

Exercise hemorheology as a three acts play with metabolic actors: is it of clinical relevance?

Jean-Frédéric Brun.

Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie 34295 Montpellier-cédex 5, France; Fax: 04 67 33 89 86; Telex: CHR MONTP 480 766 F; Phone 04 67 33 82 84; Email: drjfbrun.@aol.com

Corresponding author: Dr JF Brun, MD, PhD, Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie 34295 Montpellier-cédex 5, France; Fax: 04 67 33 89 86; Telex: CHR MONTP 480 766 F; Phone 04 67 33 82 84; Email: drjfbrun.@aol.com.

1. Abstract

Hemorheological effects of exercise are a triphasic phenomenon including: a) short-term effects (hyperviscosity mostly due to fluid shifts and alterations of erythrocyte rigidity and aggregability); b) middle-term effects (ie, the reversal of acute effects due to plasma volume expansion (autohemodilution) that lowers both plasma viscosity and hematocrit; c) long-term effects that further improve blood fluidity, parallel with the classical training-induced hormonal and metabolic alterations. Red cell rheology during these 3 stages is affected by white cells and oxidant stress. On the other hand, most metabolic and hormonal alterations play a role in exercise-induced hemorheological changes: among them, blood lactate appears to have opposite effects according to the training status, since it generally impairs erythrocyte fluidity while it improves it in some subgroups of highly trained athletes, a difference that could be related to membrane monocarboxylate transporter status. Body composition (mostly hydration status and the amount of fat mass) as well as its major hormonal regulating system (the growth-hormone-IGF-I axis) are both markedly modified by training and these modifications are correlated with hemorheology. Nutritional disturbances affecting caloric and proteic intake, lipids, iron, zinc, etc.. also modulate the hemorheologic effects of exercise. The overtraining syndrome represents a situation of unbalance between body's possibilities, nutrition, and work load, and is associated with metabolic, hormonal, immunologic and hemorheologic disturbances. The clinical relevance of these data is underlined by studies showing that exercise training in patients suffering from metabolic and/or cardiovascular disorders (such as the insulin resistance syndrome) results in a parallel improvement of metabolism, risk factors, blood rheology and fitness. Hemorheological measurements require to be studied, at least as sensitive markers of training, and possibly as "true" risk factors highly sensitive to exercise intensification.

Key words: Blood viscosity, hematocrit, exercise, VO_{2max} , training, overtraining, metabolic fitness, hemorheology, erythrocyte deformability, erythrocyte aggregation, blood lactate.

2. Introduction

Although a quite large body of literature exists now on exercise and hemorheology [1-2], there remains clearly a lot of unresolved questions [1] concerning both the physiological mechanisms and the functional consequences of the hemorheological alterations observed during and after exercise.

First of all, there are acute effects of exercise that increase blood viscosity. However, this effect which was mostly described as a phenomenon of 'hemoconcentration' [3] is quite complex and appears to be modified by several factors (eg, training status, nutrition, hydration) [1-2]. In addition it is clear that its exact physiological meaning is largely unknown.

On the other hand, blood viscosity is reduced after exercise and even more after regular training [5-8]. These effects result in an increased blood fluidity in regularly exercising individuals, which contrasts to the hyperviscosity syndrome of sedentary people. Clearly, while inactivity is characterized by a downward spiral in all physiologic functions [9], reflected by an increased viscosity, an improvement of blood rheology occurs parallel with the correction of metabolic and body composition disturbances when people are submitted to training. These observations are potentially important since blood viscosity is now considered to play a role in cardiovascular risk [10-17]. Moreover, viscosity could be a marker of training status and 'metabolic fitness' in these patients [18-19].

These issues are also potentially important in sports medicine. First, there is a large body of literature demonstrating that aerobic working capacity, but also some other markers of fitness like isometric strength, are fairly correlated to blood fluidity, as we will summarize in this review. Moreover, there is a reversal of this improvement in fluidity when athletes are found to be on the edge of the 'overtraining syndrome'. That leads to the concept of the 'paradox of hematocrit' which will be also summarized in this review: while doping frequently aims at increasing hematocrit, physiological training decreases it, unless overtraining occurs, then increasing slightly viscosity while the subject becomes unfit.

Finally, some mysterious and controversial issues of exercise physiology like lactate kinetics or exercise-induced hypoxemia have been recently investigated from an hemorheologic scope, and a possible involvement of factors of blood viscosity in their complex and multifactorial mechanism has been hypothesized.

Since this review follows a preceding one we published some three years ago [1], we shall emphasize, in this paper, on the most recent findings and research trends in this field. The more classical literature is thoroughly analyzed in our preceding review which includes 164 bibliographic references [1], most of which will not be given again here.

3. The three phases: acute, delayed and late effects of exercise on blood rheology.

We thoroughly reviewed in our previous article [1] the sequence of the hemorheologic effects of exercise. Analyzing all the body of literature concerning this issue, we proposed to describe them as a triphasic phenomenon: acute, delayed and chronic effects. Besides, effects of excess exercise or excess training (eg, the overtraining syndrome) may be considered as a fourth phase in this process.

Acute effects: a short-term increase in blood viscosity.

