Boletim Hemorreologia nº 3/2002
Pista: Bole-1

# FROM EXERCISE HEMORHEOLOGY TO HEMORHEOLOGIC FITNESS

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## 1. ABSTRACT

Exercise has several hemorheological effects that we previously proposed to classify as a triphasic phenomenon: acute effects (hyperviscosity mostly due to hemoconcentration 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 (eg, 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. On the whole, we conclude that, according to the training volume, there are at least four different aspects of this chronic hemorheologic effect of regular exercise.

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

## 2. INTRODUCTION

Exercise hemorheology has been the subject of a lot of studies in athletes, sedentary people and patients suffering from various diseases (1-3). However, there remains still several unresolved questions (3). In preceding reviews on this topic we proposed several concepts aiming at synthesizing 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 our previous articles (1-3) the sequence of the hemorheologic effects of exercise. Analyzing all the body of literature concerning this issue, we proposed to describe them as a triphasic phenomenon: acute, delayed and chronic effects. Besides, effects of excess exercise or excess training (eg, the overtraining syndrome) may be considered as a fourth phase in this process.

## 3. THE ACUTE EFFECTS: A SHORT-TERM INCREASE IN BLOOD VISCOSITY

### a) Fluid shifts

Both maximal and submaximal exercise, either they are of short or long duration, appear to always increase blood viscosity, due to a rise in plasma viscosity and hematocrit. In most cases (eg, short acute exercise) these two events virtually explain all the observed increase in whole blood viscosity (4). Actually, some studies failed to detect these changes (5), but when looking at their protocol one can notice that only postexercise (eg, recovery) values are measured so that these short-timed alterations have probably been not detected, due to a rapid return to preexercise values (1) This rise in plasma viscosity and hematocrit is sometimes interpreted as a "*hemoconcentration*" (5). 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; spleno-contraction that increases the number of circulating erythrocytes; enrichment of plasma in several proteins, coming presumably from lymphatics (9); a loss of water in the sweat for thermo-regulation (10); entrapment of water into muscle cells (11).

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 (12). These positional fluid shifts should be taken into account in the analysis of exercise-induced alterations in water status.

### b) Red cell rheology

In most (but not all) exercise protocols there are also changes in the rheological properties of erythrocytes (4). 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 (13), videofilm-induced emotional stress (14), and endogenous depression (15). These effects are generally not found at exercise when red cell rheology is investigated after resuspension of cells on a buffer, indicating that they are

mostly due to plasma factors rather than to intrinsic red cell properties (1-3).

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 $mmol.L^{-1}$, ie, a value which has been proposed to represent approximately the point where lactate induces acidosis (1-3). Some other studies suggest however that lactate exerts also some effects at lower concentrations, either in vivo or in vitro.

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 uncompletely clarified. Presumably, fluid status has also a major influence on erythrocyte rheology during exercise, as suggested by the preventive effect of drinking on red cell rigidification (16).

There are also acute changes in erythrocyte aggregability (which increases) and disaggregability (which decreases) (17-18). Little is known about the mechanisms of these latter modifications which are not found in all exercise protocols and are generally not detected by the most widely used technique, ie, the light transmission analysis (Myrenne aggregometer) (19). While preexercise fibrinogen concentrations are correlated to the extent of these changes in aggregation (18), there is no evidence either in vivo or in vitro that lactate may play a role in this change in aggregation properties of the red cells. Thus, the most important extracellular determinant of this event is likely to be fibrinogen. However, as discussed below, aggregation changes may also reflect leukocyte activation.

**c) paradoxical increase of red cell deformability during exercise in athletes**

While red cell rigidity was generally found to be either increased or unchanged during exercise, there was a surprising report of a decrease of this parameter, when assessed after exercise with the LORCA (20). This paradox has recently been explained by a study on highly trained athletes during a progressive exercise test conducted to $VO_{2max}$. In this case red cell rigidity was found to paradoxically *decrease* (21). Moreover, in vitro experiments (3) showed that lactate at concentrations ranging from 2mM to 10 mM *increased* red cell deformability in such athletes while it classically decreased it in blood from sedentary subjects. Thus, in highly trained subjects, the exercise-induced increase in blood lactate does not rigidify the red cell as observed in sedentary subjects or in moderately trained ones (like soccer players (22)) but actually improves red cell deformability.

