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Blood Doping, Erythropoietin and Altitude

Bjorn Ekblom

Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

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1. INTRODUCTION

Physical performance in sport is determined by biomechanical, physiological, psychological and other factors. Maximal aerobic power, anaerobic capacity, aerobic/anaerobic metabolic efficiency, muscle strength and co-ordination are the most important ones. Their relative importance depends on the individual demands within different sports. Nowadays the differences in these parameters between world class athletes in a specific sport are fairly small. Minor changes in any of these physiological factors, due to internal or external influences, can help explain and cause important changes in physical performance and, thus, success in sport. In this context the energy turn-over during exercise is without doubt of utmost interest. It is fairly well-known that changes in energy expenditure can have a great influence on competitive results. Over the years athletes have searched for both legal and illegal methods and substances to help increase maximal aerobic power, anaerobic capacity, or metabolic efficiency during severe exercise, thus improving their physical performance. The following discussion concerns some of the factors that influence energy yield during exercise.

2. EFFECT OF HYPOXIA

Reduction of arterial oxygen content, whether it is a consequence of or through anaemia or different types of hypoxia, causes a reduction in physical performance and can induce many different physiological reactions. It is evident that a stay at altitude (hypobaric hypoxia) causes a reduction in maximal aerobic power and physical performance. During maximal exercise no other factor within the oxygen transport system chain can compensate for the reduced oxygen content in the arterial blood. During submaximal exercise at altitude, compared to sea level, there are several signs of increased energy stress in the working muscles, especially at higher rates of submaximal exercise. Thus, the energy yield during exercise is very sensitive to changes in the oxygen availability during submaximal and maximal exercise.

Hypoxia can also be achieved by reducing the exogenous oxygen environment by living in special "flats", in which the partial oxygen content in the inspired air is reduced by increasing the nitrogen content of the room air (normobaric hypoxia). The latter makes it possible to "stay high - train low" - see below. There is no doubt that training during a prolonged stay at high altitude improves performance at altitude. In fact, prolonged physical training and living at high altitude is a prerequisite for successful performance at altitude. A more interesting question, however, is how physical training and staying at altitude affects performance at sea level. Athletes, particularly those in endurance sports, have used training during hypoxic conditions- such as during a stay at high altitude - for many years to improve physical performance at sea level. The concept behind this is that relative hypoxia should stimulate the erythropoietic system and increase the haemoglobin concentration ([Hb]) and total haemoglobin mass. An increased buffer capacity and enhanced muscle enzyme concentrations may also be a consequence of hypoxic training. Although many athletes claim that their sea level performance is improved by such training, the scientific evidence for improved sea level performance after a period of staying and training at high altitude is not convincing, and the physiological investigations of such training have produced conflicting results [1-4].

Whilst there seems to be a number of athletes from different sports who benefit from staying and training at medium high altitude (2 000 - 2 500 m), an equal or higher number of athletes do not ("non-responders"). One cannot exclude that different types of training, sports and genetic prerequisites may account for these differences. Studies have suggested, however, that the reduction in maximal oxygen uptake at altitude reduces the training intensity. This, therefore, means that the benefit of increased oxygen carrying capacity is negatively balanced by a reduction in both training intensity and training volume at altitude. Furthermore, it has been suggested that intense training at altitude may have a negative effect on muscles and other organ systems [5,6]. To avoid these potential negative consequences of altitude training, modern hypoxic training is performed in one of two conditions. The first is either as a stay at altitude, which stimulates erythropoiesis, combined with training in normoxia conditions (in the valley), which helps to maintain the training intensity. Secondly, athletes may train outdoors in a normal way and during the rest of the day they stay in normobaric hypoxia conditions in a room low in oxygen. The latter system seems to enhance factors important for maximal aerobic power and performance [7].

3. MANIPULATION OF BLOOD VOLUME AND RED CELL MASS

Both blood volume and red cell mass are important factors for maximal aerobic power and physical performance. The blood volume is controlled through a complicated series of regulating hormones. Hormones from the kidney and the heart are essential for keeping the blood volume within the limits of the present training status. When the individual increases

his/her level of physical activity there is a parallel increase in blood volume, which also contributes to increased maximal aerobic power.

