Endothelial dysfunction in hypertension: implications for treatment

Stefano Taddei[a] and Rosa Maria Bruno[b]

See original paper on page 1128

In a review article appearing in the current issue of the *Journal of Hypertension* [1], the authors critically discuss several aspects of nitric oxide signaling, which characterize experimental models of hypertension. In particular, they considered the known mechanisms of endothelial nitric oxide synthase (eNOS) dysfunction, the consequences of eNOS uncoupling in hypertension, and novel therapies potentially targeting uncoupled eNOS in hypertension.

A large body of evidence invariably demonstrates that endothelial dysfunction is a hallmark of the hypertensive patient [2,3]. So far, the main cause of hypertension-related endothelial dysfunction, in humans as well as in experimental animals, has been identified with an increased nitric oxide breakdown. In particular, hypertension-related endothelial dysfunction has been demonstrated to be the consequence of increased production of reactive oxygen species (ROS) [3]. ROS, mainly superoxide anions, are highly reactive and destroy nitric oxide, thus reducing its bioavailability and producing peroxynitrites [4]. Various enzymatic and nonenzymatic sources of ROS have been described to be activated in endothelial cells, smooth muscle cells, and inflammatory cells within the arterial wall of the hypertensive patients, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, cyclooxygenase, and uncoupled eNOS, as nicely discussed in the review by Li *et al.* [1].

In hypertensive patients, endothelial function has been associated with vascular target organ damage: this is physiopathologically sound, since endothelial function is considered the first step of atherosclerosis. The first observation of a relationship between increased carotid intima-media thickness (IMT) and endothelial dysfunction was shown in the forearm microcirculation of untreated hypertensive patients [5]. In a cross-sectional study in middle-aged healthy men, there was no evident correlation between brachial flow-mediated dilation (FMD) and IMT [6], whereas FMD predicted IMT progression in hypertensive, postmenopausal women [7]. Similarly, endothelial function is not related with arterial stiffness, measured as pulse wave velocity, in healthy individuals [8] and in nondiabetic hypertensive individuals, whereas the relationship is significant in hypertensive patients with diabetes [9]. In contrast, a weaker relationship has been found with cardiac and renal organ damage. For example, Treasure *et al.* [10] found that left ventricular hypertrophy is associated with impaired endothelium-mediated relaxation in human coronary resistance vessels of hypertensive patients, whereas in other studies, no significant difference in FMD was observed between patients with or without left ventricular hypertrophy or among patients with different geometric patterns [11]. Furthermore, despite both microalbuminuria and endothelial dysfunction are considered as expressions of endothelial pathology, no correlation between urinary albumin excretion and vasodilatation in response to acetylcholine or to sodium nitroprusside in the forearm microcirculation was found in essential hypertensive patients [12].

It is worth noting that hypertension-related endothelial dysfunction does not seem to represent a pathogenetic mechanism for the increased blood pressure values, as there is no association between the degree of endothelial dysfunction and blood pressure values [13]. The condition seems rather to be partly genetically determined, and accordingly, offspring of hypertensive patients, although normotensive, show impaired endothelial function [14]. Finally, endothelial dysfunction is not a specific feature of hypertension, but it is also a feature of other pathological conditions, namely diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, and obesity, not characterized by high blood pressure, in which reduced nitric oxide availability occurs [15]. A small hypotensive activity was demonstrated in short-term trials with ascorbic acid [16] or flavanol-rich food [17], but it needs to be confirmed in long-term trials. However, other mechanisms beyond endothelial function restoration might be responsible for the blood pressure-lowering effect of antioxidants [18].

Taken together, these studies suggest that the role of endothelial dysfunction in directly causing hypertension

Journal of Hypertension 2015, 33:1137–1138

[a]Department of Clinical and Experimental Medicine, University of Pisa and [b]Institute of Clinical Physiology – CNR, Pisa, Italy

Correspondence to Stefano Taddei, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 67 56126, Pisa, Italy. Tel: +39 050 993458; fax: +39 050 992409; e-mail: stefano.taddei@med.unipi.it

DOI:10.1097/HJH.0000000000000609

is still a matter of debate. However, the possibility of ameliorating endothelial dysfunction in hypertensive patients might have an important prognostic value beyond the direct impact on blood pressure values. Indeed, in 172 prospectively identified uncomplicated hypertensive patients, followed up for 95 months, a low flow-mediated vasodilatation conferred an increased risk of cardiovascular events after controlling for classical risk factors including left ventricular mass [19]. Lack of restoration of endothelial function despite conventional treatment might identify a subset of 'nonresponders', who might be suitable for more intensive or new therapeutic approaches, such as those targeting eNOS uncoupling [1]. In a study conducted in 251 Japanese men with newly diagnosed stable coronary artery disease and concurrent endothelial dysfunction, FMD was repeated after 6 months of optimized individualized therapy. Those patients with persistently impaired FMD had significantly higher event rates in the follow-up period compared to those with normal FMD [20]. In a similar study, endothelial function was assessed in 400 postmenopausal hypertensive women without evidence of coronary artery disease at baseline and 6 months after effectively treating blood pressure. In those women whose FMD had not improved, there was an almost seven-fold increase in cardiovascular events over the average 67-month follow-up [21].

