Exercise hemorheology: Classical data, recent findings and unresolved issues

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Abstract. The present review focuses on the past and recent knowledge in the field of exercise hemorheology and presents some unresolved issues for opening discussion. Acute exercise is associated with a rise in hematocrit which results in an increase in blood viscosity. Whereas increased blood viscosity was previously viewed as having negative consequences for cardiovascular function and aerobic performance, recent findings suggest dynamic changes in blood viscosity might be useful for vascular function during exercise by increasing nitric oxide production. Other determinants of blood viscosity are altered by exercise (e.g., decreased red blood cell deformability, increased red blood cell aggregation and plasma viscosity) and may, independent of the associated effect on blood viscosity, directly modulate aerobic capacity. However, the data published on the effects of exercise on the hemorheology are not consistent, with some studies showing decreased, unchanged, or increased red blood cell deformability/aggregation when compared with rest. These discrepancies seem to be related to the exercise protocol investigated, the population tested or the methodology utilized for hemorheological measurements. Finally, this review focuses on the effects of exercise training (i.e. chronic physical activity) on the hemorheological profile of healthy individuals and patients with cardiovascular and metabolic disorders.

Keywords: Exercise, training, blood viscosity, plasma viscosity, red blood cell deformability, red blood cell aggregation

1. Introduction

During states of increased energetic demand, a continuous rise in the rate of oxygen delivery and utilization may be observed until, at least in moderate-to-heavy intensity efforts, aerobic metabolism completely supplies the required energy cost. While highly trained individuals demonstrate faster rises in the rate of oxygen uptake, various disease states impair the capacity for performing work aerobically, when compared with untrained, healthy individuals. Consequently, the properties that influence oxygen transport and distribution (e.g., blood rheology) during exercise are important for understanding the mechanisms for reduced/improved aerobic exercise performance. Progression in hemorheological techniques improved the ability of performing blood rheological studies, and coupling hemorheological approaches with exercise physiology resulted in a renewal of interest in this scientific field. The present review will

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address classical findings in exercise hemorheology and will present new directions. In addition, some unresolved issues will be presented for opening discussion.

2. Acute effects of exercise on hemorheology and relationships with performance

2.1. Blood viscosity

Increased blood viscosity during exercise has been well reported (see [12]) and is caused by the rise of hematocrit induced by several mechanisms including fluid shift, water loss, release of sequestered RBCs from spleen and water trapping in muscle [2, 12, 22]. It appears that moderate dehydration ($\approx 2\%$ of weight loss) occurring during exercise has a limited impact on blood viscosity in healthy sportsmen [1, 85]. The changes in plasma viscosity, red blood cell (RBC) deformability and aggregation during exercise may also contribute to the changes in blood viscosity. However, the hemorheological response to exercise appears to be specific to the mode and intensity of the effort, and the training status of the individual.

Cycling exercise usually increases blood viscosity by 15–20% [11–12], due to an increase in plasma viscosity (+5–10%) and hematocrit (+10–15%). In contrast, prolonged running exercise performed in an outdoor environment does not alter blood viscosity or hematocrit [38, 60, 84]. Senay and Pivarnik [73] proposed that blood and plasma volumes are usually well maintained during such exercise, unless athletes lose a considerable amount of water (around 4–5% of total body weight). In addition, the footstrike hemolysis that occurs during running has been suggested to be responsible for the lack of change in the hemorheological profile observed in these studies. The most rigid RBCs could be destroyed during footstrike hemolysis, and the typical rise in hematocrit could be partially blunted [82, 84]. Further studies investigating the effects of cycling and running exercise on blood rheology in the same population (e.g., triathletes) may assist with definitively addressing this issue.

2.2. Blood viscosity, shear rate and nitric oxide

According to the Poiseuille law, increased blood viscosity may raise vascular resistance and increase the risks for cardiovascular complications. From an exercise physiology point of view, having high blood viscosity has been classically suspected to negatively impact on performance. Indeed, significant correlations have been reported between resting blood fluidity and indices of physical fitness such as endurance time, physical work capacity at a heart rate of 170 bpm or maximal oxygen consumption ($\text{VO}_{2\text{max}}$) [12]. Brun et al. [14] proposed that decreased resting blood viscosity could improve O_2 delivery to muscle during exercise in trained individuals.

