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Exercise-induced changes in hematocrit and hematocrit/viscosity ratio in male rugby players

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Abstract. We investigated whether the concept of hematocrit/viscosity (h/η) ratio explains the "paradox of hematocrit in athletes", by calculating a "theoretical optimal hematocrit" (*i.e.,* associated with the higher h/η value predicted with Quemada's equation from plasma viscosity, and erythrocyte rigidity index) before and after exercise. 14 rugby players (19–31 yr; weight 65.8–109.2 kg; height 1.7–1.96 m; BMI 21.7–33.1 kg/m^2) underwent a standardized submaximal exercise session on cycloergometer corresponding to 225 kjoules over 30 min. The rheologic response to exercise was measured with the MT90 viscometer and the Myrenne aggregometer. After exercise there was an increase in whole blood viscosity ($p < 0.05$) and hematocrit ($p < 0.005$) and a decrease in h/η ratio (from 14.7 ± 0.34 to 12.9 ± 0.37, $p < 0.005$). There was an increase in viscometric RBC rigidity indexes "Tk" and "k" in 9/14 subjects. Predicted and actual h/η are fairly well correlated (preexercise $r = 0.998$, $p < 0.001$; postexercise $r = 0.985$ $p < 0.001$) but actual h/η was lower than predicted (preexercise $p = 0.005$; postexercise $p = 0.02$). This discrepancy between predicted and measured hematocrit was not correlated to dehydration or plasma viscosity but was correlated to red cell rigidity ($r = 0.774$, $p < 0.01$) and its exercise-induced change ($r = 0.858$, $p < 0.01$). This study suggests that h/η, although it is not directly correlated to parameters of exercise performance, is precisely regulated during exercise according to the classic concept of "viscoregulation", and that the prediction of the theoretical optimal values of h/η and hematocrit by models may help to interpret the actual values of these parameters. However, these models need to be more extendedly tested and improved.

Keywords: Blood viscosity, hematocrit, exercise, rugby, erythrocyte deformability

List of symbols

BMI	body mass index
WHR	waist-to-hip ratio
RBC	red blood cell
SEM	standard error on the mean

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1. Introduction

Whether there is an "optimal hematocrit" has been over the last decades a matter of controversy [12]. Since hematocrit is the major determinant of blood viscosity it appeared obvious that excessively high values of this parameter can be associated with a reduction of blood flow [21, 22, 38] resulting into an impairment in oxygen delivery and thus, presumably, a decrease in exercise performance [4].

An experimental approach of this "Optimal hematocrit" in isolated muscles indicated that, due to reduced vasodilatory reserve in working skeletal muscle compared to resting muscle the optimal hematocrit is shifted to higher values [17].

However a 'paradox of hematocrit in trained athletes' was pointed out several years ago [4]. This paradox is that, on one hand, physiological training decreases hematocrit parallel to increased exercise performance, while on the other hand blood transfusion or erythropoietin (EPO) doping, that both increase hematocrit, are widely used procedures employed for improving performance. Theoretically it should be the opposite and hematocrit-increasing procedures would be expected to impair performance. We proposed to explain this paradox according to percolation theory applied by Schmid-Schönbein to blood circulation in muscles [31]. According to this theory, hematocrit has little or no hemodynamic influence in high shear-high pressure conditions (*i.e.*, exercise) explaining that a subject with supraphysiologic hematocrit (*e.g.*: an EPO doped athlete) may realize outstanding performances, but, in low shear – low pressure conditions (*i.e.*, at rest) it leads to hyperviscosity and impairs blood flow [18].

Furthermore it has been shown that the body can cope with hypererythrocythemia via an homeostatic phenomenon that implies a decrease in red cell rigidity [40]. To what extent this mechanism is efficient in humans is not known.

The most classical way to delineate the positive from the negative effect of hematocrit on circulation and oxygen supply is to calculate the h/η ratio as proposed by the pioneers of hemorheology, S. Chien [8] and J. Dormandy [16] and later popularized by J.F. Stoltz [35]. According to this author "blood's overall oxygen transport capacity is proportional to the ratio hematocrit/blood viscosity."

A recent assessment of the validity of this concept was provided by Stark and coworkers [33] who systematically used the various published formula describing the dependence of viscosity on hematocrit. They evidenced a good agreement between theoretical and observed values.

Over the last years the interest for the h/η ratio has been renewed by some interesting studies [9, 10, 25].

