The role of nitric oxide signaling in pulmonary circulation of high- and low-altitude newborn sheep under basal and acute hypoxic conditions

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Nitric oxide (NO) is the main vasodilator agent that drives the rapid decrease of pulmonary vascular resistance for the respiratory onset during the fetal to neonatal transition. Nevertheless, the enhanced NO generation by the neonatal pulmonary arterial endothelium does not prevent development of hypoxic pulmonary hypertension in species without an evolutionary story at high altitude. Therefore, this study aims to describe the limits of the NO function at high-altitude during neonatal life in the sheep as an animal model without tolerance to perinatal hypoxia. We studied the effect of blockade of NO synthesis with L-NAME in the cardiopulmonary response of lowland (580 m) and highland (3600 m) newborn lambs basally and under an episode of acute hypoxia. We also determined the pulmonary expression of proteins that mediate the actions of the NO vasodilator pathway in the pulmonary vasoactive tone and remodeling. We observed an enhanced nitrergic function in highland lambs under basal conditions, evidenced as a markedly greater increase in basal mean pulmonary arterial pressure (mPAP) and resistance (PVR) under blockade of NO synthesis. Further, acute hypoxic challenge in lowland lambs infused with L-NAME markedly increased their mPAP and PVR to values greater than baseline, whilst in highland animals under NO synthesis blockade, these variables did not show additional increase in response to low PO2. Highland animals showed increased pulmonary RhoA expression, decreased PSer188-RhoA fraction, increased PSer311-p65-NF?? fraction and up-regulated smooth muscle ?-actin, relative to lowland controls. Taken together our data suggest that NO-mediated vasodilation is important to

keep a low pulmonary vascular resistance under basal conditions and acute hypoxia at low-altitude. At high-altitude, the enhanced nitrergic signaling partially prevents excessive pulmonary hypertension but does not protect against acute hypoxia. The decreased vasodilator efficacy of nitrergic tone in high altitude lambs could be in part due to increased RhoA signaling that opposes to NO action in the hypoxic pulmonary circulation.