S44 ORTHODEOXIA, AND POSTURAL ORTHOSTATIC TACHYCARDIA, IN 165 CONSECUTIVE, UNSELECTED PATIENTS WITH PULMONARY ARTERIOVENOUS MALFORMATIONS

V Santhirapala, JT Springett, H Wolfenden, HC Tighe, JE Jackson, CL Shovlin; *Imperial College London, London, UK*

Background Patients with pulmonary arteriovenous malformations are often quoted as displaying orthodeoxia, that is, a fall in oxygen saturation on standing. It is unclear how common this phenomenon is, and how patients would compensate for any acute fall in SaO_2.

Methods Postural changes in oxygen saturation and pulse were examined in a series of 165 prospectively-recruited patients with radiologically-proven PAVMs. Self-reported exercise at presentation was graded using a modified MRC dyspnoea scale. SaO_2 and pulse measurements were made in both erect and supine postures on 1–8 separate occasions through presentation to post-embolisation follow up. These 522 sets of postural measurements displayed very high within-patient reproducibility.

Results Age ranged from 17–87 (median 49) ys, 62 (37.6%) were male, and for 159 (96%), PAVMs were attributable to HHT. 18.9% were obese with a body mass index (BMI) >30, including one with morbid obesity (BMI>40). At presentation, the SaO_2 fell by at least 2% on standing in 51(33%) patients, compared to the equivalent average supine reading. A smaller fall of 1–2% was present in a further 28 (17%) of patients. Patients with higher BMI had significantly higher supine SaO_2 for their erect SaO_2, and significantly lesser falls in SaO_2 on standing. A postural tachycardia consistently exceeded the increment required to sustain oxygen delivery at rest, across all SaO_2.12/163 (7.4%) of individuals met the pulse definition for postural orthostatic tachycardia syndrome with an increase on standing of more than 30 beats per minute. Once adjusted for baseline supine pulse and age, the erect pulse was lower in patients with higher BMI (adjusted regression coefficient 0.23 (95% confidence interval 0.026, 0.48), p = 0.011). Using the pre-specified 5 group grading system, exercise tolerance was worse in patients with lesser postural tachycardias (regression coefficient -2.19 (-3.74, -0.65) p = 0.006)).

Conclusions Orthodeoxia and postural tachycardia are common in PAVM patients. More pronounced postural tachycardias were associated with improved exercise tolerance. Further studies will be required to assess if this is because it is a surrogate of lower BMI, with obesity effectively limiting a further fall in SaO_2 on standing because of obesity-related lower supine SaO_2.

S45 SPECIFIC VENTILATION INEQUALITY AND DEAD SPACE COMPONENTS OF LUNG CLEARANCE INDEX IN PATIENTS WITH ASTHMA AND CYSTIC FIBROSIS

[1]S Gonem, [1]S Natarajan, [1]A Singapuri, [1]Ce Brightling, [2]P Gustafsson, [3]A Horsley, [1]S Siddiqui; [1]*Institute for Lung Health, University of Leicester, Leicester, UK;* [2]*Department of Paediatrics, Central Hospital, Skövde, Sweden;* [3]*Manchester Adult Cystic Fibrosis Centre, Manchester, UK*

Background Lung clearance index (LCI) is a widely reported marker of gas mixing inefficiency within the airways that is derived using the multiple breath inert gas washout (MBW) technique. We developed two novel parameters, LCI_{vent} and LCI_{ds}, to reflect the components of increased LCI due to (i) unequal convective ventilation between relatively large lung units, and (ii) increased respiratory dead space, respectively. We hypothesised that these parameters would be repeatable, would effectively discriminate between healthy controls and patients with asthma and cystic fibrosis (CF), and would distinguish between different sub-phenotypes of these diseases.

Methods Washout data from sixty-six healthy control subjects, seventy-four patients with asthma, and forty-one patients with CF were fitted to a two-compartment model of gas mixing, and the parameters LCI_{vent} and LCI_{ds} were calculated.

