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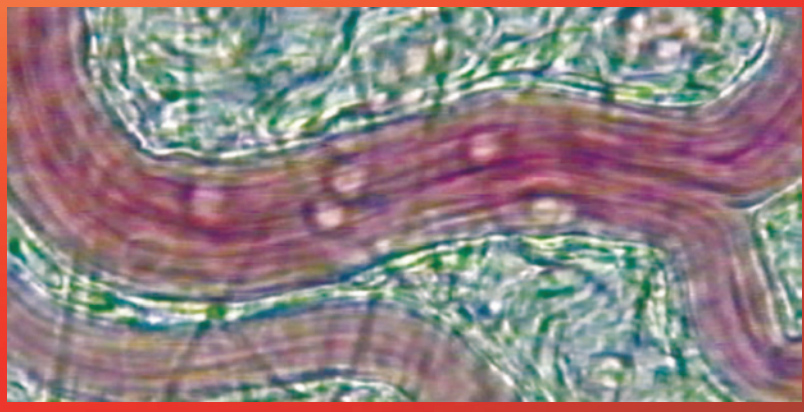

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Boletim da Sociedade Portuguesa de Hemorreologia e Microcirculação

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Sociedade Portuguesa de Hemorreologia e Microcirculação

Presidentes Honorário: Prof.ª Doutora Carlota Saldanha e Prof. Doutor João Martins e Silva

Referência da capa: Vénula pós-capilar (diâmetro aproximado: 30 mm) de rede microvascular em mesentério de rato (*Rattus norvegicus*), observada por microscopia intravital de transiluminação. No interior do vaso sanguíneo visualizam-se leucócitos a interagir com a parede vascular. Imagem obtida por Henrique Sobral do Rosário (Instituto de Biopatologia Química – Prof.ª Doutora Carlota Saldanha, Faculdade de Medicina de Lisboa; Unidade de Biopatologia Vascular, Instituto de Medicina Molecular)

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UM NOVO NORMAL…

Uma expressão que tanto se ouve nos dias que correm e que nos chama a atenção para estes tempos diferentes em que vivemos e que em tanto nos afeta. Mas mais ou menos prejudicados, afetados ou até mesmo cansados deste "novo normal" aqui está mais um boletim da SPHM, porque tudo o que queremos é voltar a fazer tudo igual. E o segundo boletim deste ano da SPHM traz já os novos órgãos desta nossa sociedade. E por isso deixem-me apresentar-me brevemente. Sou formada em Química Aplicada, o que à partida não se relaciona com hemorreologia ou microcirculação, mas após um fantástico estágio na área da microcirculação ganhei o gosto por esta área do conhecimento. Mas foi, sem dúvida, o constante entusiasmo da Professora Carlota Saldanha que me motivou a procurar, estudar e aprender mais; e é por isso que hoje aqui estou como Presidente da SPHM. E não estou por ser mais um cargo, ou porque até fica bem no CV, estou porque sinto que tenho algo a dar à comunidade científica ao divulgar e fazer crescer a hemorreologia, a microcirculação e a SPHM. Tal como disse a Professora Carlota Saldanha no nosso anterior boletim, todos e cada um dos eleitos em conjunto está motivado, atento e apto a contribuir com perguntas e propostas de estudos nestes campos tão vastos e fundamentais que são a hemorreologia e a microcirculação. Gostaríamos de ver esta sociedade a ser mais falada e mais acariciada pela sociedade científica em geral. Gostaríamos de apoiar mais jovens cientistas em congressos nacionais e internacionais. Gostaríamos de ter mais apoios financeiros para projetos de hemorreologia e/ou microcirculação. Aqui fica a nossa motivação e o que gostaríamos de fazer e para o qual vamos trabalhar. Afinal, quando um homem sonha, o mundo pula e avança. Precisamos, é claro, da ajuda de todos e todas as contribuições são bem-vindas, por isso ficamos à espera das vossas ideias, dos vossos comentários, dos vossos artigos. Até breve!

Ana Silva-Herdade
Presidente das SPHM

HEMORHEOLOGICAL PROFILES OF PERSONS WITH DIFFERENT LEVELS OF AEROBIC POTENTIAL OF THE ORGANISM: CELLULAR MICRORHEOLOGICAL MECHANISMS OF CHANGES

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ABSTRACT

Aim: The study of hemorheological profiles of persons with different levels of aerobic potential of the organism and analysis of mechanisms of cellular microrheological alterations. **Method:** 36 subjects were divided into three groups according to the level of maximum oxygen consumption (VO_2-max). The groups were selected: group 1 with a relatively low VO_2-max, group 2 with an average VO_2-max and group 3 with a relatively high VO_2-max. The parameters of the hemorheological profile were recorded. In experiments in vitro, red blood cells (RBCs) were incubated with hormones (adrenaline, insulin, and glucagon), with prostaglandins and donors of gasotransmitters (GT): sodium nitroprusside, sodium hydrosulfide, and CO donor (CORM-3). After incubation with GT, the deformability RBCs (RBCD) and their aggregation (RBCA) were recorded. **Results:** It was found that in individuals with a higher VO_2-max, the blood viscosity is significantly lower due to the lower plasma viscosity (PV) and the greater RBCD. Reduced RBCA was also observed. A significant contribution of erythrocyte microrheology to the improvement of blood fluidity and its O_2- transport efficiency in has been shown. A significant positive effect on RBCD of epinephrine, insulin and glucagon, as well as prostaglandin E_1 was established. At the same time, epinephrine and the alpha-1-AR agonist phenylephrine increased RBCA; the same effect was exhibited by prostaglandin $F_{2\alpha}$. All three gasotransmitter donors (NO, H2S and CO) increased RBC deformability and decreased aggregation. **Conclusion:** This study showed a certain degree of relationship between O_2-transport and blood rheology. Since the role of RBC microrheology with the whole blood fluidity and its transport potential has been established, the possibility of a short-term regulatory change in the microrheological RBC characteristics under the influence of different classes of signaling molecules has been demonstrated.

