RESPIRATORY CHANGES AT HIGH ALTITUDE

By

RICHARD L. RILEY

Department of Environmental Medicine, The Johns Hopkins School of Hygiene and Public Health, Baltimore 5, Md., U. S. A.

It is convenient to discuss the respiratory changes at high altitude in terms of the changes in the ventilatory response to CO_2. The classic work of Haldane and Smith, published in 1893, marked the beginning of quantitative studies of this kind. CO_2 response curves are determined by having the person breathe a given concentration of CO_2 until a steady ventilatory response is obtained. This requires about 15 minutes. Successive points on the curves of ventilation vs. Pco_2 are obtained using different concentrations of inspired CO_2. Ordinarily ventilation is plotted against alveolar P_{CO_2} because this is closer than inspired Pco_2 to the level which reaches the chemosensitive cells.

In the presence of hypoxia the ventilatory response to CO_2 is enhanced in a very special way. At ventilation levels higher than the resting level, the slope of the CO_2 response curve becomes steeper, and the change in slope is a function of the severity of hypoxia (Fig. 1). When the upper linear portions of curves determined at different alveolar P_{O_2} values are extrapolated to the Pco_2 axis, the intercepts at zero ventilation all fall at practically the same point (Fig. 2). The ventilatory response to hypoxia is thus characterized by increased sensitivity to CO_2 at levels of ventilation above the resting level and by almost complete insensitivity to CO_2 at alveolar P_{CO_2} values below that existing at the inflection point of the curve (Fig. 1). In the latter region ventilation appears to be controlled predominantly by arterial P_{O_2} alone.

The hypoxic stimulus to ventilation is mediated by peripheral chemoreceptors in the carotid and aortic bodies (Heymans and Neil, 1958). These receptors are sensitive to lowering of P_{O_2} in the arterial blood. During air breathing at sea level the chemoreceptor fibres show a low level of activity, and their contribution to the total ventilatory stimulus is small. The rate of firing and the intensity of the ventilatory stimulus increase progressively as arterial P_{O_2} is lowered. After chemoreceptor denervation hypoxia causes depression of breathing. The chemoreceptors are thus essential to the positive respiratory response to hypoxia.

Ventilatory adjustments constitute an essential part of the process of adaptation to the hypoxia of high altitude. In order to bring the P_{O_2} of the alveolar gas, and hence of the blood and tissues, closer to the P_{O_2} of the inspired air, ventilation must increase. This increase must depend on involuntary mechanisms and must not be associated with excessive respiratory alkalosis. The peripheral chemoreceptors

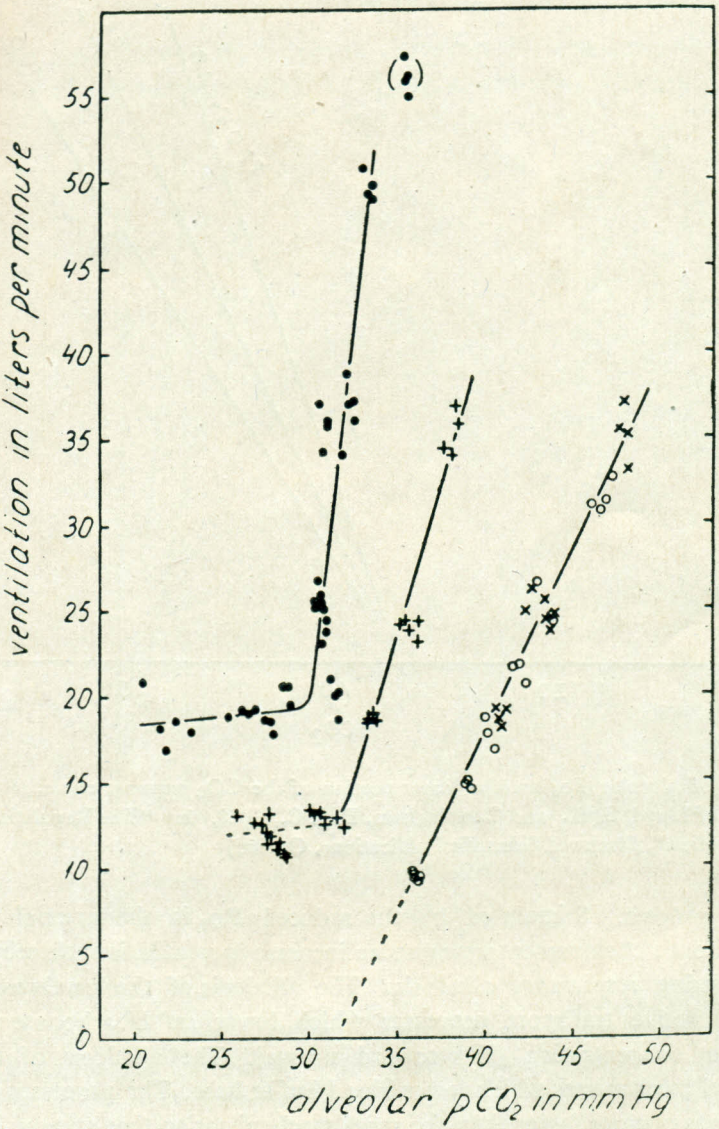

Fig. 1. Man. Subject P.G. pulmonary ventilation (37 degrees, prevailing bar. pressure saturat.) in relation to alveolar P_{CO_2}.

