twins, have concluded that heredity component to the inter-individual variability was not demonstrated for the slope of ventilatory response to CO_2, while 80-90% of the variability in tidal volume response to CO_2 could be attributed to genetic factors and the variability in the frequency response is attributed mainly to environmental differences. Collins *et al.* (1978)[3] have also reported that no correlation could be found for ventilatory response to hyperoxic hypercapnia. In this study, however, correlation ($r=0.82$, $p<0.01$) was found between the slope of ventilatory response line for monozygotic twins and it was maintained when corrected for body size by dividing the slope by body surface area (Fig. 2). Furthermore, it was interesting to note that there was a strong correlation ($r=0.90$) between respiratory frequency which was measured from 3 to 3.5 min during rebreathing in monozygotic twins (Fig. 3). Our results are basically agree with the data of Kawakami *et al.* (1980)[6] and Yamamoto *et al.* (1981)[23], but not of Arkinstall *et al.* (1974)[1] and Collins *et al.* (1978)[3].

The discrepancy described above may be due to the difference in the age of subjects or in the technique of determining the CO_2 response line. Concerning to first reason, Yamamoto *et al.* (1981)[23] have found that intrapair variances for the slope of ventilatory response to CO_2 corrected by body surface area (S/BSA) was significantly smaller in MZ than DZ either for young or adult twins, while intrapair variances for S/BSA in adult MZ was significantly larger than in young MZ. From these results, they suggested that environmental factors play a more important role in S/BSA. Although the subjects ranged in age from 11 to 22 yr and from 12 to 26 yr in the studies of present and Collins *et al.* (1978)[3], respectively, it does not written in the paper of Arkinstall *et al.* (1974)[1].

We determined the slope of ventilatory response to hypercapnia using the so-called Read's rebreathing method. Collins *et al.* (1978)[3] have measured the ventilatory response to hypercapnia by simple rebreathing method; this method differs from that of Read in that no CO_2 is initially present in the system and data collection begins when inspired CO_2 approaches the initial P_{ACO_2}. According to Collins *et al.*, a rise in P_{ACO_2} of approximately 10 mmHg over control was produced over approximately 10 min, and this technique produces linear responses with slopes similar to those obtained with Read's method[4]. At present no definite explanations for the discrepancy in the results between Collins's and our studies can be given with physiological reason. Since the slope of ventilatory response to CO_2 is changing by P_{aCO_2} levels (Loeschke and Gertz, 1958)[12], it is possible to assume that the P_{aCO_2} level in each subject may be differ more or less during rebreathing.

On the other hand, Arkinstall *et al.* (1974)[1] measured hypercapnic ventilatory drive using Read's rebreathing method 4 times with a 15- to 20 min interval between run, and it seems to be averaged to determine the slope for each subject. However, we found in the previous study (Miyamura *et al.*, 1980)[16] that the slope of the high responders decreased in repeated experiment with 30 min intervals. This is indicating that CO_2 response curve by rebreathing should be determined carefully, especially in high responders, taking into consideration the time interval in consecutive measurements.

From these results, it was suggested that genetic factors are important determinants of hypercapnic ventilatory response in the young subjects.

A part of this study has been reported in the elsewhere[15].

This study was supported in part by Grant-in-Aid for Scientific Research (No. 358037) from the Ministry of Education of Japan.

We are greatly indebted the cooperations of the twins, who were participated in this study as subjects. We are also expressed our gratitude to Miss N. Kato for her cooperations during the preparation of the manuscript.

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(Received January 30, 1982)