5. G. I. Kositskii and I. A. Chernova, The Heart as a Self-Regulating System [in Russian], Moscow (1968).
6. B. S. Kulaev, The Reflexogenic Zone of the Heart and Self-Regulation of the Circulation [in Russian], Leningrad (1972).
7. M. D. Mashkovskii, Therapeutic Substances [in Russian], 7th edn. Vol. 1, Moscow (1972), p. 212.
8. Textbook of Physiology: Physiology of the Circulation: Physiology of the Heart [in Russian], Leningrad (1980), pp. 425-438.
9. M. G. Udel'nov, Physiology of the Heart [in Russian], Moscow (1975).

RELATIONSHIP OF BREATHING VARIABILITY TO VENTILATORY RESPONSE TO CARBON DIOXIDE

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UDC 612.216-06:612.223.11

KEY WORDS: breathing variability; ventilatory response to carbon dioxide; rebreathing.

Periodic fluctuations of the frequency and depth of breathing, repeated without any evident cause with a varied period, were described long ago [12]. Investigations have shown that to study the parameters of external respiration it is essential to know not only their mean values, but also the character of variations of the parameters, which is subject to the action of both physiological and stress factors [10, 11]. The nature of breathing variability has not yet been explained. It has been suggested that changes in the regularity of breathing are due to fluctuations in the activity of certain central mechanisms [6] or to manifestation of the search for energetically optimal conditions of pulmonary ventilation. Hence it is interesting to study dependence of breathing variability on the functional state of the system regulating breathing. Correlation between the partial pressure of carbon dioxide in the alveolar air (the stimulus parameter) and ventilation (the response parameter) still remains the most physiological criterion for evaluation of the function of the breathing control system in general and its sensitivity to hypercapnia in particular [1].

The aim of this investigation was to study relations between breathing variability and the ventilatory response to carbon dioxide.

EXPERIMENTAL METHOD

Tests were carried out on 35 subjects aged 25-54 years with no neurological diseases and no pathology of the respiratory and cardiovascular systems. During the investigation 13 subjects had a marked pain syndrome due to identical pathology in the hepatogastroduodenal region; nine subjects were investigated before operation, 25-45 min after receiving premedication with Moradol, whereas 13 subjects were free from complaints. To increase the accuracy of the data and to reduce the load on the subjects, the entire routine part of the investigations was automated. A program was written for the "Élektronika NTs-80" microcomputer whereby the initial signals of the pneumatochogram and capnogram could be introduced and analyzed on a realtime scale. The tests were carried out at the same time of day, when the subjects were in a state of psychoemotional rest, and seated. To prevent the subjects from drowsing, they were requested to keep their eyes open. Each investigation consisted of two parts.

1) When the breathing variability was determined, the coefficient of variation (CV = $\sigma \cdot 100\%$ M, where σ is the standard deviation and M the mathematical expectation) was chosen as the criterion to characterize this parameter, for it is independent of the absolute values of the parameters studied and can be used to compare variability of parameters differing in dimensionality.

To determine CV, after a short rest the subject was instructed to breathe through a mask connected to the transducer of a pneumotachograph. The pneumotachogram was recorded

Laboratory of Clinical Physiology, A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 104, No. 8, pp. 137-139, August, 1987. Original article submitted January 26, 1987.

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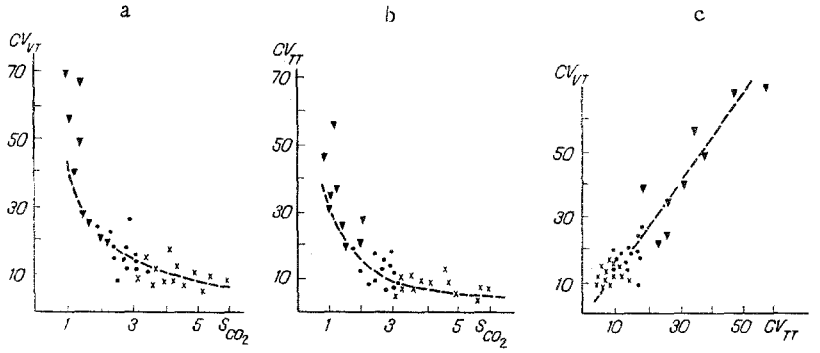

