61

APPLICATION OF CELLULAR AUTOMATA: CLASSIFICATION & QUALIFICATION OF PULMONARY PARENCHYMAL INJURY IN ARDS

Joalin P-K Lim and Jerome Abrams
University of Minnesota, Dept. of Surgery & BioMed Eng. Institute

Diagnosis and improving the treatment outcome in patients with Adult Respiratory Distress Syndrome (ARDS) have been a challenging goal of clinicians for many years. It is commonly agreed that ARDS is manifested clinically by an acute respiratory failure that evolves shortly after the onset of a predisposing clinical condition associated with: sepsis, long bone fracture, gastric aspiration, trauma, burns, ischemia-reperfusion injury and pancreatitis. All the ARDS patients required mechanical ventilator support. Reports have suggested ventilator therapy may induce injury to the patient through pressure volume stresses. In this research, we demonstrate that it is possible to separate the intra-pulmonary gas exchange injury resulting from the ventilator as well as the injury that results from the patient's lung parenchyma. In our approach, each gas exchange unit of the lung is viewed as a computer. In each computer, a piece of information about the state of perfusion or ventilation in that gas exchange unit is calculated. The operation of each alveolus on the retentions and excretions of the inert gases produces a measured information that represents the aggregate function of the alveoli. The mathematical derivation is based on 1-dimension Cellular Automata (CA) theory. Analyzing lung function in terms of the information content of gas exchange permits improved stratification of patients on the basis of a functional measure of pulmonary parenchymal injury. CA allows a rich mathematical structure and requires few assumptions. By stimulation of the partial pressure of the inert gases in the trachea, we obtained the measurement of the global lung function.

62

A FAST-RESPONDING HALOGEN GAS DETECTOR FOR NON-INVASIVE DETERMINATION OF Cl_2 DOSE DISTRIBUTION IN THE HUMAN AIRWAYS

V. Nodelman, A. Ben-Jebria and J.S. Ultman
Penn State University, Department of Bioengineering, University Park, PA.

Risk assessment of Cl_2 exposure requires knowing the relationship between the inhaled Cl_2 concentration and local tissue dose. The bolus-inhalation technique may be used to determine this relationship in human subjects provided that a Cl_2 detector with a fast dynamic response and high sensitivity is available. Such a detector was developed by utilizing a commercially available thermionic transducer. Operation of the transducer at 500°C and an absolute pressure of 120 torr resulted in a dry-air sensitivity 5 pA/ppm Cl_2 and signal-to-noise ratio of approximately 10 at a Cl_2 mole fraction of 0.1 ppm. The detector had a response time of less than 100 ms when the sampling flow was 0.5 L/min. The calibration was linear in the range of 0.03 to 4.0 ppm Cl_2 and insensitive to temperature and to CO_2 mole fraction variations which exist in expired air. Preliminary bolus-inhalation data collected employing the detector indicate that the Cl_2 dose delivered to the lower airways was influenced by the ambient Cl_2 concentration as well as the mode of breathing.

(Funded by CIIT and the Chlorine Institute).

63

THE INFLUENCE OF SURFACTANT ON PULMONARY AIRWAY REOPENING UNDER BULK EQUILIBRIUM CONDITIONS

Darren Y.K Yap and Donald P. Gaver.
Tulane University, Department of Biomedical Engineering, New Orleans, LA

During pulmonary airway reopening, surfactant sorption to and from the air-liquid interface modifies the lining fluid surface tension. Our goal is to determine how changes in surfactant physicochemical properties influence airway reopening behavior. Airway reopening is modeled as a semi-infinite, inviscid finger of air progressing steadily at velocity U, separating elastically-supported flexible walls in a planar channel. Downstream, fluid with viscosity μ holds the channel at a film thickness $2H$. Surfactant exchange is a serial processes involving convection, diffusion, and adsorption. The surfactant surface concentration (Γ^*) modifies the surface tension (γ^*). We assume bulk-equilibrium conditions where the bulk surfactant concentration C_0 is uniform due to rapid bulk diffusion, and the Henry isotherm is used. Several dimensionless parameters govern the system: Ca, comparing the viscous to surface tension stresses; St_λ, relating the surfactant adsorption rate with convection; El, the surfactant's ability to modify the surface tension; β, comparing wall elastic to surface tension stresses; η, a ratio of the wall tension to surface tension; and Pe_{int}, relating surface convection to diffusion.Our simulations show that $St_\lambda > 10$ is sufficient for interfacial remobilization, which reduces airway reopening stresses. Furthermore, Marangoni stresses on the interface are reduced by increasing the surfactant concentration, reducing El.