**d) white cells and free radicals**

Both white cell activation (54) and oxidant stress (55) are likely to play an important role in the hemorheologic effects of exercise. The marked increase in oxygen utilization that occurs during exercise results in production of free radicals by several sources, including the mitochondria

and the white cells (23). In addition, there may be an autoxidation of hemoglobin & catecholamines. Transient tissue hypoxia due to rapid accelerated consumption of oxygen in exercising muscles and to inadequate oxygen supply at the pulmonary level in some trained people has been also demonstrated and may lead to free radical formation. Whatever the mechanism, it is well established that oxidative stress during acute exercise is associated with a hemorheological impairment (23). According to Ajmani (23), exercise-induced oxidative stress can also produce an increase in mean red cell volume and increase plasma fibrinogen levels, thus increasing also aggregation.

However, until recently, little was known about the involvement of leukocyte activation in these rheological changes. Number of leukocytes increase after strenuous exercise. This increment is attributed to increased blood flow that recruits the leukocytes from the marginal pool and/or hormonal changes which are likely to be mediated by beta-2 adrenergic receptors. More interestingly, a decrease in filterability of white cells during exercise has been evidenced (24), reflecting some degree of leukocyte activation that may surely interact via several circulating factors with red cell properties. Transient hypoxia might also result cytokine release and leukocyte activation. When leukocytes (especially polymorphonuclear leukocytes) are activated, they reduce molecular oxygen enzymatically to generate metabolites such as superoxide anions, hydrogen peroxide or hydroxyl radicals (25). 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 (25). A Temiz investigated the leukocyte activation and RBC damage after exhaustive exercise in untrained rats. Significant increments in RBC membrane protein oxidation and lipid peroxidation, and decreased membrane enzyme activities were observed during early and late phases after the exercise episode. RBC transit times measured by a cell transit analyser failed to indicate significant changes in RBC deformability, despite the biochemical evidences of oxidant damage (26). These alterations were correlated with increased leukocyte phagocytic activity.

**e) 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 (27). 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 (28), ie, 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 (29) 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-Delamaire (30) 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 yr old marathon runner who underwent a thrombosis of the central vein of retina after a marathon run and exhibited during a standardized submaximal exercise-test a disproportionate increase in blood viscosity, hematocrit, and mostly red cell aggregation and disaggregation thresholds. While some of this postexercise hyperviscosity pattern may be due to the previous vascular event, these findings may support the hypothesis of a role for hemorheological disturbances during exercise in the pathogenesis of this marathon-induced retinal thrombosis (31). 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 (3). This leads to suppose that simple changes in hematocrit, red cell rigidity, and plasma viscosity are physiological adaptative modifications which occur during many kinds of exercises and do not imply a risk by themselves. Presumably such changes can be easily overcome by vasodilatation. In our opinion, the risk of strong maximal or exhausting work loads is more related to other factors, including wide muscular damage, modifications of hemostasis and white cell activation. According to Ajmani (23) these adverse rheological effects may be responsible in part for the enhanced incidence of myocardial infarction and sudden death associated with exercise.

## 4. TRAINING INDUCED IMPROVEMENT 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 (32-35). As summarized by E. Ernst (36) "*the fitter the athlete the more fluid his blood*". Koenig (37) 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 visco-sity across all age groups.

### a) the explanation: an "autohemodilution" phenomenon

During the hours following exercise, there is an increase in plasma volume (38) that represents a

reversal of the acute hyperviscosity described above, resulting in an "autohemodilution" (39).

**b) the paradox of hematocrit (40)**

This autohemodilution results in a lower hematocrit that explains the negative correlations which are found in sportsmen between hematocrit and fitness (1-3-19).

Therefore, one should point out an important paradox concerning hematocrit in exercise physiology (40).

Since sports performance depends on the capacity of oxygen transport to the exercising skeletal muscles (41,42), it is not surprising to observe that performance may be increased thanks to an artificial hematocrit augmentation (43). As pointed out in a recent review (43), this can be performed by either training in high altitude, blood transfusions, or injecting erythropoietin. Since the synthesis of erythropoietin by bioengineering, doping with recombinant human erythropoietin has become popular in sports in general, and in cycling in particular (43). Ho-wever, these data fully contrast with physiological informations reported above. In normal conditions there is a strong negative correlation between hematocrit and fitness which is explained by the effect of regular trai-ning (39).

