481. Lung injury, respiratory muscles and mechanical ventilation

P4634
Effect of imatinib and nilotinib on lipopolysaccharide-induced acute lung injury during neutropenia recovery in a mouse model
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Objective: Neutropenia recovery is associated with deterioration in oxygenation and exacerbation of pre-existing pulmonary disease. We aimed to evaluate effect of imatinib and nilotinib on lipopolysaccharide (LPS) - induced acute lung injury (ALI) during neutropenia recovery in a mouse model.

Method: We developed a mouse model of ALI during neutropenia recovery. Cyclophosphamide was administrated to induce neutropenia. During neutropenia recovery, ALI was induced by intratracheal instillation of LPS. Imatinib or nilotinib was administrated during neutropenia recovery.

Result: The numbers of inflammatory cells and neutrophil in bronchoalveolar lavage fluid in imatinib or nilotinib group were significantly lower than LPS group. Imatinib or nilotinib administration significantly reduced wet/dry ratio and ALI score. The level of myeloperoxidase and tumor necrosis factor-α in imatinib or nilotinib group were significantly lower than LPS group. Attenuation of ALI by imatinib or nilotinib was associated with PDGFRβ and C-kit pathway.

Consult: Imatinib or nilotinib effectively attenuated LPS-induced ALI during neutropenia recovery.

P4635
Effect of curcumin on LPS-induced neutrophil activation and acute lung injury
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Curcumin has antioxidant, antitumor, and anti-inflammatory properties. Neutrophils play an important role in the development of organ dysfunction associated with severe infection. This study was performed to evaluate the effects of curcumin on lipopolysaccharide (LPS) - induced neutrophil activation and acute lung injury. To assess the anti-inflammatory effect of curcumin on LPS induced neutrophil activation, neutrophils from human blood were incubated with various concentrations of curcumin (0, 1, 10, 50 and 100 nM) and LPS (100 ng/ml). The protein levels for interleukin (IL)-6, 8 and tumor necrosis factor (TNF)-α were measured using ELISA 4 hr after incubation period. To elucidate the intracellular signaling pathway, We measured the levels of phosphorylation of p38 mitogen activated protein kinases (p38), extracelluar signal-regulated kinase (ERK)1/2 and c-Jun amino-terminal kinases (JNK) with western blot analysis and nuclear levels of nuclear factor (NF)-κB with electrophoretic mobility shift assays 0.5 hr after incubation period. We also examined the effect of curcumin (60mg/kg, IP) on acute lung injury and mortality of mouse treated with LPS(20 mg/kg, IP) to determine whether these effects of curcumin also have in vivo significance.

Curcumin attenuated LPS - induced neutrophils activation including expression of p38, JNK, NF-κB, IL-6, 8 and TNF-α. Mouse treated by Curcumin were protected from LPS-induced lung injury, as determined by wet/dry weight ratio, lung injury score and IL-6, 8 and TNF-α in bronchoalveolar lavage fluid (BALF) levels and mortality.Curcumin can attenuate LPS - induced acute lung injury and mortality via the attenuation of neutrophil activation caused by LPS.

P4636
Hydrogen gas inhalation ameliorates direct lung injury and indirect contralateral lung injury in a murine aspiration pneumonia model
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Aim: Accumulated leukocytes in the lungs produce several inflammatory cytokines and reactive oxygen and nitrogen species (ROS and RNS), which will induce ALI/ARDS. It has been reported that hydrogen (H2) gas has potential as...
eliminating highly reactive ROS and RNS. The aim of the present study was to clarify the effect of H₂ gas inhalation on direct lung injury and indirect contralateral lung injury.

Methods: Anesthetized C57BL/6J male mice were intubated, and 5 μl of 0.1% HCl was administered to the left lung. Mice were randomly grouped to saline treatment instead of HCl (Sham), HCl-treatment (HCl), and 2% H₂ gas inhalation with the HCl-treatment (HCl-H₂) groups. Extra-vascular wet to dry ratio, myeloperoxidase (MPO) activity in the treated left lung and untreated right lung, and serum IL-6 level were evaluated 4 hrs after the treatment.

