Comparison of occlusion pressure and ventilatory responses

D. H. LEDERER, M. D. ALTOSE, S. G. KELSEN, AND N. S. CHERNIACK

From the Cardiovascular-Pulmonary Division, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA

Lederer, D. H., Altose, M. D., Kelsen, S. G., and Cherniack, N. S. (1977). Thorax, 32, 212-220. Comparison of occlusion pressure and ventilatory responses. The airway pressure 100 msec after the onset of an inspiratory effort against a closed airway (P_{100} , occlusion pressure) is theoretically a more accurate index of respiratory neuron motor output than ventilation. Occlusion pressure and ventilation responses to hypercapnia were compared in repeated trials in 10 normal subjects while in the seated and supine positions. During progressive hypercapnia changes in P_{100} were also compared to changes in tidal volume and inspiratory airflow. These studies show that occlusion pressure increases linearly with hypercapnia in both sitting and supine subjects. Changing from the seated to the supine position, or *vice versa*, had no significant effect on either ventilation or occlusion pressure responses to CO_2 . Correlations between P_{100} and ventilation or airflow rate were significantly higher than correlations between P_{100} and tidal volume or breathing frequency. Intermittent random airway occlusion had no effect on either ventilation or pattern of breathing during hypercapnia. Occlusion pressure responses were no less variable than ventilation responses in groups of subjects whether studied seated or supine. However, maintenance of a constant moderate breathing frequency (20 breaths per minute) reduced the interindividual variability in ventilation and occlusion pressure responses to hypercapnia.

Respiratory sensitivity to CO_2 is generally evaluated by the change in ventilation during hypercapnia. Ventilation, however, is an imperfect measure of respiratory neural efferent activity since the level of ventilation may be affected by alterations in the mechanical properties of the lung and chest wall independently of changes in respiratory activity (Cherniack and Snidal, 1956; Eldridge and Davis, 1959; Brodovsky *et al.*, 1960; Milic-Emili and Tyler, 1963). Even in normal individuals in whom pulmonary performance is unimpaired, ventilatory responses to hypercapnia vary markedly from person to person, and in the same individual ventilatory responses differ widely from day to day (Read, 1967; Kallos *et al.*, 1972; Patrick and Howard, 1972; Saunders *et al.*, 1972; Hirshman *et al.*, 1975).

Recently, occlusion pressure, the mouth pressure during airway occlusion 100 msec after the onset of inspiration (P_{100}), has been proposed as a more accurate index of respiratory neural efferent activity (Grunstein *et al.*, 1973; Whitelaw *et al.*, 1975; Altose *et al.*, 1976b; Kelsen *et al.*, 1976). The re-

lationship between respiratory output and occlusion pressure, determined during periods of arrested airflow, should not be affected by changes in the flow resistive and elastic properties of the ventilatory apparatus. However, occlusion pressure, at any level of respiratory activity, may be substantially altered through changes in functional residual capacity which in turn affect the resting length of the inspiratory muscles (Evanich *et al.*, 1973). Changes in functional residual capacity could also alter the relationship between occlusion pressure and ventilation.

Because ventilation and not occlusion pressure determines arterial blood gas tensions, it is important to ascertain the relationship between occlusion pressure and ventilation and its various components.

In the present study, occlusion pressure and ventilatory responses to hypercapnia were compared in a group of subjects, in the same individuals on different days and at different levels of functional residual capacity achieved by changing from the supine to the seated position or *vice versa*.

Since airway occlusion, a maximal load on the respiratory muscles, could excite spinal reflexes or supraspinal mechanisms which might alter the level of respiratory activity for any given chemical drive (Corda *et al.*, 1965; Knill *et al.*, 1976), the effect of intermittent airway occlusion on the level and pattern of ventilation during hypercapnia was also assessed.

Methods

Ten subjects, eight men and two women, ranging in age from 20 to 35 years were studied. All were in good health and none smoked cigarettes or had symptoms or physical signs of lung disease. Informed consent for the study was obtained in all subjects.

