The Hematocrit Paradox – How Does Blood Doping Really Work?

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Abstract

The wide-spread assumption that doping with erythropoietin or blood transfusion is only effective by increasing arterial blood O_2 content because of rising hematocrit is not self-evident. "Natural blood dopers" (horses, dogs) increase both hematocrit and circulating blood volume during exercise by releasing stored erythrocytes from the spleen. Improvement of aerobic performance by augmenting hemoglobin concentration may be expected until the optimal hematocrit is reached; above this value maximal cardiac output declines due to the steep increase of blood viscosity. Therefore an enlarged blood oxygen content might only be useful if the normal hematocrit of man during exercise is suboptimal. However, recent studies suggest that cardiac power rises after erythropoietin allowing an unchanged cardiac output in spite of increased viscosity. Other factors underlying improved performance after blood doping might be: augmented diffusion capacity for oxygen in lungs and tissues, increased percentage of young red cells with good functional properties (after erythropoietin), increased buffer capacity, increase of blood volume, vasoconstriction, reduced damage by radicals, mood improvement by cerebral effects of erythropoietin. Also the importance of placebo is unknown since double-blind studies are rare. It is suggested that blood doping has multifactorial effects not restricted to the increase in arterial oxygen content.

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Introduction

It is a widespread assumption (e.g. [22,33]) that blood doping augments peak oxygen uptake entirely by enhancing the oxygen transport capacity of blood through an increase of hemoglobin concentration ([Hb]) or hematocrit (Hct) value. In support for this concept are results of various studies investigating blood doping effects (blood infusion or erythropoietin application). These investigations show improvements of $\dot{V}O_2$ peak apparently without increases in blood volume and at least partly reversible after isovolemic hemodilution [15,23,33,34,48].

Apparently this contrasts to a variety of observations which led to the formulation of "a paradox of hematocrit in exercise physiology" (13):

1. Endurance training with increase in $\dot{V}O_2$ peak leads to a small reduction of [Hb], since the red cell volume increases, but less than the plasma volume (training hemodilution, e.g. [24,36,52]). Also for competitions lasting between some hours and several days a decrease in [Hb] and Hct [51,55] has been reported. In contrast overtraining is accompanied by a rise of [Hb] (e.g. [13]). Why is there no increase in the concentration of Hb as reaction to chronic exercise? Neither a lack of iron nor of proteins is likely in most athletes due to the large intake of nutrients and frequent use of dietary supplements. A small decrease in ferritin concentration at constant soluble transferrin receptor concentration [45] might result from incorporation of iron into the augmented Hb mass and from the increase of plasma volume (approximately by 15%).
2. Generally a correlation between [Hb] and $\dot{V}O_2$ peak for untrained as well as endurance-trained subjects is lacking or weak in cross-sectional studies (e.g. [8,13,24]). Only if confounding additional effects of training are excluded by considering nonathletes and athletes separately an increase of 0.3% in $\dot{V}O_2$ peak for 1% (relative) rise in Hct can be estimated in females [8]. Wagner [61] has theoretically deduced an even smaller change: according to

his calculations a 20% rise in [Hb] causes only a 2.9% increase in $\dot{V}O_2$ peak. Also success in endurance competition is not principally correlated with [Hb] concentration [31]. The correlations with total Hb mass and especially blood volume, however, are significant [8,29,47]; an increase of 1% in these quantities is accompanied by a 1% rise in $\dot{V}O_2$ peak [7,53].

3. The decrease of $\dot{V}O_2$ peak upon phlebotomy is essentially reversible after 1–2 weeks in spite of still lowered [Hb] most likely by a compensatory rise of plasma volume [15,38,39].
4. A rapid fall in [Hb] is a regular phenomenon after return from altitude training to sea level (rev in [7]). Also in Kenyan runners [Hb] decreased to values typical for lowlanders within the first week after descent [4,40]. The main cause is hemodilution by an increase of plasma volume [9,40]. Therefore suggested improvements of performance capacity after descent during normoxia cannot be caused by a high [Hb]. In a recent review Gore et al. [26] also question the importance of [Hb] changes for increases in sea-level performance after hypoxic exposure.

To clarify these puzzling differences it might be helpful to compare "natural blood doping" in athletic animals, to discern differences in oxygen transport and to analyse additional mechanisms influencing performance after doping.

