pulmonary endarterectomy (PEA) surgery to remove the thromboembolic material. We also examined the surgically excised PEA material and measured neovessel density in distal regions of the specimens.

Methods and results Serum VEGF-A levels were measured by Luminex array in paired serum samples from n = 44 patients at baseline (before PEA surgery) and following PEA surgery. Following PEA surgery, serum VEGF-A levels were significantly reduced compared to baseline measurements (159.5 ± 174.8 vs. 194.4 ± 198.2, p = 0.0182). Distal regions of excised PEA material were cross sectioned and processed for histopathological examination. Neovessel density was calculated by counting the absolute number of vascular channels present within a cross-sectional area and normalised to tissue area using Image J. We also measured the time between documented VTE and subsequent PEA surgery (VTE-PEA time) in patients with a documented VTE (n = 40/44 [90%] patients), and identified an inverse correlation between neovessel density and VTE–PEA time.

Conclusions Extensive angiogenesis was evident in distal PEA material from patients with CTEPH. VEGF-A is known to be a key regulator of angiogenesis and serum levels were significantly reduced following PEA surgery. Interestingly, a significant inverse correlation between neovessel density and VTE-PEA time was observed indicating that in the early stages following VTE, extensive angiogenesis is evident within the thromboembolus. Taken together these data provide further evidence that angiogenesis is an important mechanism in the attempted resolution of a VTE.

S38 THE BRD4 INHIBITOR, JQ1 DECREASES PROLIFERATION AND ARRESTS THE CELL CYCLE OF PULMONARY VASCULAR CELLS: IMPLICATIONS FOR PULMONARY ARTERIAL HYPERTENSION

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Background Pulmonary arterial hypertension (PAH) is an incurable disease characterised by raised pulmonary resistance, resulting from vascular remodelling which leads to right heart failure and death. Recently NF-kB mediated inflammatory gene expression and vascular proliferation/remodelling have been shown to be involved in the pathogenesis of PAH. The expression of subsets of NF-kB-induced inflammatory genes is dependent upon the recruitment of the bromodomains and extra-terminal (BET) family of proteins to the transcriptional activation complex. We hypothesise that inhibition of BET proteins which bind acetylated lysine residues on histones and non-histone proteins will attenuate the hyperproliferative and proinflammatory phenotype of vascular cells.

Methods Primary human pulmonary vascular endothelial cells (P-EC) were serum starved for 24 h prior to treatment with the Brd4 mimic JQ1+ or JQ1- (inactive enantiomer) in complete (5% FCS) media. P-EC cell proliferation was measured by BrdU incorporation and apoptosis was determined using caspase 3/7 activity. Cell cycle progression was determined by FACs analysis. mRNA levels of cell cycle genes and inflammatory cytokines were measured by RT-PCR. MTT assay was used to measure cell viability.

Results JQ1+ caused a significant ($p < 0.001$) and concentration-dependent decrease in P-EC proliferation and an increase in caspase 3/7 activity compared to P-EC treated with JQ1- for 24 h. JQ1+ (1 μM) significantly arrested the cell cycle of P-EC at the G1 phase. This was additionally evidenced by a decrease in the cell cycle genes CDK2, 4 and 6 mRNA levels and a significant increase in the mRNA of the cell cycle inhibitor CDKN1A (p21/cip1) at 4 h. Finally, JQ1+ significantly ($p < 0.01$) inhibited the mRNA levels of the inflammatory cytokines IL-6 and 8 in P-EC compared to JQ1–.

Conclusion Inhibition of Brd4 with JQ1 decreases remodelling and inflammation in P-EC via a decrease in proliferation, cell cycle arrest and an increase in apoptosis. Further work is required but Brd4 inhibition may provide therapeutic drugs for the treatment of PAH.

S39 THE ROLE OF SOLUBLE GUANYLATE CYCLASE STIMULATOR BAY 41–2272 ON REMODELLING PROCESSES RELEVANT TO THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION

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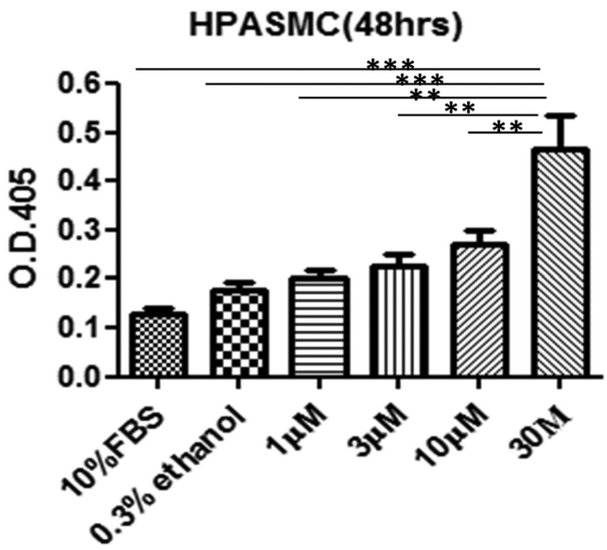
Introduction and objectives Pulmonary arterial hypertension (PAH) is characterised by remodelling of small, muscular precapillary blood vessels. The subsequent rise in pulmonary vascular resistance leads to right ventricular failure and death. The aetiology of the remodelling process is largely unknown although defects in the bone morphogenetic protein receptor II (BMPR II) pathway are likely to be involved. Most of the therapies used thus far are aimed at pulmonary vasodilation. However it is unclear how much of the benefit seen with these medications is related to reverse remodelling. Riociguat is a "first in class" drug that stimulates soluble guanylate cyclase, with a consequent increase in cyclic GMP (and vasodilation). Riociguat has recently been shown to improve haemodynamics and exercise capacity in patients with idiopathic PAH and chronic thromboembolic PH (PATENT and CHEST). Here we sought to



Abstract S39 Figure 1 Bay41–2272 induces HPASMCs DNA fragmentation (apoptosis), data were presented as mean±SEM n = 3. **p < 0.005; ***p < 0.001