165.17

HARD METAL DISEASE: EFFECTS OF CATIONIC METALS ON NEUROGENIC RESPONSES OF GUINEA-PIG ISOLATED AIRWAYS. J.S. Fedan, D. Cutler and A. Rengasamy. Pathol. & Physiol. Res. Br., Health Effects Lab. Div., NIOSH, Morgantown, WV 26505.

Inhalation of the dust of industrial hard metal (IHM), which consists of tungsten carbide, Co and other metals, causes asthma and interstitial fibrosis in workers. Dissolution of the metals may occur in the lungs. Intratracheal instillation of guinea pigs with IHM causes up-regulation of NO pathways and hyporeactivity to inhaled methacholine (MCh). To determine if neural regulation of airway diameter is also affected by IHM, we examined the effects of Co^{2+}, Cd^{2+} and Ni^{2+} on electrical field stimulation-induced neurogenic contractile and relaxant responses of guinea-pig tracheal strips. The effects of the metals (10^{-6} M; 30 min) were examined in strips at resting force or contracted with MCh (3×10^{-7} M), either in the absence or presence of indomethacin (In, 10^{-6} M). No metal had any effect on the eNANC contraction phase or relaxation responses under any condition, or affected contractions or relaxations obtained in the absence of In. Co^{2+} inhibited contractions in MCh-contracted strips (+In). Cd^{2+} and Ni^{2+} potentiated slightly contractions obtained in MCh-contracted strips (+In), but inhibited contractions obtained in the absence of MCh (+In). We conclude that following dissolution in the airway wall, metals contained in IHM may alter cholinergic neurogenic pathways.

165.18

ROLE OF THE AIRWAY EPITHELIUM ON ACETYLCHOLINE-INDUCED CONTRACTION OF RAT ISOLATED TRACHEA UNDER CONDITIONS OF LOW TEMPERATURE. O.González and G.E. Santacana. Dept. of Physiology. Univ. of Puerto Rico-Sch. of Med., San Juan, P.R. 00936-5067

In this study, isolated "in vitro" intact rat tracheas were stimulated with acetylcholine (ACH) at 37 and 18°C in the presence and absence of epithelium. Dose-response curves (DRC) with ACH were generated under these conditions. Our results indicate that at 37°C, epithelium removal shifted the DRC leftwards (EC50 from 6.4 to 2.2uM), but the ACH maximal effect remained unchanged. In epithelium-intact tracheas, low temperature also produced a significant leftward shift (EC50 from 6.4 to 2.9uM) in the DRC, without diminishing the ACH maximal effect. Epithelium-denuded tracheas exposed to low temperature showed a significant leftward shift in the DRC similar to the one observed in epithelium-intact tracheas at 37°C, but the ACH maximal effect was dampened. The results suggest that the airway epithelium may be releasing regulatory factors that diminish the sensitivity of the airway smooth muscle to ACH. At the same time, the presence of airway epithelium appears to be required to observe the maximal response to ACH under low temperature conditions. Thus, it seems that the regulatory action of the epithelium on the sensitivity and maximal response of rat trachea to ACH may be significantly altered by changes in temperature.

This study was supported by RCMI grant #G12RR03051.

165.19

EFFECTS OF LIPOPOLYSACCHARIDE ON REACTIVITY OF AIRWAY SMOOTH MUSCLE TO METHACHOLINE AND EPITHELIUM-DERIVED RELAXING FACTOR. R.A. Johnston and J.S. Fedan. Dept. of Pharmacol. & Toxicol., West Virginia University, and PPRB, HELD, NIOSH, Morgantown, WV 26505.

We examined whether lipopolysaccharide (LPS)-treatment affects reactivity of guinea-pig airway smooth muscle to the contractile effects of methacholine (MCh), and the relaxant effects of epithelium-derived relaxing factor (EpDRF), the release of which is stimulated by elevated intraluminal osmolarity. Contractile and relaxant responses of the smooth muscle were measured *in vitro* using the isolated, perfused trachea apparatus which allows pharmacological agents to be added separately to the mucosal or serosal surfaces. Due to the epithelium, serosal reactivity to MCh is greater than mucosal reactivity. Eighteen hours after LPS (4 mg/kg, i.p.) there were no differences in the EC_{50} and maximum response values for contraction to serosally- and mucosally-applied MCh between saline- and LPS-treated guinea-pigs. After precontraction of the smooth muscle with 3×10^{-7} M MCh, EpDRF-induced relaxation was initiated with cumulative additions of NaCl to the mucosal bath. The EC_{50} for relaxation remained unchanged; however, the maximum relaxation response to NaCl was increased in LPS-treated animals. These results suggest that LPS-treatment does not alter reactivity of the smooth muscle to MCh, but does enhance responsiveness to intraluminal hypertonicity by increasing the synthesis and/or release of EpDRF, or altering EpDRF's relaxant effect on the smooth muscle. (Supported, in part, by NIH 5T32 GM07039)

