$USRF_{CSA}$ was significantly reduced in stage I COPD patients compared to controls (530 mm^2 vs 640 mm^2; p=0.0002) (Abstract S94 figure 1); $USRF_{CSA}$ was also reduced in stages II (526 mm^2), III (503 mm^2) and IV (509 mm^2) disease (p=0.0001). Daily physical activity was reduced in stage I patients (steps; p<0.0001, PAL; p=0.002) and stage II–IV COPD (steps and PAL; p<0.0001) compared to healthy subjects. Using multivariate linear regression, $USRF_{CSA}$ (p=0.0003), FFMI (p=0.0003) and the impedance ratio (p=0.001) were all independent predictors of quadriceps strength in COPD. In stage I patients, only $USRF_{CSA}$ was shown to be independently associated with daily physical activity (steps, p=0.03; PAL, p=0.003), while in stage II–IV disease, FEV_1% predicted was retained as the only independent correlate with daily physical activity (steps and PAL, p<0.0001).

Conclusions Quadriceps wasting identified by $USRF_{CSA}$ exists in patients with early, as well as advanced, COPD when compared to healthy age-matched controls. Quadriceps bulk is associated with daily physical activity independent of airflow obstruction, in early but not advanced disease. Our data suggest that, rather than being an end-stage phenomenon, quadriceps wasting is present in a substantial minority of COPD patients and is related to physical inactivity in the absence of severe airflow limitation.

S95 EFFECT OF PULMONARY REHABILITATION ON CARDIOVASCULAR RISK FACTORS IN COPD

doi:10.1136/thoraxjnl-2011-201054b.95

[1]S S C Kon, [2]A L Clark, [2]K A Ingram, [2]R P Fowler, [2]P Marns, [1]J L Canavan, [1]M S Patel, [1]M I Polkey, [1]W D C Man. *[1]Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, Harefield, Middlesex, UK; [2]Harefield Pulmonary Rehabilitation Team, Harefield Hospital, Harefield, Middlesex, UK*

Background Cardiovascular disease accounts for 27% of excess mortality seen in patients with chronic obstructive pulmonary disease (COPD). This may be attributed to the coexistence of cardiovascular risk factors such as smoking exposure and physical inactivity. Increased arterial stiffness has been demonstrated in patients with COPD, and this is an independent predictor of adverse cardiovascular events. Recent studies have shown that pulmonary rehabilitation (PR) can reduce blood pressure and arterial stiffness in COPD patients (Vivodtzev *et al*, 2009; Gale *et al*, 2011). However these studies comprised small numbers of highly selected patients. We investigated the effect of PR on resting blood pressure and heart rate in an unselected COPD population.

Methods 179 consecutive COPD patients completing an 8-week outpatient pulmonary rehabilitation programme were recruited. Resting blood pressure, heart rate, incremental shuttle walk (ISW) and Chronic Respiratory Disease Questionnaire (CRDQ) were measured immediately before and after PR. Paired t test (or non-parametric equivalent) was used to test the effect of PR.

Results Following PR, there was no significant change in systolic, diastolic, mean arterial pressure and heart rate in all patients with COPD, although ISW and CRDQ improved significantly (see Abstract S95 table 1). Subset analysis in 124 COPD patients with no coexisting cardiovascular disease, diabetes or malignancy, and 31 patients with known hypertension also showed no significant change in blood pressure or heart rate.

Conclusions An 8-week outpatient PR programme has no effect upon resting heart rate or blood pressure in unselected patients with COPD.

Abstract S95 Table 1 Effect of PR on haemodynamic variables in patients with COPD

	Before PR mean	After PR mean	Mean difference (95% CI)	p Value
Systolic BP (mm Hg)	138.7	138.6	−0.0(−2.7 to 2.6)	ns
Diastolic BP (mm Hg)	86.2	86.0	−0.1 (−10.8 to 1.6)	ns
MAP (mm Hg)	103.7	103.6	−0.1 (−1.8 to 1.6)	ns
Heart rate (bpm)	81.8	80.8	−1.0 (−2.7 to 0.6)	ns
ISWT (m)	203.4	262.6	60.5 (48.6 to 72.5)	<0.0001
CRDQ	74.5	91.2	16.7 (13.9 to 19.5)	<0.0001

