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The Effect of Exercise Induced Hemorheological Adaptation on Respiratory Function and Sport performance

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ABSTRACT: Exercise hemoreology is the issue of many studies done on athletes, sedentary people and patients who suffer different illnesses. Changes in red blood cells' properties occur in most exercise methods that one of the most incident one is changes in RBC deformability which happens in most sports events and intense exercises. Blood lactate that reduces number of RBC and their flexibility is a result of exercise induced RBC rigidity and reduced flexibility. Thus, there might be a relationship between blood lactate concentration and RBC rigidity during exercise. In other hand, it has been confirmed that excessive usage of oxygen in active muscle and inadequate pulmonary oxygen supply in well exercised athletes leads to hypoxemia which cause the formation of free radicals. Studies have shown that oxidative stress during acute exercise accompanies by hemorheological disorders, but its mechanisms haven't been clarified yet. Since sport performance relates to oxygen carrying capacity to active muscles, increased performance as a result of increased hematocrit by exercising in high altitude, blood doping or erythropoietin injection isn't surprising. Because of biological engineering, erythropoietin has been very accessible and erythropoietin doping has been very popular as a result. But, logic of this kind of doping contradicts with physiological information. In normal conditions, there is a negative correlation between hematocrit and physical fitness. So, in various kinds of sports, different hemorheological patterns are observed.

Key words: Hemorheology, Exercise, Respiratory Function

REVIEW ARTICLE

INTRODUCTION

Hemeorheological disorder was considered as an independent risk factor for vascular and heart disease, meanwhile increased blood viscosity has an important role in artery stenosis disease (Lowe et al., 2000). Increased blood viscosity can have inappropriate effect on blood flow and oxygen delivery to tissues. By the way, Increase of oxygen utilization during exercise leads to production of free radicals from various sources like mitochondria and leukocyte. Temporary hypoxemia in tissue as a result of harried use of oxygen in the muscle involved in activity, and insufficient provision of oxygen in pulmonary level in some exercised individuals has been proved and may cause to the formation of free radicals. Although its mechanism is not clear yet, oxidative stress during acute exercise is accompanied with hemorheological disorders (Ajmani et al., 2000). According to Ajmani et al. (2000), exercise induced oxidative stress also causes to increase of the numbers of RBC and plasma fibrinogen level and accordingly leads to increase of aggregation.

Exercise whether in maximal or submaximal intensity, short-term or long-term, regular or warm and humid weather always increases blood viscosity because of increase in plasma viscosity and hematocrit (El-Sayed et al., 2010; Galy et al., 2005). Studies have shown these two hemorheological variables justify the observed increase in total blood viscosity (Brun et al., 1993). Increased plasma viscosity and hematocrit is usually interpreted as hemoconcentration (Teillet et al., 1991). But, such an interpretation is incomplete because the observed changes happen under the effect of at least five mechanisms: redistribution of red cells (RBC) in vascular bed (Martins and Silva, 1988), splenocontraction that increases the number of RBC, plasma proteins increase presumably via the lymphatic system, loss of water because of sweating for adjusting body temperature (Stephenson and Kolka, 1988) and trapping of water between or inside the muscular cells (El-Sayed et al., 2010; Brun et al., 2007; Brun and Khaled, 1999; sjogaard et al., 1985). Thus, these changes in body fluids must be kept in mind when we study hemorheological changes.

Dintenfass (1971), one of the pioneers of clinical rheology, investigated physically fit groups and less fit ones. He stated physical fitness is accompanied by hemodilution and lower fibrinogen levels. While the ratio of fibrinogen to albumin is higher among athletes (Brun, 2002). Exercise hemoreology is the issue of many studies done on athletes, sedentary people and patients who suffer different illnesses. In spite of broad spectrum of researches

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in field of exercise hemorheology, many questions are remained unanswered. In this review it has been attempted to integrate and link present knowledge to explore physiological mechanisms and understand the practical results of hemorheological changes during and after exercise.

2. Hemarheology and its influencing Factors: Rheology is a science that studies the materials flow and movement through the liquids (Zinngg and Shepley, 1970). Biorheology is a branch of biology that studies the flow and deformation of biological materials under the effect of pressure (Brun and et al., 2007). In the case of blood, rheology is considered as a study of blood flow through the vascular system which is called hemorheology. In another word, hemorheology describes the features of the blood flow. The rate of blood flow through the circulation system of the body is indicated by the rate of heart pressure, peripheral vessels and the friction gradient between endothelial cells and blood. This power causes the appearance of shear-stress on the endothelium. Because of the existing viscosity forces between the endothelium and blood and also in the blood itself, the speed of the blood near the endothelial surface is lower in contrast to the center of vessels which is described as a shear rate (Brun et al., 2007). The ratio of shear stress to shear rate indicates viscosity which its definition from the mathematical viewpoint is included in the domain of fluid mechanic and is an indicator of internal resistance of a fluid against the flow (Nikookheslat, 2010). Blood viscosity has been well described by Quemada's classic equation:

Blood viscosity = shear stress / shear rate

The viscosity unit is poise which indicates the ratio of shear stress to shear rate. Its applied unit is almost centi-Poise which is 0.01 Poise. For example, in the room temperate, water has a viscosity equal to one centi-Poise (west, 1990). Blood flow speed in the vicinity of the endothelium is zero and this speed progressively increases toward the center of the vessel (Prisco et al., 1998). Because two layers of liquids slips on each other with different speeds, the power which is called viscosity is appeared. The amount of this power is different, depending on the features of different liquids (West, 1990). In fact, in the viscometer, the rate of the liquid resistance against the circling cone shows the liquid viscosity (Smutok et al., 1993). Poiseuille mentioned the law of viscosity determination of fluids using capillary pipes, for the first time. He presented a formula in which the relationship of viscosity (ηe), amount of flow (Q), pressure fall through the capillary (P), capillary radius (R) and capillary length is observable:

In fact Hagen-Poiseuille's law presents a traditional picture of physiological blood circulation. Because, if dilation of blood vessel doesn't take place, blood viscosity as a peripheral resistant factor will act against the blood flow. According to the theoretical explanation of viscosity effect on oxygen carrying, the variables of this equation can be replaced in order to deliver oxygen to the tissues (Schmid-Schönbein et al., 2002 and 2001)

The researchers had indicated that, biological liquids such as blood and mucosa have abnormal flow characteristics and are not like simple liquids. Such fluids are called non-Newtonian fluids which usually contain macromolecule solution (such as protein) and in case of blood, a lot of suspended ingredient such as RBC exist (wells et al., 1961). Plasma almost functions as a liquid but the existence of RBC causes that the changes of the blood viscosity aren't linear with the changes at the shear rate (West, 1990). The lower the speed of the flow, viscosity of the blood will increase and vice versa (Moller and Kristensen, 1991; Handa et al., 1989).

