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Fibrinogen is negatively correlated with aerobic working capacity in football players

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Abstract. While it is well established that blood viscosity is decreased in sportsmen and related to fitness, the involvement of fibrinogen in this relationship is less well defined. Relationships among fitness, rheology and fibrinogen were investigated in 32 football players (age 17–33 years: 19 professionals and 13 leisure players). A submaximal 25 min exercise-test was performed and allowed the calculation of aerobic working capacity. Aerobic working capacity (W_{170} and $VO_{2\ max}$) was negatively correlated to fibrinogen ($r = -0.531$, $p < 0.01$ and $r = -0.623$, $p < 0.01$), while on the whole sample the correlation to viscosity and erythrocyte aggregation was not significant. When subjects were divided into two subgroups according to their plasma fibrinogen concentration, the aerobic working capacity (either expressed as W_{170} or $VO_{2\ max}$) is higher when plasma fibrinogen level is lower than 2.7 g/l. Thus, there is a highly significant negative correlation between fibrinogen and fitness in these sportsmen, independent of blood rheology. These data suggest that rheology and fibrinogen are to some extent separate determinants of an individual's fitness.

Keywords: Fibrinogen, sport, fitness, hemorheology, plasma viscosity

1. Introduction

Recent literature has largely demonstrated the pivotal role of fibrinogen as a risk factor for cardiovascular diseases [1–3]. High plasma fibrinogen has been shown to be associated with coronary heart disease [2–4], peripheral vascular disease [5] and stroke [6]. By contrast, while regular muscular exercise improves blood fluidity [7–15] its effects on fibrinogen are less well defined. Training has been reported either to improve [16], to impair [17] or to have no effect on fibrinogen [18–20]. On the whole, the beneficial effects of exercise on blood rheology are well demonstrated, but its effects on fibrinogen remain to be better clarified. However, there is no doubt that fibrinogen and blood rheology are closely related, e.g., fibrinogen is a major determinant of red blood cell aggregability [21].

Therefore, we aimed at investigating relationships between fitness (as a marker of training) and fibrinogen in sportsmen as well as the possible involvement of blood rheology in this relationship.

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Table 1
Characteristics of study subjects

Age (Yr)	23 ± 0.9
Weight (kg)	73.95 ± 1.53
Height (cm)	178.0 ± 1.1
Fibrinogen (g/l)	2.88 ± 0.12
Body mass index (kg/m^2)	23.3 ± 0.3

(n = 32); Mean ± SEM.

2. Materials and methods

2.1. Subjects

We studied 32 professional and leisure football players (Table 1). They were divided into two subgroups: first subgroup (G1: n = 18, with 16 being professional players) with a plasma fibrinogen concentration [Fg] lower than 2.7 g/l; second subgroup (G2: n = 14, with 3 of them being professionals) with a [Fg] higher than 2.7 g/l. Characteristics of each subgroup are shown on Table 2. Major exclusion criteria were tobacco use, muscle or joint diseases, cardiorespiratoy diseases. Inclusion criteria were age and baseline plasma [Fg].

2.2. Exercise-test

A cycloergometer (Bodyguard, Jonas Oglaend A.S., N4301-Sandnes, Norway) was employed. Subjects were asked to perform a 25 min submaximal exercise (5 min at 50 W, 5 min at 100 W and then 15 min at 85% of their theoretical maximal heart rate assumed to be 220 beats/min minus age in years). Heart rate was continuously monitored with four electrodes set on the subject's thorax. Pedal speed was 50 rpm. The morning before the test each subject ingested a standardized breakfast composed of 2070 kJ (9.1% proteins, 27.5% lipids and 63.4% carbohydrates) in order to standardize both fuel and fluid intake. Exercise started 120 min after the breakfast was eaten. In each subject an indwelling venous catheter was set in the cephalic vein at the level of the cubital fossa. Samples were drawn during the exercise-test at 0, 10, 20, 25 and 35 min. Time 0 was just before starting exercise, time 25 was just before it stopped, and time 35 was after 10 min recovery. This cycling exercise was performed in a room maintained at a temperature of 25 ± 0.5°C. Aerobic working capacity was calculated from the submaximal steps with two very classical procedures: a software derived from Astrand's nomogram [22] for an indirect evaluation of $VO_{2\ max}$ and W_{170} [23], i.e., the work in watts that subjects were able to perform at a heart rate of 170 b min^{-1}.

