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# EFFECT OF EPIGENETIC INHIBITORS ON LUNG FIBROBLAST PHENOTYPE CHANGE IN IDIOPATHIC PULMONARY FIBROSIS

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**Introduction and objectives** Idiopathic Pulmonary Fibrosis (IPF) is a fatal interstitial lung disease with unknown aetiology. Lung myofibroblasts (activated fibroblasts) are the major effector cells in the pathogenesis of IPF. Transforming growth factor- $\beta$  (TGF- $\beta$  1) is a potent activator of fibroblasts. Lack of effective treatment options necessitates novel therapeutic approaches. Epigenetic drugs, by inhibiting chromatin modifying enzymes involved in gene expression control, represent promising agents capable of modulating the cellular phenotype.

We previously demonstrated that the cyclooxygenase-2 (COX-2) gene is epigenetically silenced in lung fibroblasts from IPF patients (F-IPF)<sup>1</sup> and epigenetic inhibitors can restore COX-2 expression. However, whether epigenetic inhibitors can alter fibroblast phenotype remains unknown. This study aimed to investigate the effect of four different epigenetic enzyme inhibitors on fibroblast phenotype change in IPF.

**Methods** F-IPF and fibroblasts from non-fibrotic lung (F-NL) treated with TGF- $\beta$ 1 were cultured to test the effects of the epigenetic inhibitors BIX01294 (BIX, G9a histone methyltransferase inhibitor), 3-deazaneplanocin A (DZNep, EZH2 histone methyltransferase inhibitor), SAHA (histone deacetylases inhibitor) and Decitabine (DAC, DNA demethylating agent), in comparison with the COX-2 products prostaglandin E2 (PGE2). The expression of COX-2 and myofibroblast markers collagen 1 (COL1) and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) was assessed. The COX-2 DNA promoter methylation level was analysed by bisulfite sequencing.

**Results** TGF- $\beta$ 1 induced a myofibroblast phenotype in F-NL characterised by COL1 and  $\alpha$ -SMA upregulation and COX-2 downregulation, similar to F-IPF. PGE2 and SAHA were able to maintain/restore COX-2 expression in TGF- $\beta$ 1-induced myofibroblasts and F-IPF. DAC demonstrated similar effect in TGF- $\beta$ 1 treated F-NL only. SAHA also reduced COL1 and  $\alpha$ -SMA expression. But DZNep and BIX showed no effect. No differences in the COX-2 promoter methylation was detected between F-NL and F-IPF.

**Conclusions** Among the epigenetic inhibitors tested, SAHA shows a promising antifibrotic effect by inhibiting fibroblast activation and the underlying molecular mechanisms are currently under investigation.

## REFERENCE

- Coward WR, Feghali-Bostwick CA, Jenkins G, *et al.* A central role for G9a and EZH2 in the epigenetic silencing of cyclooxygenase-2 in idiopathic pulmonary fibrosis. *FASEB J* 2014;**28**(7):3183–96.

