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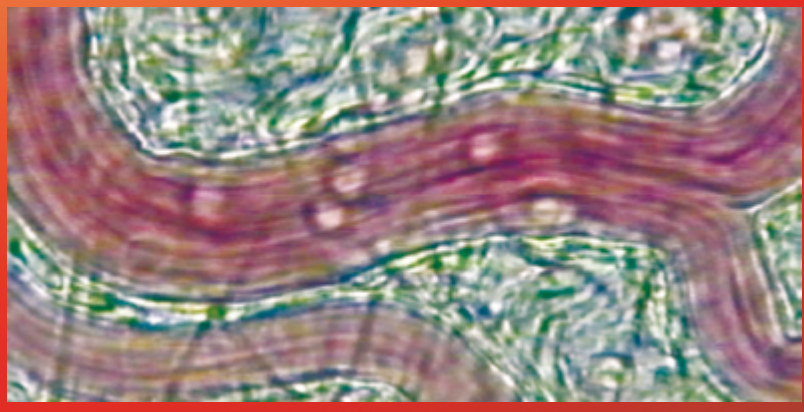

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Sumário / Summary

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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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APLICAÇÕES E EFEITOS FISIOLÓGICOS DA ACETILCOLINA

A viscosidade sanguínea é um dos factores determinantes na resistência periférica total, a qual, em conjunto com o débito cardíaco, influenciam a tensão arterial média. A microcirculação controla a resistência vascular e, consequentemente, a tensão arterial.

A resposta dos vasos da microcirculação à perfusão com acetilcolina fornece a capacidade de vasodilatação dependente do endotélio. Ao ser perfundido, o nitroprussiato de sódio, sendo um relaxante muscular, induz uma resposta vasomotora independente do endotélio. Ambas as respostas, a dependente e a independente do endotélio, permitem inferir do grau de funcionalidade do endotélio microvascular e podem contribuir para a análise de associação com os dados obtidos da funcionalidade do endotélio na macrocirculação. A correlação positiva, verificada em humanos saudáveis entre a função vascular na micro- e na macrocirculação, apresenta resultados contraditórios quando avaliada em doentes com disfunção vascular, consoante o tipo de estudo, a dimensão da amostra e a metodologia empregue.

A acetilcolina é uma molécula catiónica que actua no sistema nervoso central como neuromodulador com efeito anti excitatório e, ainda, no sistema nervoso periférico, com activação do músculo-esquelético e, consequentemente, com efeito excitatório. No entanto, o reconhecimento da acetilcolina pelo receptor muscarínico da fibra do músculo cardíaco tem, como efeito, a inibição da contracção com diminuição do batimento cardíaco. A acetilcolina foi o primeiro neurotransmissor a ser descoberto pelos premiados com o Nobel em Fisiologia e Medicina, Otto Loewi e Henry Dale, em 1936. A acetilcolina continua a ser considerada o neurotransmissor preponderante no sistema nervoso autónomo e na medula da supra-renal, onde induz a libertação da epinefrina e norepinefrina.

Todavia, a acetilcolina existe, também, numa variedade de células não neuronais, onde igualmente é sintetizada com a intervenção da isoenzima transferase de acetilcolina. e libertada quando necessária. O seu efeito é reconhecido por um conjunto de receptores e controlado pela isoenzima acetilcolinesterase. Toda esta panóplia de biomoléculas constitui o sistema colinérgico não neuronal (NNCS).

Na placenta, por exemplo, o efluxo da acetilcolina ocorre através do sistema de proteína de membrana" da classe dos canais orgânicos.

Os linfócitos T sintetizam e libertam a acetilcolina que, ao actuar de modo autócrino, induz o aumento de expressão da isoenzima transferase de acetilcolina e do receptor muscarínico M5.

A nível do endotélio íntegro, a acetilcolina actua de modo autócrino

e parácrino, sinalizando a via de síntese de monóxido de azoto (NO) endotelial que, ao passar para a célula do músculo liso, induz vasodilatação. A descoberta da acção vasodilatadora mediada pelo NO na dependência da acetilcolina deve-se a Ferid Murad Robert Furchgott e Louis Ignarro , laureados com o prémio Nobel de Fisiologia e Medicina em 1998. Tanto os linfócitos T como as células endoteliais contribuem para a concentração sanguínea de acetilcolina, que se situa na ordem do picograma (em condições fisiológicas) no humano, com variações consoante a espécie animal. A activação dos linfócitos T é responsável pelo aumento de concentração da acetilcolina na circulação sanguínea.