Key words: hemorheological profile, red blood cells, deformability, aggregation, oxygen transport, signaling molecules

INTRODUCTION

Oxygen is transported to the tissue microregions by the vascular system and blood. The most important function of the blood is its fluidity, as inverse value of blood viscosity. There is a close inverse correlation exists between changes in viscosity and blood flow[1]. In turn, viscosity as an integral blood rheological characteristic depends on plasma viscosity, hematocrit, aggregation, erythrocyte deforma-

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bility and on shear conditions[2]. Red blood cell (RBC) aggregation and deformability refer to the microrheological characteristics of blood[3]. Despite the simplicity of the construction, mature erythrocytes retained many elements of signaling cascades[4]. Consequently, for the solution of short-term adaptive tasks – for the transport of respiratory gases in the blood oxygen delivery system, erythrocytes are target cells for the action of signaling molecules. In this case, both endocrine signaling pathways and para--and autocrine signaling pathways can be realized. The presence of adrenergic receptors and insulin receptors on the RBC membranes[5,6] allows cells to respond to adequate stimuli with microrheological changes[7]. In recent decades, gaseous mediators (gasotransmitters, GT), such as nitric oxide, hydrogen sulfide and carbon monoxide, have been of great interest[8,9]. There is evidence of a positive effect of these compounds not only on blood vessels, but also on blood cells [10-12]. GT can enter the cell from outside, as well as be synthesized by cells in the course of metabolism and implement autocrine pathways for the delivery of signaling molecules[9].

METHODS

Ethical approval

The study was approved by the local Ethical Committee of the University (Protocol no. 4 of 12.06.2020). The Informed consent of all donors was obtained in accordance with the recommendations of the Helsinki Declaration (WMA Helsinki Declaration on Ethics. Principles of human health research, as amended by the 64th General Assembly of the WMA, Fortaleza, Brazil, October 2013).

Selection of Subjects

A total of 36 healthy male volunteers, aged 20 to 30 years were enrolled in the study. Of these, 3 groups were formed based on the determination of the maximum oxygen consumption (VO_2-max): 1) group 1 (VO_2-max from 30 to 40 ml O_2 kg/min, n=12); group 2 (VO_2-max from 41 to 50 ml O_2/ kg/min, n=12); group 3 (VO_2-max from 51 to 60 ml O_2/kg/min, n = 12). VO_2-max was determined by exercise testing on a bicycle ergometer (Monarh 939E).

Sample preparation and hemorheological measurements

Whole blood samples (9 mL) from healthy donors (n = 20) were drawn via venipuncture into vacuum tubes with EDTA. The RBCs were separated from plasma by centrifugation (15 min at 1500 rpm), washed in isotonic NaCl solution and resuspended in Ringer's solution with the addition of dextran 150 (10% HAES--steril, Fresenius Kabi, Germany) up to 40% hematocrit (Hct) for the following incubation with drugs and registration of macro- and microrheological parameters. The viscosity of this fluid was 1.30 mPas.

Whole blood (BV) and plasma (PV) viscosity were measured with Brookfield viscometer (DV2T LV; torque is equal to 0.0673 mNm). Blood viscosity was measured at high, 300 sec^{-1} (shear stress = 1.29 N / m2) and low shear rates, $5c^{-1}$ (shear stress = 0.06 N/ m^2). Plasma viscosity (PV) was measured at a high shear rate (250 s^{-1}). The hematocrit/blood viscosity ratio (Hct/BV_h), an index of oxygen supply to tissue, was calculated according to J.F. Stoltz[13].

Red blood cell aggregation in native plasma was assessed by the Myrenne aggregometer which provides an index of RBC aggregation facilitated by low shear. In brief, the suspension was subjected to a short period of high shear to disrupt pre-existing aggregates, following which the shear was abruptly reduced to 3 s^{-1} and light transmission through the suspension that was integrated for ten seconds; the resulting index, termed «M2» by the manufacturer and «RBCA» herein, increased with enhanced RBC aggregation.