2.1. Shear stress and shear rate: In order to determine viscosity of a fluid like blood, there is a need for application of certain amount of force on the certain amount of blood. The applied force on this fluid is called shear stress, the minimum force is needed to initiate the fluid flow is called yield stress, and the amount of blood which starts to flow under the effect of this yield stress is called shear rate. The more viscosity, the more shear stress is needed to make certain amount of shear rate or flow. The first concept of viscosity has been presented by Newton in this way, the more force on the fluid, the more flow the fluid will have. Viscosity of whole blood is about three to five times more than viscosity of water in the shear rates more than 100 cm2/s. In the lower shear rates (0.1 cm2/ s); viscosity of whole blood will be 50 to 200 times more than water.The effective factors on the blood viscosity are plasma viscosity, hematocrit, plasma proteins (fibrinogen and albumin), and deformability and aggregation ability of red blood cells which are discussed as below:

2.2. Plasma viscosity: Plasma viscosity is considered as one of the main determinant of blood viscosity. By increasing the density of the plasma protein, plasma viscosity will also increase but different proteins have different effects on the rate of plasma viscosity. Although there are high correlations between fibrinogen and plasma globulin with plasma viscosity, the increase of albumin level has less effect on the plasma viscosity (Rand et al., 1970). Increased plasma viscosity is one of the important characteristics of the rheological disorders. Two major reasons for this are:

a- Because plasma is Newtonian liquid, its viscosity measuring is done easily but artificial surface of the measuring tools can affect the accuracy of the measurement b- Its high ability in determining the rate of the acute reactive proteins such as fibrinogen. In laboratory situations, plasma viscosity shows close relationship with hemodynamic state too, in a way that

decreased viscosity causes to decrease in the diameter of the vessels. Of course, some researches referred to the beneficial effects of viscosity, because the increased viscosity can increase the density of the capillaries, taking place by nitric oxide (Herbert et al., 2006).

The percentage of RBC volume in total blood is called hematocrit, and it is reported in the shape of percentage (usual) or decimal (SI unit). There is a linear logarithmic relationship between hematocrit and plasma viscosity but this linear logarithmic state is true in hematocrit range of 20 to 60 percent. Out of this range, the rate of plasma viscosity increases with the increase of hematocrit in a non-linear manner (Chien et al., 1996). There is a high correlation between RBC aggregation and hematocrit. Hematocrits Over 55 percent and fewer than 35 percent cause lots of changes in the rate of RBC aggregation. The changes of RBC aggregation in the range of 35 to 55 percent are trivial for hematocrit and in this range the rate of RBC aggregation is independent of hematocrit (Gustavsson et al., 1981). By its major effects on blood viscosity from one patient to another and from one participant to the others, hematocrit shows big differences which make it hard to compare viscosity without considering the hematocrit rate (Neuhaus et al., 1992). In other hand, hematocrit increase can affect the increase of aggregation (Frank et al., 1997). Findings demonstrated that there is optimal point for hematocrit in which the maximum capacity of ventilated oxygen diffusion takes place. When hematocrit decreases in high rate, RBC can't get the enough regular oxygen for maintaining the artery oxygen pressure. This situation happens in the same way when hematocrit is very high with this difference that there will be competition for receiving and carrying the oxygen among RBC (Frank et al., 1997). Since decrease of hematocrit in tissue has less affectivity from the hematocrit rate in blood vessels, capillary viscosity is less affected by blood hematocrit (Mirhashemi et al., 1988). This subject represents the issue that decreased hematocrit up to 50 percent doesn't have effect on the oxygen receiving of the tissue. Also, Buerk (2001) pointed out that decreased number of RBC can increase available Nitric oxide (Buerk, 2001).Hematocrit is considered as an important parameter of viscosity which has negative correlation with physical fitness (Gaudard et al., 2003). This situation shows that why physical fitness is accompanied by dilution of blood and why decreased hematocrit leads to increased heart output (Brun et al, 2007).

2.3. Deformability and aggregation of blood cells: RBC have high ability in deformability and flexibility and this physical advantage has significant effect in facilitating the blood flow. This physical advantage makes the blood flow possible even in high hematocrit conditions (Brun et al., 2007). If RBC were rigid, blood could have been like a solid material in high hematocrits. Decreased RBC deformability reduces its life time and accordingly leads to ischemia. Low viscosity in high shear rate is because of the high RBC deformability. RBC deformability depends on geometry, flexibility and intra plasma viscosity of RBC. Physical and mechanical damage of RBC significantly affects the fluency and diffusion state of blood flow (Brun et al., 2007). RBC deformability relates on their surface to volume ratio, internal viscosity and its membrane elastic properties (Kon et al., 1983). Plasma proteins, specially fibrinogen, is considered as transmitting bridges of RBC for their adhesion to each other and this situation often takes place by decreased speed of blood flow. Connection of plasma fibrinogen to RBC surface causes to negative recharging of these cells. This state is related to non-Newtonian feature of RBC. RBC aggregation depends on the shear rate. Nonetheless, this effect would be trivial in shear rate of more than 100 / sec. RBC aggregation or disaggregation ability according to shear rate is considered as a reheological advantage (Charm et al., 1974).

2.4. Plasma proteins: Proteins regarding their size are effective in plasma viscosity. The bigger and more asymmetric the protein, the more its effect on plasma viscosity (Lowe, 1987). Fibrinogen is very asymmetric, the ratio of its length to width is equal to 20 to 1 and its synthesis is done in liver. Fibrinogen is considered as the biggest plasma protein with molecular weight of 350 to 400 kilo Dalton with concentration of 5.5 percent and has the most effect on plasma viscosity. Fibrinogen is considered as a risk factor for clogged arteries and cardiovascular diseases (Dormandy, 1970). The issue that the increased fibrinogen concentration in individuals is related to ischemia or to the existence of an acute secondary reactant is a challenging discussion. Fibrinogen with its key role in blood hemostasis has a significant role in RBC aggregation (charm et al., 1974). Fibrinogen increases non-Newtonian feature of blood and is effective in the rate of RBC deposition (Rand, 1970). Thus, Fibrinogen influences plasma viscosity. The effect of fibrinogen on plasma viscosity can be seen during the evaluation of serum viscosity. In a way that plasma viscosity is 20 percent higher than serum viscosity. In addition to its effect on the RBC aggregation and plasma viscosity, fibrinogen increase can influence arteriosclerosis by interacting with platelet in endothelium and platelet activities. So, fibrinogen can show its inappropriate effects via other than rheologic pathways like system or by its direct effect on endothelium (Temiz et al., 2000). Generally, fibrinogen increase makes the risk possibility for healthy and unhealthy individuals up to 2 times (Maresca et al., 1999).

