**Role of Prior Mechanical Ventilation on Ischemia-Reperfusion-Induced Lung Injury**

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**Rational.** Events occurring in the donor prior to lung harvesting may modulate ischemia-reperfusion-induced lung injury (IRLI). We hypothesized that mechanical ventilation prior to ischemia-reperfusion may prime the lungs for development of IRLI.

**Methods.** We studied four Sprangue Dawley rats. Two rats were mechanically ventilated (MV) with a tidal volume ($V_T$) of 12 ml/kg and without positive end-expiratory pressure (PEEP) for two hours prior to inducing ischemia. The other two control rats (CRL) were not mechanically ventilated before ischemia. Warm ischemia was induced by clamping the left lung hilum for 60 minutes. Then animals were followed by four hours of reperfusion. For both groups, animals were ventilated with a $V_T$ of 6 ml/kg and a PEEP of 6 cm $H_2O$ during the ischemia and reperfusion periods. We analyzed $PaO_2/FiO_2$ and compliance (Crs) 10 minutes and 4 hours after reperfusion, and total cell count, cell differential, and total proteins in bronchoalveolar lavage fluid (BALF) at the end of the experiment. Data are expressed as mean ± SD.

**Results.** During reperfusion Crs decreased more in MV rats (0.41±0.08 to 0.33±0.07 ml/cm $H_20$) than in CRL ones (0.39±0.02 to 0.34±0.09 ml/cm $H_20$). We did not observe differences in oxygenation between groups. MV rats had higher BALF cell count than CRL rats ($8.8x10^6±3.2x10^6$ *vs* $3.1x10^6±1.1x10^6$) and a higher percentage of neutrophils (14±16 *vs* 11±2 %). Total proteins in BALF were mildly lower in MV rats than in CRL rats (1.9±0.2 *vs* 2.1±0.6 mg/ml).

**Conclusions.** Our preliminary data suggest that prior mechanical ventilation may prime the lungs for development of IRLI. Identification of prior mechanical ventilation as an injury factor in donors may support the testing of different ventilatory strategies to prevent or attenuate IRLI.

This Abstract is Funded by: NIH HL24163, FIS 01/F015.

**Drotrecogin-alpha Infusion Protects Against Hypoxia-Induced Microvascular Injury**

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[illegible]tory cascade that results in injury to the [illegible]th leukocyte adhesion to the endothelium, [illegible]leak . Drotrecogin-alpha (activated protein [illegible]erties. Its protective role is best described during sepsis. Its usefulness in hypoxic injury has not been examined. Our experiments are designed to characterize the effects of activated protein C on the microvasculature during systemic hypoxia. **METHODS:** Experiments utilize intravital microscopy of the intact rat venular bed. Four groups were utilized: saline control, activated protein C infusion alone (100mcg/kg bolus), hypoxia alone (10% O2), and simultaneous hypoxia + activated protein C infusion. Measurements of leukocyte adherence (# per 100um venule), leukocyte emigration (# per 4000 um2), and venular leak by fluorescein isothiacyanate-labeled albumin (Fi/Fo) are reported below. **SUMMARY:** Infusion of activated protein C attenuates hypoxia-related injury in the microvasculature, as evidenced by measurements of leukocyte adherence and emigration. Furthermore, the quantity of vascular leak is reduced. These findings may have particular importance in the development of therapeutic targets within the inflammatory cascade initiated by hypoxia.

**RESULTS:** ± SEM

| | Leukocyte Adherence | Leukocyte Emigration | Vascular Leak |
|---|---|---|---|
| Normoxia | 1.6 ± 0.5 | 2.6 ± 0.2 | .14 ± .04 |
| Hypoxia | 14.5 ± 1.2 | 12.3 ± 2.2 | .82 ± .14 |
| Activated Protein C | 3.0 ± 1.4 | 3.7 ± 0.5 | .28 ± .06 |
| Activated Protein C / Hypoxia | 4.4 ± 1.5 | 3.5 ± 0.3 | .25 ± .14 |

This Abstract is Funded by: ALA-Kansas, Joseph Cates Lung Research Fund, Hak Soon Chang Fund for Pulmonary Disease, NIH HL64195

**Glutathione S-Transferase P1 Genotype and Lung Function: Evidence for a Gene-Environment Interaction**

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Genetic and environmental factors determine lung function. We have reported associations between lung function and individual[1] and maternal *GSTP1* genotype[2] in children with asthma. We sought evidence for gene-environmental interaction using exposure to environmental tobacco smoke (ETS) as a marker of environmental oxidative stress. **Method:** 221 Caucasian families were recruited via an asthmatic proband 7-18 yrs. Data collected included: questionnaire; lung function and anthropomorphic measurements. Genotype-lung function associations were assessed in probands with/without ETS exposure. **Results:** Probands homozygous for *GSTP1* $val^{105}$ had a trend towards ↑$FEV_1$. This effect was limited to children UNEXPOSED to ETS (p=0.058). Probands whose mothers were homozygous for *GSTP1* $val^{105}$ had significantly less airways obstruction (↑$FEV_1$:FVC). This effect was also limited to children UNEXPOSED to ETS (p<0.01). **Conclusion:** Individual and maternal *GSTP1* val/val genotype are associated with ↑ lung function in asthmatic children. This benefit is lost in children exposed to ETS suggesting a gene x environment interaction.

