359. Important new developments in paediatric respiratory physiology

3216

Micron-sized particle deposition in the developing rodent lung

Holger Schulz[1,2], Gunter Eder[2], Ines Bolle[3], Akira Tsuda[4], Stefan Karrasch[5,2]. *[1]Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg/München, Germany; [2]Comprehensive Pneumology Center, Institute of Lung Biology and Diseases, Helmholtz Zentrum München, Neuherberg/München, Germany; [3]Zentrale Versuchstierhaltung, Ludwig-Maximilians-University Munich, München, Germany; [4]Molecular and Integrative Physiological Sciences, Department of Environmental Health, Harvard School of Public Health, Boston, MA, United States; [5]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-Maximilians-University Munich, Germany*

Background: Little is known about the effects of postnatal developmental changes in lung architecture and breathing patterns on intrapulmonary particle deposition. We measured deposition on postnatal days (P) 7, 14, 21, 35 and 90 in WKY rats, whose lung development largely parallels that of humans.
Methods: Intrapulmonary deposition of 2 μm sebacate particles was determined in anaesthetized, intubated, spontaneously breathing rats. Continuous measurement of aerosol concentration as a function of respired volume was accomplished by aerosol photometry (Karrasch et al. 2009). Respiratory parameters were determined by whole-body plethysmography.
Results: Tidal volume increased more than 10-fold from P7 (0.19 mL) to P90 (2.1 mL) while respiratory rate declined from 182 to 113/min. Deposition per breath was lowest (9%) at P7 and P90 and markedly higher at P35 (almost 16%). Structural changes of the alveolar region include an increase in surface area from 744 cm^2 at P7 to 6536 cm^2 at P90 (Bolle et al. 2008). Consequently, particle deposition per unit time and surface area (D_{ST}) peaked at P35 and showed a minimum at P90 indicating that D_{ST} is always higher in the developing than in the adult lung. At an inhaled particle number concentration of 10E5/cm^3 an estimated 450, 690 and 290 particles are deposited per min*cm^2 at P7, P35 and P90, respectively.
Discussion: Micron-sized particle deposition was dependent on the stage of postnatal lung development in rats. A maximum was observed during late alveolarisation (P35), which corresponds to human lungs of about 8 years of age. Children at this age may therefore be more susceptible to airborne environmental health hazards.*Supported by NIH-Grant HL070542*

3217

Newborn airway compliance is correlated with amniotic fluid soluble leukocyte-associated Ig-like receptor-1 (LAIR-1)

Michiel Houben[1], Marloes Olde Nordkamp[2], Kors Vd Ent[1], Jan Kimpen[1], Linde Meyaard[2], Louis Bont[1]. *[1]Pediatrics, University Medical Center Utrecht, Utrecht, Netherlands; [2]Immunology, University Medical Center Utrecht, Utrecht, Netherlands*

Background: Poor airway function at birth is an important risk factor for childhood asthma. The mechanisms determining newborn airway function are unclear. In preterms, intra-uterine inflammation has been associated with enhanced lung maturation. To date, pro-inflammatory cytokines were studied as markers of intra-uterine inflammation. LAIR-1 is a collagen receptor that increases the threshold for activating signals on immune cells. Secreted LAIR-1 (sLAIR-1) is considered a distinct marker of immune activation.
Hypothesis: High amniotic fluid sLAIR-1 is associated with normal newborn airway function and low infant airway morbidity.
Methods: In a healthy birth cohort, 152 newborns underwent lung function measurement. Amniotic fluid was collected during labor and sLAIR-1 was measured. To determine whether amniotic fluid sLAIR-1 could be spill-over from the neonatal circulation, cord blood and amniotic fluid sLAIR-1 were measured in parallel. At age 1 month airway compliance and resistance were assessed with the single occlusion technique. Wheeze during follow-up was determined using a parental log.
Results: sLAIR-1 was detected in all amniotic fluid samples. Airway compliance and amniotic fluid sLAIR-1 were positively correlated (ρ=0.29, P=.001). This correlation did not change by adjustment for sex or maternal smoking. Resistance was not correlated. Amniotic fluid sLAIR-1 was lower in children who wheezed at ages 6 and 9 months (P=.04 and.05). Cord blood and amniotic fluid sLAIR-1 concentrations were not correlated.
Conclusion: The association between amniotic fluid sLAIR-1 and newborn airway compliance underscores the long-term clinical impact of intra-uterine immune activation.

