ARTICLE

Impact of Alterations in Total Hemoglobin Mass on $\dot{V}O_{2max}$

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SCHMIDT, W. and N. PROMMER. Impact of alterations in total hemoglobin mass on $\dot{V}O_{2max}$. *Exerc. Sport Sci. Rev.*, Vol. 38, No. 2, pp. 68–75, 2010. *Training and hypoxia-associated changes in maximal oxygen uptake are mediated by different blood adaptations. Training increases blood volume because of plasma and red cell volume expansion, resulting in increased cardiac output, whereas hypoxia increases only red cell volume, leading to increased hemoglobin concentration and oxygen transport capacity. Blood doping mimics the altitude effects, however, by far exceeding its magnitude.* **Key Words:** hemoglobin concentration, blood volume, cardiac output, training, altitude, blood manipulation

INTRODUCTION

Maximal oxygen uptake ($\dot{V}O_{2max}$), which, in a way, represents endurance performance, is, according to Fick's equation, determined by the oxygen supply of the blood and by the oxygen consumption of the skeletal muscle. Depending on the performance state, one of the two factors gains importance. It has been shown that, in untrained subjects, the oxygen consumption dominates $\dot{V}O_{2max}$, whereas in endurance-trained athletes, the oxygen supply is the main limiting factor (16,33).

The oxygen transport to the muscle underlies a complex regulation, which depends on hemoglobin concentration ([Hb]) and muscle perfusion. The latter adapts to the actual metabolic situation and can be modulated by a systemic or local regulation of the vascular diameter as well as by a change in cardiac output ((CO); for review, see (25)). The most important factor for a high CO is a compliant heart and a distensible pericardium (16), which permits a high end diastolic volume and herewith a high stroke volume. Furthermore, an efficient muscle pump (25) and a fast diastolic filling (for review, see (16)) is prerequisite, which, however, is only possible with an adequate high blood volume. Therefore, an augmentation of blood volume leads to a higher CO and an increase in $\dot{V}O_{2max}$, provided that [Hb] is high enough.

Therefore, under normoxic conditions, $\dot{V}O_{2max}$ mainly depends on CO and [Hb]. In hypoxia, however, the prevailing oxygen (O_2) partial pressure gains importance, and the O_2 diffusion rate in the lungs and the skeletal muscle become the limiting factor (33).

In this context, hemoglobin mass (tHb-mass) is important in two ways. On one side, its total mass in combination with the total volume of blood determines [Hb] and herewith O_2 transport capacity. On the other side, it increases blood volume via the increase in erythrocyte volume. This double role explains the higher correlation with $\dot{V}O_{2max}$ compared with blood volume or [Hb] (15).

The relationship between blood volume and tHb-mass and the influence of both parameters on [Hb] are illustrated in Figure 1. It is obvious that tHb-mass linearly depends on blood volume over a broad range in a sex-related manner. The scattering of tHb-mass related to a certain value of blood volume reflects different [Hb]. [Hb] and tHb-mass are therefore different physiological parameters, which may exert different effects on endurance performance.

Because of methodological issues related to tHb-mass determination, it has been difficult for a long time to determine the contributions of tHb-mass versus [Hb] to parameters such as $\dot{V}O_{2max}$ and endurance performance. With the routine application of the well-known CO-rebreathing method optimized by Burge and Skinner (4) and later on by Schmidt and Prommer (30), new insight regarding the relationship of these parameters with $\dot{V}O_{2max}$ and endurance performance has been gained (30).

We hypothesize that $\dot{V}O_{2max}$ can be increased by two different hematological adaptations. The first involves a balanced increase in blood volume and tHb-mass leading to increased cardiac output, and the second involves a relatively constant blood volume with an increase in tHb-mass resulting in an elevated [Hb] and herewith improved oxygen diffusion.

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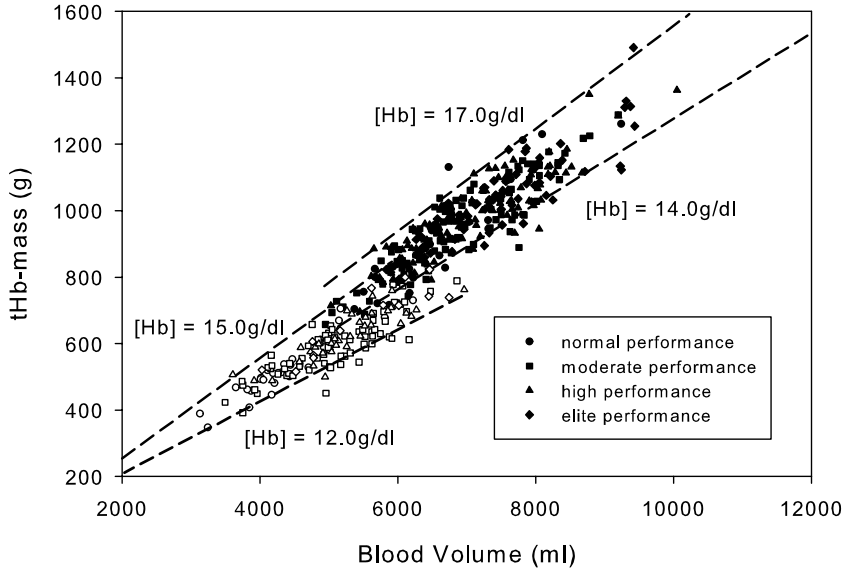