## Lungs and Inflation

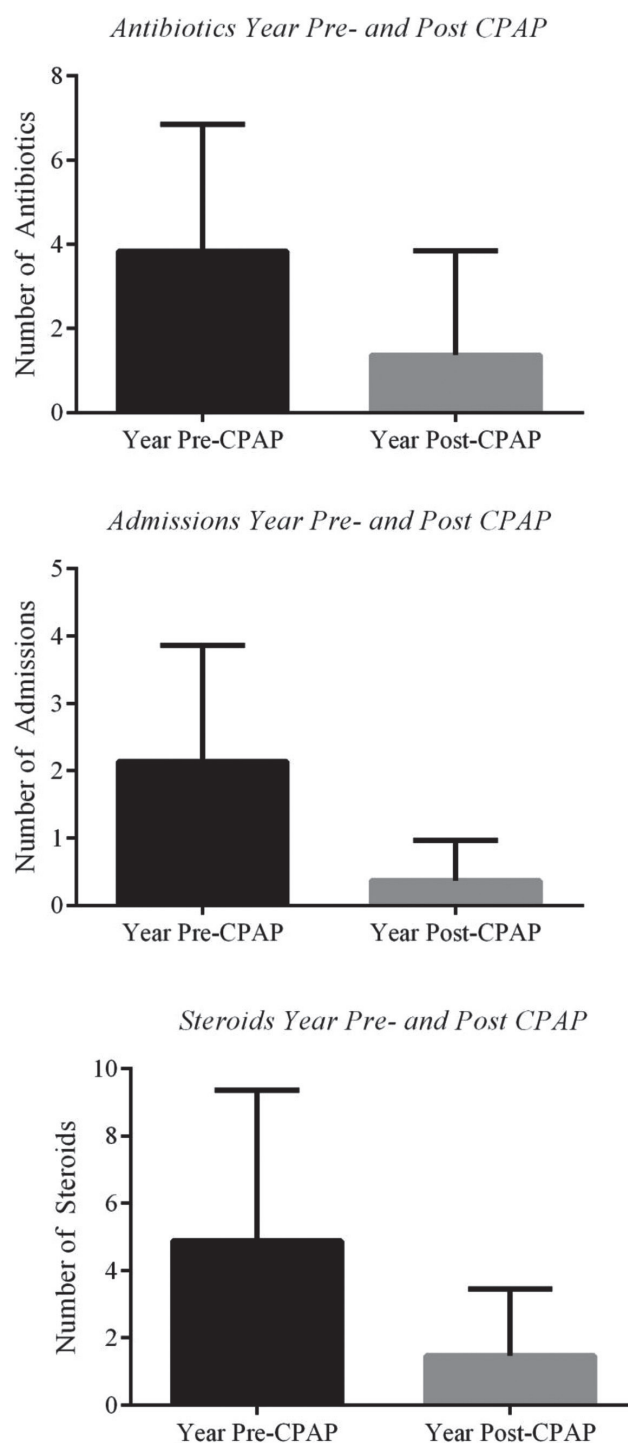
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# CPAP REDUCES EXACERBATIONS IN TRACHEOBRONCHOMALACIA

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**Overview** Tracheobronchomalacia (TBM) is increasingly recognised as a significant diagnosis in patients diagnosed with “severe asthma”. Continuous Positive Airway Pressure (CPAP) is used as first line treatment to stent the airway in TBM patients in order to clear mucus and prevent irritation, inflammation and bacterial overgrowth thereby reducing the number of exacerbations experienced by patients. However, there is currently no published data which evaluates whether this intervention has an impact on outcomes in. This study describes a cohort of patients referred to a regional centre for severe asthma patients, who were



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subsequently diagnosed with TBM and analyses the impact of CPAP on exacerbations caused by TBM.

**Methods** 20 TBM patients were identified at the North West Lung Centre in University Hospital South Manchester (UHSM) through clinics and department databases. Patient case notes and general practice medication prescriptions were used to obtain data on antibiotic and steroid prescriptions as well as hospital admissions (one year before and one after treatment). Exacerbations were analysed pre- and post-CPAP. Patient demographics were also recorded and compared to the cohort in the national severe asthma registry.

**Results** TBM patients were found to have increased weight and BMI compared to the cohort described in the national severe asthma registry; weight  $92.4 \pm 28.8$  in TBM compared to  $81.2 \pm 19.9$  and BMI  $35.5 \pm 8.1$  compared to  $28.0$ . Analysis of CPAP data showed that with an average of 6 hours of CPAP daily at average pressures of 11 cm H<sub>2</sub>O significantly reduced the number of annual exacerbations experienced by over 50% for antibiotic and steroid prescriptions and significantly more for hospital admissions. Figure 1 shows the reduction in exacerbations in the year following the initiation of CPAP compared to the year before.

**Conclusions** The severe asthma cohort with TBM are likely to have an increased weight and BMI. CPAP is an effective treatment option for TBM patients whilst awaiting the availability of more definitive surgical options and reduces antibiotic and steroid prescriptions as well as hospital admissions. It is recommended that all symptomatic TBM patients are considered for CPAP and monitored for exacerbations thereafter.

