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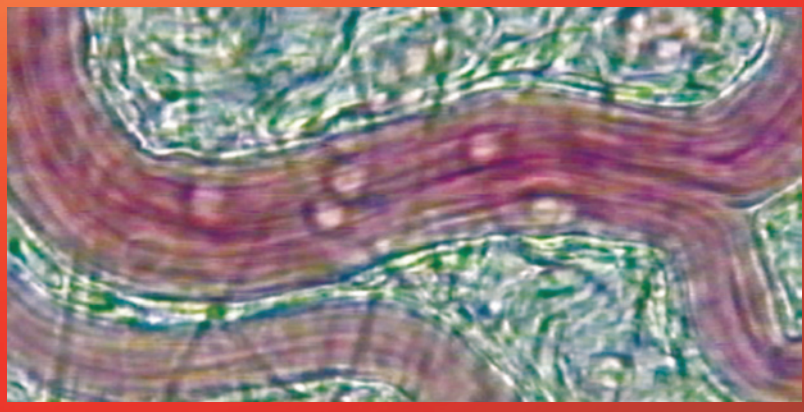

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BOLETIM

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Sumário / Summary

Sociedade Portuguesa de Hemorreologia e Microcirculação

Presidente Honorário: Prof. Doutor João Alcindo 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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MICROCIRCULAÇÃO

As notas de abertura do BSPHM têm focado o eritrócito mas importa também referir a rede vascular circulatória da microcirculação, com propriedades estruturais e funcionais que influenciam o fluxo sanguíneo.

A microcirculação está associada à Hemorreologia, à inflamação e ao controlo da resistência vascular, tornando-se o alvo da doença vascular. Há evidência que a disfunção da microcirculação precede o início da doença cardiovascular, renal e cerebral. A hipertensão tem como fenótipos o estreitamento das arteríolas, e a rarefacção capilar. Uma abordagem génica verificou que o diâmetro das arteríolas da retina dos doentes com hipertensão arterial está associado ao polimorfismo do gene do receptor do tipo 2 da angiotensina.

A alteração da perfusão sanguínea está descrita e evidenciada na sepsis severa e no choque séptico, como factor preponderante na falência multi-órgão. A observação sublingual da microcirculação tem demonstrado que a heterogeneidade da rede capilar está amplificada na sepsis, sendo menos severa nos sobreviventes. A gravidade acentua-se com a falta de controlo local do fluxo sanguíneo por menor vasodilatação arteriolar. Verifica-se que a diminuta reactividade microvascular está associada ao grau de gravidade da disfunção dos vários órgãos. Modificações estruturais da superfície luminal do endotélio como, por exemplo, a reduzida quantidade de glicocálice presente na sepsis,facilita a interacção do conteúdo celular sanguíneo com a parede do vaso e ainda faculta o "alojamento" de biomoléculas que desequilibram os mecanismos da coagulação, anticoagulação e fibrinólise. Apesar do exagerado contacto dos neutrófilos pelo rolamento e pela adesão à superfície endotelial, há diminuta transmigração para os tecidos As plaquetas rolam e aderem, com grande frequência e permanência, ao endotélio dos vasos dos doentes com sepsis que apresentam glóbulos vermelhos com reduzida deformabilidade.

A disfunção da microcirculação na sepsis está potenciada por modificações hemodinâmicas, hemorreológicas, inflamatórias e hemostáticas.

A intervenção para melhorar a perfusão tecidual parece ser efectiva a nível da microcirculação, quando feita nas primeiras horas do diagnóstico de sepsis, mas o mecanismo ainda não está totalmente esclarecido. Naturalmente que a intervenção com fluidos resulta na diminuição da viscosidade sanguínea, da adesão dos glóbulos brancos e diluição, isto é, hipoconcentração de agentes vasoconstritores. No entanto, qualquer alteração da hemodinâmica sistémica nos doentes com sepsis que manifestam hipotensão suscita muitas dúvidas sobre o benefício hemodinâmico na microcirculação, em que a par de capilares com fluxo sanguíneo parado, encontram-se outros com perfusão correcta. Haverá

zonas de estase, com consequente deficiente troca de gases e de fornecimento de nutrientes resultantes, ou de hiperagregação eritrocitária, ou deformabilidade diminuída,ou aumento de viscosidade plasmática. Na sepsis, onde a hipotensão é um parâmetro persistente, a hiperagregação eritrocitária reforça a estase microvascular. A disfunção da microcirculação mantida é um mau prognóstico na evolução dos doentes com sepsis. Isto significa que os parâmetros determinantes do fluxo capilar, nomeadamente o diferencial de pressão, o tónus arteriolar, a desobstrução capilar e os parâmetros hemorreológicos estão desregulados. O mesmo é dizer que os mecanismos miogénicos, neurohumorais e metabólicos não funcionam de modo a normalizar o fluxo capilar. Naturalmente, a célula endotelial é a interface necessária aos mecanismos da hemostase e da resposta imune e, também, à transmissão a montante das condições hemodinâmicas ocorrentes a juzante, e à correcta função microvascular.

Foi uma simples abordagem de alerta sobre a microcirculação, completamente aquém de uma centrada em características genéticas ou de outra focada nos mecanismos de comunicação biomolecular reguladores da função microvascular. Teve apenas o objectivo de deixar a mensagem sobre a necessidade de se efectuarem estudos de translação com monitorização da função/disfunção microvascular em doentes com sepsis.

