# Role of angiopoietin-2 in venous thrombus resolution and chronic thromboembolic disease

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**These findings in patients and mouse models reveal a new role for angiopoietin-2 in the pathophysiology of CTEPH, suggesting that its overexpression in pulmonary endothelium may contribute to defective angiogenesis and persistent vascular occlusion** https://bit.ly/3gotczC

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## Abstract

***Background*** Defective angiogenesis, incomplete thrombus revascularisation and fibrosis are considered critical pathomechanisms of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism. Angiopoietin-2 (ANGPT2) has been shown to regulate angiogenesis, but its importance for thrombus resolution and remodelling is unknown.

***Methods*** ANGPT2 plasma concentrations were measured in patients with CTEPH (n=68) and acute pulmonary embolism (n=84). Tissue removed during pulmonary endarterectomy (PEA) for CTEPH was analysed (immuno)histologically. A mouse model of inferior vena cava ligation was used to study the kinetics of venous thrombus resolution in wild-type mice receiving recombinant ANGPT2 *via* osmotic pumps, and in transgenic mice overexpressing ANGPT2 in endothelial cells.

***Results*** Circulating ANGPT2 levels were higher in CTEPH patients compared to patients with idiopathic pulmonary arterial hypertension and healthy controls, and decreased after PEA. Plasma ANGPT2 levels were elevated in patients with pulmonary embolism and diagnosis of CTEPH during follow-up. Histological analysis of PEA specimens confirmed increased ANGPT2 expression, and low levels of phosphorylated TIE2 were observed in regions with early-organised pulmonary thrombi, myofibroblasts and fibrosis. Microarray and high-resolution microscopy analysis could localise ANGPT2 overexpression to endothelial cells, and hypoxia and transforming growth factor-β1 were identified as potential stimuli. Gain-of-function experiments in mice demonstrated that exogenous ANGPT2 administration and transgenic endothelial ANGPT2 overexpression resulted in delayed venous thrombus resolution, and thrombi were characterised by lower TIE2 phosphorylation and fewer microvessels.

***Conclusion*** Our findings suggest that ANGPT2 delays venous thrombus resolution and that overexpression of ANGPT2 contributes to thrombofibrosis and may thus support the transition from pulmonary embolism to CTEPH.