# Regular exercise (3 × 45 min/wk) decreases plasma viscosity in sedentary obese, insulin resistant patients parallel to an improvement in fitness and a shift in substrate oxidation balance

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**Abstract.** Exercise training decreases blood viscosity in athletes parallel with metabolic improvements mostly characterized by an increase in insulin sensitivity. Patients with low insulin sensitivity exhibit a host of metabolic disorders that may also benefit from regular training. However, the hemorheologic aspects of training in such subjects are not known and we aimed at characterizing them. Subjects: Thirty-two obese insulin resistant subjects were tested before and after 2 months. Twenty-one of them were trained (3 × 45 min/wk) at a level defined by exercise calorimetry and corresponding to the power at which lipid oxidation reaches a maximum (LIPOX$_{max}$) and eleven served as controls. The two groups were matched for age and body mass index. There was no weight change in controls while the 2 months training period decreased weight by 2.5 kg ($p < 0.02$). This change was totally explained by a loss in fat mass ($-2.7$ kg, $p < 0.02$) while fat free mass remained unchanged. Blood rheology was unchanged in the control group while training improved plasma viscosity $\eta_{pl}$ (before: $1.43 \pm 0.03$ mPa.s; after: $1.35 \pm 0.03$ mPa.s, $p < 0.02$). There was no change in either hematocrit, red cell rigidity or red cell aggregation. The balance of substrates oxidation shifted towards a higher use of lipids (point of crossover where subjects oxidize 70% carbohydrates 30% lipids: before $39.3 \pm 6.9$ watts; after $70.8 \pm 6$ watts, $p < 0.001$; point where lipid oxidation is maximal (LIPOX$_{max}$) before: $16.5 \pm 1.4$ watts; after: $21.4 \pm 1.3$ watts, $p < 0.001$) and $V_{O_2\,max}$ increased by 74% ($p < 0.01$). Consistent with observations in athletes, the metabolic and ergometric improvements induced by training reduces $\eta_{pl}$ 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 $\eta_{pl}$ as simple and unexpensive marker of efficiency of training in insulin resistant patients should be further evaluated.

Keywords: Blood viscosity, plasma viscosity, hemorheology, erythrocyte deformability, erythrocyte aggregability, insulin sensitivity, insulin resistance, minimal model

## 1. Introduction

The importance of prevention and treatment of obesity for public health is now fully recognized [1], since even a modest degree of excess weight is associated with an increased risk of hypertension [2,3]

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and diabetes [4]. In a recent study by Stevens [5], the range of body-mass index that was associated with the greatest longevity was found to be between 19 and 22 kg/m$^2$. Obviously, weight loss is thus a major issue in the treatment of obesity [1]. Reportedly, a loss of as little as 10 to 15% of body weight can ameliorate hyperglycemia, hyperlipidemia, and hypertension [6]. However, these disorders can also be markedly counteracted with little, if any, weight loss [7]. For example, when 72 obese (mean body-mass index, 30 kg/m$^2$) men and women consumed a low-fat diet high in complex carbohydrates and fiber and exercised daily for three weeks, significant reductions were observed in serum cholesterol (22%), triglycerides (26%), insulin (32%), and glucose (13%) during fasting, and in systolic (6%) and diastolic (8%) blood pressure [7].

This can be interpreted by the concept of the insulin-resistance syndrome first suggested by Vague [8] and more recently developed by Reaven [9]. According to this concept, obesity, and more precisely abdominal adiposity, decreases insulin sensitivity, mostly by impairing glucose disposal in the muscle [10], resulting in metabolic disturbances that induce a high risk for both atherogenesis and diabetes [10]. Diet and exercise are thus therapeutic tools that may at least in part counteract the evolution towards atherothrombosis and diabetes [10]. It is now quite well demonstrated that physical activity (PA) has a beneficial effect in reducing hyperinsulinemia among people with and without type 2 diabetes [11–13], an effect that is assumed to reflect a decrease in insulin resistance via an increase in the number and activity of glucose transporters, in both muscle and adipose tissue [11,14]. In addition, PA may indirectly reduce insulin resistance and hyperinsulinemia by promoting fat loss and preservation of lean body mass [11].

