" Optimal " vs actual hematocrit in obesity and overweight

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« Optimal » *vs* actual hematocrit in obesity and overweight

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Abstract. Equations of blood viscosity provide a prediction of the 'optimal' hematocrit' (hct) as the hct resulting in the highest value of the bell-shaped curve of hematocrit/viscosity ratio h/η. We investigated if overweight and obesity have an influence on these parameters. We compared 32 normal weight subjects, 40 overweight (BMI 25–30) and 38 obese subjects. There was no difference in the theoretical curve of h/η. The actual h/η is the same in the 3 groups but is always higher than the theoretical h/η in all groups. The actual h/η is lower in overweight than controls ($p = 0.011$). Modeling yields the same value of theoretical optimal hct across BMI classes. The 3 groups have the same values of actual hct, but actual is significantly lower than optimal in all cases ($p < 0.001$). Hematocrit is lower than predicted due to a discrepancy between predicted and actual h/η which is due to the inter-subject variability of RBC rigidity … The discrepancy between optimal and actual h/η is negatively correlated to RBC rigidity indexes even if the model uses a fixed value of these indexes. Thus keeping in mind that the optimal hct should not be the same in the various parts of the vascular bed, its theoretical prediction with Quemada´s equation appears to predict a value higher than actual hematocrit but well correlated to it, and the agreement between optimal and actual hct is dependent on RBC flexibility. This leads to think that the body sets hematocrit below its ideal value in sedentary subjects in order to cope with the need of increasing blood viscosity factors in case of exercise without impairing O_2 supply to tissues.

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

List of symbols

RBC	red blood cell
BMI	body mass index
SEM	standard error on the mean

1. Introduction

Hemorheological alterations are classically described in obesity, consisting of moderate changes in red cell rheology, plasma viscosity and hematocrit [19, 21]. The later are rather observed in association

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with increased stores of abdominal fat [18]. However hematocrit changes are not easy to simply interpret, because their *in vivo* effects of blood viscosity are biphasic, describing a "U-shaped curve" with initially a beneficial effect on blood flow for a moderate increase, and then for higher values an increase in resistance resulting in an impairment of blood flow [15]. Notwithstanding this complexity, the classical concept of 'optimal hematocrit' has recently proven its relevance as well as the concept of hematocrit/viscosity ratio (h/η) being an index of the oxygen delivery ability of blood [13]. Regarding these concepts, we recently reported that equations of blood viscosity provide a calculation of a theoretical 'optimal hematocrit' (hct) as the hct resulting in the highest value of the bell-shaped curve of hematocrit/viscosity ratio h/η. What becomes this relationship is unknown in the case of obesity despite the well known fact that obesity is a situation of increased cardiovascular risk. Therefore in this study we investigated if overweight and obesity have an influence on h/η and the value of ´optimal´ hematocrit that it allows to calculate.

2. Subjects and methods

2.1. Study subjects

We compared 32 normal weight subjects, 40 overweight (BMI 25–30) and 38 obese subjects. Characteristics of subjects are shown on Table 1.

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, (SoAGIL DEVELOPPEMENT, 8 avenue Jean-Jaurés 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 [3, 11]. 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 [12].

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, 10]. The coefficient of variation of this method ranges between 0.6 and 0.8%. With this device we measured

Table 1
Characteristics of study subjects (mean + SEM)

	Gender M/F	Age	Weight (kg)	Height (m)	BMI (kg/m^2)
Normal weight $n=26$	12/14	32.62 ± 2.14	66.82 ± 2.11	1.70 ± 0.02	23.12 ± 0.26
Overweight $n=40$	17/23	38.90 ± 2.30	75.00 ± 1.63	1.66 ± 0.02	27.05 ± 0.22
Obese $n=30$	13/17	41.18 ± 2.74	97.90 ± 4.06	1.65 ± 0.02	35.86 ± 1.45

apparent viscosity of whole blood at native hematocrit, plasma viscosity, and blood viscosity at corrected hematocrit (0.45) according to the equation of Quemada [14]. Dintenfass's 'Tk' index of erythrocyte rigidity was calculated [9]. RBC aggregation was assessed with the Myrenne aggregometer [16] 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 [17] with hematocrit (as percentage) divided by viscosity at high shear rate determined as described above.

