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ALTITUDE ADAPTATION THROUGH HEMATOCRIT CHANGES

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Adaptation takes place not only when going to high altitude, as generally accepted, but also when going down to sea level. Immediately upon ascent to high altitude, the carotid body senses the lowering of the arterial oxygen partial pressure due to a diminished barometric pressure. High altitude adaptation is defined as having three stages: 1) acute, first 72 hours, where acute mountain sickness (CMS or polyerythrocythemia) can occur; 2) subacute, from 72 hours until the slope of the hematocrit increase with time is zero; here high altitude subacute heart disease can occur; and 3) chronic, where the hematocrit level is constant and the healthy high altitude residents achieve their optimal hematocrit. In the chronic stage, patients with CMS increase their hematocrit values to levels above that of normal individuals at the same altitude. CMS is due to a spectrum of medical disorders focused on cardio-pulmonary deficiencies, often overlooked at sea level. In this study we measured hematocrit changes in one high altitude resident traveling several times between La Paz (3510 m) and Copenhagen (35 m above sea level) for the past 3 years. We have also studied the fall in hematocrit values in 2 low-landers traveling once from La Paz to Copenhagen. High altitude adaptation is altitude and time dependent, following the simplified equation:

$$Adaptation = \frac{Time}{Altitude}$$

where High altitude adaptation factor = Time at altitude (days)/Altitude in kilometers (km).
A complete and optimal hematocrit adaptation is only achieved at around 40 days for a subject going from sea level to 3510 m in La Paz. The time in days required to achieve full adaptation to any altitude, ascending from sea level, can be calculated by multiplying the adaptation factor of 11.4 times the altitude in km. Descending from high altitude in La Paz to sea level in Copenhagen, the hematocrit response is a linear fall over 18 to 23 days.

INTRODUCTION

Organic tissues require gradual changes in order to adapt to adverse conditions. Ever since the first balloon flights, exposure to extreme hypoxia has been considered potentially lethal. This has left a profound fear of hypoxia.

At sea level, vagotomized rats suddenly exposed to an inspired oxygen fraction of 10 % can die within minutes even when ventilated with a respirator (observation at Prof. Pokorski's laboratory in Warsaw, Poland). However, if the rats are slowly and gradually adapted to the hypoxic mixture, they will tolerate and develop mechanisms of adaptation. A few years back, it was believed that rats could not adapt to the high altitude of 3500 m. Today rats grow and multiply with adequate care at 4100 m (El Alto in Bolivia). Such observations, along with clinical experience of tolerance to extreme hypoxia in patients with CMS, gave rise to the theories of adaptation to life at the summit of Mount Everest (8812 m) (1).

The object of the present study was to measure changes in hematocrit when traveling both ways between La Paz and Copenhagen and to determine when full adaptation is achieved.

MATERIAL AND ETHODS

The first author was traveling between the city of La Paz (3510 m) and Copenhagen (35 m) intermittently following 2 to 3 months' stay at each place during the past 3 years. This required a frequent change in three coordinates: latitude, longitude, and altitude. Latitude implied an opposite change of station (for example, summer to winter). Longitude implied time changes with the corresponding jet lags. Altitude was the shift from the altitude of La Paz with an oxygen tension in the inspired air of 94 mmHg to Copenhagen, where the same tension is 150 mmHg. Likewise, the arterial oxygen tension (PaO_2) went from 60 mmHg to 95 mmHg, respectively. This allowed us to study the rate of hematocrit changes upon altitude changes.

Hematocrit samples in duplicate were taken with a newly developed technique. A 21 gauge needle was inserted into the ante-cubital vein with a tourniquete immediately above. Once blood began to flow to the plastic connector of the needle, it was sampled with a heparinized capillary tube. The two samples for each subject were immediately centrifuged in a microcentrifuge during 5 min at 5000 rpm. The samples were taken the first day of arrival to a new environment and then successively as shown in the results. One study was performed in the main author on his return to the altitude of La Paz, Bolivia after a 3-month stay in Copenhagen, Denmark. He was born and lived most of his life in La Paz. Upon return to Denmark, the hematocrit was also measured during more than 40 days. These studies were repeated several times. Similarly, two other studies included the second author and his wife upon return to Copenhagen, where they were born and lived almost all their life, after a 2-week sojourn to La Paz, Bolivia, living between 3100 and 4100 m.

