Basic study

Alterations of blood rheology during and after exercise are both consequences and modifiers of body’s adaptation to muscular activity

Hémorhéologie et exercice physique

J.-F. Brun, P. Connes, E. Varlet-Marie

Abstract

Objectives. – Current knowledge. Exercise has several hemorheological effects that we previously proposed to classify as a triphasic phenomenon: acute effects (hyperviscosity mostly due to hemococoncentration but also to some alterations of erythrocyte properties), delayed effects (hyperhydration resulting in hemodilution and hypoviscosity) and a chronic situation, which can be termed hemorheologic fitness. This presentation focuses on this last stage of hemorheologic effects of exercise. Some recent studies have shown that, according to the training pattern or intensity, it may result in different aspects. In endurance athletes (e.g., cyclists), there is mostly a chronic “hyperhydration–dilution status”, but some intriguing modifications of red cell properties can also be found, in connection with metabolic and hormonal changes (insulin sensitivity, growth hormone and IGF-I status...). In sports where strength is improved rather than endurance, red cell aggregation and deformability are improved without marked changes in body fluid status and are correlated to body composition (percentage of fat) and the balance of substrate oxidation at exercise. In markedly sedentary obese, insulin resistant patients submitted to a therapeutic protocol of training, the parameter which is mostly improved is plasma viscosity, which appears to reflect in this case the plasma protein pattern related to the metabolic disorders (fibrinogen, lipoproteins...). Finally, overtraining reverses this picture of “hemorheologic fitness”, mostly by inducing a reversal of the “hyperhydration–hypoviscosity” pattern. The physiological and pathophysiological importance of these observations remains unsettled, but there is increasing published evidence that these hemorheologic modifications may interfere with the physiology of the human body at exercise. In addition, exercise appears to be a rather effective “rheo-fluidifying therapy” while viscosity mirrors its metabolic effects, which are potentially beneficial on the circulatory level.

Conclusion. – Muscular activity results in marked hemorheologic alterations that reflect short and long term adaptation of a body submitted to an increase in its load of physical activity.
1. Introduction

Biorehology is the branch of biological sciences that studies flow and deformation of biological material under the influence of the constraints, which are applied to it. The branch of biorehology focusing more specifically on blood is termed hemorheology. Its purpose is therefore to study the flow of blood, in interaction with its surrounding environment, in both macro- and microcirculation.

Exercise hemorheology has been the subject of many studies in athletes, sedentary people and patients suffering from various diseases [12,17,44]. However, there remains still several unresolved questions [17]. In preceding reviews on this topic, we proposed several concepts aiming at synthesising all this information concerning both the physiological mechanisms and the functional consequences of the hemorheological alterations observed during and after exercise.

We thoroughly reviewed in some previous articles [12,17] 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 (e.g., the overtraining syndrome) may be considered as a fourth phase in this process.

2. Some fundamental concepts of hemorheology

When blood circulates through vessels, its flow is driven by a pressure gradient between heart and periphery, and results in a force of friction over the surface of endothelium. This force results in a shear stress $\tau$ applied on the vessel wall. Due to forces of cohesion between the wall and blood and within blood itself, the velocity of blood flow is lower in the vicinity of the endothelial surface than in the middle of the vessel, thus defining the shear rate $\gamma$. This difference in velocity reflects an intrinsic resistance to flow, which is termed apparent blood viscosity $\eta = \tau/\gamma$.

Blood viscosity $\eta$ is well described by a classical robust model, Quemada’s equation:

$$\eta = \eta_p \left(1 - \frac{1}{2k}\phi\right)^{-2}$$

where $\phi$ is hematocrit, $\eta_p$ is plasma viscosity, and $k(\gamma)$ is a shear-dependent parameter quantifying the contribution of erythrocyte rheological properties to whole blood viscosity. At high shear rate, $k(\gamma)$ is representative of red cell rigidity (i.e., the lower $k(\gamma)$, the higher is erythrocyte deformability), while at low shear rate $k(\gamma)$ which tends to a maximum $k_0$ that is proportional to the ability to form erythrocyte aggregates (red cell aggregability).

It is beyond the scope of this review to describe the physiology of these different parameters, but the important point for our purpose is that Quemada’s equation states that blood viscosity actually relies on three factors:

- plasma viscosity $\eta_p$, explained by plasma content in proteins;
- hematocrit $\phi$, which may rapidly vary according to the area of the circulation and the physiological condition;
- red cell deformability and aggregability, which are influenced by metabolism and hormones [18] have also a marked circulatory influence in the microcirculatory bed that is beyond its physical effects on whole blood viscosity.

Therefore, our review will focus on individual factors of viscosity ($\eta_p$, $\phi$, red cell deformability and aggregability) considered separately rather than $\eta$ alone.

All viscosity factors reviewed above are markedly modified during exercise (and after it) and those alterations appear to be related to many aspects of exercise physiology. In fact, the traditional picture of circulatory physiology provided by Hagen–Poiseuille’s law involves blood viscosity as a factor of peripheral resistance that might hamper blood flow if it were not easily overcome by vasomodulation. This equation can be written as follows:

$$Q = \frac{(\pi \times R^4 \times \Delta P)}{(8 \times \eta \times L)}$$

Where $Q$ is the suspension volumetric flow rate through a tube of radius $R$ under a pressure difference $\Delta P$ over the vessel length $L$; $\eta$ is an effective viscosity – that is, the ratio of shear stress to shear rate with shear stress corresponding to the force that moves the fluid layers or laminae and shear rate corresponding to the velocity gradient in the fluid. As discussed below, terms of this equation can be rearranged in order to describe a theoretical effect of viscosity on $O_2$ supply to tissues. Actually, this simplistic picture of circulation is not relevant to in vivo reality, and modern investigators like Holger Schmid–Schönbein have proposed more complex models in which the effect of
blood viscosity is markedly more important, as developed below [73–75].

3. The acute effects of exercise: a short-term increase in whole blood viscosity

Both maximal and submaximal exercise, either they are of short- or long duration, appear to almost always increase blood viscosity, due to a rise in plasma viscosity and hematocrit. In most cases (e.g., short acute exercise), these two events virtually explain all the observed increase in whole blood viscosity [8].