In vitro study of microrheological responses of erythrocytes to the action of signaling molecules

To assess the effects of signaling molecules on the RBC deformability (RBCD) and their aggregation (RBCA) cells were incubated for 30 min at 37°C with:

1. *Hormonos and some agonists of their membrane receptors*
   - 1.1. epinephrine (1.0 M);
   - 1.2. phenylephrine, agonist of alpha -1-adrenergic receptors (1.0 μM);
   - 1.3. metaproterenol, agonist of beta -2- adrenergic receptors (1.0 μM);
   - 1.4. insulin (0.1 μM);
   - 1.5. glucagon (10.0 μM);

2. *Prostaglandins*
   2.1. prostaglandin E1 (PGE1, 0.1 μM);
   2.2. prostaglandin F**2α** (PG F**2α,** 0.1 μM);

3. *Gasotransmitter donors*
   3.1. sodium nitroprusside, as NO donor (SNP, 100 μM);
   3.2. sodium hydrosulfide H_2S donor (NaHS, 100 μM);
   3.3. Tricarbonylchloro(glycinato)ruthenium (II) (CORM-3, 50 μM);

4. Only in Ringer's solution (without any drug) - control samples.

RBC suspension incubated the same way (duration and temperature) but in a drug-free buffer solution was used as a control sample. All analyses were performed within 4 h after the blood withdrawal. Reagents were purchased from Sigma-Aldrich (USA).

Red blood cell aggregation was assessed by the Myrenne Aggregometer. The resulting index, termed «M10» by the manufacturer and «RBCA» herein, increased with enhanced RBC aggregation.

A parallel plate microflow channel was used to estimate red blood cell deformability. In brief, the cells were attached to bottom part of the chamber with "one point" and then they were deformed by shear flow, under constant shear stress (0.54 N/m^2). The length (L) and width (W) of each of about hundred cells were measured and the elongation parameter of single RBCs elongated with shear stress was calculated as an index of red blood cell deformability (RBCD) according to:

$$RBCD = L/W,$$

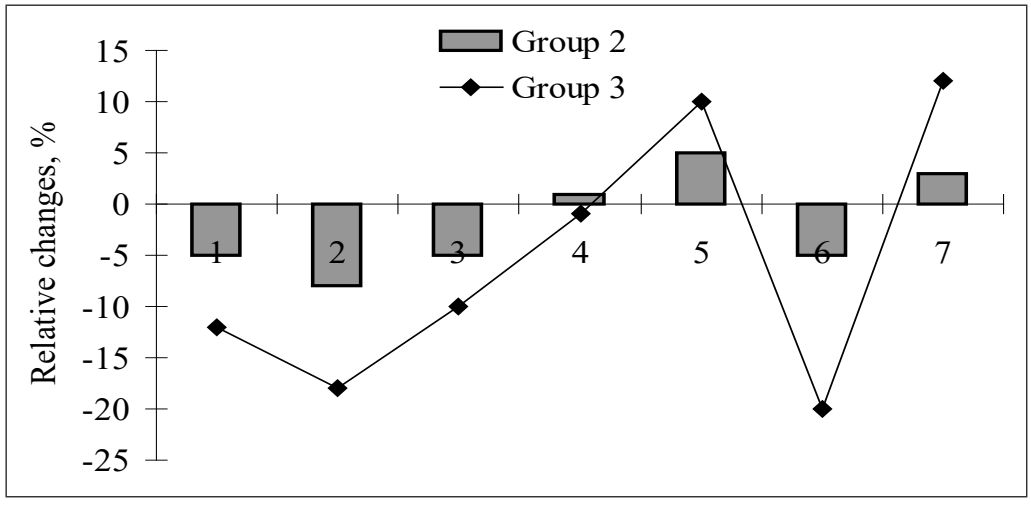
where L is length of elongated RBC, W is their width[14].

The reliability of the method for assessing erythrocyte deformability is well confirmed by the regression relationship between the specified shear stress values (from 0.36 to 1.80 N/m^2) and the obtained erythrocyte elongation indices

RESULTS

Macro- and microrheological characteristics of hemorheological profiles in individuals with different levels of aerobic potential of the body

Analysis of hemorheological profiles in individuals of three groups with different levels VO_2-max showed that the viscosity of whole blood at a high shear rate in the first group was 4.90 ± 0.11 mPa·s. In the second group, this characteristic was 5% ($p < 0.05$) less. In the individuals of group 3 with the highest O_2-transport, the BV was 12% ($p < 0.01$) lower than in the comparison group (group 1). These differences in the value of the



Note: 1 – blood viscosity under relative higher shear rate; 2 – blood viscosity under relative lower shear rate; 3 – plasma viscosity; 4 – hematocrit (Hct); 5 – red blood cell deformability (RBCD); 6 – red blood cell aggregation (RBCA); 7 – index Hct/blood viscosity (BVh at higher shear rate).

Figura 1. Relative changes (in% to the data of group 1) of the parameters of the hemorheological profile in individuals of groups 2 and 3 relative to the data of group 1 taken as the zero line in this figure.

integral hemorheological characteristic – blood viscosity were combined with a significant difference in plasma viscosity and, which is especially important, with more effective microrheological characteristics (Fig. 1).

