Oxidative stress, the capo of endothelial dysfunction in chronic renovascular hypertension

Hypertension is one of the most common chronic illnesses, along with diabetes mellitus, that the world faces. Numerous previous studies have shown that hypertension is a significant risk factor for stroke, myocardial infarction, heart failure, arterial fibrillation, aortic dissection, and peripheral arterial diseases [1,2]. Even though the development of effective pharmacological strategies for blood pressure control is a notable and worthwhile medical achievement of the 20th century, hypertension remains a leading cause of death worldwide and one of the world’s greatest public health problems [3].

A large body of evidence has shown that hypertensive patients are characterized by endothelial dysfunction and a spectrum of pathophysiological changes in the vascular endothelium at the macro- and microcirculation levels, which result in a loss of vascular homeostasis [4]. The dysfunctional endothelium gives rise to cardiovascular events. In addition, the degree of endothelial dysfunction is correlated significantly with cardiovascular outcomes [5]. Various molecules mediating vasoconstriction, vasodilatation, inflammation, and thrombosis are involved in the development of endothelial dysfunction. However, the 1998 Nobel Prize-winner Robert Furchgott proved in a pioneering report that endothelial dysfunction consists primarily of dysregulation in vasodilation [6]. Nitric oxide (NO) is a primary mediator of endothelium-dependent vasodilatation [7].

Nitric oxide is produced in the blood vessel wall through the transformation process of L-arginine into citrulline by the activity of the constitutive enzyme endothelial NO synthase. The production of NO is influenced by several agonists such as acetylcholine, bradykinin, substance P, serotonin, and other ligands acting on specific endothelial receptors and influenced by mechanical forces such as shear stress [7]. Blood vessels are physiologically maintained in a dilated state that is mediated by a stable level of NO. However, in pathological conditions, the balance of NO is jeopardized by an excessive level of reactive oxygen species (ROS), which leads to a breakdown of NO [8].

Several stimuli such as proinflammatory tumor necrosis factor-α, asymmetrical dimethyl-arginine, angiotensin II, and shear stress—all of which are associated with the development of hypertension—induce endothelial dysfunction [9]. However, the molecular mechanisms underlying the impaired endothelial modulation by these stimuli are not extensively clarified. Miyagawa et al [10] recently showed that abnormal endothelial modulation of vascular contraction in the femoral arteries of spontaneously hypertensive rats (SHR) was mostly the result of increased production of superoxide anions by nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidase. Angiotensin II type 1 receptor blockade with CV-11974 (an active form of the angiotensin II type 1 receptor antagonist candesartan) moreover had no effect on norepinephrine-induced contraction in SHR arteries, which suggested that the angiotensin II type 1 receptor was not involved in the activation of NADH/NADPH oxidase under their experimental conditions. Because the pathophysiological mechanism of hypertension in the SHR model is not fully understood, it is not easy to dissect the effect of individual stimulus on endothelial function with this animal model of hypertension [11].

In this issue of Kidney Research and Clinical Practice, Choi et al [12] try to explore further the possible mechanisms underlying impaired endothelial modulation by using two-kidney one clip (2K1C) hypertension rats as an animal model of chronic renovascular hypertension in humans. After removing the endothelium or treating specimens with Nω-nitro-L-arginine methylester (L-NAME, which inhibits the endogenous production of NO from L-arginine), norepinephrine-induced contraction was significantly more augmented in sham-operated control rats (CON) than in 2K1C rats. Furthermore, the amount of NO released during norepinephrine-induced contraction was not different between arteries obtained from the CON rats and the 2K1C rats. Based on these findings, they suggest that the production of endothelium-derived NO is impaired because of increased inactivation of NO rather than because of decreased NO production in 2K1C hypertension. Choi et al further carefully explore the pathophysiology of impaired endothelium-derived NO in 2K1C rats by measuring the contractile capacity of aorta specimens from these rats. They demonstrated that norepinephrine-induced contraction was significantly suppressed by vitamin C, diphenyleneiodonium, apocynin, or inhibitors of NADH/NADPH oxidase in aortic rings with intact endothelium from 2K1C rats, but not from CON rats. This indicates that the production of ROS is most likely involved in endothelial dysfunction in 2K1C hypertension. In addition, allopurinol had no effect on the contraction of aortic rings from 2K1C rats. This supports the
notion that ROS production in this rat model is influenced by NADH/NADPH oxidase rather than by xanthine oxidase. The authors collectively propose that endothelial dysfunction in an animal model of chronic renovascular hypertension may be because of inactivation of NO resulting from increased ROS production by NADH/NADPH oxidase.

