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**EPO or PlacEPO? Science versus Practical Experience Panel
discussion on efficacy of erythropoetin in improving performance**

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EPO or PlacEPO? Science versus practical experience

Panel Discussion

Organized by Max Hardeman and Oguz K. Baskurt at the 17th Conference of the European Society for Clinical Hemorheology and Microcirculation, Pecs, Hungary

Max Hardeman¹, Tamas Alexy², Bram Brouwer³, Philippe Connes⁴, Friedrich Jung⁵, Harm Kuipers⁶,
Oguz K. Baskurt⁷

¹Academic Medical Center, University of Amsterdam, The Netherlands

²Emory University, School of Medicine, Atlanta, GA, USA

³Open University, Amsterdam, The Netherlands

⁴UMR Inserm 1134, Point a Pitre, Guadeloupe, France

⁵Institute of Biomaterial Science and Berlin-Brandenburg Centre for Regenerative Therapies, Teltow, Germany

⁶University of Maastricht, The Netherlands

⁷Koç University School of Medicine, Istanbul, Turkey

Corresponding Author

Dr. Max Hardeman
Academic Medical Center
University of Amsterdam
The Netherlands

Introduction

Do we have evidence that erythropoietin (EPO) administration to healthy individuals improves physical performance? There has been ample publicity recently in Newspapers and radio/television programs, especially in view of the infamous Lance Armstrong doping case, stating that the positive effect of EPO administration on physical performance is primarily due to the concomitant increase in hematocrit (hct) value. The general opinion of endurance sport athletes and anti-doping agencies seems to mirror this statement: higher hct means that a higher number of erythrocytes are available to bind oxygen, thereby improving oxygen delivery and physical performance.

From a hemorheological point of view, however, it should be emphasized that a linear increase in hct leads to an exponential increase in blood viscosity. Since elevated viscosity hinders the transport of oxygen-saturated red blood cells (RBC) to tissues, the shear rate dependent hct to blood viscosity ratio (HVR) should be a better parameter to estimate the effect of EPO administration on oxygen delivery and physical performance. Conflicting the athlete's general opinion, testing the HVR concept in laboratory experiments showed that the effect of EPO on oxygen delivery, even at high shear rates, is merely minimal suggesting a primarily placebo effect on endurance. How this scientific view can co-exist with the practical experience of EPO use in competitive sport was the subject of this Panel Discussion. Expanding the scope of the discussion, two contributors from disciplines other than hemorheology (i.e., sport science and sport psychology), also participated. Unfortunately, it was not possible to have an EPO user, i.e., an athlete who admittedly used EPO for performance enhancement purposes, present to share personal experience.

Max Hardeman: Limits to human performance; is there still room for improvement?

The study discussed initially was performed by Harm Kuipers from the Department of Kinesiology, University of Maastricht, The Netherlands and entitled: "Limits to human performance; is there still room for improvement?". Kuipers won the title of World Champion in speed skating in 1975 and subsequently became a professor of Kinesiology and a doping expert. The basic question he posed was "Why is the performance of current athletes better than that of former athletes?" Objective testing shows that athletes in general have a maximal power output similar to that 20-30 years ago, suggesting that there has been no significant gain in muscle strength. Therefore, the improved performance in competitive sport, e.g., cycling, has to be explained by other factors, such as better-quality sporting materials, enhanced training facilities, introduction of fluid nutrition (enabling cyclists to maintain energy balance and continuously improved aerodynamics).

Does doping has a significant role in the observed improvement in cycling performance? The true contribution of doping is generally overestimated and no form of doping can compensate for the lack of talent and rigorous training. EPO has been shown to improve maximal power output by 3-5%, however the day-to-day variation in an athlete's performance may also reach 3-6%¹. The reason why EPO is commonly used as a doping agent is that it increases serum hemoglobin (hgb) thereby improving the maximal aerobic capacity (VO₂ max). Although some papers claim that the Rate of Perceived Exertion (RPE) is also changed with EPO, this was not confirmed in well-controlled, double blind studies. Therefore, the question remains whether a higher hgb level is indeed associated with improved sporting performance. We have mapped hgb versus ranking of the top 217 male speedskaters during the 2006 Olympic season and found no association². The same was also true for