Since classical equations of blood viscosity such as Quemada's or Dintenfass's ones [13, 27] are known to provide a quite precise model of the influence of factors of viscosity on whole blood viscosity, we used them as a physiological model to investigate viscosity and h/η ratio in athletes at rest and after exercise. More precisely we aimed at predicting in athletes which would be the optimal hematocrit value (*i.e*, associated with the higher h/η value) before and after exercise, and to compare these predicted values to the actual ones. For this purpose we used Quemada's equation of viscosity that describes viscosity as a function of plasma viscosity, hematocrit, and erythrocyte rheology (*i.e.*, at high shear rate, rigidity) and introduced in it the actual values of plasma viscosity and erythrocyte rigidity with various values of hematocrit.

2. Subjects and methods

2.1. Study subjects

We used the database of a previous paper in order to test this prediction of hematocrit [2]. Subjects used in this study were 14 male rugby players submitted daily to a physical training program. Their

main age was 19–31 yr; their main weight was 65.8–109.2 kg; their mean height was 1.7–1.96 m. Their mean waist-to-hip ratio (WHR) was 0.92+0.02.

They underwent a standardized submaximal exercise session on cycloergometer corresponding to 225 kjoules over 30 min. Pedal speed was kept constant at 60 rpm by the subjects. Dehydration was evaluated by precision weighing (Sartorius model F 150-S-F2, France).

2.2. Bioelectrical impedance measurements

Prior to the exercise-test, subjects' body composition was assessed with bioimpedance analysis with a six terminal impedance plethismograph BIACORPUS RX 4000 Biacorpus RX4000, (Healthnesslink, 8 avenue Jean-Jaurès 92130 Issy-les-Moulineaux, France) with data analysis with the software Body-Comp 8.4. This device measures total resistance of the body to an alternative electric current of 50 kHz [5, 20]. Body fat mass, fat-free mass were calculated in each segment of the body according to manufacturer's database-derived disclosed equations, and total water with published equations using the classical cylindric model and Hanai's mixture theory [23].

2.3. Hemorheological in vitro measurements

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Viscometric measurements were done at very high shear rate (1000 s^{-1}) with a falling ball viscometer (MT 90 Medicatest, F-86280 Saint Benoit) [1, 14]. The coefficient of variation of this method ranged between 0.6 and 0.8%. 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 [27]. Dintenfass' 'Tk' index of erythrocyte rigidity was calculated [13]. RBC aggregation was assessed with the Myrenne aggregometer [30] 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 h/η ratio, an index of oxygen supply to tissues, was calculated according to Chien [7] and Stoltz [34] with hematocrit (as percentage) divided by viscosity at high shear rate determined as described above.

The SEFAM aggregometer was used for a more precise assessment of RBC aggregation. This device is based upon the experiments of Mills [24, 32] 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 [6, 15, 26]. 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 sec after the shear has stopped). The aggregation index at 10 sec 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).

2.4. Blood lactate

Lactate was assayed with a kit from DuPont specially adapted to the DuPont de Nemours automatic clinical analyzer. This assay was based on NADH production by rabbit lactate dehydrogenase. Coefficients of variation range between 0.7 and 5.6%.

Table 1
Reformations (mean + SEM) of rheologic parameters during maximal exercise in study subjects

	before exercise	after exercise
Blood viscosity	2.9+0.07	3.66+0.17***
Corrected viscosity η_{45}	3.08+0.09	3.44+0.09***
Plasma viscosity	1.34+0.01	1.45+0.01***
"Tk" (RBC rigidity)	0.62+0.01	0.65+0.02***
h/η ratio	0.15+0.004	0.13+0.004****
Hematocrit (%)	42.64+0.94	46.5+1.09***
RBC aggregation 'M'	4.3+0.45	4.55+0.37
RBC aggregation 'M1'	8.08+0.6	8.12+0.65
Aggregation time (TA)	2.77+0.28	1.85+0.14***
Aggregation time (Tf)	39+2.9	28.6+2.7***

*$p < 0.05$; ***$p < 0.01$; ****$p < 0.0001$.

2.5. *Changes in plasma volume*

A formula for calculating plasma volume changes (% ΔPV) during exercise from hematocrit changes has been published by investigators of the NASA-Ames Research Center [11, 19, 39] who demonstrated its validity in moderate as well as maximal exercise. We applied this formula to our data. The equation is:

$$\% \ \Delta\text{PV} = 100/(100 - \text{Ho}) \times 100\,[(\text{Ho} - \text{H})/\text{Ho}]$$

where Ho is resting hematocrit and H hematocrit during exercise.

