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## **Shear-dependency of the predicted ideal hematocrit.**

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The ideal hematocrit is the hematocrit (Hct) value resulting in the highest value of Hct/viscosity ( $h/\eta$ ) ratio and can thus be predicted from viscometric measurements with the use of equations such as Quemada's one which yield the determination of the bell-shaped curve of  $h/\eta$  as a function of Hct. In a series of recent papers we applied this approach to various populations, using viscometry at high shear rate ( $1000\text{ s}^{-1}$ ). However the shape of this curve has been reported to be dependent on the shear rate, resulting in a right-shift in this top value when Hct increase. We present here in 11 young recreative athletes the evolution of the predicted top of the  $h/\eta$  curve and optimal theoretical Hct and the discrepancy between theoretical and optimal values over the range of shear rates 1 to  $6000\text{ s}^{-1}$ . Results show that the predicted optimal value of both  $h/\eta$  and Hct increases when shear rate increases and that the discrepancy between predicted « optimal » and actual values decreases and becomes almost asymptotic at very high shear ( $500\text{ s}^{-1}$ ). It is minimal at  $2720\text{ s}^{-1}$ . The correlation between predicted « optimal » and actual values of both parameters describes the same evolution. Therefore, it is better for assessing  $h/\eta$  and its agreement with theoretical values, and for determining the theoretical ideal hematocrit, to measure blood viscosity at shear rates equal or superior to  $500\text{ s}^{-1}$ .

**Running title:** shear rate and optimal hematocrit

**Keywords:** blood viscosity, hematocrit, hematocrit/viscosity ratio, oxygen delivery index

## 1. Introduction

The ideal Hct is the Hct value resulting in the highest value of Hct/viscosity ( $h/\eta$ ) ratio. This is a very classical concept [4] but further studies have shown that Hct varies widely across the circulation [11] so that it could seem at this time an oversimplified assumption with little actual relevance. Nevertheless, two recent lines of evidence support the relevance of this

concept of optimal Hct: (a) the fact that in erythropoietin-treated mice exercise performance displays a bell-shaped curve that closely mimics the theoretical curve of  $h/\eta$  [14]; (b) recent clinical studies showing that this  $h/\eta$  ratio is associated with the prognosis of vascular lesions [3, 7].

Therefore, although it is true that hematocrit undergoes dramatic variations across the circulatory bed, a crude value of venous Hct considered in association with the corresponding value of viscosity reflects at the level of the whole body the ability to deliver oxygen to tissues and has a prognosis value. The  $h/\eta$  ratio is thus more and more frequently called “oxygen delivery index” (ODI) [5].

This promising return of an old concept prompted us to develop a theoretical approach of  $h/\eta$  in order to predict from an individual’s viscometric data his optimal hematocrit [2]. We used Quemada’s equation [13] to reconstruct the curve of theoretical optimal  $h/\eta$  plotted vs Hct and the value of Hct corresponding to the top of this curve was considered as the “theoretical optimal Hct”. We applied this approach to various populations, using viscometry at high shear rate ( $1000\text{ s}^{-1}$ ). We observed that this prediction is quite precise for optimal  $h/\eta$  and also to a lesser extent for the corresponding Hct. Some discrepancies between the predicted optimal values and the actual ones were found in various situations and were likely to have a pathophysiological relevance [2].

However it is known that the shape of this curve is dependent on the shear rate, resulting in a right-shift in this top value when Hct increase [12]. A comprehensive picture of this dependency of on shear rate is not available. In this study we aimed at describing this relationship over a range of shear rates ranging from 1 to  $6000\text{ s}^{-1}$ .

## **2. Materials and methods**

### **2.1. Subjects**

Table 1 presents the subjects of the study. They were 11 young recreative athletes included in a protocol investigating whether simultaneous administration of low doses of epoetin-alpha (Binocrit) and growth hormone (Genotonorm) have an effect on erythropoiesis or on the aerobic performance.

The study was approved by the local Institutional Ethics Committee and the competent European authority (N°EudraCT: 2016-002742-23). Written informed consent was obtained from each volunteer prior to his enrolment in the study.

## 2.2. Hemorheological measurements and calculations

Venous blood samples for hemorheological measurements (7 ml) were drawn in the cubital fossa with a large needle, with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Viscometric measurements were then performed over the range of shear rates 1 to 6000 s<sup>-1</sup> with the RHEOMETRE Anton Paar CP 50-1 (Anton Paar Germany GmbH, Hemuth-Hirth-Strasse 6, D-73760 Ostfildern / Germany) [8-10].

Hematocrit was measured together with other hematological markers with the Coulter analysis.

From viscosity and hematocrit data we calculated the theoretical ratio  $h/\eta$

$$h/\eta = h / [\eta_p(1-1/2 k \phi)^{-2}]$$

where  $\phi$  is hematocrit,  $\eta_b$  is blood viscosity,  $\eta_p$  is plasma viscosity, and  $k$  is a shear-dependent parameter intrinsic viscosity of the red cells, *i.e.*, an index of erythrocyte rigidity which is calculated from viscometric measurements and hematocrit as follows:

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

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

## 2.3. Statistics

Results are presented as mean  $\pm$  the SEM. A value of  $p < 0.05$  was considered as significant. Comparisons were made with nonparametric tests. Pearson coefficients of correlation were tested by least square fitting.