"Natural Blood Doping" in Athletic Animals

In excellent runners like horses and dogs ($\dot{V}O_2$ peak approximately 140 ml·kg^{-1}·min^{-1}) resting hct values tend to be lower than in man (33% in horses, 40% in many dogs); during exercise hct may rise to more than 60% by expelling stored red cells from the spleen [1,65]). Hsia et al. [30] suggest that this "reversible autologous blood transfusion" increases $\dot{V}O_2$ peak by 13–30% in highly athletic species.

In contrast the small exercise induced hct increase in man by maximally 5% results mainly from hemoconcentration by water shift to the muscles; no more than 50 ml red cells (2–3% of the total volume) might be supplied to the active circulation by spleen contraction [38].

Interestingly in athletic animals with a storing spleen not only circulating cell mass but also blood volume increases during exercise [30]. If the hematocrit rises during exercise from 40 to 60%, a blood volume increase by 25% can be calculated considering accompanying water losses to tissues (about 10%).

Thus, the question is justified whether it makes sense to increase only the hct value for improvement of oxygen transport considering the rising viscosity. The concept of the optimal hct predicts that the maximum of oxygen delivery (cardiac output times arterial O_2 content) to the tissues is reached before the steep rise of in vitro viscosity at approximately 50% hct [37] beyond which the increasing viscosity limits blood flow.

In dogs and horses small erythrocytes (down to less than 40 fl) reduce flow resistance in small vessels. In addition equine red cells are very flexible [2]. Interestingly the optimal hct for dog muscle perfusion increases during exercise [25] (**Fig. 1**), probably by augmenting the vascular diameter; also hypervolemia causes a rise of optimal hct at least at rest [19]. One might speculate that hct levels of 60% and higher in exhausted horses correspond to their optimal in vivo hct at maximal cardiac performance.

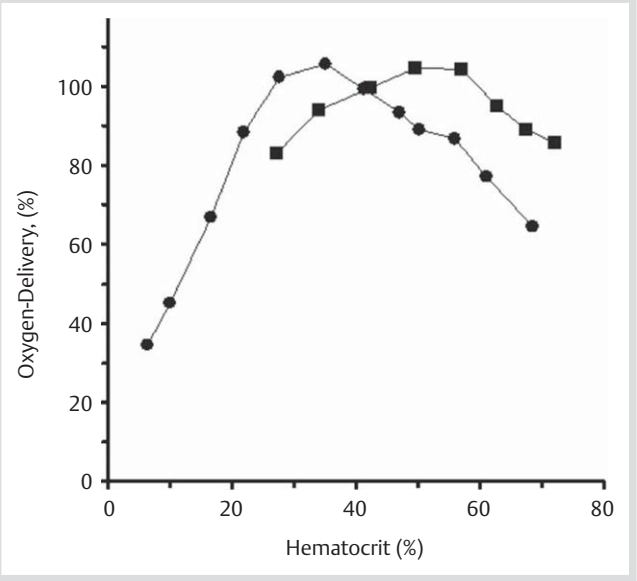

Fig. 1 Oxygen-delivery in dependence on hematocrit value for resting (filled circles) and working (filled squares) dog muscle at constant perfusion pressure (100 mmHg). O_2-delivery at 40% hct is considered as 100%. Modified from [25], Fig. 7 with kind permission from Springer Science + Business Media.

Blood Doping in Man and Mice – Optimal Hematocrit and Cardiac Power

Because of his larger red cells optimal hct should be lower in man than in dogs and horses. Robertson et al. [43,44] estimate from results of retransfusion experiments that it ranges somewhere between 43.3 and 54.8% in males (resting values), corresponding values for females are 38 and 45%. Strangely, the limits of 50% prescribed by some sport organisations might have the effect that dopers even better hit the optimal hct.

It is interesting to speculate why humans did not develop a large spleen with high storage capacity. Perhaps the corresponding genetic mechanisms were lost by non-running ancestors living on trees. The alternative option for running hunters to select high resting hcts is dangerous (thrombosis, high blood pressure, e.g. [56]) and might thus have generated a negative selection pressure during evolution. Therefore it is conceivable that the hct in humans is suboptimal for exercise. This hypothesis has already been discussed some decades ago in connection with reinfusion of own blood (e.g. [43]).