Carlota Saldanha
Presidente da SPHM

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HEPCIDIN AS THE NEW PLAYER IN INFLAMMATORY "FUNCTIONAL IRON DEFICIENCY ANEMIA" – KEY ROLES, (DE) REGULATION AND THERAPEUTIC IMPLICATIONS

António Silveira[1], Elísio Costa[2,3], Alice Santos-Silva[2,3], Flávio Reis[1 1]

ABSTRACT

Anemia of chronic kidney disease is responsible for a significant increase in morbidity and mortality among patients, as well for a poor life quality. Impairment of iron homeostasis and inflammation underlie the development of the anemia, and hepcidin is the pivotal player in this process. Ferroportin is an iron exporter present in the surface of cells that permits the absorption of iron through enterocytes and the mobilization of iron from macrophages and hepatocytes. When ferroportin is degraded by hepcidin, iron absorption is reduced as well as the mobilizion of iron for erythropoiesis, favoring the development of anemia. Many factors influence hepcidin expression and activity, including iron status, inflammatory state, tissue oxygen tension and the erythropoietic activity. The molecular mechanisms behind the regulation of hepcidin synthesis and activity became clearer during the last years due to a deep experimental and clinical investigation on this area of knowledge. In this review, we summarize the role of hepcidin in iron homeostasis, in inflammation and in the physiopathology of functional iron deficiency anemia; the molecular mechanisms behind the regulation of its expression, as well as the possibility of using hepcidin as a therapeutic target or as a diagnosis tool in functional iron deficiency anemia.

Keywords: Hepcidin; functional iron deficiency anemia; inflammation.

INTRODUCTION

The anemia that accompanies chronic renal disease (CKD) is associated with precocious mortality and morbidity rates, as well as with a decrease in life quality of patients[1-3]. The existing treatments include hemodialysis, together with the administration of iron and erythropoiesis-stimulating agents (ESA)[4]. However, about 25% of the patients require

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high doses of ESA, with potential adverse effects[5,6]. Furthermore, approximately 10% of patients develop resistance to therapy[7], complicating the treatment and the prognosis.

It is established that inflammation plays a central role in this type of anemia, as it limits erythropoiesis[8], suppresses the production of erythropoietin (EPO)[9] and, mainly, changes iron homeostasis. Hepcidin, a protein produced in hepatocytes and stimulated by inflammation, especially interleukin-6 (IL-6), plays a central role in this process since it promotes retention of iron in tissues[10]. Hepcidin degrades ferroportin, which leads to the accumulation of iron in macrophages and hepatocytes, and to a reduced flow from duodenal enterocytes to the circulation[11-13]. Thus, although there are adequate deposits of iron (thereafter normal or elevated ferritin), the circulating and available amount for hemoglobin synthesis is reduced (low serum iron, transferrin saturation and reticulocyte counts). This condition is defined as "functional iron deficiency anemia". In recent years, some authors have suggested that changes in the expression and/or activity of hepcidin may be related to resistance to ESA treatment, a process which appears to be mainly caused by disturbances in iron homeostasis and by a pro-inflammatory state[14,15]. In addition, hepcidin has been increasingly viewed as a putative therapeutic target and/or diagnosis tool in this condition of functional iron deficiency anemia.

ROLE OF HEPCIDIN IN IRON HOMEOSTASIS

Iron, an essential element for life, is involved in the transport of oxygen, as a component of heme (in hemoglobin and myoglobin) and is present in numerous enzymes essential for cellular respiration (e.g. redox mechanisms)[16], survival and growth[4]. In fact, iron is necessary for a normal hemoglobin synthesis and erythropoiesis. However, free iron is toxic[17], in a way that organisms had to develop intricate mechanisms to transport iron attached to molecules, deliver iron where it is strictly needed and store it in proteins, when in excess. There is a low iron bioavailability from human diet; iron released from senescent erythrocytes is recycled and losses are reduced to the minimum (they represent <0.1% of the 3-4 g of total iron and have to be replaced by diet)[16]. There isn't a proper pathway to excrete iron, even in the presence of high iron storages, which may lead to iron overload.

Iron is absorbed by enterocytes (approximately 1 to 2 mg per day[18]) of the duodenum and exported[19] by ferroportin to the circulation, where it binds to transferrin, that transports most of the iron to the bone narrow, for erythropoiesis. Red cell hemoglobin contains most of the iron of our body (2.5 g of iron). Reticuloendothelial macrophages from spleen phagocytize senescent erythrocytes, degrade hemoglobin and recycle iron[16]. The excess is stored as ferritin and hemosiderin (responsible for one-third of the body's iron stores) in liver and reticuloendothelial macrophages. Every time iron is needed, it is exported from iron storages through ferroportin channels into circulation[10,13].

Hepcidin is an acute phase protein that regulates iron absorption and its distribution[10]. It is produced mainly in the liver and is encoded as a pre-

propeptide, cleaved to a propeptide of 60 amino acids, and it's only secreted in its mature form, a 25 amino acid protein (convertases, like furin, PACE4, PC5/6 and PC7/LPC process hepcidin *in vitro??*)[20]. Its peptide resembles a bent hairpin held together by four disulfide bonds[20]. Its production occurs in response to a number of stimuli, like inflammation and high iron blood levels. It is excreted by the kidneys, although only 5% of the hepcidin from plasma appears intact in urine[21]. Probably, it is not freely filtered or it is reabsorbed and degraded by proximal tubular cells.