A mitose celular e a actividade ciliar são activadas pela acetilcolina.

A acetilcolina, quando interactua com o eritrócito, forma um complexo enzimático activo com a enzima de membrana, a acetilcolinesterase (AChE), favorece a deformabilidade eritrocitária e o efluxo de NO, controlando a biodisponibilidade do NO eritrocitário. Os complexos inactivos ou menos activos da enzima AChE, resultantes, nomeadamente, da ligação ao maleato de velnacrina ou ao timolol, conservam o NO dentro do eritrócito. A via de sinalização induzida pela acetilcolina que conduz à mobilização do NO envolve a AChE, a proteína banda 3, a proteína Gi e a diminuição da adenosina monofosfato cíclico.

Para além do sistema nervoso colinérgico e do NNCS, ainda existe o sistema colinérgico anti-inflamatório proposto por Tracey e cols .Os nervos aferentes e eferentes do sistema vagal são componentes de um circuito neural que modula a resposta inata imune. A activação do nervo vagal aferente, por exemplo, por uma endotoxina ou uma citocina inflamatória, estimula no eixo hipotálamo – hipófise - suprarrenal a resposta anti-inflamatória conduzida pelo nervo eferente vagal.

Assim, a activação dos neurónios adrenérgicos no baço libertam norepinefrina na vizinhança dos linfocitos T que, por sua vez, libertam acetilcolina. Este éster de colina, ao interactuar com os receptores nicotínicos existentes nos macrófagos, suprime a síntese e libertação de citocinas inflamatórias

Temos na Península Ibérica a possibilidade (no Instituto de Bioquímica, na minha unidade do Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa) de efectuar estudos “in vivo” com microscopia intravital. Com esta metodologia aplicada a um modelo animal de inflamação, foi possível demonstrar o efeito anti-inflamatório da acetilcolina pela diminuição do número de leucócitos aderentes e pela diminuta concentração de TNF- alfa em circulação.

Também foi por nós verificado que o próprio acto cirúrgico proporciona uma resposta inflamatória aguda que é protegida pela acetilcolina, por reduzir o número e a velocidade de leucócitos em rolamento e o número de aderentes, sem alterar a concentração de IL-1.

A acetilcolina, para além da sua aplicação no diagnóstico da função vascular, actua no sistema parassimpático, na junção neuromuscular, nos linfócitos T, nos macrófagos, na célula endotelial e nos eritrócitos.

A acetilcolina pertence a três sistemas, nomeadamente o neuronal, o colinérgico não neuronal e o colinérgico anti-inflamatório mas os nossos estudos acima mencionados, efectuados "in vivo", leva-nos a supor que o sistema colinérgico anti-inflamatório estabelece a ligação com os outros dois.

Esta nota de abertura daria uma imensidade de artigos de revisão e poderia ser um desafio para futuros trabalhos de investigação.

Carlota Saldanha
Presidente da SPHM

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MEMBRANE FLUIDITY AND CYTOSOLIC Ca^{2+} CONCENTRATION OF THE CIRCULATING POLYMORPHONUCLEAR LEUKOCYTES IN DIABETES MELLITUS

Caimi G., Hopps E., Lo Presti R.[1]

In the two last decades our haemorheological interest has regarded also the functional aspects played by the polymorphonuclear leukocytes (PMNs) in diabetes mellitus (DM).

Generally, the particular attention to the PMNs is related to the fact that these cells, with their geometric and biological characteristics, influence the microvascular flow and this effect is dependent in particular on their adhesion to the endothelium, on their entrapment or on their spontaneous activation. It must be also underlined the metabolic alteration that characterizes diabetic PMNs that is related to the decreased activity of phosphofructokinase and so of the glycolitic pathway, the increase in glucose metabolism via the hexose monophosphate shunt and the activation of the polyol pathway and so the increased sorbitol concentration[1].