On the other hand, the insulin resistance syndrome is associated with hemorheologic disturbances [15–22], and exercise training is known to decrease blood viscosity parallel with metabolic improvements. However the latter fact is only demonstrated in athletes [23–28]. Since the metabolic disorders of the insulin resistance syndrome are also corrected by regular exercise [10,29,30] we investigated the hemorheologic effects of training in patients with low insulin sensitivity and their relationships with metabolic improvements.

## 2. Research design and methods

### 2.1. Subjects

Thirty-two obese insulin resistant subjects (see Table 1) were studied. They were divided into two groups. Twenty-one were tested before and after 2 months of training (3 × 45 min/wk) at a level defined by exercise calorimetry as indicated below. The other eleven served as control group and were tested twice, i.e., 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 [31].

Table 1
Clinical characteristics of the study subjects

|  | Trained ($n = 21$) | Controls ($n = 11$) | Comparison |
|---|---|---|---|
| Age (yr) | $50.7 \pm 2.9$ | $52.4 \pm 3.5$ | ns |
| Weight (kg) | $88.3 \pm 4.4$ | $88.9 \pm 6.8$ | ns |
| Height (m) | $1.64 \pm 2.24$ | $1.63 \pm 0.04$ | ns |
| Body mass index (kg/m$^2$) | $33.2 \pm 1.23$ | $32.9 \pm 2.21$ | ns |

A home-made autoquestionnaire for dietary assessment was employed [32]. Body composition was evaluated with a multifrequency bioelectrical impedancemeter Dietosystem Human IM Scan that uses low intensity (100–800 $\mu$A) at the following frequencies: 1, 5, 10, 50, and 100 kHz [33–35]. Analysis was performed with the software Master 1.0 provided by the manufacturer.

## 2.2. 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 [36–38] 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 [39]. Briefly, total fat oxidation and carbohydrate oxidation were calculated from the $CO_2$ respiratory output $V_{CO_2}$ and oxygen consumption $V_{O_2}$ (in ml/min) measured at steady state at the 5th–6th min of every step, using the following equations [40]

$$\text{fat oxidation (in mg/min)} = 1.695 \, V_{O_2} - 1.701 \, V_{CO_2},$$

$$\text{carbohydrate oxidation (in mg/min)} = 4.585 \, V_{CO_2} - 3.226 \, V_{O_2}.$$

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 [41] and the LIPOX$_{max}$ [38]. The crossover point is the point where carbohydrate becomes the predominant fuel oxidized by the exercising body, i.e., it represents more than 70% of the total energy [41,42]. 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 (i.e., the so-called "anaerobic" threshold) [41,42]. Accordingly, when blood lactate data were available, we calculated by least squares fitting the blood lactate concentration at the level of the crossover point. The LIPOX$_{max}$ is the point where the increase in lipid oxidation induced by the increasing work load reaches a maximum, which will then be followed by a decrease as carbohydrates become the predominant fuel. It is calculated from the above equations, considering that the empiric formula: fat $= 1.695 V_{O_2} - 1.701 V_{CO_2}$ can be simplified as fat $= 1.7(1 - RQ)V_{O_2}$ in which $RQ$ is the respiratory quotient or respiratory exchange ratio $V_{O_2}/V_{CO_2}$. Therefore fat oxidation rate appears to be the product of two different linear relationships: the decrease of $(1 - RQ)$ and the linear rise in $V_{O_2}$ proportional to power. Derivation of this equation gives the LIPOX$_{max}$ which is the point where the value of the derived equation is equal to zero.

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 ($V_{O_2 max}$) was also indirectly evaluated from the submaximal workloads during pre and posttraining exercise tests as classically recommended by Astrand [43] with a home-made software.

## 2.3. 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) [44,45]. Accuracy of the measurements was regularly controlled with the Carrimed Rheometer "CS" (purchased from Rhéo, 91120 Palaiseau, France) [46]. The coefficient of variation of this method ranged between 0.6 and 0.8% [47]. 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 [48]

$$\eta_b = \eta_{pl}\left(1 - \frac{1}{2}kh\right) - 2,$$

where $\eta_b$ is blood viscosity, $\eta_{pl}$ 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:

$$k = 2(1 - \eta_r^{-0.5})h^{-1} \quad [48]$$

and

$$Tk = (\eta_r^{0.4} - 1)(\eta_r^{0.4}h)^{-1} \quad [49],$$

where $\eta_r$ is relative blood viscosity $\eta_b/\eta_{pl}$.

