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The triphasic effects of exercise on blood rheology: which relevance to physiology and pathophysiology?

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Abstract. The life-extending effects of regular exercise are related to a decrease in both coronary and peripheral vascular morbidity, associated with some improvements in cardiovascular risk factors. A possible link between the beneficial metabolic and hemodynamic effects of exercise could be blood rheology, which is markedly affected by exercise. We propose here a description of the hemorheological effects of exercise as a triphasic phenomenon. *Short-term effects* of exercise are an increase in blood viscosity resulting from both fluid shifts and alterations of erythrocyte rheologic properties (rigidity and aggregability). Increased blood lactate, stress, and acute phase play a role in this process. *Middle-term effects* of regular exercise are a reversal of these acute effects with an increase in blood fluidity, explained by plasma volume expansion (autohemodilution) that lowers both plasma viscosity and hematocrit. *Long-term effects* further improve blood fluidity, parallel with the classical training-induced hormonal and metabolic alterations. While body composition, blood lipid pattern, and fibrinogen improve (thus decreasing plasma viscosity), erythrocyte metabolic and rheologic properties are modified, with a reduction in aggregability and rigidity. On the whole, these improvements reflect a reversal of the so-called "insulin-resistance syndrome" induced by a sedentary lifestyle. Since impaired blood rheology has been demonstrated to be at risk for vascular diseases, the hemorheologic effects of exercise can be hypothesized to be a mechanism (or at least a marker) of risk reversal. This latter point requires further investigation. The physiological meaning of the triphasic pattern of exercise-induced alterations of blood rheology is uncompletely understood, but increased blood fluidity may improve several steps of oxygen transfer to muscle, as clearly demonstrated in hypoxic conditions. Increasing evidence emerges from the literature, that blood fluidity is a physiological determinant of fitness.

Keywords: Blood viscosity, hematocrit, exercise, $VO_{2\ max}$, training, overtraining, metabolic fitness, hemorheology, erythrocyte deformability, erythrocyte aggregation, blood lactate

1. Introduction

The importance of regular exercise in preventing most diseases is underlined by a large body of recent literature [1,2]. Protective effects of exercise have been demonstrated for coronary heart disease [3, 4] and peripheral obliterative arterial disease [5–8]. Generally, protection is associated with metabolic improvements suggesting that the beneficial effects of exercise are mediated, at least in part, by a reversal of the increase in conventional risk factors that are commonly observed in sedentary individuals [9, 10]. This metabolic improvement is found for both lipid and carbohydrate status [11,12] and accounts for a protective effect of exercise against the occurrence of non-insulin-dependent diabetes [13–15]. On the whole, a life-extending power of increased physical activity has been demonstrated by prospective studies [1]. However, it should be pointed out that strenuous exercise may sometimes be at risk for acute cardiovascular accidents [16,17].

Blood rheology, which is markedly influenced by circulating lipids [18,19] and a host of other metabolic parameters [20,21], has been shown to be an independent risk factor for cardiovascu-

lar diseases [22–27], beside the more classical markers of this risk. On the other hand, regular exercise induces several alterations of the rheologic properties of blood that could potentially be involved in its beneficial effects in several clinical situations [5–8,28]. However, there is no available study showing that the life-extending effects of exercise [1] are related to its rheological effects.

In this review, we shall attempt to analyze the literature on blood rheology and exercise, with special reference to its potential physiological and clinical relevance.

2. Acute effects of exercise on blood rheology: a short-term increase in blood viscosity

There is a general agreement that exercise, whatever its intensity, induces acute changes in the rheologic properties of blood. On the whole, both maximal or submaximal exercise sessions have been repeatedly reported to increase blood viscosity [28–46].

However, there have been some discrepancies among investigators concerning the mechanism of this hyperviscosity. These controversies can be explained by a wide variety of experimental protocols, measurements, and populations studied [29].

Models of blood viscosity such as the equations of Quemada [47] and Dintenfass [48,49] give a powerful description of the dependency of blood viscosity (η_b) upon its physiological determinants, namely plasma viscosity (η_{pl}), hematocrit (ϕ), and a structural parameter of blood cells (k) that describes erythrocyte aggregability (at low shear rates) or erythrocyte rigidity (at high shear rates). All these determinants of η_b have been reported to be acutely increased during exercise. The more constant finding, however, is that both η_{pl} and ϕ are increased [29,37], while k is frequently unchanged [34,35,37,42]. In some cases, the changes in ϕ are not evidenced since they can be short-timed and then return to preexercise values [33].