3.1. Fluid shifts

Actually, some studies failed to detect these changes [62] but when looking at their protocol one can notice that only postexercise (e.g., recovery) values are measured so that these short-time alterations have probably been not detected, due to a rapid return to preexercise values [12,17]. This rise in plasma viscosity and hematocrit is sometimes interpreted as a ‘hemococoncentration’ [78]. 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; splenocontraction that increases the number of circulating erythrocytes; enrichment of plasma in several proteins, coming presumably from lymphatics; a loss of water in the sweat for thermoregulation; entrapment of water into muscle cells [12,17,85].

It is important to stress that blood viscosity increases when recumbent subjects become orthostatic, due to an increase in hematocrit and plasma viscosity associated with a rise in plasma proteins and fibrinogen. These positional fluid shifts should be taken into account in the analysis of exercise-induced alterations in water status.

3.2. Red cell rheology

In most (but not all) exercise protocols there are also changes in the rheological properties of erythrocytes. 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, video film-induced emotional stress, and endogenous depression. 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 [8,12].

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. In one study, we interestingly found a threshold value for this effect which became apparent only when blood lactate increased above 4 mmolL⁻¹, that is a value which has been proposed to represent approximately the point where lactate induces acidosis [11]. Some other studies suggest however, that lactate exerts also some effects at lower concentrations, either in vivo or in vitro [17,18].

Actually lactate is surely 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, although this issue remains incompletely 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 [85].

There are also acute changes in erythrocyte aggregability (which increases) and disaggregability (which decreases) [12]. 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, that is the light transmission analysis (Myrenne aggregometer) [12,17]. While preexercise fibrinogen concentrations are correlated to the extent of these changes in aggregation [88], it is very likely that lactate does not play a role in this change in aggregation properties of the red cells [29]. Thus, the most important extra-cellular determinant of this event is fibrinogen. However, as discussed below, aggregation changes may also reflect leukocyte activation.

3.3. Paradoxical increase in 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. This paradox has recently been explained by a study on highly trained athletes during a progressive exercise test conducted to VO₂. In this case, red cell rigidity was found to paradoxically decrease [27]. Moreover, in vitro experiments [15] showed that lactate at concentrations ranging from 2 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 soccer players [11]) but actually improves red cell deformability.

3.4. White cells and free radicals

Both white cell activation and oxidant stress [2,76,79] 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. 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 [2]. According to Ajmani et al. [2], exercise-induced oxidative stress can also produce an increase in mean red cell volume and increase plasma fibrinogen levels, thus increasing also aggregation.

Please cite this article in press as: Brun J-F, et al., Alterations of blood rheology during and after exercise are both consequences and modifiers of body’s adaptation to muscular activity, Science & Sports (2007), doi:10.1016/j.scispo.2007.09.010
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, reflecting some degree of leukocyte activation that may surely interact via several circulating factors with red cell properties. Transient hypoxia might also result in 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 [2]. 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.

Temiz et al. [79] 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. These alterations were correlated with increased leukocyte phagocytic activity [79].

3.5. 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 [57]. Those studies have demonstrated that preventing the exercise-induced rise in erythrocyte rigidity by ω3-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.

Erythrocyte stiffening has also been shown to augment the pulmonary hemodynamic response to hypoxia [39], that is an experimental condition simulating altitude. This situation increases blood viscosity via a combination of factors (hypoxia, low pH and high values of blood lactate). This situation is associated with pulmonary hypertension. All this process is corrected by the calcium blocker flunarizine.

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 [13] 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 attractive hypothesis has been proposed by M. Guéguen-Delamair [12] when she 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 recently reported the case of a 50-year-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 these 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 [56]. 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 [14]. This leads to suppose that simple changes in hematocrit, red cell rigidity, and plasma viscosity are physiological adaptive 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. But, when drastic changes in blood rheology are associated with hemostatic perturbations and inflammatory phenomenon without sufficient vasodilation, the risks for medical complications are assumed to become no longer negligible. According to several authors [2,76,79], these adverse rheological effects may be responsible in part for the enhanced incidence of myocardial infarction and sudden death associated with exercise.

4. Training-related improvements in blood rheology

Cross-sectional studies of athletes compared to sedentary controls have repeatedly shown that athletes have a lower blood viscosity. Both plasma viscosity and hematocrit are lower [49,53,64]. As summarized by Ernst [46], “the fitter the athlete the more fluid his blood”. Koenig et al. [61] studied the self-reported regular leisure time physical activity in comparison with plasma viscosity data in 3522 men and women age 25 to 64 years from the Monica–Augsburg cohort. This population-based study shows that regular leisure physical activity is associated with a lower plasma viscosity across all age groups.

4.1. The first explanation: an “autohemodilution” phenomenon

During the hours following exercise, there is an increase in plasma volume (see refs in [12,17]) that represents a reversal of the acute hyperviscosity described above, resulting in an “autohemodilution” [46].
4.2. The paradox of hematocrit

This autohemodilution results in a lower hematocrit that explains the negative correlations which are found in sportsmen between hematocrit and fitness [12,17]. Therefore, one should point out an important paradox concerning hematocrit in exercise physiology [10].

Since sports performance depends on the capacity of oxygen transport to the exercising skeletal muscles, it is not surprising to observe that performance may be increased thanks to an artificial hematocrit augmentation that can be achieved by either training in high altitude, blood transfusions, or injecting erythropoietin. Since erythropoietin has become largely available due to bioengineering, doping with this hormone has become extremely popular in most sports. However, the rationale for this doping procedure 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 [10,12,17].

Comparisons between the extreme quintiles of hematocrit in athletes clearly illustrate this paradox [22]. 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 ergonomic 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 [17].

This issue has been further addressed by Gaudard and co-workers in our laboratory [55]. When maximal aerobic capacity was explained in power units ($W_{max}$) it exhibited a negative correlation with whole blood viscosity. When it was expressed as the power corresponding to a fixed heart rate of 170 beats/min it exhibited a negative correlation with several hemorheological factors, but the stepwise regression analysis only selected hematocrit as an independent determinant. Similarly, the best determinant of the maximal oxygen consumption ($V_{O_2}$) was also hematocrit. Therefore, it is clear that fitness is associated with a low viscosity–low hematocrit pattern while unfitness and overtraining (as discussed below) are associated with a mild hyperviscosity.

Since this physiological truth fully disagrees with the popular belief of “the more you have red cells the fitter you are”, we think that it is important to broadly disseminate this hemorheological paradigm of hematocrit among exercise physicians, coaches, and athletes.