The production of the red cells is also controlled by hormones. To maintain an adequate number of circulating red blood cells, the bone marrow must produce about 2.5 million red blood cells per second in an average man with a blood volume of 5 litres. In endurance athletes with larger blood volumes (7-8 litres) and a shorter average life span of the red blood cell than the normal 120 days, the production of the red blood cells per second is increased some 20-40 percent. The increased iron turn-over evidently does not cause any major problems in training at sea level in a well nourished athlete. The frequency of iron deficiency problems in, e.g., endurance athletes is no greater than in the general population. Thus, there seems to be an adequate supply of iron and other for the increased production of red blood cells and the increased haemolysis with strenuous athletic training [8].

Regular physical training increases blood volume and red cell mass in parallel with an increased maximal aerobic power and aerobic physical performance. It is therefore not surprising that with an acute increase in red cell mass through a reinfusion of red blood cells, there is an increase in maximal aerobic power and, thus, aerobic physical performance [9-12]. If red cell mass is increased through a reinfusion of red blood cells ("blood doping"), the blood volume remains close to its "baseline" level. There is also no increase in blood volume after injections of the hormone erythropoietin (EPO) - see below. In a study from our laboratory blood volume was measured in seven subjects in normal conditions, after reinfusion of 400 ml of packed red blood cells, and after 6 weeks of injections of EPO [13]. The results demonstrated that the blood volume was maintained at a constant average of 6.1-6.2 l in the three situations.

Increasing haemoglobin concentration ([Hb]) and haematocrit (Hct) through reinfusion of red blood cells does not seem to produce any major negative physiological side effects, such as an increased blood pressure during exercise [11]. However, medical risks such as thrombosis and transfusion complications may occur.

"Blood doping" is difficult to detect in ordinary doping tests [14]. Therefore it cannot be excluded that this manipulation - although on the IOC doping list - is used in different sports, most importantly in endurance sports.

4. ERYTHROPOIETIN

The haemopoiesis is controlled and regulated by a complex system of stimulators and inhibitors. The haemopoietic stem cell enters the cell cycle, promoted by several factors such as interleukin 1, 3 and 6. In the progression of the cells several other factors such as the granulocyte-macrophage colony-stimulation factor and erythropoietin are essential components. It is at present unknown how much the whole system can be manipulated by the stimulation

of any of these factors, but it is clear that such stimulation could cause ethical and moral problems within the sporting world.

An important regulator for the erythropoiesis is erythropoietin (EPO) - a glycoprotein (40 % carbohydrate) with a molecular weight of approximately 34 000 daltons. Erythropoietin is produced mainly in the proximal tubular cells of the kidneys. It is important to remember that it is also to some extent produced in the liver (see below). Oxygen availability in the kidneys and liver is the main regulator for the production of erythropoietin. Hypoxia due to anaemia or low plasma oxygen pressure leads to an increase of the erythropoietin secretion. Erythropoietin receptors in the bone marrow enhance the mitosis and differentiation of the red blood cells precursors, leading to a production of red blood cells.

Serum EPO concentration ([EPO]) can routinely be measured through immunoassays or bioassays. In normal conditions there is a circadian rhythm in the serum concentration with a peak during the day and lower values at night. Serum [EPO] is increased in an anaemic situation and reduced at polycythaemia. There are great inter- and intraindividual variations in serum [EPO] even in individuals with [Hb] within the "normal" limits. Strenuous physical training, transition from sea level to high altitude and other activities may cause complex changes in serum [EPO]. Since the variation in the absolute values in [EPO] are so great, quantitative determinations of [EPO] for detection of illegal administration of i.e. exogenous recombinant EPO (rhEPO) is not possible at present.

4.1. Administration of exogenous erythropoietin

Erythropoietin is now available through recombinant DNA techniques. Thus, rhepo is available to enhance the stimulation of erythropoiesis. Injections of rhEPO to patients with renal diseases has restored their physical performance to more or less to normal levels, primarily through an increased [Hb]. However, the more interesting questions regarding administration of rhEPO to healthy individuals and sport are:

- Will increased serum [EPO] in the normal athlete increase [Hb]?
- If so, will such an increase in [Hb] enhance maximal aerobic power and consequently improve aerobic physical performance ?
- What other physiological and medical consequences could a period of rhEPO injection lead to ?
- Can exogenous administration of rhEPO be detected in doping tests ?