Pulmonary function tests were performed in duplicate using a 13.5 l Collins spirometer and included the determination of vital capacity (VC), forced expiratory volume in one second (FEV_{1.0}), and maximum mid-expiratory flow rates (MMF). Functional residual capacity (FRC) was determined with the subjects in both the sitting and the supine position by the helium dilution technique. The physical characteristics of the subjects and the results of their pulmonary function tests are shown in Table 1.

Studies were performed late in the morning, and the subjects were instructed to refrain from eating and drinking coffee for at least three hours before the tests.

Progressive hypercapnia was produced by having the subjects rebreathe from a bag containing a gas mixture of 7% CO₂ in oxygen (Read, 1967). The end-tidal CO₂ concentration was sampled at the mouth and measured with an infrared analyser (Godart Capnograph). After analysis the sampled gas was returned to the rebreathing bag. Tidal volume was recorded by electrical integration of the signal from a pneumotachograph (Fleisch Pneumotachograph 2, i/a 7320, and Statham Differential Pressure Transducer, PM-5) which was connected to the rebreathing bag by a high-velocity one-way valve

(Hans Rudolf, Inc., P-308). The circuit had a resistance of 1.2 cmH₂O/l/sec at a flow rate of 2.0 l/sec. The pneumotachograph was linear over the range of airflows encountered.

During rebreathing the airway was periodically occluded for a single breath by closing the large-bore stopcock placed in the inspiratory line. At least 10 occlusions were performed during each rebreathing trial. The airway was occluded randomly but occlusions were presented no more frequently than every eighth breath. A screen prevented the subjects from knowing when airway occlusion would occur. The mouth pressure was recorded with a pressure transducer (Statham PM-131, TC), and the occlusion pressure 100 msec after the onset of inspiration (P₁₀₀) was measured. All tracings were displayed on an oscilloscopic apparatus and recorded on photo-sensitive paper (Electronics for Medicine, DR-8).

Responses to progressive hypercapnia were determined on three separate days. On the first day two rebreathing trials were performed with the subjects seated; the first with periodic airway occlusion and the second with no airway occlusion. In five of the 10 subjects the order of the rebreathing trials was reversed. The ventilatory responses during the two trials were compared.

On the second day ventilatory and occlusion pressure responses to CO₂ were determined with the subjects seated and then supine or *vice versa*, while on the third day this order in any given subject was reversed.

On another day additional studies were performed on five subjects to evaluate the effect of tidal volume and breathing frequency in contributing to the variability of ventilation and occlusion pressure responses to hypercapnia. Each subject performed five rebreathing trials: (1) adopting any breathing pattern which seemed natural to him; (2) at a fixed tidal volume of 1 litre; (3) at a fixed tidal volume of 2 litres; (4) at a constant breathing frequency of 20 breaths per minute; and (5) at a constant breathing frequency of 35 breaths per minute. To maintain

Table 1 Physical characteristics of lung function in subjects tested

Subject	Age	Sex	FVC % pred	FEV _{1.0} % pred	FEV/FVC %	FRC		% Decrease in FRC sitting to supine
						Sitting	Supine	
1	30	M	127	124	85	4.78	3.25	32
2	29	M	112	124	89	3.97	2.84	28
3	25	M	94	102	87	3.60	2.36	34
4	30	M	97	107	91	3.61	2.54	30
5	29	M	111	115	85	3.67	2.06	44
6	34	M	120	132	89	3.36	3.07	9
7	22	F	108	125	71	2.61	1.61	38
8	25	M	99	100	83	3.26	2.34	28
9	24	M	98	109	88	4.86	3.01	38
10	23	F	108	113	81	3.08	2.05	33

tidal volume constant, the subject was instructed to keep his tidal volume within the limits shown on an oscilloscope. To keep breathing frequency constant subjects breathed in synchrony with the beat of a metronome.

During progressive hypercapnia, at least three breaths after occlusion, measurements were made of respiratory frequency, inspiratory duration (t_i), tidal volume (V_T), average rate of inspiratory flow (V_T/t_i), peak inspiratory flow ($\dot{V}_{peak}$), and flow 100 msec after the onset of inspiration ($\dot{V}_{100}$). The relationships between PCO_2 , P_{100} , and these ventilatory indices were determined from the slopes of regression lines calculated by the method of least squares. The significance of differences in correlation coefficients was tested either by Student's t test or by non-parametric techniques (Mann-Whitney test) when distribution curves were skewed (Colquhoun, 1971).