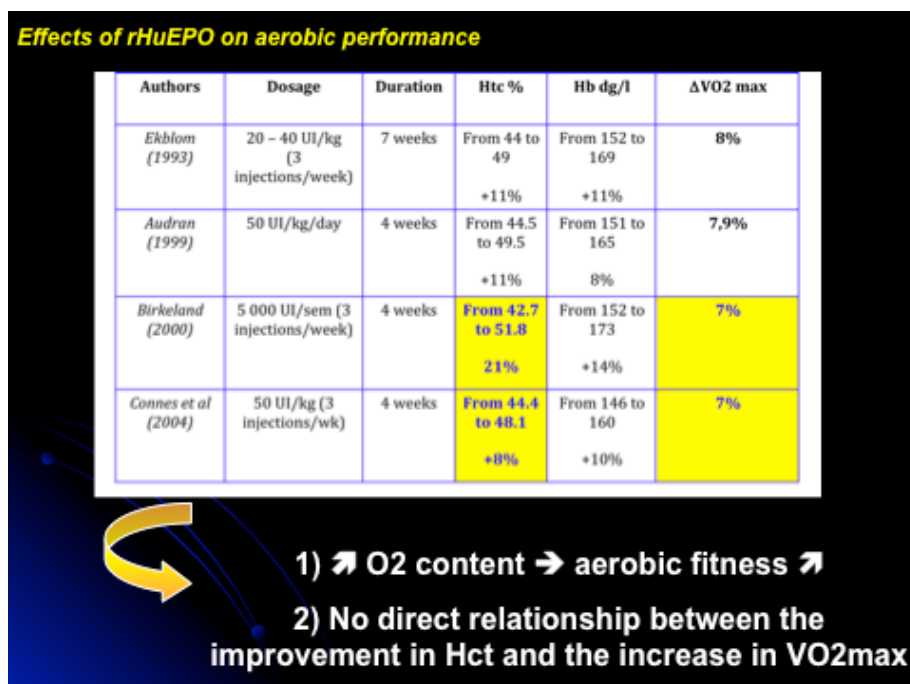
the top 200 female speedskaters concluding that the relationship between serum hgb level and skating performance was not associated. Laboratory studies indicate that there is a balance between blood oxygen carrying capacity and capillary flow. Model calculations estimate such optimum to be at around 45% hct in humans but further studies are ongoing.

There is a lot of myth and paranoia in sports regarding the effect of doping on physical performance. Not every physician working with top athletes is a true expert. Pseudo experts, like Fuentes, keep the myth alive that completing the Tour de France, Vuelta or Giro is essentially impossible without the use of performance enhancing agents. Finally the question why some athletes turn to performance enhancing agents also needs to be addressed. Their hypothesis is that doping will improve their ranking and that they are not competitive enough without its use assuming that others are doping as well. Pseudo experts reinforce this belief. Winning a race is sometimes more important than the doping-associated long term health risks, primarily due to the mental pressure and expectations of the media, coach, sponsors and public. Most athletes lack knowledge about the adverse health effects of doping; their information is mostly biased and is provided by relatives, friends, teammates and pseudo experts.

Philippe Connes: How recombinant human erythropoietin (rHuEPO) administration increases exercise performance?

While recombinant human erythropoietin (rHuEPO) was introduced in patients with renal failure with the aim to correct anemia, several studies reported an improvement in quality of life and physical fitness in this population. The latter finding inspired athletes of endurance sports to turn to rHuEPO with the goal to improve performance. VO_{2max} increases 7-8% after few weeks of rHuEPO injections. Also, a faster adaptation of aerobic metabolism was documented during submaximal exercise. However, there is no clear association between the hct increase and VO_{2max} improvement with rHuEPO supplementation (Figure 1).

Figure 1: Effect of rHuEPO injections on hct, hgb level and VO_{2max} .



The lack of association between hematological changes and VO_{2max} with rHuEPO treatment suggests that the benefits of higher hct on blood oxygen carrying capacity could partially be blunted by the exponentially rising blood viscosity that increases resistance to flow. Literature data suggests the existence of an optimum hct to blood viscosity ratio that enables the most oxygen to be delivered to tissues, hence allowing more strenuous aerobic physical performance³. In addition, the recent discovery of EPO receptors in human skeletal muscles may explain the enhanced muscle mitochondrial phosphorylation capacity described in humans after 8 weeks of rHuEPO injections, and could contribute to the performance improvement. Other studies using animal models also demonstrated that rHuEPO treatment may cause changes in tissue metabolic regulation that is beneficial during exercise. For example, EPO over-expression in EPO transfected obese mice decreases body weight, adipose tissue mass and insulin level. It causes an up-regulation of genes involved in lipid metabolism while down-regulating others responsible for glucose metabolism⁴. Whether these effects are the same in humans is currently unknown but unpublished data by Caillaud et al. suggests that 4 weeks of rHuEPO injections lead to certain metabolic changes during exercise with athletes consuming less glucose and more lipids at a target endurance level. Finally, several studies reported an increased activity and expression of the monocarboxylate transporter on the RBC membrane and a faster regulation of lactate and hydrogen ion fluxes between various tissues, which could play a role in exercise performance following rHuEPO treatment^{5, 6}.

