Direct RESEARCH JOURNALS

Direct Research Journal of Health and Pharmacology (DRJHP) Vol.1 (1), pp.1-4, October 2013
Available online at http://directresearchpublisher.org/drjhp

Case Report

Erythropoietin and physical exercise

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Accepted 17 September 2013

INTRODUCTION

Physical exercise is any bodily activity that enhances or maintains physical fitness and overall health and wellness. It is performed for various reasons including strengthening muscles and the cardiovascular system, honing athletic skills, weight loss or maintenance, as well as for enjoyment. Frequent and regular physical exercise boosts the immune system, and helps prevent the "diseases of affluence" such as heart disease, cardiovascular disease, Type 2 diabetes and obesity (Stampfer et al 2000; Hu et al 2001) .The American College of Cardiology/American Heart Association recommends at least 30 minute-moderate (at 50–70% of maximal predicted heart rate) exercise on most days to reduce the risk of cardiovascular problems(*NCEP, 2002*). Exercise also increases hemoglobin, hematocrit, platelet numbers, and interleukin-6 levels in the young healthy individuals of both genders and all fitness levels which propose a role for exercise in enhancing tissue repair mechanisms (*NCEP, 2002*).

The effect of physical exercise and training on blood volume has been known for a long time. In 1949, a group of scientists from Stockholm have reported that physical training caused and increases heamoglobin and blood volume due to physical training. In the athletically trained men and women, hemoglobin and blood volumes were reported comparatively higher than the average sedentary men's and women (*Kjeliberg,1950*) .Packed cell volume values and the concentrations of both red blood cells and hemoglobin were found to be lower in endurance athletes compared to those of untrained counterparts. Both components o f blood volume (plasma volume and red cell mass) are regulated separately and the possible mechanisms for plasma volume regulation are described elsewhere (Rocker et al., 1983).

In the course of intensive exercise, the erythrocyte mass is decreased on the one hand due to oxidative stress, defects of anti-oxidative defense, increased mechanical and/or osmotic stress (Lang et al.,2005). On the other hand, was found to be stimulated by a higher production and release of Erythropoietin full name pl.(EPO) from the kidneys, which leads further on to the release of new red blood cells from the bone marrow (~5–7 days after exercise). In the long run, this generates a higher number of red blood cells circulating in the peripheral blood. Immediately after strenuous exercise, an increased number of reticulocyctes can also be noticed in the peripheral blood.

The influence of long-distance running on the erythrocytic system (red blood cells, haemoglobin, and packed cell volume) has been reported also in many studies (ref: pl.) . Most of the investigators have found that there were increased red cell counts, haemoglobin, and packed cell volume immediately following long distance running. As shown in (Table 1). We will take one example from the table 1, In 1991 in the Institute für Leistungsmedizin , Berlin, German were they have studied Changes in red blood cells , EPO , plasma volume in 15 well-trained men before and several times after a marathon run. They have found that Immediately after the run, red blood cells were increased due to haemo-concentration, whereas 31 hours later, the values were decreased due to haemo-dilution. The EPO concentration was increased 3 hours, and more impressive 31 hours, after the run. This long-lasting effect on EPO concentration after the marathon run would seem to have been responsible for the increased red blood cell mass in long distance runners(Schwandt et al., 1991).

The above may be explained in two ways: first, by looking at EPO as a blood-volume-regulating hormone, it is well known fact that during exercise, a plasma volume decrease of about 20% can be expected due to fluid shifts from the intravascular to the extravascular

Table 1. Analysis of studies done which show the effect of exercise and blood loss on the EPO Up regulation.

	Erythropoietin	R.B.Cs &Hemoglobin	Hematocrit
Strenuous exercise in well trained athlete	Initially increase after 3 – 4 hours of exercise , Significant marked increase after 30 – 48 hours (8,9)	erythrocyte concentration, haemoglobin concentration, were significantly increased Immediately after the exercis , due to haemoconcentration , 30 – 48 hours after the exercise show erythrocyt concentration, hemoglobin concentratio decreased due to haemodilution , (another study show no significant chang in R.B.C.s after the exercise (8))	significantly higher values in the high intensity group than the REST group at 4 h after the exercises (8),
Strenuous exercise in untrained subjects , under normoxia and hypoxia condition	[EPO] was unchanged up to five hours after exercise under normoxia , but exercise under hypoxic condition(or even hypoxia at rest) ,show Initially increase after 3 hours of exercise , and Significant marked increase after 24 hours of exercise (10)	NO enough data provided	NO enough data provided
Strenuous exercise in well trained athlete , under normoxia and hypoxia condition	EPO concentration was slightly greater in hypoxic (H) conditions than in normoxic conditions in 30 minutes after high intensity interval training ; however it was similar 240 minutes after the session, (11)	NO enough data provided	NO enough data provided
Severe hemorrhage (**40% of their blood volume)** in the ovine fetus	• Mean plasma EPO concentration increased significantly 4 hours after initiating the hemorrhage, • EPO reached a maximum at 10-16 hours after the hemorrhage, • EPO decreased to 50% of maximal values at 24 hours after hemorrhage(12)	NO enough data provided	Hematocrit decreased rapidly during the 12 hours after hemorrhage (P < .0001),