Both maximal and submaximal exercise, either they are of short or long duration, appear to always increase blood viscosity, due to a rise in plasma viscosity and hematocrit. In most cases (eg, short acute exercise) these two events virtually explain all the observed increase in whole blood viscosity [20]. Actually, some studies failed to detect these changes [21], but when looking at their protocol one can notice that only postexercise (eg, recovery) values are measured so that these short-timed alterations have probably been not detected, due to a rapid return to preexercise values [1]. This rise in plasma viscosity and hematocrit is sometimes interpreted as a '*hemoconcentration*' [21]. In fact, such an explanation is far to be complete, since the observed modifications are due to at least five separate mechanisms: redistribution of red cells in the vascular bed [22]; splenocontraction that increases the number of circulating erythrocytes [23-24]; enrichment of plasma in several proteins, coming presumably from lymphatics [25-30]; a loss of water in the sweat for thermoregulation [26]; entrapment of water into muscle cells [27].

It is important to stress that there are also important fluid shifts even without any exercise, due to body position itself [31], since blood viscosity increases when recumbent subjects become orthostatic. This change is explained by an increase in hematocrit (from 41.2% to 44.2% in this paper) and plasma viscosity (from 1.55 to 1.67 mPa.s) associated with a rise in plasma proteins and fibrinogen. By contrast blood viscosity at standard hematocrit, erythrocyte deformability and erythrocyte aggregability are unchanged [31]. This mechanism may contribute to explain the "Economy class syndrome", ie, the retention of a water volume of more than 1100 ml (correlated with an increase in body weight and a moderate lower leg swelling) during 12 hr sitting in a plane during a transcontinental flight. Deep vein thrombosis and pulmonary embolism have been reported to occur in long-distance air travel passengers. However, a study simulating this situation in 12 healthy volunteers did not evidence most hemorheologic alterations, despite the wide volume of water that was retained [32]. Clearly, these positional fluid shifts should be taken into account in the analysis of exercise-induced alterations in water status.

In most (but not all) exercise protocols there are also changes in the rheological properties of erythrocytes [20]. The most classical is a decrease in erythrocyte deformability which is not a specific finding since it is also observed in most stressful events like labor [33], videofilm-induced emotional stress [34], and endogenous depression [35]. These effects are generally not found at exercise when red cell rheology is investigated after resuspension of cells on a buffer, indicating that they are mostly due to plasma factors rather than to intrinsic red cell properties [1].

Blood lactate, which experimentally shrinks the red cells and decreases their flexibility, is likely to explain in part this exercise-induced rigidification of erythrocytes, as supported by correlations between lactate concentrations and red cell rigidity at exercise [20]. In one study, we interestingly found a threshold value for this effect which became apparent only when blood lactate increased above 4 mmol.l⁻¹, ie, a value which has been proposed to represent approximately the point where lactate induces acidosis [36, 37]. However, in other experimental conditions, it was shown that even a moderate lactate increase during low intensity exercise results in a transient increase in erythrocyte rigidity [38]. Recently, in vitro experiments were conducted in order to confirm the direct role of lactate on red cell rigidity in athletes [39]. At physiological concentration (2mM, 4mM and 10 mM) red cell deformability was decreased in blood from sedentary subjects, confirming the more indirect previous studies.

Lactate is probably not the only factor explaining this rigidification. Traumatic damage of red cells due to their compression in the foot plantar circulation is likely to be important in sports like running [40], although this issue remains uncompletely clarified. Presumably, fluid status has also a major influence

on erythrocyte rheology during exercise, as suggested by the preventive effect of drinking on red cell rigidification [41, 42], and nuclear magnetic resonance measurements showing that acute exercise increases the percentage of free water in the red cell [43]. Hormones may also affect blood rheology, like glucagon [44], norepinephrine [45], leukotriene B4 [46], leukotriene C4 [47], or atrial natriuretic peptide [48].

There are also acute changes in erythrocyte aggregability (which increases) and disaggregability (which decreases) [49]. Little is known about the mechanisms of these latter modifications which are not found in all exercise protocols and are generally not detected by the most widely used technique, ie, the light transmission analysis (Myrenne aggregometer) [50]. While preexercise fibrinogen concentrations are correlated to the extent of these changes in aggregation [49], there is no evidence either in vivo [49] or in vitro [39] that lactate may play a role in this change in aggregation properties of the red cells. Thus, the most important extracellular determinant of this event is likely to be fibrinogen. However, as discussed below, aggregation changes may also reflect leukocyte activation.

Paradoxical increase of red cell deformability during exercise in athletes

While red cell rigidity was generally found to be either increased or unchanged during exercise, there was a surprising report of a decrease of this parameter, when assessed after exercise with the LORCA [51]. This paradox has recently been explained by a study on 20 highly trained athletes [52]. During a progressive exercise test conducted to VO₂max red cell rigidity was found to paradoxically *decrease* in these athletes. This decrease was not found in a subgroup in whom hypoxemia appeared at maximal exercise, as discussed below. Besides, in vitro experiments [39] showed that lactate at concentrations ranging from 2mM to 10 mM increased red cell deformability in such athletes while it classically decreased it in blood from sedentary subjects. Thus, in highly trained subjects, the exercise-induced increase in blood lactate does not rigidify the red cell as observed in sedentary subjects or in moderately trained ones (like footballers [53]) but actually improves red cell deformability.

This recent findings reconciles apparently conflicting results [51, 53] and opens new perspectives for the investigation of the role of red cell rheology in exercise physiology, as discussed below about exercise-induced hypoxemia.

White cells and free radicals.

