Probing the Effects of Lung Volume Reduction and Induced Emphysema on Dynamic Lung Mechanics in Sheep

A.C. Henderson[1], E.P. Ingenito[2], A. Hoffman[3], and K.R. Lutchen[1]
[1]Biomedical Engineering, Boston University, Boston, MA
[2]Pulm. Division, Brigham and Women's Hospital, Boston, MA
[3]Tufts Veterinary School of Medicine, Grafton, MA

Emphysema patients exhibit expiratory flow limitation, hyperinflation, air trapping, and decreased perfusion. A potential intervention is to remove significant amounts (~30%) of the lung via lung volume reduction surgery (LVRS). The goal of this study was to evaluate the mechanical consequences of LVRS itself in comparison to a papain-induced model of emphysema in two different groups of sheep. Dynamic resistance ($R_L$) and elastance ($E_L$) of the lung between 0-8 Hz were measured before and after LVRS and before and after inducing emphysema. In group 1, four healthy sheep had static and dynamic lung function measured before and after lung volume reduction. In group 2, four sheep were measured before and after the administration of papain to produce emphysema. A constant-phase model of the lung that includes airway resistance ($R_{aw}$), airway inertance ($I_{aw}$), tissue damping (G), and tissue dynamic elastance (H) was fit to the data. The results demonstrate that LVRS alone has no major impact on dynamic lung properties in healthy lungs, except that it tends to increase the dynamic elastance at functional residual capacity. The mild-to-moderate, homogeneous, papain-induced emphysema model exhibits a huge increase in the frequency dependence of $E_L$ between 0 and 0.5 Hz, such that the static elastance ($E_{stat}$) is lower but $E_L$ is higher by 0.15 Hz. This implies that there is substantial heterogeneity at the tissue level. In conclusion, these data suggest that the combination of static and dynamic mechanical properties would provide insight in evaluating the impact of LVRS on dynamic lung function in emphysematic patients.

This abstract is funded by: NIH and NSF

**MEASUREMENT AND MODELING OF LUNG ELASTICITY FOLLOWING REMODELING AND IN VITRO DIGESTION**

F.S.A. Cavalcante, H. Sakai, S. Kononov, K. Brewer, J. S. Andrade, E.P. Ingenito* B. Suki, Department of Biomedical Engineering, Boston University, *Brigham and Women's Hospital, Boston, MA 02215, Universidade Estadual do Ceara, Fortaleza, CE, Brazil Universidade Federal do Ceara, Fortaleza CE, Brazil

The elastic properties of connective tissues are an important determinant of lung function. We hypothesized that the elastic behavior of connective tissues of the lung arises primarily from two mechanisms: 1) the heterogeneity and the topology of the collagen network and 2) the mechanical interaction between collagen and proteoglycans. To test this hypothesis we measured the stress-strain curve of lung tissue strips following cellular remodeling in a rat elastase-induced emphysema model. The fiber network was also weakened by in vitro elastase digestion and the ground substance was weakened using amylase digestion. The role of proteoglycans was tested by measuring the stress-strain curves under different osmolarity conditions. Before amylase digestion, the stress-strain curve was sensitive to osmolarity, but the sensitivity decreased after digestion. We developed a two-dimensional network model based on the topology of the collagen network. The line elements were nonlinear springs corresponding to the parallel combination of elastin and collagen. The interaction between collagen and proteoglycans was based on the compressibility of the proteoglycans, which we modeled as an angular spring resisting the angular change between two line elements during uniaxial stretching. The model accounts for the loss of elasticity following remodeling by reducing either the elasticity or the fraction of collagen in the line elements and, following amylase digestion, by simply reducing the angular spring constant. We conclude that collagen is a major contributor to lung elasticity and proteoglycans serve to stabilize the collagen network at low strains.

