S. Puthenkalam[1], J. Jakowitsch[1], A. Panzenboeck[1], K.T. Preissner[2], R. Voswinckel[3], W. Klepetko[4], I.M. Lang[1]

[1]Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Vienna, Austria
[2]Institute for Biochemistry, Justus-Liebig-University, Giessen, Germany
[3]Max-Planck-Institute for Heart and Lung Research, Department of Lung Development and Remodelling, Bad Nauheim, Germany
[4]Medical University of Vienna, Department of Surgery, Division of Cardiothoracic Surgery, Vienna, Austria

ANGIOGENESIS IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

Objective:
Chronic thromboembolic pulmonary hypertension (CTEPH) is a late sequela of venous thromboembolism affecting up to 4 % patients surviving symptomatic pulmonary embolism. CTEPH is characterized by non-resolving thrombi in the pulmonary arteries leading to right heart failure and death. Previous studies in a murine model of stagnant flow venous thrombosis have shown that endothelial cell-specific deletion of vascular endothelial growth factor receptor 2/ fetal liver kinase-1 (VEGF-R2/flk-1) leads to misguided thrombus resolution. We hypothesized that thrombus non-resolution in CTEPH results from dysfunctional thrombus angiogenesis.

Methods:
CTEPH thrombi and unthrombosed pulmonary arteries as reference standards were collected from 11 CTEPH patients undergoing pulmonary endarterectomy at our institution. Patients gave informed consent. Several angiogenesis markers were investigated in CTEPH thrombi using Real Time RT-PCR, gene expression levels were normalized to endogenous 18S-RNA levels.

Results:
The gene expression levels of angiopoietin-2, VEGF, VEGF-R2/flk-1, podoplanin, platelet endothelial cell adhesion molecule-1 (PECAM-1) and vascular endothelial cadherin were decreased in CTEPH thrombi compared with pulmonary arteries. Furthermore factors involved in proliferative pathways of the vascular cells such as bone morphogenetic protein receptor type 2 (BMPR2) and transforming growth factor beta (TGF-ß1) showed also

decreased expression. By contrast, the thrombogenic molecule plasminogen activator inhibitor-1 (PAI-1) showed an increased gene expression level in CTEPH thrombi.

Conclusion:

Angiogenic molecules are downregulated in CTEPH thrombi compared with parent pulmonary arteries. Downregulation of genes involved in angiogenesis may drive venous thrombus persistence.