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CHEMOREFLEX VENTILATORY RESPONSE TO CO_2 IN MAN AT LOW AND HIGH ALTITUDES

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Abstract. On man, a peripheral chemoreflex ventilatory response curve was obtained by measuring ventilatory reactions to the transient inhalation of a CO_2-rich mixture. Experiments have been performed. 1) on lowlanders in normoxia, in acute hypoxia and during acclimatization at an altitude of 3660 m (La Paz, Bolivia). 2) on native highlanders. In lowlanders, acute and chronic hypoxia is characterized by an increase in the slope of the $\dot{V}_E/P_{A_{CO_2}}$ curve. Acclimatization is marked by a shift of this curve to a lower $P_{A_{CO_2}}$ and a higher ventilation. This shift is achieved within two days. Highland natives at high or low altitude have a very low peripheral chemoreflex CO_2 drive.

Acclimatization	Hypoxia
Altitude	Native highlanders
Control of breathing	Ventilatory response to CO_2

Ventilatory response to CO_2 during altitude acclimatization in man born at sea level has been studied by numerous authors (Rahn *et al.*, 1953; Kellogg *et al.*, 1957; Tenney, Remmers and Mithoefer, 1963; Severinghaus *et al.*, 1963; Eger *et al.*, 1968). This response has been compared to that obtained in subjects living at high altitudes (Chiodi, 1957; Forster *et al.*, 1969; Lahiri *et al.*, 1969; Sørensen and Cruz, 1969). These studies demonstrated that high altitude residence was responsible in all subjects for an increase in CO_2 sensitivity, but the origin of this mechanism remains to be understood. However, the methods used did not permit isolation of the peripheral chemoreflex response, *i.e.*, that due to arterial chemoreceptor activity from the whole response. The purpose of this work is an attempt to isolate the ventilatory peripheral response to CO_2 in man and to study it in lowlanders at sea level and during acclimatization to altitude, and in high altitude natives already known to be hyposensitive to different ventilatory stimuli (Lefrançois *et al.*, 1969a).

In 1965, Bouverot *et al.* showed that, in the dog, the inhalation of one or two tidal

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volumes of a mixture containing 7 per cent CO_2 in air (CO_2 test; Dejours *et al.*, 1958) caused, after a delay of 10–15 sec, a transient hyperventilation due to stimulation of the arterial chemoreceptors. This early response disappears after chronic chemoreceptor denervation while a delayed more prolonged response of smaller amplitude appears. Furthermore, these authors showed that the prior inhalation by normal animals of pure oxygen resulted in a response to the CO_2 test identical to that observed in the dog with denervated carotid chemoreceptors. Therefore, hyperoxygenation causes a chemical denervation which makes it possible to isolate the peripheral ventilatory response from the whole CO_2 ventilatory response, even in man. But since inhalation of CO_2 causes both an increase in Pa_{CO_2} and a decrease in the arterial pH, the ventilatory response of different subjects can be compared only if their pH variations are identical. Therefore, the buffer power of blood was determined in the different groups of subjects. Preliminary results have already been published (Lefrançois *et al.*, 1969b and 1970).

Methods

The sea level studies were performed in Rouen (altitude 25 m, mean barometric pressure 760 torr) on five healthy young subjects born at sea level (mean values: age 29 years, weight 68 kg, height 170 cm) and on three natives of 3660 m sojourning at sea level since one year (mean values: age 27 years, weight 70 kg, height 166 cm).

The altitude studies were performed in La Paz, Bolivia (altitude 3660 m, mean barometric pressure 490 torr), 1) on the five subjects native to sea level in the first hours following their arrival in La Paz and during the 6 following weeks: 2) on 10 healthy young natives of La Paz (mean values: age 21 years, weight 60 kg, height 160 cm) and 3) on three native highland patients (mean age 45 years) born and living at 3660 m, reputedly free of bronchopulmonary and cardiac diseases but showing an exercise dyspnoea and polycythemia improved by a stay at a lower altitude. Similar signs have been associated with chronic mountain sickness (Bhattacharjya, 1964).