Presumably, two separate mechanisms are involved in these changes. The increase in η_{pl} and ϕ mostly reflects fluid shifts, while changes in k at high or low shear rate are due to separate mechanisms leading to alterations in erythrocyte physiological properties. It is not surprising, therefore, to observe marked differences according to the variety of experimental conditions.

2.1. *Fluid shifts resulting in increased η_{pl} and ϕ*

A role of body fluid shifts is the more classical explanation for exercise-induced hyperviscosity. Several authors describe it as '*hemoconcentration*' [29,33,37], but it is a quite complex mechanism that includes:

(a) a redistribution of red cells in the vascular bed [42];
(b) a splenocontraction that increases the number of circulating erythrocytes [50];
(c) an enrichment of plasma in several proteins, coming presumably from lymphatics [51];
(d) a loss of water in the sweat for thermoregulation [52];
(e) an entrapment of water into muscle cells [53].

Such modifications are found in various kinds of exercise [54–59], including either maximal stress [34], short-duration submaximal bouts [51], or light, prolonged exercise [41]. When women exercise in the heat they exhibit a greater fluid loss during the follicular phase [52].

2.2. Impairment of erythrocyte rheology

Most exercise protocols are associated with a decrease in erythrocyte deformability [34,39–41]. Such a "rigidification" of erythrocytes is also found in several stressful events like labor [60], videofilm-induced emotional stress [61], and endogenous depression [62].

Several mechanisms for this rigidification of red cells during exercise have been postulated.

The first candidate was obviously blood lactate, since it experimentally shrinks the red cells and decreases their flexibility [63]. Accumulation of lactate into blood classically reflects a level of exercise which is less well tolerated, and was described as a consequence of a transition towards anaerobic processing of carbohydrates [64,65]. Recently, it has been proposed to be mostly governed by the balance between carbohydrate and lipid processing that shifts towards a higher dependency upon glucose when intensity increases [66]. Whatever the cause that increases blood lactate, correlations between its concentrations during exercise and erythrocyte rigidity have been reported [39–41,67] supporting the concept that lactate, at least when it rises above the 4 $mmol\,l^{-1}$ threshold [64] impairs red cell deformability during exercise. Even a moderate lactate increase during low-intensity exercise bouts is associated with a transient increase in erythrocyte rigidity [41]. Studies that failed to observe this relationship have frequently used washed red cells resuspended in an artificial medium that could pride this effect [39,40].

Another mechanism that may impair blood rheology during prolonged exercise is the oxidative stress induced by increased free radicals production. Yang and coworkers [46] studied deformability of erythrocytes after a 5000 m running session. Reduced deformability, as assessed with ektacytometry, was associated with alterations in the red cell shape, with a higher number of echinocytes and an increased rate of hemolysis. The malondialdehyde content of the red cell membrane was increased by 47%, thus demonstrating peroxidation. Permeability to anions was increased in the cell membrane 1 h after exercise and returned to baseline the day after [46]. To what extent an effect of free radical damage during exercise is reflected by changes in red cell deformability as assessed by viscometric or filtration techniques is unclear. In a study on light prolonged exercise we observed a kinetics of increase in red cell rigidification which is characterized by an early increase followed by a progressive return towards normal preexercise values [41]. This picture does not support the free radical explanation since oxidative stress is more likely to progressively increase with the duration of exercise. In that case changes in red cell rigidity appear to be more parallel to the transient lactate peak [41]. However, an influence of free radicals on some rheologic properties of erythrocytes during exercise remains plausible and should be further investigated.

A traumatic damage of red cells during running resulting from their compression in the plantar circulatory bed has been also suggested [68].

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 [37,68]. Nuclear magnetic resonance measurements show that water represents 62% of the red cell contents. Most of this water is "bound" to (i.e., more precisely, associated with) red cell components while a 25% of red cell water remains "free" [69]. The percentage of "bound" water in the red cell is associated with cell deformability, O_2 transport, and physical capacity. Acute exercise increases the percentage of free water [69].

Light prolonged exercise protocols at 55% of the theoretical maximal heart rate induce the same hemorheologic modifications as strong short work loads, i.e., an increase in blood viscosity explained by a rise in hematocrit, plasma viscosity and erythrocyte rigidity [41]. Preliminary experiments in our unit with force–velocity (supramaximal) exercise tests show that they are also associated with a red cell rigidification.

Little is known about the involvement of leukocyte activation in these red cell rheological changes. However, a decrease in filterability of white cells during exercise has been evidenced [70], reflecting some degree of leukocyte activation that may surely interact via several circulating factors with red cell properties.