Hepcidin binds to ferroportin and degrades it[22]. Ferroportin is a membrane iron export protein present in cells that export iron, such as, duodenal enterocytes, splenic and hepatic macrophages and hepatocytes[23], and has a fundamental role in the iron metabolism. Animal models without ferroportin expression die in the embryonic stage because they can't mobilize iron[23]. Patients with thiol residue Cys326 mutations in ferrportin (probably the binding local to hepcidin) have a form of early-onset iron overload disorder[24]. Nevertheless, it seems that hepcidin is not the only ferroportin regulator, as cellular iron can, independently, regulate ferroportin expression[25].

When attached to hepcidin, the proper degradation mechanism involves ferroportin conformational changes and endocytosis of the ferroportin-hepcidin complex, which will be degraded in the lysosomes (this is another way, apart from the renal one, to clear hepcidin)[16,22]. By doing so, hepcidin inhibits iron absorption from enterocytes and iron deliver from its reserves (e.g. liver, reticuloendothelial macrophages) to erythroid cells[11,13,22]. In fact, an injection of hepcidin in mice caused a prolonged (more than 48 hours) hypoferremia, although hepcidin was cleared in a few hours by kidneys[26]. This may be due to the fact that organism takes a longer time to resynthetize degraded ferroportin[16]. Thus, the clinical effects will be a normocytic normochromic anemia, low serum iron, low reticulocyte count, low transferrin saturation and, paradoxically, higher levels of ferritin (in contrast to iron deficiency anemia where it's low)[27,28].

This type of anemia (with high levels of hepcidin) occurs in many situations, such as in chronic infections, cancer, rheumatoid arthritis and chronic kidney disease, and is called "anemia of inflammation" or "functional iron deficiency anemia"[29]. It's hypothesized that our body developed this iron sequester mechanism to protect us against invading pathogens, many of which require iron to their growth[30,31]. In fact, patients with hereditary hemochromatosis, a disease where hepcidin levels are low, have susceptibility to infections by unusual microorganisms, like *Vibrio, Yersinia* and *Listeria*[20].

Moreover, experiments in mice with hepcidin overexpression showed that they had the classical features of functional iron deficiency anemia[32]. A report from Weinstein *et al*. (2002) showed that an hepatic adenoma resection, secreting high hepcidin levels, in a patient with a severe anemia, resolved the patient's condition[33]. In contrast, patients with hepcidin deficiency, due to hereditary or acquired causes, have a great propensity to develop iron overload[16].

Many factors can influence hepcidin production, like iron status, inflam-

mation, hypoxia, erythropoietic activity, EPO levels and anemia[4,16,18]. Iron affects hepcidin production in a feedback loop. When in excess, it can enhance its production and, when in deficiency, it can suppress it. Patients with various types of hemochromatosis have low levels of hepcidin[18]. Inflammation is a great promoter of hepcidin production. It was already tested in humans that injection of lipopolysaccharide, which increases IL-6 levels, leads to an elevation in hepcidin levels, followed by the hypoferremia[34]. Moreover, in monkeys with collagen-induced arthritis, anti-IL-6 receptor antibodies caused a diminution in hepcidin and C-reactive protein (CRP) levels in a week, with improvement of anemia parameters in 4 weeks[35]. Anemia with preserved erythropoietin production and enhanced erythropoietic activity are potent suppressors of hepcidin production, through the formation of hepcidin inhibitor proteins by erythroid precursors[36,37]. Indeed, increased erythrocyte production requires higher iron consumption and iron availability. These responses are evident in ineffective erythropoiesis, where there is an erythroid hyperplasia, although the reticulocyte count is low because of apoptosis in later stages of erythropoiesis. A perfect example is β-thalassemia, where the levels of hepcidin are very low, even in the presence of high iron serum levels and iron overload[38,39]. Hypoxia also suppresses hepcidin expression[14,15,18].

REGULATION OF HEPCIDIN EXPRESSION

Great advances in understanding the molecular mechanisms of hepcidin have been made by studying hereditary hemochromatosis[40]. These patients have mutations in hemochromatosis protein gene (HFE), in transferrin receptor 2 gene (TFR2) or in hemojuvelin gene (HFE2) and present low hepcidin levels, high iron blood and ferritin levels[4,18]. Very rare mutations in hepcidin itself cause a severe early-onset form of hemochromatosis[41].

Hepcidin is encoded by the HAMP gene[18] and it is known that its transcription is enhanced by iron "sufficiency" and inflammation and suppressed by hypoxia, anemia and iron deficiency.

Iron "sufficiency": With sufficient blood iron, transferrin-bound iron binds to transferrin receptor 1 (TfR1), displacing hemochromatosis protein (HFE), which then binds to transferrin receptor 2 (TfR2)[20]. HFE and TfR2 induce hepcidin expression through the morphogenic protein receptor complex BPM/SMAD signaling pathway[42]. The morphogenic protein receptor complex consists of BPM-6 (it's expression seems to be regulated by iron[43]), BMP receptor (BMP type I and type II serine threonine kinase receptors[4]) and hemojuvelin (HJV)[42], which, all together, activate the SMAD signaling cascade. HJV enhances the SMAD signaling and, thus, stimulates hepcidin expression[42]. This pathway leads to sequential protein activation that translocate to the the nucleus where hepcidin expression is induced through BMP responsive elements (BMP-RE) located on the promoter region of hepcidin gene[4,18]. Deletion in any of the genes that express BPM/SMAD signaling pathway molecules result in hepcidin deficiency[4,18].

