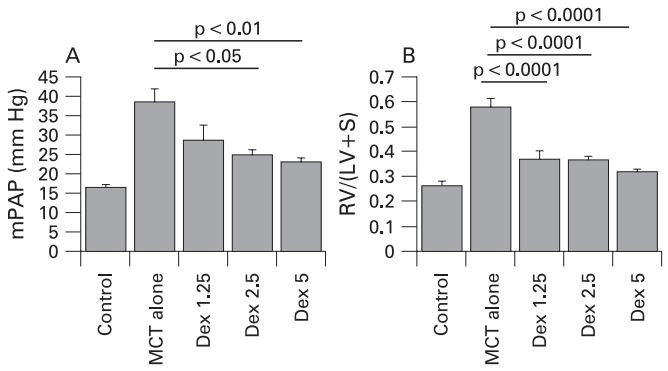

Abstract S63 Figure

rats were anaesthetised (35 mg/kg ketamine, 4 mg/kg xylasine and 0.5 mg/kg acepromazine) and haemodynamics measured using a 3.5 French umbilical vessel catheter. The ratio of right to left ventricular and septal weight was recorded (RV/LV+S).

Results: At day 28, the monocrotaline-alone rats had severe PAH with mean pulmonary arterial pressure (mPAP) (40.8 ± 6.4 mm Hg vs 16.4 ± 1.5 mm Hg, $p<0.001$), right ventricular systolic pressure (RVSP) (94.3 ± 7.8 mm Hg vs 35.2 ± 2.4, $p<0.001$) and RV/LV+S (0.6 ± 0.1 vs 0.26 ± 0.06, $p<0.001$) compared with controls. PAH was reversed in all the groups treated with dexamethasone with a suggestion of a dose–response effect, with mPAP falling to 28.7 ± 11.9 ($p = 0.07$ compared with monocrotaline alone), 24.9 ± 4.7 ($p<0.05$) and 23.1 ± 3.5 ($p<0.01$) in Dex1.25, Dex2.5 and Dex5, respectively (fig A). RVSP was also significantly lower in all three groups. Right ventricular hypertrophy as assessed by RV/LV+S was also reversed by dexamethasone compared with monocrotaline alone ($p<0.001$ in all groups, fig B). None of the measurements in the Dex5 group were statistically different to controls. There was a significant improvement in survival between all the dexamethasone groups when compared with monocrotaline alone (log rank test $p<0.001$).

Conclusions: These results suggest that monocrotaline-induced PAH can be reversed by steroids, raising the possibility that an anti-inflammatory strategy may be beneficial in some cases of pulmonary hypertension.