These questions have been addressed in a series of studies in our laboratory. Below data from these studies [13,15,16] and also unpublished data will be presented. The total number of subjects studied in these investigations was 26. All subjects were males, from a population of moderately physically active to well-trained athletes, with an average age of 27±4.6 years, body mass 77.3±8.0 kg and baseline maximal aerobic power 4.56±0.43 l/min (means ± SD). Injections of rhEPO were administrated subcutaneously 3 times a week for 6 weeks, with a dose of 20 or 40 IU/kg body weight. The variation between doses had no significant effect

on the different physiological responses. Routine laboratory methods were used in the different physiological tests. It should be noted that all subjects were familiarized with the laboratory tests before the studies started. Values presented as "before the injection period" were obtained in a second or third test before the study.

4.2. Haemoglobin concentration

Six weeks of rhEPO injections increased [Hb] and Hct in all subjects. Blood volume - as indicated above - remained unchanged, when compared to the period before injections. In Fig 1 individual values of [Hb] and Hct before and after the injection period are presented.

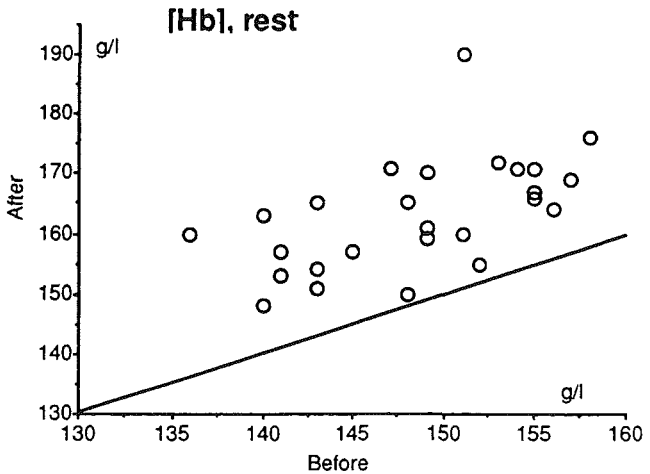

Fig 1. Haemoglobin concentration at rest before and after the injection period.

It is evident that [Hb] increased in all subjects; however, a large variation between individuals was observed. The reason for this is unknown. The conclusion is that erythropoiesis can be stimulated by rhEPO injections, even in well-trained athletes, independent of baseline [Hb]. It would also seem from these results that Hct follows this general trend.

4.3. Cardiovascular adaptation to rest.

No differences in circulatory adaptation at rest before and after the period of injecting erythropoietin were observed. The resting systolic and diastolic blood pressures were measured by a trained nurse after 5 min of supine rest with a sphygmomanometer and were 121.3±12.1 and 121.7±11.7 and 65.7±7.0 and 66.9±8.0 mm Hg ($P>0.05$) before and after the injection period, respectively. Heart rate at rest remained unchanged.

4.4. Cardiovascular adaptation to submaximal exercise.

The cardiovascular responses to submaximal exercise, comparing after to before the injection of erythropoietin, were evaluated on two standard work-rates on a mechanically braked Monark cycle ergometer - see Table 1. The work -rates averaged 120 and 190 W, corresponding to an average of 39 and 59 percent, respectively, of individual maximal oxygen uptake during running before the injection period.

	Submax I				Submax II			
	Before		After		Before		After	
	M	SD	M	SD	M	SD	M	SD
VO_2, l/min	1.78	0.40	1.77	0.39	2.68	0.26	2.69	0.22
V_e, BTPS	44.2	7.3	45.4	9.4	68.8	7.2	68.3	6.3
V_e/VO_2,	25.2	2.6	25.9	3.5	25.7	2.2	25.5	2.4
HR, beats/min	114.7	15.3	108.4 *	15.3	145.5	13.6	137.4 *	16.4
OP, ml/beat	15.5	2.8	16.4 *	3.2	18.6	2.6	19.9 *	2.9
[Hla], mM	1.88	1.02	1.70	0.56	3.01	1.35	2.95	1.2
RPEc, points	9.3	2.0	9.0	2.0	12.6	2.1	12.4	1.3
RPEl, points	8.7	1.7	8.9	1.3	12.8	1.3	13.1	2.3
SBP, mmHg	160.5	19.6	163.7	21.8	181.2	15.8	191.5 *	18.8

Table 1. Means ± SD for values obtained during two submaximal work loads (120 and 190 W, respectively). * denotes $P<0.05$ comparing after to before the injection period. VO_2 = oxygen uptake, Ve = pulmonary ventilation, HR = heart rate, OP = oxygen pulse, [Hla] = blood lactate concentration, RPEc and RPEl = rate of perceived exertion, central and local, respectively, SBP = systolic blood pressure.

