S109 ADAMTS13 PROTEIN LEVELS ARE DECREASED IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION AND IMPLICATED IN ITS PATHOBIOLOGY

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Introduction Chronic thromboembolic pulmonary hypertension (CTEPH) Results from failure of thrombus resolution following acute pulmonary embolism. Abnormalities in haemostasis are implicated in the pathobiology, including elevated levels of von Willebrand factor (VWF), which is normally regulated by ADAMTS13. Interim analysis of a genome-wide association study (GWAS) identified a significant association in CTEPH with the *ADAMTS13* and *ABO* gene loci. We aimed to determine if ADAMTS13 protein levels are altered in CTEPH.

Methods ADAMTS13 and VWF plasma antigen levels were measured by ELISA in 208 individuals with CTEPH and compared to 68 healthy controls. Levels were also measured in subjects with chronic thromboembolic disease but without pulmonary hypertension (CTED), and other disease comparator groups summarised in figure 1. In 22 CTEPH individuals ADAMTS13 and VWF levels were measured pre-operatively and at least 3 months post-pulmonary endarterectomy (PEA).

Results ADAMTS13 levels were decreased in CTEPH (median ±IQR: 0.88±0.40 μg/ml; $p=5.7x10^{-09}$) and CTED (0.83±0.22 μg/ml; $p=2.1x10^{-06}$) patients compared to healthy controls (1.15±0.30 μg/ml) (figure 1). ADAMTS13 levels remained low in CTEPH patients following PEA (pre: 0.78 ±0.27 μg/ml vs. post: 0.83±0.29 μg/ml; p=0.92) even in those with normalised mean pulmonary arterial pressures (<25 mmHg) after PEA. Furthermore, ADAMTS13 levels were lowest in the CTEPH and CTED groups when covariates (age, gender and batch) were included in multivariate rank regression models. VWF levels were increased in CTEPH (16.7±15.2 μg/ml; $p=4.0x10^{-12}$) and CTED (17.0±10.1 μg/ml; $p=3.9x10^{-06}$) compared to healthy controls (8.5±8.8 μg/ml). There was no change post-PEA (pre: 22.2±17.3 μg/ml vs. post: 19.6±14.2 μg/ml; p=0.24).

Conclusions Plasma ADAMTS13 antigen levels are markedly decreased in CTEPH. This is not secondary to pulmonary hypertension, as demonstrated by the similarly low levels in CTED, and individuals with normal pulmonary artery pressures post-PEA. Thus, the VWF/ADAMTS13 axis is implicated in the underlying disease pathophysiology. Ongoing work will clarify if there is a causal link by defining whether genetic variation at the *ADAMTS13* locus contributes to reduced ADAMTS13 protein levels and CTEPH.

S110 HIF2A DELETION IN THE PULMONARY ENDOTHELIUM PREVENTS HYPOXIA-INDUCED PULMONARY HYPERTENSION

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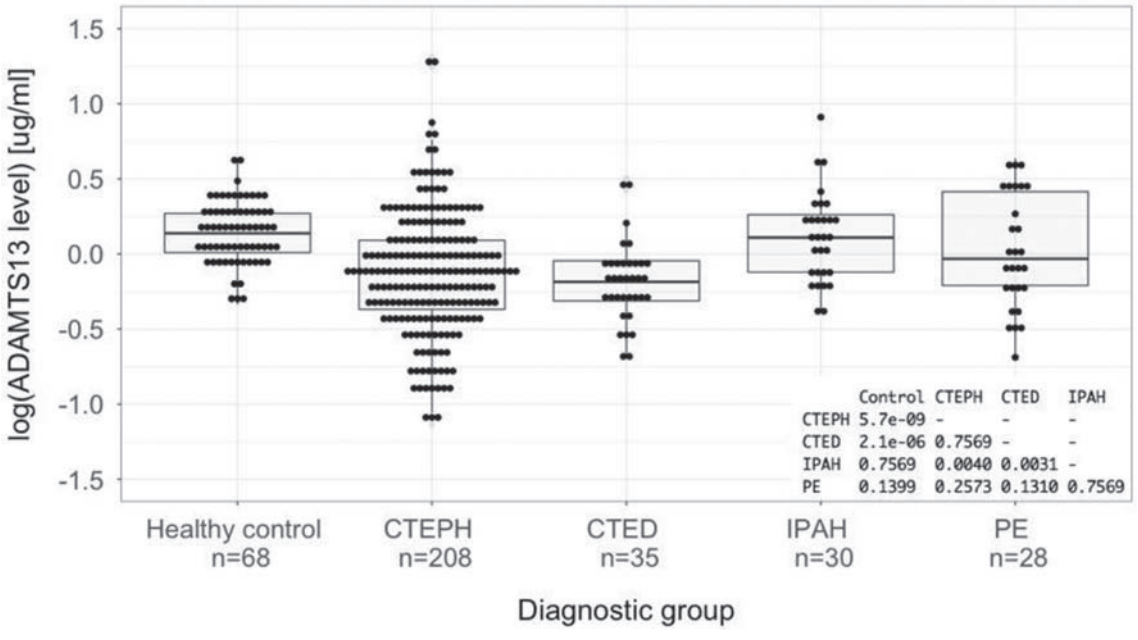
Pulmonary arterial hypertension is a progressive and irreversible disease that leads eventually to right heart failure and death. The pathogenesis of this condition involves proliferation of endothelial and smooth muscle cells resulting in vascular remodelling of the pulmonary arterioles. Several factors are implicated in the remodelling process driven by hypoxia including stabilisation of hypoxia-inducible transcription factors (HIFs), HIF1α and HIF2α. Previous studies have shown that heterozygous deletions of HIF1α or HIF2α partially attenuate many of the remodelling process associated with the development of PAH. Consistent with these observations we have



Abstract S109 Figure 1 ADAMTSI3 protein levels and diagnostic group. Log transformed ADAMTS13 antigen levels. Table of pairwise p-values displayed within figure (Dunns test). CTEPH, chronic thromboembolic pulmonary hypertension; CTED, chronic thromboembolic disease; IPAH, idiopathic pulmonary arterial hypertension; PE, pulmonary embolism.