### 3. Results

Fig.1 shows the crude viscosity data of the subjects plotted against the shear rate. Fig. 2 shows that the curve  $h/\eta$  ratio reconstructed with Quemada's model displays its classical bell-shaped profile as a function of Hct, but that the curves obtained at various shear rates are shifted on the right and toward higher values of  $h/\eta$  ratio when the shear rate increases. Optimal values of hematocrit calculated on these various curves also increase when the shear rate increases. Fig. 3 shows the evolution of Pearson's coefficient of correlation between theoretical and the actual values of hematocrit and  $h/\eta$  ratio plotted against the shear rate. For low shear rates the correlation is not significant. When shear rate increases, the coefficient of correlation improves and then reaches a plateau above  $10 \text{ s}^{-1}$ . Fig. 4 shows the evolution of the discrepancy between predicted « optimal » and actual values of the  $h/\eta$  ratio. It can be seen that the discrepancy decreases and becomes almost asymptotic at very high shear ( $500 \text{ s}^{-1}$ ). It is minimal at  $2720 \text{ s}^{-1}$ .

### 4. Discussion

This study shows that the predicted optimal value of both  $h/\eta$  and Hct increases when shear rate increases and that the discrepancy between predicted « optimal » and actual values decreases and becomes almost asymptotic at very high shear ( $500 \text{ s}^{-1}$ ). This discrepancy is minimal above  $2720 \text{ s}^{-1}$ . The correlation between predicted « optimal » and actual values of both parameters describes the same evolution and is optimal at high shear rate. All these

findings lead to think that it would be better for assessing  $h/\eta$  ratio and its agreement with theoretical values, and for determining the theoretical ideal Hct, to measure blood viscosity at shear rates equal or superior to  $500 \text{ s}^{-1}$ .

The calculation of  $h/\eta$  ratio as a function of Hct which is proposed here yields a curve which is very similar to the theoretical one assumed by classical authors and to the actual curve as recently published by Nemeth [12] and by Schuster [15]. The fair correlations observed in various populations between predicted and actual values of optimal Hct and  $h/\eta$  suggest that this model-based approach is accurate. We suggest that the fact that correlations are closer for  $h/\eta$  than Hct may lead to think that  $h/\eta$  ratio is actually the regulated parameter rather than Hct itself, in accordance with the theory of the bell-shaped curve. This would be logic if  $h/\eta$  ratio is really the “oxygen delivery index”, as assumed by various authors [1, 6].

An impressive evidence of the pathophysiological relevance of this  $h/\eta$  (or ODI) has been provided ten years ago by Kenyeres et al. [7] who performed Kaplan-Meier survival analysis on the impact of the ODI on cardiac mortality. ODI was found to be negatively correlated with the frequency of hospital admissions and low ODI appeared to be a risk factor of cardiac death in coronary heart disease.

Furthermore, our recent studies [2] lead to think that the discrepancies between theoretical and actual values of Hct and  $h/\eta$ , rather than reflecting an inaccuracy of the model, may have some physiological relevance. Actual values of both  $h/\eta$  ratio and Hct are slightly lower than predicted. In particular, predicted and actual Hct are well correlated but actual is on the average 1% lower than the predicted optimal value. Since this discrepancy between predicted and ideal values vanishes when exercise is prolonged, it can be suggested that humans have an Hct lower at rest than ideal in order to maintain the possibility to increase our Hct during exercise without impairing blood flow. Acute exercise sets  $h/\eta$  ratio closer from its predicted ideal value, *i.e.*, the value which is assumed to be associated with a higher oxygen delivery

rate. When athletes are well trained, Hct at rest is closer from ideal, and its exercise-induced rise is lower. By contrast sedentary sets Hct much lower, with a greater discrepancy with the ideal theoretical value, allowing Hct to rise during exercise in order to cope with the need for more oxygen transfer to tissues.

## 5. Conclusions

In conclusion, we show in this study that the optimal value of both  $h/\eta$  ratio and Hct predicted with Quemada's model increase when shear rate increase as a function of shear rate and that the discrepancy between predicted « optimal » and actual values also decreases when shear rate increases, and becomes almost asymptotic at very high shear ( $500 \text{ s}^{-1}$ ). This discrepancy is minimal at  $2720 \text{ s}^{-1}$ . The correlation between predicted « optimal » and actual values of both parameters describes the same evolution. Therefore, it is better for assessing  $h/\eta$  ratio and its agreement with theoretical values, and for determining the theoretical ideal Hct, to measure blood viscosity at shear rates equal or superior to  $500 \text{ s}^{-1}$ .

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**List of symbols:** Hct: Hematocrit; ODI: oxygen delivery index; SEM: standard error on the mean.