2.6. *Statistics*

Results are presented as mean + the SEM. A value of $p < 0.05$ was considered as significant. Comparisons were made with nonparametric tests. Correlations were tested by least square fitting for linear, exponential, logarithmic and power relationships.

3. Results

Table 1 shows the main hemorheologic changes observed in study subjects before and after exercise. In responses to exercise, a 36% increase in blood viscosity ($p < 0.01$) was observed, due to a rise in hematocrit ($p < 0.005$), plasma viscosity ($p < 0.01$), and red blood cell rigidity ($p < 0.02$). There was an increase in viscometric RBC rigidity indexes "Tk" and "k" in 9/14 subjects. After exercise there was also a decrease in hematocrit/viscosity ratio (from 14.7 ± 0.34 to 12.9 ± 0.37 $p < 0.005$). Dehydration, evaluated by precision weighing, resulted in a loss of 360 to 973 g water *i.e.* 1.69 to 4.32 g/kjoule. This loss of water is not correlated to plasma volume contraction as assessed by the equation of Greenleaf.

The curve of theoretical optimal h/η plotted *vs* hematocrit was reconstructed with Quemada's equation. The hematocrit corresponding to the top of this curve was considered as the "theoretical optimal hematocrit".

Figure 1 shows the reconstructed curve of this theoretical optimal h/η plotted *vs* hematocrit with the actual individual experimental points. It can be seen that on the whole there is a good agreement

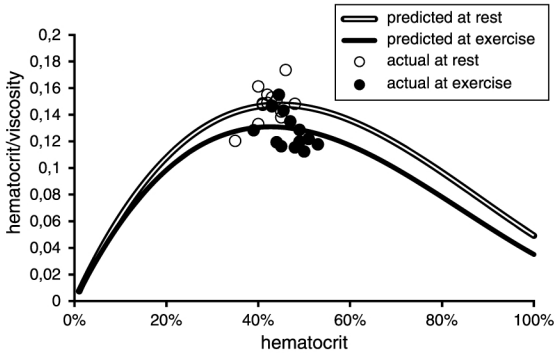

Fig. 1. Comparison between reconstructed curve of the theoretical optimal h/η plotted *vs* actual hematocrit at rest and the reconstructed theoretical curve after exercise, with actual values of h and h/η for each subject. Postexercise reconstructed curve is significantly lower compared to the curve reconstructed from values measured at rest ($p < 0.001$).

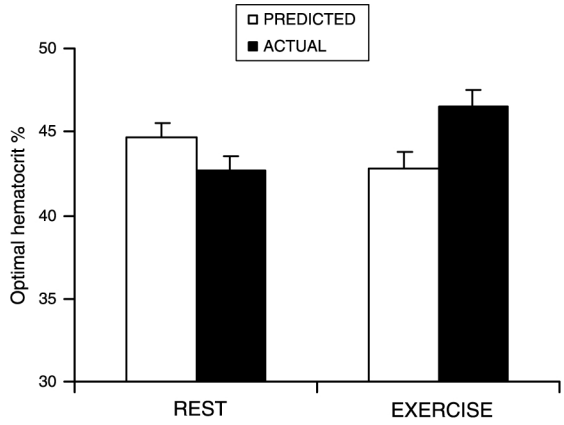

Fig. 2. Comparison between actual hematocrit and predicted hematocrit at rest and after exercise. The difference between actual and predicted is significant in both situations and there is also a significant difference between the mean of the difference at preexercise and the mean of the difference at postexercise ($p = 0.005$).

between the theoretical prediction of h/η and the value of h/η that is actually measured in true life in athletes.

However, as shown on Fig. 2, actual hematocrit was lower than predicted hematocrit at rest ($p = 0.0142$) and was higher after exercise ($p = 0.03$).

As shown on Fig. 3, predicted and actual h/η are fairly well correlated (preexercise : $r = 0.998$ $p < 0.001$; postexercise $r = 0.985$, $p < 0.001$)]. However as shown on Fig. 4, actual h/η was lower than predicted h/η (preexercise $p = 0{,}005$; postexercise $p = 0{,}02$).

As shown on Fig. 5, the discrepancy between predicted and measured hematocrit was not correlated to dehydration or plasma viscosity but was correlated to red cell rigidity ($r = 0.774$, $p < 0.01$) and its exercise-induced change ($r = 0.858$, $p < 0.01$).

