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# VENTILATORY OXYGEN DRIVE IN ACUTE AND CHRONIC HYPOXIA

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**Abstract.** Ventilatory oxygen drive has been investigated in four groups of subjects by measurement of transient changes of ventilation occurring after inhalation of two or three breaths of pure oxygen or nitrogen: 1) acutely hypoxic normal subjects, 2) lowlanders acclimatized to 3660 and 5200 m, 3) highlanders native to the same altitudes, and 4) highlanders apparently affected by chronic altitude sickness. Ventilatory oxygen drive was strong in groups one and two, slight in native highlanders and non-existent in the patients. Alveolar gases were analyzed at four altitudes, 2700, 3660, 4200 and 5200 m; at each, highlanders were significantly more hypoxic and hypercapnic than lowlanders acclimatized to the same altitude. That a third curve for highland natives can be drawn on the $O_2$-$CO_2$ Rahn and Otis diagram and is explained by the weak ventilatory oxygen drive of highlanders.

| | |
|---|---|
| Altitude acclimatization | Chronic mountain sickness |
| Alveolar gas | Control of breathing |
| Arterial chemoreceptors | Highland natives |

It is generally accepted that the hyperventilation of high altitude is initially stimulated by a decrease in the arterial oxygen tension which, acting on arterial chemoreceptors, determines the ventilatory oxygen drive (DEJOURS, 1962). The magnitude of this stimulus may be estimated in man by studying the change in ventilation following inhalation of gas mixtures containing different oxygen concentrations. Some workers have tried to examine ventilatory oxygen drive by studying the decrease in ventilation which follows prolonged inhalation of pure oxygen. But this method not only suppresses the ventilatory oxygen drive, it also provokes other changes, such as acidosis, hypercapnia and decrease of cerebral blood flow, all of which influence ventilation. Thus, the changes in ventilation during prolonged oxygen breathing cannot be interpreted simply in terms of oxygen drive (DEJOURS, 1962; TENNEY, REMMERS and MITHOEFER, 1963). In the present study, the transient ventilatory change following a short inhalation of pure oxygen ("$O_2$ test", fig. 1) was used in order to avoid the

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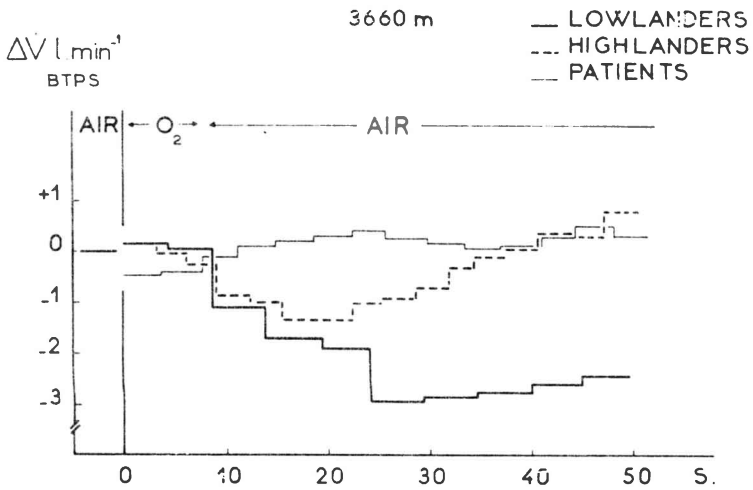


Fig. 1. Transient ventilatory effects of inhalation of two tidal volumes of pure oxygen. Note the great fall of ventilation in lowlanders, slight but significant fall in highland natives and lack of ventilatory effect in patients.

secondary effects of prolonged administration of oxygen. This oxygen test allows a direct correlation between the oxygen stimulus and the resultant decrease in ventilation.

Previous work has led to varying opinions as to the importance of the oxygen drive during hypoxia. Prolonged oxygen inhalation has not established the existence of a permanent ventilatory oxygen drive in resting subjects acclimatized to altitude (BECKER-FREYSENG *et al.*, 1942; BJURSTEDT, 1946; RAHN and OTIS, 1949; RILEY and HOUSTON, 1951; CHAPIN, 1954; ÅSTRAND, 1954; CHIODI, 1957; PUGH, 1957; HURTADO 1964). With this same method, BAINTON, CARCELEN and SEVERINGHAUS (1965) and MILLEDGE and LAHIRI (1967) have found a relative insensitivity to hypoxia in highland natives. Using the single-breath oxygen test in acclimatized lowlanders, DEJOURS *et al.* (1957) and CERRETELLI (1961) have observed a sustained ventilatory oxygen drive. Recently LEFRANÇOIS, GAUTIER and PASQUIS (1965a) used the oxygen test to compare the magnitude of the oxygen drive in acclimatized lowlanders and highlanders.