3218

Elicitability of defensive reflexes within the breathing cycle

Silvia Varechova, Bruno Demoulin, Mathias Poussel, Cyril Schweitzer, Bruno Chenuel, Anne-Laure Leblanc, Francois Marchal. *Laboratoire de Physiologie, Faculté de Médecine, Vandoeuvre-les-Nancy, France*

Background: Both the cough (CR) and the expiration reflex (ER) are usually elicited within prolonged (more than 10 s) mechanical stimulation. The use of a discrete mechanical stimulus (150 ms) has shown that the type of response is strongly dependent on the phase of the breathing cycle. CR is favoured in inspiration (I) and ER in expiration (E). The observation suggests that CR and ER exhibit different regulatory mechanisms, but it still remains unclear which mechanisms control the expression of these reflexes.
The aim of the study was to assess the elicitability of CR and ER in relation to the timing of stimulation within breathing.
Methods: 313 mechanical stimulations of the trachea were performed in 14 rabbits using stimuli lasting 50 to 600 ms. CR and ER were identified from airflow and tidal volume. The timing of the stimulus was defined within TI and TE arbitrarily divided into 4 equivalent epochs (TI1 to TI4 and TE1 to TE4) and expressed as percentage of TI and TE of the reference breath.
Results: CR incidence during TI increased from 43% in TI1 to 56% in TI4. CR was almost absent in TE1 (4%) and whenever observed, always preceded by ER. In TE2-4, CR incidence increased, e.g., 50% in T3, to a nadir of 75% at TE4, i.e. the transition from TE to TI. On the contrary, incidence of ER increased throughout inspiration (from 15% in TI1 to 50% in TI4), and further to 54% to in TE1. The incidence then decreased gradually from 53% in TE2 to 19% in TE4.
Conclusions: Elicitability of CR and ER exhibit a completely different pattern within each phase of breathing suggesting implication of distinct control mechanisms in their regulation and/or different impact of inputs from lung afferents in tuning of the CR and ER.

3219

Increased fetal growth protects against early wheeze, airway hyper-responsiveness (AHR) and current asthma in early mid-childhood: Results from the Raine birth cohort

Graham Hall[1], Lyn Chen[2], Wei Ang[3], Craig Pennell[3], John Newnham[3], Peter Sly[2]. *[1]Paediatric Respiratory Physiology, Telethon Institute for Child Health Research, Perth, Australia; [2]Queensland Children's Medical Research Institute, University of Queensland, Brisbane, Australia; [3]School of Women's and Infants' Health, University of Western Australia, Perth, Australia*

Reduced fetal growth has been associated with increased wheeze and atopy and decreased lung function in young children. This analysis of the Raine longitudinal birth cohort aimed to examine the impact of fetal growth on asthma, lung function and AHR outcomes at 6 and 14 years of age.
Methods: The Raine birth cohort enrolled women prior to 18 weeks gestation to standard (18w; n=1419) or intensive (18, 24, 28, 34 & 38w; n=1415) ultrasound monitoring groups. Children were re-assessed at 1, 2 & 3 yrs with further respiratory assessments at 6 and 14 yrs. Complete pre- and postnatal data on 1174 children are included in this analysis. Conditional fetal growth centiles were derived for head circumference, femur length and abdominal circumference. Impact of fetal growth on early wheeze (wheeze at 1, 2 or 3 years), current asthma, spirometry or AHR at 6 or 14 years was assessed using generalised estimating equations with time as repeated measures.
Results: Measures of increased fetal growth throughout pregnancy were significantly associated with a reduced risk of early wheeze, AHR at 6 yrs and current asthma at 14 yrs ($p<0.05$). In addition there was a tendency for increased FEV_1 predicted at 6 and 14 yrs and FEV_1/FVC at age 6 and 14, although these relationships were not significant.
Conclusions: In agreement with previous reports we have demonstrated increased fetal size reduces the risk for wheeze in early life. The current data suggests that the impact of fetal programming on lung health extends into early adolescence and further reinforces the need for further research to discover how fetal growth may be optimised.

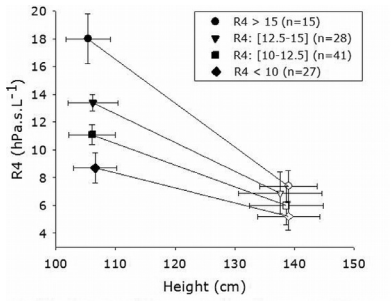
3220

Nonuniform growth in pediatric lung function between 4 and 9 years of age

Ellie Oostveen[1], Sandra Dom[2], Margo Hagendorens[3], Elke Dierckx[3], Wilfried De Backer[1], Joost Weyler[2]. *[1]Dept. of Pulmonary Medicine, Antwerp University Hospital, Antwerp, Belgium; [2]Dept. of Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium; [3]Dept. of Peadiatrics, Antwerp University Hospital, Antwerp, Belgium*

Aim: To our knowledge, the longitudinal change in respiratory resistance (R) in children at the preschool age has not been studied before.
Methods: Lung function was assessed with the forced oscillation technique at 4 and 9 years of age in 111 children (54 M: 57 F) who participated in a prospective birth-cohort in the region of Antwerp, Belgium. Respiratory impedance (4-32 Hz) was measured with a custom-built device at baseline and 15 min after bronchodilation.

Results: The drop in R at 4 Hz (R4) with increasing age was linearly related to the magnitude of R4 at 4 years of age (Pearson's correlation coefficient of 0.87 and 0.88 at baseline and after bronchodilation, respectively). Interestingly, the slope characterizing this relationship was almost similar for the baseline (0.75) and the postbronchodilator values of R4 (0.81). Division of the group of children based on the magnitude of R4 at 4 years revealed that the change in R4 with increasing age was not related to differences in growth rate (see figure). Although the differences in R4 in 4-year-old children disappeared to a large extent with the increase in age, the subgroups of children still had significantly different R4 values by the age of 9 years.