On the seated subject, after a ten minute rest period a pneumotachogram was recorded on magnetic tape. The subject breathed through a one-way respiratory valve with the inspiratory side connected to a three-way tap allowing continuous inhalation of a gas mixture with a variable concentration of oxygen or transient inhalation of a gas mixture enriched in CO_2. The end-expiratory alveolar gases were collected and analyzed at once for their CO_2 and O_2 pressures with a pH-gas analyzer (Instrument Laboratory, model 113) calibrated with gases analyzed with a Scholander 0.5 ml apparatus. Later, an electrical signal delivered by the magnetic tape permitted subsequent automatic measurements, by an analogical and digital system, of tidal volumes and corresponding ventilatory periods.

In some experiments, the subject inhaled two or three tidal volumes of a gas with various high PI_{CO_2} (CO_2 test). In other experiments, transient hypocapnia was provoked by a voluntary sigh. During each test, ventilation was recorded for one minute. This was repeated at three minutes intervals (fig. 1). All these experiments were carried out, 1) at sea level, after five minutes of inhalation of a gas mixture with $PI_{O_2} = 93$, 150, 443 or 713 torr, 2) at 3660 m, with $PI_{O_2} = 93$ or 443 torr, more severe hypoxia being

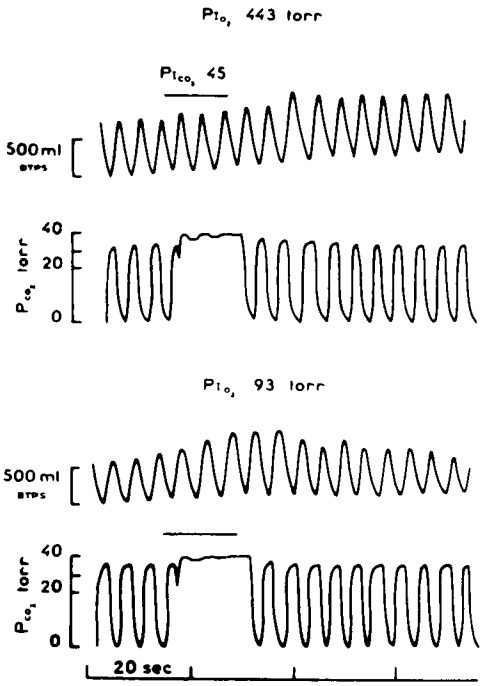

Fig. 1. CO_2 tests. Upper records during hyperoxia, lower records during hypoxia at sea level in sea level natives. Ventilatory response appears more rapidly and is more marked in hypoxia. (See Bernards *et al.*, 1966.)

obtained by transient inhalation of 2 or 3 breaths of CO_2 and nitrogen. Each subject underwent 12 tests for each experiment.

To determine the blood buffer value in the different groups of subjects, the pH and the plasma bicarbonate concentration of heparinized venous blood samples were analyzed after a ten-minute period of equilibration at 37 °C with three gas mixture in which P_{CO_2} was from 20 to 50 torr and P_{O_2} 100 torr.

Results

SEA LEVEL STUDIES (figs. 2 and 3)

1) Sea level natives. Transient hypercapnia provoked hyperventilation whose magnitude and latency were related to $P_{I_{O_2}}$. In acute hypoxia ($P_{I_{O_2}} = 93$ torr), the response (approximately 4 L.min^{-1} for $P_{I_{CO_2}} = 45$ torr) was maximum at the 15th second and then decreased rapidly. In normoxia, the same stimulus caused a lesser response appearing later and decreasing more slowly. Finally, in hyperoxia ($P_{I_{O_2}} = 443$ and 713 torr), the ventilatory response, less than 2 L.min^{-1}, was significant only from the 20th second and maximum only at the 40th second. In comparing these results with those on the dog by Bouverot *et al.* (1965), we concluded that the early ventilatory response to the CO_2 test in man was probably arterial chemoreflex and that the delayed response

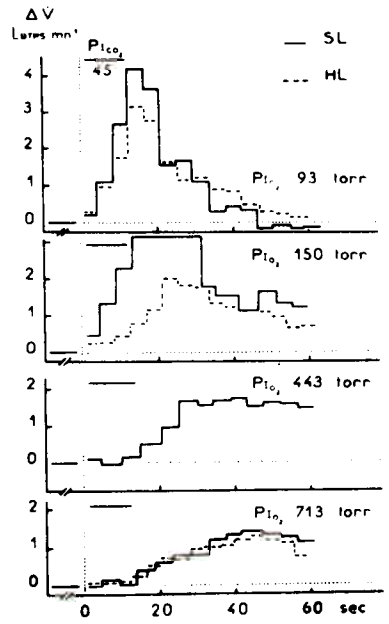

Fig. 2. CO_2 tests at sea level for different levels of oxygenation. Early peripheral chemoreflex ventilatory response to CO_2 disappears with hyperoxygenation in both highland natives (HL) and sea level natives (SL).

