European Respiratory Society
Annual Congress 2013

Abstract Number: 5071

Publication Number: P482

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Animal models **Keyword 3:** No keyword

Title: Formation of typical vascular lesions in a new experimental model of pulmonary arterial hypertension

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Body: Background: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by obstruction of small pulmonary arteries leading to increased pulmonary vascular resistance. The key pathologic finding is a negative vascular remodeling process with total vessel occlusion and a monoclonal expansion of endothelial cells. Vascular endothelial growth factor (VEGF) signaling plays a significant role in this process. Aim of our study was to investigate whether inhibition of VEGFR-2 (KDR) by gene manipulation may replicate classical pulmonary vasculopathy. Methods: We utilized mice with conditional KDR knock-out in endothelial cells (KDR-/-). KDRflox/flox/Tie-2Cre and KDRflox/flox/Tie-2 mice were injected intraperitoneally with tamoxifen for 3 weeks to induce knock-out. KDR-/- mice and wild type littermates were held in an environmental chamber with FiO2 of 0.1 or under normoxia for 2, 4, and 6 weeks. We investigated the effect of KDR deletion and chronic normobaric hypoxia on pulmonary hemodynamics and right ventricular hypertrophy. Results: KDR-/- mice showed significantly increased right ventricular pressures (RVSP's) and Fulton indices after 2, 4, and 6 weeks under normoxic conditions, compared with wild type controls. Both KDR-/- and wild type mice showed increased RVSP's under normobaric hypoxia. KDR-/- mice revealed significantly higher RVSP's and Fulton indices than controls after 4 and 6 weeks. Lung histologies demonstrated neointimal thickening and vessel occlusions in lungs of KDR-/- mice resembling human pulmonary arteriopathy. Conclusion Classical pulmonary arterial hypertension was induced in C57/BL6J mice by direct ablative gene manipulation of KDR.