Pulmonary Vascular Disease

P1 CLINICAL AND ECONOMIC BENEFIT OF CARDIOPULMONARY EXERCISE TESTING (CPX) IN PULMONARY HYPERTENSION

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Rationale The exercise response in pulmonary hypertension (PH) has characteristic features, including decreased peak oxygen consumption, increased ventilatory inefficiency (VE/VCO2 slope) and widened alveolar-arterial gradient. These features can be used in diagnosing PH or distinguishing it from other causes of breathlessness. Many of the measurements from CPX are effort-independent, unlike the 6-min walk test, and can be used to discriminate uncontrolled PH from other factors which may affect peak capacity, such as obesity. We wished to evaluate the clinical and economic impact of CPX in PH.

Methods We performed a retrospective analysis of 552 studies performed between August 2007 and August 2010. The impact of these tests was assessed by reviewing clinic letters and multidisciplinary team minutes.

Results As a direct consequence of CPX, (1) 69 (13%) new non-PH diagnoses were made leading to changes in management and non-PH therapy in 18 (3%); (2) cardiac catheterisation was avoided in 69 (13%) and identified as necessary in 5 (1%), with a net saving of £179.5k; (3) 33 non-PH causes for patients' symptoms were identified, preventing the addition of unnecessary and expensive therapies, saving £318.9k; 4) four patients were identified as needing additional therapy, albeit at greater cost (£26.6k); 5) finally, CPX facilitated confident discharge of patients in 38 (7%). The total saving using CPX over 3 years was £457.9k. Appropriate charging structures are not in place for CPX and testing was carried out using research facilities, however, a new national tariff for CPX is set at £235/test. This would still result in net saving of £328.2k (a *gain* of £594/test) in addition to the clinical benefit. We identified further savings of £93.6k which could have resulted from use of CPX earlier in the diagnostic process, increasing the net gain from £594 to £764 per test.

Conclusion CPX provides clinical and financial benefit by directing investigations and treatments in a substantial number of cases. CPX prevented patients undergoing expensive and invasive investigations to establish diagnoses and monitor progression. CPX also improved appropriate use of therapies by characterising patients' functional capacity and identifying when alternative conditions were responsible for patients' deterioration.

P2 IN-FLIGHT HYPOXAEMIA IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)

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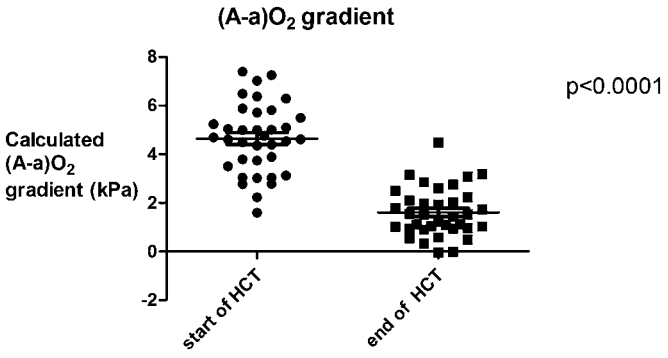
Background and Aim Aircraft travel can worsen hypoxaemia in patients with PAH since pressurised cabins reduce inspired oxygen (FiO_2) to the equivalent of breathing 15.1% at sea level. The British Thoracic Society (BTS) recommends assessing these patients for additional oxygen before air travel, but the criteria used are based on studies of people with COPD (*Thorax*, 2004). New recommendations, in press, suggest that all patients with PAH in WHO Functional Class III and IV have in-flight oxygen (*Thorax*, In Press). The aim of this study was to determine the impact of current and future recommendations on PAH patients, with the hypothesis that more PAH patients will fail a hypoxic challenge test (HCT) than seen in other respiratory conditions.

Methods Patients with SpO_2 >90% on air underwent a HCT using a 40% Venturi mask driven with nitrogen generating an FiO_2 of 15.1%. This was stopped after 20 min or if SpO_2 <85%. Capillary blood gas (CBG) measurements were made at the start and end of HCT. Current criteria suggest that an arterial partial pressure of oxygen (PaO_2) <6.6 kPa or a SpO_2 <85% represents failing the test and in-flight oxygen is needed.

