

European Respiratory Society Annual Congress 2012

Abstract Number: 4224

Publication Number: P1498

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Embolism **Keyword 3:** Circulation

Title: Involvement of the pulmonary micro-vasculature in chronic thromboembolic pulmonary hypertension (CTEPH)

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Body: Introduction: Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH. However, a limited subset of CTEPH patients present with persistent PH after PEA. Aims: To assess microvascular lesions and clinical characteristics in CTEPH-patients with persistent PH after PEA. Methods: We analyzed lung histology available from 8/10 patients with persistent PH after PEA and compared them with 10 randomly selected CTEPH-patients with successful PEA. Results: Histopathology from 8 persistent PH patients revealed thrombotic lesions, intimal fibrosis and medial hypertrophy in peripheral small muscular pulmonary arteries of all analyzed lungs. 7/8 persistent PH patients displayed moderate pulmonary venous involvement, including intimal fibrosis of small pre-septal venules, foci of capillary multiplication, and hemosiderosis. All cases presented hypertrophy of bronchiolar systemic arteries. Hemodynamic data, exercise testing and medical history exhibited non-significant but by-trend discriminating values between the persistent PH and the successful PEA group for PVR (1199 ± 154 dynes•s•cm⁻⁵ versus 825 ± 98 dynes•s•cm⁻⁵), DLCO ($63 \pm 5\%$ versus $75 \pm 4\%$), 6-minute-walk-distance (6MWD) (272 ± 48 m versus 415 ± 31 m), history of vascular implants (6/10 versus 0/10), and presence of subpleural septa on chest scanner (6/10 versus 2/10). Conclusion: We report conspicuous remodeling of the pre- and post-capillary microvasculature in CTEPH-patients with persistent PH after PEA. Group-related

discrepancies of PVR, DLCO, 6MWD, vascular implant-history, and one radiologic criterion were observed in CTEPH patients with persistent PH, as compared with CTEPH-patients with successful PEA.