Both white cell activation [54] and oxidant stress [55] are likely to play an important role in the hemorheologic effects of exercise. The marked increase in oxygen utilization that occurs during exercise results in production of free radicals by several sources, including the mitochondria and the white cells [56]. In addition, there may be an autoxidation of hemoglobin & catecholamines. Transient tissue hypoxia due to rapid accelerated consumption of oxygen in exercising muscles and to inadequate oxygen supply at the pulmonary level in some trained people has been also demonstrated and may lead to free radical formation. Whatever the mechanism, it is well established that oxidative stress during acute exercise is associated with a hemorheological impairment [56]. This clearly appears in a study by Yang and coworkers [57] who observed after a 5000m running session a decrease in red cell deformability, as assessed with ektacytometry, associated to a 47% increase in the malondialdehyde content of the red cell membrane and to alterations in the red cell shape, and to a higher number of echinocytes and an increased rate of hemolysis. According to Ajmani [56], exercise-induced oxidative stress can also produce an increase in mean red cell volume and increase plasma fibrinogen levels, thus increasing also aggregation.

However, until recently, little was known about the involvement of leukocyte activation in these rheological changes. Number of leukocytes increase after strenuous exercise. This increment is attributed to increased blood flow that recruits the leukocytes from the marginal pool and/or hormonal changes which are likely to be mediated by beta-2 adrenergic receptors. More interestingly, a decrease in filterability of white cells during exercise has been evidenced [54], reflecting some degree of leukocyte activation that may surely interact via several circulating factors with red cell properties. Transient hypoxia might also result cytokine release and leukocyte activation. When leukocytes (especially polymorphonuclear leukocytes) are activated, they reduce molecular oxygen enzymatically to generate metabolites such as superoxide anions, hydrogen peroxide or hydroxyl radicals [58]. These metabolites can injure the surrounding tissues by oxidative damage. Red blood cells (RBC) are vulnerable to oxidative damage, although they are equipped with antioxidant defense mechanisms. Recent studies have indicated that RBC that are in close contact with activated leukocytes can be damaged, at least in part by oxidative mechanisms, resulting in significant structural and functional alterations [58]. A Temiz investigated the leukocyte activation and RBC damage after exhaustive exercise in untrained rats. Significant increments in RBC membrane protein oxidation and lipid peroxidation, and decreased membrane enzyme activities were observed during early and late phases after the exercise episode. RBC transit times measured by a cell transit analyser failed to indicate significant changes in RBC deformability, despite the biochemical evidences of oxidant damage [59]. These alterations were correlated with increased leukocyte phagocytic activity.

Pathophysiological relevance of this short-term exercise-induced increase in viscosity.

Theoretically, most of the rheologic changes reviewed above are likely to exert negative effects on exercise performance. This assumption is supported by experiments conducted on both healthy volunteers and rats under hypobaric hypoxic conditions [60-61]. Those studies have demonstrated that preventing the exercise-induced rise in erythrocyte rigidity by ω 3-fatty acids improves maximal aerobic capacity. Thus, in conditions of hypoxia, a rigidification of red cells may represent a limiting factor for muscle oxygen supply and thus impair performance.

Tong et al [62] hypothesize that erythrocyte rigidification during a maximal triangular exercise may exacerbate lactic acidosis via a microcirculatory impairment and a decrease in O₂ transfer to tissues, thus representing a 'vicious circle'.

Erythrocyte stiffening has been shown to exert an effect at the pulmonary level [63-65]. Stiffened red cells augment the pulmonary hemodynamic response to hypoxia [65]. In rats hypobaric hypoxia (an experimental condition simulating altitude) increases blood viscosity via a combination of factors (hypoxia, low pH and high values of blood lactate) that is corrected by the calcium blocker flunarizine. In such conditions the above-mentioned effects of exercise on blood rheology are exacerbated. This situation is associated with pulmonary hypertension in rats. According to Cortinovis [63] the increase in viscosity (resulting from cell damage and plasma hyperviscosity induced by inflammation) is a more important factor than polycythemia for inducing pulmonary hypertension. Experiments have provided some evidence that the increase in pulmonary arterial resistance during hypoxia is due to a large extent to RBC stiffness [64].

Exercise-induced changes in blood rheology have been reported to be related to the rating of perceived exertion. The factor correlated with exertion was hematocrit [66] which was hypothesized to represent a signal among the other well-characterized ones (*e.g.* heart rate, lactate, blood glucose) that are integrated at a conscious level to generate the feeling of exertion.

An interesting hypothesis has been proposed by M. Guéguen-Delamaire [67] who suggested that such an impairment of blood rheology may be involved in the cardiovascular risk of maximal exercise,

together with changes in hemocoagulatory parameters. In agreement with this hypothesis we reported the case of a 50 yr old marathon runner who underwent a thrombosis of the central vein of retina after a marathon run and exhibited during a standardized submaximal exercise-test a disproportionate increase in blood viscosity, hematocrit, and mostly red cell aggregation and disaggregation thresholds. While some of this postexercise hyperviscosity pattern may be due to the previous vascular event, these findings may support the hypothesis of a role for hemorheological disturbances during exercise in the pathogenesis of this marathon-induced retinal thrombosis [68]. However, it should be pointed out that we observed during a light, very safe exercise quite the same rheologic changes than during strong work loads [38]. This leads to suppose that simple changes in hematocrit, red cell rigidity, and plasma viscosity are physiological adaptative modifications which occur during many kinds of exercises and do not imply a risk by themselves. Presumably such changes can be easily overcome by vasodilatation. In our opinion, the risk of strong maximal or exhausting work loads is more related to other factors, including wide muscular damage, modifications of hemostasis and white cell activation. According to Ajmani [56] these adverse rheological effects may be responsible in part for the enhanced incidence of myocardial infarction and sudden death associated with exercise.