The oxygen uptake before and after the injection period was, as expected, unchanged. Ventilatory responses also remained unchanged. Heart rate was reduced from 115 to 108 beats/min on the low submaximal work load and from 146 to 137 beats/min on the high submaximal work-rate, both $p<0.05$. The oxygen pulse increased significantly from 15.5 to 16.4 ml/beat on the low and from 18.6 to 19.9 ml/beat on the high submaximal work -rate. The reduced heart rate after the injection period during the submaximal work rate was the same as after the reinfusion of red blood cells with a corresponding increase in [Hb].

In comparison to the studies regarding the reinfusion of red blood cells, the concentration of blood lactates ([Hla]) did not changed after vs before the injection period. The [Hla] remained at 1.88 and 1.70 mM, respectively, on the low submaximal work-rate and 3.01 and 2.95 mM, respectively, on the higher. No significant change was found in the rating of perceived exertion (RPE) as evaluated with the Borg scale for central or peripheral fatigue

[17]. A possible explanation for the unchanged values on [Hla] and RPE could be that the work loads were too low and therefore potential changes during higher submaximal work-rates were not investigated.

An unexpected finding was the increased arterial systolic blood pressure during submaximal exercise. During the higher work-rate the systolic blood pressure increased significantly from 181.2 to 191.5 mmHg. At the lower work-rate there was also an increase from 160.5 to 163.7 mmHg. This, however, was not significant. The individual values are presented in Fig 2.

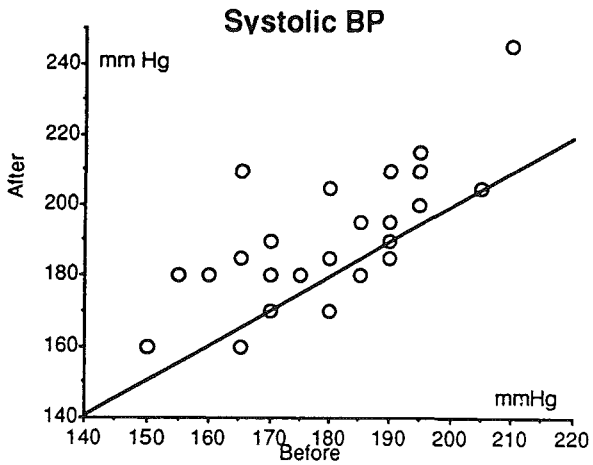

Fig 2. Systolic blood pressure at the higher submaximal rate of work (average 190 W) before and after the injection period.

The explanation for the increased systolic blood pressure during the higher submaximal work-rate is unknown and can only be speculated upon. The increased blood Hct can not be the main explanation since there was no correlation between the increase in Hct and the increase in systolic blood pressure over the rhEPO treatment period. Furthermore, the corresponding increase in Hct after reinfusion of red blood cells did not induce any increase in systolic blood pressure during submaximal exercise [11]. One possible explanation for this is that the increased serum [EPO] may have a direct effect on the peripheral vasculature, causing an increased vasoconstriction, which together with the increased Hct could increase peripheral resistance and systolic blood pressure.

4.5. Maximal exercise:

Data during maximal exercise were obtained before and after the injection of erythropoietin during running on a motor driven treadmill using conventional laboratory techniques. Fig 3 illustrates values obtained for maximal aerobic power. All subjects increased their maximal aerobic power irrespective of their baseline values. The average maximal aerobic power

increased from 4.56±0.43 to 4.90±0.44 l/min (+7.5%, $p<0.05$). The average increase in maximal aerobic power was 0.34±0.13 (range 0.11-0.62) l/min.