Inflammation: Inflammation also plays a central role in hepcidin gene

expression. The proinflammatory cytokine IL-6 activates the JAK/STAT3 signaling pathway (binding to IL-6 receptor) and promotes hepcidin expression through STAT3 responsive element (STAT3- RE) on the promoter region of hepcidin gene[44-46]. Other proinflammatory cytokines, such as interleukin-1 (IL-1) may play a similar role[47], as shown by the increased expression of hepcidin mRNA independently of IL-6 in mouse hepatocytes and in IL-6 knockout mice with chronic inflammation[20]. Zhang *et al.* (2006) and Vecchi *et al.* (2009) reported another possible pathway to induce hepcidin expression, in inflammation. Proinflammatory cytokines and bacterial lipopolysaccharide (LPS) are thought to cause endoplasmic reticulum (ER) stress and, thus, activate CREBH (cyclic AMP response element-binding protein H) which, in turn, activates numerous acute phase genes and induces hepcidin production, by binding to the promoter gene[48,49]. The available data suggests there's an interaction between JAK/STAT3 and BPM/SMAD signaling pathways, as they cooperate to promote hepcidin expression. Inhibition or abolishment of BMP/SMAD pathway resulted in blunted responses to hepcidin transcription by the IL-6 pathway[44].

Iron deficiency: In contrast, iron deficiency, is linked to low hepcidin levels because it seems to activate TMPRSS6 or matriptase-2, a hepcidin suppressor[50]. TMPRSS6 is a liver transmembrane serine protease that cleaves membrane-bound HJV into soluble HJV. This may result from inhibition of hepcidin induction by HJV in the BMP complex or by the action of soluble HJV that, presumably, binds competitively to the BMP receptor complex, inhibiting the signaling pathway and impairing hepcidin expression[50-52].

Anemia with preserved EPO production: hepcidin production may be also inhibited in the presence of anemia with preservation of EPO production[36,37]. The proteins mainly involved in these mechanism are growth differentiation factor 15 (GDF15) and twisted gastrulation protein (TWSG1), produced by erythroid precursors[36,37]. The intact erythropoiesis activity (with normal EPO levels) is essential for hepcidin suppression, as shown by some *in vivo* experiments, in which cytotoxic agents or irradiation suppressed erythropoiesis, leading to normal hepcidin levels, even in the presence of anemia[53]. GDF15 interferes with the BPM/SMAD signaling pathway, by an unknown mechanism, thus inhibiting hepcidin expression. Curiously, GDF15 knockout mice didn't have iron homeostasis impairment, suggesting that its action may be limited to anemias (like β-thalassemia) with ineffective erythropoiesis, where there is GDF15 overproduction[20,36]. TWSG1, *per se*, is thought to interfere with BMP protein, disrupting BPM/SMAD signaling pathway[18,20].

Hypoxia: Hypoxia is a potent suppressor of hepcidin. The complete physiological regulation is still incomplete but it seems to be related with the hypoxia-inducible factor (HIF) pathway[54]. In normoxic conditions, HIF pathway proteins are degraded by oxygen hydroxylase and von Hippel-Lindau protein oxygenases, but, in case of hypoxia, those enzymes are inactivated and HIF accumulates. Evidence suggests that activated HIF pathway proteins bind to hepcidin pro-

moters impairing their expression[54]. In fact, mice with deletion of von Hippel–Lindau protein (thus, simulating hypoxia conditions) had, consistently, low levels of hepcidin, but when added a new deletion to a gene encoding HIF, hepcidin levels where restored to normal (the inhibitory effect of HIF ended)[55]. Interestingly, furin (which cleaves HJV) and TFR1 are encoded by HIF target genes[56,57], suggesting that HIF could indirectly lower hepcidin through inhibition of BPM/SMAD signaling pathway[56,57]. Finally, hypoxia stimulates EPO production, which, as referred above, inhibits hepcidin, and may act as a bias factor in understanding HIF-induced hepcidin suppression.

CONCLUSIONS: HEPCIDIN AS A THERAPEUTIC TARGET OR DIAGNOSIS TOOL IN FUNCTIONAL IRON DEFICIENCY ANEMIA?

Functional iron deficiency anemia is very common among patients with inflammatory conditions (such as CKD, cancer, chronic infection and autoimmune diseases)[29] and is a predictor of poor prognosis (longer hospitalization, cognitive impairment, heart failure, and increased morbidity)[1-3]. The recent discover of new molecular pathways regulating hepcidin expression allowed the development of hepcidin targeting drugs. Treatments that attempt to lower the levels of hepcidin or its activity (inhibitors of synthesis, antagonists of their action, stabilizers of ferroportin and soluble hemojuveline[4,14]) or inhibitors of inflammation (IL-6 antagonists, statins and others[4,14,15]) are becoming very promising options to manage and/or treat the "functional iron deficiency anemia" and the resistance to ESA therapy. Although some of them have shown good potential in preliminary pre-clinical or clinical trials, more studies concerning their efficacy and adverse effects, namely in humans, need to be done.

The recent advances in this field have also brought the light on hepcidin measurement as a diagnostic and follow-up tool. Although the urgent need of standardization of the methods to measure hepcidin, most of the used assays correlated very well and have reported higher hepcidin levels in CKD patients compared with healthy ones, suggesting that, if further confirmed, could be viewed as good tools to improve diagnosis and/or to a better follow-up on the efficacy of treatments. In any case, new perspectives have been rising with the improved knowledge on this area and we may expect further developments in a short-time.