Results: This aspiration pneumonia model induced direct lung injury and contralateral lung injury. The extra-vascular wet to dry ratios of the left and right lungs were significantly larger in the HCl group compared to the Sham and the HCl-H₂ group (n=10, P<0.01), suggesting that H₂ gas was effective not only in the direct injured lung but also in contralateral lung. MPO activity of the left lung was also significantly larger in the HCl group compared to those in the Sham and HCl-H₂ groups (n=3, P<0.05). IL-6 was increased in the HCl group, but it did not statistically differ to the level in the HCl-H₂ group, suggesting H₂ gas did not interfere in the cytokine production.

Conclusion: H₂ gas inhalation ameliorated direct lung injury and indirect contralateral lung injury in a murine aspiration pneumonia model.

P4637

Respirative breathing (RB), encountered in obstructive airway diseases, is associated with large negative intrathoracic pressures and has been recently shown to induce acute lung injury and inflammation. Matrix metalloproteinases (MMP)-9 and -12, implicated in the pathogenesis of both asthma and COPD, are upregulated by inflammation and by mechanical stress per se. We hypothesized that RB induces MMP9 and -12 expression and activity in the lung. Anesthetized, tracheostomised rats were breathing through a 2-way valve. The inspiratory line was connected to a resistance setting peak tracheal pressure at 50% of maximum (RB). Quietly breathing animals served as controls. After 3 and 6hrs of RB, bronchoalveolar lavage (BAL) was performed to measure cell count and cytokine levels by ELISA. MMP9 lung levels were measured by zymography and immunohistochemistry (IHC). MMP12 was detected by IHC. Alveolar macrophages from normal rats were incubated with BAL fluid from rats that underwent RB. MMP9 activity was measured in cell supernatants by zymography. After 3 and 6hrs of RB, lung injury was detected by histology. Increased numbers of alveolar macrophages and neutrophils (p<0.05) and increased levels of IL1β and IL6 (p<0.01) were measured in the BAL following 6hrs of RB. MMP9 activity raised by 2-fold after 6hrs of RB (p<0.001). MMP9 was detected in alveolar macrophages and epithelial cells. After 3 and 6hrs of RB, increased levels of MMP12 were detected in alveolar macrophages. BAL fluid from animals that underwent 6hrs of RB, induced MMP9 in supernatants by 7.5-fold (p<0.001).

In previously healthy rats, RB resulted in increased MMP9 and -12 expression in the lung.

P4638

Study of cardiac and hemodynamic changes with airway pressure release ventilation and pressure control ventilation in children with acute respiratory distress syndrome

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Background: Acute respiratory distress syndrome (ARDS) is associated with high morbidity and mortality. Airway pressure release ventilation (APRV) was suggested to be a suitable mode for ventilating such patients with less liability of lung injury.

Aim: To compare the effect of APRV and pressure control ventilation (PCV) on cardiac and hemodynamic functions in children with ARDS.

Patients and Methods: Twenty children aged 1-14 years fulfilling ARDS criteria were included. The following parameters were recorded after ventilating the patients on PCV and APRV: ventilation parameters [peak inspiratory pressure (PIP) and mean airway pressure (MAP)], oxygenation parameters PaO₂/FiO₂ ratio and oxygen delivery, hemodynamic parameters and urine output.

Results: PIP significantly decreased from 29±7 to 24±4 cmH₂O with APRV, while MAP was significantly higher during APRV(17±5) than during PCV (13±3 cmH₂O). PaO₂/FiO₂ ratio increased significantly from 256±25 during APRV to 295±33 during APRV. Oxygen delivery increased significantly from 865±98 during PCV to 1196±127 ml/min during APRV. Cardiac index increased significantly from 3.2±0.2 during PCV to 4.1±0.3 l/min/m² during APRV. Urine output increased significantly from 0.78±0.12 ml/h during PCV to 0.97±0.2 ml/kg/h during APRV.