In conclusion, improved exercise performance with EPO use is primarily due to the increased blood oxygen carrying capacity but other effects, such as muscle and RBC membrane changes, may also play a role.

Friedrich Jung: Erythropoietin, optimal hematocrit and microcirculation

In several theoretical approaches, the hct to achieve maximal systemic oxygen delivery – as a product of cardiac output and arterial oxygen content – was calculated to fall between 30% and 42%. An optimal hct of 30% was suggested in the early seventies in an animal study⁷. This initiated a longstanding dispute between clinicians about the optimal hct for patients with peripheral occlusive artery disease (POAD) receiving hemodilution therapy – a popular therapy at that time (later also for patients receiving rHuEPO) – because POAD patients seemed to have a greater benefit with hct values at around 40%. This was fostered by Zander after analysis of different animal studies resulting in an optimal hct of 40%⁸.

Ehrly's group later studied the association between tissue oxygen tension in the anterior tibial muscle before and after exercise in POAD patients with different baseline hct values. At a baseline hct of 40%, the oxygen tension in the muscle improved after pedalgometric exercise as well as after treadmill test, while at baseline hct values of 50.6% or 33.8% the skeletal muscle oxygen tension and pedalgometric performance were clearly lower⁹. It is, however, still an unresolved question how these results obtained in POAD patients can be translated to healthy athletes.

Our group studied 20 patients with chronic dialysis-dependent renal failure and very low hematocrit values receiving rHuEPO injections at a dose of 3 x 80 U/kg body weight per week over six months. The study revealed that capillary perfusion improved significantly over time compared to the group without rHuEPO treatment, despite a significant increase in hct (over 10%) and plasma viscosity¹⁰. Recently, our group performed a study in pigs to check the association between systemic hct and tissue oxygen tension values in the left ventricular myocardium¹¹. The data revealed that

increasing hct too high deteriorated tissue oxygen tension, a finding similar to that at extremely low hct values (Figure 2).

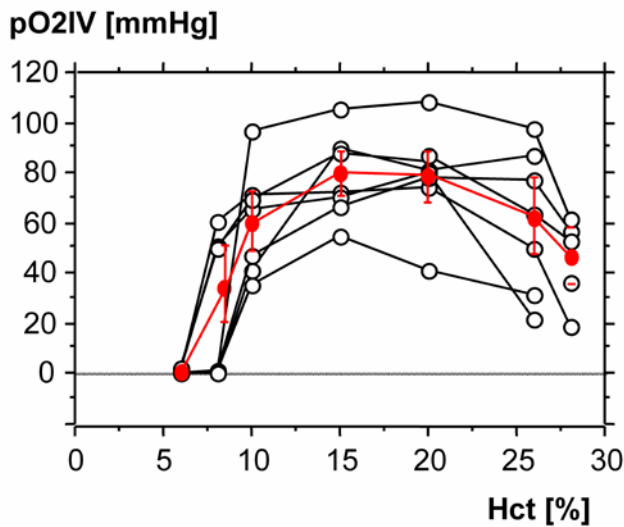


Figure 2: Association between the oxygen tension (pO_2) of the left ventricular myocardium and the systemic hct. Reprinted from [11], Copyright 2010, with permission from Elsevier. (o = individual values, ● = mean value (n=7)).

These data, however, only apply to pigs (with clearly lower baseline hct values than humans) under resting conditions. It should be noted that vessels dilate during endurance training allowing an increased volume of blood and oxygen can be delivered to muscles. Vascular dilation also leads to some degree of hemodilution with a consequent decrease in measured hct. Importantly, under resting conditions, the use of high rHuEPO doses led to reduced tissue oxygen tensions owing to the high hct. During exercise, when vessels supplying large muscles are dilated, the increased amount of RBCs available to deliver oxygen can clearly represent an advantage. However, no reliable laboratory data is currently available for conditions under strenuous exercise.

