

Hemorheologic effects of low intensity endurance training in sedentary patients suffering from the metabolic syndrome.

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1. Abstract

Hemorheologic effects of exercise training (« hemorheologic fitness ») are very different according to the mode and the intensity of this training. We previously reported that low intensity endurance training in sedentary patients suffering from the metabolic syndrome simultaneously improved blood rheology, body composition and lipid oxidation at exercise. We aimed at analyzing the link among these improvements in 24 patients submitted to a 2 months targeted training designed for increasing exercise lipid oxidation. Variations of whole blood viscosity at high shear rate ($\eta_b 1000 \text{ s}^{-1}$) were explained here by two statistically independent determinants : hematocrit and red cell rigidity. η_b decreased in 16 subjects, but increased in 8, due to a rise in hematocrit. 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 $\text{VO}_{2\text{max}}$ but not to lipid oxidation. Red cell aggregability (Myrenne) reflected both the circulating lipids (Chol, HDL and LDL) and the ability to oxidize lipids at exercise. Factors associated to a post-training decrease in aggregability (M1) were weight loss and more precisely decrease in fat mass, improvement in lipid oxidation, rise in HDL-Chol, and decrease in fibrinogen. On the whole the major determinant of hemorheologic improvement was an increase in cardiorespiratory fitness ($\text{VO}_{2\text{max}}$), correlated with a decrease in plasma viscosity, rather than an improvement in lipid metabolism, although RBC aggregability and deformability exhibited clear relationships with lipid metabolism. For which reason Hct increased in 30% of the patients during this kind of training remains unclear.

Key words: Blood viscosity, plasma viscosity, hemorheology, erythrocyte deformability; erythrocyte aggregability; insulin sensitivity, insulin resistance, minimal model.

2. Introduction

Hemorheologic effects of exercise training (« hemorheologic fitness ») are very different according to the mode and the intensity of this training [1]. We previously reported that low intensity endurance training in sedentary patients suffering from the metabolic syndrome sumultaneously improved blood rheology, body composition and lipid oxidation at exercise [2]. However the link among these metabolic and hemorheologic improvements is unclear and our working hypothesis that plasma viscosity is an integrated marker of the metabolic status in these patients [3] and could be useful for their follow-up remains undemonstrated. We thus aimed at further analyzing the effects of this kind of training on blood rheology in patients submitted to targeted training protocol designed for increasing exercise lipid oxidation.

3. Research design and methods

Subjects

Twenty four obese insulin resistant subjects (see Table 1) were studied. They were divided into two groups. Sixteen were tested before and after 2 months of training (3x45 min/wk) at a level defined by exercise calorimetry as indicated below. The other ten served as control group and were tested twice, ie before and after 2 months of conventional follow-up including dietary and exercise advice. Subjects taking insulin medication were excluded from the study. A subject was classified as having type 2 diabetes if his blood glucose value was >126 mg/dl or he had physician-diagnosed diabetes [4]. A home-made autoquestionnaire for dietary assessment was employed [5]. Body composition was evaluated with a multifrequency bioelectrical impedancemeter Dietosystem Human IM Scan that uses low intensity (100-800μA) at the following frequencies: 1, 5, 10, 50, and 100 kHz. Analysis was performed with the software Master 1.0 provided by the manufacturer.

Table 1

Clinical characteristics of the study subjects.

	Trained (n=16)	Controls(n=8) comparison	
Age (yr)	56.1 ± 9.5	54.5 ± 4	ns
weight (kg)	82.0 ± 1.8	93.6 ± 8.5	ns
height (m)	1.60 ± 0.10	1.67 ± 0.05	ns
body mass index (kg/m ²)	31.9 ± 5.1	32.7 ± 2.8	ns

Exercise testing.

Subjects were asked to fast overnight before testing. At 9 am, after baseline samples for laboratory measurements (see below) were drawn, subjects underwent a standardized submaximal exercise-test [6] consisting of four 6-min submaximal steady-state workloads,

with calculation of carbohydrate and lipid oxidation rates from gas exchange measurements according to the nonprotein respiratory quotient technique. Briefly, total fat oxidation and carbohydrate oxidation were calculated from the CO₂ respiratory output V_{CO2} and oxygen consumption V_{O2} (in ml/min) measured at steady state at the 5th-6th min of every step, using the following equations.

$$\text{fat oxidation (in mg/min)} = 1.695 V_{O2} - 1.701 V_{CO2}$$

$$\text{carbohydrate oxidation (in mg/min)} = 4.585 V_{CO2} - 3.226 V_{O2}$$

After smoothing of the curves, we calculated two parameters representative of the balance between fat and carbohydrate oxidation at different levels of exercise: the crossover point [7] and the LIPOXmax. The crossover point is the point where carbohydrate becomes the predominant fuel oxidized by the exercising body, ie, it represents more than 70% of the total energy. This point is assumed to be the point where lactate production increases, and is thus generally closely associated with the lactate threshold and the ventilatory threshold (ie, the so-called 'anaerobic' threshold).