Plasma viscosity is affected by total protein and the percentage of comprising proteins. Albumin is a small protein than fibrinogen which has less effect on plasma viscosity (Jung et al., 1992). Although fibrinogen has less

concentration in plasma, it has the most effect on plasma viscosity (Temiz et al., 2000). In contrast, albumin with its highest amount as a plasma protein has least effect on plasma viscosity (Maresca et al., 1999).From mathematic view point, certain correlation between plasma proteins and blood viscosity is unknown. Anyhow, Jung and et al., (1992) in the study of evaluating the relationship of triglycerides, globulin, fibrinogen and cholesterol with plasma viscosity in 2821 participants, reported that each of them needs 2 to 3 times changes in contrast to fibrinogen changes, in order to make fibrinogen like changes in plasma viscosity (Maresca et al., 1999). Harkness (1971) has reported that 98 percent of plasma viscosity in contrast to water is because of plasma proteins and the other two percent is related to other small molecules (Harkness, 1971).

Fibrinogen has an important rheological effect on blood flow with high and low shear rates. In high shear rates, fibrinogen will affect plasma viscosity while in low shear rates it will act on blood viscosity via the RBC aggregation. Fibrinogen is considered as the most increasing protein of the aggregation process (Maeda et al., 1987). The cases such as whether the rate of RBC aggregation is generally dependent on the plasma fibrinogen hasn't clarified completely yet (Boisseau, 2006).Moller and Kristensen (1991) have done some studies in about the relationship of fibrinogen and cardiac ischemia related factors. Information of the individuals has been gathered by questionnaires. Questionnaire includes question about social variables such as social level, occupation, mental and psychosomatic variables like economic problems and abdomen aches, behavioral variables like smoking, drug use and physical activities and also physiological variables like HDL-C and LDL-C levels, physical fitness and systolic blood pressure. The purpose of this study was to find correlation between mentioned variables and plasma fibrinogen level. The highest correlation has been observed between fibrinogen level and smoking, HDL-C and LDL-C and it has concluded that smoking creates the most danger for individuals who have high fibrinogen level (Moller and Kristensen 1991).

3. Hemorheology and cardiac function: Blood viscosity has a Considerable effect on cardiac output and local blood flow as well as capillary blood flow. Cardiac output is equal to multiply of stroke volume in heart rate. Stroke volume shows reverse relation with blood vessels resistance against blood flow. When blood viscosity increases and no compensation is done to vasodilation, heart load increases to keep the cardiac output. In the same way, vasoconstriction increases heart load and decreases cardiac coronary blood flow and accordingly causes to development of heart disease. In other hand, increased coronary viscosity besides increased heart load can create similar pathophysiological results (Gustavsson et al., 1994). Patients suffering angina have indicated increased blood viscosity in contrast to the individuals who doesn't have it. The rate of increased blood viscosity can be referred to increased plasma proteins which is the result of myocardium damage. The rate of increased blood viscosity can show the rate of myocardium damage. Lowe (1995) measured individuals' blood viscosity rate before facing heart disease and got a high relationship between increased blood viscosity and heart disease. From the physiological and also clinical point of view, decreased blood viscosity causes remedial effects and also improvement of heart disease (Lowe, 1995). Hemeorheological disorder was considered as an independent risk factor for vascular and heart disease, meanwhile increased blood viscosity has an important role in artery stenosis disease (Lowe et al., 2000). Increased blood viscosity can have inappropriate effect on blood flow and oxygen delivery to tissues. Laboratory experiments are applied for measuring rheological variables of blood, as instruments for recognizing and identifying disease and their progress. To predict blood flow state in increased blood viscosity syndrome, measurement of rheological properties is used (Gustown et al., 1981).

4. Acute effect of exercise on hemorheology:

4.1. Temporary increase in blood viscosity: Exercise always increases blood viscosity because of increase in plasma viscosity and hematocrit whether in maximal or submaximal intensity, short-term or long-term, regular or warm and humid weather (El-Sayed et al., 2010). In most cases, these two hemorheological variables justify the observed increase in total blood viscosity (Brun et al., 1993). In an only research that hasn't reported such a change in viscosity (Lacombe et al., 1991), by a little contemplation, it could be understood that, blood viscosity has been measured after exercise (in the recovery period). Therefore, perhaps these short-term changes (in plasma viscosity and hematocrit) haven't been identified because of quick return to pre-exercise amount (Brun, 2002; Brun et al., 1998). This increase in plasma viscosity and hematocrit is usually interpreted as hemoconcentration (Teillet et al., 1991). But such an interpretation is incomplete because the observed changes happen under the effect of at least five mechanisms: redistribution of red cells (RBC) in vascular bed (Martins and silva 1988), splenocontraction that increases the number of , plasma proteins increase presumably via the lymphatic system, loss of water because of sweating for adjusting body temperature (Stephenson and Kolka, 1988) and trapping of water between or inside the muscular cells (El-Sayed et al., 2010; Brun et al., 2007; Brun and Khaled, 1999; sjogaard et al., 1985).

4.2. Changes in deformability and aggregation of RBC: In most of the exercise protocols (not all of them), some changes happen in rheological features of RBC. The most classical change is decreased RBC deformability which is not special finding about exercise; because this decrease is also the result of stressful events such as laboratory, exciting stress caused by watching movie and endogenic suppress (Brun, 2002 b). These exercise induced changes are not observed usually when rheology of RBC is observed in buffer after suspension of these cells, so it shows these changes happen under the effect of plasma factors rather than natural properties of RBC (Brunet al., 1993; Brun et al., 1998). Also, when blood lactate increases to over 4 mmol (anaerobic conditions) RBC rigidity increases and accordingly blood viscosity increases significantly (Brun et al., 1993). Study of relationship between RBC aggregation and lactate has shown that when lactate increases, RBC aggregation increases. These results suggest that increased RBC aggregation affects the accumulation of lactate. This situation is caused because increased RBC aggregation causes to some problems in oxygen carrying in tiny capillaries (Varlet and Brun, 2004).

Since blood lactate causes to wrinkling and decreasing of RBC deformability in laboratory condition, possible increased RBC rigidity is justified which is supported with the correlation between lactate accumulation and RBC rigidity during exercise. The lactate threshold which caused to these changes was over 4 mmol that could cause acidosis state (Brun et al., 1991). By the way, some other researches have shown that lactate in low concentration in vitro or in vivo can also have some effects. In fact lactate is not the only factor for RBC rigidity. Traumatic Damage of RBC in plantar muscle is perhaps considered as an important factor in endurance activities for RBC rigidity, (Galy et al., 2005) which is not determined completely (Behn et al., 1991). Perhaps body fluids status affects more in RBC rheology during the exercise activity via preventive effect of fluid intake on RBC rigidity.

In addition, there is an acute increase in RBC aggregation and disaggregation shear stress (Brun et al., 1998). The mechanism of such changes is not clear yet, because these changes exercise hasn't been observed in all exercise protocols and usually it is not identifiable by already used techniques, i.e. the light transmission analysis (Myrenne aggregometer) (Brun, 2002; Brun et al., 1998). In the situation in which pre-exercise fibrinogen concentration shows correlation with the exercise induced changes, it is possible that lactate isn't a determinant factor in RBC aggregation and the most important extra cellular factor of this process may be fibrinogen (Connes et al., 2007). However, as it will be discussed, changes of RBC aggregation my show leukocyte activation (Brun et al., 2000).

