Factors controlling respiration during muscular exercise at altitude

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PREVIOUS PAPERS on the effect of altitude on muscular exercise concerned mainly the energetic aspect of this problem. Moreover, since the classical observations of Zuntz and colleagues, 1906 (quoted by Dejours (4)), few authors have attempted to explain the mechanism controlling breathing during muscular exercise at altitude and the papers published concerned mainly the role of the ventilatory oxygen drive. Thus, these ventilatory effects following inhalation of oxygen-enriched mixtures were studied in acute hypoxia (1), in acclimatized lowlanders (3, 12), and in highland natives (14). Recently, Lahiri et al. (9) compared the ventilatory oxygen drive in four Sherpas and five acclimatized lowlanders.

In other studies, Dejours (4) proposed a neurohumoral theory which takes into account all the factors thought to control breathing during exertion. At the start of an exercise, the minute volume increases abruptly and shows a relatively constant value for about 30 sec, then the ventilation increases progressively to reach a plateau for moderate exercises. Similarly, at the end of an exercise, the ventilatory output falls immediately and then does not change during about 30 sec, before decreasing progressively to a resting value during the recovery period. According to Dejours' theory (5), rapid changes in ventilation at the start and at the end of exercise are related to the neurogenic factors of ventilatory control whereas slow changes are related to the humoral factors.

Until now, slow and fast components in ventilation have been studied during muscular exercise at altitude only in acclimatized lowlanders (7). In this paper, this last work has been developed and extended to naturally acclimatized subjects, i.e., highland natives.

METHODS

Subjects

All the subjects were healthy adults, either sea-level natives sojourning for 1 month at an altitude of 3,660 m (at La Paz, Bolivia) or highland natives born and living at this altitude. Biometric data of these subjects are shown in Table 1.

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Ventilation Measurements

During all the experiments, consecutive tidal volumes were recorded by electronic integration of the pneumotachogram. Ventilation was expressed in liters BTPS/min⁻¹. The subjects breathed through a one-way respiratory valve with the inspiratory side connected to a three-way tap which allowed transient or continuous inhalation of a given gas mixture. The expiratory side allowed the collection of either expiratory gas in a Douglas bag or end-expiratory alveolar gas by the Haldane method. All the gases were analyzed immediately for CO_2 with an infrared analyzer (type Onera 80) and for O_2 with the Beckman C2 apparatus.

Ventilatory Components

The neurogenic factors controlling breathing were studied by the following two methods: *1*) measurement of fast changes in ventilation at the onset and at the cessation of exercise performed on the Collins pedal mode ergometer; *2*) measurement of the increase in ventilation occurring during active or passive motion of legs (6).

Humoral factors were estimated as follows: *1*) by the magnitude of the slow ventilatory changes observed during exercise and recovery periods; *2*) by the decrease in ventilation following inhalation of three breaths of pure oxygen during steady-state circumstances (the O_2 test); *3*) by the composition of alveolar gas before and during exercise.

Protocol

Bicycling experiments. The subjects sat on the bicycle for a 10-min resting period during which time alveolar gas was analyzed and oxygen uptake and minute volume were determined. Five minutes after the beginning of exercise, the oxygen test was performed. At the 8th min, pulmonary ventilation was measured and expiratory gases were collected for oxygen uptake steady-state determination. At the 9th min, alveolar gases were sampled. The exercise was stopped at the 10th min and during the following 10 min of recovery period, the respiratory recording was continued. Workloads of 60 and 120 w were used.

TABLE 1. *Mean biometric values in the two groups of subjects used during bicycling and leg motion experiments*

	Subjects	No.	Age, years	Weight, kg	Height, m	SA, m²
Bicycling	Sea-level natives	5	31	72	1.72	1.84
	Highland natives	6	26	60	1.70	1.69
Leg motion	Sea-level natives	3	30	74	1.73	1.88
	Highland natives	9	26	68	1.70	1.78

Leg motion experiment. Each subject lay on a bed in a comfortable supine position with his legs hanging vertically for 10 min before the experiment began. Beginning during an expiration and for a complete breath, the subject's lower legs were alternatively raised to the horizontal position by an assistant and allowed to return to the vertical, passively, at the rate of one movement per second. The maneuver was performed in such a way that there was no visible motion of the thighs. In another series, the subject actively moved his lower legs when ordered to, in exactly the same manner. This test was repeated about 10 times for each subject with an interval of 2 min between each test. These experiments were carried out using the same $P_{I_{O_2}}$ as for the bicycling exercise and, in addition, using pure oxygen.