This point was used for exercise prescription. Subjects had to exercise 45 min three times a week at this level for 2 months until a second exercise-test (scheduled with the same work loads) was performed to assess training's effects.

In addition the maximal oxygen uptake (VO_{2max}) was also indirectly evaluated from the submaximal workloads during pre and posttraining exercise tests as classically recommended by Astrand [8] with a home-made software.

Laboratory measurements.

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Hematocrit was measured by microcentrifugation. Viscometric measurements were done at high shear rate (1000 s⁻¹) with a falling ball viscometer (MT 90 Medicatest, F-86280 Saint Benoit). The coefficient of variation of this method ranged between 0.6 and 0.8% [9]. With this device we measured apparent viscosity of whole blood at native hematocrit, plasma viscosity, and blood viscosity at corrected hematocrit (0.45) according to the equation of Quemada [10]

$$\eta_b = \eta_{pl} \cdot (1 - 1/2 k \cdot h)^{-2}$$

where η_b is blood viscosity, η_{pl} plasma viscosity, h the hematocrit and k a shear dependent intrinsic viscosity of the red cells according to Quemada.

Two indices of erythrocyte rigidity (Dintenfass' 'Tk' and Quemada's 'k') were calculated from blood viscosity, hematocrit and plasma viscosity measured at time 0 with equations derived from those given above:

$$k = 2 \cdot (1 - \eta_r^{-0.5}) \cdot h^{-1} \quad [10]$$

and:

$$Tk = (\eta_r^{0.4} - 1) \cdot (\eta_r^{0.4} \cdot h)^{-1} \quad [11]$$

Where η_r is relative blood viscosity η_b / η_{pl} .

RBC aggregation was assessed with the Myrenne aggregometer [12] which gives two indices of RBC aggregation: 'M' (aggregation during stasis after shearing at 600 s^{-1}) and 'M1' (facilitated aggregation at low shear rate after shearing at 600 s^{-1}).

The sampled blood was centrifuged and the plasma assayed for diverse parameters by well standardized and routine techniques.

Statistics.

Results are presented as mean $\pm$ the SE of the mean. Before and after training, values were compared with the paired Student t-test after verification of the normality of distribution of differences between before and after values with the Kolmogorov-Smirnov test. Correlations were assessed with Pearson's procedure (least square fitting). A value of $p < 0.05$ was considered as significant.

4. Results.

Training induced the following changes, which were not observed in the control group: weight loss with preservation of fat-free mass ($p < 0.05$), decrease in plasma viscosity ($p < 0.05$), impairment of the ability to oxidize lipids as assessed by exercise calorimetry ($p < 0.05$). Changes in lipid profile were not significant. The $\text{VO}_{2\text{max}}$ increased in trained patients and was unchanged in controls (see Table 2). Whole blood viscosity η_b (1000 s^{-1}) decreased in 16 subjects, but increased in 8, due to a rise in hematocrit.

Table 2

Effects of training in study subjects. $\text{VO}_{2\text{max}}$ = maximal oxygen consumption; LIPOXmax: level (expressed in power units) at which the lipid oxidation rate reaches a maximum; η_b whole blood viscosity; η_{pl} plasma viscosity; Hct: hematocrit. (* $p < 0.05$ vs pre-training).

	Trained (n=16) Before protocol	Trained (n=16) After protocol	Controls(n=8) Before protocol	Controls(n=8) After protocol
Weight	82.0 $\pm$ 1.8	79,4 $\pm$ 16.6*	93.6 $\pm$ 8.5	92.6 $\pm$ 7.8
Fat-free mass	48,82 $\pm$ 14	48,98 $\pm$ 13	46,77 $\pm$ 4	45,1 $\pm$ 3
Fat mass (Kg)	36,6 $\pm$ 13	35,54 $\pm$ 12	36,4 $\pm$ 5	34,32 $\pm$ 5
$\text{VO}_{2\text{max}}$ (mg.min ⁻¹ .kg ⁻¹)	16,8 $\pm$ 1	20,8 $\pm$ 1.2*	16,3 $\pm$ 2.6	19,9 $\pm$ 3.6
LIPOXmax (w)	28,6 $\pm$ 11	48,8 $\pm$ 33*	31,3 $\pm$ 3.4	54,9 $\pm$ 7.3
Fat oxidation at the LIPOXmax (mg/min)	111,3 $\pm$ 36	124,4 $\pm$ 36	124 $\pm$ 14.7	180 $\pm$ 15.9
Cholesterol (g/l)	2,37 $\pm$ 0.2	2,29 $\pm$ 0.1	2,3 $\pm$ 0.1	2,28 $\pm$ 0.1
Triglycerides (g/l)	1,85 $\pm$ 0.33	1,73 $\pm$ 0.36	1,38 $\pm$ 0.19	1,32 $\pm$ 0.20