Comparisons between the extreme quintiles of hematocrit in athletes clearly illustrate this paradox (40): athletes in the lowest quintile compared to those in the four other quintiles had a lower value of blood viscosity and a higher fitness as reflected by their aerobic working capacity, their relative maximal power output, and their isometric adductor strength. By contrast athletes in the highest quintile had higher viscosity and lower red cell disaggregability. On the whole, when hematocrit increases, there is a decrease in fitness and a higher score of overtraining. Fit athletes have a rather low hematocrit associated to other metabolic and ergometric improvements, while athletes with a high hematocrit are frequently overtrained and/or iron-deficient, and that their blood viscosity (and red cell disaggregability) tends to be increased (40).

This issue has been further addressed by Gaudard and coworkers in our laboratory (41) When maximal aerobic capacity was explained in power units (Wmax) it exhibited a negative correlation with whole blood viscosity. When it was expressed as the power correspondinf to a fixed heart rate of 170 beats/minute it exhibited a negative correlation with several hemorheological factors but the stepwise regression analysis only selected hematocrit as an independent determinant ($r=-0.66$ $p<0.001$). Similarly the best determinant of the maximal oxygen consumption ($VO_{2max}$) was also hematocrit ($r=-0.462$ $p=0.01$). Therefore, it is clear 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 thruth fully disagrees with the popular belief of "the more you have red cells the fitter you are", it is important to broadly disseminate this hemorheological concept among exercise physicians, coaches and athletes.

**c) the case for 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 (42) while in rugbymen a lower increase in ηpl during exercise seems to be the most prominent characteristic of training and fitness (43). The increase in plasma volume has been assumed to contribute to the body water pool and to help to prevent dehydration (2).

## 5. The four steps of hemorheologic fitness: delayed, metabolic-mediated, effects of exercise on blood rheology

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.

### a) Endurance training

In endurance athletes (eg, 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 trai-ning reduces body fat, increases muscular volume, and markedly modifies muscular processing of fuels. 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.

As soon as 1986, Dudaev (44) 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 trigly-ceride 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 a-daptations 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 (45). Thus, this hormonal axis may be more or less directly involved in the regulation of training-induced changes in blood rheology.

### b) 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 (43-46). In this sport, in which

body composition and blood rheology are related to each other and are both correlated to performance (43).

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, sugges-ting that training-induced alterations in body composition play a role in the specific hemorheologic profile of these athletes (43).

In female rugby players two subgroups can be considered: forward (FW) and back (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 $VO_{2max}$. Exercise calorimetry evidences 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 rugbywomen, and, as previously observed in rugbymen, RBC rheology (deformability and aggregability) are the most important factors. The correlations found between RBC defor-mability and the ability to oxidize at exercise more lipids (ie, 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 conseqences on performance (46).

### c) hemorheologic effects of training in sedentary patients (47)

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...) (48).

We recently demonstrated (47) that training in sedentary insulin resistant patients, applied 3 times a week (45 min) at a level defined by a prior e-xercise-test induces significant improvements in body composition (loss of 2.5 kg on the average, consisting only of fat mass with a stability of fat free mass), associated with improvements in exercise-test parameters. The metabolic improvements indicate a markedly increased ability to oxidize fat at exercise, although blood lipids and insulin sensitivity were not significantly improved. Actually a nonsignificant tendency to such an improvement would perhaps become significant in a higher sample. Blood rheology is also improved, as expected, but the only significant result at this time is a decrease in plasma viscosity, while hematocrit,

red cell deformability and red cell aggregation are not significantly changed. Thus, consistent with observations in athletes, the metabolic and ergometric improvements induced by training reduces ηpl 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 ηpl as simple and unexpensive marker of efficiency of training in insulin resistant patients should be further evaluated (47).

Eterovic (49), extending a previous work of Dintenfass (50) has demonstrated that ηpl value is explained by a combination of cholesterol, fibrinogen, triglycerides, hematocrit (reflec-ting the degree of dilution) and HDL that may be combined in a predictive equation (51).

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 (52,53). Exercise training improves the lipid pattern of patients suffering from this syndrome (54,55). The effect of training on fibrinogen has been more controversial, since it depends upon the genetic subtypes of this molecule (56), explaining that it was not evidenced in some studies (56). In fact, training reduces fibrinogen (56), a notion that is also supported by negative correlations of fibrinogen with both fitness (58) and insulin sensitivity (59).

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 (47).