4.3. Hemorheological effects of strength training and body building

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 [17] while in rugby men, a lower increase in $η$ during exercise seems to be the most prominent characteristic of training and fitness [6]. The increase in plasma volume has been assumed to contribute to the body water pool and to help prevent dehydration [17].

4.4. Description of hemorheologic fitness (the chronic training-induced hemorheologic improvement) as a four-step situation

Beside the profound alterations in water status described above, there are other effects of regular exercise that appear later, as a consequence of training-induced changes in metabolism.

4.4.1. Endurance training

In endurance athletes (e.g. cyclists), there is mostly a chronic “hyperhydration–dilution status”, but some intriguing modifications of red cell properties can also be found, in connection with metabolic and hormonal changes (insulin sensitivity, growth hormone and IGF-I status...). Endurance training reduces body fat, increases muscular volume, and markedly modifies muscular processing of fuels. 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 et al. [40] 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 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 with increased circulating lipids and fibrinogen, trained sportsmen who exhibit the opposite metabolic picture have an increased function of this axis [12,17]. Thus, this hormonal axis may be more or less directly involved in the regulation of training-induced changes in blood rheology.

4.4.2. Strength training

In sports, where strength is improved rather than endurance, red cell aggregation and deformability are improved without marked changes in body fluid status, and are correlated to body composition (percentage of fat) and the balance of substrate oxidation at exercise.

An example where this aspect has been extensively studied recently is rugby [6]. In this sport, in which body composition and blood rheology are related to each other and are both correlated to performance [6].

In male rugby players, the isometric adductor strength is correlated to erythrocyte flexibility and red cell aggregability is
correlated to fat mass measured by bioelectrical impedance. The aerobic working capacity is negatively correlated to the increase in plasma viscosity during exercise, suggesting that this event is less important in stronger individuals. This study shows that fat mass, even within a physiological range, is a determinant of erythrocyte aggregability, suggesting that training-induced alterations in body composition play a role in the specific hemorheologic profile of these athletes [6].

In female rugby players, [22] two subgroups can be considered: forward (FW) and backward (BW). BW are leaner, due to a lower fat free mass and a lower fat mass, while they had a faster running speed during field testing and a higher VO2. Exercise calorimetry evidence a higher ability to oxidize fat at exercise expressed by the “point of crossover” and the point of maximal lipid oxidation. Besides, comparison of hemorheological parameters indicates a higher blood viscosity in FW explained by a higher red cell rigidity while plasma viscosity, hematocrit and RBC aggregability were similar. On the whole sample, adductor strength is negatively correlated to RBC aggregability and handgrip strength is negatively correlated to RBC aggregability.

The ability to oxidize lipids at exercise is negatively correlated to whole blood viscosity and RBC rigidity. Thus, blood viscosity is negatively related to fitness in rugby women, and, as previously observed in rugby men, RBC rheology (deformability and aggregability) are the most important factors. The correlations found between RBC deformability and the ability to oxidize at exercise more lipids (i.e., a parameter of endurance performance) may be due to effects of endurance training on lipid oxidation, which may in turn modify lipid metabolism and thus influence RBC rheology, with possible consequences on performance [16].

4.4.3. Hemorheologic effects of training in sedentary patients

In markedly sedentary obese, insulin resistant patients submitted to a therapeutic protocol of training, the parameter which is mostly improved is plasma viscosity, which appears to reflect in this case the plasma protein pattern related to the metabolic disorders (fibrinogen, lipoproteins...) [71].

We recently demonstrated [41] that training in sedentary insulin resistant patients, applied three 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 non-significant 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 ηp 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 ηp as simple and inexpensive marker of efficiency of training in insulin resistant patients should be further evaluated [41].

Eterovic et al. [50], extending a previous work of Dintenfass [38] has demonstrated that ηp 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 [50].

In addition, insulin sensitivity is positively correlated to fitness, probably because training improves both glucose and lipid processing by muscle, and body composition. This contributes to explain why exercise is an effective treatment of the insulin resistance syndrome [41]. Exercise training improves the lipid pattern of patients suffering from this syndrome [3]. The effect of training on fibrinogen has been more controversial, since it depends upon the genetic subtypes of this molecule [12,17], explaining that it was not evidenced in some studies. In fact, training reduces fibrinogen [12], a notion that is also supported by negative correlations of fibrinogen with both fitness [5] and insulin sensitivity [72].

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 [17].

4.4.4. Beyond training: overtraining

The overtraining syndrome (OTS) is a condition wherein an athlete is training excessively, yet performance deteriorates. The OTS affects mainly endurance athletes. It is a condition characterized by chronic fatigue, under performance, and an increased vulnerability to infection leading to recurrent infections. It is not yet known exactly how the stress of hard training and competition leads to the observed spectrum of symptoms. Psychological, endocrinological, physiological, and immunological factors all play a role in the failure to recover from exercise. This OTS remains a controversial issue since its clinical presentation is far to be specific [51]. 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 [19]. 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. There appears to be a mild dehydration with increased hematocrit, serum Na+, and serum K+. All this seems 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 [48]. We recently investigated a possible relationship between the OTS score and blood rheology in male elite ath-
The 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 sportmen 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 [87].

Current concepts of the pathophysiology of this syndrome may explain this mild hyperviscosity and mild hemocoagulation pattern, since cytokines released by the “over-stressed” muscle appear now to be responsible for most of the symptoms [7]. According to this “cytokine hypothesis of overtraining” recently proposed by Smith [77], high volume/intensity training, with insufficient rest, will produce muscle and/or skeletal and/or joint trauma. Circulating monocytes are then activated by injury-related cytokines, and in turn produce large quantities of pro-inflammatory IL-1 beta, and/or IL-6, and/or TNF-alpha, producing systemic inflammation. Elevated circulating cytokines then co-ordinate the whole-body response by:

• communicating with the central nervous system (CNS) and inducing a set of behaviors referred to as “sickness” behavior, which involves mood and behavior changes that support resolution of systemic inflammation;
• adjusting liver function, to support the up-regulation of gluconeogenesis, as well as de novo synthesis of acute phase proteins, and a concomitant hypercatabolic state;
• and impacting on immune function.

Theoretically, OTS is viewed as the third stage of Selye’s general adaptation syndrome, with the focus being on recovery/survival, and not adaptation, and is deemed to be “protective”, occurring in response to excessive physical/physiological stress. The interest of this conception for hemorheologists is thus that OTS appears to be a systemic inflammatory condition, which can be monitored by markers of inflammation, such as, obviously, hemorheological ones [89].

