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COMMENTARY

Insights into human hypertension: the role of endothelial dysfunction

C Giansante and N Fiotti
Department of Clinical Morphological and Technological Sciences, UCO Clinica Medica, University of Trieste, Trieste, Italy

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Atherosclerosis is considered an ubiquitous pathological process. In patients symptomatic for coronary artery or carotid or peripheral arterial disease, other localizations – still asymptomatic – of atherosclerotic lesions are often found. Despite this consideration, the patterns of arteries developing atherosclerosis can be quite diverse: for example, lesions prevalently develop in regions where the flow is either low or turbulent such as where artery bifurcates, mammalian artery are nearly unaffected by atherosclerosis.[1]

So, what makes the difference? The answer probably lies in the marked phenotypic variation between endothelial cells in the different vascular locations, and in the different responses of the vascular layers to the same stimulus in the same individual, as well.

Indeed, the vascular endothelium, once believed to be an inert edge between artery and blood, is now recognized as an *organ per se*.[2] Many studies over the past 10 years indicate that endothelial cells have important transport functions, act as the provision of an antithrombogenic interface, control of platelet adherence and thrombosis, as well as active actions in inflammation and vascular tone. Indeed, use of simple drugs such as aspirin may influence endothelial function in hypertension.[3,4] Endothelial cells also facilitate the transport of glucose by GLUT,[5] mainly present in brain barrier, of amino acids (such as L-arginine, a substrate for nitric oxide (NO)). Recent data even suggest a relationship of the endothelium to angiogenesis.[6] In addition, hypertensive patients with diabetes mellitus have endothelial dysfunction that can be related to urinary albumin excretion and inflammation, as well as modified by antihypertensive therapy.[7–9] Of note, endothelial cells may be actively involved in inflammation through the expression of Toll-like receptors –4 and –2, leading to increased expression of inflammation mediators such as chemokines, adhesion molecules and metalloproteinase.[10] Finally, endothelial cells are also intimately involved in haemostasis and coagulation by the production of substances such as tissue factor pathway inhibitor, thrombomodulin, endothelial protein C receptor and von Willebrand factor.[5]

Of particular interest, in the pathophysiology of the endothelium, is the endothelial regulation of vascular tone.[2] Endothelial cells produce several vasoactive substances, and among them is NO, the most powerful vasodilator.[2] NO is produced by endothelial cells via NOS III (eNOS) or via NOS II (iNOSII), where the former is constitutive and acts to maintain the vascular musculature in a state of vasodilatation, while the latter is inducible by immunological stimuli.[2,11] Indeed, several studies have demonstrated that low NO, whose circulating levels are considered as a surrogate of endothelial dysfunction, is an early marker in patients with common cardiovascular risk factors, such as diabetes, smoking and hypertension.[2]

In a recent issue of the *Journal of Human Hypertension,* Srivastava *et al.*[12] confirm that in patients with essential hypertension, NO is significantly lower than in healthy controls and that smoking habit markedly decreases NO production. The authors also examined the role of vascular cell adhesion molecule (VCAM)-1 and E-selectin, as well as the relationship between those and systolic blood pressure (SBP) and/or diastolic blood pressure (DBP). This study illustrates the complex endothelial interactions between several actors in a complex 'play', including cytokines, growth factors, adhesion molecules, vasoactive substances and chemokines. Their results indicate that sVCAM-1 and E-selectin are significantly increased in hypertension; however, even though they confirm the presence of endothelial dysfunction, no relationships among these markers are detailed. However, NO significantly correlated with E-selectin ($r=-0.42$) and with sVCAM ($r=-74$), both in controls and patients, but no correlation was found between SBP or DBP and E-selectin or sVCAM. Also, the relationship between NO and SBP, although significant ($P=0.045$), is very weak in patients ($r=-0.137$) and absent in controls.

Correspondence: Professor C Giansante, UCO Clinica Medica, Department of Clinical Morphological and Technological Sciences, University of Trieste, Trieste, Italy.
E-mail:giansant@univ.trieste.it
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Indeed, these data may reflect the complexity of endothelial response to different stimuli, and show that more knowledge is probably needed in the detailed pathophysiology of the endothelium.[2] Of note, endothelial dysfunction in hypertension may occur very early, even in white coat hypertension.[13]

Another aspect of this complexity emerges from the therapeutic targeting of endothelium impairment. The ACE inhibitors are well known to modulate the endothelium in hypertension and heart failure.[13] Indeed, many strategies have also been used to correct reduced synthesis or increased degradation of NO in many pathological conditions, such as heart failure.[14] To increase the availability of NO, a supplementation of L-arginine – the substrate for NO synthesis – has been administered in patients with heart failure, and a beneficial effect was found in the 6-min walk test. Another therapeutic approach consists in administering a direct donor of NO – nitroglycerin – but with more controversial results.[15] A possible new and promising approach consisted in administering atorvastatin that improves endothelial function by reducing the expression of cytokines and adhesion molecules.