Fig. 1. Value of S_{CO_2} (in liters/min/mm Hg), CV_{VT} (in %), and CV_{TT} (in %) after injection of Moradol (triangles) in healthy subjects (dots) and in subjects with a marked pain syndrome (crosses). Broken lines represent approximating curves: a) $CV_{VT} = 43.25/S_{CO_2}$ ($r = 0.72$); b) $CV_{TT} = 29.84/S_{CO_2}$ ($r = 0.68$); c) $CV_{VT} = 1.33 \cdot CV_{TT} + 0.36$ ($r = 0.9$).

2-3 min after the beginning of breathing for 5-6 min, and the recording stopped before the subject began to feel any signs of discomfort. The coefficient of variation of the tidal volume (CV_{VT}) and the coefficient of variation of the duration of the respiratory cycle (CV_{TT}) were calculated automatically from the sequence of 100-120 respiratory cycles thus obtained.

2) The ventilatory response to a hypercapnic stimulus was next determined by the rebreathing method 5-10 min after determination of breathing variability [2-12]. A gas mixture (7% CO_2, 70% O_2, and 23% N_2) and a rubber bag (5 liters) with three-way cock were used for rebreathing. The ventilatory sensitivity of the breathing control system to hypercapnia was estimated from the slope of the $\dot{V}_E/P_{ET}\ CO_2$ curve (the parameter S_{CO_2}). This parameter was calculated in the manner described in [8], where it was shown that its most reliable estimate can be obtained by the method of least squares on values of ventilation ($\dot{V}_E$) and CO_2 concentration at the end of expiration ($P_{ET}\ CO_2$) for each respiratory cycle. To ensure accuracy of the investigation, the instruments were calibrated automatically before each test by means of a calibration syringe (1 liter) and gas with a known CO_2 concentration, and the delay of the capnogram relative to the pneumotachogram also was determined automatically. The error of measurement of volume when the calibration syringe was used was ±0.6% of the predicted value.

EXPERIMENTAL RESULTS

Comparison of the data showed that breathing variability is inversely proportional to the ventilatory response to carbon dioxide. It will be clear from Fig. 1a, b that with an increase in ventilatory sensitivity to hypercapnia breathing variability falls, and, conversely, in subjects with a low value of S_{CO_2} the coefficient of variation was higher than in the other subjects. This rule was characteristic both of CV_{VT} and CV_{TT}. This negative correlation between breathing variability (CV) and the ventilatory sensitivity (S) could be approximated by the equation of a hyperbola of the $CV = K/S$ type. Assuming that $C = 1/CV$, the linear functions $S = K \cdot C$ is obtained, by which, using the available data, the coefficient of correlation (r) can be determined for the relationship thus obtained. Types of approximating curves and coefficients of correlation are shown in Fig. 1 and they show that the dependence of CV_{VT} on S_{CO_2} is stronger than the dependence of CV_{TT} on S_{CO_2}. The character of the connection between CV_{VT} and CV_{TT}, as Fig. 1c shows, can be well approximated by a linear function.

Comparison of the mean values of S_{CO_2}, CV_{VT}, and CV_{TT} in the groups tested (Table 1) shows that in the group of subjects with a marked pain syndrome the ventilatory response to hypercapnia was increased, but the breathing variability was less marked than in healthy subjects with no complaint. Conversely, after Moradol premedication the mean value of the parameter S_{CO_2} was lower, and the coefficients of variation were higher than in healthy subjects. All differences were statistically significant ($p < 0.05$). The increase in the ventilatory response to hypercapnia in subjects with a marked pain syndrome may have been due to increased tone of the sympathicoadrenal system of these patients, for as has been shown [7], this may lead to an increase in ventilatory sensitivity to a hypercapnic stimulus. Low values of S_{CO_2} after injection of Moradol are evidently connected with the central action of drugs of this group.