In the present article, the ventilatory chemosensitivity to oxygen of subjects living at high altitude was determined by comparing their oxygen-ventilatory response curves to those of the lowlander at sea level and the lowlander acclimatized to high altitude. Oxygen-ventilatory response curves were constructed by plotting the $P_{A_{O_2}}$ observed after inhalation of two breaths of oxygen or nitrogen against the resulting ventilation.

## Methods

In seated subjects, after a ten minutes rest period, consecutive tidal volumes were recorded by electronic integration of the pneumotachogram. The subject breathed

through a one-way respiratory valve with the inspiratory side connected to a three-way tap which allowed transient or continuous inhalation of the chosen gas mixture. All minute volumes are expressed in liters BTPS · $min^{-1}$. End expiratory alveolar gases were collected by the Haldane method and were analyzed at once for $CO_2$ with an infrared analyzer (Onera 80) and for $O_2$ with the Beckman C2 apparatus.

In all experiments, the subject inhaled two or three tidal volumes either of pure nitrogen ($N_2$ test) or of pure oxygen ($O_2$ test), which produced a transient change in $P_{A_{O_2}}$. This was repeated at three minute intervals. During each test, either ventilation was recorded for one minute, or an alveolar gas sample was collected at the end of the last breath of the test. Each subject underwent 12 tests in all.

### ACUTE HYPOXIA

The sea-level studies were performed in Rouen, France (altitude, 25 m), on three healthy young subjects. Several $O_2 - N_2$ mixtures ($F_{I_{O_2}} = 0.21$, 0.16, 0.13 and 0.115) were administered to each subject. During these experiments, $P_{A_{CO_2}}$ was recorded continuously with a Spinco Beckman $CO_2$ analyzer and kept at its control value by adding $CO_2$ to the inspired gases. After a 10 min equilibration period with each new mixture, the $O_2$ and $N_2$ tests were performed (fig. 2).

### CHRONIC HYPOXIA

Three groups were investigated at two different altitudes in Bolivia: 3660 m (La Paz) and 5200 m (Chacaltaya); 1) seven healthy sea-level residents (mean age 27) sojourning for three weeks at La Paz and then for 2 days at 5200 m, 2) 46 healthy highlanders from these two altitudes (mean age 28), 3) 9 native highlander patients (mean age 52) living at 3660 m, reputedly free of bronchopulmonary or cardiac disease but showing an exercise dyspnoea and polycythemia improved by a stay at lower

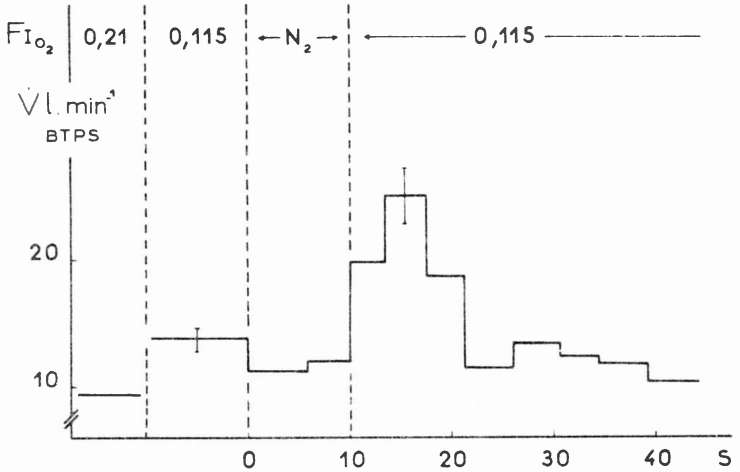


Fig. 2. Effect of $N_2$ test in acute hypoxia. After 10 min of acute normocapnic hypoxia ($F_{I_{O_2}} = 0.115$) the subject inhales two tidal volumes of pure nitrogen. Each vertical bar represents ± 2 SE.