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EXERCISE HEMORHEOLOGY: MOVING FROM OLD SIMPLISTIC PARADIGMS TO A MORE COMPLEX PICTURE

Brun JF, Varlet-Marie E, Romain AJ, Guiraudou M, Raynaud de Mauverger E.[1]

Abstract

Classic studies on exercise hemorheology evidenced that blood fluidity is impaired during exercise (short term exercise-induced hyperviscosity) and is improved as a result of regular exercise practice (hemorheologic fitness). Extensive description of these events led to the concepts of "the triphasic effects of exercise", "the paradox of hematocrit", and "the hemorheological paradox of lactate". However, some results obtained in training studies do not fit with this classical picture and cannot be explained by a simplistic paradigm based on the Hagen-Poiseuille law. Taking into account the non-linearity of the effects of viscosity factors on blood flow and oxygen delivery helps to elaborate another picture. For example, moderately high values of hematocrit and erythrocyte rigidity induced by high intensity exercise are likely to trigger a physiological vasodilation improving circulatory adaptation (rather than limiting performance as was previously assumed). This may apply to the acute rise in red cell rigidity observed during strenuous exercise, and also to the paradoxical rise in hematocrit or red cell rigidity observed after some training protocols and that did not fit with the previous (simplistic) paradigms. The "healthy primitive lifestyle" hypothesis assumes that evolution has selected genetic polymorphisms leading to insulin resistance as an adaptative strategy to cope with continuous low intensity physical activity and a special alimentation based on lean meat and wild herbs (i.e., moderately high in protein, rich in low glycemic index carbohydrates, and poor in saturated fat). We propose here that this model may help to explain on an evolutionary perspective these apparently inconsistent findings. The pivotal explanation is that the true physiological picture would be that of an individual whose exercise and nutritional habits are close from this lifestyle, both sedentary subjects and trained athletes representing situations on the edge of this model. **[Clin Hemorheol Microcirc. 2013 Mar 11. [Epub ahead of print]]** PMID:3478223

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PLASMA HYALURONAN AND HEMORHEOLOGY IN PATIENTS WITH SEPTIC SHOCK: A CLINICAL AND EXPERIMENTAL STUDY

Sallisalmi M, Tenhunen J, Kultti A, Tammi M, Pettilä V.[1]

Abstract

Background: Total plasma hyaluronan concentration is increased in septic shock. High-molecular-weight hyaluronan has a high intrinsic viscosity. Excessive release of high-molecular-weight hyaluronan in sepsis may induce hyperviscosity.

Methods: Plasma viscosity and the molecular size of plasma hyaluronan were determined in 20 patients with septic shock and in 20 healthy controls. Ex vivo, the effects of 0.4% and 0.047% high-molecular-weight hyaluronan 1560 kDa, 0.9% saline, and 6% hydroxy-ethyl-starch 130 kDa were compared to plasma and whole blood viscosity and red blood cell aggregation at a systemic hematocrit of 0.4, and at a microcirculatory hematocrit of 0.2.

Results: Plasma viscosity and total plasma protein content were low in septic shock patients on days one and four of treatment. Hyaluronan concentration was 10-fold higher in sepsis on day 1. Molecular weight of hyaluronan was relatively low, mostly 50-500 kDa, and did not change significantly in sepsis. Ex vivo, 0.4% high-molecular-weight hyaluronan 1560 kDa increased blood viscosity but did not promote red blood cell aggregation. Dilutions of 6% hydroxyl-ethyl-starch 130 kDa and 0.047% high-molecular-weight hyaluronan 1560 kDa had comparable effects on blood viscosity and red blood cell aggregation.

Conclusions: Plasma viscosity of the septic patients remained low for four days despite markedly elevated concentration of relatively small-molecular-weight hyaluronan. **[Clin Hemorheol Microcirc. 2013 Feb 4. [Epub ahead of print]]** PMID:23380965

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RED BLOOD CELL FLOW IN THE CARDIOVASCULAR SYSTEM: A FLUID DYNAMICS PERSPECTIVE

AlMomani TD, Vigmostad SC, Chivukula VK, Al-zube L, Smadi O, BaniHani S.[1]

Abstract

The dynamics of red blood cells (RBCs) is one of the major aspects of the cardiovascular system that has been studied intensively in the past few decades. The dynamics of biconcave RBCs are thought to have major influences in cardiovascular diseases, the problems associated with cardiovascular assistive devices, and the determination of blood rheology and properties. This article provides an overview of the works that have been accomplished in the past few decades and aim to study the dynamics of RBCs under different flow conditions. While significant progress has been made in both experimental and numerical studies, a detailed understanding of the behavior of RBCs is still faced with many challenges. Experimentally, the size of RBCs is considered to be a major limitation that allows measurements to be performed under conditions similar to physiological conditions. In numerical computations, researchers still are working to develop a model that can cover the details of the RBC mechanics as it deforms and moves in the bloodstream. Moreover, most of reported computational models have been confined to the behavior of a single RBC in 2-dimensional domains. Advanced models are yet to be developed for accurate description of RBC dynamics under physiological flow conditions in 3-dimensional regimes**. [Crit Rev Biomed Eng. 2012;40(5):427-40]** PMID: 23339650 [PubMed

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PARTICIPAÇÃO NACIONAL EM ARTIGOS RECENTES NA ÁREA DA HEMORREOLOGIA E MICROCIRCULAÇÃO

TISSUE OXYGEN DEMAND IN REGULATION OF THE BEHAVIOR OF THE CELLS IN THE VASCULATURE

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Abstract

The control of arteriolar diameters in microvasculature has been in the focus of studies on mechanisms matching oxygen demand and supply at the tissue level. Functionally, important vascular elements include endothelial cells (EC), vascular smooth muscle cells (VSMC) and red blood cells (RBC). Integration of these different cell types into functional units aimed at matching tissue oxygen supply with tissue oxygen demand is only achieved when all these cells can respond to the signals of tissue oxygen demand. Many vasoactive agents that serve as signals of tissue oxygen demand have their receptors on all these types of cells (VSMC, EC, and RBC) implying that there can be a coordinated regulation of their behavior by the tissue oxygen demand. Such functions of RBC as oxygen carrying by hemoglobin (Hb), rheology, and release of vasoactive agents are considered. Several common extra- and intracellular signaling pathways that link tissue oxygen demand with control of VSMC contractility, EC permeability, and RBC functioning are discussed.