Regarding PMNs, our attention has been directed in particular towards the determination of the membrane fluidity and the cytosolic calcium concentration, both under basal condition and after in vitro activation with chemotactic agents, such as 4-phorbol 12-myristate 13-acetate (PMA), non receptor-mediated, and N-formyl-methionyl-leucyl-phenylalanine (fMLP), receptor-mediated.

PMN membrane fluidity depends in particular on membrane lipid and proteic composition and it is a component of the PMN deformability, influenced also by cytosolic Ca2+ concentration. Both these two PMN parameters alter some functional expressions of these circulating cells, such as phagocytosis, and the increase in cytosolic Ca2+ content is considered a PMN activation marker[2]. As it is known, the PMN calcium concentration depends on the activity of the membrane pumps and this activity is also regulated by the membrane fluidity[3].

Now, we evaluated PMN membrane fluidity and PMN cytosolic Ca2+ concentration in 53 type 1 diabetic subjects (34 men and 19 women; age range 14-58 yrs; fasting blood glucose level 189.6±82.9 mg/dl, total cholesterol 187.7±34.00 mg/dl, serum triglycerides 105.5±61.2 mg/dl), in 68 type 2 diabetic subjects without macrovascular complica-

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tions (33 men and 35 women; age range 20-77 yrs; fasting blood glucose level 181.9±56.8 mg/dl, total cholesterol 210.9±34.8 mg/dl, serum triglycerides 133.4±61.8 mg/dl), and in 60 type 2 diabetic subjects with macrovascular complications (45 men and 15 women; age range 41-77 yrs; fasting blood glucose level 163.8±53.7 mg/dl, total cholesterol 227.7±45.1 mg/dl, serum triglycerides 188.4±89.9 mg/dl). All type 1 diabetic subjects followed a controlled carbohydrate diet and received three daily injections of insulin. All type 2 diabetic subjects followed a controlled carbohydrate diet and received oral hypoglycaemic agents. In type 2 diabetic subjects the presence or absence of macrovascular complications was determined with both physical and instrumental (Doppler, Echo-Doppler, ECG, etc) examination. An unfractioned leukocyte sospension was prepared from fasting venous blood according to the method described by Mikita et al[4]. Leukocytes were separated into mononuclear cells and polymorphonuclear cells using a density gradient[5]. PMN membrane fluidity was obtained by marking PMNs with the fluorescent probe 1-(4-[trimethylamino]phenil)-6-phenyl 1,3,5-hexatriene (TMA--DPH). PMN cytosolic Ca2+ concentration was obtained marking polymorphonuclear cells with the fluorescent probe Fura 2-AM and considering the ratio between the Fura 2-Ca2+ complex fluorescence intensity and the unchelated Fura-2 fluorescence intensity.

The same PMN parameters were examined in 48 normal controls (32 men and 16 women; age range 22-52 yrs; fasting blood glucose level 91.5±8.8 mg/dl, total cholesterol 196.7±35.8 mg/dl, serum triglycerides 102.8±55.5 mg/dl).

The values were expressed as mean s± S.D.. The difference between normal controls and diabetic subjects was evaluated according to the one-way ANOVA model integrated with the Bonferroni multiple post-test. The relationships between PMN membrane fluidity and PMN cytosolic Ca2+ concentration was evaluated using linear regression. Linear regression was also employed for the correlations between PMN membrane fluidity and age and between PMN calcium concentration and age. In normal controls, in type 1 diabetic subjects (DM1) and in type 2 diabetic subjects (DM2) without and with macrovascular complications (MVC) no statistical correlation between age and PMN cytosolic Ca2+ concentration was observed. Between PMN fluidity and age we observed only a significant negative relation DM1 subjects.

No significant difference (Figure 1) in PMN membrane fluidity was observed among normal controls, DM1 subjects, DM2 subjects without and with MVC (N= 0.341±0.024; DM1= 0.343±0.015; DM2 without MVC= 0.345±0.020; DM2 with MVC= 0.345±0.021).