**d) 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, underperformance, 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, endocrinogical, 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 (60). 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 (61). 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 (62). We recently investigated a possible relationship between the OTS score and blood rheology in male elite athletes (63). 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 sportsmen are associated with a hemorheologic pattern that suggests some degree of reversal of the fitness-associated "autohemodilution" discussed above. In addition, overtrained athletes are frequently iron depleted, a mechanism that may induce additional hemorheological alterations but is unlikely to explain the early hemorheologic tableau of the overtraining syndrome (63).

Current concepts of the pathophysiology of this syndrome may explain this mild hyperviscosity and mild hemoconcentration pattern, since cytokines released by the "over-stressed" muscle appear now to be responsible for most of the symptoms (64). Accor-ding to this "cytokine hypothesis of overtraining" recently proposed by Smith, 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 proinflammatory IL-1beta, and/or IL-6, and/or TNF-alpha, producing systemic inflammation. Elevated circulating cytokines then co-ordinate the whole-body response by: a) communicating with the CNS and inducing a set of behaviors referred to as "sickness" behavior, which involves mood and behavior changes that support resolution of systemic inflammation: b) 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 c) 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 (64).

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 also a sign of chronic venous insufficiency where it can be corrected by rheo-active drugs we recently investigated whether the FHL is associated with a hemorheologic profile. It appeared that FHL subjects complaining from OTS signs had higher plasma viscosity (1,43±0,047 vs 1,32±0,02 mPa.s $p<0.05$) and a higher red cell aggregation as measured with laser bacscattering (65). These findings suggest that the feeling of heavy legs in overtrained

athletes is related to OTS-related hemorheologic disturbances.

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

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

### a) from the viewpoint of classical circulatory physiology

The pioneer of clinical hemorheology L. Dintenfass evidenced differences between high-fitness and low-fitness groups, the high-fitness group showing a lower plasma viscosity, lower fibrinogen level, and higher albumin/fibrinogen ratio. Later, such correlations were reported many times (3). Red cell flexibility is correlated to adductor isometric strength (43). Correlations of blood fluidity with aerobic working capacity $W_{170}$, time of endurance until exhaustion (66), blood lactate response (67-69), maximal exercise-test derived $VO_{2max}$ (69), and 4 $mmol.l^{-1}$ lactate thresholds (69) have been demonstrated.

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 (3). 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 ω3 fatty acid supply (see below) there is an increase in $VO_{2max}$ under hypobaric hypoxia, suggesting that a prevention of RBC rigidification during exercise improves aerobic capacity in these conditions (27).

On a theoretical point of view, increased blood fluidity may improve $O_2$ delivery to muscle during exercise in trained individuals. However, this question remains uncompletely clarified. There are several biological indicators of fitness, which are relevant to different kinds of exercise. The most popular is maximal oxygen uptake ($VO_{2max}$), which has not been widely studied in connection to blood rheo-logy despite the theoretical link between $O_2$ supply and rheology indicated above. In one study, $VO_{2max}$ was negatively correlated to blood visco-sity, due to a negative correlation with plasma viscosity (69). Another important parameter is the ability to avoid hyperlactacidemia, indicated by the so-called “anaerobic thresholds” or “lactate thresholds” (37-69). In three separate studies, we observed that blood viscosity and erythrocyte aggregation were positively correlated to lactate accumulation into blood during exercise (136-138). The possible meaning of the relationships between resting blood fluidity and lactate response will be discussed later.

Hemorheological determinants of the maximal oxygen consumption ($VO_{2max}$) and of the areobic working capacity ($W_{170}$) are quite the same (69) since these two parameters are highly correlated to each other and are both indices of arerobic exercising capacity. Plasma viscosity is the best statistical determinant of these two measurements of aerobic performance (71). However, hematocrit is also negatively correlated with aerobic performance (40-69-71), reflecting the importance of the beneficial effect of autohemodilution. The maximal oxygen consumption ($VO_{2max}$) is a measurement of body's ability to

increase $O_2$ transfer from the surrounding atmosphere to muscles and depends on several steps. The limiting step is not the same in all sportsmen. When arterial circulation is considered, $VO_{2max}$ is equal to the maximal value of $Q.CaO_2$, Q being cardiac output and $CaO_2$ the $O_2$ content of blood. This formula $VO_{2max} = Q.CaO_2$ can be written as a function of hematocrit $\phi$ and viscosity $\eta$ if one applies Hagen--Poiseuille law. It becomes $VO_{2max}$ = constant x $(\phi/\eta)$ x $(\Delta P/Z)$ with $\Delta P$ being the drop in blood pressure and Z being hindrance. Thus the value $(\phi/\eta)$ should be a limiting factor for $VO_{2max}$. Actually, in experimental studies, $VO_{2max}$ is not correlated to $(\phi/\eta)$ but is negatively related to $\phi$, ie, in these subjects $\phi$ is mainly a factor of viscosity that is negatively related to fitness (40). 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 (1-3).