RESULTS

Bicycling Experiment (Table 2)

Oxygen uptake. Both at rest and during exercise, the oxygen uptake was not significantly different ($P > 0.1$ at 120 w) in the two groups of subjects studied and consequently, the efficiencies of each were similar.

Minute volume (Figs. 1 and 2).

TOTAL VENTILATION. During exercise, for a given load, the minute volume of the highlanders was always significantly lower than that of the sea-level natives ($P < 0.05$). This accounts for the reduced values observed for the oxygen ventilatory equivalent ($\dot{V}_E/\dot{V}_{O_2}$) in highland natives.

COMPONENTS OF THE VENTILATORY RESPONSE TO EXERCISE. *1)* Neurogenic control. Most of the subjects were untrained and therefore did not immediately attain the workload required. Consequently, the values obtained for the sudden changes in ventilation at the start of exercise were more scattered than those observed immediately the exercise had been terminated. These recovery ventilatory changes are shown (Neur. $\Delta\dot{V}_E$) in Table 2 and on Fig. 2. The higher the workload, the more important was the neurogenic component and, furthermore, for a given workload it was always greater in sea-level natives than in highland natives ($P < 0.02$).

2) Humoral control. In all subjects, the higher the load, the greater the decrease in the minute volume found following oxygen inhalation (VOD $\Delta\dot{V}_E$). In addition, the ventilatory change was significantly more important in sea-level natives than in highland natives.

For lowlanders, the alveolar gases were not found to be appreciably modified during exertion, but resting high-

TABLE 2. *Results of bicycling experiments in the two groups of subjects*

Subjects	Highland Natives	Sea-Level Natives
Rest		
$\dot{V}_{O_2}$	0.33±0.015	0.32±0.02
$\dot{V}_{O_2}$ (kg⁻¹)	5.6±0.3	4.6±0.5
$\dot{V}_E$	13.0±1.4	15.0±1.3
f	15.3±1.7	14.6±0.75
$P_{A_{O_2}}$	61±3	63±1.5
$P_{A_{CO_2}}$	29±2.5	27±0.5
R	0.77±0.04	0.75±0.04
60 Watts		
$\dot{V}_{O_2}$	0.85±0.10	0.86±0.05
$\dot{V}_{O_2}$ (kg⁻¹)	14.8±2.0	12.4±1.20
$\dot{V}_E$	29.5±1.0	32.3±1.0
f	21.7±1.0	16.8±1.1
$P_{A_{O_2}}$	58±2	63±1
$P_{A_{CO_2}}$	34±0.6	29±1
R	0.93±0.03	0.84±0.05
Neur. $\Delta\dot{V}_E$	4.4±0.6	8.0±0.65
VOD $\Delta\dot{V}_E$	5.2±0.7	8.2±1.4
$\dot{V}_E/\dot{V}_{O_2}$	34.8	37.6
120 Watts		
$\dot{V}_{O_2}$	1.24±0.10	1.58±0.15
$\dot{V}_{O_2}$ (kg⁻¹)	20.6±1.6	22.2±2.4
$\dot{V}_E$	43.9±1.2	60.2±2.1
f	25.6±1.3	20.8±1.5
$P_{A_{O_2}}$	56±1.5	61±1.5
$P_{A_{CO_2}}$	38±2.5	29±2
R	1.03±0.01	0.91±0.03
Neur. $\Delta\dot{V}_E$	6.7±0.9	10.4±0.85
VOD $\Delta\dot{V}_E$	7.8±1.1	16.5±2.8
$\dot{V}_E/\dot{V}_{O_2}$	35.4	38.0

