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A new rat model of chronic thromboembolic pulmonary hypertension induced by repeated intravenous administration of biodegradable alginate microspheres

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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is life-threatening complication of pulmonary embolism (PE) with insufficiently understood mechanisms. Several rodent CTEPH models based on i.v. administration of non-biodegradable microparticles have been validated for preclinical studies. Major limitation of these models is the lack of partial dissolution of emboli following their entrapment in the lung vasculature.
Purpose: The study was aimed at development and validation of rat CTEPH model based on recurrent embolization of (sub)segmental pulmonary artery branches with biodegradable microspheres.
Methods: Male Wistar rats were used for the experiments. Pulmonary vasculature was embolized either with sodium alginate microspheres (MS) or with autologous blood clots (AT). The animals were randomized into the following groups: i) controls: saline at a volume of 50 μL was injected 4 times with 8-day interval into the tail vein; the same regimen was used in two next groups; ii) AT; iii) MS4; iv) MS8: MS were administered 8 times with 4-day interval. Histological examination of the lungs was performed after 2 and 6 weeks after the last injection. 6 weeks after the last injection the following analyses were performed: treadmill test, transthoracic echocardiography (TTE), right ventricular catheterization with measurement of right ventricular systolic pressure (RVSP), determination of serum endothelin-1 level.
Results: The survival rate in the MS8 group was 50%. In the other groups, there were no animal deaths. Multiple emboli were found in the lumen of (sub)segmental pulmonary artery branches 2 weeks after the last injection in MS4 and MS8 groups. Increased diameter and thickening of the bronchial arterial wall were also registered. After 6 weeks, the index of hypertrophy of vessel wall in MS4 and MS8 groups was significantly higher than in controls (p=0.041 and p=0.006, respectively) (Fig. 1). No sign of vascular remodeling was identified in the branches of the pulmonary artery in the AT group. Exercise tolerance was significantly reduced in both MS4 and MS8 groups compared with the controls (p=0.025 and p=0.008, respectively). There were no significant differences in exercise tolerance between the AT and control groups. TTE data indicate a significant increase in the diameter of the pulmonary trunk and the right ventricular outflow tract in the MS8 group compared with controls and AT ($p<0.05$). Significant increase in RVSP as well as in endothelin-1 level versus controls was found only in the MS8 group.
Conclusion: Recurrent (×8) intravenous administration of MS in rats resulted in CTEPH development characterized by specific lung vasculature remodelling, reduced exercise tolerance, and persistent rise in RVSP. The model developed can be used for preclinical testing of promising drug candidates.

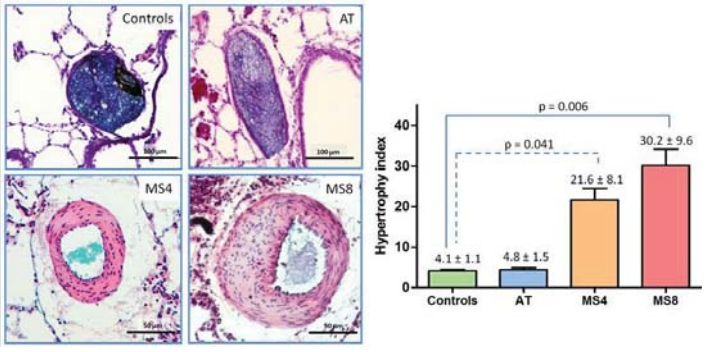

Figure 1. Histological changes in the branches of the pulmonary artery 6 weeks after the last injection of emboli.