Figure 1. Total hemoglobin mass (tHb-mass) versus total blood volume. Data of 490 subjects (male subjects, n = 314, *closed symbols*; female subjects, n = 176, *open symbols*) living and training at sea level are shown (31). Endurance state is classified by maximal oxygen uptake ($\dot{V}O_{2max}$): normal performance, less than 48 mL·min^{-1}·kg^{-1} (male subjects) or less than 37 mL·min^{-1}·kg^{-1} (female subjects); moderate performance, 48–57 mL·min^{-1}·kg^{-1} and 38–47 mL·min^{-1}·kg^{-1}; high performance, 58–67 mL·min^{-1}·kg^{-1} and 48–57 mL·min^{-1}·kg^{-1}; and elite performance, greater than 67 mL·min^{-1}·kg^{-1} and greater than 58 mL·min^{-1}·kg^{-1}, respectively. The *dashed lines* indicate the hemoglobin concentration ([Hb]) as a function of blood volume and tHb-mass.

The aim of this article is to distinguish between the effects of tHb-mass and [Hb] on $\dot{V}O_{2max}$ and illustrate how variations of these parameters alter $\dot{V}O_{2max}$.

TOTAL HEMOGLOBIN MASS AND [Hb] AS CONTRIBUTORS TO $\dot{V}O_{2MAX}$

The magnitude of blood volume and tHb-mass correlates well with anthropometric characteristics, that is, especially with lean body mass (LBM) (26). In contrast, [Hb] is not related to LBM (32). It is well known that tHb-mass and blood volume are expanded in elite endurance athletes by up to 50% compared with sedentary subjects (13). Cross-sectional (9) and longitudinal studies (15) clearly demonstrate that $\dot{V}O_{2max}$ is closely related to tHb-mass and blood volume but not [Hb] (Fig. 2). Interestingly, the relationship between $\dot{V}O_{2max}$ and tHb-mass is independent of sex and age.

The underlying mechanism for this close relationship is based on the fact that a high blood volume and its accompanying high tHb-mass can affect venous return and cardiac filling pressures resulting in elevated maximum CO (6,14). A similar relationship between tHb-mass, blood volume, and cardiac output with $\dot{V}O_{2max}$ is demonstrated in Figure 3, showing a parallel increase in the corresponding regression lines. The ratio between CO at maximum exercise and blood volume is approximately 4:1, when considering a broad performance range ($\dot{V}O_{2max}$ between 3 L and 6 L). This ratio indicates that the blood and the hemoglobin molecules circulate four times per minute through the body independent of their absolute volumes. When calculating oxygen transport by the hemoglobin molecule at maximum performance, the change in tHb-mass by 1 g is associated with a change in $\dot{V}O_{2max}$ of approximately 4 mL·min^{-1} (1 g hemoglobin binds 1.39 mL O_2; assumed is: arteriovenous oxygen difference ($avDO_2$) to be 75%, four circulation passages per minute as previously mentioned). This calculated value fits very well with the slope of the regression line obtained between $\dot{V}O_{2max}$ and tHb-mass in Figure 2a as well as with the results described in the literature in cross-sectional studies (9). These considerations demonstrate that high levels of tHb-mass and blood volume are indispensable prerequisites for a high $\dot{V}O_{2max}$, a key parameter in determining endurance performance success.

With respect to sex-related differences in [Hb] (Fig. 1), no relationship between [Hb] and $\dot{V}O_{2max}$ can be found either in very heterogeneously trained groups (Fig. 2) or within groups characterized by very similar endurance levels (13). For physiological, nonanemic conditions in normoxia, we conclude that the influences of tHb-mass on $\dot{V}O_{2max}$ are greater than that of [Hb]. This conclusion is supported by various studies using plasma volume expansion and reduction demonstrating a closer relationship between $\dot{V}O_{2max}$ and tHb-mass than between $\dot{V}O_{2max}$ and [Hb] or blood volume (15).

The impact of [Hb] on $\dot{V}O_{2max}$, however, gains importance under nonphysiological conditions, such as blood loss. In this case, the quick recovery of blood volume due to plasma volume expansion coincides with a simultaneous decrease in [Hb] and $\dot{V}O_{2max}$ (Fig. 4). The opposite effect is achieved in settings of blood transfusion and strong erythropoiesis due to recombinant human erythropoietin (rhEPO) administration. As indicated in Figure 4, mean data from antidoping studies show a similar relationship between changes in [Hb] and changes in $\dot{V}O_{2max}$, as observed after blood loss.

In both of these nonphysiological conditions, the change in tHb-mass exerts its effects on $\dot{V}O_{2max}$ via a change in O_2 transport capacity, that is, [Hb], whereas cardiac output is only marginally affected (18).

