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Is there a relationship between the hematocrit-to-viscosity ratio and microvascular oxygenation in brain and muscle?

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Abstract. The hematocrit-to-viscosity ratio (HVR) has been widely used as an estimate of red blood cell (RBC) oxygen transport effectiveness into the microvasculature or as an oxygen delivery index. However, no study investigated the possibility of HVR to truly reflect RBC oxygen transport effectiveness or to be an oxygen delivery index. We measured blood viscosity at high shear rate (225 s^{-1}), hematocrit, HVR, as well as the microvascular oxyhemoglobin saturation (TOI; tissue oxygen index) by spatial resolved near-infrared spectroscopy (NIRS) at cerebral and muscle levels in three population known to have various degrees of hemorheological abnormalities: healthy subjects (AA), patients with sickle cell SC disease (SC) characterized by moderate anemia and patients with sickle cell anemia (SS) marked by severe anemia. At both the cerebral and muscle level, HVR was positively correlated with TOI ($r=0.28$; $p=0.03$ and $r=0.38$; $p=0.003$, at the cerebral and muscle level, respectively). These findings suggest that HVR probably play a key role in blood flow and hemodynamic regulation in the microvasculature, hence modulating the amount of oxygen available for tissues. Nevertheless, the strengths of the associations are weak ($R^2 < 0.50$), suggesting that other determinants modulate microvascular blood flow and oxygenation, such as vascular geometry and vasomotor reserve.

Keywords: Microvascular oxygenation, sickle cell syndromes, hemorheology

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1. Introduction

The benefits of increased hematocrit on blood oxygen transport can be challenged, if too high, by the resulting increased blood viscosity and resistance to flow [23]. Therefore, in the last decade, the hematocrit-to-viscosity ratio (HVR) has been widely used as an estimate of red blood cell (RBC) oxygen transport effectiveness into the microvasculature [1, 3, 4, 8, 21, 27, 28, 32]. Bowers et al. [3, 4] also proposed to use the term “oxygen delivery index” to define the HVR index. Indeed, the HVR is thought to reflect a balance between blood oxygen carrying capacity (i.e., hematocrit) and blood flow resistance (i.e., blood viscosity): the highest the HVR, the greatest the RBC oxygen transport effectiveness. One may note that: 1) HVR is derived from the systemic hematocrit values and not from the lower microvascular hematocrit values [16, 18] and 2) the critical hematocrit (i.e. the minimal hematocrit which guarantees a stable and adequate oxygen partial pressure in a given tissue) is dependent on the organ considered [13]. This probably constitutes a limitation to the HVR concept. However, microvascular hematocrit in humans is not easy to measure. Except for one study which previously investigated the relationship between HVR and the transcutaneous oxygen pressure in a small group of patients with peripheral occlusive arterial disease [9], no other study investigated the possibility of HVR to truly reflect RBC oxygen transport effectiveness or to be an oxygen delivery index.

The aim of the present methodological study was to test the reliability of the HVR ratio to assess the oxygen transport effectiveness into the microvasculature. We compared the HVR, as well as the microvascular oxyhemoglobin saturation (TOI; tissue oxygen index) measured with spatial resolved near-infrared spectroscopy (NIRS) at cerebral and muscle levels, between three population known to have various degrees of hemorheological abnormalities: healthy subjects (AA), patients with sickle cell SC disease (SC) characterized by moderate anemia and patients with sickle cell anemia (SS) marked by severe anemia. HVR and NIRS parameters were tested for correlations. The TOI measured by NIRS is a robust metric of tissue oxygen supply-demand balance [10, 22].

2. Material and methods

2.1. Patients

This study is a part of the SPIR project [33, 34] and was performed on sixty-two age- and ethnicity-matched volunteers: 20 healthy subjects with no hemoglobinopathy (AA; 10 males and 10 females; 34.7 ± 11.9 yrs), 21 patients with sickle cell-hemoglobin C disease (SC; 10 males and 11 females; 35.9 ± 12.2 yrs) and 21 patients with sickle cell anemia (SS; 11 males and 10 females; 33.6 ± 11.9).