RBC aggregation was assessed with the Myrenne aggregometer [50] 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. Insulin sensitivity was evaluated as previously proposed [51–54] with the approximation SI [min$^{-1}$ · 10$^{-4}$ ($\mu$U/ml)] = 40/Ib where Ib is baseline insulin at fast.

## 2.4. Statistics

Results are presented as mean ± 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. A value of $p < 0.05$ was considered as significant.

## 3. Results

As shown in Table 1, subjects were well matched before training for age, sex, weight, height and body mass index.

Figure 1 shows the changes in body composition parameters. Trained and untrained patients were initially matched for weight and fat/fat free mass. There was no change in controls while the 2 months training period decreased weight by 2.5 kg ($p < 0.02$). This change was totally explained by a loss in fat mass ($-2.7$ kg, $p < 0.02$) while fat free mass remained unchanged.
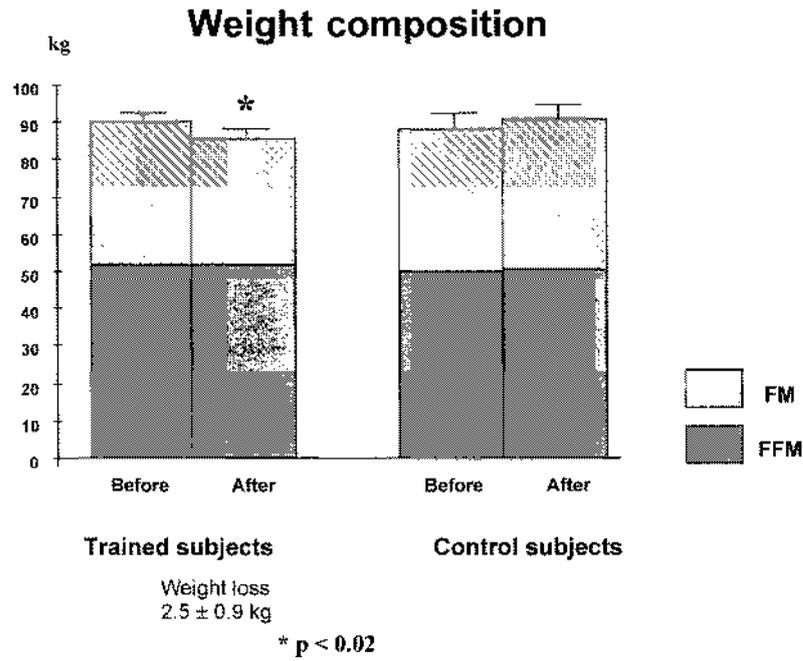
## Weight composition



Trained subjects          Control subjects

Weight loss
2.5 ± 0.9 kg

\* p < 0.02

Fig. 1. Changes in body composition parameters in subjects that completed the training sessions compared to controls that did not exercise.