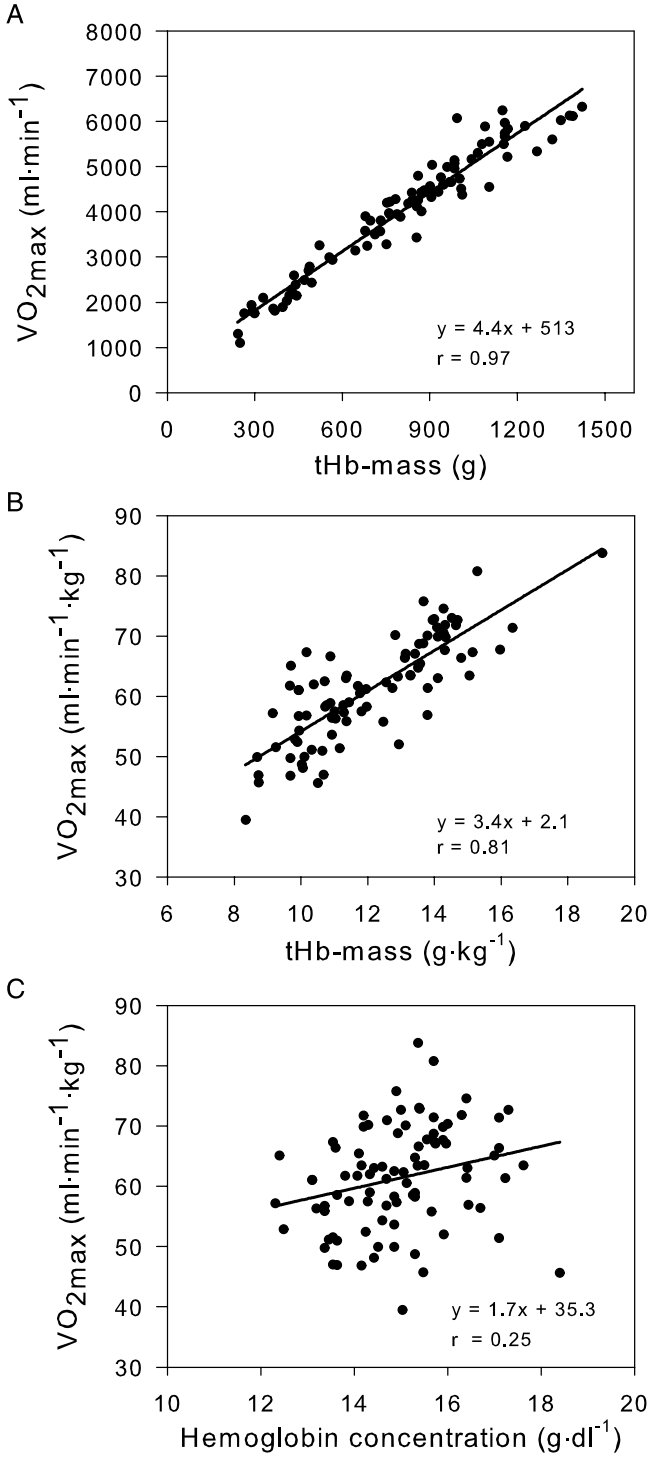

Figure 2. Relationship between absolute maximal oxygen uptake ($\dot{V}O_{2max}$) and absolute total hemoglobin mass (tHb-mass) (A), as well as between normalized $\dot{V}O_{2max}$ and body-mass related tHb-mass (B), and hemoglobin concentration (C) obtained from cross-sectional studies. Presented are data from boys aged 9–14 yr, fit untrained subjects, leisure sport athletes, elite runners, and elite rowers (32).

The slope of the regression line between tHb-mass and $\dot{V}O_{2max}$ in the settings of blood loss and erythropoietic stimulation confirms that the change of 1 g hemoglobin is related to a change in $\dot{V}O_{2max}$ of approximately 4 $mL \cdot min^{-1}$, independent of the mechanism, that is, CO or O_2 transport capacity.

EFFECTS OF TRAINING ON tHb-MASS AND [Hb]

Because elite endurance athletes possess 40%–50% higher tHb-mass, training is assumed to stimulate erythropoiesis. Data from the literature, however, are very inconsistent. Training studies lasting 4–12 wk and referring to methods using markers of red cells or hemoglobin show no increase. Those studies, however, using Evans Blue as a marker of plasma proteins and subsequently calculating red cell mass found increases between 8% and 12% after 3 and 12 wk of training, respectively ((34); for review, see (31)). Because the accuracy of the Evans Blue method for the determination of red cell volume or tHb-mass is by far lower than those methods using markers for red cells or hemoglobin (11), these latter results have to be regarded with caution. In the longest conducted training study in the literature using carbon monoxide as a marker of hemoglobin, we recently observed a 6.4% increase in tHb-mass (+60 g) in moderately trained runners ($\dot{V}O_{2max}$ = 53.1 $mL \cdot min^{-1} \cdot kg^{-1}$), following an intensive 9-month marathon training program ((31); Fig. 5). During this training period, $\dot{V}O_{2max}$ increased by 250 $mL \cdot min^{-1}$, which again confirms the dependency of $\dot{V}O_{2max}$ on tHb-mass by approximately 4 $mL \cdot min^{-1}$ per 1 g hemoglobin. Although tHb-mass significantly increased after the training program, the absolute value (12.5 $g \cdot kg^{-1}$) did not come up to the values reported for elite marathon runners (>14.5 $g \cdot kg^{-1}$; (13)), indicating that maximum tHb-mass levels can only be reached by either years of intensive training or is strongly influenced by genetic parameters. The latter point of view is supported by the identification of high $\dot{V}O_{2max}$ (65.0 $mL \cdot min^{-1} \cdot kg^{-1}$) levels in subjects with high blood volume (92.3 $mL \cdot kg^{-1}$) and tHb-mass (13.8 $g \cdot kg^{-1}$) without any training history (19). The insensitivity of the erythropoietic system to training also is mirrored by the very low oscillations of tHb-mass during a training year (1.8 ± 3.8%), including periods of recovery and high level competitions (24). Therefore, we concluded that training is not a significant factor in altering tHb-mass.

