IMPAIRMENT OF ANGIOGENESIS-DRIVEN CLOT RESOLUTION IS A KEY EVENT IN THE PROGRESSION TO CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION: VALIDATION IN A NEW RABBIT MODEL

Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition and rare complication of acute pulmonary embolism. The reason why clots do not resolve and further result in fibro-thrombotic obstruction of the pulmonary arterial bed remains poorly understood. Since defective angiogenesis is able to prevent clot resolution and has been observed in surgical material from CTEPH patients, we aimed to validate its crucial pathogenic role by local inhibition of angiogenesis in a CTEPH animal model.

Methods: Weekly embolization of autologous blood clots containing an antifibrinolytic agent, tranexamic acid, or an inhibitor of angiogenesis, SU5416, was performed in adult male New Zealand White rabbits. Right ventricular (RV) pressure was monitored by telemetry, RV function was investigated by transthoracic echocardiography and a complete pulmonary hemodynamic evaluation was performed by right heart catheterization before animal sacrifice. Circulating markers of inflammation, endothelial dysfunction, heart failure and fibrinolysis were measured in plasma. Pulmonary vessel remodeling was analyzed.

Results: Inhibition of angiogenesis within repeatedly embolized autologous blood clots resulted in elevated mean pulmonary arterial pressure (38 mmHg), increased indexed pulmonary vascular resistance and enhanced RV hypertrophy (80%, 1.9-fold and 36%, respectively compared with rabbits embolized with clots containing an antifibrinolytic agent). This was caused by both obstruction of large pulmonary arteries with fibro-thrombotic material and muscularization of pulmonary microvessels, and was accompanied by an increase in circulating endothelin-1.

Conclusion: We showed that local inhibition of angiogenesis within repeatedly embolized clots in rabbits induced more sustained and progressive pulmonary hypertension than inhibition of fibrinolysis.