VO2 max
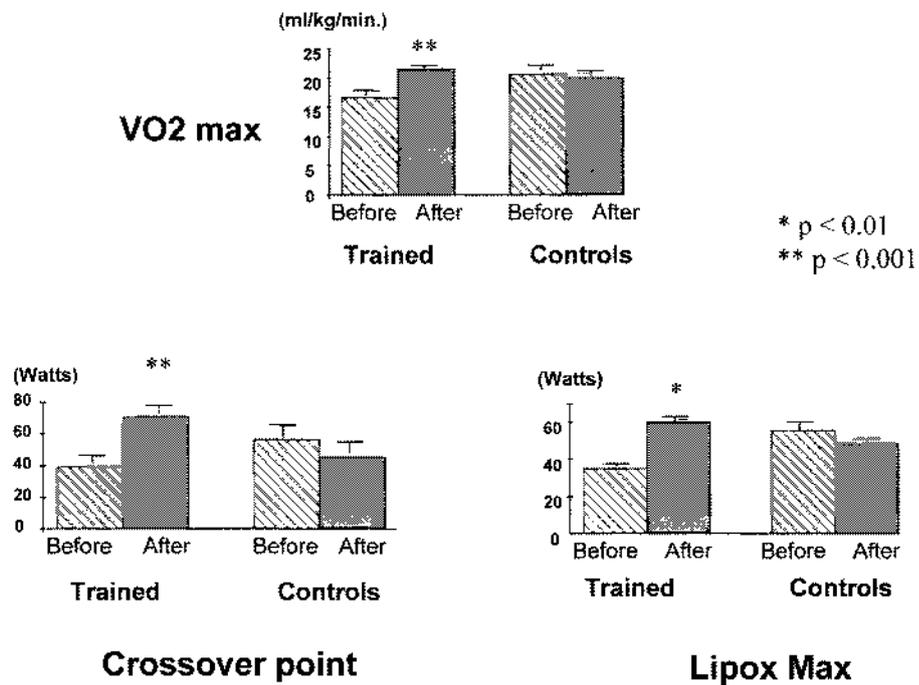
\* p < 0.01
\*\* p < 0.001



Crossover point

Lipox Max

Fig. 2. Changes in ergometric parameters in subjects that completed the training sessions compared to controls that did not exercise. $V_{O_2 max}$: maximal aerobic working capacity; crossover point and LIPOX$_{max}$: the two markers of substrate balance at exercise (see text).
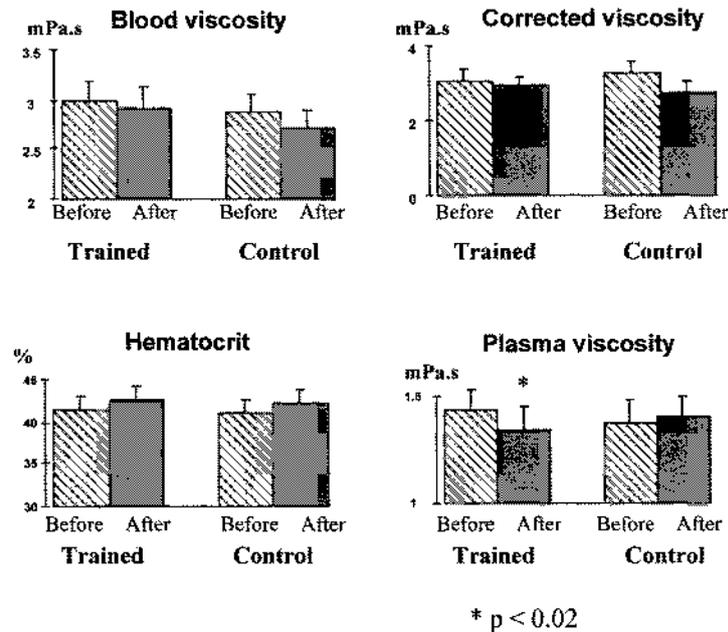
Fig. 3. Changes in hemorheological parameters in subjects that completed the training sessions compared to controls that did not exercise.

Figure 2 shows the changes in ergometric parameters. $V_{O_2 max}$ and the two markers of substrate balance at exercise (crossover point and $LIPOX_{max}$) were not different at the beginning of the study. They remained statistically unchanged (and even with a nonsignificant tendency to worsening) in controls while in trained subjects they were all markedly improved.

Figure 3 and Table 2 show that the hemorheological parameter which was significantly improved by training was plasma viscosity, while neither hematocrit, RBC deformability or aggregation were improved.

Table 3 shows values of lipids and glucose disposal parameters which are not, on this sample of subjects, yet improved. There are non significant tendencies that suggest that those improvement will perhaps become apparent on a larger sample.

## 4. Discussion

The results of this study indicate that training in sedentary insulin resistant patients, applied 3 times a week (45 min) at a level defined by a prior exercise-test induces significant improvements in body composition (loss of 2.5 kg on the average, consisting only of fat mass with a stability of fat free mass), associated with improvements in exercise-test parameters. The metabolic improvements indicate a markedly increased ability to oxidize fat at exercise. By contrast, at this stage of the study, blood lipids and insulin sensitivity are not significantly improved, although there is a nonsignificant tendency to this which could 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.