2.4. Prediction of the theoretical 'optimal hematocrit' and hematocrit viscosity ratio

The curve of theoretical optimal h/η plotted vs hematocrit was reconstructed with Quemada's equation presented above. The equation of h/η as a function of h was thus:

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

The hematocrit corresponding to the top of this curve was considered as the "theoretical optimal hematocrit". The highest value of h/η (the top of the curve) was considered as the optimal h/η.

2.5. Statistics

Results are presented as mean ± standard error of the mean (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 2 shows the main hemorheologic values in the 3 groups of subjects. Compared to controls obese had higher RBC aggregation M ($p = 0.037$) and M1 ($p = 0.000028$), and lower theoretical optimal hematocrit ($p = 0.05$). Compared to controls overweight subjects had higher RBC rigidity "k" ($p = 0.007$), higher blood viscosity at corrected hematocrit 45% ($p = 0.03$), higher hematocrit/viscosity ratio ($p = 0.011$). Compared to obese overweight subjects had higher RBC aggregation "M" ($p = 0.028$) and "M1" ($p = 0.0022$).

As shown on Fig. 1 there was no difference in the theoretical curve of h/η among the three groups. The actual h/η is lower in overweight than controls ($p = 0.011$). Figure 2 shows the comparison between actual and predicted h/η in the 3 groups of subjects. It can be seen that the model gives the same predicted value and of h/η and a higher actual h/η in controls compared to the other groups with excess weight. As shown on Fig. 3, modeling yields the same value of theoretical optimal hct across BMI classes. The values of actual Hct were lower in obese ($p = 0.052$) and overweight ($p = 0.001$) compared to controls and the actual actual hematocrit is significantly lower than optimal in all cases ($p < 0.001$). Figure 4 shows that there is a good agreement between theoretical and optimal h/η in all the subjects as shown by the correlation curve (in all subjects: $r = 0.677$; $p < 0.01$; in controls: $r = 0.613$; $p < 0.01$; in overweight: $r = 0.714$; $p < 0.01$; in obese: $r = 0.698$; $p < 0.01$). For hematocrit the coefficients of correlation are: in all subjects: $r = 0.624$; $p < 0.01$; in controls: $r = 0.473$; $p < 0.01$; in overweight: $r = 0.672$; $p < 0.01$; in obese: $r = 0.666$; $p < 0.01$. The Bland-Altman plot on the same figure shows that all values of hematocrit (except one) of this sedentary population range below the predicted optimum.

On Fig. 5 are shown the correlation between red cell deformability index 'k' and the discrepancy between optimal and actual hematocrit. When this prediction of hematocrit is performed with the full

Table 2

Hemorheological parameters in the three groups of study subjects (mean + SEM)

	η_b	η_p	Tk	k	M	M1	η45	Theoretical h/η	Actual h/η	Theoretical optimal hct	Actual hct (%)
Normal weight $n=26$	2.55 ± 0.06	1.37 ± 0.01	0.52 ± 0.01	1.38 ± 0.006	4.25 ± 0.49	7.24 ± 0.42	2.66 ± 0.05	15.77 ± 0.15	16.74 ± 0.29	49.15 ± 0.25	42.25 ± 0.52
Overweight $n=40$	2.61 ± 0.06	1.36 ± 0.02	$0.55 \pm 0.01^{***}$	$1.40 \pm 0.007^{***}$	7.02 ± 0.75(&)	11.30 ± 0.72(&)	$2.77 \pm 0.05^{*}$	15.65 ± 0.21	$16.06 \pm 0.31^{***}$	$48.43 \pm 0.26^{***}$	41.63 ± 0.65
Obese $n=30$	2.64 ± 0.05	1.35 ± 0.01	0.56 ± 0.01	1.41 ± 0.006	5.22 ± 0.40	$8.32 \pm 0.49^{***}$	2.81 ± 0.05	15.60 ± 0.14	15.75 ± 0.24	$48.21 \pm 0.17^{*}$	41.18 ± 0.51

Abbreviations: η_b: whole blood viscosity at native hematocrit (%); η_p: plasma viscosity; Tk an k: red cell rigidity indexes; M: red cell aggregation after stop flow; M1: red cell aggregation at low shear rate; η45: whole blood viscosity at hematocrit 45% calculated with Quemada's equation; h/η: hematocrit/viscosity ratio; hct: hematocrit (%). Comparisons: $^{*}p<0.05$ *vs* controls; $^{***}p<0.01$ *vs* controls; (&) $p<0.05$ *vs* obese.