During exercise, an excessive increase in blood viscosity was proposed to be potentially dangerous for the cardiovascular system because it is suspected to increase vascular resistance and increase the post-load work of the heart [28, 98]. However, blood vessels are not rigid tubes and their diameter may react and adjust in relation to the instantaneous hemorheological state. Experimental results demonstrated that increased blood viscosity may, in fact, decrease vascular resistance and increase tissue perfusion [17, 86] because the resulting increased wall shear stress may stimulate nitric oxide (NO) production by endothelial cells to create a vasodilatory compensation [69–71]. Connes et al. [27] recently studied the relationships between the changes in blood viscosity, vascular resistance, NO production and vascular hindrance in healthy sportsmen performing submaximal cycling exercise. The authors observed: 1) a

Fig. 1. Comparison between blood viscosity measured at rest at 90 s^{-1} (PRE 90) and blood viscosity measured at the end of a 15 min submaximal cycling exercise (105% ventilatory threshold 1) at either 90 s^{-1} (POST 90) or 225 s^{-1} (POST 225). The data used for this figure were those from Connes et al. [27] + 1 additional subject ($n = 10$). *Statistical difference ($p < 0.05$).

positive correlation between the increase in blood viscosity and the increase in NO production during exercise; 2) a negative correlation between the increase in NO production and the decrease in vascular hindrance; 3) a negative correlation between the increase in blood viscosity and the decrease in systemic vascular resistance. These findings suggest that a marked rise in blood viscosity during exercise could be necessary for NO production and adequate vasodilation. We suspect that greater vasodilation could be beneficial for improving peripheral blood distribution and thus allowing for optimal aerobic performance during exercise. Having decreased resting blood viscosity could be a way to obtain the largest rise in blood viscosity in response to exercise; that could explain why decreased baseline blood viscosity is also related to improved aerobic fitness. But, of course, this compensatory response is dependant on the “health status” of the endothelium [91] and a rise in blood viscosity might be more detrimental for vascular system in the case of endothelial dysfunction [19].

When measuring the effects of exercise on blood viscosity, the results are reported and interpreted for a given shear rate. Blood is a shear-thinning fluid and its viscosity decreases when the shear rate increases. It is difficult to ascertain how blood viscosity changes measured *in vitro* may impact on the vascular system *in vivo* but the shear rate is not constant at rest and during exercise. Padilla et al. [62] reported a resting shear rate of $\approx 100\text{ s}^{-1}$ at the brachial artery level. During a semi-recumbent cycling exercise at 120 W, the shear rate increased to $\approx 250\text{ s}^{-1}$. At the femoral artery level, Gonzales et al. [39] reported a rise from $\approx 60\text{ s}^{-1}$ at rest to $\approx 200\text{--}250\text{ s}^{-1}$ during a progressive single-leg knee extensor exercise. If we re-analyze the effects of exercise on blood viscosity taking into account the changes in shear rate occurring with exercise in the largest arteries (resting shear rate = 90 s^{-1} ; exercising shear rate = 225 s^{-1} ; Fig. 1), we observe no significant change of blood viscosity (PRE 90 vs POST 225) whereas for a given shear rate (90 s^{-1} at rest and during exercise; Fig. 1), the viscosity of blood increases (PRE 90 vs POST 90). Indeed, the effects of hematocrit increase and other RBC rheological changes on blood viscosity could be blunted *in-vivo* because the increase of shear rate (as a consequence of the increased blood flow) may thin blood. Nevertheless, even by taking into account the changes in shear rate occurring during exercise (90 s^{-1} to 225 s^{-1}), the non-statistically significant changes in blood viscosity (Fig. 1) are still associated with the changes in NO production (Fig. 2). Both the increase in shear rate and a positive change in blood viscosity may increase shear stress to stimulate NO production. Further studies are required to study these associations in detail. In addition, it remains unknown whether the magnitudes of changes in shear rate

Fig. 2. Relationships between the changes in blood viscosity (taking into account the changes in shear rate occurring during exercise) and NO production (NOx) during exercise. NOx and blood viscosity were measured at rest and at the end of a 15 min submaximal cycling exercise (105% VT). The changes in NOx and blood viscosity between rest and the end of exercise were calculated and plotted on this figure. To calculate the changes in blood viscosity, resting values were determined at a shear rate representing a baseline state (i.e. 90 s^{-1}) and values obtained at the end of exercise were measured by using a shear rate reflecting what happens during exercise (i.e. 225 s^{-1}). The data used for this figure were those from Connes et al. [27] +1 additional subject ($n = 10$).

occurring in the microcirculation during exercise are comparable with those occurring in large vessels. Further studies are needed to address this issue.