Both SS and SC patients recruited are regularly followed by the Sickle Cell Unit of the Academic Hospital of Pointe-à-Pitre (Pointe-à-Pitre, Guadeloupe). All participants were over 18 yrs and were Afro-Caribbean native from Guadeloupe. Patients with sickle cell disease (SCD) were in clinical steady state at the time of the study (i.e., without vaso-occlusive crisis, recent infectious episode, acute medical complication or blood transfusion/phlebotomies within the last 3 months). Exclusion criteria for all subjects were α -thalassemia, stroke or cerebral vasculopathy history, pregnancy or breast-feeding. Patients taking medication that could affect the hemorheological parameters studied, such as hydroxyurea, were also excluded. All participants received verbal and written explanation of the objectives and procedures of the study and subsequently provided written informed consent. This study was approved by the Regional Ethics Committee (CPP Sud-Ouest Outre-Mer III, Bordeaux, France). The experiments were performed in accordance with the guidelines set by the Declaration of Helsinki.

2.2. Protocol

For each participant, venous blood was sampled in EDTA tubes from the antecubital vein to measure hematocrit and blood viscosity. Then, healthy subjects and SCD patients were placed in a normalized sitting position (thighs-trunk angle of 110° and forearm at heart level to avoid venous pooling of the blood) for 10 min prior the near-infrared spectroscopy (NIRS, NIRO-200, Hamamatsu Photonics, Hamamatsu City, Japan) measurements. The experiment started with a 10-min muscle tissue oxygenation index (TOI) measurement at a sampling frequency of 6 Hz.

2.3. Near-infrared spectroscopy (NIRS) and determination of the muscle and cerebral microvascular oxygenation (TOI)

NIRS techniques have been described elsewhere [10, 22]. Briefly, NIRS principle is based on the relative transparency of tissue to light in the near-infrared region between 700 nm and 1000 nm, and on the oxygen-dependent absorption changes of hemoglobin. NIRS can be used in sickle cell patients since the near-infrared spectra absorbance of hemoglobin S is similar to the one of normal hemoglobin [20].

The tissue oxyhemoglobin saturation expressed as a tissue oxygenation index (TOI) was measured continuously and simultaneously throughout the experiment at the flexor digitorum superficialis muscle and prefrontal cortex level at 6 Hz using two channels of a three-wavelength (775 nm, 810 nm, 850 nm) high temporal resolution NIRS device (NIRO-200, Hamamatsu Photonics, Hamamatsu City, Japan). The TOI is given by (oxyhemoglobin/total hemoglobin) \times 100. The TOI value reflects oxygen saturation in the whole microcirculation (i.e., pre-capillary arterioles, capillaries and post-capillary venules) at the local region between emission and detection optodes. TOI has been shown to be independent of skull thickness and of the area of the cerebrospinal fluid layer underlying the probe since this variable is measured by spatial resolved spectroscopy [35]. To maintain the oxygen demand constant in order to evaluate oxygen supply only (i.e., oxygen transport effectiveness), we made the TOI measurements at rest.

At muscle level, the center of the NIRS probe was placed on the flexor digitorum superficialis muscle at the proximal third of the forearm. At brain level, the probe was fixed on the forehead at prefrontal cortex level between Brodmann Area 10 and Brodmann Area 46 to avoid sagittal and frontal sinuses. The two probes were firmly attached with an inter-optode distance of 4 cm by means of a medical adhesive (Hamamatsu Photonics, Massy, France).