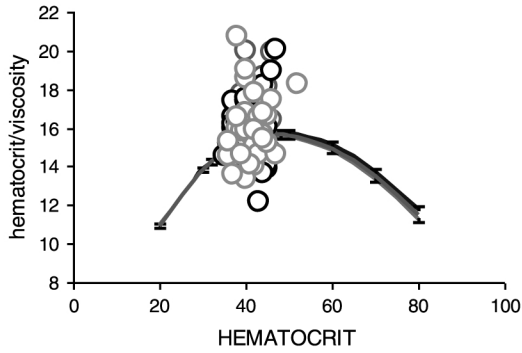

Fig. 1. Comparison between reconstructed curve of the theoretical optimal h/η plotted *vs* actual hematocrit in the three groups of subjects showing that the three theoretical profiles cannot be distinguished. In open circles are shown the actual values.

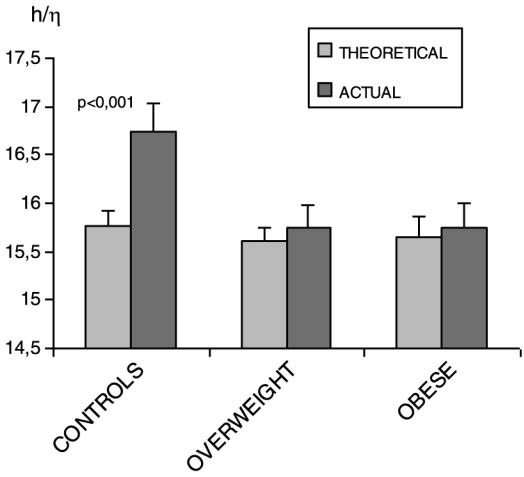

Fig. 2. Comparison between actual and predicted h/η in the 3 groups of subjects showing the same predicted value and a higher actual value in controls compared to the other groups with excess weight.

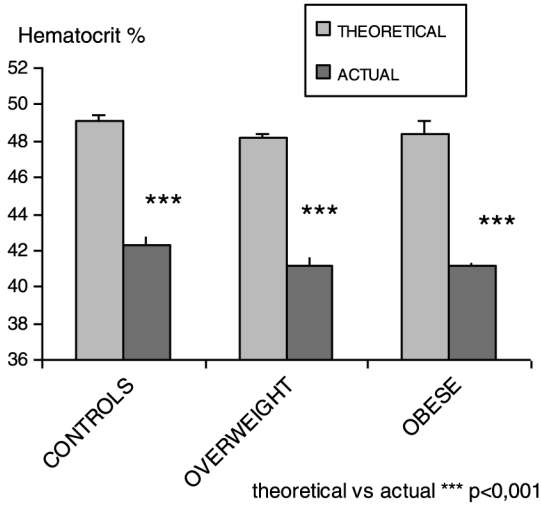

Fig. 3. Comparison between actual and predicted optimal hematocrit in the 3 groups of subjects showing the same predicted value and a value lower than predicted in all groups. No significant difference for actual hematocrit among groups.