TABLE 1

Biometric values and pulmonary function data in the four groups of subjects. § = Vital capacity is calculated as a percent of normal values at sea-level residents of same age and height as given by C.E.C.A. (1961). Hct+ = hematocrit. Values for subjects in chronic hypoxia are given with ± 2 standard errors.

| Subjects groups | Subjects number | Ht cm | Wt kg | S.A. $m^2$ | Hct+ % | VC lBTPS | VC§ % | FEV1 %VC |
|---|---|---|---|---|---|---|---|---|
| Acute Hypoxia | 3 | 170 | 69 | 1.81 | 44 | 5.10 | 101 | 75 |
| Chronic Hypoxia 3660 m | | | | | | | | |
| Lowlanders | 7 | 173 ±4 | 71 ±5 | 1.84 ±0.11 | 49 ±3 | 5.00 ±0.43 | 99 ±7 | 77 ±4 |
| Highlanders | 29 | 164 ±6 | 63 ±4 | 1.68 ±0.12 | 50 ±4 | 4.48 ±0.65 | 99 ±3 | 75 ±5 |
| Patients | 9 | 168 ±8 | 78 ±11 | 1.88 ±0.10 | 72 ±4 | 3.33 ±0.65 | 73 ±8 | 60 ±4 |

altitudes. These signs are similar to those which some workers have associated with chronic mountain sickness (BHATTACHARJYA, 1964). Biometric data of the different groups of subjects are given in table 1. 4) Oxygen tests were also performed in four highland native dogs anesthetized with Nembutal (25 $mg \cdot kg^{-1}$): A) before, B) after denervation of carotid bifurcations, C) after denervation of carotid bifurcation and section of vagus nerves. Completeness of denervation was determined by absence of ventilatory effects following intravenous injection of 0.1 $mg \cdot kg^{-1}$ of KCN (LEFRANÇOIS *et al.*, 1966).

## Results

### ACUTE HYPOXIA

The average maximal ventilatory change for the $N_2$ test, as shown in fig. 2, was plotted against the corresponding $P_{A_{O_2}}$. The sea-level ventilatory response curve constructed from the combined results of the $O_2$ and $N_2$ tests (fig. 3,A) consists of 3 distinct sections: 1) a slight increase in minute volume when $P_{A_{O_2}}$ falls from 145 to 55 mm Hg, 2) a steeper increase between 55 and 45 mm Hg and 3) no significant change in ventilation when $P_{A_{O_2}}$ changes from 45 to 35 mm Hg (LEFRANÇOIS, GAUTIER and PASQUIS, 1965b).

### CHRONIC HYPOXIA

1) In acclimatized lowlanders, after a three-week stay at 3660 m, the well-known altitude hyperventilation was observed. The mean minute volume was 10.6 $l \cdot min^{-1}$ as compared with 7.1 $l \cdot min^{-1}$ at sea level. At 5200 m, the mean resting ventilation increased to 11.2 $l \cdot min^{-1}$. At both altitudes, oxygen and nitrogen tests produced significant changes of ventilation in these subjects (fig. 3, B and C). It was not possible without danger to obtain a hypoxia severe enough to show whether or not the plateau