2.3. Plasma viscosity

When sedentary or endurance trained subjects perform short-duration maximal or submaximal exercise (mainly cycling), plasma viscosity usually increases by up to 5–10% at the end of the exercise, when compared with resting values [13, 23, 34, 36, 81]. This increase contributes, with the other blood rheological changes, to the increase of blood viscosity at a given shear rate during exercise. Increased plasma viscosity has been attributed to the rise in plasma protein content, such as fibrinogen, $\alpha 1$ -globulins, $\alpha 2$ -globulins, β -globulins and γ -globulins [87, 96], and probably, at least in part, to water loss. In contrast, several studies reported no change in plasma viscosity during prolonged running [38, 59, 60, 84] and the reasons are not fully understood.

2.4. Red blood cell deformability

The effects of acute exercise on RBC deformability have been examined in several studies, with most reporting a decrease [13, 36, 38, 61, 67, 97, 98]. This decrease may contribute to the rise in blood viscosity during exercise. Several factors might be involved in this reduction. Lactate and hydrogen ion accumulation within RBCs [53, 78] and oxidative stress [98] have been hypothesized to decrease RBC deformability during exercise. In contrast, few studies observed improved RBC deformability during acute exercise [23, 29, 43, 92]. Findings from Bor-Kucukatay et al. [9] support that NO could positively influence RBC deformability. Although very few studies investigated the effects of NO on RBC deformability during exercise, Suhr et al. [80] suggested that changes in the RBC eNO-synthase activity could positively regulate this hemorheological property. Nevertheless, findings from Bateman et al. [6] suggest that NO could decrease RBC deformability. Mesquita et al. [55] demonstrated that there

is probably a dose-dependent effect of NO on RBC deformability with normal concentration having beneficial effect on RBC deformability whereas high concentration could be deleterious. Additional studies are clearly required to examine the relationships between RBC eNO-synthase activity or expression, and the effects of NO concentration on RBC deformability during exercise.

The mechanisms at the origin of the increase in RBC deformability during exercise are not well understood but it has been shown that a rise in lactate concentration was able to cause RBC rigidification in sedentary people while it resulted in RBC deformability improvement in endurance-trained athletes [24]. It seems that RBC from endurance sportsmen could better cope with lactate than RBC from sedentary subjects. However, a recent study in our laboratory of well-trained cyclists demonstrated that during cycling exercise that increased lactate concentration (i.e., heavy-intensity exercise), RBC deformability was decreased more than during moderate-intensity exercise that did not induce changes in lactate concentration (Simmonds et al., unpublished). Endurance training also protects RBC from oxidative damage. Yalcin et al. [97] reported that the time course of RBC deformability impairment induced by exercise differed between trained and untrained rats. The alterations in RBC deformability and RBC lipid peroxidation after 60 min of swimming exercise were attenuated in the trained group suggesting that physical fitness limits lipid peroxidation during exercise and the associated hemorheological alterations. Nevertheless, training and physical fitness are not sufficient to explain why RBC deformability can differentially decrease or increase with a given exercise bout, in different individuals. RBC deformability reduction has also been reported in well-trained athletes performing various physical efforts [38, 67]. Methods for RBC deformability measurements might account for some of these discrepancies with studies having used viscosimetry, filtration techniques or ektacytometry. More efforts of standardization are needed for future investigations on RBC deformability and exercise. In addition, more studies focusing on comparisons of RBC rheology at rest and during exercise are needed.