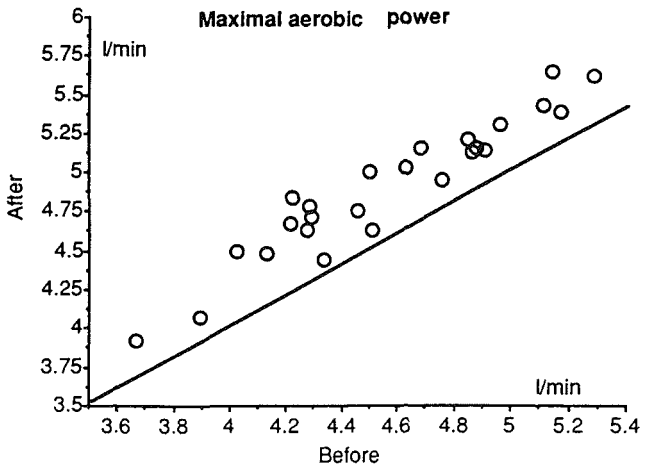

Fig 3. Maximal aerobic power before and after the injection period.

The average increase in maximal aerobic power per gram increased[Hb] was 14.8 ml 0_2/min/g, which is not statistically different from the value obtained when [Hb] was increased with blood reinfusion [9, 10]. Individual values for the increase in maximal aerobic power and increase in [Hb] are shown in Fig 4.

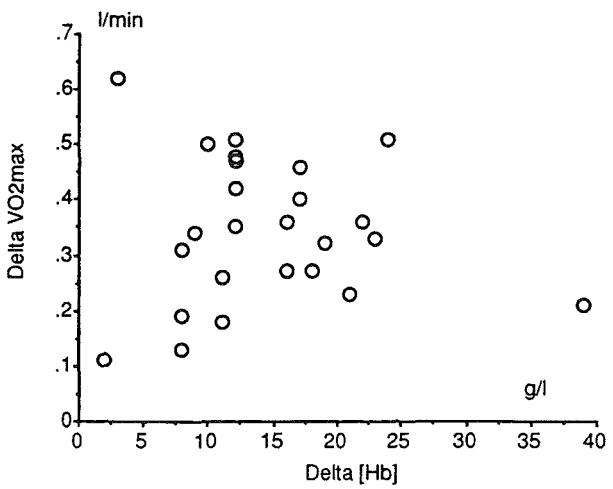

Fig 4. The increase in maximal aerobic power compared to the increase in haemoglobin concentration from before to after the injection period.

It has been proposed that a prolonged increase in [Hb] would induce compensatory changes in the circulatory adaptation to maximal exercise, such as increased peripheral vascular resistance, due to increased blood viscosity, peripheral vasoconstriction. One has to remember that the systolic blood pressure was increased after the injection period during the high submaximal exercise. Since no differences were found in the increase in maximal aerobic power, whether the [Hb] was increased acutely after blood reinfusion or more chronically after injections of rhEPO, these postulations seem to be invalid during maximal exercise.

After the cession of the rhEPO injections the maximal aerobic power decreased. This may be due to the fact that the endogenous production of erythropoietin is reduced during the injection period. There is nothing to suggest that after the injection period this production of endogenous erythropoietin will return to normal when the individual«s [Hb] has returned to its baseline value.

No significant changes were found during maximal exercise, comparing before and after the injection period, in pulmonary ventilation (166.4±16.4 to 168.3±17.1 l/min BTPS), peak heart rate (194 to 195 beats/min), peak [Hla] (13.3 to 13.8 mM), and rating of perceived exertion (19.0±0.8 to 19.3±0.6).

4.6. Muscle physiology data

Muscle biopsies from M.Vastus Lateralis were obtained before and after the injection period in 19 subjects. Table 2 summarises these results.

It is clearly shown that during this short period of increased serum [EPO] no significant changes were induced in any of the muscle physiological data. There was no change in myoglobin or enzyme concentration, which may have taken place if the suggestion had been valid that oxygen availability could increase muscle aerobic enzyme concentration during i.e. endurance training.

	Before		After	
	Mean	SD	Mean	SD
Type I, %	46.1	14.0	44,7	15,2
SDH	1.69	0.72	2.09	1.23
PFK	38.7	6.0	39.8	9.7
CS	19.6	6.2	19.2	9.4
Cytox	5.7	2.6	6.7	1.7
m-GPDH	63.9	8.2	62.4	10.3
Myoglobin	3.43	0.83	2.96	0.82
Protein	0.18	0.03	0.19	0.04

Table 2. Means ±SD for measurements from muscle biopsies before and after the injection period. SDH = succinate dehydrogenase, PFK = phosphofructokinase, CS =citrate synthase, m-GPDH = mitochondrial glycerol-3-phosphate dehydrogenase.