Results Thirty-six patients were recruited: 10 failed (28%), 26 passed (72%). The alveolar-arterial oxygen (A-a)O_2 gradient significantly fell during the HCT (4.64 vs 1.61 kPa, p<0.0001 [see Abstract P2 figure 1]). Univariate analysis showed pre-test SpO_2 (95 vs 92.5, p=0.027), PaO_2 (10.63 vs 9.15 kPa, p=0.0021) and (A-a)O_2 gradient (4.32 vs 5.48 kPa, p=0.026) to differ significantly between those who passed and failed. Three patients who failed the HCT would be missed by current BTS recommendations and one patient would receive in-flight oxygen despite passing the HCT. According to the new recommendations, 15 people would have been given in-flight oxygen who did not require it according to their HCT result.

Conclusions PAH patients are no more likely to fail a HCT than other respiratory patients. The narrowing of the (A-a)O_2 gradient during the test may suggest an improvement in V/Q matching, protecting patients from severe hypoxaemia. Both current and new BTS recommendations missed patients who might require supplementary oxygen, with new recommendations suggesting the need for in-flight oxygen in many patients who do not require it according to the result of their HCT.



Abstract P2 Figure 1

P3 ARE INFLAMMATORY CYTOKINE LEVELS ALTERED BY TREATMENT OF PULMONARY ARTERIAL HYPERTENSION?

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Introduction and Objectives Markers of immune activation and inflammation are raised in pulmonary arterial hypertension; the degree of elevation of levels of pro-inflammatory cytokines in idiopathic pulmonary arterial hypertension has recently been shown to predict long term survival (Soon *et al*, Circulation, 2010). Much less is known of the role of cytokines in disease monitoring. We assessed levels of serum cytokines in patients at initial assessment prior to commencement of targeted therapy for pulmonary hypertension, and when the patient returned to the hospital for follow-up. We also examined if changes in serum cytokines correlated with changes in 6-min walk test (6MWT).

Methods 19 patients with a diagnosis of Group I PAH or Group IV chronic thromboembolic pulmonary hypertension in a distribution inaccessible to surgery were included. Patients with inflammatory conditions other than an associated connective tissue disease or a musculoskeletal condition that would interfere with the 6MWT

were excluded. 11 healthy volunteers acted as a control group. Serum levels of interleukin (IL) 1ß, 2, 4, 6, 8, 10, 12p70 and tumour necrosis factor α (TNFα) were measured using a multiplex analyser. A Wilcoxon matched pairs test was used to compare differences between baseline and follow-up samples.

Results Patient and control demographics are presented in the Abstract P3 table 1. Levels of IL 2,6,8,10 and TNFα were elevated in the patient group compared to controls. Average time to repeat patient sampling was 4.7±1.8 months. There were no significant differences between the levels of any cytokines between baseline and follow-up in the patients and no overall correlation existed between change in 6MWT and change in any cytokine. When patients who had improved their 6MWT on follow-up were analysed as a separate group, there was a significant (p=0.0068) drop in IL6 levels on follow-up.

Abstract P3 Table 1 Patient and control demographics

	Patients	Controls
N	19	11
Male	6 (32%)	3 (27%)
Age (years) (Mean ± SD)	58±14	43±8
NYHA Class (III/IV)	15 (79%)/4 (21%)	
Aetiology of PH		
IPAH	7 (37%)	
Connective tissue disease	5 (26%) (3× SSc, 2× MCTD)	
Congenital heart disease	3 (16%) (2× Unrepaired, 1× Repaired)	
Distal CTEPH	3 (16%)	
Veno-occlusive disease	1 (5%)	
Medication on follow-up		
Endothelin antagonist	8 (43%)	
Prostanoid (Nebulised)	1 (5%)	
Sildenafil	9 (47%)	
Combination	1 (5%)	
mPAP (mm Hg)(Mean ± SD)	51.8±13.5	
CI (L/min/m^2)(Mean ± SD)	1.89±0.62	

CI, Cardiac index; MCTD, Mixed connective tissue disease; mPAP, Mean pulmonary artery pressure; SSC, Scleroderma.