This research was supported by NIH HL-51334 and NSF BES-9358207

Pulmonary Remodeling

64

BLOOD FLOW AND ANGIOGENIC GROWTH FACTOR GENE EXPRESSION IN SKELETAL MUSCLE

P.D. Wagner, J. Roca, T. Gavin, M. Jordan, N. Siafakas, H. Benoit, H. Wagner, and E. Breen
University of California San Diego, Dept. of Medicine, La Jolla, CA

Repeated exercise invokes a well-described training response in skeletal muscle, a major component of which is new capillary growth around muscle fibers. Angiogenic growth factors such as VEGF are probably important contributors to this response, and VEGF mRNA abundance is increased several fold immediately after a single bout of exercise. What links exercise to growth factor transcription is an important question of basic as well as disease-related significance. One hypothesis is that intracellular hypoxia stimulates transcription, another is that the increased shear stress and/or wall tension resulting from high blood flow during exercise is responsible. To test the latter, we compared VEGF mRNA responses to a) 5-fold, passively increased muscle perfusion with b) electrically stimulated exercise in the same muscles achieving the same 5-fold increase in flow. Exercise increased VEGF mRNA abundance some 3-fold, but passive perfusion had no effect at all. These results do not support the hypothesis that physical factors in the muscle microcirculation are direct stimuli of angiogenic growth factor responses to exercise.

65

MECHANISMS IN THE GENESIS OF HYPOXIC PULMONARY HYPERTENSION. S.S.Sobin. Dept. Bioengineering Univ. Calif., San Diego. La Jolla, CA 92093

Hypoxia is a facile agent to elicit pulmonary hypertension (HT) in most mammals. We have studied the rat with 5-10% O_2 normobaric hypoxia and 1/2 atm hypobaric normoxia . With acute resulting pulmonary hypertension, within 4 min of hypoxia the intra-acinar arterioles show endothelial cell activation, with protuberance of nuclei, adluminal spherical electron-dense membrane-bound bodies, increasing pseudopodia of the adlumenal cell membrane & edema within & beneath the cell. Lumenal platelets and leucocytes are activated with progressive marked accumulation of platelets at the endothelium. Arteriolar wall edema rapidly increases & at 1 h dissection of wall with exaggeration of activation response. Fibroblasts at arteriolar-septal wall intercept are 2x at 8 h and 3x at 24 h, with areas of basal lamina. At 48 h fibroblasts within the arteriolar wall show increased basal lamina, dense bodies and few microfilaments & are termed *transitional cells*; at 72 h smooth muscle in wall & at 7 days arterioles are muscularized. Platelet activating factor (PAF) antibody staining shows PAF in arteriolar wall and lumen at 10 min hypoxia. Findings suggest activated endothelial cell with PAF release may be an initial event in hypoxic response & subsequent events may be cytokine and autocrine related & result in vascular remodeling of lung.

66

THE RESPONSE OF AIRWAY EPITHELIUM TO MECHANICAL STRESS AND ITS IMPLICATIONS IN ASTHMA

B. Ressler*, R. T. Lee+, J. M. Drazen+ and R. D. Kamm*
*Massachusetts Institute of Technology, Cambridge, MA
+Brigham and Women's Hospital, Boston, MA

The airway wall remodels in asthma; all regions of the wall thicken, including the subepithelial collagen layer. Repeated smooth muscle constriction in asthma places mechanical stress on airway epithelium. Since the epithelium in a constricted and buckled airway is subjected to normal stresses, we investigated the response of primary rat tracheal epithelial cell cultures (RTE) to elevated pressures. After placing the cell cultures under 10 or 20 cmH_2O transmembrane pressure, we determined by Northern blot analysis changes in gene expression. We examined genes involved in regulating extracellular matrix production and early response genes known to be mechanically transduced in other cell systems. We found several different regulation patterns in response to mechanical stress. Egr-1 was quickly upregulated by pressure after one hour and then returned to baseline levels. Et-1 was also quickly upregulated by pressure, and remained at elevated levels throughout the experiment. TGF-β1 levels increased after six hours of pressure stimulation. Our results show that RTE are highly responsive to mechanical stress, and that the epithelial response may lead to airway wall remodeling as seen in asthma. Supported by the Whitaker Foundation, the NIH (HL33009), and the Freeman Foundation.

