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

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Reply to Shi Qi Li and co-workers:

We thank Shi Qi Li and co-workers for their interest in our work [1] and comments allowing us to extend the knowledge gained from our data. Our experiments in cultured human endothelial cells have shown that intermittent hypoxia (IH) directly leads to increased endothelial VE-cadherin cleavage, increased sVE release and endothelial permeability, without involvement of systemic inflammatory processes. Endothelial permeability is a key event in early vascular alterations leading to remodelling and atherosclerosis, and it is of crucial importance to decipher this initial process. Although endothelial adhesion markers have already been studied in obstructive sleep apnoea (OSA) patients [2, 3], this is the first time to our knowledge that VE-cadherin regulation and its consequences in terms of endothelial permeability has been addressed in OSA.

In our population consisting of relatively healthy OSA patients without comorbidities, there was no endothelial dysfunction as documented by normal peripheral arterial tonometry. We think that VE-cadherin might represent an early stage biomarker, detectable before the occurrence of cardiovascular complications related to endothelial dysfunction. We therefore agree with Shi Qi Li and co-workers that future studies will be needed in larger cohorts, including more advanced stages or comorbidities, to determine whether sVE remains associated with patient endothelial dysfunction and its severity, as assessed by peripheral arterial tone or flow-mediated dilation.

In our study we reported that 24-h systolic and diastolic blood pressures were statistically associated with an increase in circulating sVE level ($p=0.0002$) [1]. We found a correlation between levels of 24-h systolic blood pressures and sVE: slope 0.02, 95% CI 0.01 to 0.03; intercept −3.09, 95% CI −4.47 to −1.72; $R^2=0.20$, $p<0.01$. Similar results were also obtained with 24-h diastolic blood pressures, suggesting a correlation between circulating sVE level and blood pressure as a key trigger for endothelial dysfunction.

As suggested by Shi Qi Li and co-workers, sVE could additionally be a marker of inflammation, which is itself related to endothelial permeability. It is indeed known that VE-cadherin can be cleaved after enhancement of tumour necrosis factor-α signalling leading to sVE release and increased permeability [4, 5]. However, Sidibé *et al.* [5] found no correlation between C-reactive protein (CRP) and sVE in patients with rheumatoid arthritis at early stage (mean CRP 6 $mg{\cdot}L^{-1}$). Similarly, in our study, OSA patients presented only low burden of inflammation (mean CRP 1.4 $mg{\cdot}L^{-1}$) and there was no correlation between CRP and sVE levels ($p=0.94$ in univariate analysis). These results suggest that, at least in these cohorts with low inflammatory status, sVE release could mainly be a marker of permeability rather than a marker of inflammation.

We agree with the suggestion of Shi Qi Li and co-workers that the functional role of sVE should be questioned in future studies. To date, this has been only sparsely studied. First, studies suggested that sVE can bind to full-length VE-cadherin expressed on endothelial cells to increase permeability [4] or to modulate adhesion and angiogenesis [6], suggesting that sVE may indeed have a functional role by interfering with full length VE-cadherin homophilic interactions. Second, it was shown that fibrin can also bind to the extracellular domain of VE-cadherin, thereby promoting the formation of capillary-like structures [7, 8]. Interestingly, fibrinogen seems to be elevated in OSA patients [9]. Circulating sVE could thus act as a competitor of the interaction of fibrin with the full-length VE-cadherin and thereby modulate endothelial cell dynamics.

Shareable abstract (@ERSpublications)
In relatively healthy OSA patients devoid of comorbidities, sVE could be related to early modifications of endothelial permeability without relation to inflammation, and may have an impact on endothelial cell physiology that could be further explored https://bit.ly/3BURMA3

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Beside its role in cell–cell adhesion, Morini *et al*. [10] showed that VE-cadherin triggers the expression of a set of genes involved in endothelial differentiation and vascular stabilisation. Whether sVE, by binding to the extracellular domain of VE-cadherin, could regulate gene expression remains an open question.

To conclude, we thank Shi Qi Li and co-workers for emphasising the potential importance of our data on VE-cadherin cleavage and sVE release in the cardiovascular consequences of OSA. Our first results suggest that, in relatively healthy OSA patients devoid of comorbidities, sVE could be related to early modifications of endothelial permeability without relation to inflammation. Future studies are needed to explore more precisely whether, in other OSA populations with comorbidities or higher systemic inflammation, sVE could be a biomarker and/or actor of inflammation participating in vascular dysfunction by modifying endothelial cell physiology.

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