TABLE 1. Mean Values of S_{CO_2} (in liters/min/mm Hg), CV_{VT} (in %) and CV_{TT} (in %) in Different Groups of Subjects (M ± m)

Parameter	Group of subjects		
	after injection of Moradol	healthy subjects	patients with a marked pain syndrome
S_{CO_2}	1,46±0,13	2,74±0,10	4,29±0,29
CV_{VT}	45,3±6,74	16,4±1,47	10,97±0,99
CV_{TT}	32,5±4,09	12,8±1,44	7,85±1,07

It was because of these marked differences in the ventilatory response to hypercapnia in the groups tested that significant correlation could be obtained between S_{CO_2} and CV in a comparatively small number of tests. Had we used only one group, because of the considerable scatter of the values studied, the dependence would have been obscured. The character of dependence of breathing variability on ventilatory sensitivity thus obtained is in good agreement with known physiological and clinical data. For instance, when the sensitivity of the respiratory center is pathologically depressed, irregular, so-called periodic breaching arises, and its variability is very great. At the same time, a rigid and frequent respiration characteristic of patients with burns has been described, and attributed to overexcitation of the respiratory center due to direct impulsation from the burned surface, and mediated by stimulation by the low tissue pO_2 and acidosis [3, 4].

Newsom and Stagg [10], who studied the relations between the respiratory times and volumes during breathing of mixtures with different CO_2 concentrations, found that when mixtures with a high CO_2 concentration were breathed, the increase in the mean velocity of inspiration flow ($\dot{V}_I$) was accompanied by a simultaneous decrease in the coefficients of variation CV_{VT} and CV_{TT}. The value of $\dot{V}_I$ is used to estimate central inspiratory activity and, consequently, it follows from the results obtained by these workers that with an increase in chemoreceptor stimulation of breathing, i.e., an increase in functional activity of the respiratory control system, the variability of breathing is reduced.

To sum up the data it can be concluded that changes in breathing variability are due to changes in functional activity of the respiratory center, which may arise both by a reflex mechanism through chemoreceptors and as a result of the influence of central structures located outside the respiratory center. Breathing variability is inversely proportional to ventilatory sensitivity. Variations in the parameters of long ventilation are perhaps important when optimal values of alveolar pCO_2 are determined [5] and the higher the ventilatory sensitivity to CO_2 the faster they are abolished.

LITERATURE CITED

1. I. S. Breslav and V. D. Glebovskii, Regulation of Respiration [in Russian], Leningrad (1981).
2. R. S. Vinitskaya and N. A. Koganova, Byull. Éksp. Biol. Med., 83, No. 2, 245 (1977).
3. M. I. Kuzin, V. K. Sologub, and V. V. Yudenich, Burns [in Russian], Moscow (1982).
4. V. Rudovskii, V. Nadilovskii, and V. Zytkevich, Theory and Practice of Treatment of Burns [in Russian], Moscow (1980).
5. L. L. Shik, The Physiology of Respiration [in Russian], Leninbrad (1973), p. 279.
6. J. A. Doubenspeck and M. W. Farnham, Resp. Physiol., 47, 97 (1982).
7. L. A. Engel and B. Ritchie, J. Appl. Physiol., 30, 173 (1971).
8. N. W. Goodman and J. S. H. Curnow, Br. J. Anaesth., 57, 311 (1985).
9. D. B. Jennings and P. C. Szlyk, Can. J. Physiol. Pharmacol., 63, 148 (1985).
10. D. J. Newsom and D. Stagg, J. Physiol. (London), 245, 481 (1975).
11. I. P. Priban, J. Physiol. (London), 166, 425 (1963).
12. D. J. C. Read, Austr. Ann. Med., 16, 20 (1967).