67

HEMODYNAMIC STRESS AND SIGNALING FOR ARTERIOLAR PATTERN FORMATION IN SKELETAL MUSCLE.

Richard J. Price, Peter J. Zeller, and Thomas C. Skalak.
University of Virginia, Department of BME, Charlottesville, VA.

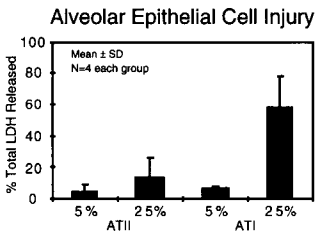
New arterioles form when fibroblasts on the abluminal surface of existing capillaries differentiate into smooth muscle (SM). In skeletal muscle, this arterialization process occurs in a controlled proximal-to-distal gradient along the capillary, consistent with a pressure-growth mechanism. TGFβ is a potential molecular mediator of arteriolar pattern formation because it is a blood pressure responsive factor that is localized to SM contractile protein expressing microvessels. *In vitro*, TGFβ enhances the production of SM α-actin by fibroblasts. Direct *in vivo* application of TGFβ to mesenteric windows increases vascular density within individual networks and the percentage of vessels with SM α-actin positive cells after 1 to 3 days. SM α-actin expression appears, however, to be limited to cells on abluminal surfaces of the vascular network. These results suggest that while TGFβ stimulates arteriole formation *in vivo*, contact between the microvessel endothelium and differentiating fibroblast may be required for the transformation of the fibroblast into SM. Supported by NIH HL49146 and HL52309. RJP is a Postdoctoral Fellow of the AHA, VA, Inc.

68

DEFORMATION-INDUCED INJURY OF ALVEOLAR EPITHELIAL CELLS IS DEPENDENT ON MORPHOLOGY

D.J. Tschumperlin and S.S. Margulies
University of Pennsylvania, Dept. of Bioengineering, Philadelphia, PA.

Mechanical ventilation with high lung volumes can compromise the blood-gas barrier. This barrier, composed of type I (ATI) and type II (ATII) alveolar epithelial cells, experiences large biaxial deformations at high lung volumes. We hypothesized that ATII cells, the progenitors for ATI cells in vivo, are more resistant to deformation-induced injury. Primary ATII cells were isolated from rats (N=4 for each group), seeded on fibronectin-coated silastic membranes, and stretched 1 or 5 days later. At 5 days, the cells are morphologically similar to ATI cells, and express many of the phenotypic characteristics of ATI cells. Cells were exposed to 5 or 25 % equi-biaxial strain for 1 hour at 15 cycles/min. Injury was assessed by lactate dehydrogenase (LDH) released into the media, relative to unstretched controls. LDH varied significantly ($p \leq .05$) with strain and cell morphology. Consistent with our hypothesis, ATII cells were significantly less sensitive to strain magnitude than ATI cells. Supported by: Whitaker Foundation



69

EFFECT OF CYCLIC COMPRESSION AND ELONGATION ON AIRWAY EPITHELIAL CELL SIZE AND SPREADING IN WOUND CLOSURE.

Ushma Savla and Christopher. M. Waters
Departments of Biomedical Engineering and Anesthesiology, Northwestern University, Chicago, IL.

Airways are continuously subjected to both tensile and compressive deformation during the respiratory cycle, but little is known about how such forces affect wound healing. We investigated whether physiological levels of stretch, provided by the Flexercell Unit would affect repair in wounded human airway epithelium. Due to the radially-dependent strain profile in Flexercell wells, we examined both cyclic compression and elongation. Elongation significantly slowed closure of wounds and compression inhibited closure to an even greater degree. This attenuation was dependent upon the time of relaxation (TR) during the cycle. When wells were stretched at 10 cpm (6 sec cycle) with TR=5 sec, wounds closed similarly to wounds in static wells, whereas in wells with TR=1 sec, significant inhibition was observed. We measured the effect of stretch at various TRs on cell area and internuclear distance (ID) since spreading and migration are two key steps in the healing process. While cell area and ID in static wells significantly increased over time, the area and ID of cells in the elongated regions did not change. Cells being compressed were significantly smaller with significantly lower ID. Cell area and ID became progressively larger with increasing TR. These results suggest that the duration and magnitude of cyclic stretch determine the extent of wound closure. Supported by NSF and the Whitaker Fnd.