The use of sedatives and inotropics were decreased significantly during APRV compared to PCV.

Conclusions: APRV may be a suitable mode for ventilating ARDS patients providing better lung recruitment and oxygenation, avoiding more lung injury and cardiac compromise compared with pressure control ventilation.

P4640

Protease-antiprotease imbalance in airway secretions in subjects with acute respiratory failure

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Studies have shown that in the acute respiratory distress syndrome (ARDS) there is protease-antiprotease imbalance, reflected as an increase in the ratio of Human Neutrophil Elastase (HNE) to several protease inhibitors in BAL and plasma. This imbalance can be related to the pathophysiology of ARDS and may correlate with clinical outcomes. The purpose of the study was to determine if similar protease-antiprotease imbalance could be detected in airway secretions in subjects at risk of developing ARDS.

Free HNE activity (HNEA) and levels of the protease inhibitors alpha-1 antitrypsin (AAT) and secretory leukocyte protease inhibitor (SLPI) were measured in...
samples of endotracheal aspirates samples collected serially in subjects intubated because of acute respiratory failure in a medical ICU (n=42 subjects, 10 eventually developed ARDS).

Contrary to reports studying BAL, we observed that free elastase activity is reduced in airway secretions of subjects that develop ARDS compared to subjects that did not. No differences were noted in AAT and SLPI concentrations in airway secretions between these groups. HNEA/AAT and HNEA/SLPI ratios were reduced in 19 subjects. In ARDS subjects, levels of HNEA returned to normal the first day after the onset of ARDS. There were no differences in survival between subjects who had notable free HNEA compared with those that did not.

Analysis of protease-antiprotease balance in airway secretions of subjects with acute respiratory failure is not useful to discriminate subjects who develop ARDS and does not correlate with survival.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical success</th>
</tr>
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<tbody>
<tr>
<td>Sex M/F</td>
<td>234/195 (n=429)</td>
</tr>
<tr>
<td>Age</td>
<td>79.02±10.3 (n=429)</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>32.49±7.19 (n=399)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>107.19±23.24 (n=429)</td>
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<tr>
<td>PAM (mmHg)</td>
<td>116.15±25.69 (n=429)</td>
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<tr>
<td>pH</td>
<td>7.29±0.12 (n=429)</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>51.08±15.61 (n=428)</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>23.65±6.95 (n=424)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.95±2.32 (n=429)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.24±2.49 (n=419)</td>
</tr>
<tr>
<td>Device O2 p</td>
<td>90/426 (21%)</td>
</tr>
<tr>
<td>Device MV</td>
<td>336/426 (79%)</td>
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</tbody>
</table>

Conclusions: We observed that in ACPE patients HLL on admission are not predictive of clinical failure but reduction of lactate independently of baseline levels is associated with clinical success.
Recordings were repeated at 3 weaning stages: A) tracheostomy and invasive ventilation; B) tracheostomy and non-invasive ventilation (NIV); C) decannulation and NIV. The compartment with the highest % contribution to VT at the start of weaning (stage A) was defined as predominant compartment (PC), the other as secondary compartment (SC). PC was the rib cage in 5 patients and AB in 2.

During SB, the contributions of PC and SC became progressively similar from stage A to C, with no significant differences at stage C (see figure).

Our results show that in difficult-to-wean patients the contribution to tidal volume of RC and AB becomes progressively more homogeneous as MV dependency decreases during weaning. Accurate monitoring of RC and AB contributions to VT provides therefore useful indications for weaning assessment.

P4645 Abdominal muscle action during sustained hypoxia

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Introduction: Classical studies suggest that expiratory neuronal activity is inhibited by hypoxia, and action of expiratory muscles during hypoxia is controversial. Isocapnic hypoxia sustained 20-60 minutes elicits a biphasic ventilatory response (roll-off), with initial peak followed by decline to a plateau. We demonstrated during sustained hypoxia, parasternal muscle activity rolls off with ventilation (ERJ 2011;38.S55).