| | ETS EXPOSED* | | | NO ETS EXPOSURE | | | P† |
|---|---|---|---|---|---|---|---|
| Child *GSTP1* genotype | ile/ile n=35 | ile/val n=41 | val/val n=10 | ile/ile n=65 | ile/val n=53 | val/val n=17 | |
| $FEV_1$ | 94.9±14.5 | 98.5±16.8 | 96.1±13.6 | 96.9±18.4 | 98.4±16.3 | 104.5±12.3 | 0.058 |
| $FEV_1$/FVC | 98.2±9.5 | 97.8±11.1 | 96.4±11.3 | 97.0±10.9 | 98.1±8.1 | 101.2±9.3 | 0.075 |
| Mother *GSTP1* genotype | ile/ile n=39 | ile/val n=36 | val/val n=11 | ile/ile n=61 | ile/val n=57 | val/val n=16 | |
| $FEV_1$ | 96.0±15.9 | 96.5±13.8 | 99.9±20.0 | 95.4±17.1 | 100.9±17.3 | 101.5±15.4 | 0.099 |
| $FEV_1$/FVC | 98.3±9.7 | 96.9±11.1 | 98.6±11.0 | 95.9±10.1 | 99.0±9.1 | 102.5±9.0 | <0.01 |

*All p>0.2 †ile/ile vs val/val.

**Ref:** 1.Carroll W *et al. ATS* 2004. 2. Carroll W *et al. Ped All Imm* 2004 (in press).

This Abstract is Funded by: GSK

**Microsomal Epoxide Hydrolase Gene Polymorphisms, Endotoxin Exposure and Lung Function Decline in Textile Workers**

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Occupational exposed to endotoxin in organic dust may induce acute and chronic lung function decline. Microsomal epoxide hydrolase (mEH) detoxifies reactive oxygen species generated by endotoxin exposure. Polymorphisms of this gene are associated with altered enzyme activity. We investigated the associations between *mEH* polymorphisms, endotoxin exposure, and lung function decline in a prospective study of 265 workers exposed to endotoxin and 234 controls. The population was divided into rapid and slow decline groups by the annual decline rate of lung function (FEV1 greater or less than 40 ml) during the 20 year follow up. *mEH Tyr113His* and *His139Arg* polymorphisms were genotyped by the 5' nuclease assay (TaqMan). Results were analyzed using multiple logistic regression models, adjusting for relative covariates.A stronger association between endotoxin exposure and rapid lung function decline was found among *mEH* genotypes associated with lower enzyme activity, with an adjusted odds ratios (AORs) of 1.74 (95% confidence interval, 0.71-4.28), 2.07 (0.99-4.33), and 4.79 (1.31-17.60) for *Tyr/Tyr*, *Tyr/His*, and *His/His* genotype groups, respectively, for the *Tyr113His* polymorphism; and 2.31 (0.72-7.41) and 2.25 (1.27-3.99) for *Arg/Arg* + *His/Arg* and *His/His* genotypes, respectively, for the *His139Arg* polymorphism. We conclude that *mEH* polymorphisms may modify the association between occupational endotoxin exposure and lung function decline.

This Abstract is Funded by: CDC (NIOSH)

**Exposure to Increasing Numbers of Different Animal Species Is Positively Associated with Gene Expression of Toll-Like Receptors**

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**Rationale:** As previously shown in a small sample gene expression of TLR2 and CD14 was higher among farm children compared to non-farm children. We aimed at replicating this finding in a larger independent dataset and intended to evaluate other factors of the farming environment affecting the expression of receptors of the innate immune system.

**Methods:** In the Swiss sub-sample of the PARSIFAL study questionnaire data and blood samples were available from 201 farm and 217 non-farm children aged 4 to 14 yrs. Gene expression (mRNA) of TLR2, CD14 and TLR4 of peripheral blood cells was assessed by quantitative real-time PCR (TaqMan®) and normalized for the endogenous control (18SrRNA). Associations between the amount of log mRNA and farm exposures were analyzed by multivariate regression models and expressed as means ratios (MR).

**Results:** Expression of the genes for TLR2, CD14 and TLR4 was significantly higher among farm children compared to non-farm children. MRs (95% CI) of the normalized values were 1.58 (1.34-1.85), 1.69 (1.43-2.00) and 1.18 (1.03-1.35), respectively.

Expression of TLR2 and TLR4 significantly increased when children were exposed to higher numbers of different farm animal species. MRs for exposure to each additional species for TLR2 and TLR4 were 1.11 (1.07-1.15) and 1.05 (1.02-1.08), respectively. No significant trend was seen for CD14. After adjustment for farming and potential confounders the association remained significant for TLR2 MR: 1.06 (1.01-1.11) and borderline significant for TLR4 MR: 1.04 (0.99-1.08).

**Conclusion:** Contact to different stable animal species seems to be crucial for the stimulation of the innate immune system, indicating higher and/or more diverse microbial exposure.

This Abstract is Funded by: Swiss National Science Foundation

AMERICAN THORACIC SOCIETY | 100th ANNIVERSARY


VOLUME 2
ABSTRACTS ISSUE
2005

www.thoracic.org

# Proceedings of the American Thoracic Society

## ABSTRACTS

1905 2005

## ATS 2005 International Conference

May 20–25, San Diego, California

AN OFFICIAL PUBLICATION OF THE AMERICAN THORACIC SOCIETY