Until recently the optimal hct during exercise has only been measured in dogs and under artificial conditions. Blood was supplied to submaximally working muscles with constant perfusion pressure from a transfusion bag, not by the heart [25]. For the first time the optimal hct during exercise in the whole organism has been investigated by Schuler et al. [54]. In mice doped with Epo the value amounted to 58% at $\dot{V}O_2$ peak. However, this value results from at least 3 factors. In addition to the changes in hct, blood volume and the rate pressure product (an estimate of the heart power) rose, thus the effect of an isolated hct increase remains to be determined.

At a first glance a change of the heart function after Epo is surprising. One might suggest that at exhaustion the heart is working to its limit because it reaches similar maximal heart rates under different conditions. However, in his review Ekblom [22] mentions that Epo causes an increase in arterial blood pressure

Table 1 Relevant circulatory variables during maximal aerobic exercise before Epo, after Epo and after subsequent hemodilution (HD) with artificial plasma published in [33].

Epo	Before	After	HD
[Hb] (g l^{-1})	14.7 ± 0.4	16.4 ± 0.4*	14.8 ± 0.4
$\dot{V}O_2$ (l min^{-1})	3.95 ± 0.16	4.26 ± 0.18*	4.06 ± 0.16
cardiac output (l min^{-1})	25.0 ± 1.0	25.2 ± 1.2	26.8 ± 1.1*
heart rate (min^{-1})	177 ± 6	180 ± 3	181 ± 3
systolic pressure (mmHg)	119 ± 5	139 ± 11*	117 ± 11
rate-pressure product (mmHg min^{-1})	21 145 ± 1 193	25 027 ± 1 916*	21 157 ± 2 157
calculated cardiac power (W)	6.67	7.81	6.94

Values are means and standard deviations. * Significant difference to Before. Cardiac power in watts was calculated from the means by multiplying the rate pressure product with stroke volume and inserting the respective units [10], therefore standard deviations and significance levels cannot be given

during exercise in contrast to blood infusion. Also in Lundby's et al. [33] doping experiments in humans, blood pressure but not heart rate at $\dot{V}O_2$ peak was increased after Epo: The heart delivered a markedly higher mechanical power (+18%) estimated from the rate pressure product as well as calculated from stroke volume, systolic pressure and heart rate [10] at equal cardiac output as before Epo (**Table 1**). The latter product seems to be an adequate measure of mechanical power, since the systolic pressure – volume area is the sum of positive and negative work of the heart and linearly correlated to its $\dot{V}O_2$ [3]. In contrast to Epo, red cell reinfusion in women (probably without a rise in blood volume) did not increase cardiac power but improved aerobic performance [43].

Unfortunately one has to doubt how far the interesting new findings on cardial effects of Epo [33,54] are fully reliable in a quantitative aspect. In man mean maximal systolic pressures during exercise between 120 and 140 mmHg communicated by Lundby et al. [33] are improbably low; therefore one might speculate on a calibrating error in their experiments. In mice the maximal heart rates (160 beats per min compared to 514 beats per min at rest) and even more the rate pressure products published in ref. 54 are much too low; according to the authors this was caused by mislabelling which will be corrected (personal communication M. Gassmann).

If the cardiac effects are real, what might be the underlying mechanism? Possibly the heart does not work at its utmost limit without doping because of unknown reasons; interestingly plasma noradrenalin concentration doubled after Epo in humans [33]. After hemodilution following Epo application cardiac output increased markedly (concomitantly with an additional noradrenalin rise) but not sufficiently to compensate for the reduced arterial O_2 content [33]. Perhaps stroke volume could not be further increased because of mechanical restriction of diastolic filling; such a possibility has been discussed recently in another context [21,32]. Based on these results one might suggest that cardiac stimulation is an important component of Epo doping.

The optimal hct might also be increased by an elevated fraction of young flexible red cells shortly after Epo application (e.g. [60]). However, in a recent Epo-doping study in humans no changes were detected in erythrocyte elongation at physiological shear rates [34]. In the case of autologous blood infusion the observed effects depend on the time schedule of application after blood storage: while the conserved red cells age continuously, regeneration in vivo produces a lot of young erythrocytes.

Additional Effects of Blood Doping

There remains a series of possibly also important physiological effects of Epo or blood transfusion. A systematic search reveals the following influential mechanisms.