The adaptation of blood to training is not a simple reaction to frequent periods of high oxygen demand in the muscle. In the kidney, where oxygen availability is sensed, arterial oxygen partial pressure is likely not decreased. Exercise-induced reductions in renal perfusion and oxygen supply may be completely compensated by reductions in renal oxygen consumption because of lower sodium reabsorption and a right-shifted oxygen dissociation curve, which improves oxygen supply to the tissue. As a consequence, erythropoietin concentration ([EPO]) remains constant after exercise at different intensities and durations (27).

The small adaptation in tHb-mass to long-term training may be mediated by adjustments in blood volume to a new set point and a slow and only partially occurring recovery of the individual characteristic [Hb] by an increase in tHb-mass (Fig. 6, arrow a). This behavior can be observed in the above-mentioned training study in which tHb-mass increased by 6.4% after 9 months, whereas [Hb] did not completely recover during that time (31). In this case, [Hb] should have

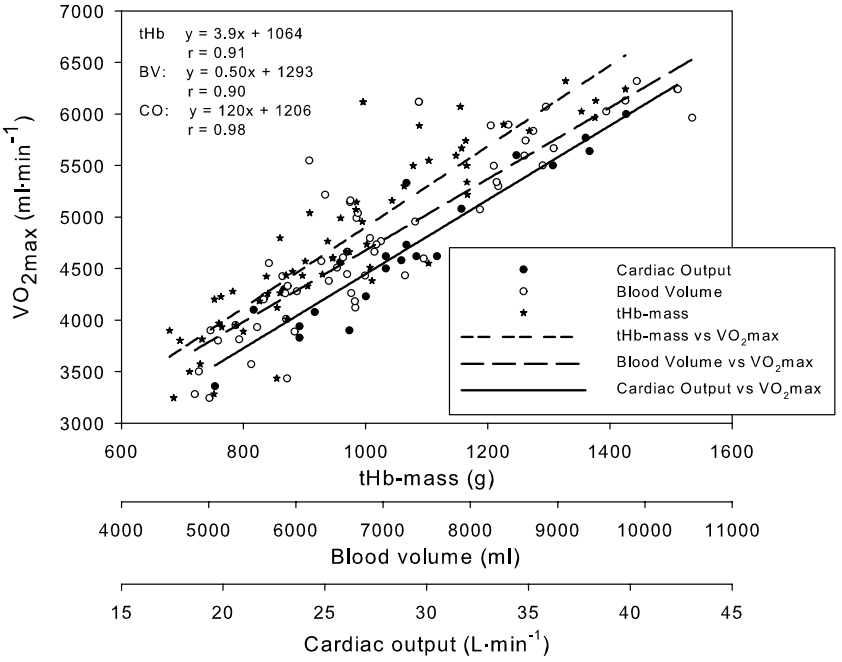

Figure 3. Relationship between maximal oxygen uptake ($\dot{V}O_{2max}$) and total hemoglobin mass (tHb-mass), blood volume (BV), and cardiac output (CO). Data for cardiac output are obtained from (6); data for tHb-mass and BV are obtained from (32).

decreased from 15.2 g·dL^{-1} to 13.8 g·dL^{-1} as a result of plasma volume expansion; however, because of the increased tHb-mass production, [Hb] only dropped to 14.7 g·dL^{-1} (Fig. 5).

Repeated intensive endurance efforts are accompanied by plasma volume overcompensation reaching up to approximately 1000 mL during the Tour de France ((20); Fig. 6, arrow p). Despite a transient overshoot in plasma volume and herewith reduced [Hb], the erythropoietic activity is not increased, and tHb-mass does not change in these situations.