Results LCI_{vent} and LCI_{ds} were markedly elevated in patients with CF, and mildly elevated in patients with asthma, compared to controls, as illustrated in Figure 1. LCI_{vent} and LCI_{ds} were weakly correlated in controls (R = 0.36, p < 0.01), moderately correlated in patients with asthma (R = 0.51, p < 0.0001), and strongly correlated in patients with CF (R = 0.89, p < 0.0001). LCI_{ds} was significantly raised in CF patients with chronic *P. aeruginosa* colonisation compared to those without chronic colonisation (1.49 vs 1.34, p = 0.004). LCI, LCI_{vent} and LCI_{ds} were significantly raised in CF patients with a severe genotype compared to those with a mild genotype. No significant differences were observed between any of the asthma sub-phenotypes (severe vs non-severe, poorly-controlled vs not poorly controlled, exacerbator vs non-exacerbator, and eosinophilic vs non-eosinophilic) with respect to any MBW parameter. The intraclass correlation coefficients of LCI_{vent} and LCI_{ds} exceeded 0.85 in the asthma and CF groups, and 0.60 in controls.

Conclusion The novel parameters LCI_{vent} and LCI_{ds} are repeatable and effectively discriminate between sub-phenotypes of CF, although their utility in asthma is currently unproven. Further studies are required to determine their utility in other airway diseases such as chronic obstructive pulmonary disease, to investigate their role as outcome measures in clinical trials, and to delineate their structural correlates.
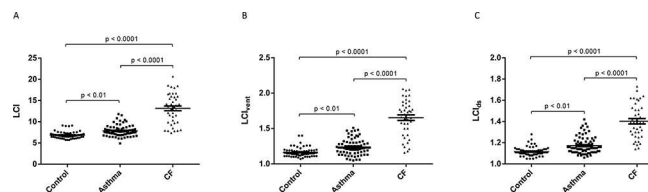
Abstract S45 Figure1 Multiple breath washout parameters across groups. Error bars denote mean +/- standard error of the mean. Groups compared using one-way analysis of variance with Bonferroni correction

Clinical studies in pulmonary vascular disease

S46 OUTCOME AFTER PULMONARY ENDARTERECTOMY (PEA): LONG TERM FOLLOW-UP OF THE UK NATIONAL COHORT

J Cannon, K Page, M Roots, A Ponnaberanam, C Tracy, D Taboada Buasso, K Sheares, C Ng, J Dunning, S Tsui, J Pepke-Zaba, D Jenkins; *Papworth Hospital, Cambridge, UK*

Introduction Chronic thromboembolic pulmonary hypertension (CTEPH) is a life threatening condition that historically has a poor outcome with supportive medical treatment. Pulmonary endarterectomy (PEA) is the treatment of choice and offers the

Abstract S47 Table 1. Median treatment effects on PVR and CI

	PVR, dyn·sec/cm^5 (relative benefit* to placebo expressed in %)				CI, L/min/m^2			
	Macitentan 3mg	p-value	Macitentan 10mg	p-value	Macitentan 3mg	p-value	Macitentan 10mg	p-value
All	-28.7 (-32.2,-19.2)	<0.0001	-37.4 (-46.3,-26.6)	<0.0001	0.5 (0.3,0.8)	<0.0001	0.6 (0.4,0.9)	<0.0001
Treatment Naïve	-19.9 (-34.2,0.8)	0.06	-40.3 (-52.0,-22.3)	0.0002	0.4 (0.1,0.8)	0.01	0.6 (0.2,1.0)	0.004
Treated	-34.4 (-45.6,-22.3)	<0.0001	-33.3 (-45.6,-20.7)	0.0001	0.6 (0.4,1.0)	<0.0001	0.6 (0.2,1.0)	0.005
FC I/II	-35.2 (-49.2,-21.6)	<0.0001	-46.0 (-57.2,-28.8)	<0.0001	0.5 (0.2,0.9)	0.002	0.7 (0.2,1.1)	0.005
FC III/IV	-21.8 (-37.8,-9.2)	0.002	-29.0 (-43.8,-16.6)	0.0003	0.5 (0.3,0.9)	0.0001	0.6 (0.3,1.0)	0.001

Median (95% CL) placebo-corrected change from baseline and Wilcoxon test p-values; *based on the log of Month 6/baseline values

only chance of cure. Data on the long term survival after PEA are limited.

Method All patients who have undergone a PEA for CTEPH at Papworth hospital were included between January 1997 and November 2012. Patients who had a re-do operation were excluded. Pre- and post-operative data on haemodynamics, exercise capacity, functional class and targeted PAH therapies taken were obtained from our PH database and from other UK PH centres. The long-term survival of patients who returned for follow-up at 3 months post PEA was determined using the NHS spine summary care record tracking system. Overseas patients were censored when last seen.