Poster Presentations

70

REPEATABILITY OF BRACHIAL ARTERY AREA MEASUREMENT

Michael D. Whitt and Dr. Gary M. Drzewiecki
Cardiovascular Research Laboratories, Dept. of Biomedical Engineering, Rutgers University, Piscataway, NJ 08855-0909
Guidant Corporation, Temecula, CA 92591

Brachial arterial lumen area measurements are made by means of a standard occlusive arm blood pressure cuff. Since the cuff compliance is not constant, its compliance variation is calibrated using a mechanical model and external pump. Human preliminary results measuring the vascular pressure-area curve have shown repeatable area measurements over the entire transmural pressure range. Following a 120 sec. occlusion reactive hyperemia is created. The results show a lumenal area increase due to decreased smooth muscle activation. The lumen area change was found to be +6% of the resting value at the subject's diastolic pressure. Results were repeatable (N=3,Mean=0.11 cm^2, SD= 0.01) at 80 mm Hg for a single subject. The in vivo experiments are employed to investigate the validity of a collapsible blood vessel model that will be applied to study blood pressure determination and the detection of lumen narrowing due to peripheral vascular stenosis.

71

HOW DO TEMPERATURE AND HUMIDITY ERRORS AFFECT MEASUREMENT OF OXYGEN UPTAKE PER BREATH?

Peter H. Breen
Dept. of Anesthesiology, University of California – Irvine, Orange, CA

Measurement of pulmonary O_2 uptake usually uses mass balance of N_2 to correct for differences between inspired and expired volume due to temperature (T) and humidity. Often during anesthesia, N_2 balance cannot be invoked due to high inspired O_2 fraction (FI_{O_2}) or non-steady state conditions. Then, O_2 uptake per breath ($V_{O_2,br}$) must use assumed or measured T and humidity differences between inspirate and expirate. This numerical analysis study examines how errors in inspired relative humidity (RH) and T can affect $V_{O_2,br}$. Equations were developed to simulate a baseline metabolic and ventilatory condition. An arithmetic error in inspired RH of 0.5 caused percent errors in $V_{O_2,br}$ of 5.6% during FI_{O_2}=0.2 and 28.8% during FI_{O_2} of unity. Percent error in $V_{O_2,br}$ = (-57.6 •FIO_2-0.115)•(change in RH) (R^2>0.999). Errors in inspired T had similar effects on percent error in $V_{O_2,br}$ (= -8.75•FI_{O_2}-0.093)•(change in T) (R^2=0.999). As FI_{O_2} increased, a progressively larger fraction of the resultant error in inspired volume is applied to $V_{O_2,br}$. Errors in T and RH are more significant during lower tissue O_2 consumption (at constant minute ventilation) because the error in inspired volume affects a smaller $V_{O_2,br}$. Errors in RH magnify at lower barometric pressure because water vapor volume occupies a larger fraction of total inspirate. Because inspired RH and T can vary significantly during anesthesia, a fast-response humidity and T sensor, combined with flow and F_{O_2} measurements, are needed to measure accurate $V_{O_2,br}$.

72

CENTRAL AND PERIPHERAL CHANGES IN AIRWAY AREA BY ACOUSTIC REFLECTION (AAAR) METHOD.

K. Pyon, P. Pandit, S. Courtney, G. Chang, L. Brooks and R. Habib.
Dept. of Pediatrics, The Children's Regional Hospital/UMC and Robert Wood Johnson Medical School, Camden, NJ 08103.

Serial changes in airway caliber can be estimated by AAAR. Its theoretical requirements, however, may limit its applicability. If AAAR measurements of tracheobronchial changes are reliable, then corresponding changes in airway resistance (Raw) should correlate with changes in lung resistance (RL). In 7 [4 newborn, 3 mature] tracheotomized piglets, we measured RL and AAAR during histamine infusion (H: 0.2, 0.5,2,5,10,20 mg/Kg/min). Changes in Raw were predicted from a tube model whose cross-section equals the mean AAAR. Raw was systematically decreased during H infusion and for higher doses. Peripheral constriction was comparable in both groups, and was more pronounced than in central airways. Central airways of mature piglets were more constricted at all H doses. The correlation between the maximal changes in Raw and RL from newborn and mature piglets were 0.70 and 0.72, respectively. The higher regression slope (1.20 vs 0.52) in newborns is consistent with the larger airway component (60% vs 30%) of RL. We conclude that, in tracheotomized subjects, AAAR can provide estimates of serial airway changes. Supported by The Whitaker Foundation.