The paradox of hematocrit in exercise physiology: which is the "normal" range from an hemorheologist's viewpoint?

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Abstract. The paradox of hematocrit in exercise physiology is that artificially increasing it by autotransfusion or erythropoietin doping improves $V_{O_2 max}$ and performance, while in normal conditions there is a strong negative correlation between hematocrit and fitness, due to a training-induced "autohemodilution". We aimed at investigating: (a) which is the physiological range of hematocrit in highly trained professional footballers; (b) what are the characteristics of athletes with high vs low hematocrit? We determined in 77 healthy male footballers the physiological range (mean $\pm$ sd) of hematocrit: 42.3 ± 2.74, (range $-2\sigma/+2\sigma = 36.8$–47.8%) thus defining boundaries of quintiles of distribution for this parameter: 40, 41.6, 42.9, 44.6. In another sample of 42 male footballers we compared three groups: lowest quintile ($n = 8$), highest quintile ($n = 5$) and the three middle quintiles considered together ($n = 29$). Athletes in the lowest quintile compared to those in the four other quintiles had a lower value of blood viscosity (-8%, $p < 0.01$) but this difference disappeared after correction for hematocrit. These subjects with low hematocrit had also higher values of the following parameters: aerobic working capacity ($p < 0.01$); isometric adductor strength ($p = 0.02$); crossover point of carbohydrate oxidation (70% carbohydrates/30% lipids) ($p < 0.05$); insulin like growth factor binding protein 1 ($p < 0.0001$). Athletes in the highest quintile had higher red cell aggregability (Myrenne index "M1" 8.45 ± 0.38 vs 6.82 ± 0.62, $p < 0.04$) and a higher disaggregability threshold γ_D (72.6 ± 22.63 vs 44.49 ± 1.37, $p < 0.01$) and a lower percentage of water in fat-free mass ($p < 0.02$). On the whole sample hematocrit was negatively correlated with aerobic working capacity (W_{170} $r = -0.329$, $p = 0.007$; W_{max} (% of expected value) $r = -0.552$, $p = 0.008$; $V_{O_2 max}$ (% of expected value) $r = -0.543$, $p = 0.009$) and with ferritin ($r = -0.33$, $p = 0.031$), and positively correlated with the overtraining score ($r = 0.352$, $p = 0.019$) which was in turn negatively correlated with ferritin $r = -0.312$, $p = 0.02$). Besides, hematocrit behaves as a major determinant of blood viscosity (correlation with blood viscosity $r = 0.997$, $p < 10^{-7}$) and erythrocyte disaggregability γ_D ($r = 0.384$, $p = 0.03$), but the hematocrit/viscosity ratio (h/η index of O_2 delivery) remains maintained almost constant over the range of values studied. These results show that (a) physiological values of hematocrit in these athletes are comprised between 36 and 48%; (b) "low" hematocrit ($<40\%$) was associated with a higher aerobic capacity; (c) subjects with the higher hematocrits ($>44.6\%$) were frequently overtrained and/or iron-deficient, and their blood viscosity (and red cell disaggregability) tended to be increased.

Keywords: Hematocrit, blood viscosity, hemorheology, erythrocyte deformability, human, male, exercise training, overtraining, body fluids, lipid oxidation, glucose oxidation

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1. Introduction

There appears to be a paradox concerning hematocrit in exercise physiology. Since sports performance depends on the capacity of oxygen transport to the exercising skeletal muscles [1,2], it is not surprising to observe that performance may be increased thanks to an artificial haematocrit augmentation [3]. As pointed out in a recent review [3], 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 [3]. However, these data contrast with normal conditions where there is a strong negative correlation between hematocrit and fitness [4–6]. This correlation is explained by the effect of regular training which has been demonstrated to induce a "autohemodilution" which decreases blood viscosity [6–8]. Thus, the physiological effects of training are not to increase hematocrit but rather to decrease it. This decrease in hematocrit is likely to be beneficial for the performance via its circulatory effects that include a decrease in peripheral vascular resistance and ventricular postload [6,9]. Moreover, this autohemodilution-related decrease in hematocrit is associated with an increase in blood volume which increases cardiac output via a Frank–Starling effect [8].

Therefore, there is a "hematocrit paradox" which is somewhat puzzling for a hemorheologist. Clearly, athletes with higher hematocrits are likely to have a more viscous blood. However, we were not aware of any study specifically describing the hemorheological and physiological profile of athletes with high or low hematocrit. In addition, there are no clear reference ranges for "physiological" values of hematocrit in trained people [10–12]. Thus, we aimed at investigating: (a) which is the physiological range of hematocrit in highly trained professional footballers; (b) what are the characteristics of athletes with high vs low hematocrit?

2. Methods

2.1. Study subjects

We used for the calculation of hematocrit normal values and statistical distribution a first sample of 77 healthy male footballers submitted daily to a physical training program. Their characteristics are shown in Table 1. They underwent a standardized submaximal exercise session on cycloergometer over 25 min [13]. Physical working capacity W_{170} was calculated as the work in watts that subjects were able to perform at a heart rate of 170 b.min^{-1} [14,15]. The maximal aerobic power (W_{max}) and the maximal oxygen uptake ($V_{O_2 max}$) were calculated by fitting the linear relationship between heart rate and power, with a home-made software which includes the classical Astrand nomograms [1].

We then studied another sample of 42 male footballers (Table 2) which were divided into quintiles of distribution according to data of the previous series of 77 athletes. In these subjects we studied blood rheology, body composition, and the metabolic adaptation to exercise as indicated below. In addition to a complete clinical examination, the French questionnaire of early symptoms of overtraining developed by the French Society for Sports Medicine (SFMS) was employed [16,17]. A nutritional questionnaire especially designed for athletes [18] was also administered. Isometric strength was measured with home-made devices which are designed to assess handgrip strength and tight adductors isometric strength.