Regarding PMN cytosolic Ca2+ concentration, among normal controls (0.805±0.057), DM1 subjects (0.837±0.058), DM2 subjects without MVC (0.826±0.066), and DM2 subjects with MVC (0.865±0.034) we found a significant difference (Figure 2) even if, employing the Bonferroni multiple post-test, a significant difference was evident only between normal controls and DM1

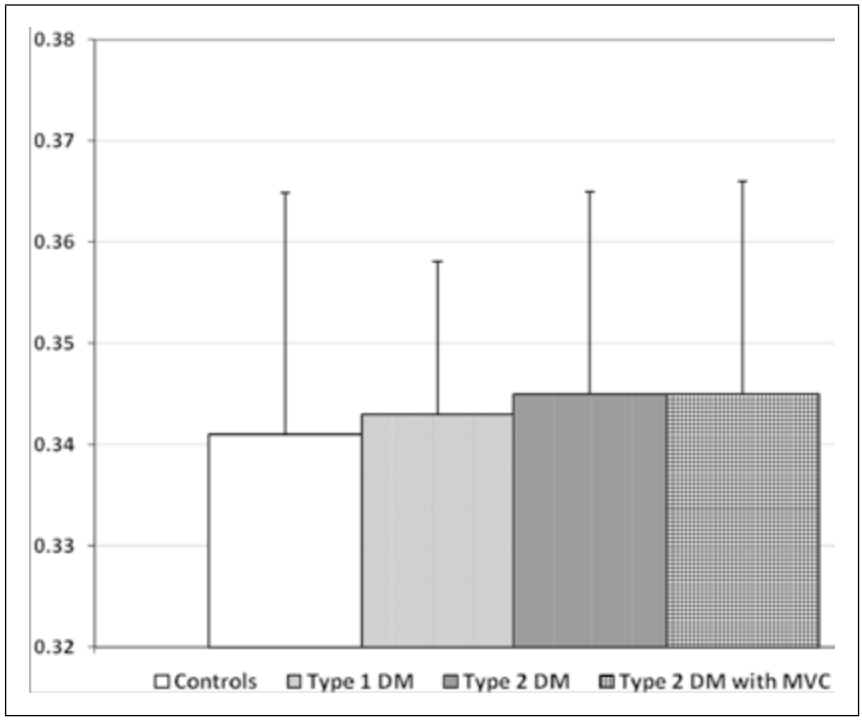
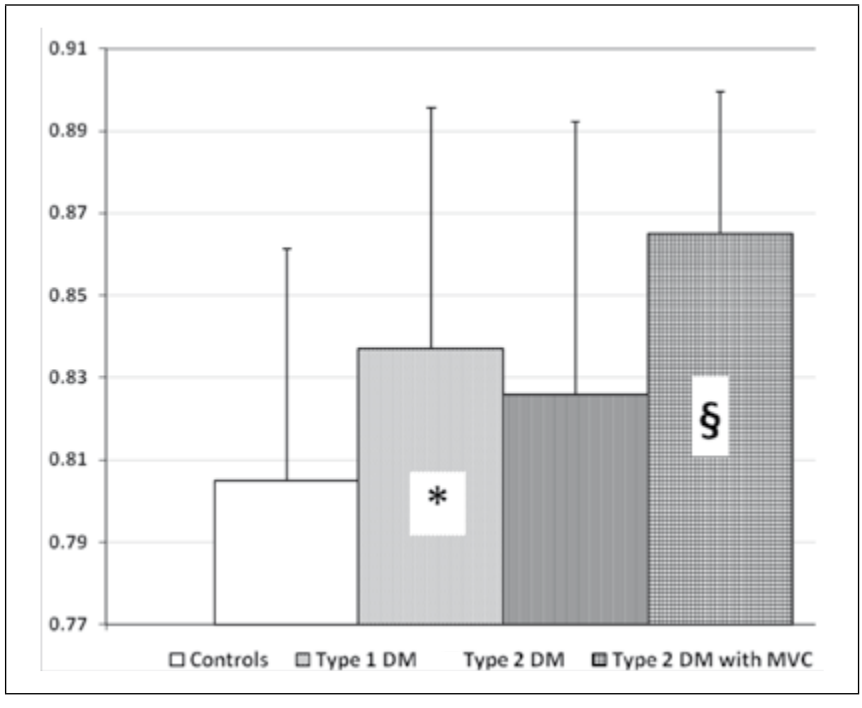