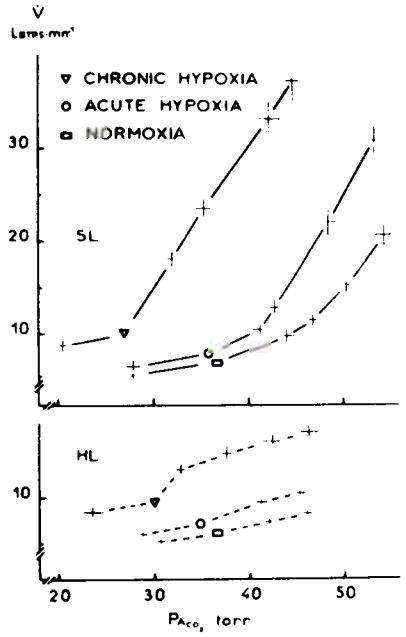

Fig. 3. Maximal ventilatory response to CO_2 tests plotted against the corresponding $P_{A_{CO_2}}$ in normoxia and acute and chronic hypoxia ($P_{I_{O_2}}$=93 torr). Upper part, sea level natives (SL); lower part, highland natives (HL). Means values of all subjects ± 1 SE.

was centrogenic. The early maximal response plotted against the corresponding $P_{A_{CO_2}}$ gives a "peripheral chemoreceptor CO_2 response curve" (fig. 3).

2) Highland natives. CO_2 tests during hypoxia resulted an early ventilatory response having the same latency as in sea level natives but a lower amplitude. On the other hand, in hyperoxia, only the late response, analogous to that of the sea level natives, persisted.

3) Sighs lowered $P_{A_{CO_2}}$ to approximately 30 torr and produced in these two groups of subjects a slight decrease in ventilation.

ALTITUDE STUDIES (figs. 3 and 4)

1) Sea level natives. In the subjects acclimatized for two or three weeks, the response to CO_2, as at sea level, was dependent upon the inspired $P_{I_{O_2}}$. In effect, for the same $P_{I_{CO_2}}$, with $P_{A_{O_2}}$ of approximately 400 torr, the ventilatory response was about 2 L.min^{-1}. For $P_{A_{O_2}} = 62$ torr (room air), it appeared earlier and was about 8 L.min^{-1}. The response attained 29 L.min^{-1} for $P_{A_{O_2}} = 34$ torr during a more severe hypoxia provoked by the inhalation of 2 or 3 breaths of CO_2 and nitrogen. In fig. 3, the peripheral chemoreflex CO_2 response curve was displaced towards the left. However, the late response is similar in amplitude and latency to that observed in the same subjects at sea level (figs. 2 and 4).

2) Highlanders. At high altitude, the early response of highlanders was not as great as that of acclimatized lowlanders. Furthermore, this response had a tendency to be

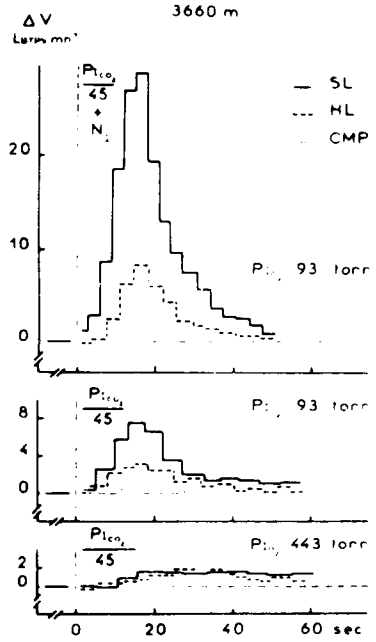

Fig. 4. CO_2 tests at different levels of oxygenation at 3660 m in acclimatized lowlanders (SL), in highland natives (HL) and in highland natives showing a chronic mountain polycythemia (CMP).