165.20

Bronchial Wall Stiffness May Limit Airway Closure in the Pig
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Fisher *et al* [Am J Resp Crit Care Med 151: A814, 1995], have reported that stimulation of vagal efferents can produce closure of canine bronchi *in vivo*. One of the factors opposing closure is the after load on airway smooth muscle. Since porcine airways are extremely cartilaginous compared to the dog, we hypothesised that airway closure would be uncommon in pigs because of the after load of the airway wall. Three month old pigs (30Kg) were anaesthetised, ventilated and the chest opened. A bronchoscope was positioned to view the right lower lobe stem bronchus (10-12 generation, 4-5mm). Vagal stimulation (18V, 2ms, 20Hz) was applied at lung volumes produced by 2.5, 5, 7.5, 10 and 15cmH_2O transpulmonary pressure. Frequency response curves for 5, 10 and 20Hz were performed at 5cmH_2O. In a limited number of experiments β-adrenergic (popranolol 2 mg/Kg) and nitrergic (L-NAME 20 mg/Kg) innervation were blocked to eliminate the possibility that closure was prevented by inhibitory innervation. Porcine bronchi narrowed following stimulation however, closure was not observed. Elevation of lung volume appeared to have little effect on bronchoconstriction in the pig. This is in contrast to the dog where closure is commonly produced by stimulation at low lung volumes but were inflation significantly inhibits closure. Blockade of inhibitory nerves did not produce closure during stimulation suggesting that closure was not prevented by activation of inhibitory nerves. We conclude that airway narrowing in the pig is limited by the stiffness of the airway wall and this prevents closure. Supported by the MRC, OTS and John Alexander Stewart postdoctoral fellowship.

165.21

The dependency of expiratory airway closure on pump system and flow rate in total liquid ventilated rabbits
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INTRODUCTION: To evaluate different expiration modes for total liquid ventilation (TLV), the occurance of expiratory airway closure, as indicated by excessive negative dynamic airway pressures, was investigated by directly comparing different pump systems and flow rates. METHODS: In a prospective, controlled laboratory study, in 16 New Zealand rabbits (2.3 +/- 0.1 kg) lungs were filled with 40 mL/kg perflubron(TM), the endotracheal tube was connected to both a piston (PP) and a roller pump (RP) system, both were used in a constant-flow suction mode and servo-controlled to shut off at an intratracheal pressure of -25 cm H2O. Drainage trials were performed pairwise with PP and RP using identical average flow; 20 flow rates (2.6-20 mL/second) were applied successively. Outcome measure was drained volume at pump shut-off. RESULTS: Relationship between flow rate and drained volume was linear for both pumps. At a flow rate of 2.6 mL/second 33.7 +/- 1.3 mL/kg (RP) and 35.1 +/- 1.3 mL/kg (PP) and at 19.1 mL/second 0 mL/kg (RP) and 1.9 +/- 0.9 mL/kg (PP) were drained. Higher flow was not possible with either pump. PP drainage volumes were significantly higher when compared to RP volumes for all flows between 4.4 and 18.3 mL/second ($p<0.05$). CONCLUSIONS: Onset of expiratory airway closure in TLV is dependent on both flow rate and pump system. Regarding the higher drainage volumes, piston pump has advantages over roller pump as the drainage force for TLV.

165.22

MECHANISMS OF AIRWAY RESISTANCE vs TISSUE RESISTANCE CHANGES IN PULMONARY EMBOLISM.
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Pulmonary embolism increases lung resistance (R) by increasing both airway resistance (Raw) and tissue resistance (Rti). Whether these changes result from local mechanical factors or from reflex factors is unknown. We therefore investigated separately in the left and right lungs the Raw and Rti changes induced by unilateral pulmonary embolism (PE) in 5 pentobarbital-anesthetized and mechanically ventilated dogs. Autologous blood clots were injected to increase the mean pulmonary arterial pressure to about 40 mmHg over 15 min. Dynamic compliance (C), R, Raw and Rti were calculated from instantaneous signals of tracheal flow, tracheal pressure, and alveolar pressures measured with alveolar capsules [Brusasco et al., J Appl Physiol 1989; 66: 1190]. PE decreased C by 23 ± 5% ($P < 0.01$) and increased R by 30 ± 13% ($P < 0.01$). In the embolized lung, PE increased Raw by 35 ± 6% ($P < 0.01$) and Rti by 19 ± 14% (NS). In the non-embolized lung, PE increased Raw by 33 ± 5% ($P < 0.01$) and Rti by 18 ± 16% (NS). The similarity of changes observed in both lungs suggests that these changes are not due to local mechanical factors (vascular obstruction, edema) but to the pulmonary hypertension and/or to neurohumoral factors. This abstract is funded by the Belgian National Fund for Scientific Research (NFWO).

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Experimental Biology 99®
Washington, D. C.
April 17-21, 1999

ABSTRACTS
PART I

Abstracts 1.1-486.12

Official Publication of the Federation of American Societies for Experimental Biology

Volume 13, Number 4, March 12, 1999