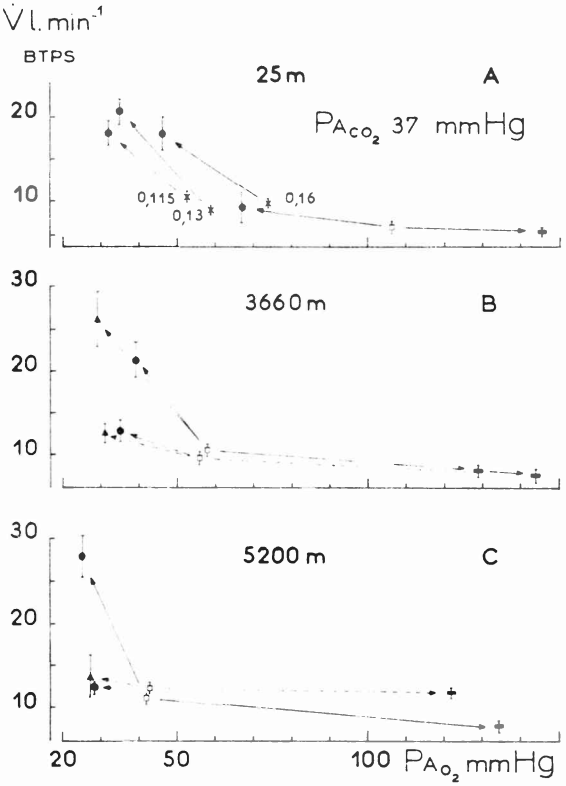


Fig. 3. Oxygen ventilatory response curve, A in acute hypoxia (mean of 12 values in one subject), B and C in chronic hypoxia. Open squares = control values; horizontal rectangles = 2-breath $O_2$ test; closed circles = 2-breath $N_2$ test; closed triangles = 3-breath $N_2$ test; crosses = acute hypoxia with $F_{IO_2}$ as indicated. Solid lines, lowlanders; broken lines, highlanders. Each vertical bar represents ± 2 SE. Note that the chemosensitivity of lowlanders is little affected by a stay in altitude and is comparatively greater than that of highlanders.

observed in the low $PA_{O_2}$ ranges of the acute hypoxia curve was present.

2) At 3660 m the mean resting ventilation of the highland native was slightly lower than that of acclimatized lowlanders. The oxygen test produced a significant ($P < 0.01$) decrease of minute volume in all these highland subjects. The inhalation of two tidal volumes of nitrogen, causing an increase in ventilation from 9.5 to 12.9 l · min$^{-1}$, reduced the $PA_{O_2}$ from 56 to 35 mm Hg. Inhalation of three tidal volumes of nitrogen decreased the $PA_{O_2}$ to 31 mm Hg but caused no further significant increase in ventilation (fig. 3,B). At 5200 m (fig. 3,C), minute volume was significantly reduced by the oxygen test, but neither two nor three breaths of nitrogen significantly altered minute volume, although the $PA_{O_2}$ fell to 27 mm Hg. In summary, the oxygen test in natives always produced a decrease in ventilation, thus demonstrating the existence of an oxygen drive. A lowering of $PA_{O_2}$ below 45 mm Hg causes no further augmentation of minute volume.

TABLE 2

Ventilatory and alveolar gas values in chronic hypoxia for acclimatized lowlanders, highlanders and patients. Minute volume in $l_{BTPS}$. $min^{-1}$. Pressures in mm Hg. All values are given with ± 2 standard errors. Number of values in parentheses.

| Subjects | Altitude | Number of Subjects | CONTROL VALUES | | | | | 2 BREATHS $O_2$ | | | 2 BREATHS $N_2$ | | | 3 BREATHS $N_2$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $\dot{V}$ | $\dot{V}.m^{-2}$ | f | $P_{AO_2}$ | $P_{ACO_2}$ | $P_{AO_2}$ | $\dot{V}$ | $\Delta\dot{V}$% | $P_{AO_2}$ | $\dot{V}$ | $\Delta\dot{V}$% | $P_{AO_2}$ | $\dot{V}$ | $\Delta\dot{V}$% |
| Lowlanders | 3660 m | 7 | 10.6 ± 0.6 (112) | 5.8 | 12 ± 1.6 (112) | 58 ± 2 (48) | 28 ± 1 (48) | 144 ± 17 (11) | 7.6 ± 0.9 (26) | − 28 | 39 ± 2 (11) | 21.3 ± 2.1 (56) | + 101 | 29 ± 2 (10) | 26.1 ± 3.4 (30) | + 146 |
| | 5200 m | 4 | 11.2 ± 0.6 (45) | 6.1 | 14 ± 1.8 (45) | 42 ± 2 (18) | 24 ± 1 (18) | 135 ± 18 (7) | 7.5 ± 0.6 (26) | − 33 | 25 ± 2 (7) | 28.0 ± 2.5 (19) | + 150 | | | |
| Highlanders | 3660 m | 29 | 9.5 ± 0.3 (398) | 5.4 | 17 ± 1.3 (398) | 56 ± 1 (103) | 31 ± 1 (103) | 129 ± 20 (10) | 8.1 ± 0.5 (157) | − 14 | 35 ± 3 (10) | 12.9 ± 1.1 (165) | + 37 | 31 ± 2 (9) | 12.6 ± 1.0 (76) | + 33 |
| | 5200 m | 17 | 12.3 ± 0.7 (174) | 7.4 | 18 ± 1.6 (174) | 43 ± 2 (30) | 25 ± 1 (30) | 119 ± 16 (7) | 10.3 ± 0.5 (96) | − 16 | 28 ± 2 (7) | 12.8 ± 0.5 (60) | + 4 | 27 ± 2 (7) | 13.8 ± 2.4 (18) | + 13 |
| Patients | 3660 m | 9 | 12.1 ± 2.1 (107) | 6.4 | 17 ± 3 (107) | 54 ± 2 (44) | 33 ± 2 (44) | 132 ± 24 (30) | 11.8 ± 1.6 (77) | − 3 | 32 ± 2 (17) | 12.7 ± 1.2 (30) | + 5 | | | |