Thus, red blood cell deformability (RBCD) in individuals with high VO_2-max was 10% ($p < 0.01$) more than that of group 1, and their aggregation (RBCA) was 20% less ($p < 0.01$). The index of blood oxygen transport efficiency (Hct/BV ratio) in groups 2 and 3 was 3 and 12%, respectively, higher than in group 1. This indicator significantly correlated with the RBCD ($r = 0.76$). In addition, a correlation between RBCD and VO_2-max was established with a coefficient of 0.58. It should be noted that the Hct/BV index also significantly correlated with the VO_2-max ($r = 0.66$). Another microrheological characteristic – RBCA, although it was significantly lower in individuals with a high aerobic potential of the body, did not significantly correlate with the value of the VO_2-max (the correlation coefficient did not exceed 0.23).

It should be noted that some RBC microrheological characteristics and especially their deformability significantly correlated with the viscosity of whole blood. In three different groups, the correlation coefficients were from 0.48 to 0.62. Therefore, it can be assumed that a change in the RBC microrheology contributes to the whole blood fluidity and its O_2-transport capabilities. It is important to note that in the flowing blood, only cells (erythrocytes in this case) can change their properties under the action of signaling molecules. It can be investigated on models RBC microrheological responses to the action of endo-para- and autorcrine signaling agents.

Molecular mechanisms of red blood cell microrheology changes

Effects of epinephrine

An increase in the body's activity, for example, under stress or muscle exercising, occurs when catecholamines are mobilized. They enter the general blood flow and become available to blood cells, including RBCs. The latter have both types of adrenergic receptors - alpha and beta-adrenergic receptors[15,16]. Therefore, it can be assumed that, for example, epinephrine will have a direct effect on the RBC microrheology. Indeed, it was found that after incubation with epinephrine at a micromolar concentration, the RBCD increased by 8-10%. Whereas their aggregation increased more significantly by 26% compared to control (Table 1, $p<0.05$).

Selective stimulation of alpha-1-AR with phenylephrine was accompanied by a pronounced increase in aggregation, by 50% ($p < 0.01$), while the deformability of the cells was almost unchanged (Table 1). On the other hand, if beta-2-adrenergic receptors are stimulated, then there is a pronounced increase in deformability by 14% and a decrease in their aggregation by 10% ($p < 0.05$).

The alterations the RBC microrheological characteristics under insulin and glucagon

On mature erythrocytes, insulin receptors are exposed[17]. The RBC incubation with insulin was accompanied by a pronounced increase in RBCD by 15% and a decrease in aggregation by 32% (Table 2; $p < 0.01$).

Table 1. Alterations of the red blood cell microrheological characteristics under epinephrine, pphenylephrine and metaproterenol (M±m, n=18)

Indexes	Control	Epinephrine 1.0 μM	Phenylephrine, 1.0 μM	Metaproterenol, 1.0 μM
RBCD, units	2.09±0.02	2.26±0,03**	2.03±0.03	2.39±0.03**
RBCA, units	6.98±0.14	8.79±0.76*	10.49±0.52**	6.28±0.19*

* $p < 0.05$ versus appropriate control; ** $p < 0.01$ versus appropriate control.
Notes: RBCA – red blood cell aggregation index (M10 – Myrenne Aggregometer); RBCD – red blood cell deformability (elongation index).

Table 2. Alterations of RBC microrheological characteristics under insulin and glucagon (M±m; n=18)

Indexes	Control	Insulin, 0.1 μM	Glucagon, 10.0 μM
RBCD, units	2.04±0,02	2.34±0.03**	2.18±0.04*
RBCA, units	6.32±0.24	4.29±0.28*	6.97±0.24*

* $p < 0.05$ versus appropriate control; ** $p < 0.01$ versus appropriate control.
Notes: RBCA – red blood cell aggregation index (M10 – Myrenne Aggregometer); RBCD – red blood cell deformability (elongation index).

In metabolic reactions, glucagon is a functional insulin antagonist[18]. It affected the RBCD in a manner similar to insulin, but less pronounced. The increase in this characteristic was 7%, which is two times less than under the action of insulin. As for the aggregation, after incubation with glucagon it increased by 10% (Table 2).

The alterations the RBC microrheological characteristics under prostaglandins

The receptors for prostaglandins of group E and prostacycline are coupled with adenylate cyclase[19] and, therefore, it can be expected that these paracrine agents, which are vasodilators, will have a significant effect on red blood cell microrheology. Indeed, RBC incubation with prostaglandin E_1 (PGE_1) significantly decreased their aggregation (by 24%, $p<0.05$), while deformability, on the contrary, significantly increased by 19% ($p<0.01$; Table 3). $PGF_{2\alpha}$ is a potent stimulator of calcium entry into cells, so its effects may be similar to that of phenylephrine. The results of the study showed that, in fact, $PGF_{2\alpha}$ strongly stimulated the RBC aggregation, by 77% ($p<0.01$), while their deformability slightly decreased, by 5% ($p<0.05$; Table 3).

The alterations the RBC microrheological characteristics under gasotransmitter donors (SNP, NaHS, CORM-3)

Para- and autocrine signaling molecules – gaseous mediators or gasotransmitters (GT) are present in RBCs and have a positive effect on their microrheological properties [20, 21]. RBC incubation with the NO donor sodium nitroprusside (SNP) resulted in an increase in cell deformability by 10% ($p<0.01$). Another microrheological characteristic, their aggregation decreased by 30% ($p<0.01$, Table 4).