Oxygen uptake is expressed in liters STPD/min⁻¹. $\dot{V}_{O_2}$ (kg⁻¹) is the oxygen consumption expressed in milliliters per minute per kg of body weight. Minute volume is expressed in liters BTPS/min⁻¹ and alveolar pressures in mm Hg. f is respiratory rate per minute. $\dot{V}_E$ is steady-state minute volume. Neur. $\Delta\dot{V}_E$ represents the rapid changes in ventilation observed at the end of the exercise. VOD $\Delta\dot{V}_E$ represents the decrease of ventilation following inhalation of three breaths of pure oxygen. Values are given with ±1 SE. (Number of subjects is seen in Table 1.) R = $\dot{V}_{CO_2}/\dot{V}_{O_2}$.
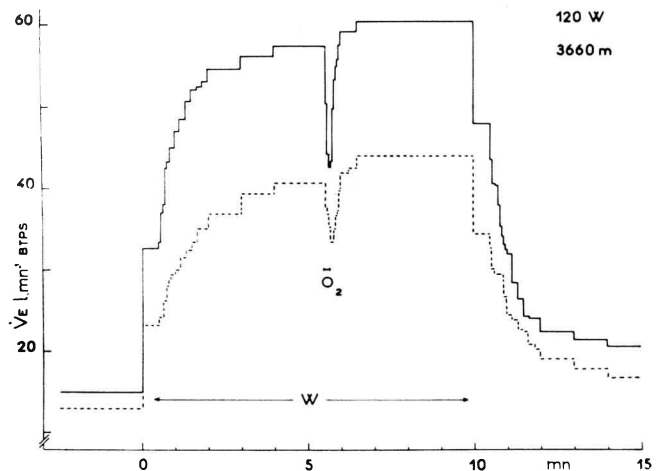

FIG. 1. Mean ventilation of the two groups of subjects during bicycling exercise with load at 120 w. Solid line, lowlanders; broken line, highlanders. Exercise begins at 0 and ends at the 10th min as indicated by W. Horizontal bar marked O_2 represents the inhalation of three breaths of pure oxygen.
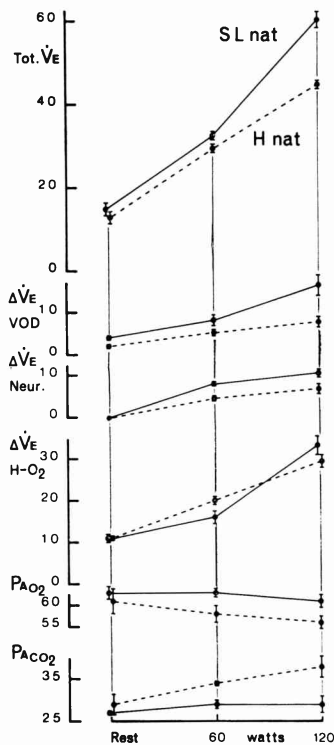
FIG. 2. Ventilatory components are plotted against workload in sea-level natives (solid line) and in highland natives (dashed line). $\dot{V}_E$ represents total minute volume; Neur. $\Delta\dot{V}_E$ fast change in ventilation observed when the exercise is stopped; VOD is the decrease of ventilation following the oxygen test; and $H-O_2$ represents that part of ventilation not controlled by neurogenic and oxygen drives. At the lower part of the figure are alveolar pressures at rest and during steady-state exercise.

land natives, as is well known, were more hypoxic and hypercapnic than sea-level natives. During exercise, these differences were even more marked.

Leg Motion Experiment (Table 3)

In all tests, the increase in ventilation, due essentially to the higher respiratory rate, was greater during active motion than passive motion. These changes were not related to P_{IO_2}. They were significantly more important in sea-level natives than in highland natives ($P < 0.001$).

DISCUSSION

Energetic Aspect

The resting values were relatively high because, first, the subjects used were untrained and the experiments were performed at any time of the day; second, the subjects were in a sitting position on the saddle of the bicycle; finally, the dead space of the respiratory apparatus was relatively large (150 ml) due to the size of the valve (inner diameter 35 mm).