RESULTS

The initial increase of the hematocrit value upon ascent reflects the maximum possible production and release of red blood cells due to a high stimulation

through increased erythropoietin. A gradual flattening of the curve until the stable peak plateau is reached would correspond to a gradually increasing feedback mechanism (*Fig. 1*). A 50% of the adaptation is reached when the hematocrit is at 43% (starting Ht of 36% + 7% that is half of the overall 14% increase). This point (A_{50}) is achieved at around 1 week. There is a greater degree of adaptation in the initial stages due to the exponential shape of the curve and erythropoietin described below.

On the contrary, upon descent to sea level, the decrease in hematocrit is gradual and almost linear (*Fig. 2*). The solid rhombus is a male high altitude native (first author) after 2 months' stay at high altitude. The solid square is a male sea level native (second author) and the empty triangle is a female sea level native both after a 2 weeks' stay at high altitude. This is suggestive of normal red blood cell destruction due to red blood cell life span along with the new theory of neocytolysis, i.e., selective destruction of the youngest circulating red cells (see discussion). The initial 18-23 days decay is linearly correlated, because there is no new replacement of red cells. Other factors could possibly be involved - yet not clearly defined. The slope, however, will reach a plateau once the cardio-pulmonary systems are able to sustain the most energy efficient level.

Fig. 3 shows the three hematocrit stages after arrival to La Paz: 1) Acute adaptation (from the time of arrival up to 3 days), where acute mountain sickness can occur, 2) Subacute adaptation, where subacute mountain sickness such as
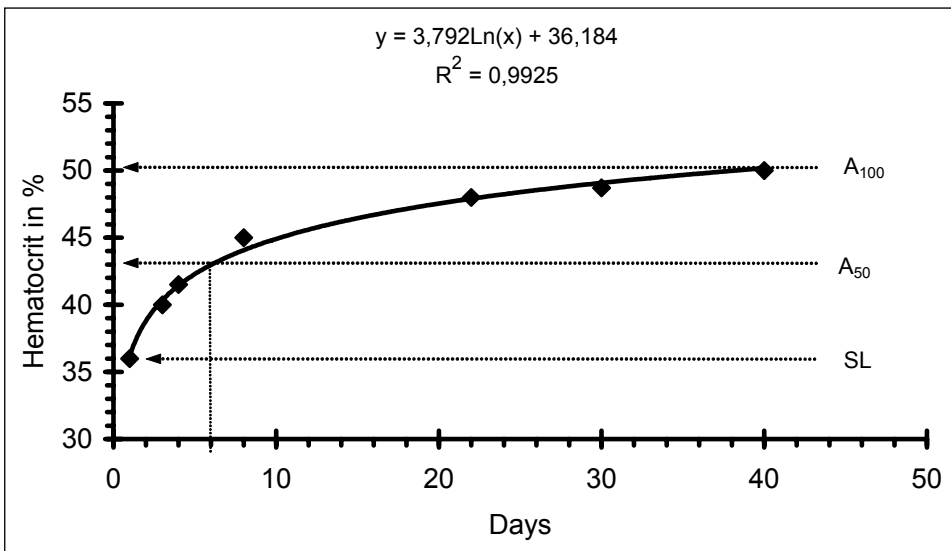
Fig. 1. Hematocrit changes after altitude travel from sea level (35 m) to high altitude (3510 m) in a male high altitude native (first author) who spent 3 months at sea level. A_{100} = 100 % adaptation.
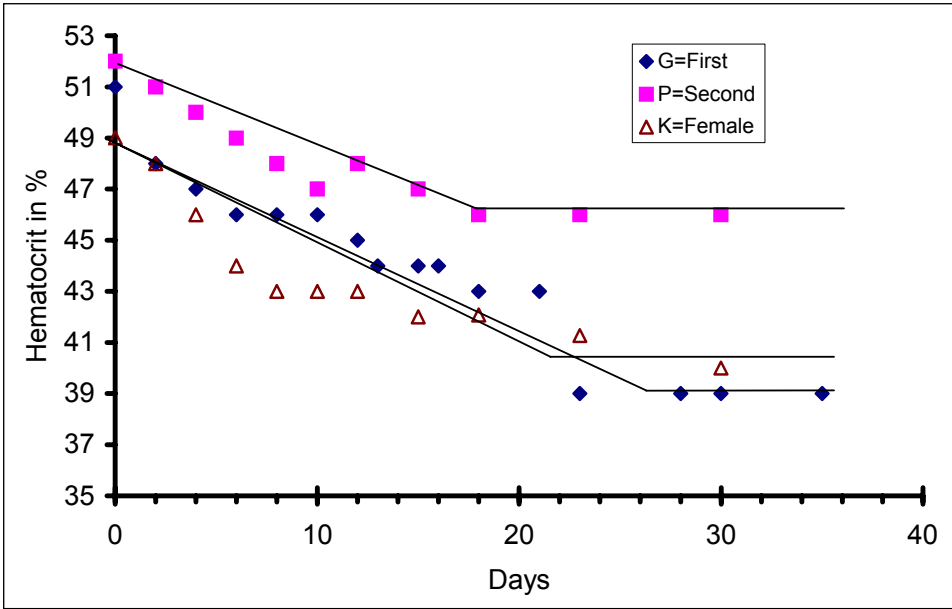
Fig. 2. Hematocrit changes on descent from high altitude (3510 m) to sea level (35 m) in three subjects.
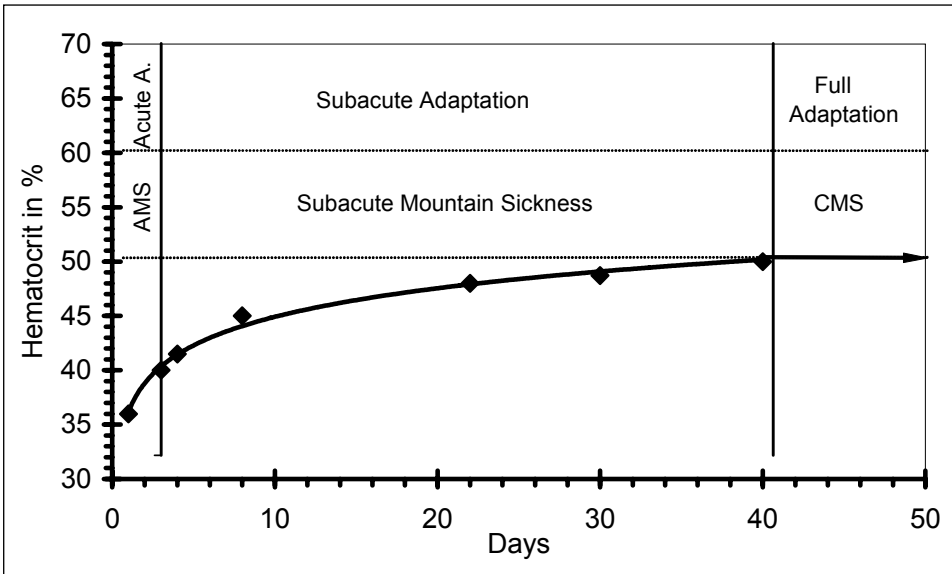

Fig. 3. The three hematocrit adaptation stages after ascent from sea level to high altitude.

high altitude subacute heart disease occurs, and 3) chronic adaptation where CMS is observed.

DISCUSSION

High altitude adaptation is altitude and time dependent following the previously described (2) simplified equation:

$$Adaptation = \frac{Time}{Altitude}$$

where High altitude adaptation factor = Time at altitude in days/Altitude in kilometers (km). Complete hematocrit adaptation to 3500 m was achieved after 40 days (*Fig. 1*). Hence, 40 days/3.5 km = 11.4 days/km for the altitude of La Paz. Assuming that this linear factor is generally acceptable, we can calculate the number of days necessary to achieve a complete adaptation to other fixed altitudes, when ascending from sea level.

