

Abstract S106 Figure 1 a. Statistically significant increase in the% of viable neutrophils and a decrease in apoptotic neutrophils in bronchiectasis; * $p = 0.02$, *** $p = 0.0003$, **** $p < 0.001$. b. Cytospin from a bronchiectasis patient after 20 hours apoptosis showing large numbers of viable neutrophils. c. Statistically significant increase in the% of phagocytosis in bronchiectasis patients at baseline and increase with Lipoxin in a dose dependent manner; * $p = 0.02$, ** $p = 0.004$. d. Confocal image of phagocytosed GFP labelled *Pseudomonas* by neutrophil.

Conclusion Serum neutrophils in bronchiectasis are primed and activated compared to healthy volunteers. The pro-resolving mediator LXA₄ stabilised the neutrophil whilst promoting neutrophil phagocytosis.

Pulmonary Hypertension

S107 GENOTYPE-PHENOTYPE ASSOCIATIONS IN PULMONARY ARTERIAL HYPERTENSION CAUSED BY *BMPR2* AND *EIF2AK4* VARIANTS

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Introduction Idiopathic pulmonary arterial hypertension (IPAH) is a rare and incurable disease. Causal mutations in *BMPR2* are found in 17% of patients. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) are rarer forms of pulmonary hypertension and have a worse prognosis. Biallelic mutations in *EIF2AK4* have been described in PVOD and PCH. We hypothesised that mutations in these genes are associated with specific phenotypes or endotypes.

Methods Whole genome sequencing was performed on genomic DNA from PAH patients recruited to the NIHR BRIDGE Study ($n = 679$). Rare (absent from BRIDGE control cohorts [$n = 5906$] and minor allele frequency < 0.0001 in the ExAC database [<http://exac.broadinstitute.org>]) and predicted deleterious (CADD score > 15 and Polyphen not benign) variants were selected for association testing with phenotypic and metabolomic data. Plasma samples from 288 patients were sent to Metabolon (USA) for a high-throughput metabolomic screen.

Results Mutations in *BMPR2* (82 single nucleotide variants and 13 deletions) were identified in 14% of PAH patients. Unexpectedly, 22 rare and predicted deleterious *EIF2AK4* variants were found in 17 patients with IPAH. Biallelic *EIF2AK4* variants were found in 1% of patients (5 homozygous variant carriers and 4 potential compound heterozygotes). Additionally, there were 8

heterozygous *EIF2AK4* variant carriers in the cohort (1%), suggesting a 3-fold over-representation of heterozygous *EIF2AK4* variants compared to ExAC ($p = 0.005$).

BMPR2 mutation carriers presented at a younger age and with more severe pulmonary haemodynamics compared to those without identified variants in the known PAH genes. Biallelic *EIF2AK4* variant carriers had a significantly reduced transfer coefficient for carbon monoxide compared to patients with *BMPR2* mutations or no identified variants. Heterozygous *EIF2AK4* variant carriers were similar to patients with no identified variants. There were no differences between groups in functional class or walk test distances assessed longitudinally.

BMPR2 and *EIF2AK4* genotype did not influence the plasma metabolome.

Discussion Biallelic *EIF2AK4* variants are the second most common genetic defect in patients with apparent IPAH, after *BMPR2*. Variants in both genes are associated with characteristic phenotypes. Additional, non-coding variants may be present in heterozygous *EIF2AK4* variant carriers. These findings have important implications for the clinical and molecular classification of PAH.

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	<i>BMPR2</i> mutation carriers	<i>EIF2AK4</i> biallelic variant carriers	<i>EIF2AK4</i> heterozygous variant carriers	Patients with no identified variants	<i>p</i>
Female (%)	68	44	80	72	0.282
Caucasian (%)	81	22	80	85	<0.001
Age (years)	39.79 ± 12.97	30.10 ± 9.26	54.43 ± 21.04	51.30 ± 16.57	<0.001
mPAP (mmHg)	60.71 ± 11.54	54.11 ± 16.29	48.25 ± 19.57	52.65 ± 13.6	<0.001
CO (L/min)	3.55 ± 1.15	4.39 ± 1.48	4.25 ± 2.17	4.26 ± 1.47	<0.001
FEV1 (% pred)	88.68 ± 15.77	92.00 ± 13.83	82.98 ± 22.26	82.36 ± 17.93	0.055
FEV1/FVC	0.78 ± 0.08	0.79 ± 0.07	0.78 ± 0.12	0.74 ± 0.10	0.004
KCO (% pred)	83.54 ± 16.86	33.84 ± 6.48	60.99 ± 41.77	67.76 ± 22.91	<0.001

Phenotypic characteristics of patients with idiopathic pulmonary arterial hypertension by genotype. Data presented as mean ± sd unless stated. mPAP – mean pulmonary artery pressure; CO – cardiac output; FEV1 – forced expiratory volume 1 second; FVC – forced vital capacity; KCO – transfer coefficient for carbon monoxide.