Respiratory physiology

S64 CLINICAL VALIDATION OF THE SEVERINGHAUS OXYGEN DISSOCIATION CURVE

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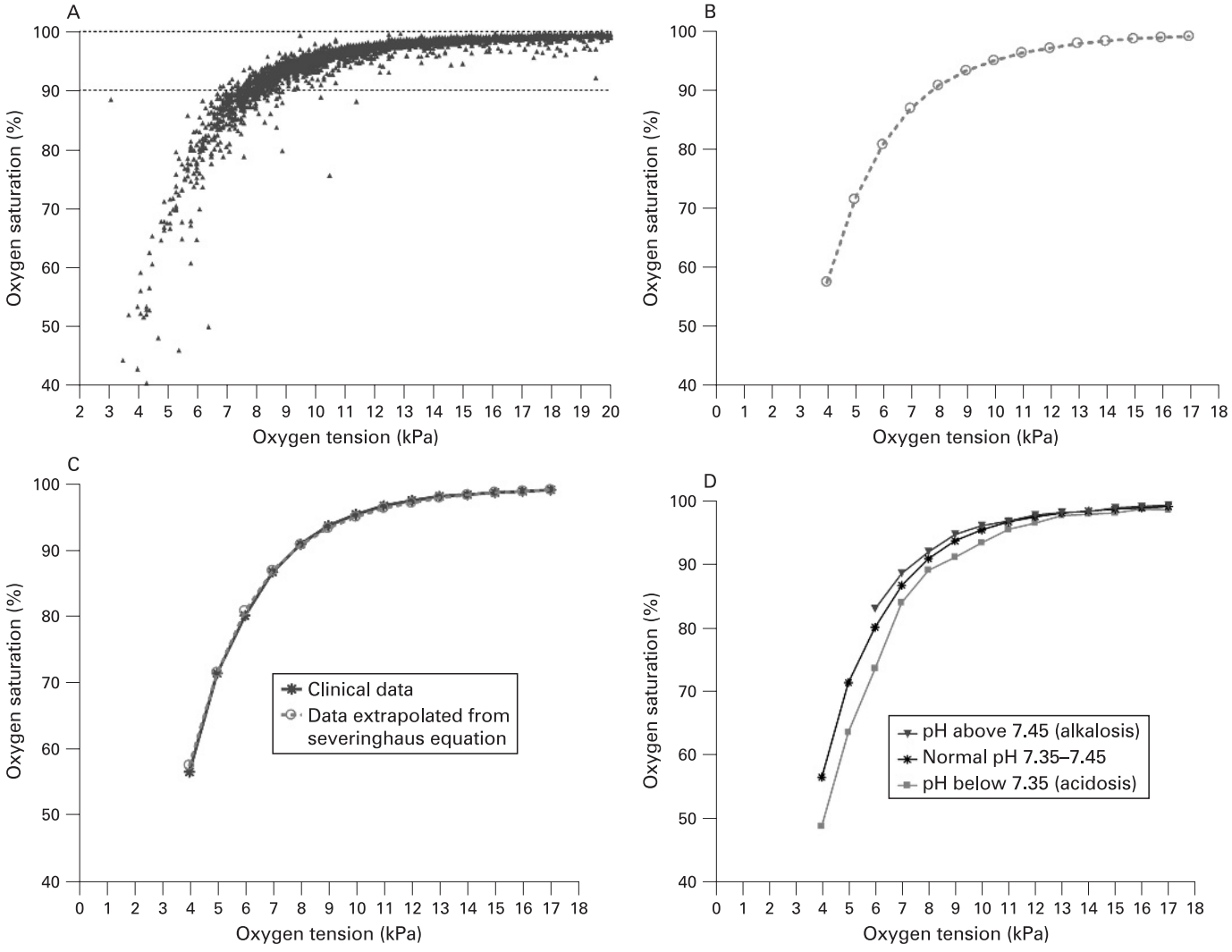
Background: Severinghaus has described a widely used mathematical model to calculate the oxygen dissociation curve for human blood. (*J Appl Physiol* 1979;**46**:599). This model is based on the



Abstract S64 Figure (A) Saturation and oxygen tension of 3524 blood gas specimens; (B) Dissociaton curve calculated from Severinghaus equation; (C) Clinical data compared with Severinghaus equation; (D) Clinical samples at normal, low and high PH.

results of laboratory tests using blood from a limited number of volunteers, which was adjusted to various predetermined oxygen tensions in vitro. We are unaware of any validation of the oxygen dissociation curve using blood samples from seriously ill patients with a wide range of oxygen tension values.
Methods: We audited 3524 anonymised blood gas results from patients treated at this university hospital (2255 specimens with normal pH (7.35–7.45), 558 acidotic specimens with pH <7.35 and 711 alkalotic specimens with pH >7.45). For each blood gas specimen, the oxygen saturation obtained by the laboratory co-oximeter was compared with the calculated value derived from the Severinghaus equation.
Results: The mean SaO_2 was 94.98% (SD 5.9%) using the laboratory co-oximeter and 94.82% (SD 5.3%) using the Severinghaus equation. The mean difference was only 0.16%, which is not clinically relevant. The raw clinical data are shown in panel A of the figure and the Severinghaus curve is shown in panel B. Panel C shows that the mean of the clinical values is almost identical to the Severinghaus result throughout the clinically relevant saturation range at normal pH. Panel D shows the effect of pH on clinical specimens, confirming the Bohr effect of rightward shift with acidosis and leftward shift with alkalosis.
Conclusion: The mathematical equation of Severinghaus predicts the oxygen saturation of human blood from patients with a range of diseases with remarkable precision. We believe this to be the first large-scale clinical validation of this equation.