2.3. Hemorheological measurements

Plasma fibrinogen was measured with the Clauss Method. Blood samples (7 ml) for hemorheological measurements were drawn with a large bore needle (Venoject Luer Adaptater, set into an indwelling catheter) with a diameter large enough to avoid erythrocyte damage. Blood was collected in a vacuum tube (Vacutainer) with potassium EDTA as the anticoagulant. Hematocrit was measured by microcentrifugation. Blood and plasma viscosities were measured at high shear rate (1000 s^{-1}) with a falling ball viscometer (MT 90 Medicatest, 37 rue de l'Ermitage, F-86280 Saint Benoit) [24]. Measurements were performed at a temperature of 37°C. With this device we measured apparent viscosity of whole blood at

Table 2
Characteristics of 2 groups of footballers

	[Fg] < 2.7 g/l ($n = 18$)	[Fg] > 2.7 g/l ($n = 14$)
Plasma fibrinogen (levels [Fg] (g/l))	2.40 ± 0.05	3.5 ± 0.13
Professionals/leisure	16/2	3/14***
Age (Yr)	24.06 ± 0.96	21.80 ± 1.72 (NS)
Weight (kg)	75.35 ± 2.09	71.13 ± 2.32 (NS)
Heigh (cm)	179.7 ± 1.60	176.4 ± 1.48 (NS)
Body mass index (kg/m^2)	23.33 ± 0.29	23.30 ± 0.75 (NS)

$n = 32$; Mean ± SEM; (NS), no significant difference; $p > 0.1$ (Mann–Whitney test); $^{***}p < 0.001$.

Table 3
Modifications (mean ± SEM) of rheologic parameters during 25 min of submaximal exercise (85% maximal heart rate) in 30 footballers (Wilcoxon test)

	Before exercise	After exercise
Plasma viscosity (mPa s)	1.32 ± 0.01	1.43 ± 0.01**
Blood viscosity (mPa s)	2.69 ± 3.24	3.24 ± 0.07**
Blood viscosity at corrected hematocrit 45 l/l	2.75 ± 0.07	3.10 ± 0.08**
Hematocrit (l/l)	44.37 ± 0.87	48.7 ± 0.96**
Erythrocyte rigidity index T_k	0.55 ± 0.02	0.59 ± 0.01**
Erythrocyte aggregation index M	4.00 ± 0.33	4.72 ± 0.39**
	$n = 29$	$n = 26$

$^{**}p < 0.01$; $^{*}p < 0.05$; $n = 30$.

native hematocrit η_s, plasma viscosity η_{pl}, and blood viscosity at corrected hematocrit (0.45) according to the equation of Quemada [25]:

$$\eta_s = \eta_{pl}(1 - 1/2 \times k \times h)^{-2},$$

where k is parameter that describes the rheological behavior of red cells, i.e., at high shear rate, their rigidity. k can be calculated with the following formula:

$$k = 2(1 - \eta_r^{-0.5}) \times h^{-1}.$$

From the same measurements of hematocrit, η_s, and η_{pl}, the Dintenfass' T_k index of erythrocyte rigidity was also calculated [26] as follows:

$$T_k = (\eta_r^{+0.4} - 1) \times (\eta_r \times h)^{-1}$$

with η_r being relative blood viscosity η_s/η_{pl}.

2.4. Statistics

Results are presented as mean ± the SE of the mean. Comparisons were made with nonparametric tests. In all subjects the effect of exercise was tested with the Wilcoxon rank sum test for paired data,

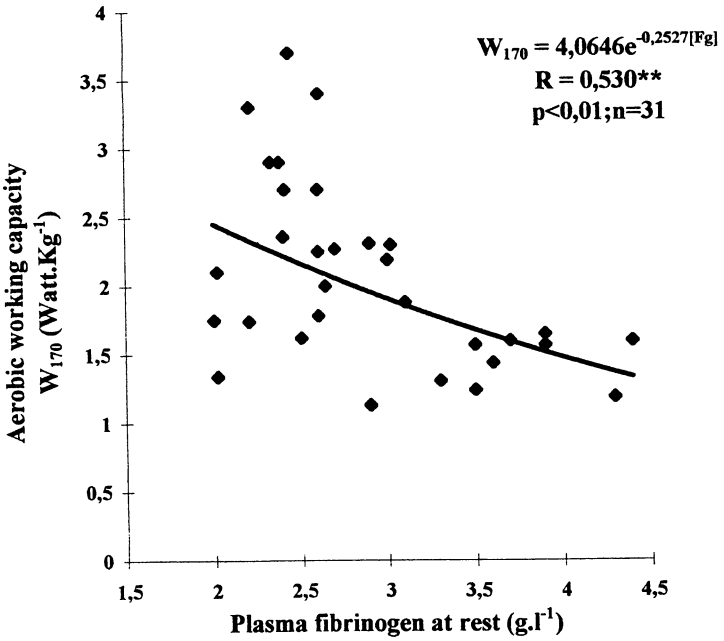

Fig. 1. Correlation ($^{**}p < 0.01$) between baseline fibrinogen and the aerobic working capacity (W_{170}).

while between-groups comparisons were performed with the two-tailed Mann–Whitney test for unpaired data. Correlations were tested by least square fitting for linear relationships. A value of $p < 0.05$ was considered as significant.

