EDITORIAL

ADVANCEMENT REGARDING THE ROLE OF ENDOTHELIUM IN ARTERIAL WALL DYSFUNCTION

We have been working in vascular research for almost thirty years. Now, starting from some of our latest contributions in the field, we attempt here to detect and highlight just a few of the most promising current directions of scientific advancement regarding arterial wall function and dysfunction. This is a most wide and intense field of biomedical research and practice. Two major issues could be approached here altogether: (a) the arterial smooth muscle contractile activity, with the multiple factors and mechanisms that influence it; (b) the key antithrombotic mechanisms, based on a healthy endothelium and lipid composition of the blood plasma. Simply stated, given all the many causes, mechanisms, and pathological consequences of endothelial dysfunction, the unhealthy endothelium is a threat via reduced vasodilation and mainly via prothrombotic trend. The reader should keep this in mind, although we focus here only on endothelium-dependent relaxation (EDR), without specifically following atherosclerosis, or any issue in vascular remodeling. In this context, we have chosen a few recently established or detailed key points, from certain physiological and pathological chains. Five years have already passed since our reviews on the following: endothelial vasomotor control (1), evaluation of endothelial dysfunction in chronic kidney disease (CKD) (2), and arterial calcification in CKD (3). Progress in these areas has been substantial ever since, but here we refer only to endothelial vasomotor control and we try to highlight just some of the issues that have been successfully addressed most recently, also opening the most interesting perspectives.

For example, regenerated endothelium (e.g. following angioplasty) is dysfunctional, at least regarding activation of endothelial nitric oxide synthase (eNOS) and the subsequent production of nitric oxide (NO) in response to platelet products and thrombin (4, 5). This local NO based protection against vasospasm, thrombus extension, and atherosclerosis is deficient in the case of regenerated endothelium, because these cells are less responsive to serotonin and thrombin, due to the loss of transplasmalemmal transduction via inhibitory G protein (4, 5). Based on the discussion in these papers and on other studies in the field, we consider that such mechanisms could be relevant for other situations of perturbed turnover of endothelial cells and/or of increased oxidative stress.

In the complex picture of endothelium-derived vasodilators and vasoconstrictors, we constantly highlight the variability of the relative contributions of endothelium-derived relaxing factor(s) (EDRF) and of the K⁺ channels involved, due to multiple factors, such as: species, sex, age, vascular bed, arterial size, resting tension, contracting and relaxing agents (1, 6, 7). Among others, Paul Vanhoutte largely shares this view, including the importance of the involved K⁺ channels (1, 4, 8). For example related to endothelial dysfunction in aging and hypertension, in males vs females (8); the molecular mechanisms discussed therein (involving Ca²⁺-dependent K⁺ channels, adenosine monophosphate-activated pro-
tein kinase, and silent information regulator T1) deserve full attention, as one good example of possible basis for the development of new therapeutical strategies.

We always underline that, for any EDRF established so far (including NO), its arterial smooth muscle relaxing effect is accompanied by hyperpolarization. Recently Paul Vanhoutte has been using the terms "endothelium-dependent hyperpolarization" and "EDH-mediated response" referring strictly to the EDR which is independent of NO and prostacyclin (4, 8). This was previously described (and still is) as the EDR mediated by various substances acting as endothelium-derived hyperpolarizing factor (EDHF), e.g. EDHF-mediated EDR (1, 4-8). The role of epoxyeicosatrienoic acids (EET) in EDH seems well established (9), including human arteries (10), but other aspects, such as the role of endothelium-derived H₂O₂ in EDH, are more and more documented (4). We have a long-term interest in the vascular effects of H₂O₂ and the mechanisms involved (11) and we are currently examining the relative contributions of certain K⁺ channels in the EDH and subsequent relaxation induced by H₂O₂. Another well established mechanism involved in EDH and EDR (especially important in smaller distal arteries and in arterioles) is the propagation of membrane potential changes via gap junctions, which is another reason for using the generic term EDH instead of EDHF (1, 4, 12). Anyway, one should note again that the relative importance/contribution of each factor/mechanism within EDR depends on multiple conditions, so that the main EDH mechanism(s) can be quite different among species, vascular beds, etc. However, we could not spot a novel EDHF or a novel mechanism of EDH described over the last few years, so we just mention that indeed there are for example vascular beds and/or species where the EDHF role is played by substances different from those mentioned above, such as: natriuretic peptide C, anandamide, extracellular K⁺, etc.