Training induced improvement in blood rheology: the "autohemodilution" phenomenon.

Cross-sectional studies of athletes compared to sedentary controls show that athletes have a lower blood viscosity. Both plasma viscosity and hematocrit are lower [68-71]. Longitudinal studies have confirmed this finding [70, 72, 73], even in previously trained sportsmen [73].

Ernst [74] observed in first-league soccer players compared to matched controls a lower η_{pl} and higher deformability of red cells, and concluded that "*the fitter the athlete the more fluid his blood*". Koenig [75] studied the self-reported regular leisure time physical activity in comparison with plasma viscosity data in 3521 men and women from the Monica-Augsburg cohort. This population-based study shows that regular

physical activity is associated with a lower plasma viscosity across all age groups. However, when a multivariate analysis is performed, the influence of regular exercise on plasma viscosity remains significant only in men while in women it is suppressed by the parameters smoking and age.

Results concerning red cell flexibility and aggregability are less clear, since according to techniques, kinds of patients and kinds of sports those factors are found to be either unchanged or improved. However, on the whole, it seems likely that at least some training regimens are able to reduce red cell rigidity and red cell aggregability [70, 73]. We think that most of this effect is actually due to more delayed effects of exercise, associated with metabolic and body composition improvements after prolonged training, that will be discussed later in this review. Since athletes blood has more young RBCs than untrained people, it is interesting to compare the rheological properties of the red cells not only between athletes and untrained people, but between old red cells from trained vs untrained people and between young red cells from trained vs untrained people. As extensively investigated by Muravyov and coworkers [76] the difference in aggregability of red cells between athletes and sedentary subject is even more pronounced when investigated on young and old red cells studied separately.

During the hours following exercise, there is an increase in plasma volume [77] that represents a reversal of the acute hyperviscosity described above, resulting in an "autohemodilution" [78, 79]. This autohemodilution results in a lower hematocrit that explains the negative correlations which are found in sportsmen between hematocrit and fitness [50]. It is important to point out that in most sportsmen, a decrease in hematocrit is thus a sign of fitness rather than a marker of 'sports anemia'. Obviously, the latter situation is rather associated with a decrease in performance. Some potential hemorheologic

mechanisms of anemia have been hypothesized, including intramuscular red cell damage [79] or traumatic destruction of erythrocytes in the foot circulation during running [40]. Nuclear magnetic resonance measurements show that exercise training increases also the water content in red cells, with a proportional decrease in "free" water and increase in "bound" water while red cell volume does not change [42]. This percentage of "bound" water in the red cell seems to be linked with an improved cell deformability, O₂ transport, and physical capacity [42].

It should be noticed that training in several sports is associated with a specific hemorheologic pattern that differs from the general picture. Body-builders have been reported to have no improvement of blood rheology after training [80] while in rugby men a lower increase in η_{pl} during exercise seems to be the most prominent characteristic of training and fitness [81-82]. The increase in plasma volume has been assumed to contribute to the body water pool and to help to prevent dehydration [2].

The delayed, metabolic-mediated, effects of exercise on blood rheology.

Little attention seems to have been given to the role of training-induced changes in metabolism in these hemorheologic improvements. However, endurance training reduces body fat, increases muscular volume, and markedly modifies muscular processing of fuels [83]. We would want to emphasize in this part of this review the potential importance of these delayed effects of training in the hemorheologic status of athletes and fit persons.

As soon as 1986, Dudaev [84] reported the effects of 30 daily cycling sessions in male coronary patients compared to controls. Results indicated that regular exercise decreased erythrocyte membrane levels of triglycerides, fibrinogen and cholesterol while it increased the level of high density lipoprotein cholesterol. Interestingly, fibrinogen and triglyceride concentrations were correlated to hemorheologic and hemodynamic improvements, showing that the alterations of lipid metabolism induced by training were probably involved in the improvement of blood rheology, with possible beneficial hemodynamic effects.

A pivotal concept for understanding these delayed effects of exercise is the concept of insulin sensitivity. Insulin sensitivity is the dose response relationship between insulin and its biological effects in the whole body [85-86]. There is clearly a wide distribution of this parameter within the whole population [85] with two extreme situations: the insulin resistance syndrome [87-88] and the states of elevated insulin sensitivity found in both athletes [89-90] and patients prone to reactive hypoglycemia [91-92]. Therefore it appears to be a continuum among trained sportsmen, sedentary subjects, and patients with the insulin-resistance metabolic syndrome [1]. Optimal lipids, fibrinogen, glucoregulatory and rheologic patterns are found in trained subjects while there is a worsening of all these parameters when subjects become sedentary [88]. Intra-abdominal accumulation of fat, either associated with obesity or not, plays a pivotal role in this syndrome [94-95], but metabolic defects at the muscular level are even more important [96-97]. In addition, muscles of subjects prone to obesity and who will develop this syndrome are less able to metabolize large amounts of lipids [98-99].