LDL-Chol (g/l)	1,61±0.08	1,46±0.13	1,38±0.09	1,42±0.09
HDL-Chol (g/l)	0,47±0.09	0,47±0.04	0,61±0.05	0,59±0.05
$\eta_b 1000 \text{ s}^{-1}$	2,9±0.65	2,90±0.54	3,2±0.22	3,03±0.22
η_{pl}	1,44±1.10	1,39±1.11*	1,41±0.02	1,40±0.04
Hct	40,9±1.1	42,5±1.4	41±1.3	43,2±1.1
RBC rigidity "Tk"	0,59±0.13	0,58±0.11	0,64±0.04	0,57±0.04
Aggregation "M"	6,33±0.54	5,48±0.42	5,4±0.4	4,99±0.3
Aggregation "M1"	10,7±0.5	11,4±1	9,4±0.8	10,6±0.4
Fibrinogen	3,48±0.17	3,58±0.18	3,50±0.4	3,83±0.2

Variations of whole blood viscosity at high shear rate ($\eta_b 1000 \text{ s}^{-1}$) were explained here by two statistical determinants : variations of hematocrit ($r=0.5796$ $p=0.023$) and variations of red cell rigidity ($r=0.5866$; $p=0.0169$). They are statistically independent from each other ($r=0.0749$; $p=0.7907$).

Changes in RBC rigidity are not significantly correlated to other changes but there was a nonsignificant tendency to a correlation with weight loss (fat loss) and decrease in LDL cholesterol. This correlation would presumably become significant on a larger sample.

Besides, plasma viscosity was related at baseline to cholesterol levels ($r=0.4714$; $p=0.0483$) and its training-induced changes are related to those of the $VO_{2\max}$ ($r=-0.692$) (see fig. 1) but not to those of the lipid oxidation rate. Red cell aggregability (Myrenne) before training reflected both the circulating lipids (Chol, HDL and LDL) and the ability to oxidize lipids at exercise ($r=-0.5142$ $p=0.0171$, see fig. 2). Factors associated to a post-training decrease in aggregability (M1) were weight loss ($r=0.471$) and more precisely decrease in fat mass, improvement in lipid oxidation rate exercise ($r=0.433$), rise in HDL-Chol ($r=0.595$), and decrease in fibrinogen ($r=0.886$).

5. Discussion

As previously reported we observe an improvement in plasma viscosity after low intensity endurance training targeted at the level of the LIPOXmax [2]. The new findings of this study are the statistical relationships among the training-induced changes.

First, variations of whole blood viscosity at high shear rate ($\eta_b 1000 \text{ s}^{-1}$), which are explained by changes in hematocrit and red cell rigidity, are not always directed towards an improvement. Beside the expected decrease there is also an increase in some subjects, due to a surprising rise in hematocrit. Changes in RBC rigidity are probably related to the metabolic status since they seem to reflect weight loss and decrease in LDL cholesterol. By contrast, this unexpected rise in hematocrit has no clear statistical explanation, neither it corresponds to any pathophysiological concept. It requires more investigations.

Besides, plasma viscosity was related at baseline to cholesterol levels, consistent with our previous report that this parameter is a mirror of the metabolic syndrome [3]. However, its training-induced changes are related to those of the $VO_{2\max}$ but not to those of the lipid oxidation rate. This finding is not simple to interpret. In athletes, parallel improvements in

aerobic working capacity and plasma fluidity are classical [1] and may reflect mostly a training-induced increase in body fluid volumes (autohemodilution) which is beneficial for the circulation. In this case the picture is probably more complex. This decrease in plasma viscosity is mostly the correction of a hyperviscosity resulting from metabolic disturbances (mostly hyperlipidemia). Its close correlation with VO_{2max} in this case may indicate that plasma viscosity is really an important determinant of this parameter.