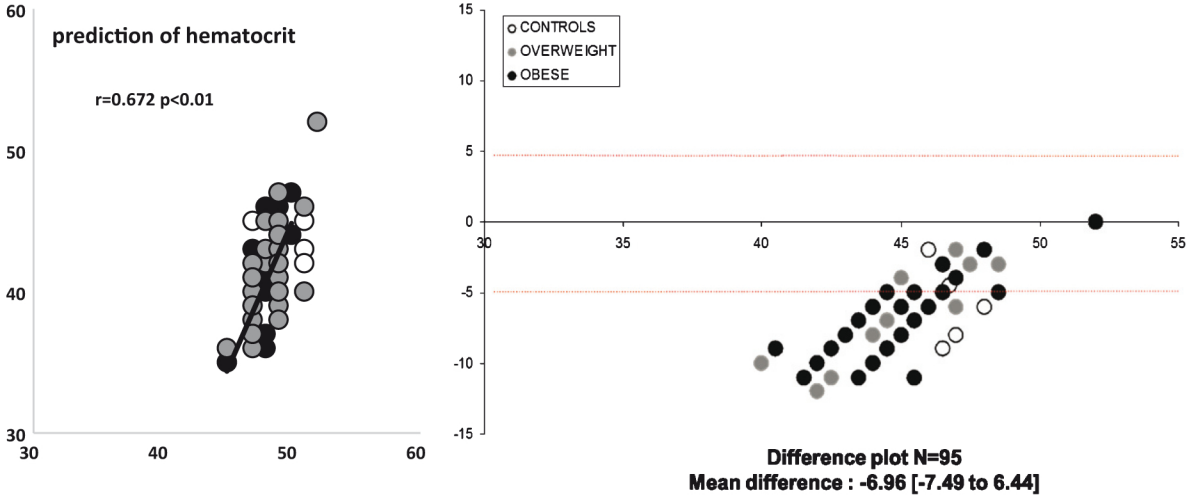

Fig. 4. Agreement between theoretical and optimal h/η and theoretical and optimal hematocrit. Left panel: Correlation curve (left: h/η; right: hematocrit). Right panel: Bland Altman plot. The correlations are less close than previously found in athletes and all values of this sedentary population range below the predicted optimum.

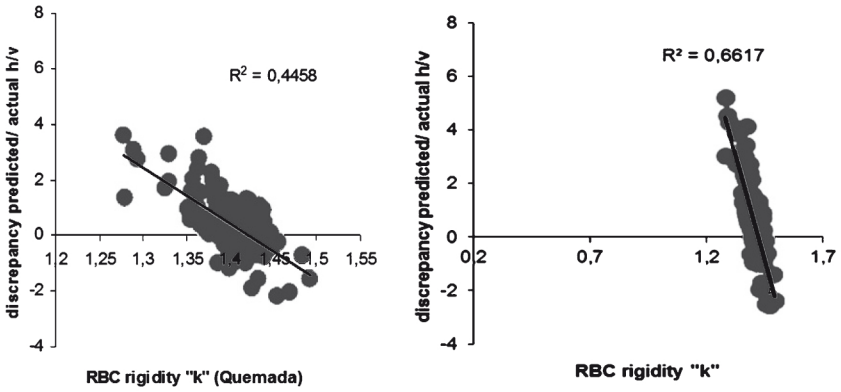

Fig. 5. Correlation between red cell deformability index 'k' and the discrepancy between optimal and actual hematocrit. Left: Prediction of hematocrit with the full Quemada model. Right: Prediction with a simplified model assuming a fixed value of k = 1.42. The two pictures show that even if red cell rigidity does not enter in the model for prediction, it remains a determinant of the discrepancy between predicted and actual optimal hematocrit.

Quemada model it shows that RBC rigidity is a major determinant of this discrepancy. This raises the question of whether the prediction of optimal hct with the Quemada's model (i.e., taking into account red cell rigidity) is the most accurate. For answering this question we performed another prediction with a simplified model assuming a fixed value of k = 1.42 which was the mean of values in the study. Actually results showed that even if red cell rigidity does not enter in the model for prediction, it remains a determinant of the discrepancy between predicted and actual optimal hematocrit. With the model at fixed 'k' agreement between predicted and actual values for both h/η and hct is markedly decreased. Correlations between predicted and actual h/η became with this simplified model; in all subjects: $r = 0.370$; $p < 0.01$; in controls: $r = 0.281$; $p < 0.01$; in overweight: $r = 0.405$; $p < 0.01$; in obese: $r = 0.466$; $p < 0.01$). For the prediction of 'optimal hematocrit'; in all subjects: $r = 0.154$; NS; in controls: $r = 0.136$; NS; in overweight: $r = 0.098$, NS; in obese: $r = 0.216$, NS). Furthermore, with this model using a fixed

value of 'k', actual RBC rigidity remains a predictor of the discrepancy between actual and predicted h/η (Fig. 5). The model with fixed 'k' gives a prediction of 'optimal hematocrit' completely different from that of the full model (correlation between the two predictions). Nevertheless discrepancies for h/η (with both models are strongly related ($r = 0.981$; $p < 0.001$) to each other, as did discrepancies for optimal hct with both models ($r = 0.976$; $p < 0.001$) to each other. Thus fixing 'k' has not suppressed them.