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EFFECTS OF ACETYLCHOLINE ON AN ANIMAL MODE OF INFLAMMATION

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Abstract

Acetylcholinesterase (AChE) is found both on the membranes of neuronal and non-neuronal cells. In this study we performed intravenous administrations of velnacrine (VLN) and acetylcholine (ACh), respectively, AChE inhibitor and substrate, in an animal model of lipopolysaccharide (LPS)-induced inflammation in Wistar rats. Using intravital microscopy the number of rolling and adherent leukocytes in post-capillary venules was monitorized and blood samples were collected for TNF-α plasma concentrations determination. Our results showed that in presence of LPS, ACh has an anti-inflammatory effect, seen by a decrease in TNF-α plasma levels and maintains the number of rolling and adherent leukocytes. The presence of VLN before LPS almost blocked the LPS-induced rolling and TNF-α releasing. Thereby VLN seems to have, like ACh, an anti-inflammatory effect by diminishing TNF-α concentrations.

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doi: 10.3233/CH-121646.

FIBRINOGEN INTERACTION WITH THE RED BLOOD CELL MEMBRANE

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Abstract

A brief review of the fibrinogen molecule composition and structure is presented like as an introduction to the effects of this plasma protein on the red blood cell hemorheoplogical properties namely erythrocyte aggregation tendency and deformability ability. The protein membrane RBC target for fibrinogen is also highlight as well as the erythrocyte signal transduction pathway associated with nitric oxide mobilization resulting from its binding.

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CXCL8 (IL-8) MEDIATES NEUTROPHIL RECRUITMENT AND BEHAVIOR IN THE ZEBRAFISH INFLAMMATORY RESPONSE

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Abstract

Neutrophils play a pivotal role in the innate immune response. The small cytokine CXCL8 (also known as IL-8) is known to be one of the most potent chemoattractant molecules that, among several other functions, is responsible for guiding neutrophils through the tissue matrix until they reach sites of injury. Unlike mice and rats that lack a CXCL8 homolog, zebrafish has two distinct CXCL8 homologs: Cxcl8-l1 and Cxcl8-l2. Cxcl8-l1 is known to be upregulated under inflammatory conditions caused by bacterial or chemical insult but until now the role of Cxcl8s in neutrophil recruitment has not been studied. In this study we show that both Cxcl8 genes are upregulated in response to an acute inflammatory stimulus, and that both are crucial for normal neutrophil recruitment to the wound and normal resolution of inflammation. Additionally, we have analyzed neutrophil migratory behavior through tissues to the site of injury in vivo, using open-access phagocyte tracking software PhagoSight. Surprisingly, we observed that in the absence of these chemokines, the speed of the neutrophils migrating to the wound was significantly increased in comparison with control neutrophils, although the directionality was not affected. Our analysis suggests that zebrafish may possess a subpopulation of neutrophils whose recruitment to inflamed areas occurs independently of Cxcl8 chemokines. Moreover, we report that Cxcl8-l2 signaled through Cxcr2 for inducing neutrophil recruitment. Our study, therefore, confirms the zebrafish as an excellent in vivo model to shed light on the roles of CXCL8 in neutrophil biology.

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CROSSTALK BETWEEN INFLAMMATION, IRON METABOLISM AND ENDOTELIAL FUNCTION IN BEHÇET'S DISEASE

Oliveira R, Napoleão P, Banha J, Paixão E, Bettencourt A, da Silva BM, Pereira D, Barcelos F, Teixeira A, Patto JV, Viegas-Crespo AM, Costa L.

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Abstract

Behçet's disease (BD) is a rare chronic vasculitis of unclear etiology. It has been suggested that inflammatory response has an important role in BD pathophysiology. Herein, we aimed to study the interplay between inflammation, iron metabolism and endothelial function in BD and search for its putative association with disease activity. Twenty five patients clinically diagnosed with BD were selected and twenty four healthy age-sex matched individuals participated as controls. Results showed an increase of total number of circulating white blood cells and neutrophils, serum transferrin, total iron binding capacity, mieloperoxidase (MPO), ceruloplasmin (Cp), C reactive protein, β2 microglobulin and Cp surface expression in peripheral blood monocytes in BD patients comparatively to healthy individuals ($p < 0,05$). Of notice, the alterations observed were associated to disease activity status. No significant differences between the two groups were found in serum nitric oxide concentration. The results obtained suggest an important contribution from innate immunity in the pathogenesis of this disease. In particular, surface expression of leukocyte-derived Cp may constitute a new and relevant biomarker to understand BD etiology.

Clin Hemorheol Microcirc. 2013 Apr 25.
[Epub ahead of print]

PARTICIPAÇÃO NACIONAL EM CONGRESSO INTERNACIONAL

Decorreu no passado mês de Abril, de 15 a 17, a 3rd International Conference On Clinical Experimental Ophtalmology, no HiltonChicago/ Northbrook, USA.