Table 1

Clinical characteristics (anthropometry and ergometry) of the 77 healthy male footballers used for the calculation of the hematocrit statistical distribution

age (years)	24.3 ± 0.8
weight (kg)	76.6 ± 1.1
height (cm)	179.1 ± 0.92
body mass index (kg/m^2)	23.9 ± 0.25
percentage of fat (%)	13.4 ± 0.3
W_{170} (w.kg^{-1})	2.79 ± 0.1
$V_{O_2 \, max}$ (ml.min^{-1}.kg^{-1})	45.8 ± 1.9

Abbreviations: W_{170}: physical working capacity normalized for a heart rate of 170 min^{-1}; $V_{O_2 \, max}$: maximal oxygen uptake.

Table 2

Clinical characteristics (anthropometry and ergometry) and selected biological data in the 42 healthy male footballers used for the rheologic study

age (years)	24.82 ± 0.8
weight (kg)	77.22 ± 1.22
height (cm)	180.1 ± 0.94
body mass index (kg/m^2)	23.7 ± 0.28
percentage of fat (%)	13.3 ± 0.3
W_{170} (w.kg^{-1})	2.9 ± 0.1
$V_{O_2 \, max}$ (ml.min^{-1}.kg^{-1})	47.6 ± 3.1
W_{max} (watts)	327.5 ± 18.9
creatine kinase (UI/l)	418.9 ± 55.8
ammonia (μmol/l)	68.5 ± 4.4
ESR first hr (mm/hr)	2.5 ± 1.5
ESR 2nd hr (mm/hr)	7.5 ± 4.5
fibrinogen (g/l)	2.32 ± 0.06
ferritin (ng/ml)	76.3 ± 7.1

Abbreviations: see Table 1.

2.2. Body composition

Body composition was assessed with a multifrequency bioelectrical impedancemeter Dietosystem Human IM Scan that uses low intensity (100–800 μA) at the following frequencies: 1, 5, 10, 50, and 100 kHz [19–21]. Analysis was performed with the software Master 1.0.

2.3. Metabolic adaptation to exercise

Subjects were asked to fast overnight before testing. At 9 am, after baseline samples for laboratory measurements (see below) were drawn, athletes underwent an improved version [22–24] of our preceding exercise-test [13] 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 [25]. 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 5–6th min of every step, using the following equations [26]

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

$$\text{carbohydrate oxidation (in mg/min)} = 4.585 V_{\text{CO}_2} - 3.226 V_{\text{O}_2}.$$

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 [27] and the LIPOX-max [24]. 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 [27,28]. 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) [27,28]. 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 LIPOXmax 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 $= 1.695\ V_{\text{O}_2} - 1.701 V_{\text{CO}_2}$ can be simplified as fat $= 1.7(1 - \text{RQ})\ V_{\text{O}_2}$ in which RQ is the respiratory quotient or respiratory exchange ratio $V_{\text{O}_2}/V_{\text{CO}_2}$. Therefore fat oxidation rate appears to be the product of two different linear relationships: the decrease of $(1 - \text{RQ})$ and the linear rise in V_{O_2} proportional to power [24]. Derivation of this equation gives the LIPOXmax which is the point where the value of the derived equation is equal to zero.

In addition more classical ergometric parameters were also measured during this test. Physical working capacity W_{170} was calculated as indicated above [14,15]. The maximal aerobic power ($W_{\max}$) and the maximal oxygen uptake ($V_{\text{O}_2\,\max}$) were also measured at the end of exercise after the 4 submaximal steps. There were expressed both as crude values and as percentages of the theoretical value expected for age, sex and anthropometry (respectively $W_{\max}/W_{\text{maxtheor}}$ and $V_{\text{O}_2\,\max}/V_{\text{O}_2\,\text{maxtheor}}$). When blood lactate data were available we also calculated by least squares fitting the power output (and the percentage of theoretical and actual $W_{\max}$) at the conventional levels of 2 mmol.l^{-1} and 4 mmol.l^{-1}, in order to quantify the lactate-power relationship (so-called "anaerobic" thresholds).

2.4. 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) [29,30]. Accuracy of the measurements was regularly controlled with the Carrimed Rheometer "CS" (purchased from Rhéo, 91120 Palaiseau, France) [31]. The coefficient of variation of this method ranged between 0.6 and 0.8% [32]. 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 [33]. Dintenfass' "Tk" index of erythrocyte rigidity was calculated [34]. RBC aggregation was assessed with the Myrenne aggregometer [35] 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 hematocrit/viscosity (h/η) ratio, an index of oxygen supply to tissues, was calculated according to Chien [36] and Stoltz [37], with hematocrit (as percentage) divided by viscosity at high shear rate determined as described above.

The SEFAM-AFFIBIO aggregometer was used for a more precise assessment of RBC aggregation. This device is based upon the experiments of Mills [38,39] on cell disaggregation behavior in shear flow. This device measures the changes in backscattered light which are observed when sheared RBC suspensions are abruptly brought to a full stop. The decrease in the optical signal reflects the formation

of RBC aggregates [40–42]. Some parameters are derived from the curve of light intensity as a function of time. The aggregation time is the reciprocal of the initial slope (calculated between 0.5 and 2 s after the shear has stopped). The aggregation index at 10 s is a measurement of the extent of erythrocyte aggregation and is the relative surface area above the curve calculated over the first 10 seconds. This device measures also disaggregation thresholds, by submitting blood to a succession of shear rates from $600 \, s^{-1}$ to $7 \, s^{-1}$. The total disaggregation threshold is the shear rate below which the backscattered light intensity starts to decrease, indicating that the shear stress applied to aggregates is no longer sufficient for allowing complete dispersion of RBC aggregates. The partial disaggregation shear rate is defined as the shear rate corresponding to the intersection point of the two asymptotes drawn from the extremes (maximum and minimum shear rate).

The sampled blood was centrifuged and the plasma assayed for diverse parameters by well standardized and routine techniques, on an automatic clinical analyzer (DuPont de Nemours). Both lactate and ammonia were assayed with the kits from DuPont specially adapted to this analyzer. Blood lactate assay was based on NADH production by rabbit lactate dehydrogenase. Coefficients of variation range between 0.7 and 5.6%. Plasma ferritin was measured by the solid phase two-site immunoradiometric assay kit "FER-CTRIA". Assay sensitivity defined as the amount significantly different from zero with a probability of 95%, is 1 ng/ml. With this assay, normal values for men range between 75 and 300 ng/ml.

