Alterations in pulmonary artery NO and O2- balance associates with remodeling in rats exposed to chronic and long term intermittent hypoxia

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Purpose: Humans working in shifts at high altitude are submitted to a form of chronic intermittent hypoxia, different from obstructive sleep apnea, with still unknown health consequences. We have established a rat model resembling this situation, which develops right ventricular hypertrophy and pulmonary artery remodeling. We aimed to assess the possible implication of alterations in NO and superoxide anion balance and to compare the alterations induced in pulmonary arteries from rats exposed to intermittent or chronic hypoxia.

Methods: Wistar rats were exposed for 46 days to normoxia or hypobaric hypoxia in a chamber mimicking 4600 mt altitude, either continuously (CH) or intermittently (2 days in hypoxia and 2 days in normoxia, CIH2x2). At day 46 the rats were euthanized and 3rd order pulmonary arteries and the heart were dissected. Heart was weighted. In pulmonary arteries we assessed: 1) NO and superoxide anion availability by using the fluorescent indicators DAF2-DA and Dihydroethidum (DHE), respectively, and confocal microscopy; 2) expression of phosphorylated endothelial NO synthase (eNOS), NADPH-oxidase (p22phox) and 3-nitrotyrosine (3-NT) by western blotting and 3) cellular alterations in adventitial cells including NADPH-oxidase and inflammatory cell location by immunohistochemistry and confocal microscopy.

Results: Compared to rats in normoxic conditions: 1) NO availability was reduced and superoxide anion was increased in both continuous or intermittent hypoxic groups, with a larger effect in CH, 2) regarding expression eNOS was only reduced in CH; NADPH-oxidase was similarly increased in both hypoxic groups and 3-NT was increased in both groups, but to a larger extent in CH, 3) adventitia exhibited a larger cell density together with increased NADPH oxidase positive and inflammatory cells in both hypoxic groups, but to a larger extent in CH.

Conclusions: Intermittent hypoxia reduces NO availability through superoxide anion destruction, without reducing its synthesis, while continuous hypoxia affects both processes, producing a larger nitrosative damage. These alterations can be linked to the more severe cardiovascular alterations in chronic hypoxia.