These findings of an hemorheological pattern in OTS can also be relevant to some aspects of the clinical symptomatology of overtraining. For instance, the feeling of having “heavy legs” (FHL) is one of the most commonly reported signs. Since FHL is associated with a hemorheologic profile. It appeared that FHL subjects complaining from OTS signs had higher plasma viscosity \((1.43 \pm 0.047 \text{ vs. } 1.32 \pm 0.02 \text{ mPa.s}; P < 0.05)\) and a higher red cell aggregation as measured with laser backscattering [87]. These findings suggest that the feeling of heavy legs in overtrained athletes is related to OTS-related hemorheologic disturbances.

We recently addressed the question of whether hemorheologic measurements may provide a marker of the early stages of overtraining. The most logic candidate for this, plasma viscosity [90], appeared actually to be a rather specific, although poorly sensitive predictor of overreaching but has no interest in the diagnosis of the overtraining syndrome itself, since predictive value of \(\eta_p\) for early stages (overreaching) or chronicized stages (overtraining syndrome) was as follows:

• prediction of overreaching: sensitivity 28.57%; specificity 90%; positive predictive value 80%; negative predictive value 47.4%;
• prediction of chronicized overtraining: sensitivity 2.70%; specificity 18.2%; positive predictive value; 10.00%; negative predictive value 5.3% [90].

5. Speculations about a possible physiological meaning of all this: is blood rheology a physiological determinant of exercise performance?

5.1. From the viewpoint of classical circulatory biophysics

We already reminded the well-known classical observations that evidenced differences between high-fitness and low-fitness groups, the high-fitness group showing a lower plasma viscosity. Such correlations were reported many times [12,17]. Red cell flexibility is correlated to adductor isometric strength [6]. Correlations of blood fluidity with aerobic working capacity \(W_\text{170},\) time of endurance until exhaustion [12], blood lactate response [12,17], maximal exercise-test derived \(V_{\text{O2}}\) [17], and 4 mmol l\(^{-1}\) lactate thresholds [17] have been demonstrated.

Studies on patients with the sickle cell trait (SCT) have demonstrated a reduced capacity for prolonged competitive exercise under hypobaric hypoxia, which seems to result from reduced erythrocyte flexibility [54]. In addition, Connes et al. [31] recently reported lower aerobic capacity in SCT carriers performing submaximal exercise at sea level; a finding probably attributed to the reduced RBC deformability, increased RBC aggregability, reduced blood fluidity and increased vascular adhesion phenomenon observed in that population in comparison with healthy subjects [33,34,65,67,82]. On the other hand, when RBC fluidity is improved by \(\omega 3\) fatty acid supply (see below) there is an increase in \(V_{\text{O2}}\) under hypobaric hypoxia, suggesting that a prevention of RBC rigidification during exercise improves aerobic capacity in these conditions.

On a theoretical point of view, increased blood fluidity may improve \(O_2\) delivery to muscle during exercise in trained individuals [35]. However, this question remains uncompletely clarified. There are several biological indicators of fitness, which are relevant to different kind exercise. The most popular is maximal oxygen uptake \((V_{\text{O2max}})\), which has not been widely studied in connection to blood rheology despite the theoretical link between supply and rheology indicated above. As reminded above, \(V_{\text{O2max}}\) has been reported to be negatively correlated to blood viscosity, due to a negative correlation with plasma viscosity [10]. Another important parameter is the ability to avoid hyperlactacidemia, indicated by the so-called ‘anaerobic thresholds’ or ‘lactate thresholds’ [12]. In three separate studies, we observed that blood viscosity and erythrocyte aggregation were...
positively correlated to lactate accumulation into blood during exercise [17]. The possible meaning of the relationships between resting blood fluidity and lactate response will be discussed later.

Hemorheological determinants of the maximal oxygen consumption (VO2) and of the aerobic working capacity (W170) are quite the same [17] 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 [10,17]. However, hematocrit is also negatively correlated with aerobic performance [10,55], reflecting the importance of the beneficial effect of autohemodilution. The maximal oxygen consumption (VO2) is a measurement of body’s ability to increase O2 transfer from the surrounding atmosphere to muscles and depends on several steps. The limiting step is not the same for all sportmen. When arterial circulation is considered, VO2 is equal to the maximal value of Q × CaO2, Q being cardiac output and CaO2 the O2 content of blood. This formula VO2 = Q × CaO2 can be written as a function of hematocrit Φ and viscosity η if one applies Hagen–Poiseuille law. It becomes VO2 = constant × (Φη) × (ΔP/ΔZ) with ΔP being the drop in blood pressure and ΔZ being hematocrit. Thus, the value (Φη) should be a limiting factor for VO2. Actually, in experimental studies, VO2 is not correlated to Φ/η but is negatively related to Φ, that is, in these subjects Φ is mainly a factor of viscosity that is negatively related to fitness [10]. 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 [55].

5.2. Hemorheology and pulmonary oxygen diffusion capacity

Several studies have reported evidence that hemorheology could be a determinant of normal pulmonary oxygen diffusion capacity. Pulmonary Hct might influence pulmonary gas exchange. Deem et al. [37] recently reported interesting results regarding the relationship between Hct, arterial pressure in O2 (PaO2) and the alveolar to arterial O2 difference (A–aDO2) and they found that decreased Hct from 30 to 11% by hemodilution improved PaO2 and A–aDO2 and enhanced the ratio between alveolar ventilation and perfusion (i.e. VA/Q mismatch). Franck et al. [52] also studied the effects of pulmonary Hct on pulmonary oxygen diffusion capacity for O2 (DLO2) by using a two-dimensional finite-element model developed to represent the sheet-flow characteristics of pulmonary capillaries. Although, DLO2 increased as the Hct increased, DLO2 reached a plateau near an Hct of 35% [52]. Altogether, results from Deem et al. [37] and Franck et al. [52] indicate that there is an optimum value for Hct, which allows the highest pulmonary oxygen diffusion capacity. If Hct is too low, RBCs cannot uptake enough O2 to maintain normal arterial pressure in O2, but if Hct is too high, the same phenomenon is possible due to competition between RBCs for O2 influx [52]. Moreover, by testing the effects of RBC shape and deformability on DLO2 and resistance to flow in rabbit lungs, Betticher et al. [4] have demonstrated that impairment in RBC deformability decreased DLO2 and increased blood flow resistance whereas improvement in RBC deformability caused the opposite. A better RBC deformability allows a more homogeneous RBC distribution within pulmonary capillary and other microvessels that might explain the beneficial effects of RBC deformability on pulmonary oxygen diffusion [58]. Hsia et al. [58] have reported that membrane diffusing capacity for carbon monoxide (DMCO) and diffusive uptake for CO (DLCO) were affected by both elements: local Hct and RBC distribution at a given Hct. It has been shown that a rearrangement of RBC at a given Hct within a capillary segment allowing a more homogeneous distribution of RBC could increase DLCO by up to 33% [58].