● Alveolar P_{O_2} 36.9 ± 1.3 mm. Hg
\+ „ 47.2 ± 1.5 „
0 „ 110.3 ± 1.9 „
X „ 168,7 ± 2.1 „

(M. Nielson and H. Smith, 1951, Acta physiol. scand. 24 : 293)

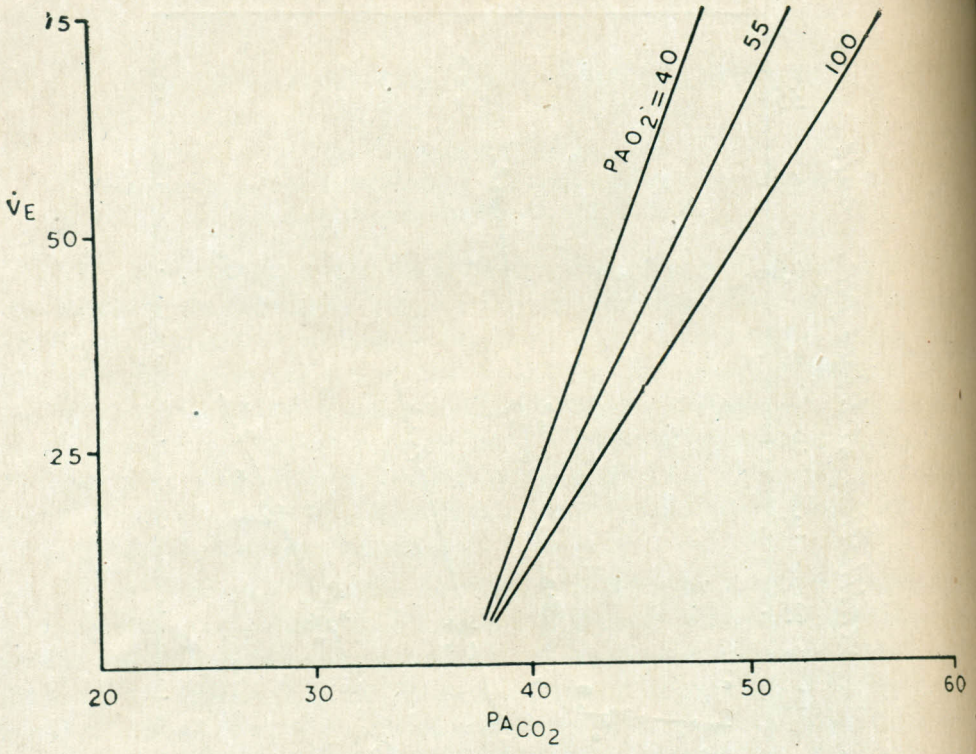

Fig. 2. Effect of alveolar P_{O_2} on the linear portion of the CO_2 response curve. (Redrawn from Fig. 5 of Lloyd, B. B., and Cunningham, D. J. C., 1963, in "The Regulation of Human Respiration", Blackwell Scientific Publications, Oxford)

initiate the process. Stimulated by the reduced P_{O_2} in the arterial blood, the carotid and aortic chemoreceptors cause an increase in ventilation, thereby lowering P_{CO_2} and causing respiratory alkalosis. The alkalosis of the cerebrospinal fluid (csf) initiates active transport processes which lower csf bicarbonate and restore hydrogen ion concentration (H^+) toward normal. The alkalosis of the blood initiates renal mechanisms which lower blood buffer base. The processes controlling csf bicarbonate operate faster than the renal mechanisms so that at any given time during acclimatization to high altitude csf (H^+) is virtually normal while arterial (H^+) is low (Severinghaus et al., 1963). During this period the reduced arterial (H^+) partially counteracts the hypoxic stimulus. As the renal adjustment of blood buffer base proceeds, ventilation progressively increases and P_{CO_2} progressively decreases. Arterial P_{O_2} rises by an amount which is approximately equal to the fall in P_{CO_2}, thus progressively reducing the hypoxic stimulus. After several weeks an equilibrium is reached in which ventilation is regulated by the combined stimuli related to arterial (H^+), csf (H^+) and arterial P_{O_2}.