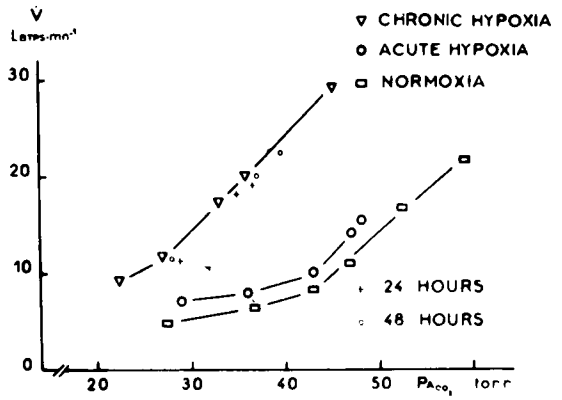

Fig. 5. Peripheral chemoreflex ventilatory response curves of one sea level native in normoxia, in acute hypoxia and during acclimatization at the altitude of 3660 m. The curve obtained after 24 h of acclimatization cannot be distinguished from that following three weeks acclimatization. Dotted line shows the modification of resting ventilatory values during altitude acclimatization.

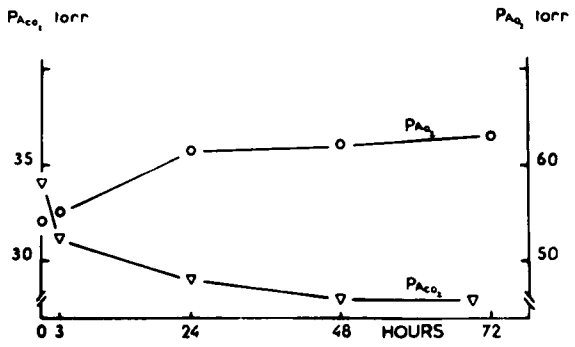

Fig. 6. Alveolar O_2 and CO_2 pressures during the first days of acclimatization of native lowlanders to 3660 m. Steady state is observed after 48 h of residence.

nearly maximum and did not show any apparent variation when the PA_{CO_2} went from 35 to 45 torr. The late response was the same as in altitude-acclimatized sea level natives.

3) Sighs at high altitude caused a slight decrease in ventilation, comparable to that observed in the two groups of subjects at sea level.

4) Highland patients reputed to be afflicted with chronic mountain polycythemia had practically no ventilatory response to the inhalation of CO_2 (fig. 4, middle).

5) Acclimatization. Ventilation at rest increased rapidly as soon as the subject was exposed to high altitude and reached a stable value in 24 to 48 h (fig. 5). Values of PA_{O_2} and PA_{CO_2} (fig. 6) also moved towards those observed in chronic hypoxia within 48 h. The $\dot{V}E/PA_{CO_2}$ curve plotted in the first 48 h at high altitude was practically the same as that observed in chronic hypoxia. In general, acclimatization was responsible for a shift upwards and towards the left of the $\dot{V}E/PA_{CO_2}$ curve.

BLOOD BUFFER VALUE

Blood buffer value was determined as the slope of the straight line relation (fig. 7) between plasma bicarbonate concentration and pH of tonometred blood. Increased hemoglobin concentration after exposure to altitude caused an increase in the value of this slope which went from -29 to -37 mEq · L^{-1} · (unit pH)$^{-1}$ after a sojourn of

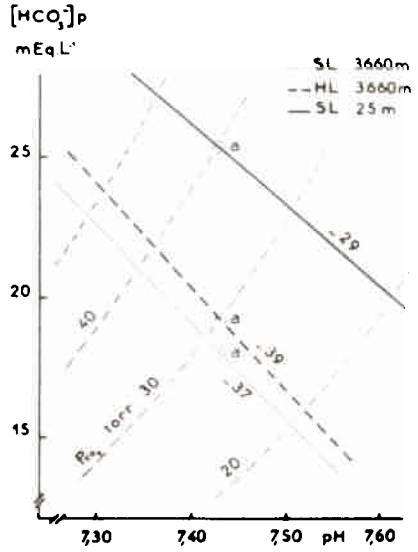

Fig. 7. Buffer power lines referred to [HCO_3^-]p/pH diagram. a represents the arterial resting point. The slope is greater at high altitude that at sea level. No significant difference is observed between acclimatized lowlanders and highland natives.

three weeks at 3660 m. This last value was not significantly different from that measured in highlanders, -39 mEq · L^{-1} · (unit pH)$^{-1}$. Arterial pH being the same at sea level and after 3 weeks at high altitude, acclimatization was accompanied by urinary bicarbonate elimination (Rahn and Otis, 1949), so that the buffer line was displaced downwards by approximately 5 mEq · L^{-1} for a pH of 7.40.

