study, for the first time, MV with and without recruitment manoeuvres (RM) was compared in healthy mice. The effects of RM on a variety of physiological parameters and pulmonary inflammation were studied over 6h.

C57Bl/6 mice were ventilated for 6h at low-VT=8mL/kg, f=180/min or high-VT=16mL/kg, f=90/min and 3% inspiratory CO2. Fio2 was 0.5 and PEEP 2cmH2O. RM were performed with 30cmH2O for 1s every 5min, 60min or not at all. Lung mechanics were followed by the forced oscillation technique. Blood pressure (BP), ECG, heart frequency (HF), oxygen saturation and body temperature were monitored. Blood gases, histopathology, neutrophil recruitment, microvascular permeability and pro-inflammatory cytokines were examined. MV with recurrent RM resulted in stable respiratory mechanics. Ventilation without RM worsened lung functions due to alveolar collapse, leading to impaired gas exchange. HP and BP were not affected. Microvascular permeability was highest in atelectatic lungs, whereas neutrophil recruitment and structural changes were strongest in lungs ventilated with high VT. Although IL-6 and KC were markedly elevated in all ventilated mice, levels were clearly reduced by recurrent RM. In contrast, TNF-α and IP-10 remained at baseline, indicating that only moderate lung injury was induced.

We conclude that recurrent RM are required to prevent atelectasis and resulting lung injury during mechanical ventilation of healthy mice.

P800
Patterns of plasma membrane disruptions distribution in mechanically ventilated lungs
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Rationale: Abnormally high stresses applied to a cell can result in the loss of cell membrane integrity and the formation of direct communications between intracellular and extracellular spaces, called plasma membrane disruptions (PMD). These lesions could be involved in the genesis of biotrauma as upregulators of pro-inflammatory mediators expression. Observations limited to the subpleural alveoli only indicate that PMD take place during mechanical ventilation with large tidal volumes (VT) and a normal end-expiratory lung volume (EELV). It is unknown if PMD develop during low EELV ventilation with physiological VT.

Objectives: To see if a) mechanical ventilation with physiological VT at low EELV causes PMD; and b) the parenchymal distribution of PMD differs between ventilation with large VT at normal EELV and ventilation with physiological VT at low EELV.

Methods: PMD have been detected as red spots in gelatin included slices of rat lungs stained with ethidium homodimer-1 shortly after anesthesia, after prolonged ventilation at low EELV followed or not by the restoration of physiological EELV, and after prolonged ventilation with large VT and normal EELV.

Main results: PMD increased during ventilation at low EELV, mainly at broncholar level. Re-sealing of most PMD occurred on restoration of a normal EELV. Ventilation with large VT caused the appearance of PMD both bronchial and parenchymal, the latter to a much greater extent than with ventilation at low EELV. The increase of PMD correlated with the concomitant increase of intermittent resistance with both modes of mechanical ventilation.

Conclusions: Entity and distribution of PMD depends on the type of injurious mechanical ventilation.

P801
Dexamethasone reduces lung inflammation induced by alveolar stretch in mice
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Background: Although mechanical ventilation is a lifesaving procedure, the associated alveolar stretch can provoke lung injury (ventilator-induced lung injury, VILI). At present, it is thought that ventilator-induced lung inflammation may precede lung injury. Activated granulocytes are known to induce oxidative stress, and pro tease activity in alveoli, causing alveolar-capillary barrier disruption and lung dysfunction.

Aim: To study the anti-inflammatory action of dexamethasone, a widely used glucocorticoid, in mice exposed to either low or high alveolar stretch.

Methods: C57Bl/6 mice were mechanically ventilated for 5 hours with either an inspiratory pressure of 10 cmH2O ("low" tidal volumes (VT) ∼7.5 ml/kg, LVT) or 18 cmH2O ("high" VT ∼15 ml/kg, HVT). Dexamethasone was intravenously administered at initiation of ventilation. Non-ventilated mice served as controls. Inflammatory mediator expression and granulocyte influx were determined in lung homogenates. Differential cell counts were done on BALI cytosin preparations.