S65 INSULIN STIMULATES GLUCOSE UPTAKE AND GLUCOSE TRANSPORTER EXPRESSION IN H441 HUMAN AIRWAY EPITHELIAL CELLS

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Background: Hyperglycaemia leads to elevated glucose levels in airway surface liquid (ASL) (Baker *et al*. *J Appl Physiol* 2007;**102**:1969–75), increasing the risk of infection with bacteria such as methicillin-resistant *Staphylococcus aureus* (Philips *et al*. *Thorax* 2007;**60**:761–4). Inhaled insulin has been developed for the treatment of diabetes (Crotty and Reynolds. *Pediatr Emerg Care* 2007;**23**:903–5), but its effect on glucose transport in the airway is unknown. This study aimed to investigate the effect of insulin on glucose uptake by cultured human airway epithelial cells.
Methods: H441 monolayers were cultured on porous filters at air interface. Insulin was added (0–7 μmol) either to basolateral or apical sides of the monolayer for an hour. Uptake studies were performed using 10 mmol glucose with radiolabelled [^{3}H]-D-glucose. Glucose transport was inhibited with 1 mmol phloretin (GLUT inhibitor). Western blotting and immunocytochemistry detected changes in GLUT2 expression.
Results: The basolateral insulin concentration dose–response effect was fitted with a variable sigmoidal curve with an EC_{50} of 1.4 μmol. Basolateral glucose uptake was 52.14 ± 19.84 nmol/mg protein with no insulin. Maximal uptake was 484.46 ± 131.97 nmol/mg protein when 1.7 μmol insulin was added to the basolateral side of the monolayer ($p<0.05$, n = 5–9). In the presence of 1.7 μmol insulin, phloretin significantly reduced uptake to 53.74 ± 9.55 nmol/mg protein ($p<0.001$, n = 3). Apical glucose uptake in the presence of 1.7 μmol basolateral insulin was 31.6 ± 2.0 nmol/mg protein compared with 11.7 ± 1.2 nmol/mg with no insulin ($p<0.001$, n = 3). Western blotting detected a band for GLUT2 at 56 kDa. Increasing insulin concentration evoked the emergence of a second band at 46 kDa. Immunocytochemistry demonstrated the movement of GLUT2 to the cell membrane with increasing insulin concentrations.
Conclusions: Insulin stimulated glucose uptake across both apical and basolateral membranes, indicating the presence of insulin-sensitive transporter(s) in the membranes of airway epithelial cells. These transporters are probably GLUT, as phloretin inhibited insulin-induced glucose uptake and insulin stimulated GLUT2 expression and translocation to the cell membrane. Insulin stimulation of glucose uptake by airway epithelial cells could increase glucose uptake from ASL, potentially reducing the risk of infection.

S66 REDUCTION IN TOTAL LUNG CAPACITY IN OBESE MEN: ROLE OF TRUNK FAT

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Background: Obesity is consistently associated with a reduction in functional residual capacity (FRC) and sometimes with reduction in total lung capacity (TLC). The factors causing this restrictive pattern are uncertain but are presumed to relate to the mass of trunk fat; one hypothesis is that inspiratory descent of the diaphragm is limited by increased abdominal volume.
Methods: Using a 1.5 T Philips magnetic resonance imaging scanner we have measured trunk volumes (total intrathoracic and intra-abdominal volumes and the surrounding subcutaneous fat) and the distribution and volumes of trunk fat (Thomas *et al*, *JAP* 1998). Images were acquired during breathholding at full inflation in 14 supine, moderately obese, middle aged men (mean (SD) age 53 years (12), body mass index (BMI) 39 kg/m^2 (7)) and seven control men (mean (SD) age 50.1 years (9.3), BMI 25 (2.2)). Gas lung volumes (TLC, FRC and subdivisions) were measured by multibreath helium dilution. Men were chosen for this exploratory study because of their predisposition to central obesity.
Results: Mean trunk volumes were 30.4 litres in control and 42.0 litres in obese men with trunk fat averaging 7.0 litres in control and 16.6 litres in obese men. In both control and obese men visceral fat (over 85% of which was intra-abdominal) only accounted for approximately a third of total trunk fat. Despite the narrow range of BMI, the volume of visceral abdominal fat in the obese men varied widely (range 2.8–8.1 l) and accounted for much of the variation in total intra-abdominal volume. Mean TLC (84 (23)% predicted), and FRC (63 (23)% predicted) were reduced in the obese men, but values of TLC varied greatly between subjects, with six men having a classic restrictive pattern with TLC less than 80% predicted. Restriction was associated with reduced expansion of the total thoracic cavity (105% predicted TLC vs 120% predicted TLC in control men) but this pattern was not related to total trunk fat volume, nor to a particularly large abdominal volume, nor to an increase in intra-thoracic fat.
Conclusion: The total volume and distribution of trunk fat varied widely in these men but could not be related directly to reduction in TLC.
Funding: Supported by the Medical Research Council UK.