A SPHM esteve representada pela sua presidente que, além e *co-chair* da sessão de abertura, apresentou a comunicação intitulada "**Modulation of Erythrocyte Nitric Oxide Bioavailability",** em que foram co-autores Pedro Teixeira, Teresa Santos-Freitas e Patrícia Napoleão.

Abstract

Changes in tissue oxygen partial pressure are sensed by erythrocyte contributing to vasodilation or vasoconstriction through its nitric oxide bioavailability. Endogenous or exogenous compounds modulate the erythrocyte nitric oxide bioavailability through the membrane targets molecules such as band 3 protein and acetylcholinesterase. Binding of acetylcholine to erythrocyte membrane acetylcholinesterase originates a signal transduction mechanism involving Gi protein and band 3 protein that stimulates nitric oxide efflux. The bioavailability of nitric oxide in presence of velnacrine maleate an acetylcholinesterase inhibitor is preserved. Timolol maleate used in patients with primary open angle glaucoma is an erythrocyte acetylcholinesterase inhibitor. In primary open angle glaucoma the total nitric oxide in retina was consistently higher and associated with intraocular pressure. The aim of this study was to assess the effect of timolol maleate in erythrocyte nitric oxide bioavailability of healthy humans. Human venous blood samples were collected from the forearm vein of fifteen healthy Caucasian men after informed consent. Each blood sample was divided in three 1mL samples, centrifuged, and erythrocyte suspensions were performed in order to achieve 10μM final concentration either of acetylcholine or timolol. Levels of nitric oxide were evaluated by amperometric method. S-nitrosoglutathione, nitrites and nitrates were assessed using the spectrophotometric Griess reaction. Timolol do not change erythrocyte nitric oxide efflux in relation to the control but significantly decreased it when compared to the acetylcholine. Timolol decreased erythrocyte S-nitrosoglutathione significantly in relation to control and to acetylcholine Erythrocyte preserves, in vitro, its bioavailability in healthy humans in presence of timolol maleate. Extrapolating our results to primary open angle glaucoma patients under timolol maleate therapeutic lower levels of reactive nitrogen species may be expected that may explain the impairment oxidative stress previously evidenced by others.

Keywords: erythrocyte; nitric oxide; timolol maleate; acetylcholine, S-nitrosoglutathione, sodium chloride(NaCl)

PRÓXIMOS CONGRESSOS

17TH CONFERENCE OF THE EUROPEAN SOCIETY FOR CLINICAL HEMORHEOLOGY AND MICROCIRCULATION (ESCHM)

July 6-9 2013, Pecs, Hungary
Convention Budapest Ltd.
Mailing Address: H-1461 Budapest, P.O.Box.11,
Office Addres: H-1097 Budapest, Tóth Kálmán u. 33/b., VI.5-6.
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www.convention.hu; www.eschm2013.hu
Programa e outras informações: http://www.eschm2013.hu

Welcome Note

Fourteen years after the Hungarian joint meeting of the International Society of Biorheology (ISB) and the International Society of Clinical Haemorheology (ISCH), we are pleased to announce that the 17th Conference of the European Society for Clinical Hemorheology and Microcirculation (ESCHM) is also going to be held in Pécs, Hungary in 2013. As Pécs has the pleasure of hosting international experts of rheology for the second time, the Organising Committee hopes to welcome even more participants at the ESCHM congress than we did during the joint meeting of 1999.

Since 1999 Pécs's welcoming atmosphere has not changed much, although many of its buildings and streets have been renovated. In 2010 it was awarded the title "European Capital of Culture" which further strengthened its position and importance both as a cultural and as a scientific centre. Several international conferences of different disciplines have been held in Pécs recently, therefore we are honoured to be the hosts of the ESCHM conference in 2013.

The 17th Conference of the European Society for Clinical Hemorheology and Microcirculation (ESCHM) is going to be held on 6-9 July 2013 in Pécs, Hungary. We hope that it will be the platform of fruitful discussions for the international community of rheologists, where keynote speeches of outstanding scholars will encourage and inspire the participants to present their findings, introduce their latest developments and share their views during the different symposia.

We are convinced that Pécs's atmosphere will provide a pleasant background for an intensive exchange of views and opinions of distinguished scientists of haemorheology coming from Europe and from different countries all over the world. We would appreciate your active participation in this conference and look forward to welcoming you in Pécs in 2013.

Prof. Kalman Toth MD, PhD, ScD
President of the Conference

Gabor Kesmarky MD, PhD
President of the Hungarian Society of Haemorheology

Prof. Nadia Antonova PhD
President of the European Society for Clinical Hemorheology and Microcirculation

Prof. Lajos Bogar MD, PhD, ScD
President of the Local Scientific Committee
Vice-President of the European Society for Clinical Hemorheology and Microcirculation

JOINT MEETING 27TH EUROPEAN MICROCIRCULATION SOCIETY AND 7TH EUROPEAN VASCULAR BIOLOGY

Birmingham, UK,21-26 July, 2013.

On behalf of the European Society for Microcirculation (ESM) and the European Vascular Biology Organisation (EVBO), we are pleased to announce that our two societies will hold a joint meeting under the auspices of the International Union of Physiological Sciences (IUPS) conference in Birmingham International Conference Centre from July 21-26, 2013. The Physiological Society will be responsible for management of the IUPS conference, including site hire, organisation of the professional trade exhibition, online submission of symposia and abstracts, registration, accommodation and advertising. Importantly, IUPS registration fees for our members are modest: £295 for full fee delegates and only £90 for young or retired delegates.