Discussion

METHODS

1) CO_2 *test*. In past studies of CO_2 sensitivity, the ventilatory response to prolonged inhalation of experimental gas mixtures has been measured. The mixtures used, more or less highly oxygenated and enriched in CO_2, were chosen to eliminate the interaction of CO_2 and O_2 stimuli, or to decrease arterial chemoreceptor activity. But at a $P_{I_{O_2}}$ of 200 torr, frequently employed, the peripheral chemoreflex is still present (fig. 2), and the relative contributions of the peripheral and central mechanisms hard to assign. The peripheral ventilatory response to CO_2 can be isolated, even at 3660 m, by the

transient inhalation of CO_2 in ambient air and pure oxygen. Since hyperoxygenation suppresses the peripheral CO_2 response, authors who have given transient inhalations of CO_2 in pure oxygen only have not studied the peripheral chemoreflex (Sørensen and Cruz, 1969).

2) *Effects of the blood buffer value* (fig. 7). Because of the well-known increase in the hemoglobin concentration, the blood buffer value was increased in the subjects living at high altitude. Our results show that, after acclimatization, the slope of the straight line representing the blood buffer value was the same in natives and altitude-acclimatized lowlanders studied at 3660 meters. Under these conditions, the arterial pH at rest was the same, and the same variations of $P_{A_{CO_2}}$ caused the same variations in pH. At sea level, in all subjects, the blood buffer value was less, but because of the position of the P_{CO_2} isobars on the $[HCO_3^-]p/pH$ diagram (fig. 7), an hypercapnia starting from the rest Pa_{CO_2} caused a comparable variation of the pH at sea level and in altitude. Therefore, the peripheral chemoreceptor CO_2 response curve enabled us to compare and evaluate the CO_2 sensitivity in all subjects. The blood buffering value *in vivo* was definitely different from that measured *in vitro*, however this last value is still of importance as far as the peripheral chemoreflex studies were concerned.

CO_2 SENSITIVITY

1) *Peripheral chemoreflex CO_2 sensitivity*. When the early ventilatory response is plotted against $P_{A_{CO_2}}$ (fig. 3), an arterial chemoreflex CO_2 response curve is obtained. Its configuration is similar to that described for continuous inhalation of CO_2 but the values of ventilation are lower. With the continuous inhalation method, peripheral and central chemoreceptors are both activated (Nielsen and Smith, 1951). In sea level natives at sea level, small variations in $P_{A_{CO_2}}$ on both sides of the normal resting value caused a small variation in ventilation, and it was only for a marked hypercapnia that ventilation was high, the whole having the typical dog-leg shape within the limits of the hypercapnia studied. For a moderate hypercapnia, the slope of the curve was greater in acute hypoxia than in normoxia, as a consequence of O_2 CO_2 interaction. Following acclimatization to altitude, every level of hypercapnia caused a ventilatory response proportional to the variation in P_{CO_2}, and the slope of this curve was the same as in acute hypoxia.

In highland natives who had lived for one year at sea level, the CO_2 response curve was very flat in normoxia as well as in acute hypoxia for hypercapnia up to 45 torr. At 3660 m, the configuration of the $\dot{V}E/P_{A_{CO_2}}$ response curve was quite different from that in sea level natives acclimatized to high altitude. A slight hypercapnia caused a relatively important ventilatory response but, for a greater hypercapnia, the sensitivity decreased and was comparable to that observed at sea level in highland subjects. This hyposensitivity to CO_2 could be compared to that observed for other ventilatory stimuli (ventilatory oxygen drive and neurogenic factors of ventilatory control during muscular exercise) (Lefrançois *et al.*, 1969). Chiodi (1957), Forster *et al.* (1969) and Lahiri *et al.* (1969) had observed a global response to CO_2 in highland natives; our results show the peripheral chemoreflex contribution to this phenomenon.