Serum Somatomedin C/IGF-I was assayed with the INCSTAR IGF-I RIA (from INCSTAR Corporation, Stillwater, MN 55082-0285 USA, purchased from Sorin Biomedica France SA). This is a double antibody desequilibrium assay which includes an ODS-silica extraction procedure from serum samples. After the extraction procedure the RIA is performed employing addition of sample and rabbit anti-IGF-I, followed by a 2 hr incubation at 2–8°C. Iodine-125 IGF-I is then added followed by a second incubation for 20 hr at 2–8°C. Pre-precipitated carrier, second antibody and polyethylene glycol are added in a single step. The assay is centrifuged after the 2 hr second antibody incubation at 2–8°C. Detection limit is 2 nmol/l. This assay does not cross-react (<1%) with IGF-II, hGH, FGF, TGR, PDGF. Within assay CVs range between 9.1–10.1%, between-assay CVs range between 10.3–15.2%.

Serum IGF binding protein-1 was assayed with the DSL ACTIVE IGFBP-1 coated tube immunoradiometric assay kit (from Diagnostic system laboratories Inc., PO Box 57946, Webster, TX 77598, USA, purchased from Chiron Diagnostics BP109, 95613 Cergy Pontoise France SA). This is a two site immunoradiometric assay (IRMA) in which the analyte to be measured is "sandwiched" between two antibodies. The first antibody is immobilized to the inside wall of the tubes. The other antibody is radiolabelled for detection. The analyte present in the patient samples, standards and controls is bound by both of the antibodies to form a "sandwich" complex. Unbound materials are removed by decanting and washing tubes. Detection limit is 0.01 ng/ml. Within assay CVs range between 3.4–6%, between-assay CVs range between 1–3.5%. No cross reactivity with IGFBP-2, 3 and 4 has been detected.

Serum IGF binding protein-3 was assayed with the DSL IGFBP-3 radioimmunoassay kit (from Diagnostic system laboratories Inc., PO Box 57946, Webster, TX 77598, USA, purchased from Chiron Diagnostics BP109, 95613 Cergy Pontoise France SA). This is a classical radioimmunoassay where there is competition between a radioactive and a non-radioactive antigen for a fixed number of antibody binding sites. The separation of free and bound antigen is achieved by using a double antibody system. Detection limit is 0.01 ng/ml. Within assay CVs range between 3.4–6%, between-assay CVs range between 1–3.5%. No cross reactivity with IGFBP-2, 3 and 4 has been detected.

2.5. Statistics

Results are presented as mean $\pm$ the SE of the mean. Normality of data distribution was tested by the Kolmogorov–Smirnov test. Correlations were tested by Pearson linear regression analysis, after tests of normality and homoscedasticity had been verified, with the software package "Statview" from Jandel scientific. After one way ANOVA was performed to assess an hematocrit effect on tested parameters across the different quintiles, lower and upper quintiles were compared using the Student's t-test. A value of $p < 0.05$ was considered as significant [43].

3. Results

In the first group of 77 healthy male footballers (Table 1) the physiological range (mean $\pm$ sd) of hematocrit was: 42.3 ± 2.74, (range $-2\sigma / + 2\sigma = 36.8$–$47.8\%$). Thus the boundaries of the quintiles of distribution of this parameter were: 40, 41.6, 42.9, 44.6.

We used these values in order to divide into subgroups the other sample of 42 male footballers presented in Table 2. We then compared three subgroups: lowest quintile ($n = 8$), highest quintile ($n = 5$) and the three middle quintiles considered together ($n = 29$). As shown in Table 3, the three subgroups had similar weight, height, body mass index and percentage of fat. There was a slight difference in age ($p < 0.04$) since athletes with low hematocrit were 5 yr older than the others (29 vs 24 yr), a difference which is not likely to have any influence on our findings as discussed below. On the other hand there was no difference in nutritional habits as indicated by the autoquestionnaire (Table 3).

Table 3
Comparison of subjects according to the quintile of hematocrit

	Quintile of hematocrit		
	Lowest ($n = 8$)	2nd, 3rd, 4th ($n = 29$)	Highest ($n = 5$)
Anthropometry and body composition			
age (years)	28.7 ± 3.4	23.6 ± 0.8	23.4 ± 2.3
weight (kg)	73.8 ± 3	78 ± 1.4	76 ± 1.22
height (cm)	177.9 ± 2.5	180.2 ± 1.06	182.1 ± 2.8
body mass index (kg/m^2)	23.2 ± 0.5	24 ± 0.35	24 ± 0.48
fat mass (kg)	10.3 ± 0.7	10.2 ± 0.5	10.4 ± 0.8
percentage of fat (%)	13.9 ± 1.7	13 ± 0.9	13.7 ± 1.5
water in fat-free mass (%)	72.5 ± 1.7	70.3 ± 0.5***	63.3 ± 2.8**
extracellular water (kg)	18.2 ± 1	19.2 ± 0.6	19.1 ± 1.3
intracellular water (kg)	28.5 ± 0.8	27.7 ± 0.9	29 ± 1.6
extracellular/total water (%)	38.85 ± 0.7	41 ± 1.5	39.5 ± 1
extracellular/total weight (%)	24.7 ± 0.8	24.8 ± 0.9	25 ± 2.4
Nutritional questionnaire			
daily intake (kcal/24h)	2786 ± 577	2631 ± 220	2646 ± 451
proteins (g.kg^{-1}.d^{-1})	1.07 ± 0.21	1.02 ± 0.11	0.97 ± 0.32
% proteins	11.5 ± 1.5	12.5 ± 0.7	11.3 ± 1.9
% lipids	48.2 ± 5.8	42.8 ± 5.2	53 ± 12.3
% carbohydrates	38.7 ± 6.8	44.6 ± 4.9	25 ± 15

** $p < 0.02$ vs lowest quintile; *** $p < 0.0001$ vs the lowest quintile.

Table 4
Comparison of ergometric parameters in subjects classified according to the quintile of hematocrit