compartments because of: (i) raised hydrostatic pressures, (ii) heightened muscle blood flow (that is more filtration surface), furthermore (iii) increased metabolites in the exercising muscles leading to a rise in the osmotic outward shift from the intravascular towards the intracellular compartments of the muscle cells. Taken together, all these lead to a rapid diminution in blood volume (plasma volume) of about 150–350 mL. Combined with an increased compliance of the venous systems (that is increased capacity of the low-pressure system due to the thermal stress from exercise) (Kirsch et al.1986), these all lead to a prolonged decrease in central blood volume.

This prolonged decrease in central venous pressure

might be an adequate stimulus not only for plasma-volume-regulating hormones such as vasopressin (antidiuretic hormone, ADH) but for EPO production and release from the kidneys as well. And indeed, studies in dogs could show that solely changes in central venous pressure are involved in modulating EPO production and release from the kidney . In general, such a pathway of EPO modulation would also explain the rapid decrease in EPO production and release after autologus (check the spellingpl.) blood transfusions in which serum EPO was found to be depressed by 62% one day following transfusion, or the rapidly depressed serum EPO in the supine, head-down tilt position, a simulation for spaceflight under terrestrial conditions (Gunga.,1996).

The second way to explain the raise to EPO after the exercise is the hypoxia theory , as hypoxia is the primary physiological stimulus for erythropoietin EPO production. Thus , depending on the hypoxic condition, increases serum EPO level could be up to several hundred-fold (Ebert and Bunn 1999).

As physical exercise results in both hemodynamic and electrophysiologic changes within normal tissue, during intense aerobic exercise, the oxygen consumption of muscle tissue increases markedly, and cardiac output must rise to meet the demands. Over time, among other effects, aerobic training results in increased left ventricular mass, heart rate during exercise, ventricular stroke volume and increased cardiac output.(Kjeliberg et al.,1950)

The electrophysiologic changes that are caused by exercise are also enhanced by emotion and competitive stress. The release of circulating catecholamines stimulates heart rate, myocardial contractility, and blood pressure, all resulting in increased myocardial oxygen consumption(Robertson.,1988). Since oxygen is transported by red blood cells, a slow response to increased demand for oxygen will lead to Hypoxia (which can be defined as reduction of oxygen supply to a tissue below physiological levels despite adequate perfusion of the tissue by blood. As demand for greater oxygen carrying capacity (the maximum volume of oxygen which can be carried by hemoglobin in the blood.), in blood increases, there is recruitment of EPO-producing cells in the more superficial cortex of the kidney. Oxygen sensing probably occurs within the same cells that produce EPO.

Transcription of the EPO gene is regulated by a hypoxia-inducible factor (HIF) and its level increase by reductions in atmospheric O2 (2 down) , blood volume, hemoglobin concentration, reduced O2 (2 down) affinity, and cardio-pulmonary causes of hypoxia. Kidney is also responsible for the regulating red cell mass through erythropoietin and plasma volume by excretion of salt and water, to maintain the hematocrit at a normal value of 45%. The balance of the oxygen consumption for sodium re-absorption and the oxygen delivery to the proximal covulated tubules in the kidney is reflected by the tissue oxygen pressure that determines red blood cell mass adjusted to plasma volume.

Increased EPO blood levels stimulate erythropoiesis in the bone marrow by accelerating the rate and number of colony-forming units (CFU-E) undergoing differentiation into red blood cells.The effect of increase in red blood cell mass leads to a reduction in the stimulus for EPO production. Metabolic hypoxia is lowering of the oxygen content of the tissues when there is more demand for oxygen as in exercise,inflammation and hyperthermia .

Since there is a time interval between stimulation and production of EPO in the kidneys – which takes at least some hours – and the occurrence of newly formed red blood cells in the peripheral blood (several days), the effects of long-term exercise on EPO are worthwhile to be investigated.And what makes that more interesting, , sub- maximal exercise in normal or acute hypoxic condition leads to increase in the demand of oxygen by the tissues in need more than usual , which if not fully compensated by increasing cardiac output , will lead to up regulate of the erythropoietin , to increase oxygen transport to the tissue in need , our concern that the failure of the up-regulaion of the EPO can lead to ischemia or other major unpredictable consequences.

This relation between the failure of the EPO to upregulate and the death after exercise needs careful investigation, as in one study, 90% of the athletes collapsed during or immediately after exercise, highlighting the tragic events that existed however, underlying mechanisms had not been fully uncovered . (Refsum.,1976).

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