Results

RESPONSES TO HYPERCAPNIA

Minute ventilation, tidal volume, and V_T/t_i increased linearly with hypercapnia. Similarly, P_{100} , $\dot{V}_{100}$ and $\dot{V}_{peak}$ also increased linearly with increasing PCO_2 during rebreathing. Frequency distributions of the linear correlation coefficients of the relation of PCO_2 and minute ventilation, tidal volume, V_T/t_i , P_{100} , $\dot{V}_{100}$, and $\dot{V}_{peak}$ during all rebreathing trials performed in the 10 subjects are shown in Fig. 1. Linear correlation coefficients greater than 0.9 were most commonly obtained from the minute ventilation- PCO_2 , V_T/t_i - PCO_2 , P_{100} - PCO_2 , and $\dot{V}_{peak}$ - PCO_2 relations, whether measured in the sitting or supine positions.

EFFECTS OF INTERMITTENT AIRWAY OCCLUSION

The effects of intermittent airway occlusion on ventilatory responses during progressive hypercapnia are summarised for all subjects in Table 2. There was no significant effect of airway occlusion on the changes in minute ventilation, tidal volume, V_T/t_i , $\dot{V}_{100}$, and $\dot{V}_{peak}$ during hypercapnia.

In two subjects, ventilatory responses to CO_2 were higher in rebreathing trials which included intermittent airway occlusion, while in three other subjects ventilatory responses were lower when airway occlusion was performed during rebreathing. Ventilation at a PCO_2 of 60 torr averaged $3.1 \text{ l/min} \pm 1.8 \text{ SE}$ higher in the studies in which airway occlusion was performed. This increase occurred in only six of the 10 subjects and, when noted, was due to a shortening of expiratory duration with consequent increase in breathing frequency. For the group as a whole, however, these changes (t test for paired observations) were not statistically significant ($P > 0.05$). There was no consistent effect of the order in which the trials were performed.

Plots of the relation of minute ventilation and tidal volume as described by Hey *et al.* (1966) were constructed to evaluate the effects of airway occlusion on the pattern of ventilation during rebreathing. The results in a representative subject (Fig. 2) show that intermittent airway occlusion during rebreathing had no effect on the tidal volume to ventilation relationship. The mean slope of the tidal volume to ventilation relationship in all subjects was $27 \text{ ml/l/min} \pm \text{SE } 5$ during rebreathing with intermittent airway occlusion and $31 \text{ ml/l/min} \pm \text{SE } 4$ in trials where the airway was not occluded. This difference was not statistically significant.

Fig. 1 Frequency distribution of the linear correlation coefficients of the relation of $\dot{V}$, V_T , V_T/t_i , P_{100} , $\dot{V}_{100}$, and $\dot{V}_{peak}$ to hypercapnia in all rebreathing trials in all 10 subjects. R = correlation coefficient.

Table 2 Effect of airway occlusion on ventilatory responses to CO₂ (mean $\pm$ SE)

	$\dot{V}$ (l/min/torr CO ₂)	V_T (ml/torr CO ₂)	V_T/t_i (ml/sec/torr CO ₂)	$\dot{V}_{peak}$ (ml/sec/torr CO ₂)	$\dot{V}_{100}$ (ml/sec/torr CO ₂)
Occlusion	2.64 $\pm$ 0.2	72 $\pm$ 8	78 $\pm$ 6	97 $\pm$ 8	63 $\pm$ 7
No occlusion	2.57 $\pm$ 0.3	63 $\pm$ 10	76 $\pm$ 7	100 $\pm$ 11	60 $\pm$ 8

Fig. 2 Relationship between tidal volume (V_T) and ventilation ($\dot{V}$) in a representative subject in two rebreathing trials. Results obtained from trials without occlusions ($\bullet$) and with occlusions ($\times$).