	Quintile of hematocrit		
	Lowest (n = 8)	2nd, 3rd, 4th (n = 29)	Highest (n = 5)
Ergometry and exercise parameters			
W_{max} (watts)	384 ± 55	315 ± 20	282 ± 23
$W_{max}/W_{maxtheor}$ (%)	$153.8 \pm 10.9^{****}$	109.4 ± 6.1	97.5 ± 16.3
W_{170} (w.kg^{-1})	$3.36 \pm 0.25^{**}$	2.75 ± 0.1	2.69 ± 0.24
theoretical $V_{O_2\,max}$ (ml.min^{-1}.kg^{-1})	38 ± 1.6	41.9 ± 0.5	42.9 ± 0.7
actual $V_{O_2\,max}$ (ml.min^{-1}.kg^{-1})	$56.4 \pm 4^{*}$	45.44 ± 2.5	41.75 ± 5.7
$V_{O_2\,max}/V_{O_2\,maxtheor}$ (%)	$148.9 \pm 10^{****}$	108.4 ± 5.6	97.6 ± 15.1
lactate threshold 2 mmol (watts)	93.3 ± 5.4	111.4 ± 17.9	81.5 ± 49.5
lactate threshold 4 mmol (watts)	178.3 ± 13.3	217.7 ± 29.4	180.5 ± 93.5
lactate threshold 2 mmol (%W_{max})	28.1 ± 3	32.8 ± 4.5	27.6 ± 15.3
lactate threshold 4 mmol (%W_{max})	53.7 ± 6.5	65.5 ± 7.3	61.7 ± 28.1
lactate threshold 2 mmol (%$W_{maxtheor}$)	40 ± 6	37 ± 7	29 ± 19
lactate threshold 4 mmol (%$W_{maxtheor}$)	76 ± 24	77 ± 11	65 ± 37
isometric handgrip strength (N)	516.8 ± 32.6	536.9 ± 23.9	460.3 ± 71.75
isometric adductor strength (N)	$1188 \pm 417.3^{***}$	602 ± 68.8	793 ± 50.5
overtraining score	5.1 ± 1.8	7.9 ± 1.35	8 ± 3
LIPOXmax (%W_{max})	28.2 ± 4	30.5 ± 3.7	31.6 ± 4

* $p < 0.05$ vs the 2-3-4th quintiles; ** $p < 0.02$ vs the 2-3-4th quintiles; *** $p < 0.03$ vs the 2-3-4th quintiles; **** $p < 0.01$ vs the 2-3-4th quintiles.

By contrast, athletes in the highest and lowest quintiles exhibited some differences in biological data, ergometry and hydration status when compared to the other subjects.

Athletes in the lowest quintile compared to those in the four other quintiles had a lower value of blood viscosity at native hematocrit (2.79 ± 0.04 vs 3.00 ± 0.05 mPa.s, $p < 0.01$). This difference disappeared after viscosity was corrected for hematocrit (hematocrit fixed at 45%): (3.32 ± 0.1 vs 3.13 ± 0.05 mPa.s, ns). All other factors of blood viscosity were similar when compared to subjects in the other quintiles. Consistently, the h/η value remained constant among all quintiles (Table 5) and was thus the same in subjects from the lowest quintiles compared to all others (13.7 ± 0.3 vs 14.72 ± 0.19 mPa^{-1}.s^{-1}.10^2). These subjects with low hematocrit had also a higher aerobic working capacity expressed as W_{170} (3.36 ± 0.25 vs 2.74 ± 0.1 watt.kg^{-1}, $p < 0.01$). This difference did not reach significance when aerobic power was expressed as as W_{max} or as $V_{O_2\,max}$, although there was a nonsignificant tendency. By contrast, when W_{max} and $V_{O_2\,max}$ were expressed as a percentage of the theoretical value predicted for age and anthropometry ($V_{O_2\,max}/V_{O_2\,maxtheor}$ and $W_{max}/W_{maxtheor}$), this difference became significant and confirmed an increased aerobic power ($+50\%$, $p < 0.01$) in the subgroup of subjects with low hematocrit. Actually, value of both parameters was close from the predicted value in all the quintiles $> 40\%$ while it was increased by 50% in the lowest quintile (see Table 5). By contrast, there was a weakly significant difference between these athletes from the lowest quintile and others concerning the crossover point in the fuel balance (i.e., the percentage of maximal power where carbohydrate become predominant and represent $>70\%$ of the oxidized substrates): this point is significantly higher in athletes from the lowest quintile ($52.7 \pm 8\%$ vs $34 \pm 4.3\%$, $p < 0.05$). There was no difference in lactate kinetic parameters, with the 2 mmol lactate threshold at 43 ± 6 vs $44.4 \pm 3.3\%$ W_{max} (ns) and the 4 mmol lactate threshold 4 mmol at