Our knowledge continues to expand in anti-inflammatory and antiatherosclerotic effect of endothelial function. As an example, Yamawaki *et al.*[16] identified a molecule (thioredoxin interacting protein) whereby shear stress exerts beneficial effects in the endothelium; therapeutic efforts targeting to this pathway could be a new, and hopefully efficient, approach to endothelial dysfunction. What are the implications for our everyday management of this common condition? Almost certainly, a greater understanding of the detailed pathophysiology of endothelial dysfunction in hypertension, and the extensive inter-relating processes, such as angiogenesis, thrombogenesis and inflammation, may allow us to identify new therapeutic targets and improve management options,[17] to reduce the great burden of hypertension on cardiovascular disease and stroke.[18] We can only hope that detailed assessment of the endothelium would help us in this way!

References

1 Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* 1988; **112**: 1018–1031, Review.
2 Chowdhary S, Townend JN. Nitric oxide and hypertension: not just an endothelium derived relaxing factor!. *J Hum Hypertens* 2001; **15**(4): 219–227.
3 Magen E, Viskoper JR, Mishal J, Priluk R, London D, Yosefy C. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. *J Hum Hypertens* 200; **19**(9): 667–673.
4 Felmeden D, Nadar SK, Lip GY. Aspirin and endothelial function in hypertension. *J Hum Hypertens* 2005; **19**(9): 663–665.
5 Mann GE, Yudilevich DL, Sobrevia L. Regulation of amino acid and glucose transporters in endothelial and smooth muscle cells. *Physiol Rev* 2003; **83**: 183–252.
6 Karter Y, Aydin S, Curgunlu A, Uzun H, Erturk N, Vehid S *et al.* Endothelium and angiogenesis in white coat hypertension. *J Hum Hypertens* 2004; **18**(11): 809–814.
7 Varughese GI, Lip GY. Hypertension in patients with type-II diabetes: relation to urinary albumin excretion, endothelial function and inflammation. *J Hum Hypertens* 2005; **19**(6): 421–424.
8 Czarnecka D, Kawecka-Jaszcz K, Stolarz K, Olszanecka A, Dembinska-Kiec A, Kiec-Wilk B. Ambulatory blood pressure, left ventricular mass and vascular phenotypes in relation to the endothelial nitric oxide synthase gene Glu298Asp and intron 4 polymorphisms in a population-based family study. *J Hum Hypertens* 2005; **19**(5): 413–420.
9 Schram MT, van Ittersum FJ, Spoelstra-de Man A, van Dijk RA, Schalkwijk CG, Ijzerman RG *et al.* Aggressive antihypertensive therapy based on hydrochlorothiazide, candesartan or lisinopril as initial choice in hypertensive type II diabetic individuals: effects on albumin excretion, endothelial function and inflammation in a double-blind, randomized clinical trial. *J Hum Hypertens* 2005; **19**(6): 429–437.
10 Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol* 2001; **1**: 135–145.
11 Bautista LE. Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. *J Hum Hypertens* 2003; **17**(4): 223–230.
12 Srivastava K, Narang R. Nitric oxide and cell adhesion molecules in Essential Hypertension, a case control study. *J Hum Hypertens*, in press.
13 Coban E, Timuragaoglu A, Ozdogan M. Edothelial dysfunction in patients with white coat hypertension. *J Hum Hypertens* 2004; **18**(1): 71–72.
14 Neutel JM. Effect of the rennin–angiotensin system on the vessel wall: using ACE inhibition to improve endothelial function. *J Hum Hypertens* 2004; **18**(9): 599–606.
15 Tousoulis D, Charakida M, Stefanadis C. Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure. *Int J Cardiol* 2005; **100**: 347–353.
16 Yamawaki H, Pan S, Lee RT, Berk BC. Fluid shear stress inhibits vascular inflammation by decreasing thioredoxin-interacting protein in endothelial cells. *J Clin Invest* 2005; **115**: 733–738.
17 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF *et al.* British Hypertension Society. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**(3): 139–185.
18 He FJ, MacGregor GA. Cost of poor pressure control in the UK: 62000 unnecessary deaths per year. *J Human Hypertens* 2003; **17**: 455–457.