EFFECTS OF CHANGES IN BODY POSITION

On changing from the sitting to the supine position functional residual capacity fell an average of 1.2 l. However, changing body position had no significant effect on the relation of changes in P_{CO_2} to changes in minute ventilation, tidal volume, V_T/t_i , $\dot{V}_{peak}$, $\dot{V}_{100}$, and P_{100} . The responses to hypercapnia with subjects sitting and supine are summarised in Table 3. At a P_{CO_2} of 60 torr, P_{100} was 0.5 cmH₂O $\pm$ SE 0.3 higher, and ventilation was 2.7 l/min $\pm$ SE 2.2 lower in the supine as compared to the sitting position, but neither of these differences was statistically significant. Changing body position also had no significant effect on the relation of tidal volume to ventilation, which averaged 33 ml/l $\pm$ SE 2

with the subjects seated and 34 ml/l $\pm$ SE 3 with the subjects supine. There was no systematic effect on the duration of inspiration or expiration. No consistent effect on the responses to hypercapnia could be attributed to the order in which the rebreathing trials were performed.

RELATION OF OCCLUSION PRESSURE TO VENTILATORY INDICES

Linear correlation coefficients of the relation of P_{100} and minute ventilation, tidal volume, respiratory frequency, V_T/t_i , $\dot{V}_{100}$, and $\dot{V}_{peak}$ as respiratory drive was increased by progressive hypercapnia are shown in Fig. 3 for all trials in all 10 subjects. The correlation coefficients of the P_{100} -ventilation relationship exceeded 0.80 in 47 of 50 trials and exceeded 0.90 in 37 of 50 trials. Similarly, the correlation coefficients of the P_{100} - $\dot{V}_{peak}$, P_{100} - V_T/t_i , and P_{100} - $\dot{V}_{100}$ relationships exceeded 0.80 in 47, 44, and 40 of the 50 trials, respectively. Correlation coefficients of less than 0.90 occurred with equal frequency in the sitting and supine positions. As determined by the Mann-Whitney test (Colquhoun, 1971), P_{100} -ventilation, P_{100} - $\dot{V}_{peak}$, P_{100} - V_T/t_i , and P_{100} - $\dot{V}_{100}$ correlations were significantly better than the correlations between P_{100} and V_T and P_{100} and respiratory frequency ($P > 0.01$).

VARIABILITY IN RESPONSES TO HYPERCAPNIA

The variability of each response to hypercapnia in a given individual was determined from the coefficient of variation (standard deviation divided by the mean, expressed as percent). The variability of the responses during three rebreathing trials in a single subject while seated is shown in Fig. 4 where the responses are ranked in order of increasing variability. The coefficient of variation of the ventilatory response to CO₂ was 39%. The coefficient of variation of changes in V_T/t_i and $\dot{V}_{peak}$ during hypercapnia were smaller, indicating greater reproducibility, while changes in

Table 3 Effect of body position on ventilatory and pressure responses to CO₂ (mean $\pm$ SE)

Body position	$\dot{V}$ (l/min/torr CO ₂)	V_T (ml/torr CO ₂)	V_T/t_i (ml/sec/torr CO ₂)	$\dot{V}_{peak}$ (ml/sec/torr CO ₂)	$\dot{V}_{100}$ (ml/sec/torr CO ₂)	P_{100} (cm H ₂ O torr CO ₂)
Sitting	3.03 $\pm$ 0.4	65 $\pm$ 12	91 $\pm$ 8	111 $\pm$ 16	85 $\pm$ 15	0.60 $\pm$ 0.08
Supine	2.98 $\pm$ 0.3	85 $\pm$ 14	90 $\pm$ 7	115 $\pm$ 12	74 $\pm$ 11	0.56 $\pm$ 0.06

Fig. 3 Frequency distribution of linear correlation coefficients obtained during all rebreathing trials in 10 subjects showing the relationship between ventilatory indices and P_{100} . R = correlation coefficient.

Fig. 4 Variability of ventilatory and occlusion pressure responses to hypercapnia in all rebreathing trials in a single subject. In this subject V_T/t_I , $\dot{V}_{peak}$, and ventilatory responses to CO_2 show the least day-to-day variability.

$\dot{V}_{100}$, P_{100} , f , and V_T during hypercapnia were less reproducible.

