Cutting edge pulmonary hypertension

S1* DOES PARADOXICAL EMBOLI OF PARTICULATE MATTER THROUGH PULMONARY ARTERIOVENOUS MALFORMATIONS PRECIPITATE MIGRAINES?

[1]T Patel, [2]A Elphick, [3]JE Jackson, [4]CL Shovlin. *[1]St George's, University of London and Imperial College School of Medicine, London, UK; [2]Imperial College School of Life Sciences, London, UK; [3]Imperial College Healthcare NHS Trust, London, UK; [4]Imperial College London, London, UK*

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Introduction and objectives Pulmonary arteriovenous malformations (PAVMs) are an example of a right-to-left shunt resulting in deoxygenated, unfiltered venous blood bypassing the pulmonary capillaries to re-enter the systemic arterial circulation. Patients with PAVMs are known to have an increased incidence of migraines, reducing following PAVM treatment by embolisation. This study aimed to examine if paradoxical embolism of particulate matter through PAVMs may precipitate migraines.

Methods A structured survey was designed for online completion by people with hereditary haemorrhagic telangiectasia (HHT), the most common cause of PAVMs. Question logic directed participants through a series of unbiased questions that asked about HHT features including presence of PAVMs; variables in relation to migraines; and whether participants had undergone imaging tests. Stratified by whether contrast had been given, participants reporting migraines were asked whether any difference in migraines had been noted following scans, by ticking that "migraines were no different really"; "seemed a bit better"; "seemed a bit worse"; "seemed to bring on a migraine"; "seemed to stop a migraine". Participants were recruited from 26/07/2013- 21/04/2015, yielding 702 consented responses. Data were downloaded to an Excel spreadsheet for participant stratifications, and statistical analyses using GraphPad Prism 6.0 and STATA 13.1 (Statacorp LP).

Results Overall, 557 participants had HHT, of whom 180 (32.3%) reported features consistent with migraines. HHT participants with migraines more commonly reported PAVMs than those without migraines (62.8% vs 38.5%, $p < 0.00001$). For computerised tomography (CT) scans, images "with injection of contrast" were associated with a higher proportion of participants reporting worsening migraines than "without injection of contrast" CT scans (11.7% vs 3.4%, $p = 0.0065$). This association strengthened following paired analysis of participants who had undergone both methods (13.6% vs 3.2%, $p = 0.0032$). In multiple regression analyses, there was no additional contribution from other participant demographics such as alcohol consumption or smoking habit. Analysis of magnetic resonance imaging (MRI), contrast echocardiography and ultrasound data is ongoing.

Conclusion This study strongly indicates that an association between injecting contrast media and the worsening of migraines, in participants with right-to-left shunts due to PAVMs, exists. Further research is required to establish the exact mechanism responsible for this phenomenon.

*S1- BTS Medical Student Award Highly Commended.

S2 VASCULAR QUIESCENCE FACTOR BMP9 IS REGULATED BY INFLAMMATION AND NEUTROPHIL ACTIVATION

W Li, L Long, K Hoenderdos, PD Upton, X Yang, AM Condliffe, ER Chilvers, NW Morrell. *University of Cambridge, Cambridge, UK*

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Introduction Endothelial bone morphogenetic protein type II receptor (BMPR-II)-mediated signalling is essential for protecting vascular endothelium. Loss of BMPR-II predisposes human pulmonary artery endothelial cell (hPAEC) monolayers to apoptosis and increased permeability. *In vivo*, reduced BMPR-II function promotes endothelial permeability and the development of pulmonary arterial hypertension (PAH). Importantly, BMP9, the only confirmed active circulating BMP, signals preferentially via BMPR-II and induces BMPR-II expression to maintain endothelial integrity and homeostasis. It was recently shown that administration of recombinant BMP9 prevented LPS-induced lung vascular leakage *in vivo* and reversed established PAH in three rodent models.[1] However, it is not known how circulating BMP9 is regulated during LPS-induced inflammation and in PAH.

Objective To investigate whether BMP9 is regulated by inflammatory stimuli *in vivo* and *in vitro*.

Results Intraperitoneal LPS challenge in mice led to a significant increase in circulating neutrophil elastase levels with a reciprocal reduction in BMP9 levels (both measured by ELISA) within 24 h. Since this reduction in BMP9 might be due to reduced BMP9 synthesis in the liver or cleavage of BMP9 by neutrophil-derived proteases, we quantified BMP9 synthesis in the liver after LPS challenge, as well as changes in alpha-1 antitrypsin, the major elastase inhibitor in man. Synthesis of BMP9 fell sharply 3 h after LPS-challenge but recovered completely by 18 h. No increase in the synthesis or levels of circulating active alpha-1 antitrypsin was observed. Supernatants from purified human peripheral blood neutrophils activated *in vitro* degraded recombinant BMP9. Inhibition studies confirmed that the BMP9-cleavage activity released by activated neutrophils was largely attributable to neutrophil elastase.

Conclusions and discussions Synthesis of the endothelial protective factor BMP9 is actively regulated by inflammation, and BMP9 is subject to neutrophil elastase-mediated cleavage. Since inflammation has been shown to be a second hit in the pathogenesis of PAH, this study could provide a potential link between inflammation and reduced endothelial BMPR-II signalling.

REFERENCE

1 Long L, Ormiston ML, Yang X, *et al*. Selective enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension. *Nat. Med*. 2015;**21**: 777–785

S3 REDUCED BMPR2 EXPRESSION POTENTIATES A PULMONARY ARTERY SMOOTH MUSCLE CELL SPECIFIC IL-1ß RESPONSE

[1]J Pickworth, [2]S Shay, [2]S Gladson, [1]J Iremonger, [1]AMK Rothman, [1]S Francis, [2]J West, [1]A Lawrie. *[1]University of Sheffield, Sheffield, UK; [2]Vanderbilt Instiute, Nashville, USA*

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Introduction and objectives Bone morphogenetic protein receptor type 2 (BMPR2) mutations are found in heritable and idiopathic pulmonary arterial hypertension however penetrance is incomplete implying necessity for a 'second hit'. IL-1ß and IL-6 are increased in PAH patients and animal models and are