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LOW SKELETAL MUSCLE STRENGTH AND PHYSICAL ACTIVITY ARE ASSOCIATED WITH POOR OUTCOMES IN PULMONARY ARTERIAL HYPERTENSION

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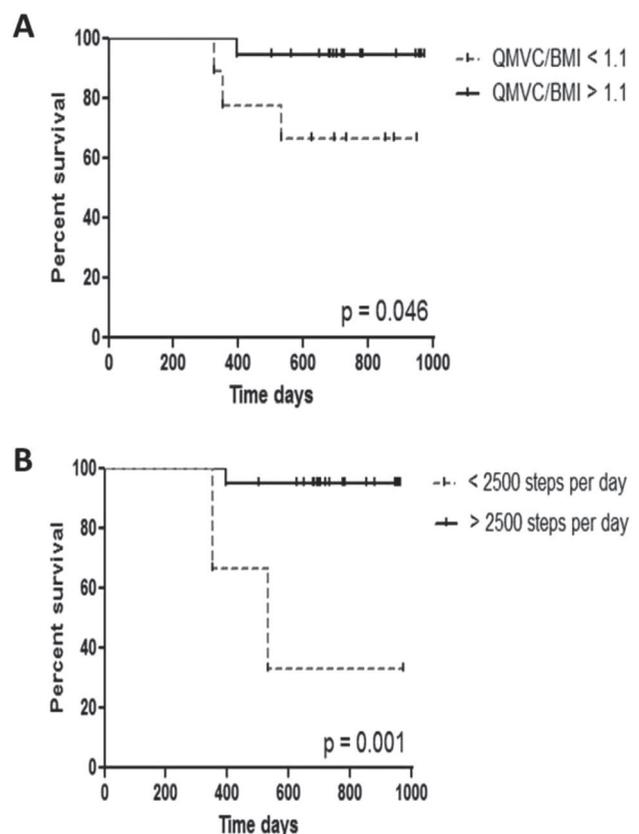
Introduction Skeletal muscle wasting and low physical activity are emerging as important potentially modifiable complications of pulmonary arterial hypertension (PAH). In other conditions, such as COPD and heart failure, low muscle strength and low levels of activity have been shown to be associated with poor outcomes. We aimed to define the association of muscle strength and

physical activity with hospital admission rates, long term quality of life and mortality in patients with PAH.

Methods Twenty-eight patients with PAH had their quadriceps maximal volitional capacity (QMVC), step count, BNP and 6MWD measured. At least 1 year later, these patients' records were reviewed and data were collected on mortality, transplantation, admission to hospital and quality of life using the EMPHASIS 10 questionnaire. QMVC was normalised to BMI and 24 patients with valid step count data were included in the analysis of activity. Kaplan-Meier plots were constructed to define mortality and ROC analysis was used to demonstrate which factors most closely predicted hospital admission. Pearson correlation was used to define the associations with follow-up quality of life.

Results Kaplan-Meier plots demonstrated that patients with a QMVC/BMI < 1.1 and those with a step count < 2500 per day were significantly more likely to die or undergo transplant than those above these cut-offs (Figure 1 A and B). ROC analysis showed that a QMVC/BMI < 1.5 predicted hospital admission over the follow up period with a sensitivity of 93% and a specificity of 62%. It also demonstrated that QMVC was superior to the 6MWD in predicting hospital admission (AUC 0.83, $p = 0.003$ vs. AUC 0.73, $p = 0.017$). Finally QMVC/BMI was significantly correlated to quality of life at follow-up in this cohort (Pearson $r = -0.47$, $p = 0.018$).

Discussion Our data suggests that, like in other chronic conditions, low muscle strength and low physical activity in PAH are associated with poor outcomes. Treatment strategies targeting the muscle and physical activity levels may improve outcomes in terms of both quality of life and mortality.



Abstract S108 Figure 1 Kaplan-Meier plots showing survival (end points being death or transplant) in patients with PAH with a: A. QMVC/BMI < 1.1 and > 1.1; B. step count < 2500 and > 2500