Impaired RBC deformability may decrease tissue perfusion and oxygenation [63]. For example, patients with sickle cell disease have very rigid RBCs which may impair blood flow into the microcirculation [3, 26]. Indeed, the surprising increase of RBC deformability found in several studies during exercise [23, 29, 43, 92] was suggested to be beneficial for tissue oxygenation and endurance performance. However, we recently reported an association between faster oxygen consumption kinetics (i.e. VO_2 -on kinetics) during a rest-work transition and slightly decreased RBC deformability in athletes [76]. A faster VO_2 -on kinetics indicates a better physiological adaptation to endurance exercise [94]. We suspect that this slightly – but not pathologically – decreased RBC deformability could paradoxically improve tissue extraction of oxygen from blood due to (i). an increased transit time for RBC to pass through capillary networks [54], and; (ii). reduced distance between the RBC and vessel wall [31], which would plausibly enhance oxygen exchange between RBC and peripheral tissues. Of course, while a slight decrease in RBC deformability may be beneficial for enhancing oxygen extraction, it is clear that the severe RBC deformability impairment observed in several diseases such as sickle cell disease [83] or diabetes [72] is deleterious.

2.5. Red blood cell aggregation

A growing interest has been recently devoted to the study of RBC aggregation and its impact on hemodynamics [5]. In addition, several studies reported association between RBC aggregation abnormalities and diseases, probably as a consequence of inflammation and/or metabolic disturbances, such as in primary open-angle glaucoma [56], type 2 diabetes [75], insulin resistance [15, 16], sickle cell disease [49, 83, 93] and others [32, 48, 58, 79, 95]. Few studies have investigated RBC aggregation

in response to exercise and contrasting results have been reported: some studies described no change [25, 84, 89], an increase, in association or not with a rise in plasma fibrinogen level [18, 36, 84], or a delayed decrease [98] with exercise. Such findings should be considered in the context that *in vitro* assessment of RBC aggregation is typically performed on blood samples adjusted to standardised hematocrit (usually 40%); increased hematocrit observed during exercise likely increases RBC aggregation *in vivo* due to an increased cell-cell contact. Nevertheless, the reasons for incongruent reports are unclear, but may be related to the differences in: 1) the population tested (athletes or sedentary subjects, population with disease); 2) the exercise performed (cycling, running, resistance exercise); 3) the technique used to measure aggregation (backscattered technique versus light transmission technique).

3. Training effects on hemorheology

3.1. Healthy population

Whereas acute exercise may increase blood viscosity at a given shear rate, chronic exercise (endurance or resistance exercise) usually results in a decrease [12, 46, 68]. Following a cessation of exercise (few hours or few days later), there is an increase in plasma volume [12] which represents a reversal of the acute hyperviscosity observed during acute exercise, resulting in an “autohemodilution” [35, 36]. The repetition of exercise during consecutive days leads to a chronic “autohemodilution” resulting in a low baseline hematocrit – low baseline viscosity patterns [12, 35, 46]. Plasma volume expansion is also responsible for the decrease of the plasma viscosity contributing to the decrease of blood viscosity [35]. In contrast, overtraining syndrome is associated with a reversal of the “autohemodilution” phenomenon with hematocrit, plasma and blood viscosities increasing above levels observed in the trained state [88, 90]. The mild chronic inflammation associated with overtraining could be responsible for these hemorheological changes [90].

Exercise training also induces adaptations of RBC aggregation [46] and RBC deformability [14]. Ernst et al. [35] reported increased RBC deformability in athletes compared to sedentary subjects, a finding later confirmed by Smith et al. [77]. A 3-month longitudinal study of initially untrained healthy volunteers performing regular training also revealed a fall of blood viscosity and an improvement of RBC deformability [35]. The reasons of the RBC deformability improvement in healthy population under training have been rarely addressed but Smith et al. [77] found higher proportion of young deformable RBCs in athletes than in untrained subjects. The higher turnover of RBCs and greater elimination of old fragile RBCs in physically active individuals might account for this finding. The production of RBCs is under the control of erythropoietin (EPO), which is up-regulated with regular exercise training [44]. It is not surprising, therefore, that Zhao et al. [99] demonstrated that increased RBC deformability in endurance-trained rats involved erythropoiesis. Specifically, exercise training caused a rise of circulating EPO which was associated with increased RBC deformability. The increased RBC deformability observed in athletes has been hypothesized to contribute, in part, to improved endurance sport performance [22, 77].