Finally, most hormones affect blood rheology, some of them being involved in exercise physiology. For instance, glucagon [71], norepinephrine [71–73], leukotriene B4 [74], leukotriene C4 [75] decrease red cell deformability while atrial natriuretic peptide [76] increases it.

There are also acute changes in erythrocyte aggregability [34,68] and disaggregability [36] during exercise, both of them resulting in an increase in viscosity at low shear rate [68]. 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, i.e., the light transmission analysis (Myrenne aggregometer) [35,40].

2.3. *Physiological 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 [77,78]. 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. [67] hypothesize that erythrocyte rigidification during a maximal triangular exercise may exacerbate lactic acidosis via a microcirculatory impairment and a decrease in O_2 transfer to tissues, thus representing a "vicious circle".

Erythrocyte stiffening has been shown to exert an effect at the pulmonary level [79–81]. Stiffened red cells augment the pulmonary hemodynamic response to hypoxia [81]. 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-mentionned effects of exercise on blood rheology are exacerbated. This situation is associated with pulmonary hypertension in rats. According to Cortinovis [79] 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 [80].

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 [82] 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 Guéguen and Delamaire [34] 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. However, we observe during a light, very safe exercise quite the same rheologic changes than during strong work loads [41]. Thus, it is likely 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.

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

Cross-sectional studies of sportsmen compared to sedentary controls show that sportsmen have a lower blood viscosity. Both plasma viscosity and hematocrit are lower [30,31,83–88]. Longitudinal studies have confirmed this finding [84,85,89], even in previously trained sportsmen [90].

Ernst [91] compared 14 first-league soccer players with 30 matched controls. He observed a lower η_{pl} and higher deformability of red cells in sportsmen. In this study, it appeared clearly that "*the fitter the athlete, the more fluid his blood*". Koenig [92] 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 [84,90]. 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.

During the hours following exercise, there is an increase in plasma volume [93] that represents a reversal of the acute hyperviscosity described above, resulting in an "autohemodilution" [94,95].

This autohemodilution results in a lower hematocrit that explains the negative correlations which are found in sportsmen between hematocrit and fitness [35]. 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 [96] or traumatic destruction of erythrocytes in the foot circulation during running [97]. 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 [69]. This percentage of "bound" water in the red cell seems to be linked with cell deformability, O_2 transport, and physical capacity [69].

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 [98], while in rugbymen a lower increase in η_{pl} during exercise is the most most prominent characteristic of training and fitness [99].

4. Overtraining

The overtraining syndrome in athletes remains a controversial topic since its clinical presentation is not specific [100]. 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 [101]. This score appears to be correlated with markers of muscular damage (creatine kinase, myosin) or neuroendocrine dysfunction (somatotropic axis), but also with some hematological markers like ferritin. We recently investigated a possible relationship between this score and blood rheology in male elite sportsmen [102]. The overtraining score was correlated with blood viscosity, this correlation being explained by a correlation with plasma viscosity and hematocrit. Subjects with a high overtraining score exhibited a higher blood viscosity explained by higher (although fully physiological) values of plasma viscosity and hematocrit. 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, but this mechanism was not likely to explain the early hemorheologic tableau of this syndrome [102]. Further studies are required to investigate whether hemorheologic measurements may provide a marker of the early stages of overtraining.

5. Long-term 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 [66]. We would want to emphasis in this part of this review the potential importance of these delayed effects of training in the hemorheologic status of athletes and fit persons.

There appears to be a continuum between trained sportsmen, sedentary subjects, and patients with the insulin-resistance metabolic syndrome. 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 [103].

The insulin-resistance syndrome represents a widely accepted explanation of the classical association of lipid disorders, obesity, impaired glucose tolerance, hypertension and increased cardiovascular risk [103–107]. Intra-abdominal accumulation of fat, either associated with obesity or not, plays a pivotal role in this syndrome [105–107], but metabolic defects at the muscular level are even more important [108,109]. In addition, muscles of subjects prone to obesity and who will develop this syndrome are less able to metabolize large amounts of lipids [110]. While the theory of insulin resistance as the common explanation of all this picture is probably an oversimplification [111], there are reports of correlations between insulin resistance and abnormalities of blood rheology [112–114]. Therefore, hyperviscosity is a symptom of insulin resistance [112–114], probably because most of the metabolic disorders which are found in this situation are likely to impair blood rheology [18–21]. For instance, Eterovic [19] extending a previous work of Dintenfass [21] 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 Le Dévéhat [115] 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, red cell aggregability is negatively associated with the percentage of body fat [99].