On the other hand, there is evidence from blood withdrawal and blood retransfusion studies that the volume regulating system quickly reconstitutes the normal individual blood

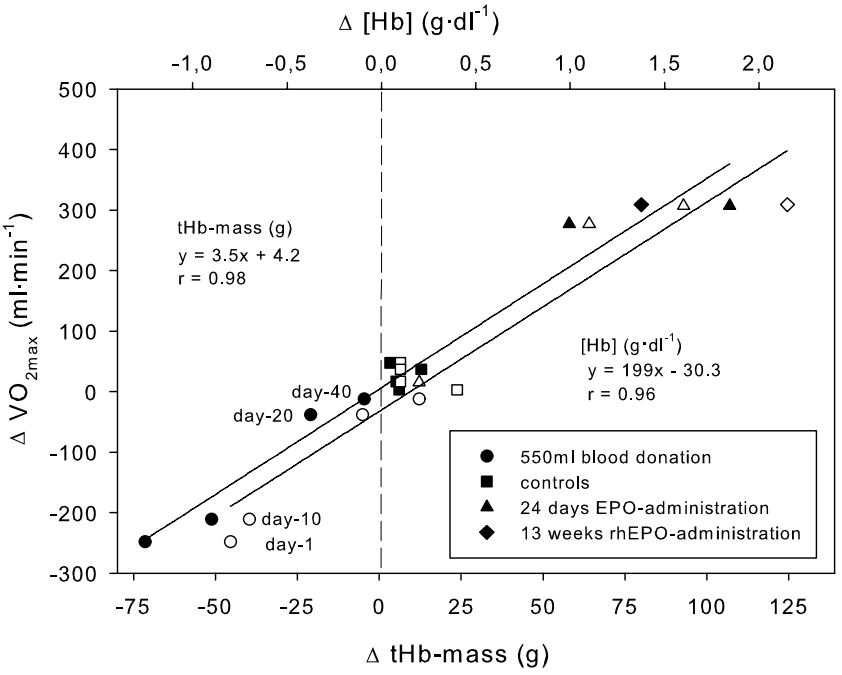

Figure 4. Relationship between changes in maximal oxygen uptake ($\dot{V}O_{2max}$) and total hemoglobin mass (tHb-mass) (*closed symbols*) as well as hemoglobin concentration (*open symbols*). Each point presents the mean values from previous studies (18,21,22). The day after blood donation is indicated in the lower left corner. Initial mean tHb-mass and hemoglobin concentration ([Hb]) was 890 g and 15.2 g·dL^{-1}, respectively, in blood donors (22); 928 g and 15.3 g·dL^{-1} in controls; 840 g/891 g and 14.8 g·dL^{-1}/15.0 g·dL^{-1} before a 24-d lasting recombinant human erythropoietin (rhEPO) administration (two groups); and 960 g and 14.2 g·dL^{-1} before a 13-wk lasting rHEPO administration.

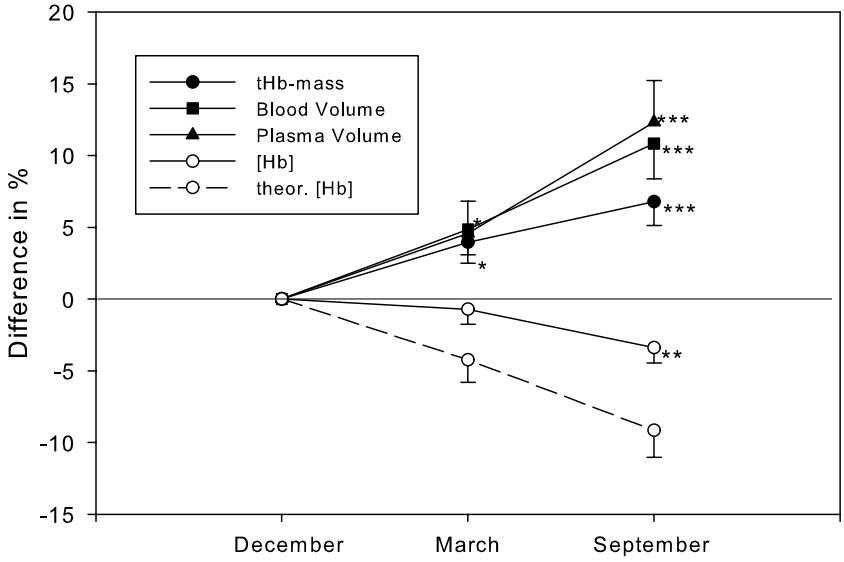

Figure 5. Influence of a 9-month endurance training program in moderately trained subjects on blood volumes, total hemoglobin mass (tHb-mass), and hemoglobin concentration ([Hb]). Presented are percentage differences from the initial values. The *dashed line* indicates the theoretical development of [Hb] if no increase in tHb-mass would have occurred. Data derived from (31).

volume, which is followed by normalization of [Hb]. Blood withdrawal leads to a decrease in [Hb] because of a rapid expansion of plasma volume compensating for the loss of blood volume and a delayed and slow increase in tHb-mass until the original [Hb] is attained again within 30 d ((22); Figs. 4 and 6, arrows b and c). In contrast, in blood transfusion studies, the erythropoietic system is suppressed within 21 d after transfusion, as indicated by a decrease in reticulocyte count, until the individual [Hb] and tHb-mass is restored ((5); Fig. 6, arrows n and o).

We conclude that endurance training is only a small and slow stimulus for the erythropoietic adaptation and is not the main reason for the high endurance performance observed in elite athletes.