Table 5

Comparison of subjects according to the quintile of hematocrit

	Quintile of hematocrit		
	Lowest ($n = 8$)	2nd, 3rd, 4th ($n = 29$)	Highest ($n = 5$)
	Laboratory parameters		
ammonia (μmol/l)	74 ± 11.2	68.7 ± 5.3	57.8 ± 4.5
creatine kinase (IU.l^{-1})	344.6 ± 112.75	451.7 ± 73	336.2 ± 80.5
IGF-I (mg/ml)	271.3 ± 29.5	246.3 ± 16	312.2 ± 51
IGF-BP3 (mg/l)	3.41 ± 0.38	3.6 ± 0.25	3.41 ± 0.14
IGF-I/IGFBP3	11.6 ± 1.9	8.8 ± 0.6	12.2 ± 2.2
IGF-BP1 (ng/ml)	28.8 ± 1.9[###]	10.3 ± 0.6	12.2 ± 2.2
Fibrinogen (mg/l)	2.3 ± 0.1	2.3 ± 0.08	2.43 ± 0.1
Ferritin	93.7 ± 17.7	72.7 ± 8	65.4 ± 24.5
	Hemorheological parameters		
hematocrit (%)	38.7 ± 0.8[***]	42.3 ± 0.2	45.5 ± 0.3[***]
h/η mPa^{-1}.s^{-1}	13.7 ± 0.3	14.2 ± 0.2	14.7 ± 1
blood viscosity η_b (mPa.s)	2.8 ± 0.04	2.98 ± 0.04	3.16 ± 0.23
η_b at corrected hct 45%	3.32 ± 0.11	3.13 ± 0.05	3.12 ± 0.22
plasma viscosity η_p (mPa.s)	1.37 ± 0.02	1.39 ± 0.02	1.31 ± 0.06
erythrocyte rigidity "Tk"	0.65 ± 0.02	0.61 ± 0.01	0.65 ± 0.04
erythrocyte aggregation "M"	4.6 ± 0.7	4.7 ± 0.4	4.2 ± 1.5
erythrocyte aggregation "M1"	9.7 ± 0.75	8.9 ± 0.4	7.3 ± 1.3
aggregation kinetics "TA"	3.61 ± 0.7	3.2 ± 0.3	2.7 ± 0.5
aggregation kinetics "Tf"	34.4 ± 1.85	37.8 ± 2.4	35.5 ± 12.8
aggregation kinetics "S_{10}"	20.55 ± 1.5	22.3 ± 1.1	23.2 ± 3.1
aggregation kinetics "S_{60}"	38.8 ± 1	39.8 ± 1	40.35 ± 3.4
disaggregation γ_S (s^{-1})	107.3 ± 2.1	77.8 ± 7.3	83.9 ± 12.7
disaggregation γ_D (s^{-1})	47.6 ± 2.2	43.9 ± 1.6	72.6 ± 22.6[***]

[###] $p < 0.0001$ vs the 2-3-4th quintiles.

[***] $p < 0.01$ vs the 2-3-4th quintiles.

68.4 ± 5.9 vs $74.4 \pm 3.7\%$ W_{max} (ns). While the isometric handgrip strength was similar at 516.9 ± 32.6 vs 525 ± 21.8 N, the isometric adductor strength was markedly higher at 1188 ± 417.3 vs 627.6 ± 58 ($p = 0.02$). For the overtraining score the tendency towards a lower value did not reach significance (5.1 ± 1.8 vs 8.7 ± 1.3 ns). As shown in Table 5, subjects from the lowest quintile exhibited also a higher value of IGFBP1 ($p < 0.0001$) than others.

Athletes in the highest quintile of hematocrit had higher red cell aggregability (Myrenne index "M1" 8.45 ± 0.38 vs 6.82 ± 0.62, $p < 0.04$) and a higher disaggregability threshold γ_D (SEFAM-AFFIBIO 72.6 ± 22.63 vs 44.49 ± 1.37, $p < 0.01$). While the percentages of fat and fat-free mass were similar, there was a significant difference for the percentage of water in fat-free mass which was lower in this quintile than in the others ($p < 0.02$).

On the whole sample hematocrit was negatively correlated with both aerobic working capacity W_{170} (Fig. 1; $r = -0.329$, $p = 0.007$) and ferritin (Fig. 2; $r = -0.33$, $p = 0.031$), and positively correlated with the overtraining score (Fig. 3; $r = 0.352$, $p = 0.019$) which was in turn negatively correlated with
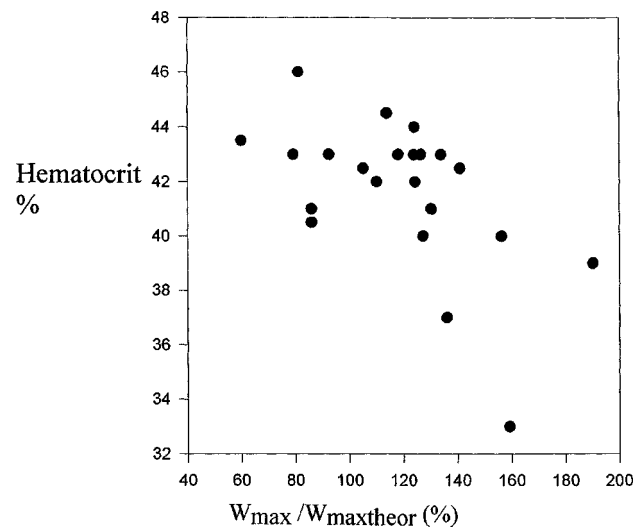
Fig. 1. Correlation between hematocrit and fitness expressed as the ratio aerobic working capacity $W_{max}/W_{maxtheor}$ ($r = -0.552$, $p = 0.008$).
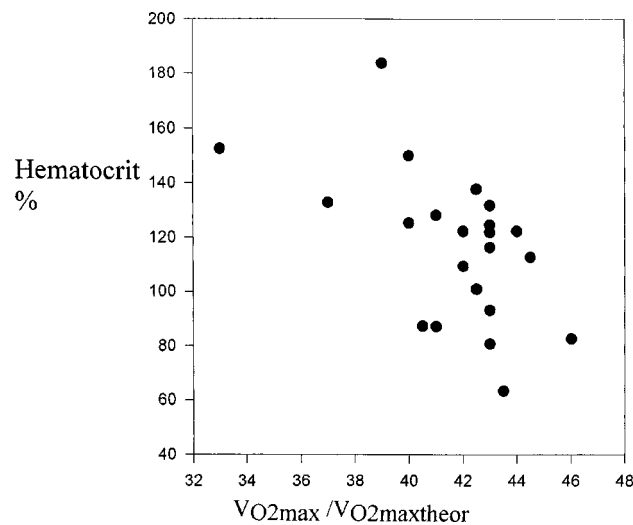

Fig. 2. Correlation between hematocrit and the ratio maximal oxygen uptake $V_{O_2\,max}/V_{O_2\,maxtheor}$ ($r = -0.543$, $p = 0.009$).

ferritin ($r = -0.312$, $p = 0.02$). Hematocrit was negatively correlated with the ratio aerobic working capacity $W_{max}/W_{maxtheor}$ ($r = -0.552$, $p = 0.008$) and with the ratio maximal oxygen uptake $V_{O_2\,max}/V_{O_2\,maxtheor}$, ($r = -0.543$, $p = 0.009$). The percentage of water in fat-free mass was not correlated to hematocrit although there was a nonsignificant tendency ($r = -0.288$, $p = 0.08$). Hematocrit exhibited also a negative correlation with blood lactate concentration at the level of the crossover point (15 values available $r = -0.543$, $p = 0.036$) and with baseline values of growth hormone ($r = -0.341$, $p = 0.031$).