#### S55 USING CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) IN EXCESSIVE DYNAMIC AIRWAY COLLAPSE (EDAC)

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EDAC is a term that refers to the pathological collapse of respiratory airways during expiration as a result of posterior wall muscle laxity leading to a >50% loss of airway cross-sectional area. This muscle laxity leads to a loss of airway patency which results in symptomatic dyspnoea. CPAP has been suggested as a method to ameliorate the difficulties associated with EDAC where standard medical care has failed, ameliorating the need for further invasive treatments such as endobronchial stenting or tracheoplasty. Demonstrating its effectiveness is difficult as many of those who suffer with EDAC have co-morbid disease such as COPD, asthma or EGPA which may mask the impact of CPAP when measuring response with subjective criteria such as the WHO functional impairment scale. We set out to determine whether we could objectively demonstrate improvements in airway diameter using CPAP in patients with EDAC, in addition to COPD and EGPA, using firstly bronchoscopy and secondly dynamic computed tomography (CT). In both cases we used a Philips Respironics Trilogy 200 CPAP device to deliver positive airway pressure at 5 cm increments up to a pressure of 20 cmH<sub>2</sub>O. Figure 1a shows a bronchoscopic example of this process with an increase in airway area from  $1.54\text{cm}^2$  to  $5.35\text{cm}^2$  equating to a 400% increase in volume at 20 cm H<sub>2</sub>O. Figure 1b shows a CT example with a 52.9% increase in airway area, with the RMB increasing in diameter by 3 mm. CPAP was objectively shown to be an effective,

Figure 1a

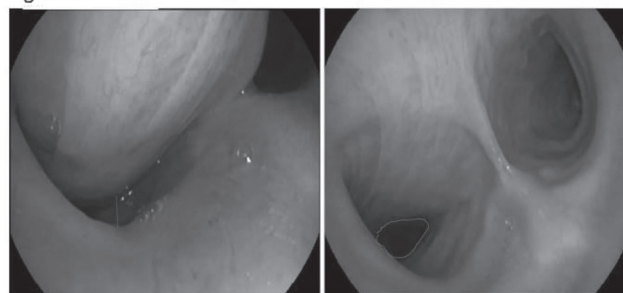
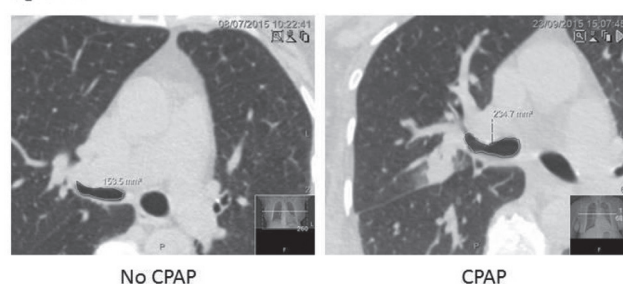


Figure 1b



Abstract S55 Figure 1

relatively inexpensive, treatment for EDAC via bronchoscopy or CT imaging and it is hypothesised such independent measures enhance existing assessments of improvement.

#### S56 NEURAL RESPIRATORY DRIVE AND CARDIAC FUNCTION IN PATIENTS WITH OBESITY-HYPOVENTILATION-SYNDROME FOLLOWING SETUP OF NON-INVASIVE VENTILATION FOR HYPERCAPNIC RESPIRATORY FAILURE

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**Background** Chronic hypercapnic respiratory failure in obesity hypoventilation syndrome (OHS) is commonly treated with non-invasive ventilation (NIV). We hypothesised that treatment of OHS would improve neural respiratory drive (NRD) and improve cardiac function.

**Patients and methods** A prospective, observational single-centre study was conducted. OHS patients were assessed recording NRD, as measured by the electromyogram of the parasternal intercostals (EMGpara) before, during and after NIV set-up and cardiac function with trans-thoracic echocardiography (TTE) before and after NIV set-up. Follow up appointments were planned at 6-weeks (6W-FU) and 3 Months (3M-FU). The tricuspid annular plane systolic excursion (TAPSE) score was used to assess the right ventricular (RV) function and EMGpara%max and neural respiratory drive index (NRDI) were recorded to assess NRD. The Wilcoxon test was used to compare baseline with follow-up results.

**Results** 10 patients (age 55.9 (7.6) years, females 50%, weight 126.6 (29.1) kg, BMI 48.1 (7.5) kg/m<sup>2</sup>) were studied. 3 patients were non-compliant with NIV. NRDI and EMGpara%max significantly improved following NIV set-up, and this effect was maintained at 3M-FU (EMGpara%max 24.4 (12.9)%, 16.9 (5.4)%