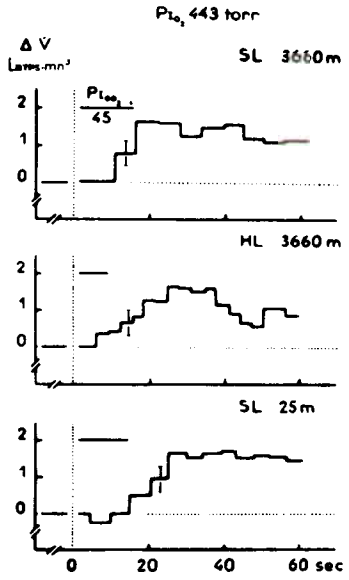

Fig. 8. CO_2 tests in hyperoxygenated subjects ($P_{I_{O_2}}$ = 443 torr.) There is no chemoreflex ventilatory response but a delayed (central) response appears and is the same in all groups of subjects.

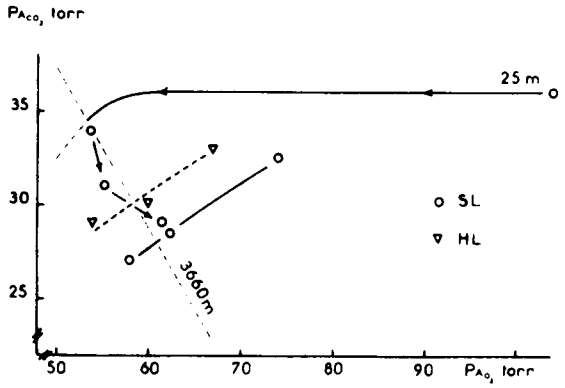

Fig. 9. Alveolar gas values are plotted on a $P_{A_{O_2}}$ $P_{A_{CO_2}}$ diagram during three weeks altitude acclimatization of lowlanders (SL) and in highland natives (HL). Arrows show the pathway of alveolar gases during acclimatization.

Patients showing chronic mountain polycythemia were insensitive to CO_2 as well as to oxygen (Lefrançois, Gautier and Pasquis, 1968).

2) *Central sensitivity.* The late ventilatory response appearing after inhalation of two or three tidal volumes of a hyperoxygenated CO_2-mixture was the same in all the subjects studied at low and high altitude (fig. 8). This method cannot be used to quantify the central sensitivity, as the amount of CO_2 inhaled is insufficient. The results can, however, be related to those of Severinghaus, Bainton and Carcelen (1966) who found no notable change of central CO_2 sensitivity in different groups of subjects at high altitude.

ACCLIMATIZATION

Acclimatization does not change the sensitivity to CO_2 of subjects who have recently arrived at high altitude (fig. 5). Twenty-four hours after arrival, their $\dot{V}E/PA_{CO_2}$ response curves have practically the same slope as those taken after a month's stay : only, they exhibit a hyperventilation which stabilizes in less than 48 h. This hyperventilation is accompanied by a transient respiratory alkalosis (Kronenberg *et al.*, 1971) which causes a renal elimination of bicarbonates ; the urine was alkalotic in the first days of the stay. Acclimatization is demonstrated by a rapid displacement upwards and towards the left of the $\dot{V}E/PA_{CO_2}$ response curve (Kellogg *et al.*, 1957 ; Severinghaus *et al.*, 1963). The progressive consequences of hyperventilation can be represented on a PA_{O_2}/PA_{CO_2} diagram (fig. 9). This figure shows also the relative hypoxia and hypercapnia of highland natives due to their lower sensitivity to ventilatory stimuli.

References

Bernards, J. A., P. Dejours and A. Lacaisse (1966). Ventilatory effects in man of breathing successively CO_2-free, CO_2-enriched and CO_2-free gas mixtures with low, normal or high oxygen concentration. *Respir. Physiol.* 1 : 390–397.

Bhattacharjya, B. (1964). Mountain Sickness. Bristol, J. Wright ed.