During the last decade, correlations between insulin resistance and abnormalities of blood rheology have been described [100-106]. Therefore, hyperviscosity is a symptom of insulin resistance [107], probably because most of the metabolic disorders which are found in this situation are likely to impair blood rheology [100-106]. For instance, Eterovic [108], extending a previous work of Dintenfass [109] has demonstrated that η_{pl} value is explained by a combination of cholesterol, fibrinogen, triglycerides, hematocrit (reflecting the degree of dilution) and HDL that may be combined in a predictive equation. The concept of insulin resistance as a factor of impaired blood rheology provides a pathophysiologic support to the findings of LeD ev hat [110] who reported that isolated obesity is associated with hemorheologic disturbances. The importance of body composition as a factor involved in the

hemorheologic profile of an individual is further supported by studies showing that even in sportsmen, while the percentage of fat is not pathologic but is normal or low, red cell aggregability is negatively associated with the size of fat mass [81-82].

In addition, insulin sensitivity is positively correlated to fitness [111-113], probably because training improves both glucose and lipid processing by muscle, and body composition [114]. This contributes to explain why exercise is an effective treatment of the insulin resistance syndrome [88]. Exercise training improves the lipid pattern of patients suffering from this syndrome [115-116]. The effect of training on fibrinogen has been more controversial, since it depends upon the genetic subtypes of this molecule [117], explaining that it was not evidenced in some studies [118]. In fact, training reduces fibrinogen [117], a notion that is also supported by negative correlations of fibrinogen with both fitness [119] and insulin sensitivity [120-122].

On the whole it is thus clear that training decreases the blood concentrations of the main parameters known to impair blood rheology, and induces a body composition pattern characterized by a low percentage of fat. All these modifications are likely to play a major role in the improvement of blood rheology induced by regular physical activity [123].

A pivotal mechanism in these adaptations is probably the growth hormone - somatomedin axis. While growth hormone-deficient adults have a low insulin sensitivity associated with an increased percentage of body fat [124] with increased circulating lipids [125] and fibrinogen [126], trained sportsmen who exhibit the opposite metabolic picture have an increased function of this axis [127]. Thus, this hormonal axis may be more or less directly involved in the regulation of training-induced changes in blood rheology.

4. Beyond training: Overtraining.

The overtraining syndrome in athletes remains a controversial issue since its clinical presentation is far to be specific [129]. Recently, the French consensus group on overtraining of the *Société Française de Médecine du Sport* (SFMS) proposed a standardized questionnaire of early clinical symptoms of this elusive syndrome, allowing the calculation of a 'score' that may help to classify on a clinical basis sportsmen submitted to a heavy training program [130]. This score appears to be correlated with markers of muscular damage (creatinine kinase, myosin) or neuroendocrine dysfunction (somatotrophic axis), but also with some hematological markers like ferritin.

We recently investigated a possible relationship between this score and blood rheology in male elite athletes [131]. The overtraining score appeared to be correlated with blood viscosity. This correlation was explained by higher plasma viscosity and hematocrit in individuals with a high overtraining score. By contrast, there was no difference in RBC deformability and aggregation. Therefore, the early signs of overtraining in elite sportsmen are associated with a hemorheologic pattern that suggests some degree of reversal of the fitness-associated 'autohemodilution' discussed above. In addition, overtrained athletes are frequently iron depleted, a mechanism that may induce additional hemorheological alterations but is unlikely to explain the early hemorheologic tableau of the overtraining syndrome [131].

There has been an earlier report of mild dehydration after four weeks of daily exhaustive endurance training (six days/week), but the authors did not classify this situation as overtraining. Results showed an increased hematocrit, serum Na⁺, and serum K⁺. All this was proposed to be due to an excess plasma water loss. Since concentrations of blood urea nitrogen and serum glutamic-oxaloacetic transaminase were also increased, without any evidence for water-electrolyte deficiency syndrome,

renal dysfunction, or liver cell damage, the authors interpreted these findings as reflecting a persistent mild degree of dehydration and catabolic state noted after intense training [132].

Further studies are required to investigate whether hemorheologic measurements may provide a marker of the early stages of overtraining.

5. Physiological meaning: is blood fluidity a physiological determinant of aerobic capacity?

The pioneer of clinical hemorheology L. Dintenfass [133] first reported in cardiovascular patients and normals higher cardiac work or higher fitness being related to low blood viscosity or lower aggregation of red cells. He evidenced differences between high-fitness and low-fitness groups, the high-fitness group showing a lower plasma viscosity, lower fibrinogen level, and higher albumin/fibrinogen ratio [133]. Later, such correlations were reported many times [1]. Red cell flexibility is correlated to adductor isometric strength [82]. Correlations of blood fluidity with aerobic working capacity W_{170} [134], time of endurance until exhaustion [135], blood lactate response [136-138], maximal exercise-test derived VO_{2max} [138], and 4 mmol.l⁻¹ lactate thresholds [138] have been demonstrated. The increase in body water and plasma volume after training [77] which explains most of the rheologic changes is likely to exert major hemodynamic effects that can improve performance [77]. However, hemorheologic factors have been hypothesized to be by their own physiological determinants of muscular performance [135].

Studies on patients with the sickle cell trait have demonstrated a reduced capacity for prolonged competitive exercise under hypobaric hypoxia, which seems to result from reduced erythrocyte flexibility [139]. This abnormality is no longer found at sea level or at moderate altitude and may result from a decrease in oxygen delivery by sickle cells under hypoxic conditions. On the other hand, when RBC fluidity is improved by $\omega 3$ fatty acid supply (see below) there is an increase in VO_{2max} under hypobaric hypoxia, suggesting that a prevention of RBC rigidification during exercise improves aerobic capacity in these conditions [60-61].