On the other hand, insulin sensitivity is positively correlated to fitness [116–118], probably because training improves both glucose and lipid processing by muscle, and body composition [15]. This can explain why exercise is an effective treatment of the insulin-resistance syndrome [11,12,15]. Exercise training improves the lipid pattern of patients suffering from this syndrome [119]. The effect of training on fibrinogen has been more controversial, since it depends upon the genetic subtypes of this molecule [121], explaining that it was not evidenced in some studies [122]. In fact, training reduces fibrinogen [121], a notion that is also supported by negative correlations of fibrinogen with both fitness [123] and insulin sensitivity [124].

On the whole, it is 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.

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 [125] 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. This aspect remains to be investigated.

6. Is blood fluidity a physiological determinant of aerobic capacity?

A correlation between blood fluidity and several indices of fitness has been reported by several investigators [29,35,128–130]. Red cell flexibility is correlated to adductor isometric strength [99]. Correlations of blood fluidity with aerobic working capacity W_{170} [29,35,129], time of endurance until exhaustion [128], blood lactate response [131–133], maximal exercise-test derived $VO_{2\ max}$ [132], and 4 mmol l^{-1} lactate thresholds [132] have been demonstrated. The increase in body water and plasma volume after training [93] which explains most of the rheologic changes is likely to exert major hemodynamic effects that can improve performance [93]. However, hemorheologic factors have been hypothesized to be by their own physiological determinants of muscular performance.

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 [130]. 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 ω_3 fatty acid supply (see below), there is an increase in $VO_{2\ max}$ under hypobaric hypoxia, suggesting that a prevention of RBC rigidification during exercise improves aerobic capacity in these conditions [77,78].

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 ($VO_{2\ max}$), 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, $VO_{2\ max}$ was negatively correlated to blood viscosity, due to a negative correlation with plasma viscosity [132]. Another important parameter is the ability to avoid hyperlactacidemia, indicated by the so-called "anaerobic thresholds" or "lactate thresholds" [64–66]. In three separate studies, we observed that blood viscosity

and erythrocyte aggregation were positively correlated to lactate accumulation into blood during exercise [131–133]. The possible meaning of the relationships between resting blood fluidity and lactate response will be discussed later.

Hemorheological determinants of the maximal oxygen consumption ($VO_{2\ max}$) and of the aerobic working capacity (W_{170}) are quite the same [132] 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 [88,132]. However, hematocrit is also negatively correlated with aerobic performance [35,132], reflecting the importance of the beneficial effect of autohemodilution. The maximal oxygen consumption ($VO_{2\ max}$) 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, $VO_{2\ max}$ 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 $VO_{2\ max} = Q \cdot CaO_2$ can be written as a function of hematocrit ϕ and viscosity η if one applies Hagen–Poiseuille law [139]. It becomes $VO_{2\ max} = \text{constant} \times (\phi/\eta) \times (\Delta P/Z)$, with ΔP being the drop in blood pressure and Z being hindrance. Thus the value (ϕ/η) should be a limiting factor for $VO_{2\ max}$. Actually, in experimental studies, $VO_{2\ max}$ is not correlated to (ϕ/η) but is negatively related to ϕ, i.e., in these subjects ϕ is mainly a factor of viscosity that is negatively related to fitness [132]. 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 [93]. However, systemic hematocrit influences blood flow in tissues [140]. Murray and Escobar [141] 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 [140,142–145]. It has been showed that hematocrit directly reduces blood flow in some tissues [142–145]. The whole body of literature [35,39,40,129,132] 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 (e.g., "sports anemia" [146]). 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.

7. Is erythrocyte aggregability a modulator of muscle oxygen delivery during exercise?

Three papers from our group have demonstrated a link between erythrocyte aggregability at baseline and the rise in blood lactate during exercise [131–133]. These papers suggest that red cell aggregation may influence muscular lactate metabolism. As experimentally shown by Vicaut [147], increased RBC aggregation may impair microcirculation in muscles. Although aggregation is beneficial to some extent for microvascular perfusion [148], 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" [64,65], but is rather explained nowadays by a shift in the balance of fuel oxidations [66], could be influenced by the aggregation-related alterations in microcirculatory supply of O_2. While the microcirculatory effects of red cell aggregation are a matter of controversy, experiments by Johnson and coworkers [149] 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 [149]. However, Popel [150], comparing a wide series of animals, shows that red cells from athletic animals aggregate more. This author postulates that their capacity to

aggregate would regulate postcapillary hindrance, i.e., a parameter that is not likely to be modified by size changes and thus depends rather on rheology. Across mammals, these studies demonstrate a correlation between $VO_{2\ max}$ and aggregability [150]. Such a zoologic observation is not in agreement with literature on red cell aggregation and fitness in humans.

