Is increased hematopoiesis needed at altitude?

The increased hemoglobin concentration in high-altitude dwellers is a double-edged sword. Increasing hemoglobin concentration is a response long considered to be a beneficial adaptation, whereby an increase in the oxygen-carrying capacity of the blood compensates for the arterial hypoxemia of altitude. Without such an adaptation, maintenance of the arterial oxygen delivery to the tissues would require an increased cardiac output, an energy-intensive response. Furthermore, the body seems to go to considerable lengths to raise hemoglobin when the arterial oxygen levels fall. As one goes to high altitude, plasma volume immediately begins to contract, quickly raising the hemoglobin concentration. As one remains at altitude, erythropoiesis increases both the hemoglobin concentration in the blood and the total amount in the body. Thus, by different mechanisms, both acute and chronic hypoxemia serve to increase blood hemoglobin concentration.

However, at some point, the increase in hemoglobin concentration ceases to be a benefit and becomes a curse. That is, some individuals lose their ventilatory acclimatization to hypoxia after a decades-long residence at high altitude. They cease to hyperventilate, suffer central depression of respiration particularly at night, and develop severe hypoxemia, which over time stimulates excessive polycythemia. With hemoglobin concentrations usually above 23 g/100 ml, these individuals develop a potentially fatal syndrome called chronic mountain sickness. The combined effects of hypoxemia and impaired microcirculatory perfusion result in organ malfunction, particularly of the brain and lung. Dizziness, mental confusion, and even cerebral infarction occur. Pulmonary hypertension and impaired ventilation-perfusion relationships, leading to degradation of pulmonary gas exchange and further hypoxemia, also occur. The hypoxemia-polycythemia cycle can be interrupted by lowering the hemoglobin concentration (decreasing the degree of polycythemia), causing the patients to feel better, the arterial oxygen saturation to increase, and the pulmonary and systemic oxygen transport to improve at rest and during exercise.

In altitude dwellers, there is a cost-benefit balance for an increased hemoglobin concentration, and the question arises as to the optimal hemoglobin level for the most favorable balance. It is not an idle question. Many millions of people are living at higher and higher altitudes, driven by world population pressures and the increasing need to retrieve mineral resources often found at high elevations. There is the opportunity, possibly even the mandate, for integrative physiologists to understand better optimal hemoglobin concentrations in response to the hypoxic stresses of residence at altitude.

In this issue of the Journal, Villafuerte et al. (2) provide a theoretical analysis to address the question of how different hemoglobin concentrations alter oxygen transport, as judged by the mixed venous PO2, in individuals living at high altitude. On the basis of their experience that cardiac output and the position of the oxygen-hemoglobin dissociation curve vary little with altitude, cardiac output and P50 were assumed to be constant. Their analysis suggests that, with increasing hypoxemia, the mixed venous PO2 is maximal at hemoglobin concentrations of ~15–18 g/100 ml; furthermore, Villafuerte et al. raise the possibility that higher concentrations of hemoglobin might offer no additional protection to oxygen transport at altitude.

However, if the cardiac output and resting oxygen uptake do not change with altitude, as the authors assume, then the arterial-venous oxygen content difference would be constant and independent of altitude. If so, this could have two possible implications. First, the increased hemoglobin could be responsible for the maintenance of the arterial-venous oxygen difference in subjects with low values of arterial oxygen content. This possibility is suggested by a study in which subjects, who were taken acutely to altitude, decreased their values of arterial-venous difference and increased their cardiac outputs (3). Possibly, the body defends itself against chronic hypoxemia by an increase in hemoglobin concentration and against acute hypoxemia by an increase in cardiac output. Second, if there is a constant arterial-venous oxygen content difference, the arterial-venous oxygen saturation difference would be an inverse function of hemoglobin concentration, which would itself then define the mixed venous oxygen saturation. If true, both of these implications point to a role for increasing hemoglobin concentration in maintaining oxygen transport during chronic hypoxemia, if the body chooses not to increase cardiac output.

Villafuerte et al. (2) do not exclude that, for mild degrees of hypoxemia, hemoglobin concentrations up to ~18 g/100 ml (PO2 of ~57 Torr, elevation of ~3,800 m) may facilitate oxygen transport. However, they point out that, as hypoxemia becomes more and more severe, increasing hemoglobin concentrations become progressively less effective in maintaining oxygen transport, in which values of ~18 g/100 ml may be optimal for all altitudes. To establish an optimal value for hemoglobin, or whether one exists for the various altitudes, measurements in populations are needed. Particularly needed are measurements during exercise to stress the oxygen transport system, but gathering these will not be easy, for investigators must access subjects, obtain permission, and design studies to answer complex questions. Exercise at altitude may promote alveolar edema, impair ventilation/perfusion relationships, and have variable effects on oxygen diffusion capacity. For example, although increases in hemoglobin concentrations may reduce pulmonary blood flow for a given exercise intensity, the diffusing capacity depends not only on hemoglobin concentration but also on alveolar oxygen tension and pulmonary blood flow. There are but few comprehensive measurements that have examined the effect of hemoglobin concentration on oxygen transport over a wide range of hemoglobin values in high-altitude residents.

The question arises as to the possible evolutionary origin of the increase in hemoglobin concentration with hypoxia and what physiological function it might serve. Although most of the world’s population do not go to altitude, everyone has survived fetal life. Compared with adult standards, the mature fetus has a low arterial PO2 and a cardiac output that may approach the maximal sustainable value (1). Thus it becomes important for survival of the species that oxygen transport be efficient, and a high hemoglobin concentration could be utilized for arterial oxygen transport to spare higher cardiac outputs. In this context, hemoglobin concentrations rise rapidly during the last third of gestation, the period of most rapid fetal
weight gain; concentrations average ~18 g/100 ml but fall rapidly when arterial oxygenation improves in the newborn (1). Evolutionary pressures may have designated efficient oxygen transport and high hemoglobin concentrations during development. One may speculate that, when humans go to high altitude, hypoxemia reactivates mechanisms for increasing hemoglobin concentration present in fetal life. And perhaps the function is the same, namely, to conserve circulatory energy by minimizing cardiac output. It may be coincidence, but it is of interest that the fetal hemoglobin concentration and that proposed by Villafuerte et al. (2) for the altitude dweller are similar.

In the altitude resident, when hemoglobin concentrations exceed 21–23 g/100 ml, microcirculatory perfusion becomes abnormal and chronic mountain sickness symptoms may appear. A challenge for physiologists is to evaluate, in chronic hypoxemia, the separate effects of high hemoglobin concentrations on oxygen transport from the polycythemia-related impairment of microcirculatory function. It seems that, for hemoglobin concentrations somewhere between 18 and 21 g/100 ml, impairment in oxygen transport and/or tissue perfusion threaten the well-being of altitude residents. The report of Villafuerte et al. (2) has served to emphasize that this is an area demanding further research.

REFERENCES


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