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Editorial

Moving Beyond the Endothelium is Still Challenging-Complex Interplay between Endothelin and Reactive Oxygen Species in Pulmonary Arterial Hypertension

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▸ See the article "Effect of Ambrisentan Therapy on the Expression of Endothelin Receptor, Endothelial Nitric Oxide Synthase and NADPH Oxidase 4 in Monocrotaline-induced Pulmonary Arterial Hypertension Rat Model" in volume 49 on page 866.

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Conflict of Interest
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Pulmonary arterial hypertension (PAH) is a complex and devastating syndrome that involves pulmonary vasoconstriction and pulmonary vascular remodeling, which results from unique pathophysiologic mechanisms involving endothelin and reactive oxygen species (ROS).[1)2)] Several factors, from molecular and cellular mechanisms to epigenetics and environmental factors, have been studied and are known to be involved in the pathophysiology of PAH. Vasoactive substances cause pulmonary vasoconstriction and increase pulmonary vascular resistance, which leads to an increase in the right ventricular (RV) pressure and finally death due to RV failure. Endothelin-1 (ET-1) is a powerful vasoconstrictor, which induces proliferation of vascular smooth muscle cells, and is a therapeutic target for pharmacological treatment.[3)] Several compounds that can block the endothelin receptors have been developed.[1)3)4)]

ROS is generated by endothelial nitric oxide synthase (eNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX), which comprise seven family members (Nox1–Nox5 and dual oxidase 1 and 2).[5)] NOX-derived ROS are key factors involved in promoting pulmonary vascular remodeling.[6)] Of these, NOX4 is prominently expressed in the pulmonary artery adventitia and contributes towards hypertensive vascular remodeling and development of PAH.[6)] In an experimental PAH rat model, NOX4 protein expression level was increased by ET-1 treatment in the pulmonary arterial smooth muscle cells; this highlights the possible interplay between endothelial cells and other cells, such as smooth muscle cells and cells in the adventitia in PAH.[7-9)]

In this issue of the *Korean Circulation Journal*, Lee et al.[10)] investigated the effects of ambrisentan treatment, which is a selective endothelin type A receptor antagonist, in the monocrotaline-induced PAH rat model. The authors report that ambrisentan treatment resulted in the recovery of the body weight and RV hypertrophy, lowered the RV pressure, and restored the ET-1 and eNOS protein expression levels, thus, proving the concept of the interplay between endothelin and ROS causing PAH and vice versa. However, the expression level of NOX4 remained unaffected.[10)] This was unexpected and may be due to the limitations of the study,

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such as fixed (low) dose of ambrisentan, inadequate treatment period, and the limited number of animals used in the study. Therefore, further studies must be conducted to clarify the relationship between endothelin and NOX4 and to prove the interplay between the different cells in the lung tissue in PAH. Better understanding of this complex interplay among different vascular cell types in PAH may contribute towards the identification of novel therapeutic targets and decreasing the PAH-related morbidity and mortality rates in the future.[8)]

REFERENCES

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67-119.
PUBMED | CROSSREF
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34-41.
PUBMED | CROSSREF
3. Chester AH, Yacoub MH. The role of endothelin-1 in pulmonary arterial hypertension. *Glob Cardiol Sci Pract* 2014;2014:62-78.
PUBMED | CROSSREF
4. Kim KH, Kim HK, Chan SY, Kim YJ, Sohn DW. Hemodynamic and histopathologic benefits of early treatment with macitentan in a rat model of pulmonary arterial hypertension. *Korean Circ J* 2018;48:839-53.
PUBMED | CROSSREF
5. Chen F, Haigh S, Barman S, Fulton DJ. From form to function: the role of Nox4 in the cardiovascular system. *Front Physiol* 2012;3:412.
PUBMED | CROSSREF
6. Barman SA, Chen F, Su Y, et al. NADPH oxidase 4 is expressed in pulmonary artery adventitia and contributes to hypertensive vascular remodeling. *Arterioscler Thromb Vasc Biol* 2014;34:1704-15.
PUBMED | CROSSREF
7. Lee H, Kim KC, Hong YM. Change of voltage-gated potassium channel 1.7 expressions in monocrotaline-induced pulmonary arterial hypertension rat model. *Korean J Pediatr* 2018;61:271-8.
PUBMED | CROSSREF
8. Nogueira-Ferreira R, Ferreira R, Henriques-Coelho T. Cellular interplay in pulmonary arterial hypertension: implications for new therapies. *Biochim Biophys Acta* 2014;1843:885-93.
PUBMED | CROSSREF
9. Barman SA, Fulton D. Adventitial fibroblast Nox4 expression and ROS signaling in pulmonary arterial hypertension. *Adv Exp Med Biol* 2017;967:1-11.
PUBMED | CROSSREF
10. Lee H, Yeom A, Kim KC, Hong YM. Effect of ambrisentan therapy on the expression of endothelin receptor, endothelial nitric oxide synthase and NADPH oxidase 4 in monocrotaline-induced pulmonary arterial hypertension rat model. *Korean Circ J* 2019;49:866-76.
PUBMED | CROSSREF