The donor of another gasotransmitter – hydrogen sulphide, NaHS, upon incubation of RBCs in its presence, caused similar changes in the direction of cell microrheology (Table 4). At the same time, RBCD changes practically did not differ from those that were during RBC with SNP. Whereas the aggregation decreased markedly less, only by 22%, although it was significant (Table 4).

Upon incubation of RBCs with the CO donor CORM-3, their deformability increased only by 7% ($p<0.01$). While the aggregation was 35% reduced after incubation with the CO donor (Table 4).

CONCLUSION

The results of the study showed that in persons with more efficient transport and metabolism of oxygen in the body, blood exhibits a higher fluidity. This was evidenced by a 12% lower blood viscosity. This is quite typical for endurance athletes[22,23]. The blood viscosity reduction was accompanied by a decrease in PV, RBCA and a significant increase in their deformability. With regard to plasma viscosity, its contribution to changes in whole blood flow in individuals

Table 3. Alterations of RBC microrheological characteristics under prostaglandin E1 (PGE1) and $F_{2\alpha}$ ($PGF_{2\alpha}$, M±σ; n=18)

Indexes	Control	PGE1, 0.1 μM	$PGF_{2\alpha}$, 0.1 μM
RBCD, units	2.08±0,01	2.48±0,02**	1,98±0.02*
RBCA, units	7.02±0.32	5.35±0.26*	12.43±0.26**

* $p < 0.05$ versus appropriate control; ** $p < 0.01$ versus appropriate control.
Notes: RBCA – red blood cell aggregation index (M10 – Myrenne Aggregometer); RBCD – red blood cell deformability (elongation index).

Table 4. Alterations of RBC microrheological characteristics under gasotransmitter donors (SNP, NaHS, CORM-3; M±σ; n=18)

Indexes	Control	SNP, 100 μM	NaHS, 100 μM	CORM-3, 50 μM
RBCD, units	2.03±0.02	2.23±0.02**	2.24±0.04**	2.17±0.04*
RBCA, units	6.64±0.36	4.65±0.44*	5.05±0.28*	4.32±0.39**

* $p < 0.05$ versus appropriate control; ** $p < 0.01$ versus appropriate control.
Notes: RBCA – red blood cell aggregation index (M5 – Myrenne Aggregometer); RBCD – red blood cell deformability (elongation index); SNP – sodium nitroprusside; NaHS – sodium hydrosulphide; CORM-3 – tricarbonylchlor (glycinate) ruthenium (II).

with high VO_2-max was more significant than in individuals with relatively low body aerobic potential. This was indicated by the lower correlation between the viscosity of blood and plasma in the latter (r = 0.56 in group 1 and 0.78 in individuals in group 3). With similar hematocrit values in all three groups, the transport efficiency of blood, assessed by the Hct/BV index[13], depended on its viscosity, which was significantly reduced in group 2 and especially in group 3. At the same time, a significant correlation was found between Hct/BV and VO_2-max, and the latter - with the index of RBC deformability. These relationships are confirmed by other authors, e.g.[24].

Thus, positive changes in red cell microrheology were combined with a high level of oxygen transport. This raises the question of the short-term cellular mechanisms of changes in the RBC microrheological properties during the adaptation of the body to muscle load. Since mature erythrocytes have functionally active α- and β-AR[5,15,16], a regulatory change in the physiological state of these cells can be expected when binding to receptors of the corresponding agonist. The obtained results indicate that epinephrine at a concentration of 1.0 μM markedly increased the RBC aggregation and their deformability. The presence of both types of adrenergic receptors on the RBC membranes raises the question of possibly different effects of their separate stimulation. Indeed, incubation of cells with an alpha--1-AR agonist, phenylephrine was accompanied by a pronounced increase in RBCA and a slight decrease in RBCD. It is known that the α-1-adrenergic receptor is associated with the Ca^{2+} signaling pathway and, when stimulated, increases the entry of calcium into the cell[25,26]. Probably, the increase in RBCA under the influence of phenylephrine was associated precisely with the activation of the calcium regulation mechanism[7]. It is known that the membrane of mature erythrocytes contains both subtypes of beta-adrenergic receptors (beta-1 and beta-2-adrenergic receptors)[5,16]. In this case, beta-2-AR is exposed on the membrane of erythrocytes twice as much as the subtype of beta-1-AR. In view of the above, this type of receptor was stimulated by their agonist - metaproterenol. During RBC incubation with this compound RBCA decreased, and the deformability significantly increased. The activation of β-adrenergic receptors stimulates adenylate cyclase (AC) and increases the level of cAMP in the cell[27]. Subsequent activation by cAMP of protein kinase A (PKA) may be responsible for the increased plasticity of erythrocyte membranes[28]. It should be noted that prostaglandin E_1 had a similar effect to metaproterenol on the RBC microrheology since it also activates the adenylate cyclase system[29]. Prostaglandin from group F ($PGF_{2\alpha}$) showed a strong pro-aggregation effect. Aggregation rise exceeded 100% ($p < 0.01$). This RBC increase can be explained by the stimulation of Ca^{2+} entry into RBCs during their incubation with $PGF_{2\alpha}$[30].