As a first example of the use of this high altitude adaptation factor, we can calculate the length of time required to adapt to 2500 m: 2.5 x 11.4 = 28.5 days. Likewise, in order to adapt to 5000 m: 5.0 x 11.4 = 57 days are needed. In order to adapt to 8812 m (the summit of Mt Everest): 8.8 x 11.4 = 100 days, excluding other factors such as temperature differences, wind, logistics, and food. However, in the case of these extreme altitudes it seems logical to require different stages of altitude adaptation, as currently done, since no airplane can land on the summit of Mt. Everest. These data indicates that most people do not take enough time to adapt when ascending Mount Everest. Hence, the complications due to altitude.

The adaptation formula should only be applied to altitudes above 2000 m, since up to this altitude, changes are insignificant. In order to plan for movements starting from higher than sea level altitudes, as in mountain climbing, this would require further studies.

Phlebotomy has been used at high altitude to treat polyerythrocythemia. However, we strongly oppose it, as the underlying cause of polyerythrocythemia is not well understood in most cases (3). Hypoventilation along with a high hematocrit in CMS has been considered the most efficient energy saving mechanism (4). So that phlebotomy would produce an unnecessary extra load on the body. But phlebotomy would be a logic choice to perform in high altitude residents going to sea level. Furthermore, the high altitude residents, after staying at sea level, are often wrongly diagnosed as suffering from anemia. This should, from now on be considered a normal adaptation process.

In this study, hematocrit was analyzed in three persons that arrived to sea level or to a fixed altitude, where they remained sedentary and in comfortable living conditions. This contrasts with mountaineers who are constantly ascending and changing altitudes. The mountaineers are also exposed to exercise, dehydration, cold, sleep loss, and are under stress. A normal diet for a high altitude visitor to a sea level city contrasts with the food ingested by mountaineers. Dehydration and/or bleeding alters the hematocrit, but these are false observations of the true hematocrit that assumes no abnormal fluid changes. Previous studies (5) have

shown that hemoglobin (Hb) concentration increases upon altitude ascent. The initial increase is attributed fundamentally to a shift of water out of the vascular system, with a decrease in the plasma volume (PV) up to 20 % and a correlated decrease of blood volume (BV), confirmed by an increase in the concentration of plasma proteins (6). Atrial natriuretic peptide, released by exposure to hypoxia is believed to be the underlying mechanism (7). However, red cell volume (RCV) has individual variations with changes, both increasing and decreasing between +20% down to –13%. After a year at high altitude, there are reports that RCV can increase up to 50 % (5). Iron supplementation in women has been shown to improve the hematocrit increase at high altitude (8). This shows that red meat ingestion is fundamental on ascent to high altitude.

Adaptation is a complex subject due to multiple variables playing their role in differently reacting individuals. Also, any disease can alter adaptation. Going from La Paz, Bolivia at 3510 m to Copenhagen at 35 m, implies a series of changes in the three coordinates: latitude, longitude and altitude, as stated above. The author suffered a serious jet lag going to sea level from La Paz towards the East. It took around twenty days for regularization of sleep hours, without medication. This is not only due to the time difference; it also compromises the oxygen increase and the carbon dioxide tension increase from 30 mmHg in La Paz to the normal sea level value of 40 mmHg. This relative CO_2 accumulation initially induces fatigue and sleepiness during the day. This lasted and correlated quite well until the full hematocrit adaptation A_{100} was achieved.

There is, likewise, swelling of the feet during long trips, due to being seated in a plane. Upon arrival to sea level, the increased oxygen tension in the inspired air induces hypoventilation and respiratory acidosis. A higher CO_2 tension in the arterial blood gives rise to vasodilatation and fluid retention during the acute adaptation stage. This has been observed in soccer players going from La Paz to compete at sea level. It is highly probable that some degree of cerebral edema may be present, but this has not been corroborated by MR scans. Just as the kidney plays a fundamental role in long-term altitude adaptation, it also functions in the sea level adaptation, regulating a new fluid retention status.