3. Results

Comparison of the two subgroups with the Fisher's exact test show that subjects are matched for age and body mass index (Table 2), but there was significantly more professionals in the low fibrinogen group (88.9 vs. 21.4%, $p = 1.01 \times 10^{-4}$). Note that professionals had a lower fibrinogen (2.48 ± 0.07 vs. 3.44 ± 0.15 g/l, $p < 0.01$) while their erythrocyte aggregation index was not different (4.12 ± 0.4 vs. 4.11 ± 0.5 ns). Exercise induces a significant increase in hemorheologic parameters (Table 3).

In the whole group of footballers put together, the mean aerobic working capacity ($W_{170} = 2.06 \pm 0.12$ W kg^{-1} and $VO_{2\ max} = 41.01 \pm 3.21$ ml min^{-1} kg^{-1}) was not correlated to viscosity and erythrocyte aggregation ($p > 0.1$).

Concerning hemorheologic parameters there is not significant difference among the two groups ($p > 0.1$). However, both W_{170} and $VO_{2\ max}$ are negatively correlated to plasma fibrinogen level at rest (Figs 1 and 2).

Moreover, the aerobic working capacity (either expressed as W_{170} or $VO_{2\ max}$) is higher when plasma fibrinogen level is lower than 2.7 g/l (Figs 3 and 4).

4. Discussion

This study investigated the relationships among fitness (aerobic working capacity), fibrinogen and blood rheology, in a sample of leisure and professional sportsmen designed to exhibit a wide range of

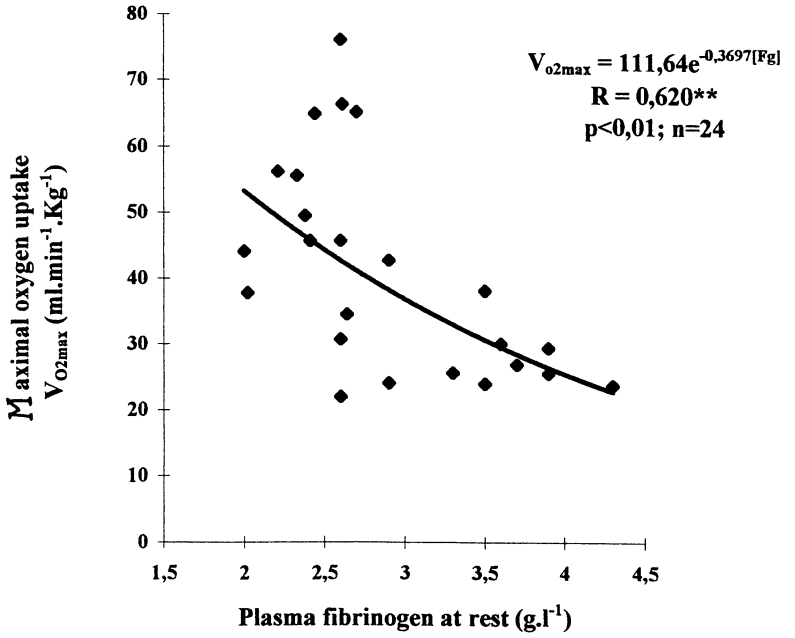

Fig. 2. Correlation ($^{**}p < 0.01$) between baseline fibrinogen and the maximal oxygen consumption ($VO_{2\ max}$) calculated from submaximal steps with Astrand's nomogram.