Insulin significantly affected the RBC microrheology, while the aggregation decreased by 30%, and the increase of RBCD was 15%. One of the mechanisms of the effect of insulin on the RBC microrheological properties may be associated with its ability to activate protein kinase C (PKC-zeta), which is present in human erythrocytes[31]. The signaling pathway that can be realized by the action of insulin on RBCs includes the activation of PKC and membrane proteins: protein 3, 4.1R, and protein 4.9[32]. Phosphorylation of these proteins at serine-trionine (band 4,1R) or tyrosine (band 3) residues is accompanied by an increase in membrane plasticity and RBCD in general[33]. After RBC incubation with glucagon the change in microrheology was similar to the response of cells to epinephrine: a moderate increase in deformability and aggregation was observed. In a number of tissues, glucagon causes an increase in the formation of cAMP that is, it has an effect similar to the action of β-adrenergic receptor agonists, but without the involvement of β-adrenergic systems in the implementation of this effect.

On muscle blood flow is significantly affected by gaseous mediators. Most information is available on nitric oxide[34]. It was found nitric oxide (NO) modulates oxygen delivery-utilization matching in resting and contracting skeletal muscle. Recent reports indicate that neuronal NO synthase (nNOS)-mediated vasoregulation during contractions is enhanced with exercise training[35]. As for the positive microrheological responses obtained in the study of the donors of hydrogen sulphide and carbon monoxide, the details of the cellular signaling cascades involved in their effects are yet to be found. In addition, although NO, H_2S and NO modulate independent signaling pathways, there is some evidence of cross-talk between these three gasotransmitters[36,37].

Taken as a whole, we can conclude that the results of the study showed a certain degree of relationship

between O_2-transport and blood rheology. Since the role of RBC microrheology with the whole blood fluidity and its transport potential has been established, the possibility of a short-term regulatory change in the microrheological RBC characteristics under the influence of different classes of signaling molecules has been demonstrated.

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The author declares no conflict of interest.

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CORONA VÍRUS-19 E HEMORRELOGIA

*Carlota Saldanha**

A contaminação dos humanos pelo SARS-CoV2 ou doentes com COVID -19 originou inicialmente um afluxo extraordinário de doentes infetados que ficaram hospitalizados nas Unidades de Cuidados Intensivos com morte subsequente. A comunidade científica ficou em alerta desviando grande parte dos investigadores das suas áreas de trabalho para dar resposta às múltiplas perguntas que desde logo apareceram. Quais o sinais e sintomas, qual a composição e estrutura do SARS-CoV2, (o que é e como é), como entra no organismo, quais as células alvo, quais os mecanismos que expressam os vários sintomas e sinais manifestados, como diagnosticar, como tratar precocemente ou durante a hospitalização bem como quais as regras para evitar o contágio.

Limitando-nos ao título deste "Comentário" o vírus entra para o eritrócito (ou glóbulo vermelho) através da proteína membranar banda 3 tradicionalmente conhecida como o canal aniónico permutador entre os iões cloreto e bicarbonato[1]. O eritrócito é único transportador sanguíneo do COVID-19 que se conhece até à data. Após a saída do RBC o COVID -19 pode infetar as células dos tecidos dos órgãos corporais através da ligação ao recetor membranar da enzima conversora da angiotensina (ACE2)[2].

O eritrócito contendo o SARS-CoV2 aumentará a viscosidade interna contribuindo para a diminuição da sua deformabilidade (ED)[3]. A possibilidade de ocorrer entupimento nos capilares, componentes da rede sanguínea microvascular, pelos eritrócitos infetados aumenta e favorece a estase, dificulta capacidade de oxigenação ou mesmo nalgumas situações induz a instalação de hipoxia[4]. Esta propicia a disfunção endotelial com a geração do fator indutivo de hipoxia, aumenta a interação dos neutrófilos e células endoteliais com produção espécies reativas de oxigénio (ROS) e azoto (NORS) iniciando-se a resposta de fase aguda da inflamação[5].

Durante a permanência do SARS-CoV2 no interior do RBC há alteração da osmolalidade interna com repercussão no aumento da agregação eritrocitária (EA)[6].

Pelo exposto a permanência do SARS-CoV2 no interior do RBC desfavorece a normalidade de duas propriedades hemorreológicas ED e EA com possíveis repercussões na viscosidade sanguínea. Eventualmente porque se desconhecem os valores dos outros parâmetros hemorreológicos tais como o hematócrito, a viscosidade plasmática (VP) e o fibrinogénio. Será de prever valores da VP acima do normal por aumento da concentração plasmática do fibrinogénio[7]. O Fib é reconhecido como uma proteína de fase aguda da inflamação que responde à cascata dos fatores pró- inflamatórios com destaque para ainterleucina-6 implicada na estimulação da síntese e libertação do Fib para a circulação sanguínea. Os valores da concentração do Fib acima do intervalo da normalidade permanece na inflamação não resolvida ou crónica[7]

Poderá ocorrer hemólise com influência no mecanismo da eritropoiese e no conjunto aparentar o quadro clínico similar ao descrito para doentes com sépsis internados nas unidades de cuidados intensivos[8,9].