S67 SNIFF AND TWITCH TRANSDIAPHRAGMATIC PRESSURES IN HEALTH AND DISEASE

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Introduction and Objectives: Contractile function of the diaphragm is best quantified by measuring transdiaphragmatic pressure (Pdi), either during a maximum volitional effort such as a sniff (sniff transdiaphragmatic pressure: Pdi,Sn) or non-volitionally following supramaximal stimulation of the phrenic nerves (twitch transdiaphragmatic pressure: Pdi,Tw). However, normal values for these tests are not well established. The objective of this study was to obtain normal values for Pdi,Sn and Pdi,Tw, to determine whether gender, height, weight or body mass index influence these values and whether Pdi,Tw offers additional information over Pdi,Sn in the clinical evaluation of diaphragm strength.

Methods: Pdi,Sn and Pdi,Tw were measured in 91 and 101 healthy volunteers, respectively, to determine normal values, and in 453 patients referred for respiratory muscle assessment. Diaphragm weakness was defined as a Pdi,Sn and Pdi,Tw below the 5th centile.
Results: Mean (SD) Pdi,Sn was 131 cmH_2O (27) for men and 114 cmH_2O (24) for women. Mean (SD) Pdi,Tw was 27 cmH_2O (6) for men and 25 cmH_2O (5) for women. Age was negatively associated with Pdi,Sn ($r^2 = -0.27$) and Pdi,Tw ($r^2 = -0.39$). Height, weight and body mass index did not independently influence Pdi,Sn or Pdi,Tw. Taking into account age and gender, 204 patients were considered to have diaphragm weakness. The addition of the non-volitional Pdi,Tw to Pdi,Sn in the identification of diaphragm weakness improved specificity from 72% to 100% and positive predictive value from 82% to 100%.
Conclusions: Normal values for Pdi,Sn and Pdi,Tw have been established. The use of both tests of diaphragm function increases diagnostic precision.