The long-term training adaptation seems to be in contrast to the acute exercise-induced hemoconcentration. This hemoconcentration is due to fluid loss from the intravascular space to the intracellular and interstitial spaces as well as a transient red cell expulsion from the spleen (Fig. 6, arrow d). The intended aim of all these mechanisms may be a combined effect of blood volume expansion and hemodilution due to long-term training and an acute hemoconcentration during exercise resulting in both increased blood volume and cardiac output and increased [Hb], that is, elevated O_2-transport capacity. This adaptation process would be equivalent to that of other mammals, for example, horses and dogs. While exercising, these mammals release red cells from the spleen and achieve significantly different hematocrit levels during exercise (~60%) and at rest (~35%) (2). The increased muscle oxygen supply is provided during periods of demand, whereas a low hematocrit, which favors the protection against thrombotic risk factors, occurs at rest.

The magnitude of this mechanism is illustrated by the following example: when [Hb] raises from 15.0 $g \cdot dL^{-1}$ to 16.5 $g \cdot dL^{-1}$ in an athlete with 7500 mL of blood and 1025 g hemoglobin (Fig. 1), an increase in [Hb] up to 0.5 $g \cdot dL^{-1}$ is a result of splenic release (66 g in 200 mL of red cells) and greater than 1.0 $g \cdot dL^{-1}$ is due to the transient loss of 500 mL of plasma volume. The resulting decrease in blood volume (from 7700 mL to 7200 mL) reduces cardiac output by 1.25 L and $\dot{V}O_{2max}$ by approximately 150 $mL \cdot min^{-1}$; on the other hand, the increase in [Hb] augments $\dot{V}O_{2max}$ by approximately 300 $mL \cdot min^{-1}$ and compensates for the lower cardiac output.

In conclusion, the combined effect of long-term training and acute exercise promotes high cardiac output due to a chronically increased blood volume and elevated [Hb] due to an acute reduction of plasma volume.

EFFECTS OF ALTITUDE ON tHb-MASS AND [Hb]

The regulation processes of tHb-mass and [Hb] at altitude are completely different to those occurring during endurance training at sea level. When commuting from lowlands to altitude, [Hb] increases to maintain an adequate $avDO_2$. This adjustment is achieved by a reduction in plasma volume occurring within hours to a few days (Fig. 6, arrow e). Within the following weeks to months at altitude, plasma volume remains low, whereas tHb-mass increases until the initial blood volume is achieved ((12); Fig. 6, arrow f). The end stage of this adaptation process can be observed in natives of the Andes ((12); Fig. 6, arrow g), who display high tHb-mass, low plasma volume, and elevated [Hb]. The magnitude of the increase in tHb-mass and [Hb] is related to the prevailing altitude. For example, the tHb-mass and [Hb] are 11% and 2.3 $g \cdot dL^{-1}$ higher at 2600 m and 14% and 3.1 $g \cdot dL^{-1}$ at 3500 m compared with lowlanders, respectively (3,12).

Interestingly, altitude populations with a long adaptation history (*i.e.*, at least 20,000 yr in Tibetans and East Africans in comparison to less than 5000 yr in the Andeans) are characterized by a similar [Hb] as populations from lowlands (1), indicating different adaptation processes (Fig. 6, arrow h).

The erythropoietic stimulation at altitude also differs from that during training. Although no change in plasma [EPO] occurs after exercise or during training periods (27), [EPO]

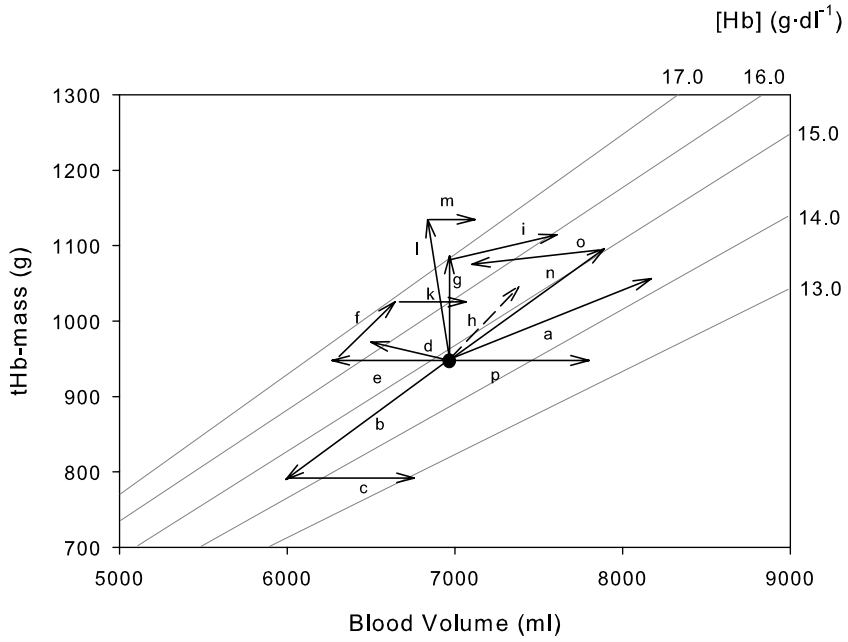

Figure 6. Schematic presentation of changes in total hemoglobin mass (tHb-mass), hemoglobin concentration ([Hb]), and blood volume under various conditions: *a* = adaptation to endurance training at sea level, *b* = acute blood loss, *c* = acute compensation of blood loss, *d* = acute exercise including red blood cell release from the spleen, *e* = acute altitude exposure, *f* = several weeks of altitude adaptation, *g* = native to altitude (Andes), *h* = possible adaptation of Tibetans and East Africans, *i* = endurance athlete native to altitude, *k* = return from altitude, *l* = manipulation with EPO, *m* = combined effect of EPO administration and training, *n* = acute effect of blood transfusion, *o* = effect of blood transfusion after several days, and *p* = plasma volume expansion during stage races.