Beside hematocrit, blood viscosity at corrected hematocrit 45% was also correlated with fitness, either expressed as W_{170} ($r = -0.348$, $p = 0.03$) as a ratio aerobic working capacity $W_{max}/W_{maxtheor}$
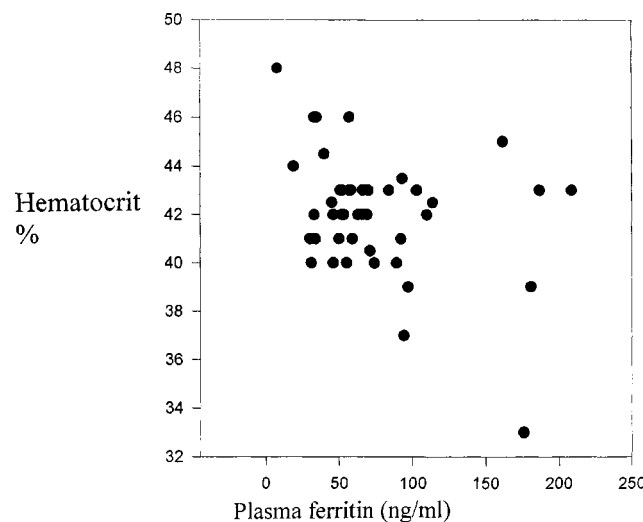
Fig. 3. Correlation between hematocrit and ferritin ($r = -0.33$, $p = 0.031$).

($r = -0.507$, $p = 0.016$) or as a ratio maximal oxygen uptake $V_{O_2\,max}/V_{O_2\,maxtheor}$ ($r = -0.494$, $p = 0.019$). Interestingly, there was no significant correlation between blood viscosity at corrected hematocrit 45% and the value of hematocrit ($r = -0.299$, $p = 0.058$), so that blood viscosity at corrected hematocrit 45% and hematocrit could be considered as independent determinants of fitness. The red cell rigidity index "Tk" exhibited a non significant tendency to be correlated with W_{170} ($r = -0.283$, $p = 0.08$), $V_{O_2\,max}/V_{O_2\,maxtheor}$ ($r = -0.398$, $p = 0.07$) and $W_{max}/W_{maxtheor}$ ($r = -0.405$, $p = 0.06$). However a stepwise regression analysis eliminated in both cases all other viscosity factors and selected only hematocrit as a statistical determinant of W_{170}, $V_{O_2\,max}/V_{O_2\,maxtheor}$ and $W_{max}/W_{maxtheor}$. Similarly, a partial correlation analysis suppresses correlations between fitness and blood viscosity at corrected hematocrit 45% when the variable hematocrit is neutralized. Thus, in this study, hematocrit is the major hemorheologic determinant of fitness, while all other rheologic parameters have only a very marginal statistical weight.

In fact, hematocrit also appeared in this sample of 42 sportsmen to be the major variable explaining blood viscosity (correlation with blood viscosity $r = 0.997$, $p < 10^{-7}$). It was also correlated to the erythrocyte disaggregability threshold γ_D ($r = 0.384$, $p = 0.03$). While the hematocrit/viscosity ratio (h/η index of O_2 delivery) remained maintained almost constant over the range of values studied, red cell rigidity ("Tk" index) exhibited a major influence on h/η as demonstrated by a strong correlation between these two parameters ($r = -0.757$, $p = 2.9 \times 10^{-13}$). By contrast the influence of plasma viscosity as a variable determining the value of blood viscosity was not found to be significant in this population, at least in terms of correlations. Actually in this sample of subjects this parameter varied over a narrow range.

4. Discussion

Our study shows boundaries for the quintiles of distribution of hematocrit in footballers and indicates that 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
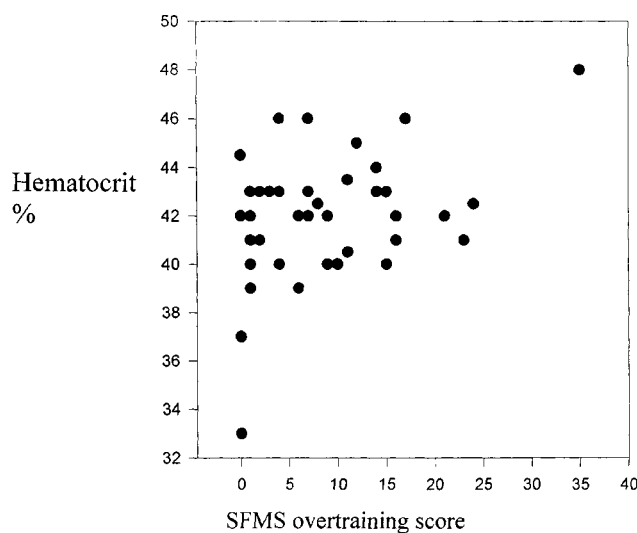
Fig. 4. Correlation between hematocrit and the overtraining score ($r = 0.352$, $p = 0.019$).

output, and their isometric adductor strength. By contrast athletes in the highest quintile had higher viscosity and lower red cell disaggregability. Although differences in fitness parameters (compared to all subjects with lower hematocrit) do not reach significance, correlations show that when hematocrit increases, there is a decrease in fitness and ferritin, and a higher score of overtraining.

These findings are also apparent on Figs 1 to 4, although some of the correlations do not reflect a so close relationship between hematocrit and these parameters across all the range of hematocrits investigated here. Actually, validity of these correlations is indicated by the normality and homoscedasticity tests which apparently rule out the possibility of spurious correlations due to outliers. Although this paper mostly focuses on extreme quintiles, these correlations require some comments.