These studies indicate that RBC deformability and Hct contribute to wall stress on pulmonary capillaries. Caillard et al. [21] proposed that a combination of high Hct level and reduced RBC deformability, particularly during exercise, might cause capillary pressure to approach the ultimate tensile length of vessel wall, particularly at level of blood–gas barrier that could lead to membrane disruptions and alter oxygen diffusion between alveoli and capillaries. From a hemorheologist point of view, we can also speculate that blood rheology impairment, like low RBC deformability or high RBC aggregation, lead to the transformation of active pulmonary capillaries into plasmatic pulmonary capillaries, that is, without oxygen, as already demonstrated into brain microcirculation. Altogether, these studies suggest that hemorheology impairment alter oxygen diffusion from alveoli to capillaries that might contribute to decrease exercise performance.

5.3. Hemorheology and cardiac function

Classical heart physiology assumes, after Hill (1923) that maximal cardiac output (Qc, i.e. the product of heart rate (HR) by stroke volume [SV]) was the primary factor explaining individual differences in maximal oxygen consumption (VO2) which is one of the main determinant of endurance performance. It is generally stated in textbooks that 70–85% of the limitation in VO2 is linked to maximal Qc. Besides, several studies showed that training induced improvement in VO2 resulted from an increase in maximal Qc rather than a widening of Da-vO2. However, any increase in ηh is likely to increase heart post-load and thus to decrease maximal stroke volume. Recently, we investigated blood rheology parameters and heart rate variability (HRV) at rest in athletes with sickle cell trait and we found a loss of parasympathetic activity associated to a hyperviscosity syndrome [30]. These results support the idea that blood rheology and cardiac function could be linked. Sickle cell trait athletes have usually lower aerobic capacity than normal athletes that suggests that blood rheology impairment and cardiac efficiency are limiting factor for endurance performance [63].

5.4. Hemorheology and cardiac function

The most important hemorheological factor affecting oxygen carrying capacity is Hct. Doping studies have shown that reinfusion of 900–1350 mL blood elevated the oxygen carry-
5.5. Hemorheology and oxygen supply to exercising muscles

Several investigators reported significant correlations between blood fluidity and indices of physical fitness such time of endurance until exhaustion, aerobic working capacity W170 or VO2 (see references in [12,17]). As underlined by Brun et al. [12,17], on a theoretical point of view, increased blood fluidity may improve O2 delivery to muscle during exercise in trained individuals. In one study, VO2 was negatively correlated to ηp, due to negative correlation with ηp [12,17]. Moreover, Charm et al. [23] reported reduced ηp among joggers compared with non-joggers. It seems that ηp could be a determinant of aerobic performance. In narrow capillaries, and so in muscle capillaries, RBCs flow in a single file and are surrounded by a plasma layer which allows normal blood flow structuring. Indeed, if ηp is too high, this could alter the normal blood flow structuring in capillaries, increase blood flow resistance, disorganize normal RBC orientation inside microvessels and thus impair O2 delivery to tissues. Hct could also play a role in O2 supply to muscles. Although higher Hct values are responsible for a greater blood oxygen carrying capacity, several studies reported negative correlations between Hct and aerobic performance [12,17]. If Hct is too high, this increases blood flow resistance in capillaries that might interfere with tissue O2 supplies [12,17]. RBC properties, that is RBC deformability and RBC aggregability, may also improve or impair O2 supply to tissues. As we have discussed earlier, a better RBC deformability allows a more homogeneous RBC distribution within pulmonary capillary and other microvessels that might allow adequate oxygen diffusion at the pulmonary level or at the muscular level. Parthasarathi and Lipowsky [70] studied the effect of reduced RBC deformability on microvessel recruitment attendant to a reduction in tissue PO2 in rat cremaster muscle and found that impairment in RBC deformability may adversely affect capillary recruitment and physiological mechanisms that ensure adequate delivery of oxygen to tissue. Studies of the rheological behavior of RBCs in the capillary network clearly demonstrated that capillary flux and velocity are strongly dependent on the ability of RBCs to deform on entry into the capillaries. RBC deformability impairment adversely affects capillary perfusion. Parthasarathi and Lipowsky [70] observed that less deformable RBCs were excluded from the bulk of the capillaries and followed more centralized pathways within the microvasculature that could alter O2 delivery to tissues.

5.6. Hemorheology and the Noakes’ hypothesis

Classic theory in exercise physiology considers that maximal exercise performance is limited by the cardiorespiratory system as a result of specific metabolic changes in the exercising skeletal muscle (i.e. peripheral fatigue). According to the classical model of Hill, peripheral fatigue occurs only after the onset of heart fatigue or failure. Thus, this hypothesis predicts that it is the heart, not the skeletal muscle that is at risk of anaerobiosis or ischemia during heavy exercise. As remembered by Noakes et al. [66], Hill proposed the existence of “governor” in either the heart or brain to limit heart work when myocardial ischaemia developed and to prevent fatal cardiac events during intense exercise. Noakes et al. [66] reviewed and reported several experimental results, which are compatible with the theory that the reduced maximal heart rate, maximal stroke volume and maximal cardiac output during acute and chronic hypoxia are due to central regulation. The central governor theory proposes that afferent sensory information from the heart, but also perhaps from the brain and respiratory muscles, informs the brain of any threat that hypoxia or ischemia may develop in those organs. In response, the central governor acts via the motor cortex to reduce the efferent neural activation of the exercising muscles, thereby reducing the mass of muscle that can be recruited, and hence, reducing the exercise intensity that can be sustained [66]. By limiting the muscle mass that can be activated, the central governor limits the peripheral peak VO2 to a level that will not induce hypoxia in any of the vital organs. The brain tissue is very vulnerable to hypoxia and its high metabolic rate needs a high oxygen supply. Because cerebral cortex capillaries are very narrow, any blood rheological impairment (increased local Hct, intensified RBC aggregation or loss of RBC deformability) alters blood flow structuring and hence adequate blood oxygenation. Blood flow structuring disturbance in cerebral cortex capillaries results in a slow down to a full stop of the blood flow, despite a preserved arteriovenular pressure difference. Indeed, we propose that blood rheological impairment induced by exercise and the subsequent metabolic changes (such as lactate acidosis and oxidative stress) could disorganize blood flow structuring in the brain which might reduce the efferent neural activation of the exercising muscles to limit metabolic changes and hence to limit further blood rheological impairment that might cause severe brain disturbance. Although afferent sensory information form the heart and others organs inform the brain to stop or reduce exercise as supposed by Noakes et al. [66], hemorheology (in relation with metabolic changes induced by exercise) could also...
play a great role in this process. Besides, Khaled et al. [59] by studying the effects of oral zinc supplementation on blood rheology behavior and Borg’s rating of perceived exertion (RPE) during exercise in healthy subjects, found that blood rheology and RPE were improved after zinc supplementation suggesting that hemorheology might influence exercise tolerance and hence, endurance performance [59]. At least, results obtained by Brun et al. [13] also comfort this hypothesis because they found a significant correlation between Hct and perceived exertion in exercising healthy subjects.