Figure 1. TMA-DPH polarization degree in PMNs of control subjects, type 1 and 2 diabetics and type 2 diabetics with macrovascular complications



*** p < 0.**05 vs Controls § p < 0.001 vs Controls and type 2 DM; p < 0.05 vs type 1 DM

Figure 2. PMN Cytosolic Ca2+ content in control subjects, in type 1 and 2 diabetics and in type 2 diabetics with macrovascular complications.

subjects and between normal controls and DM2 subjects with MVC, but not between normal controls and DM2 without MVC. It must be underlined that the values of PMN cytosolic calcium concentration observed in DM2 subjects with MVC are significantly higher in comparison with DM1 subjects and DM2 subjects without MVC. In normals, in DM1 subjects, in DM2 subjects without MVC and in DM2 subjects with MVC no significant correlation between PMN membrane fluidity and PMN cytosolic Ca2+ concentration was observed.

Even if, in our experience, the behaviour of the PMN membrane fluidity in diabetes mellitus results to be controversial[6-10] and seems to depend on the extent of survey and on the glycometabolic profile, in the re-examination of our case-record of diabetic subjects subdivided for type and for macrovascular complications this microrheological parameter has the same trend observed by us in other chronic clinical conditions, such as vascular atherosclerotic disease[10,11], essential arterial hypertension[12,13] and chronic kidney disease[14] and is different from that observed in acute clinical conditions, such as juvenile myocardial infarction[15] and ischemic stroke[16,17].

Interesting is instead the behaviour of PMN cytosolic Ca2+ concentration in all the groups of diabetic subjects now examined. From these data it is evident the different trend of PMN cytosolic Ca2+ in the two types of DM. Regarding the group of DM2 with MVC these data are in agreement with our previous observation[18] concerning a small number of subjects. However other authors found in type 2 diabetic sub-

jects without any vascular complication (19, 20) a significant increase in PMN cytosolic Ca2+ concentration.

The different behaviour of cytosolic calcium in DM1 subjects in comparison with DM2 subjects is similar to that regarding PMN membrane fluidity (lo presti 98) and β_2-integrin pattern[21] during in vitro activation with PMA and fMLP.

Several studies have regarded instead the role of leukocyte count in this metabolic condition. An elevated leukocyte count has been associated with different glucose metabolism abnormality[22], such as insulin resistance[23], impaired glucose tolerance[24], impaired fasting glucose[24], and type 2 DM[25,26,27,28]. Even in normoglicemic subjects with parental type 2 DM an elevated leukocyte count predicted the presence of several components of the metabolic syndrome and therefore the cardiometabolic risk[29]. A higher leukocyte count seems to be related to the development of micro- and macro-vascular complications in type 2 diabetic subjects and, in fact, leukocyte count results correlated with the albumin excretion rate[30] and it increases the risk of peripheral artery disease[31]. The leukocyte count, and in particular the polymorphonuclear count, is associated with the presence and the severity of diabetic retinopathy as well as DM itself[32].

Bearing in mind that a secondary hyperviscosity syndrome is present in diabetes mellitus, it is interesting to underscore the behaviour, at rest, of PMN membrane fluidity and PMN cytosolic Ca2+ concentration. As it is known, in fact, circulating leukocytes contribute to the blood hyperviscosity that characterizes this clinical condition. In our experience, however, major informations regarding these two parameters of PMN cells in diabetes mellitus may be obtained when their evaluation, including PMNs filtration, is effected during "in vitro" activation with chemiotactic agents. Employing this technique it seems also avident the different trend of these two parameters in type 1 diabetics and in type 2 diabetics.