This abstract is funded by: NIH HL-59215 AND HL-62266

**LUNG MODEL AND CT SIMULATOR TO ESTABLISH DYNAMIC VOLUMETRIC LUNG IMAGING**

Hiroko Kitaoka, Ge Wang, Zhanping Liu, Ming Jiang, Geoffrey McLennan and Eric A. Hoffman. Dept. of Radiology, Univ. Iowa College of Medicine, Iowa City, Iowa 52242

**Rationale:** Multi Slice Spiral CT Scanning has the potential to provide unprecedented longitudinal information about the normal and diseased human lung. A fundamental requirement for this to develop id the availability of accurate 4D models of the breathing lung (three-spacial plus time).

**Methods:** To take advantage of the rapidly emerging changes in this imaging technology, we have extended our mathematical, computer-based 3D human lung model (JAP 87: 2207-17) to 4D with temporal changes including both respiratory and cardiogenic-based displacement functions. Additionally, we simulate physiologically based differences in regional lung density, tumor growth, and blood flow characteristics. This model is incorporated into a CT simulator that allows for emulation of scanning parameters including table motion, gantry speed, x-ray divergence angles, and photon statistics (radiation dose). We then apply newly designed reconstruction techniques to generate 4D image data sets, allowing for objective results against which we can evaluate that imaging methodologies.

**Results:** A breathing lung has been created. The model includes the beating heart and 10,000 airway segments. This model can be visualized in 3D and all aspects of the model can be analyzed and modified.

**Conclusions:** With the development of this model and with the ability to mage the lung both dynamically and volumetrically, we can appropriately refine multislice CT scanning parameters. Such methodology, coupled with objective, computer-based quantitative tools are critical to the investigation of structural function relationships.

This abstract is funded by: NIH ROI HL64368-0l, ROI HL60158-Ol, Japan No. 12670558

ROLE OF CHOLINERGIC REFLEXES ON THE BRONCHOCONSTRICTOR RESPONSE TO NEUROKININ A IN ALLERGIC AND NON-ALLERGIC DOGS.

R.W. Chapman, A. House, C.S. Celly, J.A. Hey, S.S. Young. Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA.

Neurokinin A (NKA) potentiates airway cholinergic neurotransmission in several species. In this study, the role of cholinergic reflexes on the bronchoconstrictor response to NKA was evaluated in non-sensitized dogs (n=12) and in allergic dogs (n=12) neonatally sensitized to ragweed in which heightened bronchoconstrictor reactivity to NKA has previously been observed. Pulmonary resistance ($R_L$) was measured in anesthetized, spontaneously breathing dogs before and after increasing concentrations of aerosolized NKA. The provocative concentrations of NKA increasing $R_L$ by 25% above the baseline ($PC_{25}$) was measured before and after (~10 min) aerosolized saline or ipratropium bromide (0.01%) using a randomized cross-over design. In allergic dogs, NKA bronchoconstrictor reactivity ($PC_{25}$ = 0.050 ± 0.011%) was 2.5 times higher than that of non-sensitized controls ($PC_{25}$ = 0.177 ± 0.031%). Ipratropium bromide inhibited the bronchoconstrictor response to NKA in both sensitized and non-sensitized dogs and after ipratropium, reactivity to NKA was 5-fold less in allergic dogs ($PC_{25}$ = 0.246 ± 0.048%) as compared to 3.5 fold less in non-sensitized controls ($PC_{25}$ = 0.622 ± 0.106%). In conclusion, cholinergic reflexes are important components of the bronchoconstrictor response to NKA in dogs particularly in those sensitized neonatally to ragweed. It is speculated that heightened activity of cholinergic reflexes contributes to the bronchial hyperresponsiveness seen in allergic dogs.

This abstract is funded by: Schering-Plough Research Institute

EFFECTS OF OZONE RE-EXPOSURE ON SUBSTANCE P (SP)-INNERVATION IN AIRWAYS OF POSTNATAL RATS.