On a theoretical point of view, increased blood fluidity may improve O_2 delivery to muscle during exercise in trained individuals. However, this question remains uncompletely clarified. There are several biological indicators of fitness, which are relevant to different kinds of exercise. The most popular is maximal oxygen uptake (VO_{2max}), which has not been widely studied in connection to blood rheology despite the theoretical link between O_2 supply and rheology indicated above. In one study, VO_{2max} was negatively correlated to blood viscosity, due to a negative correlation with plasma viscosity [1, 138]. Another important parameter is the ability to avoid hyperlactacidemia, indicated by the so-called 'anaerobic thresholds' or 'lactate thresholds' [36-37]. In three separate studies, we observed that blood viscosity and erythrocyte aggregation were positively correlated to lactate accumulation into blood during exercise [136-138]. The possible meaning of the relationships between resting blood fluidity and lactate response will be discussed later.

Hemorheological determinants of the maximal oxygen consumption (VO_{2max}) and of the aerobic working capacity (W_{170}) are quite the same [138] since these two parameters are highly correlated to each other and are both indices of aerobic exercising capacity. Plasma viscosity is the best statistical determinant of these two measurements of aerobic performance [134]. However, hematocrit is also negatively correlated with aerobic performance [134, 138, 140], reflecting the importance of the beneficial effect of autohemodilution. The maximal oxygen consumption (VO_{2max}) is a measurement of body's ability to increase O_2 transfer from the surrounding atmosphere to muscles and depends on several steps. The limiting step is not the same in all sportsmen. When arterial circulation is considered, VO_{2max} is equal to the maximal value of $Q \cdot CaO_2$, Q being cardiac output and CaO_2 the O_2 content of blood. This formula $VO_{2max} = Q \cdot CaO_2$ can be written as a function of hematocrit ϕ and

viscosity η if one applies Hagen-Poiseuille law [141]. It becomes $VO_{2max} = \text{constant} \times (\phi/\eta) \times (\Delta P/Z)$ with ΔP being the drop in blood pressure and Z being hindrance. Thus the value (ϕ/η) should be a limiting factor for VO_{2max} . Actually, in experimental studies, VO_{2max} is not correlated to (ϕ/η) but is negatively related to ϕ , ie, in these subjects ϕ is mainly a factor of viscosity that is negatively related to fitness [140]. One could suggest that this comes from the fact that fitness is accompanied by blood dilution which lowers hematocrit, but results in increased cardiac output [78-79]. However, systemic hematocrit influences blood flow in tissues [142]. Murray and Escobar [143] have shown that a decrease in hematocrit is primarily responsible for the rise in cardiac output after acute experimental hemodilution. Furthermore, regional vascular beds have markedly different blood flow responses to alterations in hematocrit [142, 144-147]. It has been showed that hematocrit directly reduces blood flow in some tissues [144-147]. The whole body of literature shows that training and improved performance are associated with low hematocrit, although in some cases low hematocrit may be also found associated with a reduction of performance (eg, 'sports anemia' [148]). Thus, it remains difficult to give a simple interpretation of the relationships between hematocrit and performance, unless the clinical context is carefully taken into account.

The paradox of hematocrit.

However, there appears to be an important paradox concerning hematocrit in exercise physiology. Since sports performance depends on the capacity of oxygen transport to the exercising skeletal muscles [149,150], it is not surprising to observe that performance may be increased thanks to an artificial haematocrit augmentation [151]. As pointed out in a recent review [151], this can be performed by either training in high altitude, blood transfusions, or injecting erythropoietin. Since the synthesis of erythropoietin by bioengineering, doping with recombinant human erythropoietin has become popular in sports in general, and in cycling in particular [151]. However, these data fully contrast with physiological informations reported above. In normal conditions there is a strong negative correlation between hematocrit and fitness which is explained by the effect of regular training [78-79]. A striking example of this paradox can be found in a prospective study by Janetzko and coworkers [152] who showed that a 450-ml whole blood donation increases the submaximal physical working capacity at a heart rate of 130 min⁻¹ (PWC 130) and the maximal working capacity determined by treadmill exercise testing. Interestingly, plasma viscosity also decreased after donation, further improving blood rheology.

Comparisons between the extreme quintiles of hematocrit in athletes clearly illustrate this paradox [140]: athletes in the lowest quintile compared to those in the four other quintiles had a lower value of blood viscosity and a higher fitness as reflected by their aerobic working capacity, their relative maximal power output, and their isometric adductor strength. By contrast athletes in the highest quintile had higher viscosity and lower red cell disaggregability. On the whole, when hematocrit increases, there is a decrease in fitness and a higher score of overtraining. Fit athletes have a rather low hematocrit associated to other metabolic and ergometric improvements, while athletes with a high hematocrit are frequently overtrained and/or iron-deficient, and that their blood viscosity (and red cell disaggregability) tends to be increased [140].

5. Is blood rheology a modulator of muscle oxygen delivery during exercise?

Several lines of evidence indicate that hemorheological parameters might be by several ways involved in muscle oxygen metabolism.