Results: Both LV T and HV T-ventilation increased inflammatory mediator ex-
Pression in lung tissue which was accompanied by granulocyte influx (p<0.05). BALF neutrophil numbers and inflammatory mediator expression (KC, IL-1) were enhanced in HVT-ventilated mice compared to LVT-ventilated mice (p<0.05). Dexamethasone inhibited lung inflammation caused by LVT or HVT-ventilation (p<0.05).

Conclusion: Dexamethasone prevents inflammatory mediator expression and granulocyte influx in lungs of mice exposed to low or high alveolar stretch. Dexamethasone treatment may be considered as a potential therapeutic strategy to inhibit the inflammatory response during mechanical ventilation.

**P803**

Intermedin stabilized endothelial barrier function and attenuated ventilator-induced lung injury in mice

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Rationale: Even protective ventilation may aggravate or induce lung failure, particularly in preinjured lungs. Thus, new adjuvant pharmacologic strategies are needed to attenuate ventilator induced lung injury (VILI). Intermedin/Adrenomedullin II (IMD) stabilized pulmonary endothelial barrier function in vitro. We hypothesized that IMD may attenuate VILI-associated lung permeability in vivo.

Methods: Human umbilical vein endothelial cell (HUVEC) monolayers were incubated with IMD and transendothelial electrical resistance was measured to quantify endothelial barrier function. Expression and localization of endogenous pulmonary IMD and its receptor complexes comprising of CRLR and RAMP-3 were analyzed by qPCR and immunofluorescence in unventilated mouse lungs and in lungs ventilated for 6h. In untreated and IMD treated mice, lung permeability and pulmonary leukocyte recruitment was assessed after mechanical ventilation.

Results: IMD stabilized endothelial barrier function in HUVECs. Mechanical ventilation reduced the expression of RAMP 3, but not of IMD, CRLR, and RAMP1 and 2. Mechanical ventilation induced lung permeability, which was ameliorated by IMD treatment. IMD did not reduce VILI associated pulmonary leukocyte recruitment.

Conclusion: We showed for the first time that IMD had endothelial barrier stabilizing properties in vivo. IMD may possibly provide a new approach to attenuate ventilator-induced lung injury.

**P804**

Plasma levels of LL37 in patients with and at risk of acute lung injury

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Cathelicidins are a group of antimicrobial peptides with a wide range of functions including immunomodulation, chemotaxis, angiogenesis and antimicrobial effects. LL-37 is the active form of the only known human example of a cathelicidin, HCAP-18. It is induced by the local action of L-25-OH vitamin D. LL37 is expressed by many different cell types including lung epithelial cells, neutrophils and other immune cells. We have shown that patients with severe vitamin D deficiency have an increased risk of Acute Lung Injury post-oesophagectomy and hypothesized that this may be related to the effects of vitamin D on LL37.

Methods: Plasma levels of LL37 were determined by ELISA in a cohort of patients with Acute Lung Injury and in a cohort of patients at risk of Acute Lung Injury due to undergo oesophagectomy.

Results: Average pre-operative plasma LL37 levels in the oesophagectomy cohort were 117.2ng/ml and post operative levels are significantly lower (p=0.027, paired t test). In our ALI cohort, median levels of LL37 on day 0 lower than normal levels (p=0.017). LL37 levels correlate with vitamin D status, however, preoperative LL37 levels did not predict Acute Lung Injury.

Conclusion: LL37 levels are lower than normal in patients with Acute Lung Injury and fall progressively in patients undergoing oesophagectomy. The mechanism underlying this is unclear and requires further evaluation, but may be related to vitamin D deficiency in these patients.