As shown on Fig. 6, these discrepancies between predicted and measured hematocrit were correlated to red cell rigidity ($r = 0.774$, $p < 0.01$) and its exercise-induced change ($r = 0.858$, $p < 0.01$). By contrast they were not correlated to dehydration ($r = –0.205$ NS) or plasma viscosity($r = –0.171$ NS).

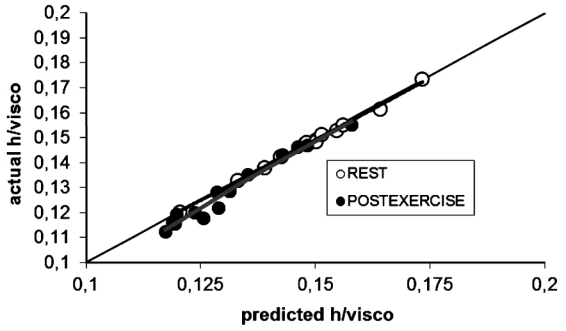

Fig. 3. Correlation between predicted and actual h/η. preexercise ($r = 0.998$, $p < 0.001$) postexercise ($r = 0.985$, $p < 0.001$).

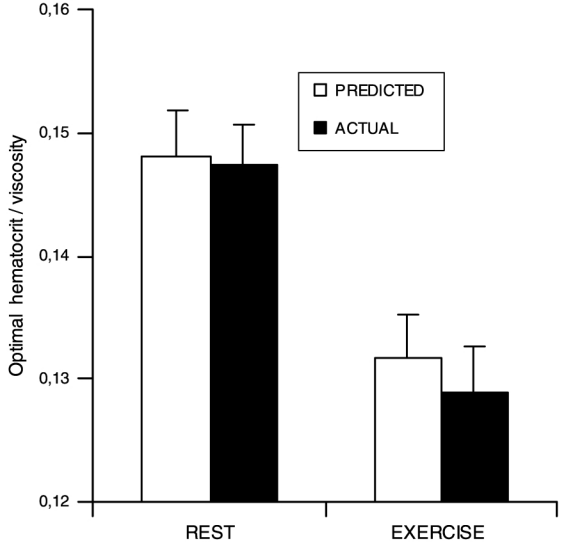

Fig. 4. Comparison between actual h/η and predicted h/η at rest and after exercise. The figure shows that actual h/η was lower than predicted h/η both before and after exercise (preexercise $p = 0{,}005$; postexercise $p = 0{,}02$).

4. Discussion

This study shows that (a) Quemada's equation yields a quite precise prediction of the h/η that will actually be measured at high shear rate in blood samples when the curve plotting it against hematocrit is reconstructed from red cell rigidity and plasma viscosity values; (b) it also predicts quite well on the average the value of hematocrit which is thus close in these athletes from the 'optimal hematocrit' given by the theoretical approach; (c) there are however some discrepancies between predicted and actual hematocrit; (d) those discrepancies are explained by red cell rigidification during exercise.

The first interesting finding of this study is that Quemada's equation, a theoretical model that was not specifically developed for blood [27] provides a rather fine prediction of the "ideal" hematocrit with viscosity measurements performed at high shear rate. This further confirms the good accuracy of this classical equation.

However the finding of discrepancies which are correlated to the parameter "k" that, at high shear rate, measures red cell rigidity, should be pointed out. It may indicate that the two variables involved in viscoregulation are plasma viscosity and hematocrit, while red cell rheology is not a signal sensed for the homeostatic regulation of viscosity. It is known that an adaptative decrease in red cell rigidity

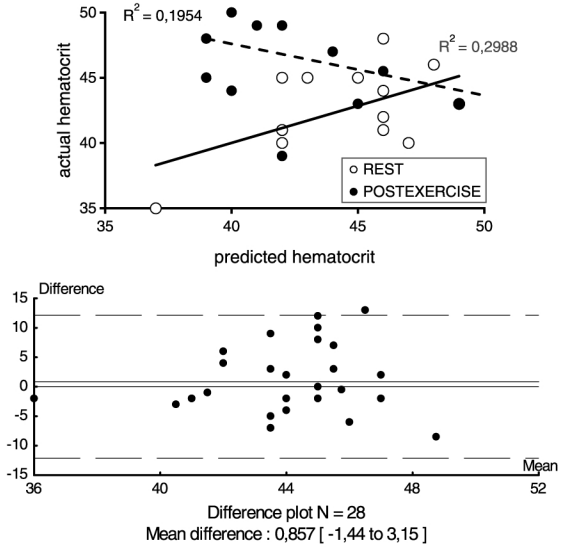

Fig. 5. Upper panel: correlation between predicted and measured hematocrit at rest and after exercise. Lower panel: Bland-Altman plot of the agreement between predicted redicted and measured hematocrit at rest and after exercise.