**b) a new concept: viscosity parameters as factors of blood low momogeneity 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 (eg, namely Ohm's, Poiseuille's, Vant'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" (72-74). 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 (75). While in classical textbooks the role of "myogenic vasomotion" has probably been grossly overemphased, 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 gastrocemius muscles evidences a drammatic 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 "fluidality" 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 (75).

These new concept 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 (67-69). These papers suggest that red cell aggregation may influence muscular lactate metabolism. As experimentally shown by Vicaut (76), increased RBC aggregation may impair microcirculation in muscles. Although aggregation is beneficial to some extent for microvascular perfusion (77), 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 $O_2$. While the microcirculatory effects of red cell aggregation are a matter of controversy, experiments by Johnson and coworkers (78), 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 (78).

Experiments of muscle hypoxia (79) 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 (79). In humans suffe-ring 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 (80).

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 (81). According to Freund, the mathematical analysis of postexercise lactate allows a fair evaluation of lactate production by muscles ($\gamma 1$) and lactate clairance ($\gamma 2$). In a sample of subjects exhibiting a wide range of $\gamma 2$ (from 2 to 7.7 x $10^{-2}$ $min^{-1}$) we observed that postexercise red cell aggregability index Myrenne "M1" (measu-red at $VO_{2max}$) was the only hemorheologic parameter correlated to $\gamma 2$. Thus microcirculatory adaptations influenced by red cell aggregation may influence lactate disposal and clea-rance (as reflected by $\gamma 2$), adding its effect to that of the balance between carbohydrates and fat oxidation which is the major determinant of blood lactate concentrations at exercise in physiological conditions (81).

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 $ml.watt^{-1}$ (82) but is higher in sedentary subjects when they exhibit a low fat-free mass or a high waist-to-hip ratio (83). Interestingly, it is increased in individuals with elevated blood viscosity parameters (84) and the improvement of these parameters by prostaglandin E1, naftidrofuryl or hemodilution partially corrects it. According to Wolff and Witte, the measurement of this waste of oxygen during submaximal steady state workloads may allow a direct clinical determination of microcircu-latory performance in involved muscle tissue as a function of blood viscosity (84).

Finally, an amazing issue in current exercise physiology is exercise-induced arterial hypoxemia (EIAH), i.e., the arterial pressure in $O_2$ decreases during intense exercise. This situation has some similarities with horse's exercise-induced pulmonary hemorrhage (EIPH) that is frequently observed during competitive races (85). 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 (86).

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 capa-city of shear-dependent rheofluidification found in horses despite their high red cell aggregability (86) indicates that horse and human rheology are extremely different. However several recent lines of evidence support a role for blood rheology in the pathophysiology of EIAH. First, comparison between hypoxemic and non hypoxemic athletes shows that exercise increases blood viscosity to higher levels in EIAH athletes, despite a similar rise in hematocrit and a paradoxical decrease in RBC rigidity. In addition, improvement of RBC deformability by dietary poly-unsaturated fatty acids reduces hypoxemia in athletes at maximal exercise (87).

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 and by the paradoxical lack of hyperviscosity at exercise sometimes reported in athletes (88). In EIAH-prone athletes, this mechanism may be blunted and hyperviscosity may thus result at maximal exercise in hypoxemia (87).

## 7. Nutritional and metabolic influences on blood rheologic changes during exercise

Nutritional factors influence he-morheologic changes associated with exercise, with possible effects on muscular performance itself.

A first important issue is water (89) dehydration reduces blood and plasma volume, increases hematocrit, plasma osmolality, plasma viscosity and plasma protein, while it dramatically

increases red blood cell aggregation proportional to a rise in plasma globulin. Accordingly, water supply almost completely prevents the increase in red cell rigidity induced by 1 hr submaximal strenuous exercise (16).