Bouverot, P., R. Flandrois, R. Puccinelli and P. Dejours (1965). Etude du rôle des chémorécepteurs artériels dans la régulation de la respiration pulmonaire chez le Chien éveillé. *Arch. int. Pharmacodyn.* 157 : 253–271.

Chiodi, H. (1957). Respiratory adaptations to chronic high altitude hypoxia. *J. Appl. Physiol.* 10 : 81–87.

Dejours, P., Y. Labrousse, J. Raynaud and R. Flandrois (1958). Etude du stimulus gaz carbonique de la ventilation chez l'Homme. *J. Physiol. (Paris)* 50 : 239–243.

Eger II, E. I., R. H. Kellogg, A. H. Mines, M. Lima-Ostos, C. G. Morrill and D. W. Kent (1968). Influence of CO_2 on ventilatory acclimatization to altitude. *J. Appl. Physiol.* 24 : 607–615.

Forster, H. V., J. A. Dempsey, M. L. Birnbaum, W. G. Reddan, J. S. Thoden, R. F. Grover and J. Rankin (1969). Comparison of ventilatory responses to hypoxic and hypercapnic stimuli in altitude-sojourning lowlanders, lowlanders residing at altitude and native altitude residents. *Federation Proc.* 28 : 1274–1279.

Kellogg, R. H., N. Pace, E. R. Archibald and E. B. Vaughan (1957). Respiratory response to inspired CO_2 during acclimatization to an altitude of 12,470 feet. *J. Appl. Physiol.* 11 : 65–71.

Kronenberg, R. S., P. Safar, J. Lee, F. Wright, W. Noble, F. Wahrenbrock, R. Hickey, E. Nemoto and J. W. Severinghaus (1971). Pulmonary artery pressure and alveolar gas exchange in man during acclimatization to 12,470 ft. *J. Clin. Invest.* 50 : 827–837.

Lahiri, S., F. F. Kao, T. Velasquez, C. Martinez and W. Pezzia (1969). Irreversible blunted respiratory sensitivity to hypoxia in high altitude natives. *Respir. Physiol.* 6 : 360–374.

Lefrançois, R., H. Gautier and P. Pasquis (1968). Ventilatory oxygen drive in acute and chronic hypoxia. *Respir. Physiol.* 4 : 217–228.

Lefrançois, R., H. Gautier, P. Pasquis and E. Vargas (1969a). Factors controlling respiration during muscular exercise at altitude. *Federation Proc.* 28 : 1296–1300.

Lefrançois, R., P. Pasquis, H. Gautier and M. F. Monconduit (1969b). Effets de l'oxygénation sur la réponse ventilatoire au CO_2 chez l'Homme à haute et basse altitude. *J. Physiol. (Paris)* 61 : 335–336.

Lefrançois, R., H. Gautier, P. Pasquis, A. M. Cevaer and M. F. Hellot (1970). Pouvoir tampon du sang humain à haute et basse altitude. *J. Physiol. (Paris)* 62 : 401–402.

Nielsen, M. and H. Smith (1951). Studies on the regulation of respiration in acute hypoxia. *Acta Physiol. Scand.* 24 : 293–313.

Rahn, H. and A. B. Otis (1949). Man's respiratory response during and after acclimatization to high altitude. *Am. J. Physiol.* 157: 445–462.

Rahn, H., R. C. Stroud, S. M. Tenney and J. C. Mithoefer (1953). Adaptation to high altitude: Respiratory response to CO_2 and O_2. *J. Appl. Physiol.* 6: 158–162.

Severinghaus, J. W., R. A. Mitchell, B. W. Richardson and M. M. Singer (1963). Respiratory control at high altitude suggesting active transport regulation of CSF pH. *J. Appl. Physiol.* 18: 1155–1166.

Severinghaus, J. W., C. R. Bainton and A. Carcelen (1966). Respiratory insensitivity to hypoxia in chronically hypoxic man. *Respir. Physiol.* 1: 308–334.

Sørensen, S. C. and J. V. Cruz (1969). Ventilatory response to a single breath of CO_2 in O_2 in normal man at sea level and high altitude. *J. Appl. Physiol.* 27: 186–190.

Tenney, S. M., J. E. Remmers and J. C. Mithoefer (1963). Hypoxic-Hypercapneic Interaction at High Altitude. Pergamon Press, pp. 263–272.