**P805**

Preventive and therapeutic effects of phosphoinositide 3-kinase inhibitors on acute lung injury

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Background: Phosphoinositide 3-kinases (PI3Ks) are involved in a number of biological processes. Recent preclinical studies demonstrated that PI3K-dominant signal pathway could play an important and critical role in the development of acute lung injury, while the number of studies are limited and the mechanism remains unclear.

Methods: CD-1 mice were intranasally or intratracheally administered with different PI3K inhibitors once a day for three days before intratracheal instillation of LPS for 4 and 24 hours. Effects of SHBM1009 on LPS-induced capillary permeability, leukocyte distribution and epithelial cells were measured. Besides, the therapeutic effects of SHBM1009 on pancreatic elastase induced lung injury was evaluated in wistar rats.

Results: Local delivery of PI3K inhibitors had more effective roles in the prevention from LPS-induced ALI than systemic delivery. PI3K inhibitors prevented both LPS- or elastase-induced lung injury in mice and rats probably through the direct inhibitory effects on airway epithelial cells, activating neutrophils and macrophages.

Conclusion: PI3K may be a therapeutic target for lung injury.

**P806**

Adenosine but not the A2A adenosine receptor agonist, CGS 21680 attenuates the endothelial cell barrier disruption induced by lipopolysaccharide

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Rationale: Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are severe disorders. Pulmonary injury is at the endothelial cell (EC) barrier with increased permeability. Our in vitro studies demonstrate that adenosine protects from the bacterial toxin lipopolysaccharide (LPS) induced barrier dysfunction.

Hypothesis: Based on the known activation of the A2A adenosine receptor (A2AR) with adenosine it was hypothesized that the A2A agonist, CGS 21680 (CGS), would attenuate the LPS disrupted EC barrier in vivo.

Methods: Control and A2AR knock out (KO) mice were given normal saline (NS) or LPS intratracheally. NS or CGS was instilled intravenously (IV) at the same time or 3hrs later. At 22 hours Evans Blue Dye albumin (EBD) was instilled IV, at 24hrs the samples were collected. Bronchoalveolar lavage (BAL) was done and the lungs harvested. Cell counts, protein and EBD extravasation were analyzed.

Results: CGS caused an increased number of cells in the LPS/adenosine treated mice and the KO mice treated with CGS at 3hrs consistently demonstrated a decreased cell count. LPS challenge increased the protein in BAL and EBD from lung, the protein and EBD were significantly attenuated in the LPS/adenosine treated mice but not in the CGS treated mice.

Conclusions: Adenosine significantly attenuates the LPS induced EC barrier dysfunction in mice. The A2AR agonist, CGS, attenuates the cell count but not the protein or EBD extravasation. Other adenosine receptors or mechanisms may be involved in the significant improvement of protein and EBD barrier disruption that occurs with adenosine treatment.
Acute lung injury (ALI) and sepsis remain major challenges in critical care. While a massive inflammation determines early sepsis, apoptosis of lymphocytes is a hallmark of late sepsis. Lipid emulsions (LE) are used in critically ill to maintain caloric intake. Fish oil (FO) based LE are considered as alternative with immunomodulatory impact. We investigated the effects of LE in a murine model of ALI.

Mice were infused with SO, FO or NaCl. 24h after intratracheal instillation of 10μg lipopolysaccharide (LPS), a bronchoalveolar lavage (BAL) was performed to determine numbers of leukocytes, protein and cytokines. Lymphocytes were isolated from spleen and apoptosis was determined by FACSCalculus.

LPS induced a massive invasion of leukocytes into the airspace compared to unstimulated controls. Infection of SO amplified whereas FO attenuated the rise. Both, in vivo experiments and isolated BAL cells revealed a rise which was further increased by SO. Infection of FO reduced protein as well as TNF after LPS.

Before LPS, infusion of SO induced a significant rise in apoptosis of lymphocytes. After LPS, a reduced number of lymphocytes accompanied with a rise in apoptosis was detected in all groups with FO infused mice showing significantly less apoptosis compared to SO.