Red cell aggregability before training reflected both the circulating lipids and the ability to oxidize lipids at exercise. Factors associated to a post-training decrease in aggregability (M1) were weight loss and more precisely decrease in fat mass, improvement in lipid oxidation rate exercise, rise in HDL-Cholesterol and decrease in fibrinogen. By contrast changes in aerobic capacity or in lipid oxidation at exercise do not seem to markedly influence them.

Once again, the complexity of the relationships between the various components of the metabolic syndrome and its hemorheological manifestations is clearly emphasized. Training seems to induce separate effects on these various symptoms. On one hand it increases cardiorespiratory fitness and this increase induces a reversal in the plasma hyperviscosity that is an integrated index of the various aspects of this syndrome. On the other hand, it decreases fat mass and this has immediate effects on red cell rheology. Finally, due to the lack of marked improvement in lipid profile at this early stage of the training process, we are unable to clearly evidence a relationship between the improvement in circulating lipid concentrations and factors of blood viscosity. However, the post-training changes in RBC aggregability index "M" are negatively correlated to those of HDL-Cholesterol. It is likely that a longer and stronger training procedure would result in unequivocal lipid improvements and that these changes would be then associated to improvements in blood rheology, since in resting condition, our study evidenced, like many others [13] clear relationships between lipids and hemorheological parameters.

On the whole the major determinant of the hemorheologic improvement after low intensity endurance training was an increase in cardiorespiratory fitness (VO_{2max}), correlated with a decrease in plasma viscosity, rather than an improvement in lipid metabolism, although RBC aggregability and deformability exhibited clear relationships with lipid metabolism. For which reason Hct increased in 30% of the patients during this kind of training remains unclear.

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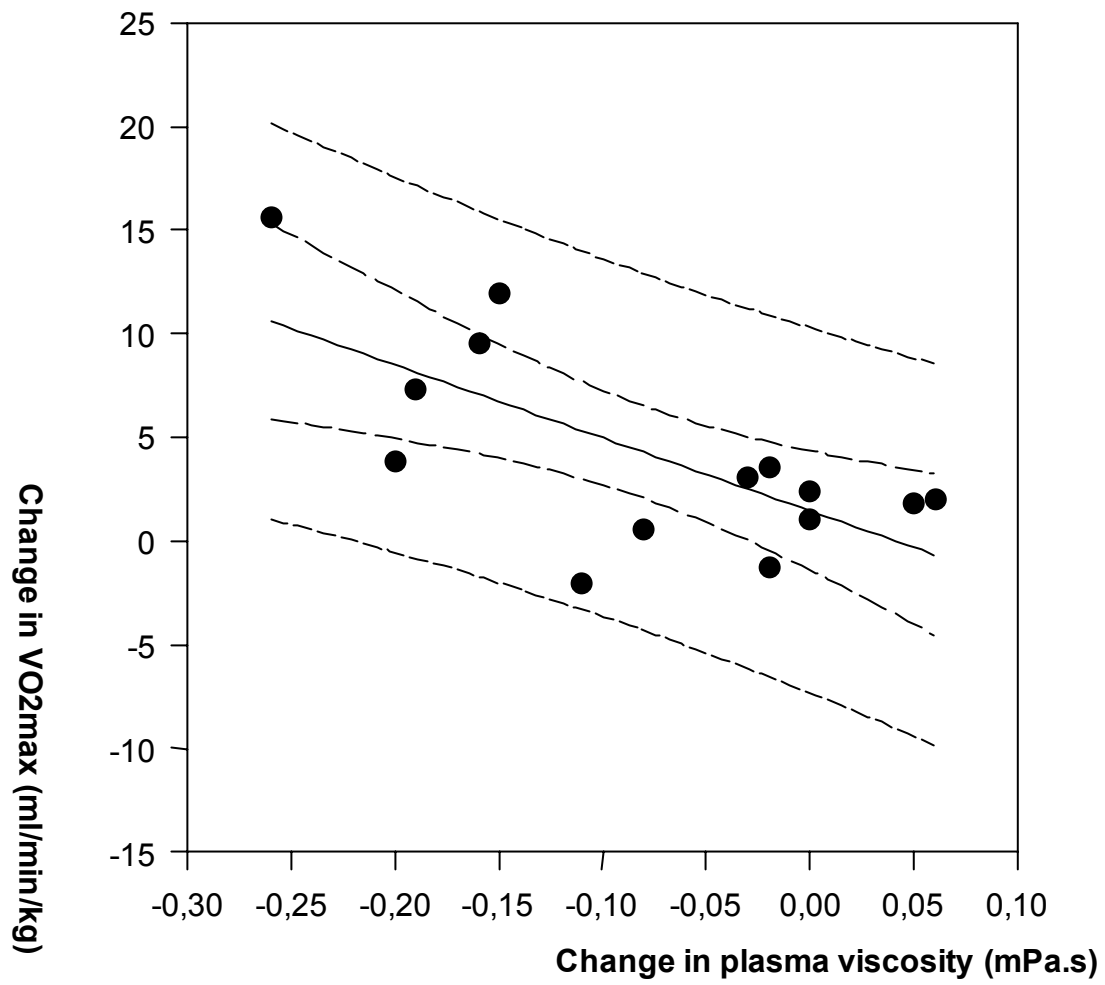