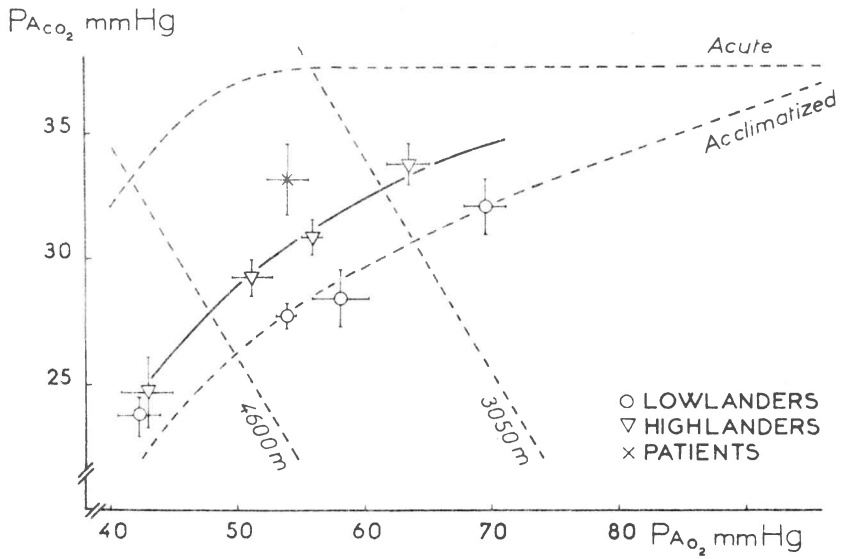


Fig. 4. $O_2 - CO_2$ diagram. Dotted lines are redrawn from RAHN and OTIS (1949). Note that the values for the acclimatized lowlanders are similar to the acclimatized line of Rahn and Otis and that this line is significantly below the points for the highland natives. Each bar represents ± 2 SE for $P_{ACO_2}$ and $P_{AO_2}$.

3) The mean resting minute volume of highland native patients was 12.1 $l \cdot min^{-1}$, only slightly different from that of healthy natives. Oxygen (fig. 1) and nitrogen tests produced no ventilatory effects (table 2).
4) The oxygen test response in native dogs diminished considerably after sinocarotid denervation and disappeared after complete chemodenervation (fig. 6).

### ALVEOLAR GASES

Alveolar gases from 56 native and lowland subjects at four different altitudes ranging from 2700 to 5200 m were collected and analyzed for $O_2$ and $CO_2$. Results are plotted on the $O_2 - CO_2$ diagram of RAHN and OTIS (1949). At each altitude, alveolar gas values were significantly different in the two groups of subjects. Furthermore, patients were more hypoxic and hypercapnic than healthy subjects living at the same altitude (3660 m). Alveolar values in the acclimatized lowlanders were identical with those of the Rahn and Otis curve for similar subjects, but the alveolar values of natives were located between the acute and acclimatized curves. Therefore, it is possible to complete the classical Rahn and Otis diagram by a third curve for highland natives (fig. 4).

## Discussion

### VENTILATION MEASUREMENT

Ventilation was recorded at any time of the day but always after ten minutes of rest.