While RBC rigidity usually increases or doesn't change during exercise (Brun, 2002; Brun et al., 1993; Brun et al., 1994; Brun et al., 1998; Vande walle et al., 1998), there is an interesting report of this parameter decrease using ektacytometry measurement method after exercise (by LORCA) (Brun et al., 1998). This contrast has been mentioned recently with study on well trained athletes during progressive exercise test up to VO2max. In this case, rigidity of RBC contrastively decreased (Connes et al., 2002). In addition, a study (Brun et al., 1995) in lab condition shows that lactate concentration of 2–10 mmol increase RBC deformability in such athletes while in the blood of less active individuals, this parameter decreases classically. Therefore in well trained participants exercise induced increase of blood lactate can't cause to increased RBC rigidity as it happens in non-athletes or individuals who have moderate fitness (like football players), but in fact it improves the RBC deformability (Temiz et al., 2000; Brun et al., 1991).

4.3. Leukocyte activation and oxidative stress: Leukocyte activation and oxidative stress (Ajmani et al., 2002; Senturk et al., 2005; Temiz et al., 2000) are more passible to have important role in hemorheological effects of sport activities. Increase of oxygen utilization during exercise leads to production of free radicals from various sources like mitochondria and leukocyte. Temporary lack of oxygen in tissue as a result of harried use of oxygen in the muscle involved in activity, and insufficient provision of oxygen in pulmonary level in some exercised individuals has been proved and may cause to the formation of free radicals. Although its mechanism is not clear yet, oxidative stress during acute exercise is accompanied with hemorheological disorders (Ajmani et al., 2000). According to Ajmani et al. (2000), exercise induced oxidative stress also causes to increase of the numbers of RBC and plasma fibrinogen level and accordingly leads to increase of aggregation.

Nonetheless, up to day there was little information about the role of leukocyte activation in these rheological changes. The numbers of leukocytes are increased after exhausting exercise. This effect is referred to the increase of blood flow that calls up leukocytes from peripheral pool and/or hormone changes which may mediated by beta adrenergic 2 receivers. It is interesting that, during exercise, reduced filtering ability of leukocyte has been reported that is somehow indicator of leukocyte activation which may interact with RBC features via some existing factors in blood flow. Temporary hypoxia may also cause to release of cytokines and activation of leukocytes. When leukocytes are active (especially polymorphonuclear leukocytes), they decrease molecular oxygen in a way to produce metabolites like superoxide anion, peroxide hydrogen or hydroxyl radicals (Ajmani et al., 2000). In the nearby tissues, these metabolites can cause oxidative damage. RBC are susceptible to oxidative damage

although they are equipped with antioxidant mechanisms. Recent studies have shown that RBC in the vicinity of active leukocyte, at least get damaged somehow with the mediation of oxidative mechanisms which causes morphological and functional changes (Brun et al., 2000). Temiz et al. (2000) have studied activation of leukocytes and RBC damage after exhausted exercise in rate. Significant increase in oxidation of protein and lipid peroxidation of RBC membrane, and decreased activation of membrane enzymes have been observed in the early and post stage of exercise. Although biochemical evidences indicated oxidant damage, RBC crossing time couldn't significantly change RBC deformability. These changes had positive correlation with increased phagocytic activity of leukocytes (Temiz et al., 2000).

4.4. RBC Rheological changes and exercise performance: Theoretically, it seems that most of the changes we have reviewed previously have negative effect on exercise performance. Experiments done on healthy subjects, volunteers and rats in hypobaric and hypoxic condition, support this hypothesis (Guézennec et al., 1989). These studies show that preventing from exercise induced increase in RBC rigidity by omega 3 fatty–acid improves maximum aerobic capacity. Therefore in the hypoxic situation, rigidity of RBC may be a limiting factor for providing oxygen for muscle and thus makes the performance interrupted.

Also, it is reported that rigidity of RBC reinforces pulmonary hemodynamic responses to hypoxia, hypobaric simulation in high altitude, (Doyle and walker, 1990). This hypobaric environment increased blood viscosity via combination of factors (hypoxia, low PH, large amount of blood lactate). These factors explicitly make RBC more rigid which is hypothetically accompanied with pulmonary hypertension. This phenomenon, low pressure environment induced pathophysiological disorder improved by the use of calcium canal blocker (Flunarizine).

It has been observed that physical activity induced changes in body rheology is related to the rate of perceived exertion. Increased hematocrit had a positive correlation with perceived exertion (Brun et al., 1990) and it has been presumed it shows a message among other recognized factors of fatigue (heart rate, lactate, and blood glucose) which are integrated in consciousness level in order to create fatigue feeling. An interesting hypothesis (Brun et al., 1998) is that, disorder in blood rheology accompanied with increased blood coagulation, may be involved in the increase of cardiovascular risk of maximal exercise. Along with this hypothesis, it has been reported recently that, one of the marathon runners suffered from thrombosis in central retinal vein (Gaudard et al., 2002). This runner showed increased blood viscosity, hematocrit, RBC aggregation, and also RBC disaggregation threshold following a standardized submaximal exercise test. While some of these involved factors in high viscosity may be because of previous thrombotic incident, these findings support our hypothesis about hemorheological disorders during marathon, which may be one of the pathogenic factors of retinal thrombosis (Gaudard et al., 2002). However it should be mentioned that these rheological changes have been observed during submaximal exercise like maximal work load (Brun et al., 1994). This finding lead us to the point that simple changes in hematocrit, RBC rigidity and plasma viscosity are adaptive physiological modifications that takes place during various exercises and are not perse indicator of risk possibility. These changes probably can be overcome with vasodilatation. However, recent researches show that perhaps increase in blood viscosity during exercise is necessary for producing NO and sufficient vasodilatation (Connes et al., 2012). It seems that maximal or exhausting workload risk is related to other factors such as severe muscular damage, change in homeostasis and activation of white blood cells. But, when wide changes in blood rheology are accompanied with hemostasis disorder and inflammation without enough vasodilatation, clinical risk are not negligible. According to some researchers (Ajmani et al., 2000; Senturk et al., 2005; Temiz et al., 2000), these inappropriate rheological changes may be responsible for part of the increase of Myocardial infarction and sudden death incidence during exercise (Brun et al., 2010).