increases transiently for some days after ascent to altitude because of the lower blood oxygen saturation in the kidney (8). After several days at altitude, [EPO] decreases and reaches a constant level slightly above the initial baseline.

EFFECTS OF TRAINING AT ALTITUDE (HYPOXIA) ON tHb-MASS AND [Hb]

Recent research efforts in the area of altitude training and endurance performance have focused on the concept of "live high–train low" (17,10). Basing from a critical evaluation of the literature, we concluded that those altitude training studies, which were performed for at least 3 wk at altitudes above 2100 m, but with less than 14 h of hypoxia per day, did not show any increases in tHb-mass. In contrast, the studies in which the subjects were exposed to similar hypoxic conditions for at least 14 h·day^{-1} reported increases in tHb-mass of approximately 6% (Fig. 6, arrow f). This magnitude is comparable to the effects achieved when performing conventional altitude training (Fig. 7; (31)).

The maximum tHb-mass ever determined in endurance athletes is derived from cyclists native to altitude living and training at 2600 m. They combine training and hypoxia-induced stimuli (Fig. 6, arrows g and i) and possess approximately 70% more hemoglobin than sedentary subjects from sea level. However, in these athletes, [Hb] concentration is lower compared with that in untrained subjects from the same altitude reflecting blood volume expansion, similar to what occurs at sea level (29).

In many of the altitude training studies conducted above 2000 m, positive effects on $\dot{V}O_{2max}$ and performance at sea level were demonstrated (for review, see (7)). The $\dot{V}O_{2max}$ response to altitude, however, was rather individual, and no clear relationship was observed between tHb-mass and $\dot{V}O_{2max}$. The mechanisms leading to this benefit several days or weeks after return to sea level have not been clarified. It has not been determined whether increased [Hb] due to elevated tHb-mass or an increased blood volume due to plasma volume expansion after return from altitude exert more influence on $\dot{V}O_{2max}$ (Fig. 6, arrows f or k).

While at sea level, an increase in tHb-mass is accompanied by improved $\dot{V}O_{2max}$, this relationship is not present at altitude. Despite 11% higher tHb-mass after 6 months of intermittent acclimatization to 3500 m, no difference in $\dot{V}O_{2max}$ could be observed compared with the matched controls at similar altitude (23). Also, infusion of 700 mL red cells in saline (~100 g hemoglobin) during acute exposure to 4300 m did not prevent the reduction in $\dot{V}O_{2max}$ (−26%), which was identical to the drop in a nontreated control group (35). These data are in accordance with calculations of Wagner (33) demonstrating that muscle and lung diffusion capacity as well as ventilation but not cardiac output and [Hb] are the limiting factors at higher altitudes.

EFFECTS OF DOPING ON tHb-MASS AND [Hb]

The magnitude of blood doping expressed as a change in tHb-mass occurring in competing elite athletes has never been published. Controlled antidoping studies investigating the effects of rhEPO and obvious cases of blood doping show increases in tHb-mass of approximately 10%. The total blood volume is not affected by rhEPO administration (18,21) and only slightly elevated by the combined effect of rhEPO administration and training ((28); Fig. 6, arrows l