Steady-state oxygen consumption was similar for the two groups both at rest and during exercise. This explains the similarity in the efficiencies calculated for highland and sea-level natives, thus confirming the ob-

TABLE 3. *Results of leg motion experiment in the two groups of subjects breathing air or pure oxygen*

Subjects	Highland Natives		Sea-Level Natives	
P_{IO_2}, mm Hg	93	433	93	433
Passive Motion				
n	83	90	31	33
Control values				
$\dot{V}_E$	7.9±0.2	7.6±0.2	8.7±0.15	7.0±0.2
f	14.2±0.5	12.7±0.6	12.4±0.7	12.2±0.6
Motion				
$\dot{V}_E$	8.5±0.3	7.9±0.2	11.5±0.2	12.2±0.25
f	14.9±0.7	12.3±0.7	14.8±0.4	14.6±0.5
$\Delta\dot{V}_E$	0.6±0.2	0.35±0.16	2.75±0.25	2.13±0.3
Active Motion				
n	97	84	30	29
Control values				
$\dot{V}_E$	7.7±0.2	8.2±0.2	8.2±0.2	6.9±0.2
f	14.5±0.5	13.7±0.3	12.7±0.8	12.5±0.6
Motion				
$\dot{V}_E$	9.4±0.3	9.8±0.4	16.1±0.8	13.7±0.9
f	17.4±0.7	15.9±0.35	17.2±0.7	16.2±0.8
$\Delta\dot{V}_E$	1.73±0.26	1.73±0.25	7.82±0.8	6.80±0.8

Values given are experimental means ± SE. n is the number of tests. Minute volume is expressed in liters BTPS/min^{-1}. f is respiratory frequency per minute. Note that the ventilatory increase is not significant during passive motion for the highlanders ($t = 1.5$) but significant in other experiments ($t > 3$).

servations of Pugh et al. (12) and Lahiri et al. (9) on Himalayan Sherpas and also Balke (2) on Andean highlanders.

Respiratory Control

For a given workload, the minute volume was unquestionably lower for Himalayan and Andean highland natives than for acclimatized lowlanders (2, 9). However, Grover and co-workers (8) did not find this result in North American highlanders born and living at 3,100 m. The difference between these subjects may be due to the fact that Andean natives have lived continually at the same altitude for centuries.

In the light of the neurohumoral theory (4), the differences in ventilatory responses between highlanders and lowlanders can now perhaps be more satisfactorily explained. According to this theory, there are two groups of factors responsible for the hyperventilation of exertion.

Neurogenic factors. As debated by Dejours (6), the neurogenic factors seem to be linked to proprioceptive stimuli originating in the mechanoreceptors of the limbs involved in exercise. It may be that during voluntary exercise, cerebral control of ventilation is superimposed on the reflex control from these receptors. Both these controls come into operation at the beginning of exercise and cease when it ends.

As has been seen from the results obtained, fast changes in ventilation during bicycling experiments and increases in the minute volume during passive and active motion are significantly lower in highland natives (Tables 2 and

3). Furthermore, for these subjects, increases in ventilation are not significant in passive motion, are small but significant during active motion of the legs without load, and become increasingly important during bicycling experiments, especially when the workload is heavy. All values for highlanders remain lower than those for sea-level natives, however. Thus, it can be suggested in consequence that highland natives are less sensitive to neurogenic stimulation.

Prolonged oxygen inhalation, moreover, did not modify the ventilatory response to active and passive motion of the legs (Table 3). Consequently, it seems that there is no interaction between neurogenic factors and the oxygen control of breathing.

Humoral factors. Humoral control of ventilation during exercise has been estimated from the magnitude of the ventilatory slow components. In this component, it is possible to distinguish on the one hand the ventilatory oxygen drive from the decrease in ventilation following inhalation of pure oxygen; on the other hand, the remaining humoral factors are determined by the difference between the total humoral control and the ventilatory oxygen drive ($H-O_2$, Fig. 2).

1) Ventilatory oxygen drive during exercise. Åstrand (1) found that breathing was 46% controlled by the ventilatory oxygen drive at a simulated altitude of 4,000 m. Cerretelli (3), using the single breath method, found that it was only 29% controlled in acclimatized lowlanders living at an altitude between 5,000 and 7,000 m. These results were confirmed by Pugh et al. (12) at 5,800 m. In Andean highlanders at 4,500 m, Velasquez and Reynafarje (14) observed that continuous inhalation of pure oxygen had a very feeble effect on their breathing. Lahiri et al. (9), working at 4,880 m, compared the ventilatory response to exercise of highland natives and acclimatized lowlanders and found that the ventilatory

oxygen drive controlled 33% of breathing in newcomers but only 14% in the Sherpa. Our results using the oxygen test confirm in general these observations. The ventilatory oxygen drive was found to be significantly higher for acclimatized lowlanders (27%) than for highlanders (only 17%). In addition, the oxygen drive was found to have the same percentage control of ventilation at rest and during exercise (10).