S96 SURVIVAL AFTER THE FIRST MYOCARDIAL INFARCTION IS SHORTER IN PATIENTS WITH COPD COMPARED TO THE GENERAL POPULATION

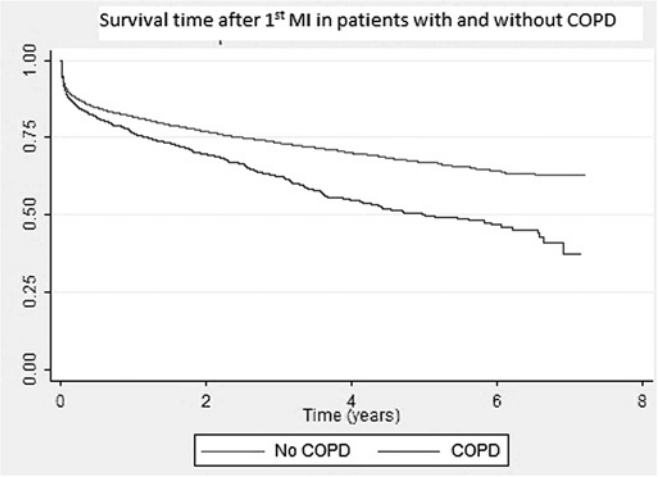
doi:10.1136/thoraxjnl-2011-201054b.96

[1]J K Quint, [1]E Herrett, [2]A Timmis, [3]H Hemingway, [1]L Smeeth. *[1]London School of Hygiene & Tropical Medicine, London, England; [2]Barts & The London NHS Trust, London, England; [3]University College London, London, England*

Background Patients with COPD are at increased risk of myocardial infarction (MI) compared to the general population and have shorter survival after any MI. We investigated whether this held true in patients with an "unanticipated" MI, defined as an MI occurring as the first manifestation of atherosclerotic disease *and* without any traditional cardiovascular risk factors *and* without any prior chest pain.

Methods All patients experiencing their first MI between 1st January 2003 and 31st December 2008 as recorded in Myocardial Ischaemia National Audit Project (MINAP), who had no previous evidence of MI in their General Practice Research Database (GPRD) or MINAP record were included. Patients under 18 years of age, not registered with GPRD at the time of MI, or with <1 year of standard follow-up before their MI were excluded. Data were provided by the "Cardiovascular Disease Research Linking Bespoke Cohorts and Electronic Records" (CALIBER) group at UCL. The primary exposure of interest was diagnosis of COPD (defined in GPRD) and the outcome death after MI. Survival analysis was done using Kaplan–Meier methods. Cox proportional hazards models were used to adjust for potential confounders (age and sex).

Results 8065 individuals were included, 968 (12%) of whom had a physician diagnosis of COPD made either before the first MI or during the follow-up period. 87 patients died on the day of admission 10 (11.5%) of whom had COPD. The overall mortality rate was 160.2 deaths (95%CI 145.5 to 176.5) per 1000 person years in those with COPD compared to 99.4 deaths (95.2 to 103.9) per 1000 person



Abstract S96 Figure 1 Survival time after 1st MI patients with and without COPD.

years in those without COPD. After adjusting for confounding by sex and stratifying for age, survival was shorter after 1st MI in patients with COPD; HR 1.37 (1.23 to 1.52, p<0.001) in those with COPD compared to those without COPD (Abstract S96 figure 1). Survival was shorter in those (n=96) who exacerbated within 6 months of their 1st MI; HR 1.72 (1.13 to 2.60, p=0.01).

Conclusions Survival is shorter after an "unanticipated" MI in patients with COPD and patients who exacerbate within 6 months of their MI have an even higher mortality rate.

BMP signalling in pulmonary hypertension

S97 BMPR2 R899X KNOCK-IN MICE DEVELOPED AGE-RELATED PULMONARY HYPERTENSION

doi:10.1136/thoraxjnl-2011-201054b.97

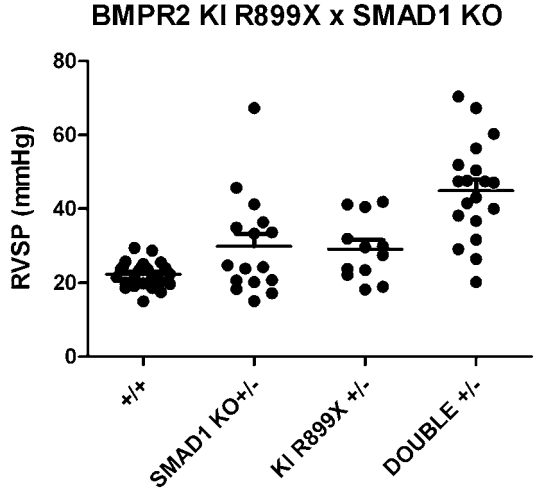
[1]L Long, [1]X Yang, [1]N W Morrell, [2]M Southwood. *[1]University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; [2]Papworth Hospital, Cambridge, UK*

Background Heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (*BMPR2*) underlie the majority (>70%) of cases of heritable pulmonary arterial hypertension (hPAH) and a variable proportion of idiopathic PAH (15%–40%). There are also reports of PAH in patients with mutations in the downstream Smad signalling proteins. However, to date there is no mouse model that mimics the genetic mutations in human disease.