5. Chronic effect of training induced adaptations on hemorheology

5.1. Adaptive exercise induced hemorheological progress and hematocrit paradox: Cross sectional studies repeatedly have shown that athletes have lower total blood viscosity, plasma viscosity and hematocrit in contrast to the sedentary group (El-Sayed et al., 2009; Ernst, 1987). Ernest and et al., (Ernst, 1985; Ernst, 1987) have expressed briefly that, the flooder the athletes' blood, the fitter the athletes is. Konig et al. (1997) have studied recreational physical activity relevant to plasma viscosity among 3522 women and men of 25-64 age and indicated that this population has lower plasma viscosity in comparison to their peers. Plasma volume increases after exercise, (Brun, 2000; Brun et al., 1998) that cause to dilution of blood and is opposite of acute increase in viscosity as described earlier. Blood dilution causes to decrease in hematocrit which explains reverse relationship between hematocrit and physical fitness (Brun, 2002; Brun et al., 1998). Thus, a big paradox can be seen about hematocrit in exercise physiology (Brun and et al., 2000).

Since sport performance is dependent on the capacity of oxygen carrying to muscle, it is not surprising to see that sport performance increases under the effect of hematocrit increase because of exercising in high altitude, blood doping or erythropoietin injection. Because of availability of erythropoietin by biological engineering

extensively, doping with this hormone has become popular. But, logic of this kind of doping has contradiction with the physiological information discussed before. There is a reverse significant correlation between hematocrit and physical fitness under the regular situation (Brun, 2002; Brun et al., 1998; Brun and et al., 2000).

Comparing different hematocrit levels among athletes show this paradox explicitly (Brun et al., 2000). Group of the athletes who had the lower hematocrit, had the highest amount in these parameters: aerobic working capacity, isometric strength of adductors, charging point of carbohydrate oxidation (fat 30% and carbohydrate 70 %), and insulin-like growth factor binding protein. Inversely, to athletes who with high hematocrit, had the most rate of RBC aggregation and disaggregation threshold and lower percentage of water in fat free mass. Generally, low hematocrit has relationship with high aerobic capacity and participants with high hematocrit (>44.6 %) have been repeatedly suffered from over training or anemia and their blood viscosity (and their RBC disaggregation threshold) had tendency to increase (Brun et al., 2000).

This subject has been paid more attention by Gaudard et al (2003). Maximum aerobic capacity which is defined in power unit (Wmax) has shown reverse relationship with total blood viscosity. When this capacity has been mentioned as power in fixed heart rate, 170 beat per minute, indicated reverse correlation with some factors but step by step regression chose only hematocrit as a determinant factor independent from aerobic power. In addition, the best predictor of maximum oxygen consumption (VO2max) was also hematocrit.

Therefore, it is clear that physical fitness is accompanied with a low viscosity and low hematocrit pattern, while lack of fitness and overtraining accompanies with a little higher viscosity. Since this physiological fact is not in the same direction with general belief (that, the more amount of RBC, the fitter you are), it seems that this hematocrit pattern should be expanded among the coaches, athletes, and physicians. In some sport fields, hematocrit pattern is different from most of the sports. Body builders don't show any improvement in blood rheology after training (Brun, 2002; Ahmadizad, 2005; Nikookheslat, 2010), and dominant index of training and fitness in rugby players is a little increased plasma viscosity (Bouix et al., 1998). Hypothesis is that, this increase of plasma volume in body water pool has a preventive role against dehydration.

5.2. Training induced chronic hemerheological fitness

5.2.1. Training induced hormonal and metabolic changes: Dudaev et al., (1986) have shown that the effects of 30-day regular cycling exercise in coronary patients in comparison to the control group, decreased fibrinogen, cholesterol and concentration of triglycerides levels of RBC membrane. An interesting point is that, concentration of fibrinogen and triglyceride show correlation with hemodynamic and hemorheologic and VO2max improvement (El-Sayed et al., 2009; Connes et al., 2004) which indicates that training cause to positive adaption in fat metabolism, and accordingly cause to improvement in blood rheology and proper hemodynamic effects.

The main mechanism of these adaptations is probably growth hormone-somatomedin axis. At the time of growth hormone decrease, low insulin sensitivity with the increase in body fat, lipids and circling blood fibrinogen can be observed. While trained individuals have shown different metabolic profile that indicates increased operation of this axis. Therefore, this hormonal axis probably cause to the regulation of training induced changes in blood rheology, less or more directly (Brun and Khaled, 1999). In these sports which improve strength more than endurance, aggregation and RBC deformability is improved without explicit changes in the distribution of blood. This improvement in rheology of RBC (aggregation and deformability) has positive relation with body composition (fat percentage) and oxidation balance (carbohydrate and fat) during exercise. This concept has been extensively studied in rugby. In this sport branch, body composition and blood rheology are related to each other and both of them have correlation with performance (Bouix and et al., 1998).

5.2.2. Endurance exercise: body fat and muscular mass: In rugby men players, flexibility of RBC had positive correlation with isometric power of adductor muscle of the tights and RBC aggregation had positive correlation with fat mass. Aerobic working capacity had reverse correlation with the increase of plasma viscosity during physical activity suggesting that strength doesn't have more importance among rugby players. This study shows that fat mass is the determinant of RBC aggregation even in physiological range, which suggests that exercise induced changes in body composition, has an important role in special hemorheologic profile of these athletes (Bouix et al., 1998).

In Rugby women players, forward players (stronger) and defend players (more enduring) have been studied in 2 groups. defend players are thin and have little fat mass and muscle mass and more running speed and aerobic capacity in contrast to forward players (Cassan et al., 2001). While comparison of hemorheologic variables in forward players showed that these players have more blood viscosity while in both groups, plasma viscosity amount, RBC aggregation and blood hematocrit were similar. It seems that high viscosity of forward rugby women players can be justified with the more rigidity of RBC. Ability of lipid oxidation during exercise has indicated negative correlation with blood viscosity and RBC rigidity. Therefore, it has been deducted that among rugby women, blood viscosity has negative relation with aerobic fitness (Brun et al., 2004). This observed negative

correlation between RBC deformability and ability of more lipid oxidation during endurance exercise, could be because of more lipid oxidation in endurance activity. This increased fat oxidation, changes fat metabolism and improves rheology of RBC besides performance.

6. Effect of hemorheological parameters on sport performance

6.1. Can rheology determine sport performance?

It has been mentioned before that, in contrast to less fit group, fit individuals have lower plasma viscosity (Brun, 2002; Brun et al., 1998). Flexibility of RBC has positive relation with isometric strength of adductors (Bouix et al., 1998). In addition, there is a positive correlation between blood fluidity and aerobic work capacity, time to exhaustion (Brun et al., 1998) and maximum oxygen consumption (Brun, 2002). RBC aggregation also has shown reverse correlation with steady state, consumed oxygen during exercise and difference of vein/arteriolar blood oxygen and positive relation with cardiac output during rest. Blood viscosity has negative relation with applied oxygen in different shear rates. RBC deformability in all shear stress has positive correlation with consumed oxygen (Simmonds et al., 2011).

In all exercise intensities, there is a significant negative correlation between RBC deformability and systemic vascular resistance and significant positive correlation between RBC deformability and vein/ arteriolar oxygen difference and between RBC deformability and consumed oxygen (Connes et al., 2009). Meanwhile, the best correlation is for plasma viscosity (Brun et al., 2010). Moreover, blood lactate response has negative relation with blood viscosity (Brun, 2002; Brun et al., 1998; varlet and Brun, 2004) and power intensity in which blood lactate reaches to 4 mmol in a liter, has reverse correlation with erythrocytes aggregation (Brun, 2002).