Tamas Alexy: The pros and cons of EPO use in the clinical practice

An overview of recent clinical trials and guidelines regarding the clinical use of EPO or recombinant erythropoiesis-stimulating agents was provided with special focus on the cardiovascular and hematology fields. EPO was isolated from human urine in 1977 and rHuEPO was first approved for clinical use in 1989. It was recommended for the partial correction of anemia with a hgb target of 9-10g/dL in patients with chronic kidney disease and anemia associated with chemotherapy or HIV with the objective to avoid transfusion therapy¹². Given the initial beneficial effects of improved quality of life, transplant success, reduced risk of iron overload and heart failure exacerbation, the target hgb was increased to a mean of 11g/dL in the First National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-DOQI) anemia guidelines¹³. However, well designed clinical studies subsequently showed a trend towards increased mortality, significantly elevated risk of vascular access thrombosis, heart failure-associated hospitalizations and hypertension in the patient group with higher hct target¹⁴⁻¹⁶. These ultimately led to an FDA black box warning that implicated rHuEPO use in increased mortality and an increased rate of adverse cardiovascular events. In addition, it is now recommended that clinicians withhold EPO products at hgb values exceeding 12g/dL. The complications related to rHuEPO use are likely multifactorial and the underlying mechanisms are

currently under investigation. It is important to emphasize that these studies only included patients using rHuEPO for therapeutic purposes with well-defined clinical indications; data on EPO use in healthy individuals and athletes for doping purposes is limited. Further studies are warranted to evaluate the possible health risks associated with rHuEPO use for performance enhancement purposes in athletes.

Bram Brouwer: Multi-angle investigation of the physiological effects of EPO

Central issue to the current study is the argument how cyclists justify the use of EPO (EPO translates to faster cycling) and how anti-doping authorities penalize its use (EPO use means unfair competition). These arguments are based on the following assumptions¹⁷: EPO use for doping results in increased hct values that leads to increased blood oxygen transport capacity. As a result, VO_{2max} increases allowing the cyclist to reach higher maximal aerobic speed.

We have investigated this model from six different angles: (1) the a priori probability; (2) a theoretical investigation into all aspects of the model, including hemorheological aspects; (3) a study on the validity of VO_{2max} as predictor of aerobic performance; (4) a meta-analysis of all 17 EPO studies that are published to date¹⁸; (5) historical statistical studies claiming that cycling performance increased following the introduction of EPO in 1989^{19, 20}; and (6) a socio-historical study on alternative explanations of the development of EPO-doping linked performance in cycling. None of these six angles supported any evidence for the model described. In a recent meta-analysis of EPO studies, Heuberger et al. confirmed our results²¹. We conclude that any ergogenic action of EPO or blood doping is not real and can be classified as a myth!

Oguz K. Baskurt: Concluding remarks^{*,*}

Most people, except for the hemorheologists, believe that EPO use increases exercise performance. The main concept we repeatedly discussed in this session is the existence of an optimum hct value for oxygen delivery. However, I believe that there are several other factors that should also be taken into account. The cardiac output of an athlete may increase up to eight-fold at the time of peak exercise. Is a change in hct, on the order of 5-10%, physiologically relevant? We must not forget additional factors such as the rheological effects of vascular changes in response to circulating neuro-humoral factors (i.e., vasodilation as pointed out by Dr. Jung) and the increase in shear forces during exercise. While still under intense research, optimal hct from the rheological standpoint, as well as vascular control mechanisms and tissue oxygen extraction, all play a critical role at maximal intensity exercise.

EPO is also likely to have physiological effects other than increasing the hct value. Studies have shown that it regulates angiogenesis, alters respiratory function, may change the ventilation pattern and affects overall metabolism. Furthermore, it may also have a psychological effect, a subjective feeling that some people experience with EPO use. Finally, let me mention a paper that we published about 15 years ago. We treated rats with rHuEPO and noticed a significant decrease in erythrocyte aggregation explained by a concomitant rise in the surface charge of RBCs²². There was also a change in RBC deformability suggesting that EPO alters inherent RBC properties. Further studies are needed to clarify the physiological and psychological effects of EPO that will help us better understand its use as a doping agent.

* Text extracted from digital sound recording.

+ Deceased unexpectedly a few days following the Conference. We dedicate this manuscript to his legacy that will stay with us forever.



Oguz K. Baskurt in Istanbul, Turkey (May, 2011)



Oguz K. Baskurt during his conclusive remarks at the "EPO or placEPO Panel Discussion"; 17th ESCHM Conference, Pecs, Hungary (July, 2013)

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