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VE-cadherin cleavage in sleep apnoea: new insights into intermittent hypoxia-related endothelial permeability

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Shareable abstract (@ERSpublications)
This study demonstrates for the first time that VE-cadherin is cleaved in sleep apnoea patients, in volunteers exposed to 14 nights of intermittent hypoxia and in endothelial cells exposed to *in vitro* intermittent hypoxia, leading to increased endothelial permeability https://bit.ly/3sAy5sc

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Abstract

Background Obstructive sleep apnoea (OSA) causes intermittent hypoxia that in turn induces endothelial dysfunction and atherosclerosis progression. We hypothesised that VE-cadherin cleavage, detected by its released extracellular fragment solubilised in the blood (sVE), may be an early indicator of emergent abnormal endothelial permeability. Our aim was to assess VE-cadherin cleavage in OSA patients and in *in vivo* and *in vitro* intermittent hypoxia models to decipher the cellular mechanisms and consequences.

Methods Sera from seven healthy volunteers exposed to 14 nights of intermittent hypoxia, 43 OSA patients and 31 healthy control subjects were analysed for their sVE content. Human aortic endothelial cells (HAECs) were exposed to 6 h of intermittent hypoxia *in vitro*, with or without an antioxidant or inhibitors of hypoxia-inducible factor (HIF)-1, tyrosine kinases or vascular endothelial growth factor (VEGF) pathways. VE-cadherin cleavage and phosphorylation were evaluated, and endothelial permeability was assessed by measuring transendothelial electrical resistance (TEER) and fluorescein isothiocyanate (FITC)–dextran flux.

Results sVE was significantly elevated in sera from healthy volunteers submitted to intermittent hypoxia and OSA patients before treatment, but conversely decreased in OSA patients after 6 months of continuous positive airway pressure treatment. OSA was the main factor accounting for sVE variations in a multivariate analysis. In *in vitro* experiments, cleavage and expression of VE-cadherin increased upon HAEC exposure to intermittent hypoxia. TEER decreased and FITC–dextran flux increased. These effects were reversed by all of the pharmacological inhibitors tested.

Conclusions We suggest that in OSA, intermittent hypoxia increases endothelial permeability in OSA by inducing VE-cadherin cleavage through reactive oxygen species production, and activation of HIF-1, VEGF and tyrosine kinase pathways.