The study by Choi et al is interesting because it provides insights on the possible underlying mechanism of angiotensin II-induced endothelial dysfunction in hypertension. The renin–angiotensin system is activated in renovascular hypertension, which results in increased circulating angiotensin II levels. Based on the findings of Choi et al, increased circulating angiotensin II may activate NADH/NADPH oxidase and enhance ROS production in the vascular endothelium. Previous findings from in vitro experiments showing that angiotensin II stimulates the generation of superoxide anion radicals in cultured vascular smooth muscle cells also support this notion [13]. However, it should be recognized that even though the levels of circulating angiotensin II are increased in 2K1C rat models, the exact mechanism for high blood pressure is still unclear. The authors moreover did not examine the direct effect of angiotensin II receptor blockade on norepinephrine-induced vascular contraction. Therefore, further investigations are needed to elucidate the exact mechanism of angiotensin II-induced endothelial dysfunction.

In summary, the study findings of Choi et al provide a proper description of the source of superoxide production, and they showed that oxidative stress is a key player related to endothelial dysfunction in chronic renovascular hypertension. In spite of the aforementioned limitations, the results are intriguing and allow us to understand further the pathophysiology of vascular endothelial dysfunction in hypertension. Judging by the given evidence, nevertheless, it is unclear whether oxidative stress is the capo or just an associate of endothelial dysfunction.

Conflicts of interest

None to declare.

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References

[1] Ibrahim MM, Damasceno A: Hypertension in developing countries. Lancet 380:611–619, 2012
[2] Kannel WB: Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 275:1571–1576, 1996
[3] Laurent S, Schlaich M, Ester M: New drugs, procedures, and devices for hypertension. Lancet 380:591–600, 2012
[4] Virdis A, Ghiadoni L, Versari D, Giannarelli C, Salvetti AT, Addei S: Endothelial function assessment in complicated hypertension. Curr Pharm Des 14:1761–1770, 2008
[5] Munzel T, Sinning C, Post F, Warnholtz A, Schulz E: Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. Ann Med 40:180–196, 2008
[6] Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376, 1980
[7] Luscher TF, Barton M: Biology of the endothelium. Clin Cardiol 20 (11 Suppl 2):II–3–10, 1997
[8] Tschudi MR, Mesaros S, Luscher TF, Malinski T: Direct in situ measurement of nitric oxide in mesenteric resistance arteries. Increased decomposition by superoxide in hypertension. Hypertension 27:32–35, 1996
[9] Esper RJ, Nordaby RA, Vilarino JO, Paragano A, Cacharron JL, Machado RA: Endothelial dysfunction: a comprehensive appraisal. Cardiovasc Diabetol 5:4, 2006
[10] Miyagawa K, Ohashi M, Yamashita S, Kojima M, Sato K, Ueda R, Dohi Y: Increased oxidative stress impairs endothelial modulation of contractions in arteries from spontaneously hypertensive rats. J Hypertens 25:415–421, 2007
[11] Horie R, Kihara M, Lovenberg W, Ben-Ishay D, Bianchi G, Iwai J, Nagaoka A, Rapp JP, Sassard J, Simpson FO: Comparison of various genetic hypertensive rat strains. J Hypertens Suppl 4:S11–S14, 1986
[12] Choi S, Shin HR, Kim SH, Lee MJ, Jun YJ, Kim HL, Chung JH: Effects of oxidative stress on endothelial modulation of contractions in aorta from renal hypertensive rats. Kidney Res Clin Pract 33:19–25, 2014
[13] Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW: Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 74:1141–1148, 1994

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