5.7. A new concept: viscosity parameters as factors of blood flow homogeneity or heterogeneity

During the last years, it has become obvious that the classical concepts of total flow and total peripheral resistance were unable to explain the relationships between blood viscosity factors and circulation. These were actually shown to violate the rules of linear physics stemming from the 19th century (e.g. namely Ohm’s, Poiseuille’s, Van’t Hoff’s and Hooke’s law). Clearly, the classical Newtonian physics was unable to explain the physiological effects of blood viscosity factors. This finding prompted the application of contemporary paradigms used in the non-linear sciences in general, namely the “percolation theory” [73–75]. Accordingly, crude measurements of blood viscosity have a poor physiological relevance, since blood may acutely undergo heterophase processes of self-potentiating viscidation or fluidification according to local flow conditions. In this context, by contrast, viscosity factors like red cell deformability, red cell aggregability, local hematocrit, plasma viscosity, and fibrinogen concentration are by contrast important regulatory factors that can govern the transition from the highly fluid towards the near-solid status. Apparently, these concepts are relevant for muscular physiology [55]. While in classical textbooks the role of “myogenic vasomotion” has probably been grossly overemphasized, the assessment of heterophase processes by ultrasound Doppler in the femoral artery of awake human subjects demonstrates the importance of these concepts. The measurement of the initiating reactions of “exercise hyperemia” in the gastrocnenius muscles evidences a dramatic flow increase in the subsequent relaxation phase: the temporal evolution of the latter during reiterating contractions leads to progressively more perfusion in the healthy controls, but leads to erratic evolutions (and rapid fatigue reactions) in patients afflicted with peripheral arterial obliterating disease. Analyses of these experiments by non-linear dynamics used to quantify these reactions show the highly relevant role of “qualitative transfer parameters”. Rather than the “pseudo–quantitative” numerical data, such as the conventional overall flow and/or the “total” peripheral resistance, the concept of “fluidity” taking into account these spatio-temporal inhomogeneities seems to explain the effects of blood rheology on muscular microcirculation. More particularly, in the specific conditions of the exercising muscle, it appears that these heterophase processes result in a very high local fluidity of blood regardless systemic hematocrit, plasma viscosity being the only hemorheological relevant factor. By contrast, in resting muscle high hematocrit or abnormal red cell rheology are likely to compromise circulatory homogeneity and to promote viscidation processes [10,55].

These new concepts provide an explanation for several clinical observations in exercise hemorheology. First, several papers from our group have demonstrated a link between erythrocyte aggregability at baseline and the rise in blood lactate during exercise [86]. These papers suggest that red cell aggregation may influence muscular lactate metabolism. As experimentally shown by Vicaut et al. [91], increased RBC aggregation may impair microcirculation in muscles. Although aggregation is beneficial to some extent for microvascular perfusion [69], 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, 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 co-workers [20], suggest that red cell aggregation represents 60% of resistance at the venous pole in cat gastrocnemius. Aggregation could be thus the major modifer of venous resistance in skeletal muscle [20].

Experiments of muscle hypoxia [92] 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. 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 [42].

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 [86]. According to Freund, the mathematical analysis of postexercise lactate allows a fair evaluation of lactate production by muscles (γ1) and lactate clearance (γ2). In a sample of subjects exhibiting a wide range of γ2 (from 2 to 7.7 × 10−2 min−1), we observed that postexercise cell aggregability index Myrenne “M1” (measured at V̇̇O2) was the only hemorheologic parameter correlated to γ2. Thus, microcirculatory adaptations influenced by red cell aggregation may influence lactate disposal and clearance (as reflected by γ2), 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 [86].

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 ml watt−1 but is higher in sedentary subjects when they exhibit a low fat-free mass or a high waist-to-hip ratio [86]. Interestingly, it is increased in individuals with elevated blood viscosity parameters [86] and the improvement of these parameters by
prostaglandin E1, naftidofuryl 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 (cited in [86]).

Finally, an amazing issue in current exercise physiology is exercise-induced arterial hypoxemia (EIAH), that is, 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 [21]. 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 but the clear demonstration of a role of blood rheology in this process is still lacking [21].

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, and the high capacity of shear-dependent rheofluidification found in horses despite their high red cell aggregability [21] 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 hypoxic and non-hypoxic athletes shows that exercise increases blood viscosity to higher levels in EIAH athletes. The greater increase in blood viscosity in these athletes was attributed to the lack of RBC deformability improvement during exercise whereas RBC became surprisingly more deformable in non-EIAH athletes. In addition, improvement of RBC deformability by dietary poly-unsaturated fatty acids reduces hypoxemia in athletes at maximal exercise [21].

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 [26] and by the paradoxical lack of hyperviscosity at exercise sometimes reported in athletes [21,36]. In EIAH-prone athletes, this mechanism may be blunted and hyperviscosity may thus result at maximal exercise in hypoxemia [25,36]. It is possible that training leads RBC to be more adapted to cope with lactate and oxidative stress, resulting in a lack of RBC deformability impairment and allowing a higher endurance performance [25].