Porquanto a sépsis pode ocorrer por ausência de tratamento de ferida aberta na pele infetada, seria de advertir a existência dessa situação na lista das precauções na prevenção na disseminação do COVID-19. A dimensão estrutural da SARS-CoV2 permite-lhe entrar pelo processo de pinocitose semelhante ao das nanopartículas[10].

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Voltando ao início desta descrição além da boca e do nariz os olhos são acessos à entrada do SARS--CoV2 expelido pela tosse e ou pelo espirro de doentes infetados como explicado no artigo "*Erythrocyte a Target for Covid-19 Infected Patientes*" cujo Resumo se encontra neste Boletim[11].Mais uma explicação para a utilização de óculos que deveria estar na listagem da prevenção da propagação do SARS-CoV2.

O aumento dos NORS presente no endotélio disfuncional pode ser corrigido por fármacos que controlam os mecanismos de sinalização para a manutenção ou libertação do monóxido de azoto (NO) no pelo glóbulo vermelho[12]. Considerando que a SARS-CoV2 sai pela mesmo canal proteico aniónico, isto é proteína banda 3 o impedimento da saída é conseguido parcialmente pela hidroxicloroquina (HCQ) que se liga à extremidade N da banda3 deixando livre a extremidade C e o fármaco em alguns infetados pode não demonstrar 100%.de eficácia[13]. Eis aqui uma fonte de perguntas!

No entanto a ligação da HCO com a extremidade N da proteína banda 3 induz a desfosforilação desta com repercussão na face externa da membrana do eritrócito, nomeadamente a inibição da enzima acetilcolinesterase (AChE)[14]. Esta proteína da família das GPi apresenta dupla função, a de enzima e de recetor, que ao adotar a conformação menos ativa impede a saída do monóxido de azoto com consequente aumento de formação de NORS e ORS intraglobular de acordo com o mecanismo de transdução de sinal[10,14].

A permanência do SARS-CoV2 no interior do eritrócito em ambiente de incontrolável excesso de stress oxidativo, a corona vírus poderá ser destruída pelas várias enzimas intraglobulares. Esta hipótese carece de confirmação.

A SARS-CoV2 pode continuar em circulação através da ligação estabelecida entre a sua proteína "espiculada spike" e a proteína 147 presente na camada externa da membrana do eritrócito e dos glóbulos brancos[15]. O antibiótico ivermetina encobre o "spike" que deixa de ser reconhecido pela proteína 147, mas inibe a AChE sem impedir o efluxo do NO pelo eritrócito.[16,17]

A ivermetina possui a propriedade de inibir a proteína transportadora do SARS-CoV2 do citoplasma para o núcleo das células dos diferentes tecidos evitando a replicação do vírus[18].

Ainda a relembrar que a ivermetina inibe a agregação eritrocitária que está aumentada nos doentes infetados com o SARS-CoV2[19].

As alterações dos valores dos parâmetros hemorreológicos associados aos doentes infetados com SARS-CoV2 serão de esperar como resultantes das características dos níveis dos estados da inflamação, da hemóstase, da disfunção endotelial dos componentes do hemograma, da idade e das comorbilidades ou comorbidade.

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LEONOR TRINDADE SOUSA

Arte é a forma usada pelo artista para manifestar a sua criatividade sendo a fonte da sua inspiração a perceção da vida. Sendo esta uma atividade /habilidade que manifesta a estética visual é a forma do artista exteriorizar sentimentos e emoções por meio de uma corrente de Estilo e Estéticas diferentes. O Estilo é a forma da obra, a Estética é o fundamento da Arte. A capacidade do artista de ler e interpretar a vida com tamanha sensibilidade e de a expressar em forma de pintura/escultura, musica, escrita é o que se denomina Arte.

A Arte em todas as suas vertentes preserva e mantêm viva os aspetos que marcam e definem as características de um povo e sua cultura.

A Arte é o bem mais precioso da humanidade.

Na minha forma de expressão, absorvo tudo o que me rodeia, eleva-me principalmente a pintura, entrego-me de corpo e alma usando a cor e o movimento, várias técnicas e materiais que conjugados entre si me permitem extravasar através de traços, manchas nuances e figuras, mostrando ao mundo o meu estado de alma. Procuro em cada traço uma nota musical... Procuro em cada traço um poema pois quando os pincéis dormem a caneta ganha vida, para além da pintura também escrevo principalmente poesia (já divulgada em várias publicações nacionais e estrangeiras).

A minha forma de me expressar é principalmente a pintura sendo esta eclética pois inspiro-me também

40x30 Óleo Ref: 015

em tendências diversificadas e radicalmente opostas, sintetizo e aplico o que entendo ser o melhor de cada técnica procurando resultados finais que acrescentem algo de novo ao que já foi feito.

Assim de uma forma coerente e fiel a mim própria tento exprimir-me com criatividade tanto no domínio da representação abstrata como na figurativa, tanto no grande formato como no pequeno percorro vários temas sendo a conjugação das cores quentes e motivos Africanos o que mais me realiza, com que o meu eu mais se identifica.

A minha pintura reúne e condensa momentos que exprimem o meu interior, a minha sensibilidade e a minha postura perante a vida, o meu desejo de alcançar os meus objetivos a minha vontade férrea que me leva a enfrentar e a ultrapassar dificuldades até sentir que cheguei a porto seguro, ao um destino final.