2) The remaining humoral factors controlling ventilation. These factors are more difficult to study and are represented mainly by changes in blood acidity and arterial carbon dioxide pressure. In this paper, only end-tidal carbon dioxide pressure measurements have been taken into account. Little change in the alveolar gas was observed in acclimatized lowlanders, but in highland natives, hypercapnia and hypoxia were found to increase with the workload. However, ventilation controlled by these factors was not significantly different in the two groups of subjects studied (Fig. 2). This can be explained by the fact that highland natives are less sensitive to hypoxic and carbon dioxide stimulation (11, 13).

CONCLUSIONS

Highland natives seem to be less sensitive to both humoral and neurogenic ventilatory stimulation, and consequently, the respiratory response to exercise is less important in these subjects. Highland natives were thus found not only able to extract more oxygen from a given ventilatory flow but also to have a better tolerance to hypoxia which could favor a greater working capacity at high altitudes.

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Discussion

DR. DEMPSEY: How much of the difference in the neural drive between the native and sojourning lowlander was due to a change in the status of the sojourning lowlander from his preascent level? Do you have measures of the neural drive in the lowlander from sea level up to altitude?

DR. LEFRANCOIS: Yes, we do. Neurological control of breath-

ing has the same value at sea level in normoxia, in acute hypoxia, and after a sojourn of 1 month at altitude.

DR. BIRNBAUM: First, we were unable to confirm your finding that the native becomes more hypoxic than the sojourning lowlander during a given exercise load; our loads developed much higher oxygen consumptions than yours. Upon measure-

ment of arterial blood gases, we were unable to find differences in arterial pO_2 between natives and sojourners, but we were able to find differences in oxygen content relative to hemoglobin for a particular oxygen consumption. I think one may not safely assume that during exercise the alveolar-arterial gradient remains the same; it does not.

Second, I am impressed by the similarity of your data for each group. The contours of the curves looked almost identical for the native and the sojourner in response both to neural drive and the steady-state drives. Are the percentages of change very different as you look at the change from where they started?

DR. LEFRANCOIS: For your first point, I think you are right; it is always better to have blood gas measurements, but unfortunately it was not possible. Concerning your second question, I think my graph is not perfect, but we have data (see text) which show that neural drive is significantly different in lowlander and native subjects.

DR. BIRNBAUM: I think your data are very good and they look very much like ours. Another interest is your breath test. When I did a hand calculation of the percent of change, I got decreases of 20% in one group and 24% in another, relative to the respective ventilatory levels prior to the three breath test. We find similar drops when we obliterate the hypoxic drive.

DR. LAHIRI: Would you like to speculate as to how the highlanders happen to have a lower neural component of the ventilatory response during exercise? Could it be through the arterial chemoreceptors or by some sympathetic control or other neural mechanism?

DR. LEFRANCOIS: I have no explanation for the mechanism.

DR. CRUZ: Many groups in different countries have shown that highlanders have a lower ventilatory hypoxic drive than the lowlanders. In terms of acclimatization, do you think they are better off than the sojourners? They do ventilate less for a given exercise and therefore have more reserve.

DR. LEFRANCOIS: I think it is better for the natives. They are more able to live at altitude for they tolerate more hypoxia and are able to extract more oxygen at a given ventilatory flow.

DR. DEMPSEY: Alveolar-capillary diffusion and the dimensions of the pulmonary capillary bed in the native are much larger than in a sojourning lowlander. Although the alveolar pO_2 is lower because of the hypoventilation, he can maintain comparable levels of arterial pO_2. I think if you could postulate a degree of inefficiency, it might be the pulmonary hypertension if this is the way they are producing a larger pulmonary capillary bed. But as far as the exchange across the lung is concerned, they definitely seem to be efficient.

DR. BANCHERO: Our experiments at 14,900 ft (4,500 m) (Morococha, Peru) indicated that natives to high altitude exercising in the recumbent position dropped their arterial oxygen saturation 9% which indicated that there was a decrease in the pO_2 of the arterial blood (1).

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