Conclusions Several cytokines were elevated in these patients with pulmonary hypertension. The role of cytokines in disease monitoring requires further study and there seems to be little relation with serum cytokines, except IL6, and a change in a patient's clinical state as measured by 6MWT. Replication of results from this pilot study and examination of longitudinal trends in cytokine levels are warranted.

P4 THE USE OF SILDENAFIL TO TREAT PULMONARY HYPERTENSION ASSOCIATED WITH SARCOIDOSIS

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Introduction and Objectives Pulmonary hypertension (PH) is increasingly recognised as a major contributor to poorer outcomes in pulmonary sarcoidosis. Current treatment guidelines for sarcoidosis associated pulmonary hypertension (SAPH) recommend the optimisation of underlying lung disease and use of oxygen when hypoxaemia is present,[1] however there is insufficient evidence to recommend advanced therapies. Limited data suggest a benefit following treatment with sildenafil in SAPH, although no randomised controlled treatment trials have been reported. We report our experience of patients with SAPH treated with sildenafil.

Methods We reviewed 22 patients (mean age 56±12 years; 10 men) with SAPH (mean pulmonary artery pressure 46±9 mm Hg) who received treatment with sildenafil. Haemodynamic measurements were evaluated by right heart catheterisation in all patients. Serial measurements of brain natriuretic peptide (BNP), pulmonary function testing and functional status were collected.

Results The mean duration of follow-up after the commencement of sildenafil was 21±14 months. Six patients died during follow-up, and four patients required the addition of an endothelin receptor antagonist due to worsening pulmonary hypertension. Patients were dichotomised into responders (those maintained on sildenafil monotherapy; n=12) or non-responders (those who died or required and escalation of PH therapy during follow-up; n=10). Compared to responders, non-responders had a significantly lower % predicted DLco (20% vs 34%; p=0.03) and % predicted Kco (46% vs 62%; p=0.05) at commencement of sildenafil (Abstract P4 table 1). Within 6 months of commencement of sildenafil, non-responders had a 21% increase in median BNP levels, while responders had a 51% reduction in BNP levels. Sildenafil was ceased in one patient after the development of ocular side-effects attributed to the drug.

Abstract P4 Table 1 Demographic and baseline clinical characteristics of patients with sarcoidosis associated pulmonary hypertension receiving treatment with sildenafil*

	Non-responders (n=10)	Responders (n=12)	p Value
Age (years)	53.5 (14)	58.5 (10)	NS
Gender, M:F	5:5	5:7	
Follow-up (months)	23 (16)	20 (12)	NS
Baseline			
mPAP (mm Hg)	50 (10)	43 (8)	NS
PaO_2 (kPa)	7.8	8.2	NS
DLco % predicted	20	34	0.03
Kco % predicted	46	62	0.05
Δ BNP at 6 months	+21%	−51%	

*Values are given as mean (SD) or median (range).

Conclusions Our observations suggest that sildenafil is safe and well tolerated in SAPH. At commencement of sildenafil, a lower % predicted DLco and Kco, and an increasing BNP level within the first 6 months of therapy, was associated with increased risk of death or requirement for additional PH therapy. Controlled trials are warranted before therapeutic recommendations can be made.

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P5 PULMONARY HYPERTENSION IN A MOUSE MODEL WITH REDUCED MACROPHAGE NUMBER (MACLOW)

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Introduction and Objectives Pulmonary arterial hypertension (PAH) is a devastating condition with high morbidity and poor life expectancy. Pathologically PAH is characterised by the medial thickening of the small distal pulmonary arteries. Early endothelial cell (EC) dysfunction and apoptosis, and the subsequent abnormal proliferation and migration of pulmonary artery smooth muscle cells are thought to be a major contributing factor. Macrophages are proposed to play an important role in regulating these processes and are recruited to remodelled pulmonary arteries but the exact role of