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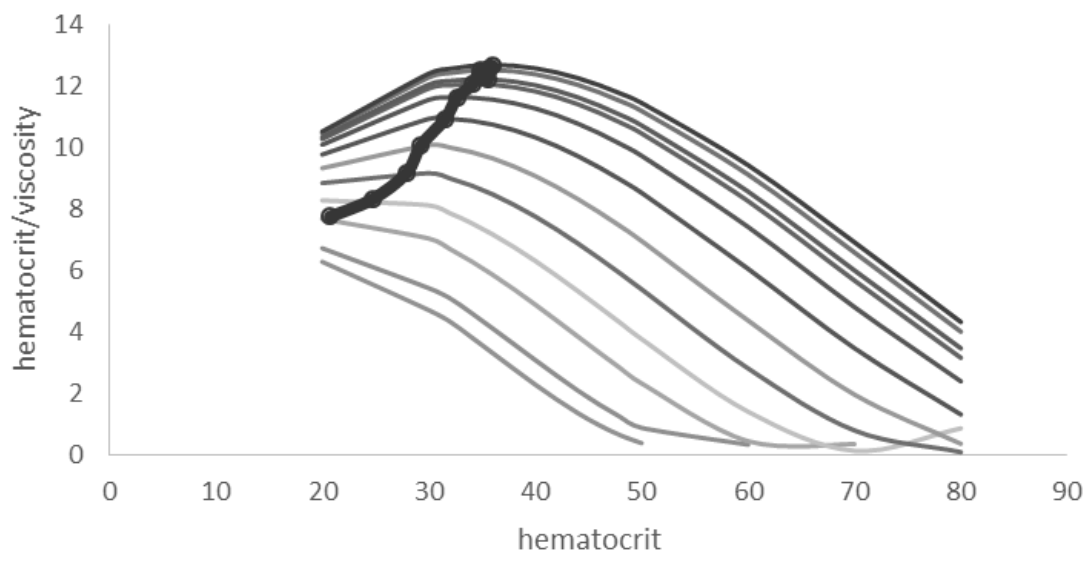
**Table 1.** Clinical characteristics of the 11 subjects of the study. Values are expressed as mean +/-SEM. BMI = Body Mass index

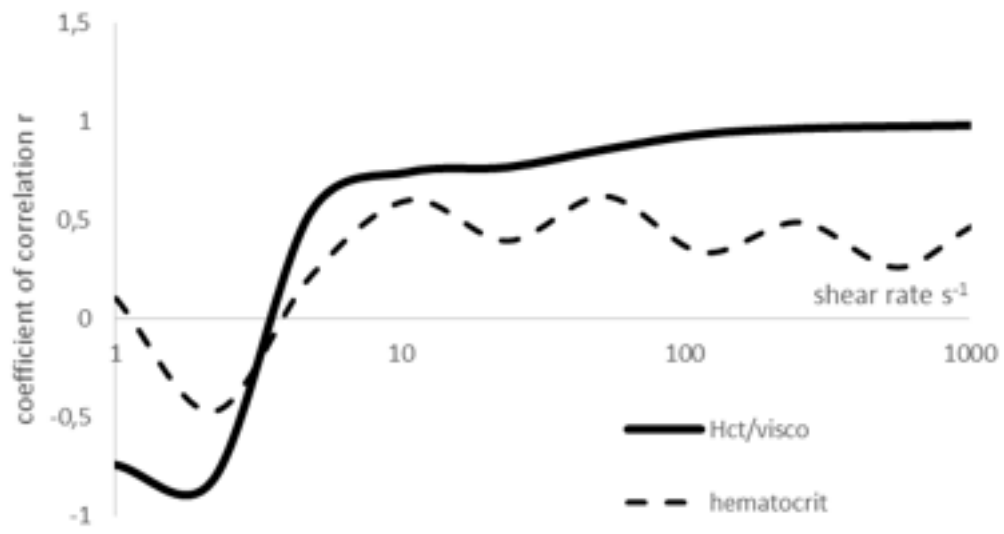
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age (years)	22.20±2.82
weight (kg)	78.77±9.53
height (cm)	175.62±5,91
BMI (kg/m <sup>2</sup> )	25.4±2.35
hematocrit (%)	43.71±2.13

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**Fig. 1.** Crude viscosity data of the subjects plotted against shear rate.

**Fig. 2.** The theoretical model of optimal hematocrit predicted with Quemada's model. The hematocrit/viscosity ratio displays its classical bell-shaped curve as a function of hematocrit. The curves obtained at various shear rates are shifted on the right and toward higher values of hematocrit/viscosity when the shear rate increases. Optimal values of hematocrit are represented by the thick black line.

**Fig. 3.** Evolution of the Person's coefficient of correlation between theoretical and the actual values of hematocrit and hematocrit/viscosity plotted against the shear rate. For low shear rates the correlation is not significant. When shear rate increases the coefficient of correlation improves.

**Fig. 4.** Evolution of the discrepancy between predicted « optimal » and actual values of the hematocrit/viscosity ratio. It can be seen that the discrepancy decreases and becomes almost asymptotic at very high shear ( $500 \text{ s}^{-1}$ ). It is minimal at  $2720 \text{ s}^{-1}$ .