T. Mulvey[1], B.E. Satterfield[1], D.G. Frazer[2], J.S. Fedan[2], and R.D. Dey[1]. Department of Anatomy, West Virginia University[1] and PPRB, NIOSH[2], Morgantown, WV 26506.

Airway infections or irritant exposures during early postnatal periods may contribute to the onset of asthma during childhood and may be associated with exposure during critical periods of postnatal lung growth. In previous studies, a possible critical period was identified during which there was heightened neural sensitivity to ozone ($O_3$) occurring around postnatal day (PD) 4. The present study examines the effects of an initial $O_3$ exposure at PD4 on airway SP innervation 24 hr after re-exposure on day PD28. Rats were exposed to 2 ppm $O_3$ or filtered air (FA) for 1 hr as follows: control (FA), single $O_3$ exposure at PD28, single $O_3$ exposure at PD4, multiple $O_3$ exposure at PD21 and PD28, and multiple $O_3$ at PD4 and PD28. At PD29, 24 hr after the last exposure, lungs were removed, fixed, and prepared for SP immunocytochemistry. Extrapulmonary (EP) and intrapulmonary (IP) airways were dissected and SP nerve fiber density (NFD) for epithelium (E) and smooth muscle (SM) was determined by image analysis. SP NFD in the IP-SM increased twofold from about 0.7% in control to 1.4% in the group exposed to ozone at both PD4 and PD28. SP-NFD was not altered in IP-E or in the EP airways of this exposure group, and was not different from control in IP or EP airways of other exposure groups. These findings suggest that an initial ozone exposure during a possible critical phase of postnatal airway growth (PD4) followed by a second irritant exposure at PD28 leads to altered airway innervation not observed after a single PD28 exposure.

This abstract is funded by: NHLBI Grant HL 61905

**THE EXTRINSIC INNERVATION OF THE MURINE LUNG AS STUDIED BY RETROGRADE TRACING AND IMMUNOHISTOCHEMISTRY**

*Q. T. Dinh[1,2], D. A. Groneberg[2], E. C. Mingomataj[2], J. Springer[2], A. Fischer[2]*
*[1]Institute of Anatomy and Cell Biology, University of Giessen, [2]Research Division of Allergy, Dept. of Pediatrics, Charité, Humboldt-University, Berlin, Germany*

The extrinsic and intrinsic innervation of the lung plays an important role in the regulation of airway function in health and disease. Despite the growing interest on neuromodulation in the murine model of airway inflammation, detailed studies on the the origin of nerve fibre types innervating the airways have not been carried out. The sensory and sympathetic innervation of the murine lung were studied by means of retrograde neuronal tracing of main stem bronchi in combination with double-labelling immunofluorescence. Fluorescent dye (Fast blue) positive sympathetic neurons (n=18276) were located in the superior cervical and stellate ganglia. More than 98% of these neurons were immunoreactive to tyrosine hydroxylase (TH) and 43% TH positive neurons contained neuropeptid Y (NPY) immunoreactivity (IR). A small number of neurons were TH-negative but NPY positive or nonreactive to TH and NPY. All possible combinations of TH and NPY co-existence were found in nerve fibres of the lung parenchyma. Sensory neurons projecting to the murine lung were located in the vagal-sensory jugular and nodose ganglia. They showed all possible combinations of neuronal nitric oxide synthase (nNOS)- and substance P (SP)- IR. About 15% were immunoreactive to nNOS, a small number of the neuronal population showed IR to nNOS and SP (3%), and the same number were only immunreactive to SP (3%). In the lung, SP-IR and NOS-IR nerve fibres surrounded blood vessels and formed a dense network in the lamina propria immediately below the epithelium. The present study provides a detailed topographical and neurochemical map of the sensory and sympathetic innervation of the murine lung.

FEDAN

AMERICAN JOURNAL OF

# Respiratory and Critical Care Medicine

Volume 163 • Number 5 • April 2001


AN OFFICIAL JOURNAL OF THE AMERICAN THORACIC SOCIETY