6. Nutritional and metabolic influences on hemorheologic changes associated with exercise

Nutritional factors influence hemorheologic changes associated with exercise, with possible effects on muscular performance itself. A first important issue is water [12] 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 h submaximal strenuous exercise [85].

Caloric intake has also a pivotal importance. In athletes, there is a tendency to consume fewer calories than expended and to avoid fats. This tendency may further compromise antioxidant mechanisms protecting red cells against the exercise stress [54]. That stress is proportional to the intensity and duration of the exercise, relative to the maximal capacity of the athlete. Muscle glycogen depletion compromises exercise performance and also increases the stress. Glycogen stores can be protected by increased fat oxidation (glycogen sparing). The diets of athletes should be balanced so that total caloric intake equals expenditure, and so that the carbohydrates and fats utilised in exercise are replenished. Many athletes do not meet these criteria and have compromised glycogen or fat stores, have deficits in essential fats, and do not take sufficient micronutrients to support exercise performance, immune competence and antioxidant defence. From all nutritional variables optimal energy supply is considered as most vital for human performance. It is postulated that lack of energy homeostasis is a basic problem in the development of overtraining [7]. Most if not all clinical symptoms of this syndrome are directly or indirectly related to the physiological mechanisms of energy homeostasis. Lack of available energy has surely a much greater impact than exercise stress by its own. Dietary insufficiencies should be compensated for by supplementation with nutrients, with care not to over compensate. In a recent study we addressed the hemorheological side of this problem [89]. In 41 elite athletes, exercising 13 ± 0.9 h per week a standardized nutritional questionnaire suitable for sports medicine was applied. We found negative correlations between fibrinogen and protein intake. Accordingly, the RBC disaggregability threshold was also correlated negatively with protein intake. Caloric intake was correlated with red cell rigidity and negatively correlated with the RBC disaggregability threshold. Lipid intake was negatively correlated with the RBC disaggregability threshold. Carbohydrate intake was positively correlated with whole blood viscosity and negatively to the hematocrit/viscosity ratio. Therefore, fibrinogen levels and red cell rheology exhibit correlations with nutritional status in athletes. Low protein intake appeared to be associated with (mildly) raised fibrinogen and aggregability and caloric restriction with lowered red cell deformability [54]. These data are thus consistent with the concept of a pivotal role of adequate nutrition to prevent the effects of the chronic exercise-induced inflammation in people on the edge of the overtraining syndrome [89].

Contrasting with these effects of nutritional status on baseline hemorheology of people submitted to more than 10 h per week of training, there are few reported effects of a preexercise feeding on blood rheological response to exercise [12,17]. In thirty-one male triathletes, Van der Brug [84] investigated the effects of different kinds of feedings on the hemorheological response to prolonged exercise. While exercise caused the expected increase in whole blood and plasma viscosity, hematocrit, and osmolality, and a very small, but significant decrease in erythrocyte deformability, irrespective of the feedings consumed, the intake of different amounts of carbohydrate had no influence on the hemorheological parameters. Therefore, if...
water supply is sufficient, carbohydrates have no major influence to the hemorheological response to exercise.

By contrast, polyunsaturated fatty acids of the omega 3 family (ω3PUFA) increase exercise performance by improving RBC flexibility [18,57]. Thoth and co-workers [81] described also that ω3PUFA 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 [68] since it shows that a three-week 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 [15]. After a 495 kcal breakfast (8.9% proteins, 27.3% lipids; 63.9 % glucids, i.e. 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 [12,17].

Recent studies have underlined the importance of mineral and trace element status in sports hemorheology. Zinc, which in vitro increases the deformability of artificially hardened red cells [18], 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 which is associated with a decrease in performance. Experimentally, a double blind randomized trial of oral zinc supply in healthy volunteers improves blood viscosity [59] while the effects on performance are not significant. Zinc seems also to reduce erythrocyte aggregation both in vitro and in vivo [18].

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 [60]. Subjects with low ferritin levels suggesting mild iron deficiency thus 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 [60]. 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 homoconcentration 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 [44].

Recently the issue of alcohol consumption and blood rheology during exercise has been extensively studied (see review in [43]). According to El-Sayed [45], alcohol continues to be the most frequently consumed drug among athletes and appears to evoke detrimental effects on exercise performance capacity. Alcohol consumption decreases the use of glucose and amino acids by skeletal muscles, adversely affecting energy supply during exercise. Although moderate alcohol consumption has favourable effects on blood coagulation and fibrinolysis, but occasional and chronic alcohol consumption is usually linked with unfavourable alterations in platelet aggregation and function and may be associated with platelet-related thrombus formation. Concerning the effects of alcohol on rheological properties of the blood evidence suggests that alcohol use following exercise is associated with unfavourable changes in the main determinants of blood viscosity [45]. In moderately active young men, alcohol (0.7 g/kg body mass) was given 1 h after exercise. During recovery, while the increase in haematocrit postexercise similarly returned to the baseline level in both control and alcohol trials, plasma viscosity and plasma fibrinogen remained significantly high during recovery in the alcohol trial compared with control condition. Authors conclude that the consumption of alcohol after exercise delays the normal return of plasma viscosity, plasma fibrinogen to resting baseline levels during recovery.

7. Exercise as a “hemorheologic therapy”

In sedentary patients, regular exercise also improves blood rheology [44]. 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. Training compensates not only for the potential damage risk factors represent but also for the physical stress provoked by vigorous exercise. 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 [47].

Non-insulin dependent diabetes represents an extreme example of the insulin-resistance syndrome in which all the metabolic abnormalities are overtly expressed. Exercise has been proposed as a preventive treatment for this disease which is mostly explained by a decrease in muscular fat and glucose processing. In these patients, there is also a link between unfitness and cardiovascular risk [83]. Recently Aloulou reported the hemorheologic effects of low intensity endurance training in sedentary patients suffering from the metabolic syndrome [3] in 24 patients submitted to a two months targeted training designed for increasing exercise lipid oxidation. Variations of whole blood viscosity at high shear rate were explained here by two statistically independent determinants: hematocrit and red cell rigidity. Changes in RBC rigidity appeared to reflect weight loss and decrease in LDL cholesterol. Plasma viscosity was related to cholesterol and its training-induced changes are related to those of VO but not to lipid oxidation. Red cell
aggregability reflected both the circulating lipids (cholesterol and its subfractions HDL and LDL) and the ability to oxidize lipids at exercise. Factors associated to a post-training decrease in aggregability were weight loss and more precisely decrease in fat mass, improvement in lipid oxidation, rise in HDL-Cholesterol, and decrease in fibrinogen. On the whole, the major determinant of hemorheologic improvement was an increase in cardiorespiratory fitness ($V_O2$), correlated with a decrease in plasma viscosity, rather than improvement in lipid metabolism, although RBC aggregability and deformability exhibited clear relationships with lipid metabolism. This study thus evidences that the return to “metabolic fitness” in such subjects prone to develop metabolic diseases and diabetes, is closely associated with a parallel improvement in blood rheology, aerobic capacity and metabolism.