In a murine model of ALI the choice of lipid emulsions is able to influence inflammatory parameters. Induction of ALI is paralleled by reduced lymphocytes with increased apoptosis in the spleen. SO leads to massive apoptosis in lymphocytes even before ALI. Infection of FO attenuated the rise in ALI-induced apoptosis. Modulating the lipid emulsions used for nutrition may be relevant for critically ill and may have impact on outcome.

P808

Eugenol dose-dependent improvement of pulmonary lesions in lipopolysaccharide acute lung injury

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Background: Eugenol, a methoxyphenol component of clove oil, inhibits NF-κB activation induced by TNF-α in LPS-stimulated macrophages.

Aim: To evaluate the effects of different doses of eugenol on lung mechanics, histology and cytokines in LPS-injured lungs.

Methods: Male CD-1 mice were randomly divided in 9 groups (5-8/group). Mice were intratracheally instilled with saline solution (0.05 ml) or LPS (10 μg in 0.05 ml of saline); 6 h later they received sterile saline (0.2 ml) and Tween 1% (C, L, and I groups) or different doses of eugenol: 16, 65, 114, 160, 650 or 1500 mg/kg in saline (0.2 ml) and Tween 1% (C1, L1, L2, E2, LE2, L5, LE5, L7 and LE7 groups, respectively) by gavage. Mice were evaluated 24 h after receiving LPS.

In another 18 mice [C6, L6, E6 = (saline solution followed by eugenol) and L6=3], in theory similar TNF-α and IL-1β were detected by ELISA in lung homogenates at 6 (C3, L3, L3, L3) and 24 h (C4, L3, L3, E3, L3, L3 and LE3) after LPS administration. One-way ANOVA followed by Tukey test was used (α=0.05).

Results: Static elasstane, viscoelastic component of elastance and viscoelastic resistive pressure were higher in L group (33.05, 5.01 cmH2O/ml, and 1.00 cmH2O/mL respectively) than in C (22.13, 3.62 cmH2O/ml, and 0.71 cmH2O/O2) accompanied by alveolar collapse and collagen fiber deposition; eugenol reduced the parameters of L groups (except alveolar collapse) and abolished them from L (23.34, 3.62 cmH2O/ml, and 0.72 cmH2O/L) onwards. LE group showed smaller TNF-α and IL-1β levels than L mice. LBE behaved similarly to C and E groups.

Conclusion: Eugenol exhibits an vivo anti-inflammatory dose-dependent action in LPS-induced lung injury. Supported by: CNPq, FAPERJ, MCT.

P809

Increased uric acid levels in bronchoalveolar lavage fluid of mice infected with H1N1 influenza

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Rationale: Lower respiratory tract infections with influenza are associated with severe inflammatory responses, which may result in ALI/ARDS. Tissue injury results in the release of damage-associated molecular patterns (DAMPs), such as uric acid and ATP, leading to NLPR1/INFLAMMATION activation and IL-1β release.

Hypothesis: We hypothesized that influenza-induced lung injury is associated with the release of DAMPs into the airway lumen.

Methods: C57Bl/6 mice were inoculated with 10ICD0 influenza A/PR/8 (H1N1) and sacrificed 4, 8 and 14 days later to collect BALF to determine uric acid, extracellular ATP and markers of inflammation and lung injury. Non-infected mice were sacrificed on day 0 for control measurements.

Results: Influenza virus infection resulted in bodyweight loss between day 6 and day 11 (p<0.05) and returned to normal values on day 14 after infection. Uric acid levels in BALF were significantly increased on day 8 after viral infection (52.7±11.9 μM ± 12.2±5.8 μM in control mice, 95% CI p<0.01), while ATP was undetectable. Uric acid in BALF was associated with increased levels of inflammatory markers (IL-6, KC and IFN-γ) as well as markers of lung injury (sRAGE and total protein in BALF). However, increased IL-1β levels, indicative for inflammation/homeostasis, were only observed on day 4 after influenza infection (p<0.01).