S68 THE RELATIONSHIP BETWEEN NEURAL RESPIRATORY DRIVE AND HYPERCAPNIA IN PATIENTS WITH NEUROMUSCULAR DISEASE

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Background: Although respiratory muscle strength is a better predictor of hypercapnic ventilatory failure than poor spirometry in neuromuscular disease (NMD), more reliable tests to monitor progression to hypercapnic ventilatory failure are required. If the respiratory muscles are weak, neural respiratory drive must increase to maintain the balance between the capacity of the respiratory muscles and the load on the respiratory muscle pump. Neural respiratory drive can be measured by quantifying the diaphragm electromyogram recorded using a multipair oesophageal electrode.
Aims and Hypothesis: The aim of the study was to investigate the relationship between neural respiratory drive, measured by quantifying the diaphragm electromyogram (EMGdi) and carbon dioxide retention in NMD. We hypothesised that there would be a positive relationship between arterial pCO_2 and diaphragm electromyogram activity in patients with NMD.
Methods: 11 patients with NMD were studied (four neuralgic amyotrophy, two amyotrophic lateral sclerosis, one muscular dystrophy, one phrenic nerve trauma, one myotonic dystrophy, one polymyositis, one polyneuropathy; eight men; mean (SD) age 53.9 years (10.1); vital capacity 76.8% predicted (20.0); pH 7.43 (0.04), pO_2 11.0 kPa (1.5), pCO_2 5.1 kPa (1.0), HCO_3 24.9 mmol/l (3.5)). Sniff nasal pressure (SNIP), and mouth inspiratory pressure (PImax) were measured. EMGdi was recorded at rest using a multipair oesophageal electrode. Resting EMGdi was normalised by expressing EMGdi as a percentage of peak EMGdi recorded during maximum inspiratory manoeuvres. Normalised EMGdi activity/minute was then calculated (''EMGdi%index''). The maximum inspiratory manoeuvres were inspiration from FRC to TLC, PImax manoeuvres, maximum sniff manoeuvres and sprint maximum voluntary ventilation over 15 s. Relationships between variables were assessed using linear regression analysis.
Results: Correlations between EMGdi%index and each variable measured are shown in the table. There were significant correlations between EMGdi%index and pCO_2 ($r = 0.67$, $p = 0.03$) and HCO_3 ($r = 0.63$, $p = 0.04$) only. Mean (SD) PImax and SNIP were 63.1 cmH_2O (33.0) and 51.0 cmH_2O (35.7), respectively, and mean (SD) EMGdi%index was 575.6 au/min (312.6).
Conclusion: The significant correlations between EMGdi%index, pCO_2 and HCO_3 suggest that the EMGdi%index could potentially be used to monitor progression towards hypercapnic ventilatory failure in NMD. The value of the EMGdi%index over other respiratory muscle function tests requires further study.

Abstract S68 Table Correlations between EMGdi%index and anthropometric/physiological variables

	r	p Value
Age	0.59	0.06
BMI	−0.03	0.9
pH	−0.42	0.2
pO_2	−0.51	0.1
pCO_2	0.67	0.03
HCO_3	0.63	0.04
Vital capacity %	−0.16	0.7
Sniff nasal pressure	−0.54	0.09
PImax	−0.61	0.1

BMI, body mass index; PImax, mouth inspiratory pressure.

Paediatric lung disease

S69 THE DEVELOPMENT OF THE BRONCHIAL SUBEPITHELIAL RETICULAR BASEMENT MEMBRANE

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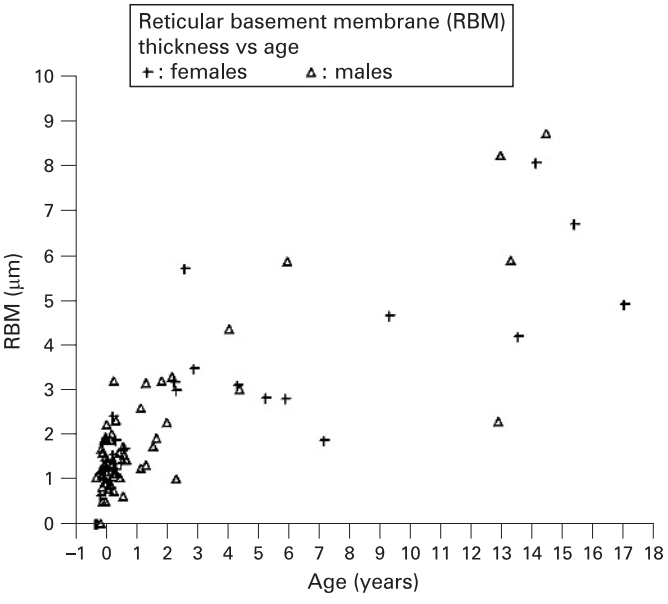
Background: Abnormal thickening of the bronchial subepithelial reticular basement membrane (RBM) is a recognised feature of airway remodelling.[1–3] However, even although the RBM is present in the airways of healthy children and adults, nothing is known about its normal development. We hypothesised that the RBM is first visible at birth and subsequently thickens normally with age for the first 3 years, when final adult thickness is reached.
Methods: Cartilaginous airways were studied in lungs obtained postmortem from 87 infants and children (22 weeks gestation to 17 years old) who had died from non-respiratory causes and had no history of asthma. RBM thickness was measured in haematoxylin and eosin stained paraffin wax sections using computer aided image analysis and a method previously validated in endobronchial biopsies.[4]



Abstract S69 Figure