ESM and EVBO members submitted a total of 52 symposia for ranking by a joint ESM/EVBO Scientific Programme Committee and, based on these rankings, we submitted 28 symposia for consideration by the IUPS scientific committee. Almost 300 proposals were submitted for consideration by the IUPS International Scientific Programme Committee (ISPC) at its meeting in Birmingham in March 2012. Giovanni Mann (ESM President 2013), Jeremy Pearson (EVBO Council member) and Ulrich Pohl (Past ESM President) represented ESM/EVBO interests on the IUPS Scientific Programme Committee.

We are pleased to have secured 18 internationally competitive symposia which will be funded by the Physiological Society and clearly identified as ESM/EVBO led symposia. We have emailed the chairs of the successful ESM/EVBO symposia to inform them that Nick Boross-Toby (Director of Events) from the Physiological Society will be liaising directly with them in the next few weeks to provide guidelines concerning financial support for the 18 symposia, arrangements for registration of chairs and invited speakers, accommodation and the banquet.

In addition, the scientific programme is enhanced greatly by designated Plenary, Keynote and Prize Lectures: www.iups2013.org/lectures.html and ESM/EVBO are sponsoring the following Plenary/Keynote Lectures:

- Plenary Lecture – Peter Carmeliet, VIB – KU Leuven, Belgium www.vrc-lab.be
- Keynote Lecture – Elisabetta Dejana, IFOM-IEO, Milan, Italy www.ifom-ieo-campus.it/research/dejana.php
- Keynote Lecture – Takayuki Asahara, Tokai University School of Medicine, Kanagawa, Japan www.cdb.riken.jp/en/labtour/people_html/asahara/index.html
- ESM Malphigi Award Lecture – nominations to be considered by ESM Executive Committee

Further information and updates will be available from IUPS website: www.iups2013.org, and we envisage that the symposium programme will be uploaded in the next few weeks. In the meantime, should you require any additional information concerning the Joint ESM/EVBO Meeting at IUPS in Birmingham, please do hesitate to contact either of us.

Giovanni E. Mann (ESM President 2013),
Email: giovanni.mann@kcl.ac.ukJeremy

D. Pearson (EVBO Council),
Email: jeremy.pearson@kcl.ac.uk

REGRAS DE PUBLICAÇÃO / INSTRUCTIONS TO AUTHORS

CONVITE

A Sociedade Portuguesa de Hemorreologia e Microcirculação (SPHM) aceita para publicação no seu BOLETIM artigos de curta extensão. O Boletim é editado quatro vezes por ano em formato de papel e electrónico (www.hemorreologia.com), sendo distribuído gratuitamente a individualidades e instituições científicas e culturais.

INSTRUÇÕES

1. Todos os textos enviados para publicação estão sujeitos a apreciação editorial e aprovação. A decisão é baseada no mérito científico e cultural dos trabalhos.

2. São aceites somente os trabalhos preparados em versão óptica (*PDF* ou *Microsoft Word*).

3. Os textos devem ser redigidos em Português ou Inglês.

4. Os manuscritos com o pedido de publicação devem ser enviados por *e-mail* ao Editor (carlotasaldanha@fm.ul.pt).

– Comunicações Originais (artigos curtos) – Os textos serão considerado para publicação rápida, com a seguinte estrutura: Sumário (50-70 palavras), Introdução, Material e Métodos, Resultados, Discussão e Conclusões. O(s) autor(es) são estimulados a englobar em conjunto os resultados, discussão e conclusões.
(Extensão máxima do texto: 5 a 6 páginas a um espaço (letra de corpo 11), incluindo figuras tabelas e quadros(e respectivas legendas),agradecimentos e até 30 referências bibliográficas).

– Artigos de Revisão – O BOLETIM terá a maior satisfação em acolher curtas revisões sobre assuntos de particular interesse, no âmbito da Hemorreologia, Microcirculação ou assuntos de âmbito médico ou de outras áreas científicas afins, que sejam submetidos directamente para publicação ou mediante convite especial do Editor.
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INVITATION

The Portuguese Society on Hemorheology and Microcirculation (Sociedade Portuguesa de Hemorreologia e Microcirculação, SPHM) is pleased to welcome short papers for publication in its BOLETIM. This publication, in paper and online (www.hemorreologia.com), is distributed four times a year free of charge to the members of the Society.

INSTRUCTIONS

1. All submitted manuscripts are subjected to editorial review and approval. The decision to publish is dependent on the scientific and cultural merit of the papers.

2. Only contributions prepared and submitted as optic version (*PDF* or *Microsoft Word*), will be accepted.

3. Texts must be written in Portuguese or in English.

4. All scientific contributions, including manuscript submission and further correspondence should be addressed by *email* to the Editor (carlotasaldanha@fm.ul.pt)

– Original Communications – Manuscripts may be considered for rapid processing as short communications. All manuscripts should be arranged in the following sections: Abstract (50-70 words), Introduction, Material and Methods, Results, Discussion, Acknowledgements and References. The author(s) may combine some of the sections normally included in a full paper, namely the results, discussion and conclusions.
(Maximum communication length – 5-6 single spaced typed pages, including figures, tables, legends, acknowledgments and up to 30 references).

– Short Reviews – The BOLETIM will publish reviews on subjects of particular interest in its field, either following a special invitation or a submission by the author, and in the latter case only after approval by an Editorial Board member. Further information can be obtained from the editor.
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29 ANOS

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