Conclusion: Uric acid in BALF is increased during influenza infection and associates with biomarkers of inflammation and lung injury, but it does not influence inflammasome activation. Whether uric acid fails to activate NLPR1/INFLAMMATION or that IL-1β is scavenged by IL-1 receptor antagonist during influenza infection remains to be determined.
Background: Alveolar epithelial damage is a critical event that leads to protein-rich edema in acute lung injury (ALI). Even though Fas activation induces apoptosis of alveolar epithelial cells, its role in the formation of lung edema is unclear.

Aim: We investigated whether inhibition of caspase-dependent apoptosis protects against Fas-mediated epithelial injury in mouse lungs.

Methods: We administered the pan-caspase inhibitor Z-VAD-fmk (10 mg/kg) or vehicle subcutaneously to mice treated with one intratracheal dose of recombinant human FasL (rh-FasL; 25 ng) or PBS, then studied the mice 16 h later. We measured alveolar fluid clearance (AFC) by intratracheal instillation of FITC-human albumin, and protein permeability by measuring IgM in bronchoalveolar lavage fluid. Caspase-3 activity and cytokines (IL-1β, IL-6, KC, TNF-α) were measured in lung homogenates.

Results: Compared with PBS-treated mice, the intratracheal instillation of rh-FasL decreased AFC (PBS: 20.1±3.1% vs rh-FasL: 19.2±2.4%, P<0.05), and increased protein permeability (PBS: 54.7±6.3 vs rh-FasL: 59.1±4.9 mg/mL, P<0.05), caspase-3 activity and cytokine production. In contrast, mice treated with rh-FasL and Z-VAD-fmk had normal AFC (17.0±2.3%, P<0.05) and a smaller increase in protein permeability (152.5±18.4 mg/mL, P<0.05), associated with a reduced caspase-3 activity and an increase in cytokine production. Z-VAD-fmk was not harmful in PBS-treated mice.

Conclusion: Activation of the Fas pathway impairs the alveolar epithelial function in mouse lungs by mechanisms involving caspase-dependent apoptosis, suggesting that targeting apoptotic pathways could reduce the formation of lung edema in ALI.

Methods: Mouse BALB/c mice were randomly divided into seven groups: saline group (RvD1+PBS group); LPS group; LPS+RvD1 (300ng) group; GW9662 (a PPARγ antagonist) group; LPS+RvD1 (600ng) + GW9662 group. LPS (50ng/mouse in 100ul saline) or saline was instilled intratracheally. RvD1 was injected intravenously 30min before RvD1 injection. Mice were killed at 6, 12, and 24h. BALF samples were collected for cell counts and cytokine analysis. Lung tissues were collected for histological analysis and western blot analysis.

Results: RvD1 significantly decreased total leukocyte counts by 44±7%, and also reduced TNF-α, IL-6 expression levels in BALF in comparison to the LPS group (P<0.05, n=9). H&E staining of histological sections showed that RvD1 markedly attenuated LPS-induced lung inflammation. Western blot analysis revealed that RvD1 activated PPARγ and suppressed IκBα degradation and p65 nuclear translocation.

Conclusions: These results suggest that RvD1 may attenuate lung inflammation of LPS-induced ALI through suppressing NF-κB activation.
P817
Effect of proteinase inhibitor from crataeva tapia (cratاب) in distal lung mechanical, inflammatory and remodeling alterations induced by elastase in mice
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Aims: The leading role of elastase in the emphysema physiopathology has been recognized. The present study aimed to evaluate if a plant proteinase inhibitor CratAb contributes to inactivation of elastase-induced mechanical, inflammatory and extracellular matrix remodelling alterations.