Our finding of a negative correlation between hematocrit and fitness is fully consistent with previous findings [4–6]. Moreover, in this study, measurement of body fluids with bioimpedance provides an explanation of this relationship: the percentage of water in fat-free mass appears to be lower in subjects with hematocrit > 44.6% than in the others. While this percentage remains stable around 71% in the four lower hematocrit quintiles, it significantly decreases by 8% when hematocrit is in the higher quintile. Obviously, this observation is consistent with the concept of a training-induced "autohemodilution" process [6–8] which is assumed to be directly related to performance [8] via its beneficial hemodynamic effect. However, we were unable in this study to demonstrate any correlation between this bioimpedance-derived index of fat-free mass hydration and any fitness parameter (data not shown). Clearly, a low hematocrit is the best correlate of fitness in this sample, consistent with previous studies [8].

It is interesting to notice how this observation is in contrast with a common athletes's belief that increasing hematocrit by various doping procedures [3] increases fitness. Two previous papers from our group may suggest an explanation for this paradox. First, we reported [44] that iron-deficient athletes have a slightly higher plasma viscosity and red cell aggregability, probably due to a reversal in the training-related "*autohemodilution*" process. In this study, ferritin tends to decrease when hematocrit increases, suggesting that some of the elevated hematocrit values of the highest quintile may reflect disorders related to iron deficiency, a very common state in athletes which impairs performance even without any defect of oxygen transfer [45]. However, in our preceding paper, hematocrit was not changed in iron-deficient athletes who rather exhibited high values of plasma viscosity and red cell aggregability.

Thus, iron status is not likely to explain our findings. By contrast, we also reported [17] that athletes with a high overtraining score suggesting early stages of the overtraining syndrome have moderately increased values of hematocrit and plasma viscosity. Since in our sample the overtraining score and hematocrit are negatively related, some degree of overtraining may be responsible for the raised hematocrit values found in the highest quintile.

In fact, as we remind above, a decrease in performance in athletes whose hematocrit is in the highest quintile is not significantly observed, although correlations suggest a tendency to this. The most significant differences are found when we compare athletes in the lowest quintile of hematocrit with athletes from all other quintiles (middle and high hematocrits). These subjects clearly exhibit a higher aerobic power and a higher isometric adductor strength. As indicated by the ratio of water to fat-free mass, these subjects have an increased water volume which is likely to explain the low hematocrit and the improved performance.

Some recent reports are consistent with our finding. A Japanese study of 20 male triathletes in the 4th Kaike Triathlon, held in Tottori during 1984, shows that lower hematocrit values correlate with excellent competition results [46]. Authors suggest that low hematocrit represents a kind of "reserve", so that the competitors' hematocrit values could be elevated during exercise if their hematocrit values are in the low normal density whilst at rest. An epidemiologic study evaluated $V_{O_2\,max}$ in a population-based study of 413 boys and 372 girls, ages 10 to 14 years and showed that $V_{O_2\,max}$ was negatively related to height, total cholesterol, and hematocrit in males [47]. In a physiological experiment Hagberg and coworkers demonstrated that expanded blood volumes contribute to the increased cardiovascular performance of endurance-trained older men [48]. They performed sophisticated isotopic measurements of peak-exercise cardiac volumes and plasma and red cell volumes in endurance-trained compared to matched lean sedentary men. Athletes had approximately 40% higher $V_{O_2\,max}$ values than did the sedentary men and larger relative plasma (46 vs. 38 ml/kg), red cell (30 vs. 26 ml/kg), and total blood volumes (76 vs. 64 ml/kg), larger peak exercise stroke volume indexes and larger end-diastolic volume indexes. Interestingly, there were quite fair correlations of $V_{O_2\,max}$ with plasma, red cell, and total blood volumes. Moreover, peak exercise stroke volume was correlated directly with the blood volume variables. Authors performed multivariate analyses that led them to the conclusion that fat-free mass and plasma or total blood volume, but not red cell volume, were independent determinants of $V_{O_2\,max}$ max and peak exercise stroke volume. On the whole, plasma and total blood volumes correlated with the stroke volume and end-diastolic volume changes from rest to peak exercise. Thus, expanded intravascular volumes, particularly plasma and total blood volumes, are likely to contribute to the higher peak exercise left ventricular end-diastolic volume, stroke volume, and cardiac output. Accordingly, these expanded fluid volumes can be considered as direct determinants of $V_{O_2\,max}$ improvement after training in master athletes. Clearly, an increase in these volumes elicits both chronic volume overload and increased utilization of the Frank–Starling effect during exercise. However, in contrast with this study, there are some cross-sectional investigations [49] on erythrocyte, plasma, and blood volume of healthy young men (as assessed by isotope dilution methods) that lead to the conclusion that neither vascular volumes nor fluid–cell ratio are closely related to aerobic fitness. The reason for this discrepancy is not perfectly clear, but we could argue that authors report only crude values of $V_{O_2\,max}$ and that these values exhibit also a rather marginal relationship with hematocrit, while when $V_{O_2\,max}$ is corrected for anthropometry and thus expressed as a percentage of expected theoretical value this relation is more significant. Therefore, we may assume that other anthropometric determinants of both fluid volumes and $V_{O_2\,max}$ may obscure this relationship and reduce its statistical significance. In our opinion, expression of $V_{O_2\,max}$ as a percentage of the expected theoretical value is useful for normalizing results and makes them easier to interpret and to correlate.

On the whole, we think that all the bulk of literature supports, consistent with our study, that increased plasma volume directly results in increased $V_{O_2\,max}$ and might be a separate, and even more important determinant of $V_{O_2\,max}$ than red cell volume itself [48]. Our finding of an inverse relationship between hematocrit and ferritin clearly confirms that hematocrit in athletes usually reflects hydration status rather than iron stores. In our sample of subjects, low ferritin is a common finding, associated with impaired performance, but it is rather associated with a moderately increased hematocrit (related to unfitness) than with a low hematocrit which could reflect a true state of sports anemia. Obviously, this does not rule out the possibility of a further evolution of iron deficiency resulting in a decrease in hemoglobin and hematocrit [50,51], but this situation is surely much more unfrequent than the physiological training-induced decrease in hematocrit associated with increased body fluid stores.