Results 880 patients underwent PEA over the 15 year period. The mean age was 57 (range 15–84) and 53% were male. The majority (89%) were in WHO functional class 3 or 4 prior to surgery with an average mean pulmonary artery pressure (mPAP) of 47 mmHg and PVR of 795 dynes. 65% of patients were taking at least 1 targeted therapy as a "bridge to surgery". Post surgery the majority of patients (86%) were in WHO functional class 1 or 2 at the 12 month follow-up with only 17% taking targeted therapy. There was a reduction in the average mPAP to 27 mmHg and PVR to 308 dynes by 12 months. The 10 year conditional survival post PEA of the first 314 patients from the cohort (Freed *et al*. J Thorac Cardiovasc Surg, 2011;141:383–7) was 74%.

Conclusion The conditional survival of a subset of the cohort at 10 years was 74%. There was a significant functional and haemodynamic improvement in the majority of patients at 12 months post surgery. Only 17% of patients at 12 months post surgery were being treated with targeted therapy.

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mortality in pulmonary arterial hypertension (PAH) patients in the SERAPHIN trial (NCT00660179), the first event-driven outcomes trial in PAH. A substudy in SERAPHIN investigated the effect of macitentan on patients' cardiac haemodynamics.

Methods 742 PAH patients were randomised to placebo, macitentan 3 mg, or macitentan 10 mg once-daily. Stable background PAH therapy, except injectable prostanoids and other ERAs, were allowed. At selected centres, patients underwent right heart catheterisation at randomisation and Month 6. Changes from baseline to Month 6 for mean right atrial pressure (mRAP), mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), cardiac index (CI) and mixed venous oxygen saturation (SvO_2) were calculated for all patients and stratified in an exploratory analysis for background PAH therapy and baseline WHO functional class I/II vs III/IV. Median treatment effects (95% CL) between placebo and macitentan are reported.

Results 187 patients participated in the substudy (51% were treatment-naïve and 56% in WHO FC III/IV). Baseline median values for all patients on placebo (n = 68), macitentan 3 mg (n = 62) and 10 mg (n = 57) were: mRAP 7.0, 8.0, 7.0 mmHg; mPAP 52.0, 54.0, 52.3 mmHg; PVR 800, 785, 789 dyn·sec/cm^5; CI 2.49, 2.23, 2.47 L/min/m^2; and SvO_2 66.0, 64.5, 66.5%, respectively. Overall, haemodynamic parameters improved at Month 6 with macitentan and worsened with placebo. Beneficial treatment effects with macitentan were statistically significant (P < 0.05) for PVR and CI for both subgroups, except for PVR in treatment naïve patients treated with macitentan 3mg (Table).

Conclusions Macitentan significantly improved cardio-pulmonary haemodynamics in PAH patients. Improvements in PVR and CI were consistent irrespective of background PAH therapy and baseline WHO FC.

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EFFECT OF MACITENTAN ON HAEMODYNAMICS IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION: RESULTS FROM THE LONG-TERM, RANDOMISED, PLACEBO-CONTROLLED SERAPHIN TRIAL

[1]G Coghlan, [2]A Torbicki, [3]N Galiè, [4]LJ Rubin, [5]L Perchenet, [6]G Simonneau; [1]*Royal Free Hospital, London, United Kingdom; [2]Department of Pulmonary Circulation and Thromboembolic Diseases, Center of Postgraduate Medical Education, ECZ-Otwock, Poland; [3]University of Bologna, Bologna, Italy; [4]Division of Pulmonary & Critical Care Medicine, University of California, San Diego, USA; [5]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [6]Service de Pneumologie, Hôpital Universitaire de Bic↓tre, Le Kremlin Bic↓tre, France*

Introduction and objectives Macitentan, a novel dual endothelin receptor antagonist (ERA), significantly reduced morbidity and

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INEFFICIENT VENTRICULO-ARTERIAL COUPLING CONTRIBUTES TO REDUCED EXERCISE CAPACITY IN PULMONARY HYPERTENSION

C McCabe, Hoole, P White, R Axell, L Shapiro, J Pepke-Zaba; *Papworth Hospital, Cambridge, United Kingdom*

Introduction Ventriculo-arterial (VA) coupling (Ees/Ea) in the right heart is defined by RV end-systolic elastance (Ees) and pulmonary arterial effective elastance (Ea) with Ees/Ea representing the mechanical efficiency of forward flow from the RV. Ees/Ea may influence exercise capacity in pulmonary hypertension (PH) because patients exhibit cardiac limitation at peak oxygen uptake (peak VO_2) and suffer impaired exercise cardiac output adaptation. We hypothesised that Ees/Ea in the RV represents a