Table 2

Effects of training on fibrinogen, red cell aggregation and red cell deformability "Tk"

| Fibrinogen (g/l) | | RBC aggregation "M" | | RBC aggregation "M1" | | RBC rigidity "Tk" | |
|---|---|---|---|---|---|---|---|
| before | after | before | after | before | after | before | after |
| subjects undergoing 2 months training (3 × 45 min/wk) | | | | | | | |
| 3.45 | 3.77 | 5.40 | 4.96 | 9.06 | 10.71 | 0.60 | 0.63 |
| ±0.18 | ±0.21 | ±0.45 | ±0.41 | ±1.05 | ±0.55 | ±0.03 | ±0.03 |
| untrained controls | | | | | | | |
| 3.25 | 3.50 | 6.59 | 5.73 | 10.77 | 11.61 | 0.60 | 0.49 |
| ±1.05 | ±0.27 | ±0.54 | ±0.38 | ±0.53 | +1.13 | ±0.06 | ±0.04 |

Table 3

Effects of training on blood lipids and glucose disposal. No significant change at this stage of the study

| Cholesterol (g/l) | | Triglycerides (g/l) | | Fasting glucose (mmol/l) | | Fasting insulin ($\mu$U/ml) | | Insulin sensitivity (min$^{-1}$ × 10$^{-4}$ ($\mu$U/ml)) | |
|---|---|---|---|---|---|---|---|---|---|
| before | after | before | after | before | after | before | after | before | after |
| subjects undergoing 2 months training (3 × 45 min/wk) | | | | | | | | | |
| 2.25 | 2.25 | 1.47 | 1.38 | 5.42 | 5.62 | 19.42 | 11.64 | 3.25 | 4.70 |
| ±0.17 | ±0.17 | ±0.25 | ±0.21 | ±0.32 | ±0.41 | ±6.89 | ±2.66 | ±0.45 | ±0.68 |
| untrained controls | | | | | | | | | |
| 2.10 | 2.29 | 1.58 | 1.44 | 5.42 | 8.38 | 12.25 | 10.00 | 3.16 | 6.11 |
| ±0.25 | ±0.12 | ±0.29 | ±0.29 | ±1.28 | ±1.48 | ±4.05 | ±2.88 | ±1.15 | ±1.79 |

Methods used in this study require some comments. The exercise-test based upon the technique of indirect calorimetry at exercise was designed in order to define in individuals the levels at which they would better oxidize lipids. The rationale for this was that muscular lipid accumulation is believed to explain a large part of the decrease in insulin sensitivity found in overweight people [10,55–60]. On the other hand, some literature indicates that obese and insulin resistant people exhibit a lower ability to oxidize lipids in muscles, both at rest and at exercise [61–63]. Thus such a test is expected to define an individual level for exercise training which would optimize lipid utilization by exercising muscle, thus helping to reduce both insulin resistance and hyperlipidemia. At this stage of the study, this procedure does not fulfills all these purposes, since the changes in lipids and insulin sensitivity is not yet significant. We expect that it will become more evident in a higher sample of trained subjects. By contrast, there is a clear effect on body fat, with a loss of weight which is moderate (2.5 kg) but is very interestingly associated to a stability of fat free mass, and a shift towards a higher ability to oxidize lipids at exercise which may lead to speculate that further training will determine even more beneficial effects on all these parameters.

Although already used by a few investigators [40,64,65] this approach remains quite new at present. However, there is now a large body of literature to support the validity of exercise calorimetry [40,66]. Actually, when exercise is performed above the lactate threshold, the validity of the technique has been a matter of discussion, since there is an extra $CO_2$ production from the bicarbonate buffer which can be assumed to interfere with the calculations. In fact, this increase in $CO_2$ is so negligible that it is very unlikely to have a measurable effect on calorimetric calculations [40], as further demonstrated by a study comparing calorimetry and stable isotope labelling [66]. Clearly, even at high intensity exercise, respiratory gases are mostly the reflect of the balance of substrate oxidation.

