

## EFFECTS OF TARGETED THERAPY ON THROMBUS MORPHOLOGY AND THE CELLULAR AND TISSUE COMPOSITION OF PULMONARY ENDARTERECTOMY SPECIMENS – A RETROSPECTIVE HISTOPATHOLOGICAL STUDY

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**Objectives** Despite recent advances in the treatment and management of patients with chronic thromboembolic pulmonary hypertension (CTEPH), relatively little is understood regarding the factors modulating thrombus integrity before or during the surgical process. Anecdotal reports suggest that targeted therapies for pulmonary arterial hypertension prior to surgery may influence the friable nature and structural integrity of the pulmonary endarterectomy (PEA) material and, as many agents act by altering smooth muscle tone and function, have a plausible role in modulating the cells and constituents of the thrombus.

**Methods** The distal tail portions from PEA specimens from treatment naive (n=5) and from patients treated with the endothelin receptor antagonist Bosentan (n=8) or the phosphodiesterase 5inhibitor Sildenafil (n=7) were examined by 2 blinded observers. Morphology of PEA samples was examined using Haematoxylin and Eosin (H&E) staining and by Elastic van Gieson (EVG) to assess types of connective tissues present with the specimen. A semi quantitative score (0= absent, 1= low, 2=medium, 3=high) was used to measure relative contribution of collagen, elastic fibre content, myxoid-type changes and density of smooth muscle cells (SMCs) through the specimen.

**Results** PEA specimens were histologically heterogeneous containing areas of loose fibromyxoid tissue as demonstrated by H&E and EVG staining. Occasional endothelial lined channels sometimes surrounded by contractile fusiform SMCs were identified and frequent SMCs of a morphologically secretory phenotype dispersed throughout the specimen. Interestingly, a similar contribution of connective tissue components (collagen, elastin, myxoid) was observed in all samples regardless of the type, if any, of targeted therapy prior to PEA surgery. A significant increase in the presence of SMCs was observed in patients treated with Bosentan (mean score 1.37, p=0.0326 vs. control) or Sildenafil (mean score 1.57, p=0.0187 vs. control) before PEA surgery compared to treatment naive patients (mean score 0.83).

**Conclusion** Despite little evidence for changes in connective tissue in PEA samples, targeted therapies for PAH were found to influence SMC expression in distal tail regions. The potential effects of targeted therapy upon thrombus organisation and revascularisation are less clear and further work is warranted to substantiate these interesting observations.