Baseline values of resistance at 4 Hz (R4) expressed as a function of height in groups of children at 4 years of age (closed symbols) and when they reached the age of 9 years (open symbols). Bars: SD.

Conclusion: Four-year-old children with high airway resistance exhibit the largest drop in resistance with growth to 9 years of age; this drop in resistance is independent of airway muscle tone at young age.

3221

Multicentre feasibility and variability of measuring the lung clearance index in healthy volunteers

Susanne Fuchs[1], Helmut Ellemunter[2], Johannes Eder[2], Uwe Mellies[3], Jörg Grosse-Onnebrink[3], Burkhardt Tümmler[4], Doris Staab[5], Andrea Jobst[5], Matthias Griese[6], Jan Ripper[6], Ernst Rietschel[7], Frank Ahrens[8]. *[1]Children's Hospital and Research Institute, Marien Hospital Wesel, Wesel, Germany; [2]Department of Paediatrics, Cystic Fibrosis Centre, Medical University, Innsbruck, Austria; [3]Paediatric Pulmonology, Medical University Essen, Essen, Germany; [4]Paediatric Pulmonology and Neonatology, Medical University Hannover, Hannover, Germany; [5]Paediatric Pulmonology and Allergology, Charité Berlin, Berlin, Germany; [6]Dr. von Haunersches Kinderspital, Medical University Munich, Munich, Germany; [7]Cystic Fibrosis Centre, University Hospital of Cologne, Cologne, Germany; [8]Cystic Fibrosis Centre, Children's Hospital Hamburg Altona, Hamburg, Germany*

The Lung Clearance Index (LCI) is superior to spirometry in detecting early lung disease in Cystic Fibrosis and correlates with structural changes seen on CT-scans. The LCI has the potential to become a novel outcome parameter for clinical and research purposes. Longitudinal studies are required to further prove its prognostic value. Multi-centre design is likely to facilitate realisation of such studies.
Therefore the aim of the present study was to assess multi-centre feasibility and inter-centre variability of LCI measurements in healthy children and adolescents.
Measurements were performed using the EasyOne Pro, MBW module (ndd, Switzerland) by 8 participating CF centres. Marien Hospital Wesel, 7 is the upper limit of normal for the LCI.
The success rate of LCI measurements was 75.5%, leaving n=102 measurements for final analysis. Mean age (range) was 12.5 (5-20) years. Mean LCI (range) was 6.3 (6.0-6.5) and thus normal. Inter-centre variability was 2.9% (p=<0.05).
Our study demonstrates good multi-centre feasibility and low inter-centre variability of the LCI in healthy volunteers when measured with the EasyOne Pro MBW module. Our data are comparable to published single-centre data. However, central coordination, quality control, regular training and supervision during the entire study appear essential for successfully performing multi-centre trials.
This project was supported by Mukoviszidose eV Germany

3222

Area under the reactance curve: Reference ranges and bronchodilator response (BDR) in healthy children

Shannon J. Simpson[1], Claudia Calogero[2], Massimo Palumbo[3], Judy Park[1], Peter Franklin[4], Enrico Lombardi[2], Peter D. Sly[5], Graham L. Hall[1,6]. *[1]Paediatric Respiratory Physiology, Telethon Institute for Child Health Research, Perth, Australia; [2]Respiratory Medicine, Anna Meyer University-Hospital for Children, Florence, Italy; [3]Department of Pediatrics, Belcolle Hospital, Viterbo, Italy; [4]School of Paediatrics and Child Health, University of Western Australia, Perth, Australia; [5]Queensland Children's Medical Research Institute, University of Queensland, Brisbane, Australia; [6]Respiratory Medicine, Princess Margaret Hospital for Children, Perth, Australia*

Introduction: Lung function in children with asthma is frequently normal during asymptomatic periods, especially when assessed using respiratory resistance and reactance (Xrs). Disease related change in Xrs may be amplified by calculating the area under the reactance curve (AX). Increased sensitivity using AX has been reported in identifying a positive BDR in asthmatic children. However, baseline reference ranges and BDR in healthy children are yet to be defined. Therefore, we developed reference ranges and defined BDR by AX in a large population of healthy children.
Methods: Impedance spectra were obtained in 760 healthy children (335 male), aged 2-13 years and with height 90-160 cm using a commercial forced oscillation device (FOT) device (I2M, Chess Medical, Belgium). AX between 6 Hz and the resonant frequency was calculated in 647 children. Backward stepwise linear regressions identified anthropometric predictors of AX, and z-score equations were generated. Absolute and relative changes in AX post bronchodilator were calculated in 496 children.
Results: AX was predicted by height ($p<0.001$) and sex ($p=0.004$). Both absolute and relative changes in AX to bronchodilator were dependent on baseline lung function and height. A significant BDR using AX was defined as a decrease in absolute or relative AX of 33.2 $hPa.L^{-1}$ and 82%, respectively.
Conclusions: We have provided healthy reference ranges for AX to aid in disease detection, and defined cut-off values for a positive BDR by AX.