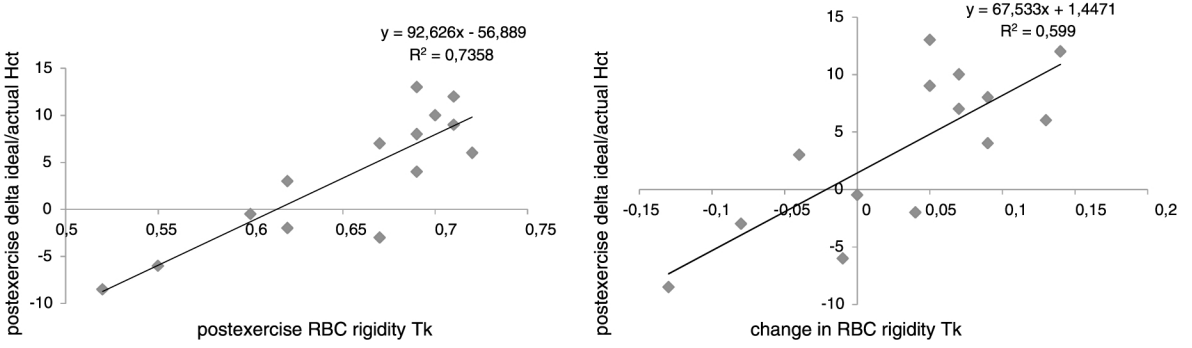

Fig. 6. Correlation of the discrepancies between predicted and measured hematocrit with post exercise red cell rigidity ($r = 0{,}774$, $p < 0.01$) and the exercise-induced change in red cell rigidity ($r = 0{,}858$, $p < 0.01$).

occurs in experimental hyperviscosity [40] but there is no evidence that erythrocyte rigidification can trigger mechanisms reducing viscosity. Even more we deal here with a short-term change in red cell flexibility that is unlikely to have an immediate effect on viscoregulatory mechanisms. This aspect of viscoregulation remains poorly known.

The current finding of a loss of accuracy of our prediction based on Quemada's equation after exercise-induced red cell rigidification suggests that it will be interesting to investigate a new modeling based on the same concept but with a fixed (or a theoretical) value of "k" rather than the actual one. In a further study (data not shown here) we observe that fixing "k" in the model does not improve the accuracy of the prediction but on the opposite decreases it without suppressing the correlation between red cell rigidity and the discrepancy between predicted and actual values, so that the use of the full Quemada's model with actual "k" values is probably better.

Finally our study provides some new information supporting the validity of the concept of h/η.

The determination of an optimal value of hematocrit that yields the highest value of h/η is an old idea, as indicated in our introduction. This concept has been found to be useful in various clinical

conditions such as blood transfusion [29, 36], sickle cell disease [10, 37], or ischemic heart disease [28]. Concerning exercise physiology we were unable 20 years ago to evidence a relationship between h/η and maximal aerobic capacity although such a relationship could be theoretically expected [3, 4]. However in a recent study in animals submitted to experimental alterations in hematocrit this relationship was clearly demonstrated [33]. The approach we propose in this paper may help to analyze more closely this parameter and its determinants in various physiological and pathophysiological situations.

This study also shows that in athletes the actual hematocrit is close of the theoretical 'optimal hematocrit' predicted by an equation of viscosity and suggests therefore, not only that this approach based on the h/η ratio is valid, but that in physiological conditions venous hematocrit is quite precisely set at its optimal value. It will be interesting to investigate whether in other physiological and pathologic contexts this remains true. The comparison between theoretical optimal and actual hematocrit values can expected to provide a means to explore viscoregulation.

5. Conclusions

Therefore, on the whole, this paper demonstrates in a sample of athletes that (a) Quemada's equation predicts h/η and the 'optimal hematocrit'; (b) this 'optimal hematocrit' is higher than actual hematocrit, but well correlated to it; (c) there are some discrepancies between predicted and actual hematocrit; (d) those discrepancies are explained by red cell rigidification during exercise which are taken into account by the model but are not likely to trigger viscoregulatory adaptations at least on the short term.

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