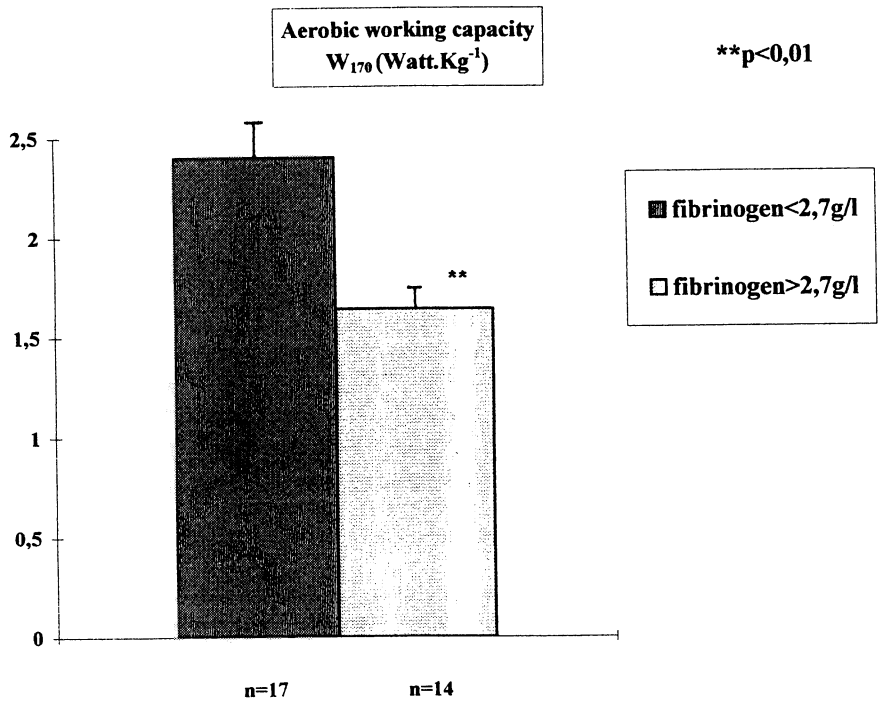

Fig. 3. Comparison of aerobic working capacity (W_{170}) between footballers classified on the basis of their plasma fibrinogen (G1: [Fg] < 2.7 g/l; G2: [Fg] > 2.7 g/l). $^{**}p < 0.01$; Mann–Whitney test.

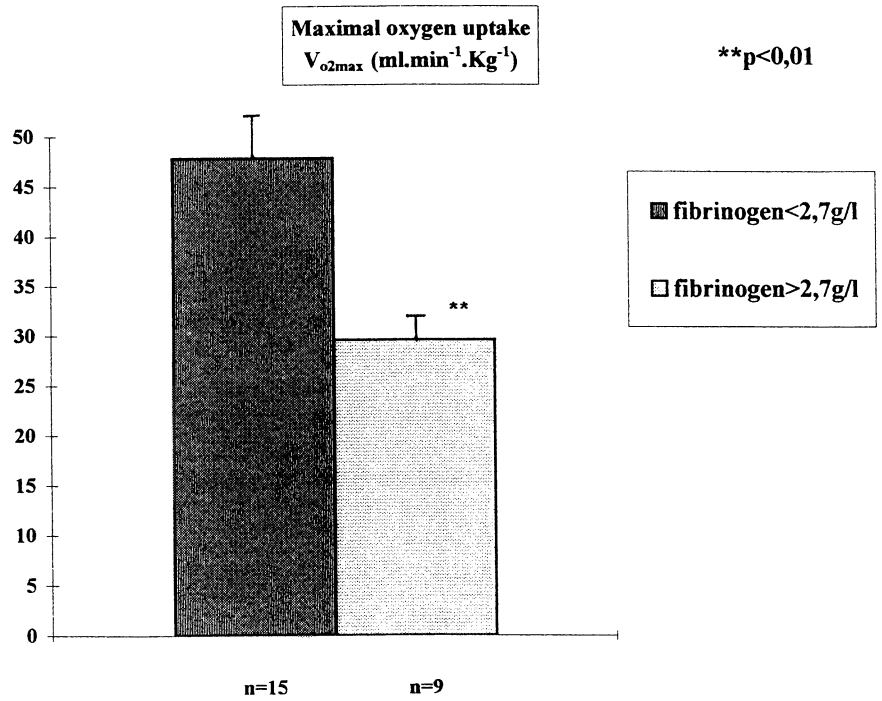

Fig. 4. Comparison of maximal oxygen consumption ($VO_{2\ max}$) calculated from submaximal steps with Astrand's nomogram, between footballers classified on the basis of their plasma fibrinogen (G1: [Fg] < 2.7 g/l; G2: [Fg] > 2.7 g/l). $^{**}p < 0.01$, Mann–Whitney test.

these parameters. To our knowledge, this is the first study investigating specifically relationships among these three parameters in sportsmen. Results show: (1) that aerobic working capacity is negatively correlated to fibrinogen (so that the subgroup with a fibrinogen lower than 2.7 g/l exhibits a stronger working capacity), and (2) that blood rheology is not clearly related to fitness in this sample of subjects.