Experiments of muscle hypoxia [151] 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 [151]. 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 [152].

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

Studies reviewed above show that blood rheology is influenced by metabolic factors, alterations in body composition and body fluid shifts. However, nutritional factors exert their own effect on these processes. Such an effect could be expected to influence hemorheologic changes associated with exercise, with possible effects on muscular performance itself.

An influence of nutrition on blood rheology during exercise has been suggested by reports concerning carbohydrates [31], water intake [37] and polyunsaturated fatty acids [77,78]. Water intake [37] has been demonstrated to reduce exercise-induced hyperviscosity by preventing RBC stiffening. Chronic changes in diet have also an effect on blood rheology during exercise, as studied by the team of Davidson [31]. A high-carbohydrate diet (85% carbohydrates) decreases by 4% plasma viscosity, mainly because it decreases the total protein content of blood, while a low-carbohydrate (2%) high-lipid (75%) high-protein (23%) diet increases it by 5% parallel with an increase in protein content [31].

Evidence has been given that essential polyunsaturated fatty acids of the omega 3 family (ω_3PUFA) increase exercise performance by improving RBC flexibility [77,78]. Thoth and coworkers [153] 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).

There is some difference in the rheologic response if patients exercise in fasting or fed condition. After a 495 kcal breakfast (8.9% proteins, 27.3% lipids, 63.9% glucids, i.e., mimicking a "french breakfast"), exercise changes in whole blood viscosity and hematocrit were similar than after fasting. However, fasting subjects underwent an increase in erythrocyte rigidity that was prevented by the breakfast. By contrast, plasma viscosity was higher and exhibited a stronger increase during cycling 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 [154]. The effect of blood rheology during exercise of special diets containing large amounts of proteins, which are widely used in some sports, remains to be studied. At rest, some of them reduce red cell flexibility and thus impair blood rheology [155].

Mineral status seems also to have some effect on blood rheology in sportsmen. Zinc, which *in vitro* increases the deformability of artificially hardened red cells [156], is frequenly low in the serum of sportsmen, this situation reflecting some degree of deficiency. Sportsmen with low serum zinc have a higher blood viscosity and an impairment in erythrocyte deformability [157] which is associated with a decrease in performance. Experimentally, a double blind randomized trial of oral zinc supply in healthy

volunteers improves blood viscosity [158], while the effects on performance are not significant. Zinc seems also to reduce erythrocyte aggregation both *in vitro* and *in vivo* (Khaled, unpublished data). On the whole, the importance of zinc on exercise performance could be in part mediated by its effects on rheology [159].

Another mineral which is frequently lacking in sportsmen is iron. Iron-deficiency anemia in rats has been reported to be associated with abnormal erythrocyte rheology [160]. In humans, regular exercise results in higher mineral losses that can lead to iron deficiency. Even without anemia, this situation is likely to impair performance, although there is still some controversy concerning the opportunity of iron supplementation in sportsmen. In elite sportsmen plasma ferritin has been observed to be negatively correlated with blood viscosity [161]. Subjects with low ferritin levels suggesting mild iron deficiency have 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 [161]. 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.

9. Exercise as a "hemorheologic therapy"?

A large literature on the therapeutic effects of exercise in peripheral obliterative arterial disease shows that the therapeutic effect of training in this disease is explained by rheologic improvements [5–8]. Whether rheologic mechanisms also explain the beneficial effects of exercise in other situations is less known. However, the protective effects of exercise on coronary heart disease are now well demonstrated [2–4] and blood rheology has recently emerged as a major determinant of risk in this disease [24–27]. Therefore, further studies should be done in order to investigate possible rheologic mechanisms in this protective effect of exercise.

Non-insulin-dependent diabetes represents an extreme example of the insulin-resistance syndrome [108] in which all the metabolic abnormalities are overtly expressed. Exercise has been proposed as a preventive treatment [15] for this disease which is mostly explained by a decrease in muscular glucose uptake [109]. Since in these patients there is a link between unfitness and cardiovascular risk [162, 163] as well as a relationship between blood rheology and working capacity, a possible involvement of blood rheology in these interactions remains to be investigated. In insulin-dependent diabetics, there is also a relationship between aerobic working capacity and rheology [164] which may be interesting for the follow-up of diabetic sportsmen.

In conclusion, the body of literature summarized above supports the concept of blood fluidity being a marker of an individual's degree of fitness or unfitness. In that respect, an evaluation of hemorheologic measurements as indices of accuracy of training in sportsmen 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.

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