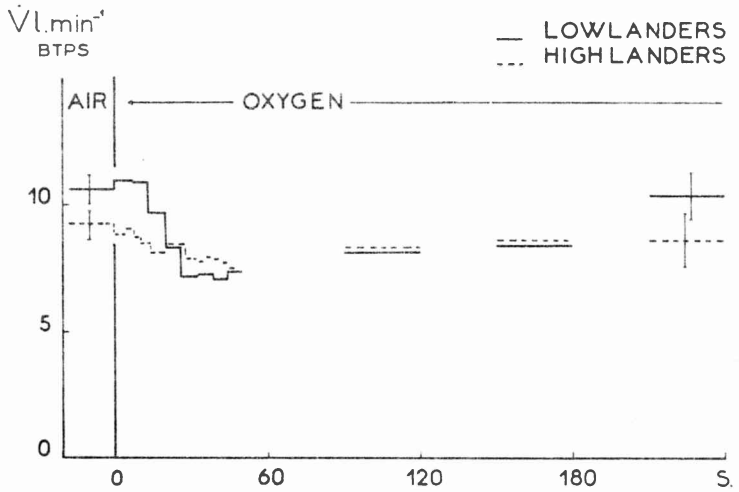


Fig. 5. Ventilatory effects of prolonged inhalation of pure oxygen at 3660 m in acclimatized lowlanders and highlanders. Ventilation was measured cycle by cycle during the first minute, then averaged for each 30 second period. Each bar represents ± 2 SE.

These values were higher and somewhat less reproducible than measurements made under more basal conditions. Although the ventilation did not differ significantly in the two groups of subjects at 3660 m, the native subjects were more hypercapnic and more hypoxic than the temporary sojourners (fig. 4). The respiratory rate of lowlanders was twelve per minute as compared with seventeen for highlanders. If it is assumed that the dead space is the same in men of similar morphology, the natives then must have a relatively lower alveolar ventilation (AKHMEDOV, 1967). This explains the similar differences in alveolar gases observed by CHIODI (1957). This difference should have been observed again at 5200 m, but the lowlanders, well acclimatized at 3660 m, spent only 30 hours at 5200 m, so that complete acclimatization was not achieved. This may explain why the observed ventilations and alveolar gas values were not significantly different in the two groups of subjects at the higher altitude.

During prolonged inhalation of pure oxygen, a fall of ventilation resulting from the suppression of oxygen drive occurs after a short delay and is maximal after 30 sec. Ventilation then increases progressively due to the action of secondary effects. After a few minutes of continuous oxygen inhalation it becomes difficult to observe any further significant change of ventilation (DEJOURS *et al.*, 1959) (fig. 5). Therefore, the different methods of studying oxygen drive do not produce similar results. The maximal fall of ventilation during continuous oxygen breathing, 33 per cent for the sojourners and 20 per cent for the natives, was greater than that observed with the transient oxygen test, *i.e.*, 28 and 14 per cent at 3660 m respectively. The oxygen test is not very accurate for quantitative determination of the oxygen drive (DEJOURS, 1962). Nevertheless, similar conclusions are reached with both methods when comparing maximal ventilation decreases in different groups of subjects.

## VENTILATORY OXYGEN DRIVE IN ALTITUDE

The diminution of ventilation observed after inhalation of two breaths of oxygen in all normal subjects living in altitude is evidence of the existence of an oxygen stimulus (fig. 1). This phenomenon was observed in both highlanders and acclimatized lowlanders at altitudes up to 5200 m. This confirms the work of DEJOURS *et al.* (1957) and CERRETELLI (1961) on lowlanders and that of CHAPIN (1954) and SEVERINGHAUS, BAINTON and CARCELEN (1966) on natives. The ventilatory oxygen drive is more important in acclimatized lowlanders (table 2 and fig. 3). Moreover, the higher the altitude, the more important is the oxygen drive for each group of subjects.

The chemoreflex origin of altitude hyperventilation has been studied in dogs by GILFILLAN *et al.* (1958). BOUVEROT *et al.* (1965), working with awake, trained, acutely hypoxic dogs observed that the oxygen test produced a ventilatory change which is similar to the decrease observed in man and which is suppressed by chemodenervation. Our experiments performed in highland native dogs show that oxygen test response must be of chemoreflex origin in dogs. Fig. 6 shows that ventilatory effects of oxygen tests were relatively more important in dogs than in men living at the same altitude. It may be a species difference, for similar observations have been made at sea-level: using the oxygen test in normoxia, DEJOURS (1962) found a decrease of 10% of ventilation in man, and BOUVEROT *et al.* (1965) of 40% in the awake dog. Since the existence of a reflex chemosensitivity in man has been previously demonstrated by GUZ *et al.* (1966), it is reasonable to assume that the variations of ventilation observed after the oxygen and nitrogen tests are of chemoreflex origin in hypoxic man.