Our rheological data require some comments. In this study, the classical exercise-induced changes in blood rheology are evidenced. Blood viscosity increases after exercise, due to a rise in both hematocrit and plasma viscosity [27–31] but also to an increase in red cell rigidity [10–12,29] and red cell aggregability [32]. By contrast, we fail to observe the well-known relationship between fitness and blood fluidity [8,13]. This seems to be explained at least in part by the overlap of plasma viscosity values between professional and leisure sportsmen, while the latter had on the whole lower levels of aerobic capacity. This is not in disagreement with studies that evidence this relationship in more homogeneous groups of sportsmen. Clearly, fitness is a highly multifactorial process, so that its relation to blood fluidity is better evidenced in more homogeneous groups of sportsmen, e.g., subjects submitted to similar training and diet protocols.

By contrast, a relationship between aerobic working capacity and fibrinogen is clearly observed. Both $VO_{2\ max}$ and W_{170} calculated from the submaximal exercise test exhibit a negative correlation with fibrinogen. This is consistent with studies showing that a 6 months training period decreases plasma fibrinogen in elderly subjects [17]. However, this aspect of fibrinogen physiology has been a matter of controversy, since other studies reported either an increase [16] or no effect at all [18–20] in fibrinogen after training. The explanation for these discrepancies has been clarified by Vaisanen and coworkers [33] who recently investigated the relationship between $VO_{2\ max}$ and fibrinogen according to the various geno-

types of this protein analyzed by polymerase chain reaction. The predictive role of $VO_{2\ max}$ in a finnish population varied across fibrinogen genotypes. Actually it was marginal in the most common genotypes and appeared more clearly in less frequent genotypes like TaqI 800 bp homozygotes or TaqI 900 bp homozygotes. In our sample of subjects, whatever the genotype, which was not investigated, the relationship between fibrinogen and fitness, nonetheless, appeared clearly. In young men, fibrinogen values over 3.5 g/l are likely to result from mild inflammatory states [1].

It is not surprising to find a higher percentage of professionals in the low fibrinogen group compared to the high fibrinogen group. Aerobic working capacity is to a large extent a marker of the training level, which is obviously higher in professionals. Thus, our findings of a higher aerobic capacity in footballers with a low fibrinogen may reflect to a large extent an influence of the training state on fibrinogen turnover. However, the hypothesis of an influence of fibrinogen on fitness cannot be ruled out and will require further investigations.

We decided to choose a cut-off value of 2.7 g/l of plasma fibrinogen on the basis of the recent follow-up studies that pointed out the prognostic significance of fibrinogen in cardiovascular events [34–37]. On the whole, in these studies, a significant increase in cardiovascular risk was seen around this value. For instance, in the ECAT study, 2.71 g/l represents the boundary between the lower and the middle tertile of fibrinogenemia [34], and the study shows that above this threshold patients with angina pectoris had a risk of cardiovascular events increased by 164%. A significant increase in cardiovascular risk above this value or a closely similar one is also found in the Gothenburg study [35], the Northwick Park Heart Study [36] and the Framingham study [5]. Interestingly, we found a lower aerobic working capacity in sportsmen whose plasma fibrinogen was above this value.

The fact that in this sample of subjects aerobic working capacity correlates with fibrinogen but not with blood rheology may suggest that the improvement in blood fluidity that is generally found in trained subjects is to some extent independent from changes in fibrinogen. Alternatively, the correlation between fibrinogen and fitness is probably not explained by the rheological importance of fibrinogen. Presumably, this relationship is better explained by alterations of fibrinogen turnover during repeated regular exercise [33].

However, it remains logic to speculate that there is probably some influence of training-induced changes in plasma fibrinogen on plasma viscosity and red cell aggregation. This influence, that is not found in this study, remains to be further investigated in other groups of subjects and with more sophisticated measurements of red cell aggregation. For example, in an other study, we reported that the acute exercise-induced impairment in red cell disaggregability was correlated to baseline fibrinogen values [15, 37]. Since red cell aggregation has been shown to influence oxygen distribution in muscle microcirculatory network [32], such relationships may be important to elucidate.

On the whole, this study confirms that fitness and plasma fibrinogen are closely related physiological characteristics of a sportsman. We think that the mechanisms of this relationship, and principally the possible involvement of fibrinogen levels in body's adaptation to exercise, require further investigations.

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