Methods: C57Bl6 mice received elastase intranasally (50ml/animal E group). Control group received saline (Ve group). Afterwards, mice were treated with CratAb (2mg/kg) at days 1, 15, 21, 28, 35 after elastase instillation (I-E group).
At day 40, mice were anesthetized and mechanically ventilated and we analyzed respiratory system resistance and elastance, tissue elastance, tissue damping and airway resistance. Afterwards, BAL was performed and lungs were removed. By morphometry, we quantified the mean linear intercept (Lm) and the collagen and elastic fibers in distal lung parenchyma.

Results: We did not observe any differences in pulmonary mechanics comparing all groups. In E group, there was an increase in BAL-total cells, BAL-lymphocytes, BAL-neutrophils, collagen and elastic fibers and Lm compared to Ve group (p<0.05). The CratAb treatment in elastase treated animals decreased Lm (105.9±10.3μm) compared to E group (p<0.05). BAL-neutrophils (7.2±1.4×105 cells/ml), and collagen content (0.59±0.02%) were decreased in I-E group compared to E animals (p<0.05).

Conclusions: This plant proteinase inhibitor (CratAb) reduced elastase-induced pulmonary inflammatory and remodeling alterations which may be considered as a new and potential therapeutic strategy for COPD treatment.

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P818
Intravenous immunoglobulin in community acquired pneumonia
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Immunity disorders play an important role in the inflammatory formation in patients with lung diseases.

The aim was to study the efficacy of i.v. immunoglobulin immunovenin (IMV) in patients with community acquired pneumonia (CAP).

Methods: The study included 35 patients with CAP. The patients blood was tested to estimate the level of CD3+, CD4+, CD8+, CD16+, CD20+ lymphocytes, the content of A,G,M immunoglobulins (Ig), circulating immunocomplexes (CIC), γ-interferon and TNFa. 17 patients with CAP were treated with standard therapy.

The other 18 patients received combined treatment with IMV.

Results: Compared to healthy subjects in patients with CAP the level of CD3+, CD4+, CD8+, CD16+, CD20+ lymphocytes was lower by 1.2-1.4 times, the content of IgA, IgG and γ-interferon was lower by 1.3 times. Conversely, the level of CD20+ lymphocytes, IgM, CIC was higher by 1.3-1.8 times, and the level of TNFa was higher by 1.9 times. Symptoms of inflammation and impairment of the immune status have been found in patients who received standard therapy. The use of IMV in patients with CAP eliminated immunity disorders, improved the results of the treatment.

Conclusion: In patients with CAP immunovenin improved the immunity status and increased the treatment efficacy.

P819
PTX3 as a component of innate immunity in the role of captopril in acute lung injury induced by bacterial endotoxin
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Objective: Innate immunity is an important mechanism for the development of acute lung injury (ALI). Lung pentraxin PTX3 is an inflammatory mediator and a component of innate immunity. Recent evidence implies that angiotensin-converting enzyme (ACE) plays an important role in the pathogenesis of ALI. We speculated that inhibition of ACE play the protective effect on ALI through the presence of PTX3, therefore, protect the lung from severe injury.

Methods: Lung injury was induced by intratracheal instillation of lipopolysaccharide (LPS) in rats, followed by i.p. administration of captopril, an ACE inhibitor, or saline control, and the PTX3 expression, fibrin deposition, tissue factor expression and lung injury were determined. Local and systemic inflammatory responses were assessed by measuring cytokines in the lung and plasma.

Results: Treatment with captopril dramatically attenuated LPS-induced lung injury, alveolar fibrin deposition and inflammatory cell infiltration 6 h after LPS challenge compared to that in the saline control rats. Local and systemic PTX3 expression were significantly decreased by the captopril therapy, accompanied by decreased interleukin (IL)-6, IL-10 and monocyte chemoattractant protein-1 levels in the plasma.

Conclusion: These results support that inhibition of ACE with its clinically used inhibitor offers protective effects on ALI. PTX3, acting as both anti-inflammation component and the component of innate immunity, may reflect severity of lung injury and serve as the potential therapeutic "target" during ALI Captopril treatment through the presence of PTX3 could be a potential mechanism that mediates lung injury.