Several factors affect NO release and/or bioavailability, by chronically decreasing it (oxidative stress, smoking, pollution, and oxidized low-density lipoproteins) or increasing it (estrogens, exercise, and appropriate diet), while it is definitely decreased in aging, diabetes, and hypertension (4). New evidence confirms the prominent EDCF role of prostacyclin (and endoperoxides), acting via the thromboxane receptors (prostanoid receptors, TP) on smooth muscle cells (4). We systematically underline that vasoconstriction is favored in all physiological and pathological situations of diminished relaxation tendency, including those of reduced EDR. In other words, increased release and/or action of constrictor prostanoids and endothelin-1 can contribute to vascular dysfunction, especially when EDR is diminished. Very recent data show that NO by itself can limit its relaxing effect, via soluble guanylyl cyclase, which in hypoxia catalyses formation of constricting cyclic inosine monophosphate (cIMP) rather than relaxing cGMP (4).

Finally, one should always remember that, although very important in small arteries and arterioles, EDH can only partially compensate NO deficit. We consider that this could be explained by a limited functional reserve of EDH. But in the perfused tissue the major aspect is the dysfunctional flow adjustment in more proximal larger arteries, because flow-mediated dilation (FMD) is impaired due to factors that reduce NO production and/or availability and/or relaxing action.
Advancement regarding the role of endothelium in arterial wall dysfunction

Overall, the above selection is clearly not a systematic approach, but one naturally driven to a certain extent by our recent studies and ongoing projects. Still, as stated in the introduction, we focused on what we consider really hot topics. These are achievements and/or trends fostering fast progress in understanding the deep mechanisms of arterial wall function and dysfunction. And they are closely linked to better perspectives in the treatment and prevention of arterial dysfunction. The latter should be considered as both cause and effect, in the frame of cardiovascular disease and in pathology in general.

We do continue to investigate the cellular calcium fluxes involved in arterial smooth muscle muscle contractile activity (7, 13) and also the arterial wall dysfunction in CKD (14, 15). Although these areas are closely related to the subject of this editorial, we decided to leave aside the recent progress therein, to be more properly addressed on other occasions.

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REFERENCES

1. Serban DN, Nilius B, Vanhoutte PM. The endothelial saga: the past, the present, the future. Pflugers Arch. 2010; 459(6): 787-792.


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**STREPTOCOCCAL MEDIASTINITIS AFTER THYROIDECTOMY – A LIFE THREATENING COMPLICATION**

Surgical site infections after thyroid surgery are mostly superficial and can be well treated. A rare and life threatening complication is streptococcal mediastinitis. More than 20 cases have been published on this phenomenon, 11 of which had a fatal outcome. The signs and symptoms are represented of high septic fever, increase of inflammation parameters and surgical site erythema in the early postoperative period after thyroid surgery. These can be signs of a GAS (group A Streptococcus) three-compartment infection, which might lead to necrotizing, descending, life-threatening mediastinitis. Early diagnosis with support of computed tomography (CT) scans, immediate therapy are vital. The therapy can be for 6 weeks or more and include repeated wound revisions (wound opening and lavage with the patient under general anesthesia), intravenous pathogen-adapted antibiotic treatment (penicillin and clindamycin). If treatment resistance occurs, cervical negative pressure treatment should be considered to control the infection. (Bures C et al. Streptococcal mediastinitis after thyroidectomy: A literature review. *Der Chirurg*, 05.02.2015, doi: 10.1007/s00104-014-2972-y. 104: 1-6).

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