Toda a minha obra é o resultado de muita luta, de muita persistência, de muito ouvir, ver e fazer, de esforços enormes que não quero guardar só para mim pois pretendo divulgar e partilhar com o mundo dando assim sentido ao meu percurso.

Poema

De saudade em saudade
Se constrói um espaço
... frio... vazio... calado
De esperança em esperança destruída
se constrói um olhar sem olhos
igual para gente e coisas....
De adeus em adeus
abafados pelo orgulho
e aberto ao egoísmo
da confusão dos sentimentos
e pela vontade dos homens
se constrói uma mulher de nome
SOLIDÃO.

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EFFECTS OF DIABETES ON MICROCIRCULATION AND LEUKOSTASIS IN RETINAL AND NON-OCULAR TISSUES: IMPLICATIONS FOR DIABETIC RETINOPATHY

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Abstract

Changes in retinal microcirculation are associated with the development of diabetic retinopathy (DR). However, it is unclear whether such changes also develop in capillary beds of other non-retinal tissues. Here, we investigated microcirculatory changes involving velocity of rolling neutrophils, adherence of neutrophils, and leukostasis during development of retinal vascular lesions in diabetes in other non-retinal tissues. Intravital microscopy was performed on post-capillary venules of cremaster muscle and ear lobe of mice with severe or moderate diabetes and compared to those of non-diabetic mice. Additionally, number and velocity of rolling leukocytes, number of adherent leukocytes, and areas of leukostasis were quantified, and retinal capillary networks were examined for acellular capillaries (AC) and pericyte loss (PL), two prominent vascular lesions characteristic of DR. The number of adherent neutrophils and areas of leukostasis in the cremaster and ear lobe post-capillary venules of diabetic mice was increased compared to those of non-diabetic mice. Similarly, a significant increase in the number of rolling neutrophils and decrease in their rolling velocities compared to those of non-diabetic control mice were observed and severity of diabetes exacerbated these changes. Understanding diabetes-induced microcirculatory changes in cremaster and ear lobe may provide insight into retinal vascular lesion development in DR.

Keywords: microcirculation; leukostasis; diabetic retinopathy.
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ERYTHROCYTE A TARGET FOR COVID-19 INFECTED PATIENTS

Carlota Saldanha*

Abstract

The questions about the Covid-19 and the discussion of the answers are the aim of the present opinion. Facing the great amount of knowledge centred in the field of red blood cells (RBC) or erythrocyte arise the principle for a diagnostic test with efficiency, accuracy, fast and cheap in order to differentiate the infected Covid-19 patients from those that are asymptomatic but with or without the Covid-19. Different results may be obtained and will be here discussed. The signal transduction mechanisms of nitric oxide in the RBC have key points that are therapeutic targets for compounds to apply in infected Covid-19 patients.

Keywords: Blood smears; Erythrocyte membrane band3 protein; Nitric oxide; Microcirculation; Systemic circulation.
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THERAPEUTIC APPROACH FOR COVID-19 PATIENTS

Carlota Saldanha*

Abstract

The biochemical effects of hydroxychloroquine, ivermectin, azithromycin molecules, and the zinc cation on functional properties of human erythrocyte will be presented. Among a wide range of therapeutically applications attributed to hydroxycloroquine the anti-inflammatory role will be herein highlight as well as for the azithromycin. The intervention of the ivermectin molecules into cell abortion mechanism of the virus replication will be described. The action of hydroxychloroquine, ivermectin, azithromycin molecules, and of zinc cation to prevent the spread and the replication SARS2-CoV2 Virus, as a first therapeutic approach for Covid-19 symptomatic patients, will be the aim of the present opinion.

Keywords: Erythrocyte acethylcholinesterase receptor; Hydroxycloroquine; Azithromycin; Ivermectin; Zinc cation

Abbreviations: ARS: Acute Respiratory Syndrome; RBC: Red Blood Cells; NO: Nitric Oxide; HCQ: Hydroxychloroquin; PTK: Protein Tyrosine Kinase; PTP: Protein Tyrosine Phosphatase; AChE: Acetylcholinesterase; ACh: Acetylcholine; NORS: Nitrogen Reactive Species

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THE INFLAMMATORY ASPECT OF MALE AND FEMALE PATTERN HAIR LOSS

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Abstract

Abstract: Male and female pattern hair loss (MPHL and FPHL, respectively), is the most common cause of hair loss affecting nearly 80 million people in the US, yet treatment options remain limited and lacking. As the need for more effective therapeutics remains unmet, this perspective offers a unique angle by directing attention to the inflammatory aspect of MPHL and FPHL. Evidence and implications of inflammation as a characteristic feature of MPHL and FPHL are highlighted through evaluation of clinical and quantitative data. Comparable results suggest the presence of significant perifollicular inflammatory infiltrates, such as lymphocytes and histiocytes, as well as the involvement of inflammatory genes, such as CASP7 and TNF, in the presentation of MPHL and FPHL. Resurfacing of the inflammatory aspect in MPHL and FPHL pathogenesis will advance future developments in MPHL and FPHL therapeutic options.

Keywords: hair loss, inflammation, male pattern baldness, female pattern baldness.
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