Soluble VE-cadherin: not just a marker of endothelial permeability

Received: 13 Aug 2021
Accepted: 19 Aug 2021

To the Editor:

Recently, the publication by HARKI *et al*. [1] in the *European Respiratory Journal* reported higher levels of serum soluble VE-cadherin (sVE) in volunteers exposed to intermittent hypoxia (IH), as well as in patients with obstructive sleep apnoea (OSA). They further demonstrated that IH induced VE-cadherin cleavage through reactive oxygen species production and activation of HIF-1, VEGF and tyrosine kinase pathway, indicating that serum sVE could be a promising biomarker of increased endothelial permeability in OSA patients. The results are meaningful since there is, as yet, no endothelium-specific biomarker for the early diagnosis of endothelial barrier disruption in OSA patients. However, it is worth noting that sVE may not be just a marker of endothelial permeability.

First, VE-cadherin is the major transmembrane adhesion molecule responsible for maintenance of endothelial barrier integrity. VE-cadherin can be cleaved from the cell surface by proteolytic cleavage, resulting in the generation of a 90-kDa fragment referred to as sVE [2]. Hence, the level of sVE may signify the presence of increased endothelial permeability in theory. HARKI *et al*. [1] have reported increased levels of sVE in patients with OSA; however, the absence of correlative data between sVE and long-term cardiovascular outcomes, such as flow-mediated vasodilation (FMD), circulating inflammatory and metabolic biomarkers, peripheral arterial tonometry, or blood pressure made it less convincing that serum sVE represents a valid marker for endothelial dysfunction in OSA patients.

Second, sVE may be a marker of inflammation in OSA patients. Notably, sVE is a marker of inflammation as elevated levels of sVE have been reported in various systemic vasculitis conditions, such as rheumatoid arthritis, Behçet's disease and Henoch–Schönlein purpura, as well as urticarial and allergic vasculitis, under conditions of chronic inflammation, and also in patients with severe sepsis [3]. Incubation of endothelial cells with pro-inflammatory cytokines such as tumour necrosis factor-α and bacterial lipopolysaccharide led to significantly increased serum sVE [2]. Meanwhile, inflammation and oxidative stress are the hallmarks of OSA, thus, it is possible that higher sVE reported by HARKI *et al*. [1] may represent increased systemic inflammation rather than endothelial permeability of OSA.

Third, sVE may participate in the pathophysiological process of OSA induced vascular injury, rather than simply being a biomarker. The authors demonstrated that IH-induced endothelial barrier disruption is accompanied by formation of sVE. However, it was unclear from the study whether sVE is only the result of the cleavage of VE-cadherin, or if sVE has a particular function of itself. It has previously been observed that sVE-cadherin contributes to inflammation-induced disruption of the endothelial barrier by interfering with VE-cadherin interaction, indicating that sVE may play a role in the pathophysiological process directly [4].

In summary, serum sVE may be an innovative biomarker of endothelial permeability; however, it would be clearer if the validity of serum sVE was be further investigated with regards to the relationship with conventional FMD or other endothelium indicators. Besides, the specificity of sVE as the biomarker of endothelial permeability is doubtful, as it may also represent systemic inflammation. Further, it should be clarified whether the generation of sVE has biological function itself, which implies a novel target for therapeutic efforts.

Shareable abstract (@ERSpublications)
Serum soluble VE-cadherin holds a promise as a marker of endothelial permeability; further investigations are still needed to confirm the sensitivity and specificity, and extend the existing findings https://bit.ly/2WujSCc

Cite this article as: Li SQ, Lin YN, Li QY. Soluble VE-cadherin: not just a marker of endothelial permeability. *Eur Respir J* 2021; 58: 2102241 [DOI: 10.1183/13993003.02241-2021].

Shi Qi Li[1,2,3], Ying Ni Lin[1,2,3] and Qing Yun Li[1,2]

[1]Dept of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [2]Institute of Respiratory Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [3]Co-first author.

Corresponding author: Qing Yun Li (liqingyun68@hotmail.com)

Conflict of interest: None declared.

References

1 Harki O, Tamisier R, Pépin J-L, *et al.* VE-Cadherin cleavage in sleep apnoea: new insights into intermittent hypoxia-related endothelial permeability. *Eur Respir J* 2021; 58: 2004518.

2 Sidibe A, Mannic T, Arboleas M, *et al.* Soluble VE-cadherin in rheumatoid arthritis patients correlates with disease activity: evidence for tumor necrosis factor alpha-induced VE-cadherin cleavage. *Arthritis Rheum* 2012; 64: 77–87.

3 Blaise S, Polena H, Vilgrain I. Soluble vascular endothelial-cadherin and auto-antibodies to human vascular endothelial-cadherin in human diseases: two new biomarkers of endothelial dysfunction. *Vasc Med* 2015; 20: 557–565.

4 Flemming S, Burkard N, Renschler M, *et al.* Soluble VE-cadherin is involved in endothelial barrier breakdown in systemic inflammation and sepsis. *Cardiovasc Res* 2015; 107: 32–44.