Individual variations are due to race, physical training, ventilatory and cardiac characteristics, genetics, and fundamentally to cardio-pulmonary disease. This is relevant for all three adaptation stages. After the initial acute phase of adaptation, acute mountain sickness may occur in susceptible individuals. Rarely, it is due to hematological disorders that are extremely serious, such as sickle cell anemia.

If the subject is exposed to intense exercise in the subacute stage, he can easily develop high altitude subacute cardiac disease. This was described by Anand et al (9) in soldiers ascending to altitudes between 5800 and 6700 m and performing intense physical exercise. According to our equation presented above, it would take at least 66 days (11.4 x 5.8) for the soldiers to adapt to that altitude. It would have been better for the soldiers to train gradually with low level exercise, since they remained only at altitude for 70 days. This would have reduced significantly

the cardiac insufficiency. The soldiers had insufficient time to adapt to the new hypoxic environment.

The final chronic adaptation stage is acquired when the hematocrit value no longer increases. This stage has previously been shown to be the most energy efficient biological high altitude condition (4). Here, the initial cardio-respiratory and renal hyperactive response gradually achieves the lowest oxygen consumption at the expense of an increase in the number of red blood cells. The chronic adaptation stage was originally described in CMS patients, but it is also pertinent to normal high altitude residents.

Going from high altitude to sea level, the hematocrit response is linear and complete adaptation is achieved at around 18-23 days. The response is linear, because it is caused by a sudden stop in new red blood cell production and a gradual decrease, possibly by neocytosis along with normal fluid changes.

Airplane cabin pressures typically correspond to around 2500 of altitude even though the exterior altitude is above 10000 m. On long flights for over 8 hours, this helps in the initial gradual adaptive process to 4100 m at the El Alto airport in La Paz, Bolivia. Short flights, in one hour or less to the same airport can lead to a greater risk of acute mountain sickness. In a controlled hypobaric hypoxia study, where subjects were exposed to 4000 m during 3 hours/day, 5 days per week in a total period of 4 weeks, the serum erythropoietin (EPO) levels doubled (10). However, there was no increase in RCV and Hb. Our study assumes a similar EPO rise.

Neocytolysis (11) originally described by Alfrey et al (12, 13) in astronauts during space sojourn, has been shown to play a role on polycythemic patients after the descent to sea level and also in polycythemic high altitude dwellers transported to sea level. Young and middle-aged RBCs were more prone to phagocytosis due to changes in their wall structure. This poses a question of whether it would be more compromising to health to go up than to go down. Going up is a building strategy of the body by increasing the number of red blood cells. Going down to sea level, the human body destructs red blood cells through hemolysis with an increased production of urobilinogen (evidenced by a regular urine test) and also fecal iron and bile pigments (evidenced by dark blue-green stools). At first glance, the descent would compromise health most.

Consequently, it is logical to propose that bleeding (phlebotomy) upon arrival to sea level is of benefit. This would, aside from constituting a resource for blood donors, mean an energy saving mechanism for the organism. The authors have opposed bleeding at high altitude in CMS patients, because we consider polyerythrocythemia a result of a spectrum of medical conditions (3). Hence, diminishing the oxygen carrying capacity by phlebotomy is an unnecessary stress to the body at high altitude. Not so, going down, where there is a "relative excess" of oxygen supply.

Our study shows that "new" full adaptation is achieved when the hematocrit reaches a new hematocrit plateau confirming complete adaptation. The authors

believe that the increase of hematocrit in response to environmental chronic hypoxia is the most efficient mechanism to allow for oxygen transport and cannot be thus classified, as some other authors propose, as excessive or unnecessary (5), and where a limit of optimal hematocrit is set. Going from sea level to the altitude of La Paz requires about 40 days to achieve a complete adaptation. Conversely, going back down to sea level requires about 20 days for the adaptation to occur.

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