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Title: Repeated embolization and fibrinolysis inhibition induce chronic thromboembolic pulmonary hypertension in rabbits

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Body: Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe disease characterized by unresolved and organized thrombi obstructing pulmonary arterial bed, resulting in pulmonary hypertension and right heart failure. Since CTEPH is notoriously underdiagnosed and its pathogenesis poorly understood, developing animal models is a major challenge. Our aim was to develop a chronic model of CTEPH in rabbits. CTEPH was induced in adult male New Zealand rabbits by performing 5 weekly embolizations of autologous blood clots, with (n=5) or without (n=5) 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. Acute embolization with tranexamic acid resulted in a 46% increase in RVSP. Repeated embolization with tranexamic acid increased systolic RVSP by 28% ($p \leq 0.05$), as well as mean pulmonary arterial pressure, pulmonary vascular resistance, RV/(LV+S) ratio and plasma ET-1 by 31%, 71%, 21% and 34%, respectively, compared to control rabbits. Distal pulmonary artery remodeling was also observed. We have shown a significant increase in RVSP, accompanied by persistently increased mPAP and PVR, and RV hypertrophy after repeated embolization and fibrinolysis inhibition in rabbits, together with remodeling of proximal and distal pulmonary arteries.