Figure 5 illustrates the intra-individual variability of each response in all the subjects. The responses are ranked in order of increasing variability. The ranking of the responses with respect to their coefficients of variations was not the same in all subjects, but overall the variability of changes in V_T/t_I , $\dot{V}_{peak}$, ventilation, $\dot{V}_{100}$, and P_{100} were relatively small (mean coefficients of variation ranged from 22 to 33%). Interindividual variability of all responses to hypercapnia on a given day were determined from the data obtained on the third test

Fig. 5 Intra-individual variability of ventilatory and pressure responses to hypercapnia. Coefficient of variations for each individual for each index of CO_2 response have been averaged. In the same individual, V_T/t_I , $\dot{V}_{peak}$, and ventilatory responses to CO_2 show the least variability from day to day.

day with the subjects seated and supine. These results are summarised in Fig. 6 which shows that the coefficient of variation of ventilatory responses to CO_2 was 42% with the subjects seated and 30% with the subjects supine, while the interindividual coefficient of variation of the occlusion pressure responses was 42% with the subjects seated and 43% while the subjects were supine.

EFFECT OF BREATHING PATTERN ON VARIABILITY OF VENTILATORY AND OCCLUSION PRESSURE RESPONSES Table 4 shows the ventilatory and occlusion pressure

Fig. 6 Interindividual variability in ventilatory and pressure responses to CO₂. Bars show average values of the coefficient of variation of each index of CO₂ response measured in all 10 subjects on a single day. Striped boxes show variation of responses measured in sitting position while unshaded bars show variation of responses measured in supine position.

responses to hypercapnia during unrestricted breathing and when either tidal volume or breathing frequency was kept constant. Holding tidal volume constant at 1 litre or 2 litres and holding breathing frequency constant at 35 breaths per minute had little effect on the variability of ventilatory or occlusion pressure responses. In contrast, when breathing frequency was kept constant at 20 breaths per minute, ventilatory responses were reduced in all subjects, and interindividual variations in both occlusion pressure and ventilatory responses appreciably narrowed.

Discussion

The present study has demonstrated that periodic, random airway occlusion has little effect on breathing pattern or on ventilatory responses to CO₂. Variations in FRC produced by changing from the sitting to the supine position or *vice versa* have no statistically significant effect on the magnitude or linearity of

ventilatory and occlusion pressure responses to CO₂. Occlusion pressure increases linearly with PCO₂ and correlates better with minute ventilation and the rate of airflow during inspiration than with tidal volume or breathing frequency. The reproducibility from day to day in a given individual as well as the inter-individual variability of the occlusion pressure responses to CO₂ are similar to that of the ventilation responses; but the variability of both responses is reduced by the performance of rebreathing tests at a constant moderate breathing frequency.

RESPONSES TO HYPERCAPNIA

Although it is agreed that minute ventilation is a linear function of PCO₂, there is controversy regarding the relationship between occlusion pressure and PCO₂. Some reports have described a curvilinear relation of P₁₀₀ and PCO₂ which can be linearised by plotting the logarithm of P₁₀₀ against PCO₂ (Grunstein *et al.*, 1973; Whitelaw *et al.*, 1975). The present study and other studies consistently find linear P₁₀₀-PCO₂ relationships (Cosgrove *et al.*, 1975; Altose *et al.*, 1976 a and b; Burki *et al.*, 1976). The reason for this discrepancy remains unclear. It may depend on the method used to produce hypercapnia. Using a rebreathing technique, a curvilinear relationship can be obtained unless care is taken to allow the CO₂ in the blood, alveoli, and rebreathing bag to reach complete equilibrium before determinations of ventilation or occlusion pressure can be made (Read, 1967). The time required for this to occur depends on the volume of gas and the concentration of CO₂ in the rebreathing bag.