Gas transport

1. The diffusion capacity for O_2 in the lungs as well as in consuming tissues increases with rising hct (e.g. [49,65]) because of the enlarged red cell surface area. This might also reduce exercise-induced arterial hypoxemia [20] which is especially marked in endurance-trained subjects.
2. The rising proportion of young erythrocytes [41] after Epo application optimizes in addition to deformability various functional properties (enzyme activities, buffer capacity, low oxygen affinity increasing capillary PO_2, (e.g. [50]); after terminating Epo injection, however, the properties rapidly deteriorate.
3. The amount of extracellular non-bicarbonate buffers increases with rising Hb mass [11].

Circulatory functions

4. An increase in red cell volume might increase the blood volume thus improving the filling of vessels and especially of the heart and producing ergogenic effects at least in untrained subjects [62]. However, this seems to be compensated by a corresponding decrease in plasma volume after Epo ([22,34]; after retransfusion slightly but not significantly increased blood volumes occasionally have been observed in males [14,57] but not in females [43]. In genetically modified mice, Epo causes a rise in blood volume since the plasma volume is not reduced [54]. If a volume effect exists, it might depend on the time lag until competition after doping (especially by blood transfusion), since the down-regulation of plasma volume by renal mechanisms needs approximately 24 h (cf. [44]). A drawback of all cited studies is that plasma volume was not measured but calculated from red cell or transfused volume and [Hb] or hct; if the ratio whole body hct/venous hct has changed, plasma volumes are not correct [59].
5. Epo causes constriction in renal and mesenteric resistance vessels [28] which might shift blood flow to other parts of the circulatory system. Also Hb influences the diameter of the vessels by binding or liberating NO or nitrite ([18]) depending on saturation (reviewed in [15]). Over extended periods Epo facilitates growing of vessels by mobilising endothelial precursor cells in bone marrow [27].
6. Epo protects erythrocytes against radicals (via binding of iron? [17]).

Miscellaneous effects

7. Epo induces a shift of muscle phenotype from fast glycolytic to slow oxidative in rats [16]. It improves force in hemodialysis patients [42] and regeneration after trauma in rat muscles [46].
8. Epo defends the brain against hypoxia, additionally it improves mood and thus probably engagement [35]. Therefore similar effects as with amphetamines or other stimulants are conceivable.

9. Finally the placebo effect has to be taken into account [5]. Astonishingly we could find only few true double-blind investigations on ergogenic effects of blood transfusion (e.g. [12,14,57,64], 33 subjects) and Epo (e.g. [6,63], 18 verum vs. 17 placebo subjects). The average rise in $\dot{V}O_2$ peak by 7% after Epo in these investigations was not significantly lower than in most not-blinded studies. However, in a study, where only the controls were blinded, the non-blinded doped subjects reached 12% higher $\dot{V}O_2$ peak [58]. It is also conceivable that placebo as well as mood improvement play a more important role for the duration of performance until exhaustion since submaximal endurance is percentually much more increased by blood doping than $\dot{V}O_2$ peak: 26% (single-blinded) after autologous red cell transfusion [44], 54% (not blinded) after Epo [58].

Conclusions

Considering this diversity of effects it remains unclear, how much of the improvement in $\dot{V}O_2$ peak of 5–10% found in most studies on blood doping can be ascribed to a single factor. In any case the augmented oxygen content of arterial blood seems not to be the sole cause for ergogenic effects of blood transfusion and Epo. In the apparent effect of hct increases, the rise of oxygen capacity of blood and at least the additional factors described under gas transport (diffusion capacity, red cell properties, buffer capacity) act together and cannot be discerned. Various circulatory functions also seem to be involved in the optimized oxygen transport. Possibly mood changes and rise of cardiac power are linked by a stimulation of the sympathetic nervous system exhausting the ultimate reserves of the organism – the classical doping mechanism. Finally, there is a probable explanation of the hematocrit paradox: for evolution survival of the fittest in health (low hct) is more important than survival of the fittest in short-lasting competitions (high hct).

Note added in proof: The authors of Ref. 54 have communicated that the heart rate at maximal oxygen uptake was 700–800 beats per minute in mice. Insertion of these values into the regression equations added to Fig. 5 of Ref. 54 yields plausible values for the rate pressure product.

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