The effects of cardiac rehabilitation and exercise training on blood rheology in patients with coronary heart disease (CHD) have been recently investigated by Church et al.[24]. After rehabilitation, patients with CHD had reductions in plasma viscosity (from $1.85 \pm 0.18$ to $1.77 \pm 0.11$ mPa.s) and whole blood viscosity. Thus, cardiac rehabilitation improves blood rheology in patients with CHD. However, whether these improvements actually contribute to the increased functional capacity and reduced morbidity and mortality that is associated with participation in cardiac rehabilitation and exercise programs remains to be demonstrated.

8. Conclusions

A major historical issue in Sports Medicine is the research of accurate “markers of fitness”, which may help to predict performance and/or under performance, and thus avoid some unexpected health problems in athletes. Although less studied than other aspects of Sports Medicine and Exercise Physiology, exercise hemorheology is likely to provide some interesting possibilities fitting with this scope. As explained above, the training-induced improvement in blood rheology provides an integrated reflect of not only “autohemodilution” (i.e. training-related decrease in hematocrit) which is clearly a sign of fitness, but also some in plasma and red cell rheology that reflect metabolic improvements and thus what we propose to term “hemorheologic fitness”. A first unresolved question is thus the exact value in sports medicine of those alterations as “integrated markers of fitness”.

The issue of overtraining is another field where clinical assessment is difficult and where there is absolutely no consensus on biological signs. Interestingly, our findings of hemorheological signs of overtraining fits with the more recent pathophysiological concepts of this disease, which involve exercise-induced muscle histologic microlesions leading to post-exercise inflammation in order to govern muscle repair. This interleukine-related “wartime economy” is likely to explain more of the behavioral and metabolic signs of this disease, and is clearly reflected by hemorheological changes. In our studies, plasma viscosity seems to be more related to overtraining itself while hematocrit is rather linked to associated variations in aerobic working capacity (i.e. fitness). The clinical relevance of these potential “markers” clearly requires more investigation. Close from this topic is the issue of so-called “sports anemia”: a quite confusing question that hemorheologists may help to clarify. Hemorheologists observe that: (a) low hematocrit in athletes does not generally mean anemia but hemodilution; (b) iron deficiency, at the beginning, impairs blood rheology in athletes, even before anemia occurs, and may be associated with a paradoxical rise in hematocrit and viscosity. That leads to what we proposed to call “the paradox of hematocrit in athletes”. According to traditional physiology, it is highly paradoxical to observe that doped athletes with high hematocrit may win races. According to Poiseuille’s law and its application to hemorheology they should not, since excess hematocrit would increase blood viscosity and thus impair perfusion. The recent understanding of non-linear acute transition between two structures of blood (highly fluid versus highly viscous) resolves this apparent paradox. According to this approach, tremendously high hematocrit would thus: (a) actually improve $O_2$ supply at exercise; (b) induce a true hyperviscosity syndrome (like polycythemia vera) at rest. This is likely to explain at least a part of recently reported fatalities in young cyclists in a clear context of hyperviscosity. However, there is clearly a need for specific studies.

Another amazing question is that of race horses that undergo pulmonary hemorrhage, which seems to be related to the story of elite athletes that undergo oxygen desaturation at peak exercise. The recent abovementioned studies by Connes and co-workers actually indicate that highly trained endurance athletes may have specially designed red cells which cope very well with blood lactate. They are able to uptake more lactate. This lactate, which impairs RBC deformability in sedentary subjects, paradoxically improves it in trained subjects. Some so-called extreme athletes who undergo oxygen desaturation at exercise actually exhibit a higher viscosity response than those who don’t, and that appears to be associated with a lack of exercise-induced red cell “fluidification”.

Studies on blood rheology in SCT carriers performing exercise might also allow resolving an important question: that is, “Do SCT carriers are really at risk for developing medical complications, such as exercise-related sudden death”. Several reports underlined that SCT could be one of the most frequent cause of exercise sudden death in black army recruits and athletes but pathophysiological mechanisms responsible of such a fatal scenario remain unclear. Some investigations demonstrated disturbed hemorheologic characteristics at rest and in response to exercise in this population that could participate to blood flow impairment into the microcirculation.

Another potentially promising area of research in exercise hemorheology is the correlations between RBC deformability and the ability to oxidize at exercise more lipids. This may reflect the fact that a low ability to oxidize and to periodically deplete triglyceride in muscle is associated with raised blood lipids. Alternatively, high carbohydrate oxidation rates in the mitochondrion are likely to promote more free radical generation. All this requires to be elucidated.

Concerning red cell aggregation, it is thus known to increase, and postexercise RBC aggregability is correlated to fibrinogen at rest. Whether other factors than fibrinogen also play a role
in this physiological, rapidly reversible process is unknown. Even more mysterious is the functional role of these exercise-related changes in RBC aggregation. G. Brook’s “crossover concept” [16] implies that blood lactate during exercise is nowadays considered rather as a mirror of the balance between oxidized carbohydrates and lipids than resulting from a “Pasteur-like” effect (so-called “anaerobiosis”). As shown above, RBC aggregability seems to be associated with a higher lactate accumulation in blood during exercise. Whether this repeatedly reported observation means that aggregation induces in muscle some degree of “anaerobiosis” remains to be clarified. Our more recent finding in this issue is that the kinetics of lactate removal from blood after exercise is related to the extent of RBC aggregation at peak exercise.

On the whole, both physiological and clinical fields of sports medicine are full of questions still to be resolved by hemorheologists, and that potentially imply clinical applications of hemorheology in this domain of biological sciences.

Uncited references

[1,9,32,80].

References


Alterations of blood rheology during and after exercise are both consequences and modifiers of body’s adaptation to muscular activity.