In conclusion, supplementation with tetrahydrobiopterin, sepiapterin, or inhibitors of NADPH oxidase may represent promising new therapeutic interventions able to preserve eNOS coupling activity in hypertension [1]. However, on the basis of the current knowledge, we should not necessarily expect a blood pressure-lowering effect from this kind of intervention. Nevertheless, restoration of endothelial function in hypertensive patients might have a relevant impact in improving their cardiovascular prognosis. When and whether drugs targeting NOS uncoupling will be available for human use, adequately powered, long-term interventional trials should assess their effects of delaying vascular aging and reducing cardiovascular events.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Li Q, Youn J-Y, Cai H. Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension. *J Hypertens* 2015; 33:1128–1136.
2. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990; 323:22–27.
3. Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation* 1998; 97:2222–2229.
4. Munzel T, Gori T, Bruno RM, Taddei S. Is oxidative stress a therapeutic target in cardiovascular disease? *Eur Heart J* 2010; 31:2741–2748.
5. Ghiadoni L, Taddei S, Virdis A, Sudano I, Di Legge V, Meola M, *et al.* Endothelial function and common carotid artery wall thickening in patients with essential hypertension. *Hypertension* 1998; 32:25–32.
6. Yan RT, Anderson TJ, Charbonneau F, Title L, Verma S, Lonn E. Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. *J Am Coll Cardiol* 2005; 45:1980–1986.
7. Rossi R, Nuzzo A, Olaru AI, Origliani G, Modena MG. Endothelial function affects early carotid atherosclerosis progression in hypertensive postmenopausal women. *J Hypertens* 2011; 29:1136–1144.
8. Koivistoinen T, Virtanen M, Hutri-Kahonen N, Lehtimaki T, Jula A, Juonala M, *et al.* Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: The Cardiovascular Risk in Young Finns Study and the Health 2000 Survey. *Atherosclerosis* 2011.
9. Bruno RM, Penno G, Daniele G, Pucci L, Lucchesi D, Stea F, *et al.* Type 2 diabetes mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction. *Diabetologia* 2012.
10. Treasure CB, Klein JL, Vita JA, Manoukian SV, Renwick GH, Selwyn AP, *et al.* Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. *Circulation* 1993; 87:86–93.
11. Muiesan ML, Salvetti M, Monteduro C, Corbellini C, Guelfi D, Rizzoni D, *et al.* Flow-mediated dilatation of the brachial artery and left ventricular geometry in hypertensive patients. *J Hypertens* 2001; 19 (3 Pt 2):641–647.
12. Taddei S, Virdis A, Mattei P, Ghiadoni L, Sudano I, Arrighi P, *et al.* Lack of correlation between microalbuminuria and endothelial function in essential hypertensive patients. *J Hypertens* 1995; 13:1003–1008.
13. John S, Schmieder RE. Impaired endothelial function in arterial hypertension and hypercholesterolemia: potential mechanisms and differences. *J Hypertens* 2000; 18:363–374.
14. Taddei S, Virdis A, Mattei P, Ghiadoni L, Sudano I, Salvetti A. Defective L-arginine-nitric oxide pathway in offspring of essential hypertensive patients. *Circulation* 1996; 94:1298–1303.
15. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, *et al.* Endothelial function and dysfunction. Part II: association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. *J Hypertens* 2005; 23:233–246.
16. Juraschek SP, Guallar E, Appel LJ, Miller ERF 3rd. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2012; 95:1079–1088.
17. Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP. Effect of cocoa on blood pressure. *Cochrane Database Syst Rev* 2012; 8:CD008893.
18. Bruno RM, Daghini E, Ghiadoni L, Sudano I, Rugani I, Varanini M, *et al.* Effect of acute administration of vitamin C on muscle sympathetic activity, cardiac sympathovagal balance, and baroreflex sensitivity in hypertensive patients. *Am J Clin Nutr* 2012; 96:302–308.
19. Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Poisa P, *et al.* Prognostic role of flow-mediated dilatation of the brachial artery in hypertensive patients. *J Hypertens* 2008; 26:1612–1618.
20. Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, *et al.* Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. *J Am Coll Cardiol* 2009; 53:323–330.
21. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol* 2002; 40:505–510.