EFFECTS OF INTERMITTENT AIRWAY OCCLUSION

Mechanical loading of the ventilatory apparatus during inspiration in normal individuals increases respiratory neural efferent activity independently of any change in chemical drive. This increase is noted by the second loaded breath but respiratory activity

Table 4 Effect of breathing pattern on ventilatory and occlusion pressure responses to CO₂

Subject	Control	Constant tidal volume		Constant breathing frequency	
		1 litre	2 litres	20 breaths/min	35 breaths/min
Ventilatory responses (l/min/torr CO ₂)					
1	3.0	2.3	1.7	2.1	2.1
2	3.4	2.1	2.4	2.7	4.2
3	2.6	1.8	1.5	2.1	1.0
4	7.7	7.8	8.6	2.4	5.3
5	1.9	0.6	0.8	1.3	1.1
Occlusion pressure responses (cm H ₂ O/torr CO ₂)					
1	0.6	0.2	0.2	0.3	0.4
2	0.6	0.5	1.2	0.3	2.0
3	0.6	0.5	0.4	0.7	0.3
4	2.3	2.4	2.1	0.9	1.3
5	0.4	0.1	0.1	0.4	0.8

returns to control values within one breath after removal of the load (Altose *et al.*, 1975). Airway occlusion, a maximal load, might be expected to produce a similar increase in respiratory efferent activity. However, since occlusions were separated by at least eight normal breaths and minute ventilation was not measured for at least five breaths after airway occlusion, any changes in respiratory activity consequent to airway occlusion would have dissipated. In infants, inspiratory efforts against an occluded airway can distort the thorax, thus producing reflex effects which could conceivably change breathing pattern. However, in the present study in adults, no effects of intermittent airway occlusion on the pattern or level of ventilation could be discerned.

CORRELATION OF P_{100} AND VENTILATION INDICES

In anaesthetised animals occlusion pressure and tidal volume are closely related (Altose *et al.*, 1976a). The present study indicates that, in conscious man, occlusion pressure also correlates well with tidal volume. However, even better correlations were obtained when occlusion pressure was compared to inspiratory airflow. This relationship is not unexpected since P_{100} , like inspiratory airflow, is a time-dependent inspiratory event.

Minute ventilation is affected by both inspiratory and expiratory events. The excellent correlation between ventilation and occlusion pressure in both the sitting and supine positions indicates that expiratory activity is usually closely linked to the preceding inspiration and that variations in expiratory duration, independent of changes in inspiration, play an insignificant role in determining the level of ventilation.

EFFECTS OF CHANGING BODY POSITION

Changing from the sitting to the supine position had little effect on ventilatory responses to CO_2 . This is in agreement with the findings in a previous study by Rigg *et al.* (1974). Additionally, changing body position had no significant effect on the pattern of breathing during hypercapnia.

Despite considerable change in functional residual capacity with changing position, occlusion pressure responses were also essentially unaffected. These results contrast with the findings in anaesthetised animals that graded increases in functional residual capacity, in a given animal, progressively decrease occlusion pressure responses (Eldridge and Vaughn, 1976). Theoretically the occlusion pressure which reflects the isometric force of contraction of the inspiratory muscles should vary directly, at any given level of stimulation, with the initial length of those muscles. Consequently, as functional residual capacity is increased, the resting length of the inspiratory

muscles decreases and the occlusion pressure should fall.

However, in groups of normal individuals of different body size and fivefold variations in FRC, occlusion pressure responses to CO_2 could not be correlated to their functional residual capacities (Cosgrove *et al.*, 1975; Shaffer *et al.*, 1976). Presumably differences in respiratory efferent activity in response to hypercapnia exceed variations in inspiratory muscle length produced by changes in functional residual capacity.

The lack of an effect of changing body position on occlusion pressure responses in the present study could be due to a compensatory increase in respiratory activity while in the sitting position as compared to the supine position which would serve to overcome the effects on the inspiratory muscles of the larger functional residual capacity (Grassino *et al.*, 1973). This would allow ventilation to be kept nearly constant despite variations in body position.

VARIABILITY OF VENTILATION AND OCCLUSION PRESSURE RESPONSES

Among the 10 subjects studied, and in any given individual from day to day, the variability of ventilatory and the P_{100} responses was quite similar and may be considered equally valid measures of respiratory CO_2 sensitivity. This suggests that measurement of P_{100} is no better than ventilation in evaluating respiratory motor neuron activity in normal subjects. However, in specific circumstances, during anaesthesia or in patients with lung disease, when the mechanical properties of the chest wall or the lung may be altered, measurement of the P_{100} may be more valuable than ventilation.