4.7. Physical performance

Endurance physical performance was evaluated by time to exhaustion during a standardised endurance test before and after the injection period in all 26 subjects. The time to exhaustion during the fixed maximal work-rates increased significantly from 493±74 s to 567±82 s. Individual data relating the change in time to exhaustion to the change in maximal aerobic power over the injection period are shown in Fig 5.

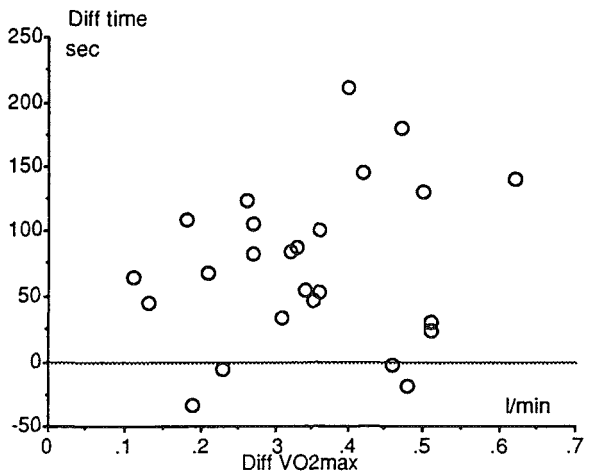

Fig 5. The change in time to exhaustion in relation to the change in maximal aerobic power.

Since there were no major changes in the muscle physiology data, as discussed above, it is obvious that the increased maximal aerobic power, caused by the increased [Hb] over the injection period, can explain most of the effect of the prolonged time to exhaustion during the maximal endurance test.

A high-intensity intermittent exercise protocol was used to investigate whether an increased maximal aerobic power over the injection period could influence the physiological responses to repeated, high-intensity sprinting. Before and after the injection period 6 subjects performed 15 6-s bouts of high-speed uphill running at a 10^0 gradient, interspersed with 24-s periods of passive recovery. The speed chosen for each subject was the highest possible speed at which the 15 bouts could be completed [15].

The maximal aerobic power in these subjects increased on average from 4.76 to 5.14 l/min. When the same test was performed after the injection of erythropoietin, the accumulation of lactate (peak post-exercise minus pre-exercise [Hla]) decreased significantly, from 10.3 to 7.9 mM. The accumulation of hypoxanthine also decreased significantly from 9.1 to 5.6 M/l. Thus, the increased maximal aerobic power reduced the anaerobic stress, as evaluated from a net reduction in the ATP resynthesis, via the adenylate kinase reaction (reduced serum hypoxanthine concentration), and a reduced anaerobic glycolysis (reduced [Hla]) during this

type of high-intensity intermittent exercise. This could be due to both a higher rate of phosphocreatine resynthesis during the recovery periods between the sprints, as a consequence of the greater oxygen availability, and also a small increase in aerobic metabolism during the sprints.

From these studies it can be concluded that there is an increased physical performance both during a maximal run on a treadmill with a duration of 5-8 min, which relies on maximal aerobic power , and in high-intensity intermittent sprinting, which relies predominately on the anaerobic energy systems. This increase in physical performance, as evaluated in these two exercise protocols, over the injection period can not be explained by changes in the peripheral characteristics of the muscles. A more probable explanation is an increased maximal aerobic power, which supports the corresponding changes in physical performance after blood reinfusion and other types of manipulation of the energy yield systems.

4.8. Is rhEPO injection possible to detect ?

To try to answer this question, blood and urine samples were taken on different days before and after the end of the injection period. The complete data are published in detail elsewhere [18].

Since the plasma [EPO] varies considerably during the day and, furthermore, since the differences between normal individuals in plasma [EPO] are so large, quantitative methods for detecting exogenous administration of rhEPO in e.g. athletes can not be used. To help solve the problem with illegal administration of rhEPO in sports, a qualitative method based on an unique electrophoretic method has been developed by Leif Wide in Uppsala, Sweden.

This method can discriminate between endogenous EPO and rhEPO, as the electric charge of these two EPO forms are different. The rhEPO, which is manufactured from hamster ovary and kidney cells and mouse fibroblast cells, is less negatively charged than the endogenous EPO. This makes it possible to measure a mean value for electrophoretic mobility of EPO in samples from both plasma and urine which are different from the endogenous one. In a sample containing both rhEPO and endogenous EPO a biphasic curve emerges.