Aim: To study ventilation and action of the abdominal expiratory muscle, Transversus Abdominis (TA), during sustained hypoxia in awake canines.

Methods: After study implantation of sonomicrometry transducers and EMG electrodes in TA, and full recovery, we measured airflow, SpO2, ETCO2, mean EMG and shortening (SHORT) of TA, during room air breathing (BASE) followed by 25 minutes of isocapnic hypoxia (mean 79.9% SpO2). The canines were awake, breathing through a mask. We report results 2-3 min after reaching SpO2 80% (PEAK) and final 5 min (PLATEAU) of sustained hypoxia, then room air breathing (RECOVERY).

Results: For N=9 (mean 28.7 kg, 27 days post implant), minute ventilation and tidal volume increased significantly from BASE to PEAK, then decreased to PLATEAU (p<0.001). Concurrently, mean EMG and SHORT of TA increased significantly from BASE to PEAK, then attenuated to PLATEAU (p<0.001).

Conclusion: During sustained isocapnic hypoxia, the abdominal expiratory muscle, TA, is markedly activated during initial hypoxia, then attenuated with prolonged hypoxia.

P4646 Transtracheal lung ventilation with a manual respiratory valve with a variable flow

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In cannot-inhale, cannot-ventilate situations, a lung ventilation through a thin transtracheal cannula may be attempted. However, it may be impossible to achieve sufficient ventilation if the lungs are spontaneously emptying and dangers of barotrauma may occur. Here we present a valve [1] as a bi-directional manual respiratory pump which low flow during inspiration (by reducing gas supply to the valve) and increased flow during expiration, by increasing gas supply to the valve, permitted more effective ventilator effect and efficient expiration, with low gas consumption.

The device is held in a hand and when squeezed, upper and lower part (A and B) move inwards and reduce the flow (A) and close the outflow (B).

The device is thus closed manually by squeezing the handle (the extent of manoeuvre should be adjustable).

A. During inspiration, when squeezed with the hand, the outflow is blocked (while the inflow to the venturi nozzle is reduced by the action of the lower part of the handle (B).

B. During inspiration, when squeezed with the hand, the flow is reduced.

C. The device is held in a hand and when squeezed, upper and lower part (A and B) move inwards and reduce the flow (A) and close the outflow (B).

D. The device is thus closed manually by squeezing the handle (the extent of manoeuvre should be adjustable).

E. The inflow is unblocked, variable gas flow is providing respiratory valve with variable gas flow.

F. The inflow is blocked, variable gas flow is provided shortening of the inspiratory time and efficient expiratory aid, and permitted IE ratios of 1:1, or even the inverse ratio ventilation. Satisfactory lung ventilation can be assured with transtracheal ventilation with a bidirectional manual respiration valve with variable gas flow.

Reference:

P4647 Effects of anesthesia, muscle paralysis and controlled ventilation on gas exchanges evaluated by DLCO and pulmonary surfactant protein B:

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Background: For patients with chronic obstructive pulmonary disease (COPD), the first acute exacerbation requiring mechanical ventilation is a breaking point in the disease.

Methods: We conducted a retrospective study to estimate the cumulative survival...
of COPD patients after their first intubation and the prognostic factors of these patients.

Results: Between January 2000 and December 2010, 110 patients (50.9% stage III and 30.6% stage IV according to GOLD) were admitted in intensive care unit (ICU) for acute exacerbation of their COPD. The main aetiologies of the acute respiratory failure were pneumonia (n=40) and acute cardiac failure (n=30). ICU mortality was 22% and the median survival time was 68 months. In cox multivariate analysis, three independent prognostic factors were found: admission in ICU for proved infectious exacerbation (HR=1.83; 95%CI [1.01-3.34], p=0.047), GOLD Stage III and IV (HR= 3.78; CI 95% [1.44-9.92], p=0.007) and acute renal failure (HR=5.79; CI95% [3.01-11.20], p<0.0001).

Conclusion: Cumulative survival of COPD patients were with acute respiratory failure depends mainly on severity of COPD, exacerbation aetiology and associated acute renal failure.