Recently the maximum rate of pressure development during airway occlusion (dP/dt max) has been used to evaluate respiratory neuron motor activity (Matthews and Howell, 1975). By the rebreathing technique the dP/dt max, like the P_{100} , increases linearly with ventilation. The response to hypercapnia, as measured by dP/dt max, correlates with the ventilatory response and is unaffected by changes in lung volume. Unlike the P_{100} , dP/dt max is unaffected in conscious individuals by experience with external flow resistive loads (Altose *et al.*, 1976b) or by relief of asthmatic bronchospasm (Matthews and Howell, 1975). Although measurement of dP/dt max requires somewhat more sophisticated equipment than is required for measurement of P_{100} , it may also show less variability from day to day in the same subject.

Our results suggest that the interindividual variability in both P_{100} and ventilatory responses to CO_2 rebreathing could be reduced by maintaining breathing frequency constant at 20 breaths per minute during the tests. This was not true at high fixed breathing

frequencies where even small changes in tidal volume can result in large changes in ventilation. Rebuck *et al.* (1974) found in four subjects that variability in response could be reduced by keeping tidal volume constant at 1 litre, but this was not observed in the present study. Both intrinsic differences in the sensitivity of the respiratory chemoreceptors and extraneous influences which produce cortical effects can influence respiratory neuron output. Arkinstall *et al.* (1974) showed in studies in fraternal and identical twins that tidal volume responses were genetically determined and frequency responses were determined by 'environmental factors'. As shown in Fig. 5, the rate of increase of breathing frequency with hypercapnia in groups of individuals showed the greatest coefficient of variation. By keeping breathing frequency constant at moderate rates, extraneous cortical influences, which can influence respiratory neuron response and can increase interindividual variability, seem to be diminished.

This study was supported by NIH grants HL-08805 and HL-01392.