3.2. Cardiovascular diseases

Diseases related to the macrovasculature and microvasculature represent the principal causes of death and disability in many countries. Accumulating evidence suggests that hemorheological disturbances

(e.g., elevated plasma and whole blood viscosity, RBC aggregation, plasma fibrinogen concentration) are integral in the development of cardiovascular disorders [47]. Kesmarky et al. [45] reported that ischemic heart disease patients presented with increased hematocrit, plasma and whole blood viscosity, and plasma fibrinogen concentration, compared with healthy controls. Moreover, the degree of hemorheological impairment was related to the number of coronary vessels with angiographic evidence of significant lesions. While the efficacy of exercise therapy in cardiac rehabilitation is clear, with significant improvements in body composition, aerobic capacity, blood chemistries and reduced health expenditure, it is less clear of the effects of exercise training on “hemorheological health” in patients with cardiovascular diseases.

Acute exercise in patients with coronary artery disease invokes what could be considered negative consequences: increased plasma viscosity, von Willebrand factor and plasma fibrinogen concentration [51]. The effect of chronic exercise in patients with cardiovascular diseases is unclear, due to conflicting reports. Ernst and Matrai [37] reported that treadmill walking 5 d/wk in claudication patients decreased blood and plasma viscosity, decreased RBC aggregation, and increased RBC filterability within 4 wk. Daily walking and regular cycling ergometry were ineffective, however, for improving whole blood or plasma viscosity in stable post myocardial infarct patients [66]. Levine et al. [52] investigated the effect of 10-wk cardiac rehabilitation that included 30–40 min of moderate-intensity exercise on 3 d/wk. This training program failed to improve hemorheological indices when compared with baseline values. In contrast, Church et al. [21] reported that a 12-wk cardiac rehabilitation program incorporating moderate-intensity exercise and dietary education, significantly decreased plasma and blood viscosity. Lack of consistent findings are likely due to differences in hemorheological techniques (e.g., tube versus rotational viscometry) and study design; for instance, the studies reporting positive effects of exercise training employed high-intensity exercise efforts [37], or provided dietary intervention in addition to exercise therapy [21].

The lack of well-designed studies investigating the effect of regular exercise on blood rheology in cardiovascular diseases limits the capacity to make definite comment regarding its efficacy. Nevertheless, the widely reported increased peak aerobic capacity following exercise training, in patients with cardiovascular diseases, coincides with increased maximal cardiac output yet unaltered mean aortic pressures: this indicates that peripheral resistance must also decrease. Hambrecht et al. [42] reported that 6-months of regular cycle ergometry reduced total peripheral resistance by ~20% in patients with chronic heart failure. Increased conductance of the vasculature is often reported following exercise training, but is likely to be endothelial-dependent and highly localized within the trained limb [40]. Moreover, recent evidence suggests that while regular exercise improved vascular function in healthy subjects, the resting diameter of vessels remained unchanged and only vessels that experienced high shears during exercise training demonstrated improvements in function [8]. Previous findings corroborate that exercise training in coronary artery bypass candidates significantly increased endothelium-dependent vasodilatory capacity and average peak blood-flow velocity of left internal mammary artery *in vivo*, when compared with sedentary, matched candidates [41]. Specimens of left internal mammary artery obtained during subsequent bypass surgery indicated that exercise training increased mRNA and protein expression of eNOS, and increased the ratio of phosphorylated versus unphosphorylated eNOS; importantly, shear-stress dependent mechanisms (i.e., Akt-dependent and Ser¹¹⁷⁷) explained the increased phosphorylation state of eNOS [41], highlighting the link between blood rheological properties (which directly influence shear stress), exercise, and vascular function. Thus, while exercise training studies utilizing hemorheology techniques are limited in cardiovascular disease patients, careful consideration of the literature implicates rheological properties of blood to be complicit with the often cited benefits following exercise training.