Methods We developed a knock-in mouse harbouring a heterozygous (±) human disease causing mutation in BMPR-II: a nonsense mutation in the cytoplasmic tail (R899X) to determine the in vivo physiologic consequences of this *BMPR2* mutation. In addition, we crossed this animal with Smad1± knockout mice to determine the effect of additional loss of signalling via this pathway. Haemodynamic, and morphometric data were collected at 3 months and 6 months of age.

Results At 3 months of age pulmonary haemodynamics and vascular morphometry of R899X± and Smad1± mice were similar to wild-type littermate controls. In contrast, at 6 months of age R899X± and Smad1± mice developed mild pulmonary hypertension with pulmonary vascular remodelling compared with wild-types. Pulmonary artery smooth muscle cells from R899X± mice were hyperproliferative in serum and exhibited defects in Smad signalling in response to BMPs. When R899X± mice were crossed with Smad1± animals, double heterozygous mice had significantly higher right ventricular systolic pressures than single heterozygous mice.

Conclusion These findings demonstrate that knockin of a human disease causing BMPR-II mutation causes age-related pulmonary hypertension in mice. In addition, we show that the accumulation of defects in the BMP/Smad signalling pathway increases the susceptibility to pulmonary hypertension, highlighting the central role of this pathway in disease.



Abstract S97 Figure 1

S98 BMPR-II MUTATIONS DO NOT PREDISPOSE TO PULMONARY ARTERIAL HYPERTENSION IN A MOUSE MODEL OF SCHISTOSOMIASIS

doi:10.1136/thoraxjnl-2011-201054b.98

A Crosby, E Soon, F Jones, M Southwood, B Dunmore, D Dunne, N W Morrell. *Cambridge University, Cambridge, UK*

Schistosomiasis is the worldwide leading cause of pulmonary arterial hypertension (PAH) and is particularly prevalent in the third-world. More than 80% of patients with PAH in the western world have a mutation in bone morphogenetic protein type-II receptor (BMPR-II), which is a member of the transforming growth receptor-β (TGF-b) superfamily and is important in cell proliferation and differentiation. The aim of the study was to determine if mice with a heterozygous null mutation in BMPR-II are more susceptible to schistosomiasis–induced PAH, compared to wild-type littermates.

Methods Wild-type and mutant C56/BL6 mice were infected percutaneously with a low dose of *S mansoni*. At 17 weeks post-infection right ventricular systolic pressure (RVSP) and right ventricular (RV) hypertrophy, liver and lung egg counts and body weight were measured. Pulmonary vascular remodelling was assessed by morphometry, following immunohistochemistry. Human and mouse pulmonary arterial smooth muscle cells (PASMC) were cultured with *S mansoni* eggs for 24 h. At 24 h the expression of cytokines in PASMC were measured by qPCR and cytokine levels in the cell supernatant were measured by ELISA.

Measurements and Main results At 17 weeks post-infection there was no significant difference in RVSP, the degree of RV hypertrophy, liver weight or body weight between wild-type or mutant mice. However, 33% of the mutant mice died prematurely. After 24 h co-culture with eggs both mouse and human PASMC showed an increase in cytokine expression and cytokine release. More specifically we saw an increase in IL-6, Kc (mouse homologue of IL-8) and IL-13 expression and an increase in IL-6 and Kc secretion. We also saw an increase in PASMC proliferation, determined by Ki67. There was a suggestion that PASMC from mutant mice may display an increase in cytokine response to egg stimulation.

Conclusions This study has shown that BMPR-II mutations do not predispose to schistosomiasis-induced PAH. We have also shown that PASMC respond to *S mansoni* eggs by an increase in expression and release of inflammatory cytokines. These may play a part in inducing pulmonary vascular remodelling by stimulating PASMC proliferation. However, this affect was not significantly enhanced by BMPR-II mutations.

S99 THE ANTI-MALARIAL DRUG AND LYSOSOMAL INHIBITOR, CHLOROQUINE, INCREASES CELL SURFACE EXPRESSION OF BMPR-II

doi:10.1136/thoraxjnl-2011-201054b.99

B J Dunmore, L Long, X D Yang, A Crosby, N W Morrell. *University of Cambridge, Cambridge, UK*

Bone morphogenetic protein receptor type II (BMPR-II) is a member of the transforming growth factor ß (TGFß) receptor superfamily.