A difference in red cell aggregation parameters is suggested by the higher partial disaggregation threshold found in the highest quintile of hematocrit. Since red cell aggregability is well known to be hematocrit dependent, comparison among samples with different hematocrits should be interpreted with caution. The hematocrit dependence of erythrocyte aggregation measurements with the Myrenne apparatus have been extensively investigated by Agosti [52]. When looking at the curves of his paper it is clear that in our range of hematocrits (37–48%) the influence of hematocrit is minimal (2–3%). Although most guidelines insist of the need of an *in vitro* adjustment, we think that such a procedure may increase the variability of the results by 8–10%, i.e., more than the effect of hematocrit itself in that range of values. By contrast, the effect of hematocrit becomes surely major beyond these limits. Possibly, a lack of hematocrit adjustment could pride some effects and other studies focusing more carefully on aggregation in extreme values of athletes' hematocrit will be required with hematocrit adjustment.

By contrast, as shown in Table 5, there is no effect of hematocrit on either h/η or on Tk. Both parameters seem to remain unchanged across all the range of hematocrits studied here. However these two variables appear to correlate quite fairly, as shown in Fig. 5, suggesting that, regardless hematocrit, red cell rigidity is a major determinant of h/η in athletes. This finding, which appears totally independent of the hematocrit issue investigated here, will require additional investigations. There is no clear explanation for it. One possible reason may relate to RBC properties such as MCHC or MCV, but these hematology data are not available.

Interestingly, there are also several metabolic and endocrine differences between subjects from the lowest quintile and the other athletes. The crossover point for oxidized fuel balance during exercise, i.e., the percentage of maximal power where carbohydrates become predominant and represent >70% of the oxidized substrates is on the average 70% higher in athletes from the lowest quintile (52.7% vs 34%). Actually, this difference is weakly significant ($p < 0.05$) so that this unexpected finding may be spurious and requires confirmation. However, a shift in carbohydrate balance in relation to hematocrit/ferritin status may be consistent with Brooks' theory of the the "crossover" concept [27,28]. According to this theory, iron stores rather than O_2 availability modulate the balance between carbohydrates and fat during exercise, which is in turn responsible for the lactate production by exercising muscles, rather than a "Pasteur-like" effect, i.e., a relative lack of O_2 at the muscular level. In fact, when the crossover point is expressed as a percentage of theoretical maximal performance rather than a percentage of the measured maximum, the difference is no longer found, suggesting that the increase in maximal power and $V_{O_2\,max}$ above the predicted value in athletes of the lowest quintile explains most of this metabolic pattern.

At the level of this crossover point, blood lactate is on the average at about 2 mmol/l, consistent with Brook's assumption that lactate threshold is mostly explained by the shift toward a predominant carbohydrate oxidation (>70%) [27]. However, we observe that this blood lactate concentration at the level of the crossover point exhibits some degree of variation and is negatively correlated with hematocrit.
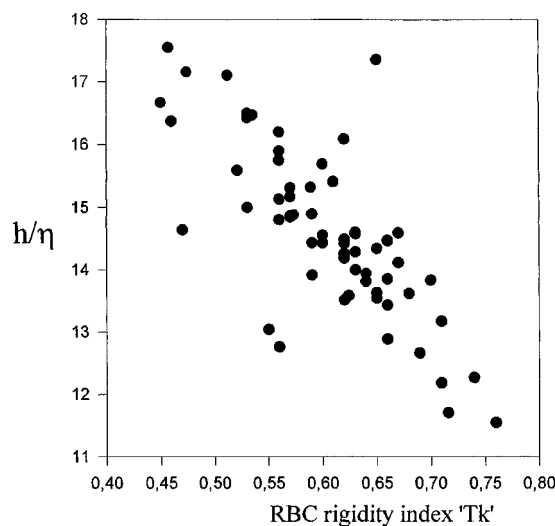
Fig. 5. Correlation between the hematocrit/viscosity ratio (h/η index of O_2 delivery) and the red cell rigidity "Tk" index ($r = -0.757$, $p = 2.9 \times 10^{-13}$).

This unexpected finding should also be considered with caution, since we observe no difference in lactate kinetic parameters (either the 2 mmol or the 4 mmol lactate threshold). However, this finding could be consistent with recent studies on recombinant erythropoietin-induced erythrocytemia in rats [53] in which a raised hematocrit (from 42 to 54%) resulted in higher muscular concentration of glycogen and free fatty acids, whereas lactate response to exercise was lowered. These results were interpreted as suggesting that energy substrate utilization during exercise is affected by enhanced oxygen availability, so that a lower overall contribution to energy production from anaerobic metabolism during exercise followed erythropoietin administration. In fact, relationships between exercise metabolism and hematocrit are not very clear in our results, since neither the LIPOXmax nor the lactate kinetics are correlated with hematocrit, while a low hematocrit seems to be associated with a higher crossover point and a higher blood lactate at this crossover point. These aspects require further studies.

Another point which requires discussion is the relationships between hormones of the GH–IGF axis and hematocrit. We find that subjects from the lowest quintile have a twofold higher value of IGFBP1, and that hematocrit is negatively correlated with baseline values of growth hormone. While growth hormone and IGF-I are involved in hematopoiesis [54] and in fluid homeostasis [55,56], such findings may have a physiological relevance. Actually, both IGFBP1 and growth hormone circulating levels are increased by training and associated with fitness [57,58], so that it is not surprising to find in our fitter subjects (who have the lowest hematocrit), higher IGFBP1 and growth hormone values. Whether there is a causal relationship between these parameters is difficult to assess from a correlational study. However, growth hormone is able to increase body fluid volumes [55], a physiological process that may explain its correlation with hematocrit in the current study. The case for IGFBP1 is less clear, since this binding protein is regulated by nutritional factors and by circulating insulin [59,60]. Higher values of IGFBP1 may reflect either a low caloric intake or low circulating insulin that may frequently be found in trained people [62]. In addition IGFBP1, which reduces the free circulating IGF-I [59,60,62], may also reduce some of its physiological effects. However, recent papers [62] show that IGFBP1 has an own stimulatory effect on erythropoiesis, synergistic with IGF1. Therefore, increased IGFBP1 may reflect some homeostatic feedback for increasing red cell mass. Clearly this point requires further investigation.

In conclusion, these data confirm that 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.

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