3.3. Metabolic disease

Metabolic diseases include a wide-spectrum of disorders stemming from autoimmune, lifestyle and genetic sources. While diverse in etiology for onset and progression, remarkable cross-over may be observed in the manifestations of the co-morbidities and complications of metabolic disorders. For instance, while type 1 and type 2 diabetes mellitus result from vastly different etiologies (autoimmune and environmental, respectively), the resultant complications are closely related (e.g., retinopathies; neuropathies; nephropathy; cardiovascular diseases). Perhaps not coincidentally, localized hypoxia has been implicated in the progression of many complications associated with metabolic disorders. Given microcirculatory blood flow is balanced by vascular tone and the rheological properties of blood, the importance of hemorheological health is obvious in the development and progression of hypoxia-related complications.

Cross-sectional studies in high-risk populations for metabolic disorders (e.g., obesity) provide evidence that hemorheological disturbances are associated with progression towards overt disease [10, 57, 65]. Whether exercise training may reverse or diminish the effects of impaired hemorheology in high-risk individuals seems to depend upon study design. While 10 d of aerobic exercise had no effect on arterial function of obese subjects with metabolic syndrome [7], 8 wk of moderate-intensity exercise by obese and insulin resistant individuals decreased plasma viscosity; however, blood viscosity, plasma fibrinogen, RBC aggregation and RBC deformability remained unchanged [33]. Coppola et al. [30] reported that twelve wk of moderate-intensity treadmill exercise reduced blood viscosity at high (450 s^{-1}) and moderate (90 s^{-1}) shear rates in older, sedentary individuals. Consequently, the limited studies investigating the effects of exercise training in individuals at risk for metabolic disorders indicates that plasma viscosity may improve within 8 wk of aerobic exercise training, while at least 12-wk of exercise training is required to induce beneficial changes in blood viscosity. Further studies investigating the mechanisms for reduced viscosity in early-stage metabolic disorders would be useful to determine whether the typical progression toward impaired hemorheology in overt-disease states may be averted using exercise training.

Blood viscosity is increased for individuals with type 2 diabetes, when compared with healthy controls [50]. Moreover, hemorheological health is markedly worse for individuals with type 2 diabetes that present with poor glycemic control and is associated with co-morbidities [75], suggesting hyperglycemia may be involved in the processes underlying increased blood viscosity and morbidity for these patients. Chronic hyperglycaemia decreases the compliance of RBCs and reduces the repulsion induced by the negative charge of the cell surface [4, 64]. Very few studies have investigated the effect of exercise training on hemorheology in type 2 diabetes. One of the few studies pertinent to type 2 diabetes demonstrated that ~ 14 wk of intensified glycemic management, incorporating insulin therapy, exercise training and dietary modification, reduced blood glucose concentration, blood and plasma viscosity, and RBC aggregation [20]. Given that insulin, dietary interventions and exercise training were concurrently implemented, the contribution of exercise training in reducing RBC aggregation was not discernable. Simmonds et al. [74] subsequently demonstrated that 12-wk of moderate-intensity treadmill walking for 120 min/wk significantly decreased RBC aggregation in plasma and a plasma-free aggregating solution (dextran 70), and increased maximal elongation index (RBC deformability) in older women with type 2 diabetes. Interestingly, no changes in anthropometry (e.g., body mass index) or glycemic control (e.g., HbA_{1c} , fasting glucose concentration) were observed during the training period, suggesting that hemorheology improved in the diabetic patients due to mechanisms independent of reduced adiposity and decreased hyperglycemia. It is likely that plasma factors may explain, in part, the reduced RBC aggregation following exercise training, as the 12-wk training in diabetic patients decreased plasma fibrinogen concentration by $-6.9 \pm 10.7\%$ (Simmonds, unpublished finding); however, given that RBC aggregability in dextran

70 was also decreased, it is plausible that intrinsic changes to the RBC (e.g., increased electronegative charge of RBC) also contribute to improved hemorheology following exercise training in type 2 diabetes.

4. Conclusion

The present review presented classic and new findings, as well as unresolved issues, in the field of exercise hemorheology. Blood rheology and vascular function interact continuously to provide adequate oxygen and nutrient delivery to tissues: they cannot be considered separately. Future studies in healthy, athletic and chronic disease populations should consider investigating blood rheology, microvascular and macrovascular function concurrently, particularly at rest, during exercise and after exercise-training programs. A full overview of cardiovascular function and hemorheological responses to exercise will assist in the optimization of disease management and athletic performance.

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