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 (90). 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 in 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 (91). It is postulated that lack of energy homeostasis is the basic problem in the development of overtraining (60,61-91). 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 (90) In a recent study we addressed the hemorheological side of this problem (92). In 41 elite athletes exercising 13±0,9 hr/wk 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 threshol. 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 (92). 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 (64-90,91).

Contrasting with these effects of nutritional status on baseline hemorheology of people submitted to more than 10 hours per week of training, there are few reported effects of a preexecise feeding on blood rheological response to exercise (1,3). In thirty-one male triathletes van der Brug investigated the effects of different kinds of feedings on the hemorheological response to prolonged exercise. (93). 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 (93).

By contrast, polyunsaturated fatty acids of the omega 3 family (ω3PUFA) increase exercise performance by improving RBC flexibility (27). Thoth and coworkers (94) describe also that ω3PUFA increase arerobic 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 (95) since it shows that a 3 wk of fish oil supplementation (6 g/day), without or with vitamin E (300 IU/day), has no effect on either RBC rheology or exercise perfor-mance.

In fact, the simple fact to take or not a breakfast before exercise has a significant influence on hemorheological response to this exercise (96). After a 495 kcal breakfast (8,9% proteins, 27,3% lipids; 63.9% glucids, ie mimicking a “french breakfast”), the increase in erythrocyte rigidity that occurs at fast is prevented, while plasma viscosity is higher and increases more when subjects were fed than when they were fasting. Therefore, such a breakfast modifies the rheologic response to exercise, by preventing a reduction in red cell deformability and increasing plasma viscosity as well as its rise during cycling (96).

Recent studies have underline the importance of mineral and trace element status in sports hemorheology. Zinc, which *in vitro* increases the deformability of artificially hardened red cells (97), is frequently low in the serum of athletes, this situation reflec-ting some degree of deficiency. At-hletes with low serum zinc have a higher blood viscosity and an impairment in erythrocyte deformability (98) which is associated with a decrease in performance. Experimentally, a double blind randomized trial of oral zinc supply in healthy volunteers improves blood viscosity (99) while the effects on performance are not significant. Zinc seems also to reduce erythrocyte aggregation both *in vitro* and *in vivo* (100).

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 (101). Subjects with low ferritin levels suggesting mild iron deficiency exhibit a higher blood viscosity explained by a higher plasma viscosity while hematocrit and red cell rigidity are unchanged. Eryt-hrocyte aggregability is also higher in iron-deficient subjects (101). These data suggest that mild iron deficiency as commonly seen in athletes, before anemia occurs, is associated with an increase in plasma viscosity and RBC aggregation, together with an increased subjective feeling of exercise overload.

Finally, studies in body builders evidence abnormalities, including hemoconcentration and alterations in cholesterol metabolism, which have been suggested to be at risk for thromboembolic phenomena because of increased blood viscosity. Those abnormalities could reflect the use of diet, exercise, and ergogenic drug regimens, which are common among competitive athletes (3).

## 8. Exercise as a "hemorheologic therapy" in cardiovascular and metabolic diseases?

In sedentary patients, regular exercise also improves blood rheology. In fact, an improvement in blood fluidity can be induced by regular physical exercise regardless of whether the blood rheology was normal or abnormal at baseline. Thus regular exercise might be a way of therapeutically increasing blood flow in ischaemic vascular diseases. 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 (102).

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 (103).

The effects of cardiac rehabilitation and exercise training on blood rheology in patients with with coronary heart disease (CHD) have been recently investigated by T Church (104). After rehabilitation, patients with CHD had reductions in plasma viscosity (from 1.85±0.18 mPa.s to 1.77±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.

In conclusion, we have tried to summarize above a body of literature which is rapidly growing. It is clear that blood fluidity mirrors the individual's degree of fitness or unfitness. Since these markers appear to be also sensitive to nutritional status and overtraining, the use of hemorheologic measurements as indices of accuracy of training in either athletes or patients submitted to training for medical purposes is attractive. Of course, the accuracy of these parameters should be further assessed, but there is a lack of relevant ones (60,61-64). There is also a growing interest about viscosity parameters as markers of metabolic and cardiovascular rehabilitation. Here again, some work remains to be done in order to assess the reliability of viscosity parameters as markers suitable for the follow-up of these patients. Finally, several physiological aspects of this question such as the paradoxical increase in red cell deformability in trained individuals, the involvement of these factors in pulmonary hemorrage in horses or in

exercise-induced arterial hypoxemia in athletes remain poorly understood.

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