First, several papers from our group have demonstrated a link between erythrocyte aggregability at baseline and the rise in blood lactate during exercise [136-138]. These papers suggest that red cell aggregation may influence muscular lactate metabolism. As experimentally shown by Vicaut [153],

increased RBC aggregation may impair microcirculation in muscles. Although aggregation is beneficial to some extent for microvascular perfusion [154], its increase, even within a physiological range, might impair aerobic metabolism in muscle, resulting in higher blood lactate. If this assumption is correct, lactate accumulation, that was classically described as an "anaerobic process", but is rather explained nowadays by a shift in the balance of fuel oxidations [83], could be influenced by the aggregation-related alterations in microcirculatory supply of O₂. While the microcirculatory effects of red cell aggregation are a matter of controversy, experiments by Johnson and coworkers [155], suggest that red cell aggregation represents 60% of resistance at the venous pole in cat gastrocnemius. Aggregation could be thus the major modifier of venous resistance in skeletal muscle [155].

Experiments of muscle hypoxia [156] show that an anemia reducing by 25 % hematocrit in dogs increases blood lactate accumulation. This increase in lactate is associated with higher muscular glucose consumption, and with an increase in glucagon, norepinephrine, epinephrine and cortisol while insulin and free fatty acids are unchanged [156]. In humans suffering from peripheral obliterative arterial disease, red cell aggregation is negatively correlated with transcutaneous oxygen pressure, further supporting the concept that aggregation impairs oxygen supply to tissues [157].

In fact, a possible explanation for the relationship between rheology and lactate blood accumulation may be, rather than a hemorheological 'Pasteur-like' effect (so-called 'anaerobiosis'), an influence of red cell aggregation on lactate removal, as evidenced by modelling of postexercise lactate kinetics [158-159]. According to Freund [160-164] the mathematical analysis of postexercise lactate allows a fair evaluation of lactate production by muscles (γ_1) and lactate clearance (γ_2). Moreover, the latter parameter (γ_2) appears to be easily measurable with simplified protocols [158-159, 165]. In a sample of subjects exhibiting a wide range of γ_2 (from 2 to $7.7 \times 10^{-2} \text{ min}^{-1}$) we observed that postexercise red cell aggregability index Myrenne "M1" (measured at VO₂max) was the only hemorheologic parameter correlated to γ_2 . Thus microcirculatory adaptations influenced by red cell aggregation may influence lactate disposal and clearance (as reflected by γ_2), adding its effect to that of the balance between carbohydrates and fat oxidation which is the major determinant of blood lactate concentrations at exercise in physiological conditions [83].

Another oxygen-related parameter which can be influenced by blood rheology could be the oxygen equivalent of the watt. This parameter is theoretically close from $10.3 \text{ ml.watt}^{-1}$ [9] but is higher in sedentary subjects when they exhibit a low fat-free mass or a high waist-to-hip ratio [166]. Interestingly, it is increased in individuals with elevated blood viscosity parameters [167] and the improvement of these parameters by prostaglandin E1, naftidrofuryl or hemodilution partially corrects it. According to Wolff and Witte, the measurement of this waste of oxygen during submaximal steady state workloads may allow a direct clinical determination of microcirculatory performance in involved muscle tissue as a function of blood viscosity [167].

Finally, an amazing issue in current exercise physiology is exercise-induced arterial hypoxemia (EIAH), i.e., the arterial pressure in O₂ decreases during intense exercise. This situation has some similarities with horse's exercise-induced pulmonary hemorrhage (EIPH) that is frequently observed during competitive races [168-169]. In both situations a ventilation/perfusion inequality and/or pulmonary diffusing capacity limitation may occur as a result of an interstitial pulmonary edema. In horses, a host of literature has investigated a possible role for blood rheology in EIPH [168-175] but the clear demonstration of a role of blood rheology in this process is still lacking [173].

In humans, episodes of pulmonary hemorrhage following ultra marathon races have been reported, supporting the hypothesis of some pathophysiological similarities between EIPH and EIAH. Actually, pulmonary capillary pressure during maximal exercise does not reach the high levels observed in horses [168-169], and the high capacity of shear-dependent rheofluidification found in horses despite their high

red cell aggregability [173] indicates that horse and human rheology are extremely different. However several recent lines of evidence support a role for blood rheology in the pathophysiology of EIAH. First, comparison between hypoxemic and non hypoxemic athletes shows that exercise increases blood viscosity to higher levels in EIAH athletes, despite a similar rise in hematocrit and a paradoxical decrease in RBC rigidity [52]. In addition, improvement of RBC deformability by dietary polyunsaturated fatty acids reduces hypoxemia in athletes at maximal exercise [176].

We can hypothesize that there is a training-induced adaptation in high level athletes that apparently decreases the exercise-induced hyperviscosity, as shown by *in vitro* experiments on the effect of lactate on red cells [39] and by the paradoxical lack of hyperviscosity at exercise sometimes reported in athletes [177]. In EIAH-prone athletes, this mechanism may be blunted and hyperviscosity may thus result at maximal exercise in hypoxemia [176].

6. Nutritional and metabolic influences on blood rheologic changes during exercise.

Nutritional factors influence hemorheologic changes associated with exercise, with possible effects on muscular performance itself.

A first important issue is water [178] dehydration reduces blood and plasma volume, increases hematocrit, plasma osmolality, plasma viscosity and plasma protein, while it dramatically increases red blood cell aggregation proportional to a rise in plasma globulin. Accordingly, water supply almost completely prevents the increase in red cell rigidity induced by 1 hr submaximal strenuous exercise [41].