2.4. Hematological and hemorheological parameters

Hematocrit and blood viscosity were measured within the four hours after sampling and after full re-oxygenation of blood for 10–15 min, as recommended by the international guidelines for hemorheological laboratory techniques [2]. Hematocrit was measured after blood microcentrifugation at 9500 g for 10 min (JOUAN-HEMA-C, Saint Herblain, France). Blood viscosity was measured at $\approx 25^\circ\text{C}$ and native hematocrit using a cone-plate viscometer (Brookfield DVII + with CPE40 spindle) at 225 s^{-1} . Then, HVR at 225 s^{-1} was calculated as follows: hematocrit/blood viscosity at 225 s^{-1} .

Table 1
Hematological, hemorheological and microvascular oxygenation parameters

	AA	SC	SS
Hematocrit (%)	41.9 ± 3.2	32.3 ± 2.8***	25.2 ± 4.2***†††
Blood viscosity (cP)	6.4 ± 1.1	7.8 ± 1.2***	6.3 ± 1.5†††
HVR	6.8 ± 1.2	4.1 ± 0.6***	4.2 ± 1.1***
Muscle TOI (%)	63.2 ± 6.0	60.9 ± 7.9	53.0 ± 6.9***†††
Cerebral TOI (%)	72.9 ± 6.4	67.9 ± 8.3	56.1 ± 11.3***†††

Values represent mean ± S.D. HVR = hematocrit-to-viscosity ratio, TOI = Tissue Oxygen Index. Different from control group (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$); different from SC group († $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$).

2.5. Statistics

All values were expressed as means ± standard deviations. The data were tested for the normality (Kolmogorov-Smirnov test) and homogeneity of variance (Levene test). Hematocrit, blood viscosity, HVR at 225 s⁻¹ and microvascular oxygenation parameters were compared between the three groups using a one-way analysis of variance (ANOVA) followed by a Newman-Keuls *post-hoc* test. When the rules for parametric test application were not fulfilled, a Kruskal-Wallis test followed by Dunn's multiple comparison tests was used. Pearson correlation tests were used to test the association between HVR at 225 s⁻¹ and muscle or cerebral TOI determined by NIRS.

The significance level was defined as $p < 0.05$. Analyses were conducted using SigmaStat (v. 3.5, Systat Software GmbH, Erkrath, Germany).

3. Results

The Table 1 shows hematological, hemorheological and microvascular oxygenation parameters. Hematocrit was different between the three groups with AA > SC > SS. Blood viscosity was higher in SC patients compared to both AA and SS patients. HVR at 225 s⁻¹ was lower in both SC and SS patients compared to AA subjects. Muscle and cerebral TOI were lower in SS patients compared to both AA and SC patients. At the cerebral level, the TOI tended to be lower in SC patients compared to AA subjects ($p = 0.08$).

At the cerebral level, HVR was positively correlated with cerebral TOI ($r = 0.28$; $p = 0.03$) (Fig. 1). At the muscle level, HVR was also positively and significantly correlated with muscle TOI ($r = 0.38$; $p = 0.003$) (Fig. 2).

4. Discussion

This study investigated the possibility of using the hematocrit-to-viscosity (HVR) ratio as an index of RBC oxygen transport effectiveness into the microvasculature or RBC oxygen delivery. We showed that the HVR measured at high shear rate was lower in sickle cell patients compared to healthy subjects. This result may be explained by the fact that HVR calculated from blood viscosity at high shear rate is largely influenced by RBC deformability, which is very reduced in sickle cell patients compared to healthy subjects. It is well known that, for a given hematocrit, sickle cell patients are characterized by higher blood viscosity than healthy subjects because of the reduction of RBC deformability. The present results are in accordance with previous studies [3, 28].

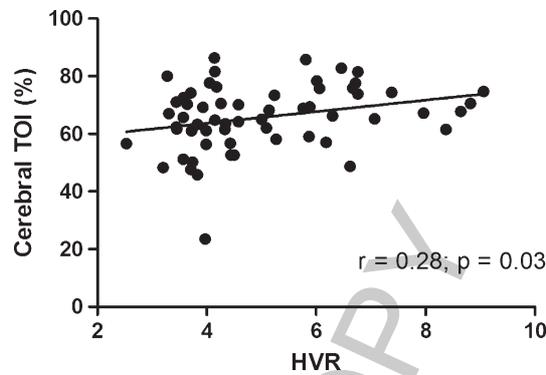


Fig. 1. Relationship between HVR and cerebral TOI.