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NITRIC OXIDE, A PROTECTIVE MOLECULE IN THE CARDIOVASCULAR SYSTEM

Lei J, Vodovotz Y, Tzeng E, Billiar TR[1]

Abstract

Nitric oxide (NO) is an intra- and inter-signaling molecule that regulates vessel dilatation, neuronal transmission, cardiac contraction, immunomodulation, and stem cell differentiation and proliferation. NO plays an important protective role in the cardiovascular system. NO inhibits smooth muscle cells proliferation and migration; enhances proliferation and migration of endothelial cell and inhibits apoptosis; suppresses platelet aggregation; and prevents platelet, leukocyte and monocyte adhesion to endothelium. NO exerts an inhibitory effect on the development of intimal hyperplasia in mechanically or immunologically injured vessel. New therapeutic approaches aimed at enhancing NO bioavailability or assisting delivery of NO locally may help patients with cardiovascular disease **[Nitric Oxide. 2013;35:175-85]. PMID: 24095696**

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A REVIEW OF METHODS TO DETERMINE THE FUNCTIONAL ARTERIAL PARAMETERS STIFFNESS AND RESISTANCE

Westerhof N, Westerhof BE[1]

Abstract

Objectives: In treatment of hypertension not only the pressure response is of interest, but also the effect on arterial parameters, for example, stiffness and resistance, is essential. We therefore reviewed what quantitative information on arterial stiffness can be obtained from pressure wave analysis.

Methods: Using data from published large cohort studies, we derived relations between stiffness and the pressure-derived variables systolic pressure, pulse pressure, augmentation index (AIx), return time of reflected wave and reflection magnitude.

Results: All pressure-derived variables give limited information on arterial function in terms of stiffness and resistance, except AIx (in low stiffness range only). Input impedance as a comprehensive description of the arterial system is too complex to derive and interpret in practice, but is accurately described by three parameters: systemic vascular resistance, total arterial stiffness, and aortic characteristic impedance (outflow tract size and proximal aortic stiffness). These parameters predict aortic pressure well in terms of magnitude and shape: with measured flow the predicted (p) and measured (m) systolic, Ps, and diastolic, Pd pressures relate as Ps,p=0.997 Ps,m-1.63 and Pd,p=1.03 Pd,m-3.12 mmHg (n=17). Therefore, methods should be developed to determine, preferably noninvasively, these three arterial parameters.

Conclusion: Variables derived from pressure wave shape alone (e.g. inflection point, AIx among others), and wave separation (e.g. reflection magnitude), while predicting cardiovascular events, give little information on arterial function. We propose to develop new, and improve existing, noninvasive methods to determine systemic vascular resistance, total arterial stiffness, and aortic characteristic impedance. This will allow quantifying the response of arterial function to treatment **[J Hypertens. 2013 Sep; 31(9):1769-75]. PMID:23777762**

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WHAT IS THE MECHANISM OF FLOW-MEDIATED ARTERIAL DILATATION

Markos F, Ruane O'Hora T, Noble MI[1]

Abstract

The present review attempts to explain the controversies concerning the mechanism of shear stress-mediated arterial dilatation, commonly called flow-mediated arterial dilatation (FMD). Flow-mediated dilatation occurs in an artery when the blood flow to the organ supplied by the artery is increased. There are two hypotheses regarding the stimulus for FMD: (i) a wave of endothelial and smooth muscle hyperpolarization, conducted in a retrograde fashion from the vasodilated peripheral vascular bed towards the relevant conduit artery; and (ii) an increase in shear stress sensed by the endothelial cells. The latter hypothesis is associated with two further postulates concerning the method of mechanotransduction of the shear stress stimulus: (i) direct transmission from endothelial cell cytoskeleton to the vascular smooth muscle to induce dilatation; and (ii) indirect transmission to the endothelial cell cytoskeleton via the glycocalyx. The virtues and inconsistencies of these hypotheses are discussed. The first hypothesis is excluded because a vasodilated peripheral vascular bed does not cause dilation of the upstream conduit artery if an increase in flow within the conduit artery is prevented and because FMD is completely blocked by inhibition of nitric oxide synthase (NOS). It is probable that the stimulus is an increase in shear stress between the blood and the adjacent layer of the arterial wall, the glycocalyx. Ultimately, a change in the endothelial cell cytoskeleton is the likely event that leads to activation of NOS and this activation does not occur without a functioning glycocalyx **[Clin Exp Pharmacol Physiol. 2013; 40(8): 489-94].PMID:23692253**

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