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Title: Hypoxia-induced pulmonary hypertension: Synergistic effects of sildenafil and erythropoietin in mice

Mr. Victor 31121 Samillan vsamillan@yahoo.com¹, Mr. Thomas 31122 Haider t.haider@access.uzh.ch MD¹, Prof. Dr Johannes 31123 Vogel jvogel@vetphys.uzh.ch¹, Prof. Dr Max 31124 Gassmann maxg@access.uzh.ch¹ and Dr. Louise 31125 Ostergaard ost@access.uzh.ch¹. ¹ Institute of Veterinary Physiology, University of Zürich, Switzerland, 8057 .

Body: The term pulmonary arterial hypertension (PAH) describes a group of diseases characterized by elevated pulmonary arterial pressure. The cause can be due to several vascular changes, including pulmonary remodeling. If left untreated, patients might die from right heart failure within an average of three years. The present study was designed to investigate single and combination therapy with erythropoietin (epo) and sildenafil on hypoxia-induced PAH. Mice were randomized, first in a normoxic and a hypoxic group and second to receive saline, epo, sildenafil or epo and sildenafil. Epo was injected three times per weekly (500 IU/kg) and sildenafil daily (10 mg/kg). The animals were exposed to three weeks of either hypoxia (10 % oxygen) or normoxia, after which they underwent the different treatments for an additional two weeks. Immunohistochemistry was performed to elucidate changes in morphology. Plasma levels of cardiotrophin-1 and atrial natriuretic peptide (ANP) were measured. The pulmonary pressure was estimated using right heart catheterization. On average the hypoxic mice lost approximately 20 % of their body weight. This was reduced to 5 % for the group receiving the combination treatment. The hypoxia-induced increase in right ventricular hypertrophy and medial wall thickness of pulmonary arterioles was significantly attenuated with the combination therapy. Similar results were also observed for cardiotrophin-1 and ANP levels. The combination treatment with epo and sildenafil demonstrated an improvement in the clinical outcome in hypoxia-induced PAH in rodents, superior to that observed for either drug given alone.