Studies on patients of sickle cell trait (SCT) indicate low capacity for long term competitive sport activities under hypobaric pressure and hypoxic condition, which seemingly is because of decreased in RBC flexibility (Gaudard et al., 2004). Also, Connes and et al., (2006) have recently reported that SCT patients who do submaximal exercise in the sea level, have lower aerobic capacity, the finding that is probably because of decreased RBC deformability, increased RBC aggregation, decreased blood fluidity and increased vascular adhesion of these patients in comparison to healthy individual (Connes et al., 2005; Tripette et al., 2007). In other hand, when RBC fluidity is improved using ω3 fatty acids, under hypobaric and hypoxic condition, Vo 2max increases suggesting that preventing from rigidity of RBC during exercise, improves aerobic capacity in this condition.

Theoretically, increase of blood fluidity increases oxygen delivery to the muscles in trained individuals during exercise (Connes et al., 2006). While this hypothesis has not become clear yet (Brun et al., 2010). There are a lot of biological indices for physical fitness which are various according to different sport activities; maximum oxygen consumption (VO2max) is the most famous of this indices which has not studied in relation to blood rheology. As we mentioned before, there is negative correlation between VO2max and blood viscosity because of reverse relationship with plasma viscosity (Simmonds et al., 2011; Brun et al., 1998; Brun et al., 2000). Another important index of physical fitness is extra accumulation of blood lactate (known as anaerobic threshold or lactate threshold) in maximal work load (Brun et al., 1998). In three separated studies (Brun, 2002; Brun et al., 1998; Varlet and Brun, 2004) it is observed that blood viscosity and RBC aggregation have positive correlation with lactate accumulation in blood during exercise. Possible meaning of relationship between resting blood fluidity and lactate response will be discussed later.

6.2. VO2max-hematocrit correlation: Since maximum oxygen consumption (VO2max) and aerobic work capacity (W 170) have high relationship with each other and both of these parameters are aerobic activity capacity indices, both are similarly affected by the same indices of blood viscosity (Brun, 2002). Researches show that viscosity statistically is the best predictor of these two measures of aerobic performance (Brun, 2002; Brun et al., 2000). But, hematocrit has also negative relationship with aerobic performance (Brun et al., 2000; Gaudard et al., 2003) which shows beneficial effect of auto-hemodilution. VO2max indicates body ability to increase oxygen carrying from atmosphere to muscles, and is dependent to several stages. Limiting step (will be mentioned below) is different among athletes. VO2max is equal to the multiple of cardiac output (Q) in oxygen content of blood (CaO2). If we use Hagen-Poiseuille law (Schmid–Schonbein et al., 2002), the equation of VO2max = Q × CaO2 can be written as a function of hematocrit (Φ) and viscosity (η). Doing this, the equation changes to:

VO2max = constant coefficient * (Φ/η) * (ΔP/Z).

In this equation ΔP is blood pressure drop and Z is vessel hindrance (dilation/contraction). So, value of (Φ/η) should be a limiting factor for VO2max. In experimental studies VO2max doesn't have relation with Φ/η, but in return it has reverse relationship with Φ which is one of the blood viscosity indices and has negative relation with physical fitness (El-Sayed et al., 2009; Brun et al., 1998; Brun et al., 2000).

This matter suggests that negative relation of VO2max with hematocrit indicates physical fitness, because physical fitness is accompanied with auto-hemodilution which decreases hematocrit and increases cardiac output (Gaudard et al., 2003). Deem et al. (1999) studying on rabbits, observed that decreased hematocrit by 11–30 percentage of auto-hemodilution, improves partial

pressure of arterial oxygen and oxygen exchange (difference of alveoli and arteries, A-a ΔO2) and increases ventilation ratio in alveoli to blood flow (VA/Q). Frank and et al. (1997) studied also the effect of pulmonary hematocrit on pulmonary oxygen diffusion. Although pulmonary oxygen diffusion capacity rises by increased hematocrit but pulmonary oxygen diffusion capacity reached to a plateau near the hematocrit of 35%. Generally, results of these studies (Deem et al., 1999; Frank et al., 1997) show that there is optimal amount for hematocrit that makes the highest capacity of pulmonary oxygen diffusion possible. It should be mentioned that according to Deem et al. (1999), pulmonary oxygen exchange is improved by hematocrit change from natural low level to anemia, While according to Frank et al. (1997) study, oxygen exchange (diffusion capacity) is improved by hematocrit change from anemia to natural low level.

These findings indicate the two phasic effect of hematocrit. When hematocrit is too low, RBC can't get enough oxygen for retaining arteriolar blood pressure. This situation also takes place when hematocrit is high with this difference that there is competition among RBC for receiving and carrying oxygen (Frank et al., 1997). Moreover by studying the effect of shape and RBC deformability on pulmonary oxygen diffusion capacity and resistance against blood flow in rabbits' lungs, Betticher and et al. (1995) demonstrated that disorder in RBC deformability decreased pulmonary oxygen diffusion capacity and increased resistance against blood flow while improvement in RBC deformability had reverse results. Optimal RBC deformability causes to homogeneous distribution of RBC in pulmonary capillaries and other tiny vessels which may explain beneficial changes of RBC deformability on pulmonary diffusion of oxygen (Betticher et al., 1995; Zhao et al., 2012). Studies show that hematocrit and distribution of RBC affects RBC membrane diffusing capacity for carbon monoxide and diffusive uptake for carbon monoxide. At a given hematocrit, homogeneous distribution of RBC increases diffusive uptake for carbon monoxide up to 33% (Hsia et al., 1997).

Caillaud et al. (2002) suggested that combination of high hematocrit and impaired rheology of RBC (especially during exercise) may cause to excessive pressure on pulmonary capillary wall leading to capillary rupture and leakage of liquid from capillary that cause to rise interstitial edema and promote the oxygen distribution limitation. Generally, these studies suggest that impaired hemorheology changes oxygen diffusion from alveolus to capillary which may reduce sport performance. Also, it seems that impairment in blood rheology such as rigidity of RBC or increase in RBC aggregation can cause clogged arteries or clinical effects such as pulmonary hypertension, ischemia, and necrosis in different organs.