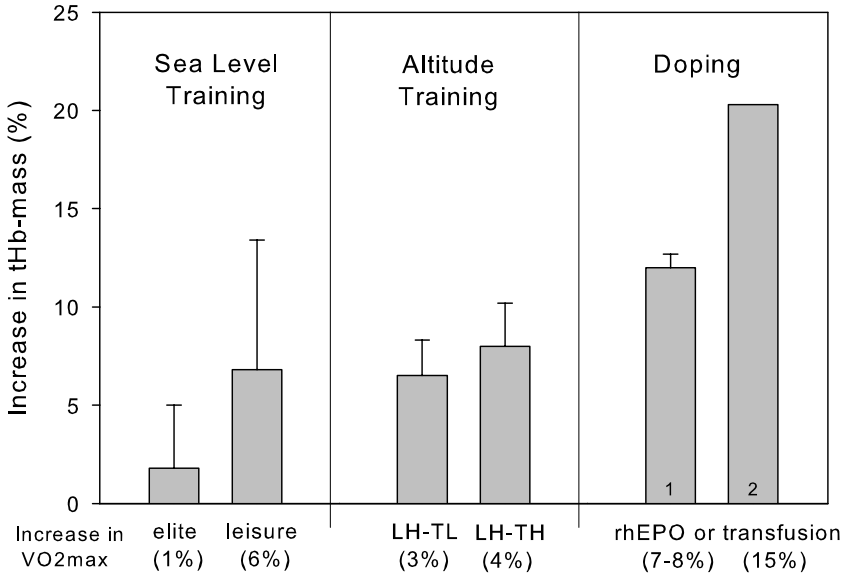

Figure 7. Effects of training in elite and leisure athletes as well as effects of altitude training (live high–train low (LH-TL) and live high–train high (LH-TH) protocols) and doping on total hemoglobin mass (tHb-mass). The columns in the section *doping* represent blood manipulation without (*column 1*) and with previous hemodilution (*column 2*). The corresponding maximal oxygen uptake ($\dot{V}O_{2max}$) is indicated in parentheses. rhEPO = recombinant human erythropoietin. Data from (28,31,17,21).

and m). The positive impact on $\dot{V}O_{2max}$ can therefore be attributed to an increase in [Hb] and not to an increased cardiac output (18).

In the mid-1990s, hematocrit values frequently oscillated by more than 10% during cycling seasons. Using published data from the internet of cyclists from the Gewiss-Ballan team from December 1994 and May 1995 (hematocrit (Hct) increased from 41.1 ± 2.4% to 53.7 ± 3.8%) and assuming that they have a mean blood volume of 7574 mL (nonmanipulated state as shown for elite cyclists (28)), tHb-mass increased by approximately 285 g, which corresponds to a hemoglobin content of 4 blood bags. After the introduction of cutoff limits (*e.g.*, Hct 50% in cycling, [Hb] 17.0 $g \cdot dL^{-1}$ in cross-country skiing), excessively high values disappeared, but mean [Hb] of the athletes increased. In a study conducted in 1999, we showed that more than 50% of the riders from a professional cycling team increased their tHb-mass by more than 100 g (28) during one season, which cannot represent a physiological adaptation to training (24). From antidoping studies, it is known that such an increase can be obtained only by a 24-d administration period of rhEPO (21). After introducing the rhEPO detection method, many athletes switched to autologous blood transfusions, which allows for similar changes in tHb-mass as obtained by rhEPO administration.

Despite the introduction of cutoff limits, the magnitude of blood manipulations is considerable. Assuming a hematocrit of 44% in the nonmanipulated state (corresponding to a [Hb] of 14.5 $g \cdot dL^{-1}$), a blood volume of 7500 mL, and a tHb-mass of 990 g, the critical Hct of 50% ([Hb] of ~16.5 $g \cdot dL^{-1}$) is reached after the administration of 136 g hemoglobin, that is, the hemoglobin content of two blood bags (Fig. 6, arrows n and o). More extreme forms of manipulation are possible during stage races because plasma volume overcompensation in the range of 1000 mL (see section "Effects of Training on tHb-mass and [Hb]") reduces [Hb] and Hct values and herewith increases the scope of action (Fig. 6, arrow p).

Changes in tHb-mass due to blood doping are not uniformly reflected by changes in [Hb]. The impact of tHb-mass expansion exerts higher [Hb] in athletes with low blood volumes compared with those with higher volumes. For instance, when transfusing 120 g of hemoglobin to a small female athlete with 4 L of blood, [Hb] increases by 3.3 $g \cdot dL^{-1}$ (*e.g.*, from 14.0 to 17.3 $g \cdot dL^{-1}$). When transfusing the same amount of hemoglobin to a tall male athlete with a blood volume of 9 L, [Hb] increases only 1.5 $g \cdot dL^{-1}$ (*e.g.*, from 15.0 to 16.5 $g \cdot dL^{-1}$). In both cases, however, the increase of 120 g augments $\dot{V}O_{2max}$ by approximately 400 $mL \cdot min^{-1}$ (Fig. 4). This magnitude of improved performance has been observed after 24 days of rhEPO administration (21). When extrapolating this relationship between $\dot{V}O_{2max}$ and tHb-mass, we calculate a benefit in $\dot{V}O_{2max}$ of up to 1000 $mL \cdot min^{-1}$ for the times before the cutoff limits (Hct 50%) were introduced and of up to 860 $mL \cdot min^{-1}$ in riders with hematocrit values close to 50% at the end of a 3-wk stage race.

CONCLUSIONS

tHb-mass determines $\dot{V}O_{2max}$ via two different mechanisms. $\dot{V}O_{2max}$ can be increased by the following: (i) a balanced increase of tHb-mass and plasma volume augmenting cardiac output and/or (ii) by increasing [Hb] due to an increase of tHb-mass accompanied by a reduced or unchanged plasma volume augmenting $avDO_2$. Mechanism (i) is achieved by endurance training; mechanism (ii), by adaptation to altitude or blood manipulation. A combination of both mechanisms is present in athletes training and living at altitude and also, but to a lesser extent, in endurance athletes from sea level during acute exercise. However, the highest impact on $\dot{V}O_{2max}$ is

obtained when athletes increase [Hb] by blood manipulation (Fig. 7). A change in tHb-mass by 1 g causes a change in $\dot{V}O_{2max}$ by approximately 4 $mL \cdot min^{-1}$.

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