With regard to time it is possible to detect exogenous rhEPO administration in all subjects within 24 hours after the last administration of rhEPO and in 75% of the subjects after 48 hours. Due to the differences in electrophoretic mobility this qualitative method is very safe. It should also be highlighted that there were no false positive samples in this study.

Thus, exogenous administrated rhEPO can be detected in most subjects within two days, and in some subjects it can be detected for several days after the end of the injection period. Within two weeks of the end of the injection period most of the effect of the exogenous administration of the rhEPO on maximal aerobic power and presumably also on physical performance had disappeared.

5. SUMMARY

Erythropoietin is a very potent hormone. Exogenous administration of rhEPO for some weeks will increase physical performance through its effect on increasing [Hb], and as a consequence its increase on maximal aerobic power. In contrast to "blood doping" exogenous administration of rhEPO can be detected in plasma and urine. This method of detection is safe and does not give any false positive results.

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Discussion: Blood Doping, Erythropoietin and Altitude

T. Reilly:
In the normobaric hypoxia situation, because of the fall in oxygen tension at night, might it be that you only need to sleep in that environment and not live in it?

B. Ekblom:
It is true. You stay in for 20-22 hours and you are outside for 2-4 hours.

P.M. Clarkson:
You have shown that iron depletion does not affect maximal performance in the laboratory and scientists have generally dismissed iron depletion as being a significant problem for athletes. However, team physicians and athletes will tell you that when an athlete is iron-deficient, he or she is not able to train hard and recover from the training, and it becomes a significant problem. Yet we are not able to measure this in the laboratory. Is there something wrong with our tests? Can you suggest something that we could do to better assess the effects of iron depletion without anaemia on performance?

B. Ekblom:
It is a difficult task because we have not seen any effect of iron deficiency, in the situation of normal haemoglobin, neither with the experiments done nor when giving iron supplements to people who are, as told, iron deficient. And if they are given iron and there is no change in haemoglobin concentration, there is no change in performance. If you have a coach saying that it has a positive effect, it will probably have a positive effect on the haemoglobin concentration, if they were truly anaemic. The problem is you have to know which haemoglobin concentration is the subnormal, because you can have a normal at 120 or 180 or even above or below these limits. What you could from a practical standpoint, is always give iron for a short period time, and see if that affects haemoglobin. If you do it, you should use tablets, never injections.

M. Gleeson:
What are the possible health risks of high dose EPO, particularly in athletes who are going to engage in exercise over a prolonged period in a hot environment?

B. Ekblom:
There is a theoretical risk of course, for thrombosis and so forth. Interestingly enough is that the subjects who have high baseline haemoglobin concentrations are not at higher risk than those with low, but that does not say that the delta is not unimportant. It might be that the higher risk is the increase in blood pressure. That is the most important point, in my view.

D.R. Mottram:
Clearly not all competitors have easy access to altitude adaptation or indeed the resources to undertake it. Blood doping is a non-pharmacological method and as we have heard throughout the day nutritional manipulation is certainly allowed in sport. As you have also

said it is not possible at the present time to detect blood doping. It could be argued therefore that blood doping should not be a banned procedure. Do you have any comment on that?

B. Ekblom:

I think it is banned now for different reasons, and I think you should keep on that, if that was the question. If you leave it free, it may be that people will try to find blood from anybody to booster now and then, and then you enormously increase the risk. I think we should keep it on the doping list.

T.D. Fahey:

Do you have data on muscle blood flow with EPO and its possible effect on lactate levels and lactate clearance?

B. Ekblom:

In our 26 subjects we did not observe any effect on plasma concentrations of lactate before and after. That might be due to the fact that the workload was too low. At a higher submaximal rate of work we might have seen an effect.

T. Reilly:

With regard to the issue of fatigue and EPO, I was wondering if you have any follow-up data on your EPO subjects, and if it ties in with the observations that when the new blood cells have run their course, and there is no longer the erythropoietic stimulus, you get in fact a semi-anaemia and fatigue.

B. Ekblom:

Yes, that is a possibility. There is in fact a downwork shift of the (Hb) after the end of the injection period but we have not systematically studied that.