4. Discussion

This study shows that construction of the bell-shaped curve of h/η with Quemada's equation is predictor of a 'theoretical optimal h/η' and a 'theoretical optimal hematocrit'. Modeling yields on the average the same value of theoretical optimal h/η and hematocrit across BMI classes. Both theoretical predictions of h/η and hematocrit are well correlated to the actual values measured in venous blood but actual h/η is always higher than the theoretical h/η in all groups and actual venous hematocrit is lower by 13% on the average compared to this optimal value. Discrepancy between optimal and actual h/η and hematocrit are negatively correlated to RBC rigidity indexes even if the model uses a fixed value of these indexes and are thus not due to inappropriate inclusion of red cell rigidity in the predictive model.

In a preceding study on rugby players [4] using the same approach for prediction optimal h/η and hematocrit with Quemada's equation, we also reported fair correlations between predicted and actual h/η with r coefficients of $r = 0.998$ (pre-exercise) and $r = 0.985$ (post-exercise), as well. Hematocrit was also well predicted by the model ($r = 0.547$). In another study on professional soccer players [5] predicted and actual hematocrit were also well correlated ($r = 0.644$). On the whole the agreement we find in this study on sedentary lean or obese subjects is similar ($r = 0.624$), but the discrepancy between theoretical and actual hematocrit is higher than in athletes.

This means that Quemada's equation provides a prediction of the optimal hematocrit that fits with what is observed in reality. However the true hematocrit is lower than the predicted optimal hematocrit, and is much lower in sedentary than in athletes.

In the study on rugby players we found that the discrepancy between predicted and measured hematocrit was strongly correlated the exercise-induced change ($r = 0.858$) in red cell rigidity. In another study on recreational athletes hematocrit response was correlated with this discrepancy [6]. This may suggest that the body sets hematocrit lower than ideal in order to maintain the possibility of increasing viscosity factors during exercise without inducing an excessively high blood viscosity that would impair O_2 transfer to tissues. Accordingly, animal studies suggest that very athletic species like camels have their hematocrit exactly set at the optimal value and do not further increase their hematocrit during exercise. We may hypothesize that the same is true in humans and that sedentarity increases the gap between theoretical and optimal hematocrit in order to cope with the need of increasing viscosity factors during exercise, and that training decreases this gap because exercise induced increase in viscosity factors will not result in values of viscosity that could impair O_2 transfer.

Interestingly, red cell rigidity in both athletes and sedentary subjects is a major determinant of this reduction of hematocrit below the ideal predicted value. Other factors observed in our previous studies were blood pressure and overtraining, that both result in an hematocrit more lower than predicted.

A surprising finding is that actual h/η is higher than predicted in our sample of sedentary subjects while it is lower in the various samples of trained athletes we studied. In fact in our three studies on athletes predicted h/η and actual h/η are quite close; in soccer players: 14.61 vs 13.88; in rugby players: 14.80 vs 14.77; in a sample of 19 recreational athletes presented in the Lisbon meeting [6]:

13.65 and 13.48. By contrast the difference in sedentaries was greater: 15.8 vs 16.74. Therefore in trained individuals the difference ranges between 0.2 and 5% while it is close to 6% in sedentaries. It is likely that this is to some extent explained by the level of training but at this time the explanation for this finding remains unclear.

We should only briefly comment the relevance of measurements performed on venous blood with viscometry at high shear rate. It is classically said that arterial hematocrit is lower than venous hematocrit but this difference is not always evidenced in recent studies, and interestingly the correlation between venous and arterials hematocrits is very high ($r = 0.990$) [2]. Therefore, venous haematocrit is a correct approach of systemic haematocrit and this is further demonstrated by the relevance of h/η to the prediction of vascular risk concerning mostly the arterial bed [8, 20]. This also gives a rationale to measurements at high shear rate which do not reflect the flow condition in the venous circulation but yield a more interpretable bell-shaped curve of h/η vs haematocrit [13] and thus a more precise calculation of the optimal hematocrit.

5. Conclusions

Therefore, keeping in mind that the optimal hct should not be the same in the various parts of the vascular bed, its theoretical prediction with Quemada's equation appears to predict a value higher than actual hematocrit but well correlated to it, and the agreement between optimal and actual hct is dependent on RBC flexibility. Mechanisms underlying discrepancies between actual vs optimal hematocrit (and actual vs optimal h/η) clearly need to be more extensively investigated. This study, put together with our other ones in athletes and fetuses, support the assumption that the prediction of ideal h/η and hematocrit with Quemada's equation and the analysis of factors explaining discrepancies between predicted and actual values is relevant to physiology and pathophysiology.

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