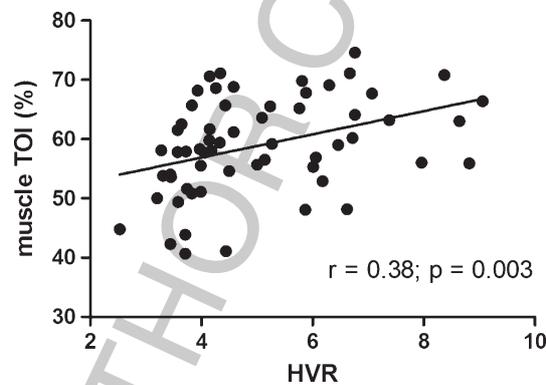


Fig. 2. Relationship between HVR and muscle TOI.

One of the major assumption in the definition of the HVR concept is that, according to the Poiseuille' law [23], the resistance to blood flow is proportional to blood viscosity. Although a rise of hematocrit may be accompanied by greater blood oxygen content, the resulting increased blood viscosity and blood flow resistance may counteract the benefits of increased hematocrit, hence resulting in the alterations of microvascular and tissue oxygenation. It has been previously shown - in patients with peripheral arterial occlusive disease [14, 15] and mice [25] - that performance and oxygen partial pressure in the skeletal muscle decrease with both increasing and decreasing hematocrit. These findings suggest the existence of an optimal hematocrit value for blood oxygen carrying capacity and delivery to tissues. A low HVR would indicate poor RBC oxygen transport effectiveness while elevated HVR would be favorable to high RBC oxygen transport effectiveness and delivery to tissue.

However, a limit to this concept could be that blood vessels are not rigid glass cylinder and vascular geometry may adapt continuously, when vascular function is intact [19], to compensate for the increase of blood flow resistance caused by the high hematocrit and blood viscosity. Several studies showed that an increase of blood viscosity is not always accompanied by an increase of blood flow resistance [6, 7, 11, 12, 24, 26] because the resulting higher shear stress exerted on the endothelium, and on RBCs, stimulates the production of nitric oxide, thus leading to vasodilation and improved blood flow and oxygen delivery to tissues [7, 11, 12, 24, 29, 31].

Nevertheless, we found significant correlations between HVR and muscle TOI or cerebral TOI in our population. These findings suggest that HVR probably play a key role in blood flow and hemodynamic regulation in the microvasculature, hence modulating the amount of oxygen available for tissues. Because blood viscosity was measured at high shear rate, RBC aggregates were probably dispersed and the associations found between HVR and TOI mainly reflect the ability of single RBCs to deform and reach the tissues to diffuse their oxygen. Further studies are needed on larger cohorts (>50 individuals per group) to test whether the associations observed in the whole population persist in each sub-population.

One of the limitations in this study is that blood viscosity was measured *in-vitro* using a cone-plate viscometer. This approach does not take into account several *in vivo* phenomena such as those occurring in the microcirculation like the Fahraeus-Lindqvist effect and the presence of a cell free plasma layer caused by the axial migration of the flowing RBCs. In this latter case, plasma viscosity plays a key role in regulating blood flow resistance in microcirculation and tissue oxygenation [5, 17, 29, 30].

In conclusion, although it is evident that HVR plays a key role in the RBC oxygen transport effectiveness into the microvasculature [14, 15, 25], the strengths of the associations found are weak ($R^2 < 0.50$), suggesting that other determinants modulate microvascular blood flow and oxygenation, such as vascular geometry and the ability of the vascular function to adapt its response to the decrease or increase of the blood viscosity.

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