We also used in this paper a simplified technique to evaluate insulin sensitivity that we recently proposed for the clinical follow-up of obese, insulin-resistant patients, the index $SI = 40/Ib$. This index was proposed after a critical analysis of several indices of insulin sensitivity (SI) calculated from baseline insulin (Ib) and glucose (G). Although the theoretical background of all them is sometimes obscure, they have been repeatedly reported to fit quite well with the golden standards that are the glucose clamp and the minimal model [54,67,68]. In fact, their validity relies on the physiological feedback loop between SI and Ib [69]: $SI \times Ib = a$ (constant). Therefore there should be in physiological (or near-physiological conditions) a simple hyperbolic relationship between SI and I: $SI = a/Ib$. However, it was rather surprising to notice that both $I \times G$ and $I/G$ are proposed as markers of insulin resistance: in fact both of them are apparently quite well correlated to "true" measurements of SI. This is due to the fact that including G in this determination does not improve the accuracy of the equations, probably because G is too narrowly regulated in normal subjects and too erratic when it becomes abnormal. We thus proposed |51–54| the crude index $a/Ib$ as a marker of insulin sensitivity which is valid in nondiabetic obese [52] but loses its accuracy in all the situations where the feedback loop $SI \times Ib = $ constant is disrupted, such as hypoglycemic states, high values of SI in athletes, or overt diabetes with marked pancreatic $\beta$-cell failure [54]. In the population studied here, this a simple and quite cheap index of SI which, as we previously reported, is quite accurate [52,54]. Whether it is sensitive to the changes in SI induced by training in such patients remains to be studied. Since the index $40/Ib$ did not significantly change in our group (despite a nonsignificant tendency), this question will require a separate study.

Another simplified index in the indirect measurement of $V_{O_2 \, max}$ from submaximal steps according to Astrand [43] which is a very classical procedure but is of course less precise than a direct measurement during a maximal test. In fact, it was hard to propose a maximal test before and after training to those very sedentary patients: in several cases this would result in the decision for them to drop out of the protocol. By contrast, the simple and unexpensive calculation of $V_{O_2 \, max}$ as used here is interesting to monitor the efficiency of training since it reflects cardiorespiratory improvement. As can be seen from our results, this is one of the parameters that were the most markedly affected by the training protocol.

Some comments should also be done about the choice of our population. At this stage of the study, it includes sedentary, overweight patients presenting various degrees of metabolic disturbances reflecting the insulin-resistance syndrome. Several patients in both the control ($n = 5$) and the training group ($n = 7$) have fasting blood glucose values above the limits currently proposed for defining diabetes [31,70]. No insulin requiring patient was included but 5 patients in the training group and 4 in the control group were treated with metformin and/or a sulphonylurea. This treatment did not change during the protocol. It will be interesting to study separately the diabetic and nondiabetic insulin resistant subjects in a further stage of this study. However, they were here considered together, as representing a "continuum" of metabolic disorders, a concept which is supported by the current literature on this topic |71|.

This paper more specifically focuses on the hemorheologic effects of training in insulin resistant sedentary patients. The interesting and surprising point is that this level of training in such subjects does not induce the classical effects observed in athletes [72,73| that mostly consisted of an "autohemodilution" with a decrease in hematocrit, plasma viscosity and whole blood viscosity. Only plasma viscosity was decreased in our patients. This parameter was already elevated before training and the protocol resulted in a partial normalization. Interestingly, in a study of our group, plasma viscosity appears to be the only hemorheological parameter which remains "independently" correlated to insulin sensitivity after multivariate analysis in a large sample of patients. It is not very sensitive but exhibits a quite high specificity to insulin resistance. Thus, the specific effect of training on this parameter may reflect an effect of training on the insulin resistance syndrome. Since this change is significantly found even before we observe a

significant change in the simplistic index of insulin sensitivity SI $= 40/\text{Ib}$ it seems that plasma viscosity is quite sensitive to the effect of our "metabolic" training procedure. We propose that it should be more extensively studied as a marker of this kind of training.

On the whole, consistent with observations in athletes, the metabolic and ergometric improvements induced by training reduces $\eta_{pl}$ 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 $\eta_{pl}$ as simple and unexpensive marker of efficiency of training in insulin resistant patients should be further evaluated.

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