## COMPARISON OF CHEMOSENSITIVITY DURING ACUTE AND CHRONIC HYPOXIA

The results of the oxygen and nitrogen tests at different levels of oxygenation were used to construct for each group of subjects an oxygen-ventilatory response curve, the slope of which can be interpreted in terms of chemosensitivity. In acute hypoxia (fig. 3,A), the curve has a sigmoid shape which is similar to the curve obtained in the dog by HONDA and KREUZER (1966). With falls in $P_{A_{O_2}}$ to 45 mm Hg, the more severe the hypoxic stress, the greater is the ventilatory response for a given dimunition of $P_{A_{O_2}}$. When $P_{A_{O_2}}$ is lower than 45 mm Hg, the curve shows a plateau and any further decrease of $P_{A_{O_2}}$ provokes no supplementary ventilatory effect, although minute volume remains below maximal breathing capacity. In order to explain the existence of the plateau, HORNBEIN, GRIFFO and ROOS (1961) have suggested that the chemoreceptors may be saturated in intense hypoxia. These conclusions are based on experiments during which electrical activity of the Hering nerves was recorded in acutely hypoxic cats.

The oxygen ventilatory response curves of sojourners at 3660 m (fig. 3,B) and 5200 m (fig. 3,C) are similar to the curves observed in the same subjects during acute hypoxia. Chemosensitivity was not modified by a stay of three weeks to two months at altitude. No definite conclusions are possible because of the small number of subjects we could

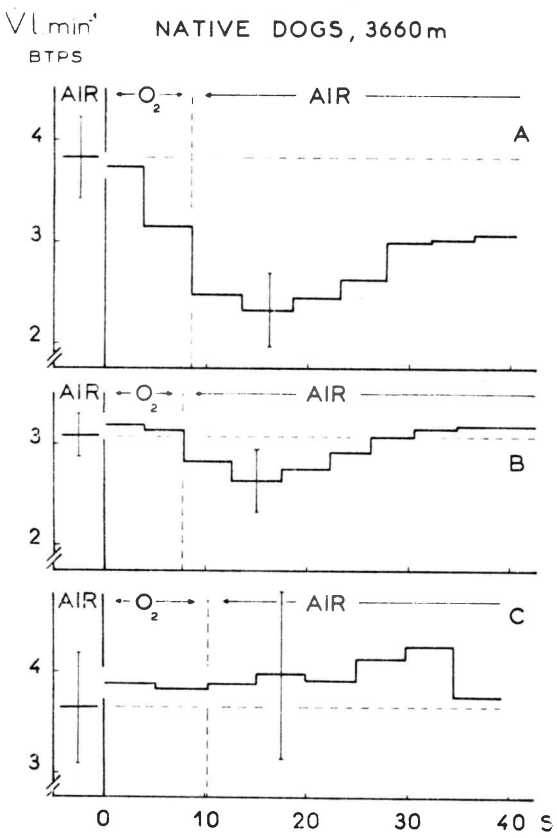


Fig. 6. Effects of oxygen tests in four native dogs anesthetized with 25 mg·kg$^{-1}$ of Nembutal. A) before, B) after denervation of carotid bifurcations and C) after section of vagus nerves. Completeness of denervation was determined by absence of ventilatory effects following intravenous injection of 0.1 mg·kg$^{-1}$ of KCN. Note that chemodenervation abolished the ventilatory response to oxygen inhalation. Mean of 45 tests. Vertical bars equal ± 2 SE.

study. We known nothing about the oxygen drive of long-term sojourners (a few years).

The comparison of the oxygen ventilatory response curves of sojourners and natives living at two levels of high altitude (fig. 3, B and C) demonstrates the lower sensitivity to hypoxia of natives. In these highlanders living at 5200 m, inhalation of two or even three breaths of nitrogen lowering $P_{A_{O_2}}$ to 27 mm Hg provoked neither significant change in ventilation nor subjective discomfort.

The hyposensitivity of chemoreceptors to hypoxia is more marked in the patients (fig. 1). This accounts for the fact that they are more hypoxic and more hypercapnic than healthy subjects at the same altitude.

## ALVEOLAR GASES

RAHN and OTIS (1949) on the $O_2-CO_2$ diagram have reported alveolar gas values

in acute and chronic hypoxia for different levels of real or simulated altitude. A distinction between the effects of hypoxia on natives and acclimatized lowlanders was not made. Our results indicate that the points for the alveolar values of natives are located on a line between the acute and acclimatized Rahn and Otis curves (fig. 4). The relative decrease in alveolar ventilation of natives can be explained by a diminution of ventilatory oxygen drive.

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