In Fig. 3 are shown CO_2 response curves performed on both acclimatized (left hand fan) and unacclimatized (right hand fan) subjects. In both cases the CO_2

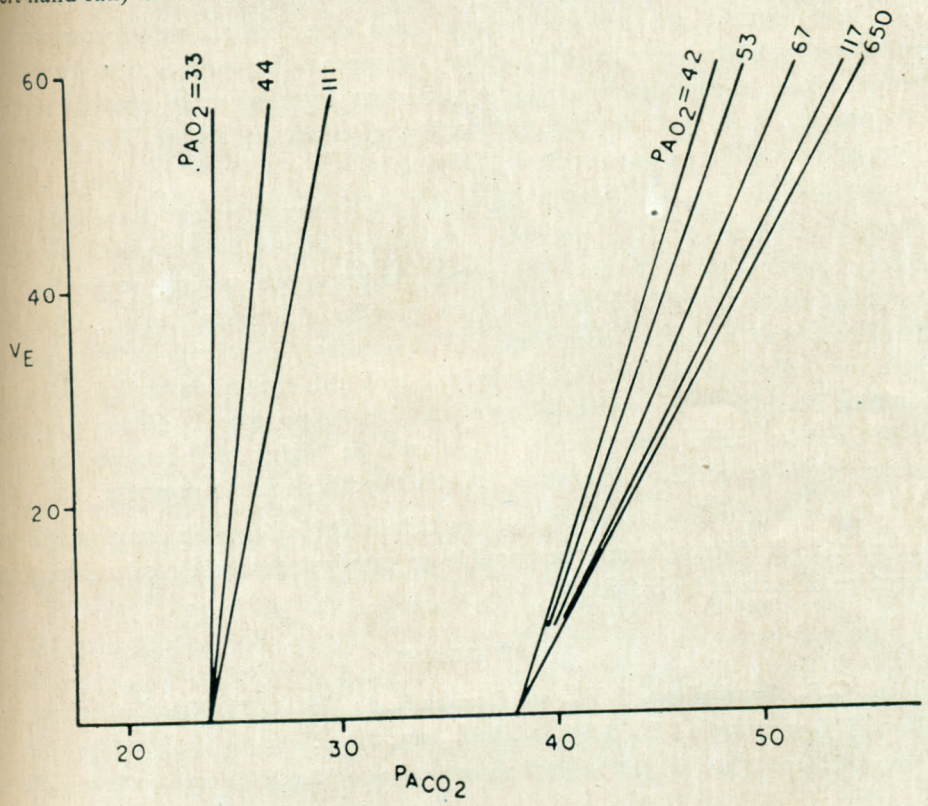

Fig. 3. Effect of prolonged acclimatization to high altitude (19,000 ft.) upon the fan of CO_2 response curves at different alveolar P_{O_2} levels. The linear portions of the curves have been extrapolated towards the base line. Fan of curves on right obtained at sea level before acclimatization. Fan of curves on left obtained after prolonged acclimatization. (Redrawn from Fig. 2 of Milledge, J. S., 1963, in "The Regulation of Human Respiration" Blackwell Scientific Publications, Oxford)

response curves become steeper when the alveolar PO_2 is lowered, but the slopes of curves at corresponding alveolar PO_2 values are steeper in the acclimatized person. The entire fan is displaced to the left by approximately 14 mm. Hg. after prolonged acclimatization to 19,000 feet.

If the hypoxic stimulation of breathing in the acclimatized person is removed acutely by administering O_2, the immediate reduction in ventilation is only slight because the control mechanism is extremely sensitive to the elevation in P_{CO_2} which accompanies any reduction in ventilation. If hypoxia is removed permanently by return to sea level, ventilation slowly returns to normal (CO_2 response curve moves

slowly to the right) as the buffer base in blood and csf rises. This requires several days.

Although the changes which have been described are well documented as applied to lowlanders going to high altitude, it appears that natives who have lived at high altitude for generations breathe somewhat less than more recently acclimatized people. As a result the natives have lower values of arterial Po_2 and higher values of arterial Pco_2 (Bainton et al., 1964).

The use of pharmacological agents to hasten the attainment of acclimatization to high altitude may well be possible. As stated above, the processes controlling csf bicarbonate normally operate faster than the renal mechanisms, suggesting that the rate at which the kidneys excrete base may be a limiting factor. By using a pharmacological agent to accelerate the renal excretion of base at high altitude, respiratory alkalosis should be minimized and the hypoxic stimulus to breathe should be freed from the counteracting effect of alkaline blood. Hence ventilation should increase more and arterial Po_2 should be higher than it would be in the absence of the drug. Experiments to test this hypothesis are in progress.

By understanding the mechanisms which lie behind the observed respiratory changes at high altitude, it may be possible to manipulate these mechanisms to the advantage of man at high altitude.

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