

Systemic and local inhibition of fibrinolysis induces chronic thromboembolic pulmonary hypertension in rabbits

R. Quarck, L. Vengethasamy, A. Ronisz, M. Delcroix.

Respiratory Division, University Hospitals Leuven & Clinical and Experimental Medicine Department, KU Leuven, Leuven, Belgium

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition due to partial obstruction of the pulmonary arterial bed by unresolved and organized thrombi, resulting in increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension and right heart failure. The disease is notoriously underdiagnosed and its pathogenesis remains poorly understood. The need of developing animal models of CTEPH remains a major challenge. The aim of the current study was to establish a stable and reliable model of CTEPH in rabbits.

CTEPH was induced in adult male New Zealand rabbits by performing 5 weekly embolization of autologous blood clots, without (n=5) or with intravenous (n=7) or within the clot (n=6) administration of tranexamic acid, a fibrinolysis inhibitor. Saline replaced clots in the control group (n=5). Right ventricular systolic pressure (RVSP) was monitored by telemetry. Right heart catheterization was performed 12 weeks after the first embolization, before animal sacrifice. RV hypertrophy, plasma endothelin-1 (ET-1) and lung vessel morphometry were analyzed.

Repeated embolization with tranexamic acid, intravenous or within clot, resulted in significant increase in systolic RVP (28% and 52%, compared to baseline), and PVR (86% and 117%, compared to control rabbits embolized with saline). Mean pulmonary arterial pressure was increased by 24% and 22% and cardiac output was decreased by 12% and 21%. This was accompanied by increase in the RV/(LV+S) ratio of 13% and 9% and circulating ET-1 levels of 25% and 37%. Moreover, repeated embolization with tranexamic acid induced remodeling of distal pulmonary arteries, and media and intima thickening of proximal large pulmonary arteries. Finally, obstruction of proximal pulmonary by fibro-thrombotic and recanalized material was observed.

We showed that repeated embolization with intravenous or within the clot administration of tranexamic acid induced pulmonary hypertension, RV hypertrophy and remodeling of both proximal and distal pulmonary arteries.