Sildenafil in pulmonary hypertension treatment: Effects in a chronic hypoxic newborn sheep.

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INTRODUCTION: The principal aim of this project was to evaluate the pulmonary function of newborn sheep gestated and born in the highlands (HL, 3,600 m, INCAS, Putre) and compares them to sheep gestated and born in the lowlands (LL, 580 m, Santiago) at Chile. This function was studied at a systemic (in vivo), myographic and molecular level between 10 and 15 days of age. With the in vivo experiments, we determine the pulmonary arterial pressure and the pulmonary vascular resistance, during basal and acute hypoxic conditions. In addition, we determine these variables inhibiting the PDE5 activity (with Sildenafil) to evaluate the use of Sildenafil as treatment for pulmonary hypertension in neonates. With the ex vivo experiments we determine the contractility of the resistance pulmonary small arteries and the response to vasomotor agonists or antagonists, particularly the NO donor (SNP) and PDE5 inhibition (sildenafil).

At a molecular level, we determine the expression of mRNA of PDE5, by quantitative RT-PCR using a semi-quantitative approach. Finally, we determine by histological studies, the vascular remodeling in conductance and resistance pulmonary arteries.

RESULTS: We observed pulmonary arterial pressure and resistance increased in the highland newborn when compared to the lowland newborn in basal and hypoxic conditions. This was correlated with a PDE5 activity in both groups that increased during hypoxia. In addition, the pulmonary arteries develop a higher contractile capacity in HL when compared with LL. Moreover, the HL has a higher vasodilator response to sildenafil in pulmonary arteries. At the mRNA level, PDE5 was similar in LL and HL. Finally, HL showed an increased smooth muscle area in resistance pulmonary arteries compared to LL.

CONCLUSIONS: Sildenafil is effective in decreasing pulmonary arterial pressure, even in presence of pulmonary vascular remodeling, and precluding a dangerous increase in pulmonary pressure in episodes of acute hypoxia. Therefore, more studies and clinical trials are necessary to consolidate sildenafil as a therapeutic tool for pulmonary hypertension, particularly in newborns that suffered chronic hypoxia during gestation.

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