6.3. The relationship of blood rheology and heart function: Classic heart physiology hypothesize that maximum cardiac output (Qmax) is multiplying of heart rate (HR) and stroke volume (SV) and is the most important factor indicating individual differences in maximum oxygen consumption (VO2max) (Silverthorn, 2009). Most of the textbooks mention that 70–85 percent of limitation in VO2max is relevant to maximal cardiac output. In addition, several studies have shown that exercise cause to improvement of VO2max as a result of increased maximal cardiac output rather than increase in A-aΔ. But more probably, any increase in blood viscosity increases cardiac after-load which causes a decrease in maximal stroke volume. Recently a study about blood rheology parameters and variability of heart rate of Sickle cell trait athletes in resting state, was indictor of loss of parasympathetic activity in hyper viscosity syndrome (Connes et al., 2006 a). These results support our claim that, blood rheology can be relevant to heart function. Sickle cell trait athletes usually have lower aerobic capacity than regular athletes, which suggests disorder in blood rheology and proper efficiency of heart are limiting factors for endurance performance (Gallais et al., 1994).

Hematocrit is the most important hemorheologic factor which influences oxygen carrying capacity. Studies on doping show that 900–1350 ml blood injection, increases oxygen carrying capacity and also athletes' VO2max 4-9 percent. Several studies have reported the effect of erythropoietin injection on sport function. One of these studies has reported that VO2max increased 7-10% after 4 weeks regular injection, the effect of erythropoietin accompanied by increase of 8-10 percent in hemoglobin and hematocrit (Connes et al., 2004). In another study Connes (2003) also reported that, 4–week treatment with erythropoietin causes to faster oxygen consumption kinetic in the start of submaximal cycling exercise. These studies (Connes 2003; Connes et al., 2004) indicate that if hematocrit doesn't exceed an optimal range, it would have an important role in endurance performance even if the increased hematocrit causes to increase in viscosity and to somehow neutralize beneficial effect of increased hematocrit on oxygen carrying capacity.

6.4. Blood rheology and oxygen delivery to tissues: Studies have shown positive correlation between blood fluidity and physical fitness indices such as time of endurance activity up to exhaustion, aerobic working capacity (w 170) or VO2max (Connes et al., 2010; Brun, 2002; Brun et al., 1998). As Brun (Brun, 2002; Brun et al., 1998) pointed, increased blood fluidity in exercising athletes, may theoretically increase delivery of oxygen to active muscles. This issue explains why VO2max has reverse correlation with blood viscosity because of negative correlation with plasma viscosity. In addition, Charm et al. (1979) reported lower plasma viscosity in joggers comparing with non-joggers. Therefore, plasma

viscosity can be one of the determinant factors of aerobic performance. In capillaries (including muscle capillaries), RBC flow in one column and are surrounded by a layer of plasma. In fact, if plasma viscosity becomes too high, movement of this blood structures in capillaries will face with problem, resistance against blood flow will increase RBC orientation inside micro-vessels disorganize and therefore delivery of oxygen to tissue will be impaired. Hematocrit can have significant role in muscular oxygen supply. Although high values of hematocrit is responsible for high capacity of oxygen carrying in blood, several studies indicated negative relation between hematocrit and aerobic performance (Brun, 2002; Brun et al., 1998). Moreover, optimal range of hematocrit cause to increased resistance against blood flow in capillary, and interfere tissue oxygen supply (Brun, 2002; Brun et al., 1998). RBC properties (aggregation and deformability) can also improve or impair tissue oxygen supply. As we discussed before high ability of deformability let the RBC distribute equally in pulmonary capillaries and other micro-vessels that may cause to enough diffusion of oxygen in pulmonary or muscular levels (Zhao et al., 2012; Brun et al., 2010). Parthasarathi et al. (1999) have reported that decreased RBC deformability has inappropriate effect on capillary recruitment and delivery of oxygen to tissue. Several studies about rheological behaviors of RBC in capillary network have indicated explicitly that capillary flux and velocity is highly dependent on RBC deformability in entry point to capillaries. Disorder in RBC deformability has inappropriate effect on capillary blood flow. It has been observed that RBC with low deformability can't enter capillaries and take the central direction through tiny vessels which can change oxygen delivery to tissues (Parthasarathi et al., 1999).

Recently, microcirculatory effects of RBC aggregation have been discussed with controversy. Still, most of evidences show that high RBC aggregation is responsible for increased blood viscosity, blocking the blood flow and increasing resistance against blood flow which probably make problem for oxygen delivery to tissues and cause to relocation of metabolism toward anaerobic metabolism and restrict endurance performance (Brun et al., 2010).

6.5. Blood rheology and central governor theory: Classic theory of exercise physiology presupposes that maximal performance in exercise is restricted as a result of metabolic changes in skeletal muscle involved the activity by cardiovascular system (peripheral fatigue). Regarding Hill's classic model (Noakes et al., 2001), peripheral fatigue happens only after starting heart fatigue or exhaustion. So, this hypothesis predicts that during heavy exercise, heart (but not skeletal muscle) face with anaerobic metabolism or ischemia risk. As Noakes et al. (2001) reported, Hill had suggested existence of one governor in heart or brain which restricts heart function when local ischemia of myocardia happens, in order to prevent fatal cardiac accidents during heavy exercise. Noakes et al. (2001) have reported some experimental studies which is along which the theory of decrease of maximal heart rate, maximal stroke volume and maximal cardiac output during acute ischemia because it is in line with central governor. Central governor theory suggests that afferent information from heart (and probably from brain and respiratory muscle) informs brain from a probable risk of ischemia or hypoxia in that organ. In response, central governor by means of motor cortex operates in a way that decreases active muscles efferent neurons activity during activity and there for, decreases active muscle mass and intensity of the activity which can be tolerated (Noakes et al., 2001). Limiting active muscle mass, central governor limits peak VO2 such that doesn't cause to ischemia of vital organs. Brain tissue has high tendency to hypoxia and high rate of its metabolism, needs a lot of oxygen supply. Because cortex capillaries are very narrow, every kind of hemorheologic disorder (increased local hematocrit, intensive RBC aggregation or decreased RBC deformability) changes the flow of these blood structures and enough content of blood oxygen accordingly. Disorder in blood flow, which is created as a result of exercise and continuous metabolic changes (lactic acidosis and oxidative stress), can interrupt brain blood flow. Oxygen deprivation can decrease activation of muscle afferent neuron during activity in order to limit metabolic changes and therefore prevent from more hemorheologic disorders which may cause to intensive local ischemia of brain. In addition, as Noakes et al. (2001) suggested, afferent information from heart and other organs, informs brain to decrease or stop exercise. Hemorheology (in relation to exercise induced metabolic changes) can have an important role in this process. Also Khaled et al. (1997) studying the effect of edible zinc supplementation on rheologic behavior of blood and Borg's rating of perceived exertion (PRE) during exercise in healthy participants noticed that blood rheology and PRE improved after zinc supplementation which suggest that hemorheology probably effects exercise tolerance and thus endurance function. Finally, Brun et al. (1990) support this hypothesis by reporting positive correlation of hematocrit and perceived exertion in healthy participants.

7. Viscosity parameters, homogeneity and heterogeneity factors of blood flow during exercise: Schmidt-Schönbein et al. (2002) noticed that classic concept of total flow and total peripheral resistance can't explain the relationship of viscosity factors of blood flow and they have tried to explain this concept with current patterns which were used in non–linear science called percolation theory. According to this approach, blood viscosity doesn't behave like a continuous variable similar to laboratory, because blood fluctuates between two opposite states: under the condition of high shear stress-

high blood flow speed, blood viscosity is very low and under condition of low shear stress-low blood flow speed, blood viscosity increases significantly. These changes in blood viscosity are because of local condition of blood flow and effective factors on viscosity such as RBC deformability, RBC aggregation, local hematocrit, plasma viscosity and concentration of fibrinogen. All of these factors cause to change of blood state from a complete liquid into a state close to a solid. Studies have shown that in muscle which is involved in exercise, local fluidity of blood remains very high disregarding systemic hematocrit level. Plasma viscosity is an only factor which probably increases local resistance under this condition. In contrast, in resting period, hematocrit, rigidity of RBC and their aggregation also cause to hyper viscosity and disorders local blood flow.

7.1. RBC aggregation and blood lactate during exercise: These new concepts explain several clinical findings about hemorheology of exercise. First, several studies have indicated correlation between RBC aggregation in base level and increased blood lactate during exercise (Varlet and Brun, 2004). These researches indicate that RBC aggregation may effect on metabolism of muscle lactate. As Vicaut et al. (1994) had shown in lab condition, RBC aggregation may prevent microcirculatory blood flow in muscle. Although, aggregation of these cells is to some extent beneficial for diffusion through microvessels (Osterloh et al., 2000), its increase even in physiologic range may disturb aerobic metabolism in muscle which increases blood lactate. If this hypothesis be true, aggregation of lactate can be influenced from RBC aggregation which blocks microvessel flow and causes to ischemia. While, effect of RBC aggregation on microvessels circulation is challenging, experiments of Cabel et al. (1997) suggests that RBC aggregation shows 60 percent of blood flow resistance in capillaries of cat gastrocnemius muscle. Therefore, RBC aggregation can be the most important modifier of venous resistance in skeletal muscle.

Hypoxic experiments of muscle on dogs suffering from ischemia as a result of exercise (25% decrease of hematocrit) indicated unequal increase in lactate aggregation (Wasserman et al., 1985). This increased lactate accompanied with more consumption of glucose in muscle and increased glucagon, norepinephrine, epinephrine, and cortisol levels while insulin and free fatty acids levels didn't change. These authors suggested that availability of muscle oxygen was involved in this finding. In individuals suffering peripheral obliterative arterial disease, RBC aggregation has reverse correlation with transcutaneous oxygen pressure which supports the concept that aggregation impairs oxygen supply of tissue (Dupuy–Fons et al., 1995).

In fact, one possible response for the relation of rheology and blood lactate aggregation can be effect of RBC aggregation on lactate removal, as it is observed in after exercise modeling of lactate kinetics (Varlet and Brun, 2004). Mathematical analysis of post-exercise lactate provides possibility of reasonable estimation of produced lactate by muscle ($\gamma 1$) and lactate clearance ($\gamma 2$). In participant who indicated vast range of $\gamma 2$ (from 2 to 7.7 ×10-2 min -1), it has been observed that Myrenne index of RBC aggregation (measured at VO2max) was the only hemorheological parameter which had negative correlation with $\gamma 2$. Therefore microcirculatory adaptations induced from RBC aggregation can alter lactate disposal and removal, because it influence balance between carbohydrate and fat oxidation (which is a major determinant of blood lactate concentration in physical activity under physiological condition) (Varlet and Brun, 2004).

Other parameter related to oxygen which can be affected by hemorheology, is oxygen equivalent of the watt. Theoretically, this parameter is close to 10.3 ml. W-1, but is even higher in sedentary participants who have low fat-free mass or high waist-to-hip ratio (Varlet and Brun, 2004). Interestingly, this index is increased in individuals with high plasma viscosity (Varlet and Brun, 2004) and improvement of these parameters by prostaglandin E1, naftidrofuryl or hemodilution partially corrects it. According to Wolff and Witte, measuring this oxygen waste in submaximal steady state workloads, may provide direct determination of microcirculatory function in the involved muscle tissue, as a feature of plasma viscosity (Varlet and Brun, 2004).

7.2. Exercise induced hypoxemia: An interesting subject in exercise physiology is exercise induced hypoxemia (EIH) in which arterial oxygen pressure decreases during intensive exercise. This state has some similarities with exercise induced pulmonary hemorrhage (EIPH) of horses which are seen frequently during the races (Caillaud et al., 2002). In both situations, an inequality in the rate of ventilation/perfusion and/or limitation in pulmonary diffusion capacity take place which is because of interstitial pulmonary edema. In horses, theoretical bases, mentioned blood rheology as the cause of EIPH but there isn't clear picture of hemorheology role in this process (Caillaud et al., 2002).

In human, some cases of pulmonary hemorrhage have been reported after marathon races which support the hypothesis of similarity between EIPH and EIH. In fact, since human pulmonary capillaries pressure during maximum exercise doesn't reach to the level that is observed in horses, and also high capacity of rheofluidification dependent to shear stress in horses in spite of high aggregation of their RBC (Caillaud et al., 2002), we can conclude that rheology of horses and human are completely different. But, recently some evidences show the role of blood rheology in pathophysiology of EIH. First, comparison of EIH and non–EIH athletes

shows that, in athletes suffering local ischemia, exercise increases blood viscosity in high rate. By the increase of these athletes' blood viscosity, RBC deformability gets impaired during activity while RBC deformability improves in athletes who don't experience EIH. In addition, improvement of RBC deformability by multi unsaturated fatty acids, decreases ischemia of tissues in maximal exercise (Caillaud et al., 2002).

It can be supposed there are some adaptations to training in elite athletes that explicitly decreases exercise–induced hyper-viscosity and evidences of this hypothesis are laboratory experiments about the effect of lactate on RBC and paradoxical lack of hyper-viscosity at exercise reported in athletes (Caillaud et al., 2002; Connes, 2005). In EIH-susceptible athletes, this mechanism may be blunted and hyper-viscosity may cause, at maximal exercise to hypoxemia (Connes, 2005; Connes et al., 2004 a).It is probable that exercise improve an adaptive mechanism in RBC which cause these structures deal with lactate and oxidative stress. Perhaps, this adaptation retains RBC deformability and helps higher endurance performance (Connes et al., 2004 a).

DISCUSSION

In sedentary people, regular exercise changes blood properties. These changes lead to lower hematocrit which reflects metabolic progressions in body. In this way, it can be said that regular exercise results in more fluid and healthier blood which can be used as a proper therapeutic method for cardiovascular patients. Studies on hemorheological changes in coronary patients have shown that rehabilitation associates with decreased plasma viscosity and regular physical activity leads to appropriate changes in RBC properties which indicates individuals' fitness and health. Generally despite numerous studies done in physiology, many questions are remained unanswered and because of their potential characteristics, their study has specific importance in biological fields.

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