Fig. 1

Correlation between the changes in plasma viscosity and those of the VO2max ($r=-0.692$).

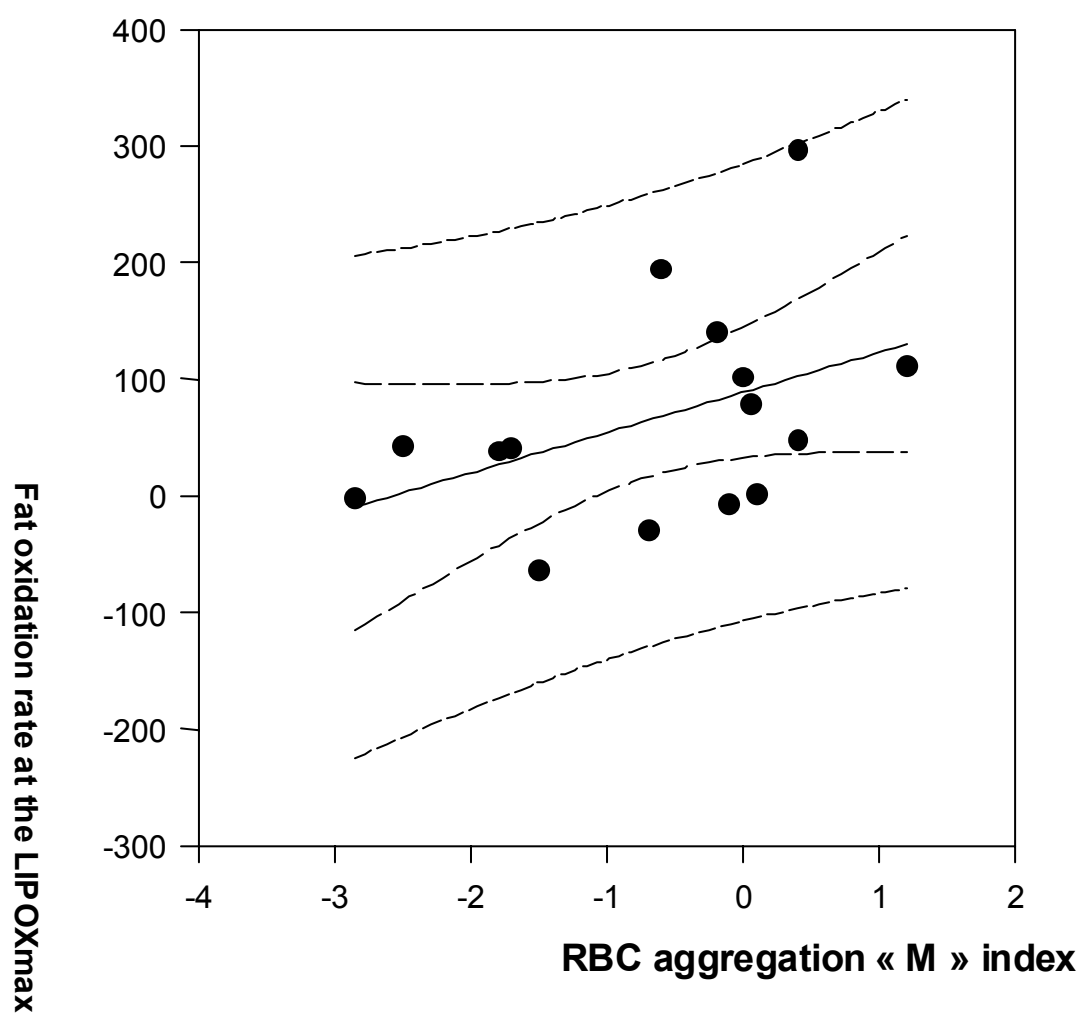


Fig 2

Correlation between the red cell aggregability index (Myrenne) before training and the ability to oxidize lipids at exercise ($r=-0.5142$ $p= 0.0171$). The more the patient is able to oxidize lipids, the lower the aggregability index.