While the influence of carbohydrates is not very clear [179] and could thus be supposed to be reduced, polyunsaturated fatty acids of the omega 3 family (ω 3PUFA) increase exercise performance by improving RBC flexibility [60-61]. Thoth coworkers [180] describe also that ω 3PUFA increase aerobic exercise capacity in patients suffering from ischemic heart disease and hyperlipoproteinemia. This increase is related to an improvement in hemorheology (whole blood viscosity) and circulation (decrease in total peripheral resistance). Actually a recent well-conducted study apparently challenges all this literature [181] since it shows that a 3 wk of fish oil supplementation (6 g/day), without or with vitamin E (300 IU/day), has no effect on either RBC rheology or exercise performance.

In fact, the simple fact to take or not a breakfast before exercise has a significant influence on hemorheological response to this exercise [182]. After a 495 kcal breakfast (8,9% proteins, 27,3% lipids; 63,9 % glucids, ie mimicking a "french breakfast"), the increase in erythrocyte rigidity that occurs at fast is prevented, while plasma viscosity is higher and increases more when subjects were fed than when they were fasting. Therefore, such a breakfast modifies the rheologic response to exercise, by preventing a reduction in red cell deformability and increasing plasma viscosity as well as its rise during cycling [182].

Recent studies have underline the importance of mineral and trace element status in sports hemorheology. Zinc, which *in vitro* increases the deformability of artificially hardened red cells [183], is frequently low in the serum of athletes, this situation reflecting some degree of deficiency. Athletes with low serum zinc have a higher blood viscosity and an impairment in erythrocyte deformability [184] which is associated with a decrease in performance. Experimentally, a double blind randomized trial of oral zinc supply in healthy volunteers improves blood viscosity [185] while the effects on performance are not significant. Zinc seems also to reduce erythrocyte aggregation both *in vitro* and *in vivo* [186].

Another mineral which is frequently lacking in athletes is iron. Even without anemia, this situation is likely to impair performance, although there is still some controversy concerning the opportunity of iron supplementation in athletes. In elite athletes plasma ferritin has been observed to be negatively correlated with blood viscosity [187]. Subjects with low ferritin levels suggesting mild iron deficiency exhibit a higher blood viscosity explained by a higher plasma viscosity while hematocrit and red cell rigidity are unchanged. Erythrocyte aggregability is also higher in iron-deficient subjects [187]. These data suggest that mild iron deficiency as commonly seen in athletes, before anemia occurs, is associated with an increase in plasma viscosity and RBC aggregation, together with an increased subjective feeling of exercise overload.

Finally, studies in body builders evidence abnormalities, including hemoconcentration and alterations in cholesterol metabolism, which have been suggested to be at risk for thromboembolic phenomena because of increased blood viscosity. Those abnormalities could reflect the use of diet, exercise, and ergogenic drug regimens, which are common among competitive athletes [188].

7. Exercise as a 'hemorheologic therapy' in cardiovascular and metabolic diseases?

In sedentary patients, regular exercise also improves blood rheology. In fact, an improvement in blood fluidity can be induced by regular physical exercise regardless of whether the blood rheology was normal or abnormal at baseline. Thus regular exercise might be a way of therapeutically increasing blood flow in ischaemic vascular diseases. [5]. Training compensates not only for the potential damage risk factors represent but also for the physical stress provoked by vigorous exercise [189]. A large literature on the therapeutic effects of exercise in peripheral obliterative arterial disease shows that the therapeutic effect of training in this disease may be largely explained by rheologic improvements [190].

Non-insulin dependent diabetes represents an extreme example of the insulin-resistance syndrome [96] in which all the metabolic abnormalities are overtly expressed. Exercise has been proposed as a preventive treatment [88] for this disease which is mostly explained by a decrease in muscular glucose uptake [97]. In these patients there is also a link between unfitness and cardiovascular risk [191].

We recently demonstrated [193-194] that training in sedentary insulin resistant patients, applied 3 times a week (45 min) at a level defined by a prior exercise-test induces significant improvements in body composition (loss of 2.5 kg on the average, consisting only of fat mass with a stability of fat free mass), associated with improvements in exercise-test parameters. The metabolic improvements indicate a markedly increased ability to oxidize fat at exercise, although blood lipids and insulin sensitivity were not significantly improved. Actually a nonsignificant tendency to such an improvement would perhaps become significant in a higher sample. Blood rheology is also improved, as expected, but the only significant result at this time is a decrease in plasma viscosity, while hematocrit, red cell deformability and red cell aggregation are not significantly changed. Thus, consistent with observations in athletes, the metabolic and ergometric improvements induced by training reduces η_{pl} in sedentary, insulin resistant patients, but at those low levels training does not appear to induce 'autohemodilution' (as reflected by hematocrit) neither it improves red cell deformability or aggregation. The reliability of η_{pl} as simple and unexpensive marker of efficiency of training in insulin resistant patients should be further evaluated [192-194].

In insulin dependent diabetics, there is also a relationship between aerobic working capacity and rheology [195] which may be interesting for the follow-up of diabetic athletes.

In conclusion, the body of literature summarized above clearly indicate that blood fluidity mirrors the individual's degree of fitness or unfitness. In that respect, an evaluation of hemorheologic measurements as indices of accuracy of training in either athletes or patients submitted to training for medical purposes remains to be done. On the other hand, the involvement of rheologic mechanisms in the beneficial effects of exercise in several situations like coronary heart disease remains to be investigated.

7. References

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