References

- Altose, M. D., Kelsen, S. G., and Cherniack, N. S. (1975). Effects of transient flow resistive loading and unloading on inspiratory muscle force. (Abstract.) *Physiologist*, **18**, 120.
- Altose, M. D., Kelsen, S. G., Stanley, N. N., Cherniack, N. S., and Fishman, A. P. (1976a). Effects of hypercapnia and flow-resistive loading on tracheal pressure during airway occlusion. *Journal of Applied Physiology*, **40**, 345–351.
- Altose, M. D., Kelsen, S. G., Stanley, N. N., Levinson, R. S., Cherniack, N. S., and Fishman, A. P. (1976b). Effects of hypercapnia on mouth pressure during airway occlusion in conscious man. *Journal of Applied Physiology*, **40**, 338–344.
- Arkinstall, W. W., Nirmel, K., Klissouras, V., and Milic-Emili, J. (1974). Genetic differences in the ventilatory response to inhaled CO₂. *Journal of Applied Physiology*, **36**, 6–11.
- Brodovsky, D., MacDonell, J. A., and Cherniack, R. M. (1960). The respiratory response to carbon dioxide in health and emphysema. *Journal of Clinical Investigation*, **39**, 724–729.
- Burki, N. K., Mitchell, L. K., Chaudhary, B., and Zechman, F. W. (1976). Mouth occlusion pressure as a measure of respiratory centre output in man. (Abstract.) *Federation Proceedings*, **35**, 634.
- Cherniack, R. M. and Snidal, D. P. (1956). The effect of obstruction to breathing on the ventilatory response to CO₂. *Journal of Clinical Investigation*, **35**, 1286–1290.
- Colquhoun, D. (1971). *Lectures on Biostatistics*, pp. 143–148. Clarendon Press, Oxford.
- Corda, M., Eklund, G., and von Euler, C. (1965). External intercostal and phrenic alpha motor responses to changes in respiratory load. *Acta Physiologica Scandinavica*, **63**, 391–400.
- Cosgrove, J. F., Neunburger, N., Bryan, M. H., Bryan, A. C., and Levison, H. (1975). A new method of evaluating the chemosensitivity of the respiratory center in children. *Pediatrics*, **56**, 972–980.
- Eldridge, F. and Davis, J. M. (1959). Effect of mechanical factors on respiratory work and ventilatory response to CO₂. *Journal of Applied Physiology*, **14**, 721–726.
- Eldridge, F. L. and Vaughn, R. Z. (1976). Effect of changing lung volume on occlusion pressures: muscular effects. (Abstract.) *Federation Proceedings*, **35**, 633.
- Evanich, M. J., Franco, M. J., and Lourenço, R. V. (1973). Force output of the diaphragm as a function of phrenic nerve firing rate and lung volume. *Journal of Applied Physiology*, **35**, 208–212.
- Grassino, A. E., Lewinsohn, G. E., and Tyler, J. M. (1973). Effects of hyperinflation of the thorax on the mechanics of breathing. *Journal of Applied Physiology*, **35**, 336–342.
- Grunstein, M. M., Younes, M., and Milic-Emili, J. (1973). Control of tidal volume and respiratory frequency in anesthetized cats. *Journal of Applied Physiology*, **35**, 463–476.
- Hey, E. N., Lloyd, B. B., Cunningham, D. J. C., Jukes, M. G. M., and Bolton, D. P. G. (1966). Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respiration Physiology*, **1**, 193–205.
- Hirshman, C. A., McCullough, R. E., and Weil, J. V. (1975). Normal values for hypoxic and hypercapnic ventilatory drives in man. *Journal of Applied Physiology*, **38**, 1095–1098.
- Kallos, T., Hudson, H. E., Rouge, J. C., and Smith, T. C. (1972). Interaction of the effects of naloxone and oxymorphone on human respiration. *Anesthesiology*, **36**, 278–285.
- Kelsen, S. G., Altose, M. D., Stanley, N. N., Levinson, R. S., Cherniack, N. S., and Fishman, A. P. (1976). Effect of hypoxia on the pressure developed by inspiratory muscles during airway occlusion. *Journal of Applied Physiology*, **40**, 372–378.
- Knill, R., Andrews, W., Bryan, A. C., and Bryan, M. H. (1976). Respiratory load compensation in infants. *Journal of Applied Physiology*, **40**, 357–361.
- Matthews, A. W. and Howell, J. B. L. (1975). The rate of isometric inspiratory pressure development as a measure of responsiveness to carbon dioxide in man. *Clinical Science and Molecular Medicine*, **49**, 57–68.
- Milic-Emili, J. and Tyler, J. M. (1963). Relation between work output of respiratory muscles and end-tidal CO₂ tension. *Journal of Applied Physiology*, **18**, 497–504.
- Patrick, J. M. and Howard, A. (1972). The influence of age, sex, body size and lung size on the control and pattern of breathing during CO₂ inhalation in Caucasians. *Respiration Physiology*, **16**, 337–350.
- Read, D. J. C. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine*, **16**, 20–32.
- Rebuck, A. S., Rigg, J. R. A., Kangalee, M., and Pengelly, L. D. (1974). Control of tidal volume during rebreathing. *Journal of Applied Physiology*, **37**, 475–478.

- Rigg, J. R. A., Rebuck, A. S., and Campbell, E. J. M. (1974). Effect of posture on the ventilatory response to CO₂. *Journal of Applied Physiology*, **37**, 487-490.
- Saunders, N. A., Heilpern, S., and Rebuck, A. S. (1972). Relation between personality and ventilatory response to carbon dioxide in normal subjects: a role in asthma? *British Medical Journal*, **1**, 719-721.
- Shaffer, T. H., Altose, M. D., Lederer, D. H., and Cherniack, N. S. (1976). The interaction of FRC and ventilation on occlusion pressure: Theoretical and experimental results for conscious man. (Abstract.) *American Review of Respiratory Disease*, **113**, (April, Part 2), 195.
- Whitelaw, W. A., Derenne, J. P., and Milic-Emili, J. (1975). Occlusion pressure as a measure of respiratory center output in conscious man. *Respiration Physiology*, **23**, 181-199.
- Requests for reprints to: Dr M. D. Altose, 281 Gibson Building, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA.