Simvastatin attenuates ventilator-induced lung injury in mice

Holger C Müller, Katharina Hellwig, Simone Rosseau, Thomas Tschernig, Andreas Schmiedl, Birgitt Gutbier, Bernd Schmeck, Stefan Hippenstiel, Harm Peters, Lars Morawietz, Norbert Suttorp, Martin Witzenrath

Abstract

Introduction: Mechanical ventilation (MV) is a life saving intervention in acute respiratory failure without alternative. However, particularly in pre-injured lungs, even protective ventilation strategies may evoke ventilator-induced lung injury (VILI), which is characterized by pulmonary inflammation and vascular leakage. Adjuvant pharmacologic strategies in addition to lung protective ventilation to attenuate VILI are lacking. Simvastatin exhibited anti-inflammatory and endothelial barrier stabilizing properties in vitro and in vivo.

Methods: Mice were ventilated (12 ml/kg; six hours) and subjected to simvastatin (20 mg/kg) or sham treatment. Pulmonary microvascular leakage, oxygenation, pulmonary and systemic neutrophil and monocyte counts and cytokine release in lung and blood plasma were assessed. Further, lung tissue was analyzed by electron microscopy.

Results: Mechanical ventilation induced VILI, displayed by increased pulmonary microvascular leakage and endothelial injury, pulmonary recruitment of neutrophils and Gr-1\textsuperscript{high} monocytes, and by liberation of inflammatory cytokines in the lungs. Further, VILI associated systemic inflammation characterized by blood leukocytosis and elevated plasma cytokines was observed. Simvastatin treatment limited pulmonary endothelial injury, attenuated pulmonary hyperpermeability, prevented the recruitment of leukocytes to the lung, reduced pulmonary cytokine levels and improved oxygenation in mechanically ventilated mice.

Conclusions: High-dose simvastatin attenuated VILI in mice by reducing MV-induced pulmonary inflammation and hyperpermeability.

Introduction

In acute respiratory failure, mechanical ventilation (MV) is a life saving treatment without alternatives, and MV is also employed following surgery or trauma. One third of all patients in intensive care units worldwide receive MV [1]. However, particularly in preinjured lungs even minimal MV-associated physical stress may evoke ventilator-induced lung injury (VILI), an important undesirable effect of respirator therapy [2,3]. VILI is characterized by a pulmonary inflammatory response with the liberation of cytokines, recruitment of leukocytes to the lung and increased lung permeability, consecutively resulting in lung edema, surfactant dysfunction, impaired lung compliance and deterioration of pulmonary gas exchange [4]. Clinical studies of Amato et al. and the ARDS Network revealed that minimization of MV-induced physical stress by reduction of tidal volumes to 6 ml/kg significantly improved the clinical outcome of mechanically ventilated patients [5,6]. However, even low tidal volume ventilation of healthy lungs causes lung injury [7], and particularly preinjured lungs are sensitive to the development of VILI even in the setting of lung-protective ventilation [2,3]. As the necessity to guarantee sufficient gas exchange limits a further substantial reduction of tidal volumes, new adjuvant pharmacological therapies in addition to lung-protective ventilation are needed to prevent VILI.

Simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor belonging to the group of statins may be a promising drug candidate for adjuvant pharmacotherapy in MV. Besides well-known lipid lowering properties, simvastatin exhibits pleiotropic
experiment. A urinary catheter was inserted. VT, RR, air-
There was no additional fluid support in any conducted
output were monitored (Pulmodyn, Hugo-Sachs-Electro-
way pressure, peripheral oxygen saturation and urine
side 0.9% containing 100 mmol/l HCO$_3^-$ was placed for blood pressure monitoring and infusion
was attenuated by simvastatin treatment [12]. Further, statin treatment was
associated with improved survival in sepsis and severe
community acquired pneumonia [13-16].

Pulmonary and systemic hyperinflammation, leukocyte
recruitment to the lungs, and the development of pul-
monary microvascular leakage are crucial components
of VILI [4,17]. We thus hypothesized that simvastatin
may reduce VILI and may be a promising adjuvant
pharmacologic strategy to limit VILI in addition to lung
protective ventilation.

In the current study, anesthetized mice were subjected
to mechanical ventilation for six hours. Simvastatin
treatment markedly attenuated ventilator-induced pul-
monary microvascular permeability and endothelial
injury, recruitment of neutrophils and Gr-1$^+$ mono-
cytes, as well as proinflammatory cytokine levels in the
lung, and improved oxygenation considerably.

Materials and methods

Mice

Female C57BL/6 mice (11 to 15 weeks, 20 to 22 g)
(Charles River, Sulzfeld, Germany) were employed. Pro-
cedures were approved by institutional and governmen-
tal authorities.

Mechanical ventilation

Mice were anesthetized by intraperitoneal injections of
Fentanyl (0.075 mg/kg), Midazolam (1.5 mg/kg) and
Medetomidin (0.75 mg/kg). Repetitive applications of
Fentanyl (0.016 mg/kg), Midazolam (0.33 mg/kg) and
Medetomidin (0.16 mg/kg) were done via an intraperi-
toneal catheter when required to guarantee adequate
anaesthesia over the whole experiment. Body-temperature
was maintained at 37°C by a heating pad. After tra-
cheotomy and intubation, mice were ventilated
(MiniVent, Hugo-Sachs-Electronics, March-Hugstetten,
Germany) with 50% oxygen; tidal volume (VT) 7 ml/kg;
respiratory rate (RR) 240 minute$^{-1}$; positive end-expira-
tory pressure (PEEP) 6 cmH$_2$O. All mice survived the protocol. At termina-
tion of the experiments mice were sacrificed by exsan-
guination via the carotid catheter. Non-ventilated mice
served as controls.

Simvastatin treatment

Simvastatin (Sigma, Steinheim, Germany) was dissolved
in ethanol and diluted with saline. Mice received i.p.
injections of 20 mg/kg simvastatin or solvent 24 h and
1 h before the VILI experiment. Non-ventilated mice
were treated in according intervals. Simvastatin treat-
ment had no impact on overall cholesterol, HDL and
LDL cholesterol in studied mice.

Blood gas analyses

Blood samples were analyzed for $p_{a}O_2$, $p_{a}CO_2$, ph,
HCO$_3^-$, SBE, Lactate, Na$^+$, K$^+$, Cl$^-$, Ca$^{2+}$ by blood gas
analyzer (ABL-800, Radiometer, Copenhagen, Denmark).
P/F ratio was calculated as $p_{a}O_2$ /FiO$_2$.

Lung permeability

Human-Serum-Albumin (HSA; 1 mg) was injected via
carotid artery catheter or tail vein in ventilated or non-
ventilated mice, respectively, 90 minutes before the
experiment termination. Mice were sacrificed and
bronchoalveolar lavage (BAL) of the right lung was per-
formed with 2 x 400 μl saline. BAL- and plasma HSA-
levels were quantified by ELISA (enzyme-linked immuno
sorbent assay) (Bethyl (biomol), Hamburg, Germany). Permeability was assessed by calculating the HSA BAL/
plasma ratio.

Electron microscopy

Lungs were flushed via the pulmonary artery, cut,
immersion-fixed (1.5% glutaraldehyde, 1.5% paraformal-
dehyde in 0.15 M HEPES), rinsed (0.1 mmol/l HEPES,
0.1 mmol/l cacodylate buffer) and osmicated (1%
osmium tetroxide in 0.1 mmol/l cacodylate buffer).
After rinsing in 0.1 mmol/l cacodylate buffer and dis-
tilled water, specimens were stained in half-saturated
aqueous uranylacetate solution (1:1). Samples were
dehydrated in ascending acetone concentrations,
embedded in epon, cut (70 nm), stained with lead citrate
and uranyl-acetate, and analyzed.

Differential cell count lung

Lungs were flushed. The left lung was digested in RPMI
containing Collagenase and DNase for 1 h. Leukocytes
were extracted by meshing the lung tissue through a cell
strainer (100 μm) and counted by haemocytometer and

Life-Sciences, Oakmont, PA, USA). After preparation, a
recruitment maneuver was performed (airway pressure
35 cmH$_2$O for 5 sec) before respirator settings were
adjusted for 6 h to $V_T$ 12 ml/kg, RR 120 minute$^{-1}$, PEEP
2 cmH$_2$O. All mice survived the protocol. At termi-
nation of the experiments mice were sacrificed by exsan-
guination via the carotid catheter. Non-ventilated mice
served as controls.
differentiated by flow cytometry according to their side-scatter/forward-scatter properties and CD45, Gr-1 and F4-80 expression.

**Differential cell count blood**

Leukocytes were quantified by flow cytometry using True-Count-Tubes and differentiated according to their side-scatter/forward-scatter properties and CD45 and Gr-1 expression.

**Quantification of cytokines**

Cytokines were quantified from total protein of flushed homogenized left lungs and blood samples (BioRad, Hercules, CA, USA).

**Measurement of Alanine transaminase levels**

Alanine transaminase (ALT) levels were measured by routine laboratory test at the Institute of Laboratory Medicine and Pathobiology of the Charité - Universitätsmedizin Berlin.

**Statistic analyses**

Groups were compared using One-Way-ANOVA following Newman-Keuls post test. For comparison of two groups Mann-Whitney U-Test was applied. P-values < 0.05 were considered significant. Data are represented as mean +/- SEM.

**Results**

**Simvastatin prevented oxygenation failure in VILI**

The decline of the peripheral oxygen saturation (SpO₂) observed in ventilated mice was prevented by Simvastatin treatment (Figure 1a). At the termination of the experiment, blood gas analysis was performed in arterial blood samples. The P/F ratio was higher in simvastatin treated mice (Figure 1b).

**Simvastatin reduced VILI-associated pulmonary vascular leakage**

MV induced a marked increase of pulmonary microvascular permeability in mice, indicated by an elevated HSA BAL/plasma ratio. Pulmonary hyperpermeability was decreased by Simvastatin treatment (Figure 2).

**Simvastatin attenuated endothelial injury in ventilated mice**

Non-ventilated, untreated or simvastatin treated mice exhibited intact alveolar epithelium and capillary endothelium (Figure 3a-d). Capillary endothelial cells of ventilated and untreated mice were swollen and showed loss of intracellular vesicles and caveolae (Figure 3e, f). In ventilated and simvastatin treated lungs, endothelial cells displayed fewer signs of injury as compared to ventilated and untreated mice. Swelling of endothelial cells occurred only sporadically, and normal distribution of vesicles and caveolae was preserved by simvastatin (Figure 3g, h).

**Simvastatin limited the recruitment of PMN and Gr-1<sup>high</sup> monocytes to the lung in VILI**

MV evoked PMN and Gr-1<sup>high</sup> monocyte recruitment to the lung, which was reduced by simvastatin treatment (Figure 4a, b). Further, MV elicited an increase of circulating PMN and monocyte counts, whereas lymphocyte counts were unaltered in the blood (Figure 4c-f). Notably, following simvastatin treatment monocyte counts were increased significantly and PMN counts were increased by trend in blood of ventilated mice (Figure 4c, d).

**Simvastatin treatment attenuated VILI-associated pulmonary cytokine production**

MV induced an increase of IL-1β, IL-6, IL-12p40, MIP-1α, MIP-2 and MCP-1 in the lung tissue. Simvastatin...
treatment attenuated the ventilation-evoked increase of IL-1β, IL-12p40 and MIP-1α in the lung tissue (Figure 5).

**Simvastatin treatment attenuated VILI-associated IL-12p40 increase in plasma**

MV evoked an increase of IL-1β, IL-6, IL-12p40, MIP-1α, MIP-2 and MCP-1 in blood plasma. Simvastatin treatment attenuated the VILI-associated increase of IL-12p40 in the plasma. All other quantified cytokines did not show statistically significant alterations due to simvastatin treatment in ventilated mice (Table 1).

**Hemodynamics, urine output electrolytes, acid-base homeostasis and markers of hepatic and renal function**

Continuous monitoring of systemic arterial blood pressure and quantification of electrolytes, parameters of acid-base homeostasis, renal and global hepatic function and urine output at the end of the experiment demonstrated standardization of experimental procedures.

Simvastatin treatment did not alter blood pressure, urine output electrolyte levels or acid-base homeostasis in mechanically ventilated mice. Further simvastatin had no impact on renal function or ALT levels in plasma (Table 2).

**Discussion**

Mechanical ventilation may evoke ventilator-induced lung injury even under employment of protective ventilation strategies. Adjuvant pharmacologic approaches to reduce VILI in addition to protective ventilation may further improve morbidity and mortality of ventilated patients. Investigating VILI in a mouse model of MV, the current study for the first time provides experimental evidence that simvastatin treatment may limit VILI in vivo. Simvastatin reduced VILI-associated hyperpermeability, endothelial injury, neutrophil and monocyte recruitment, and inflammation in murine lungs.

Mouse models have been successfully used to investigate pathomechanisms of VILI [18-20]. The currently employed mouse model allowed us to analyze key features of VILI while avoiding detrimental lung injury due to high airway pressures, tidal volumes or respiration rates. Although a V_T of 6 ml/kg is recommended for lung protective ventilation, we employed a V_T of 12 ml/kg which allowed for limitation of respiratory rates in our model, an important independent trigger of VILI in mice [21]. Further lung stress and lung strain, generated by a V_T of 12 ml/kg affecting healthy lungs in the current model may apply in ventilated areas of inhomogeneously injured lungs even under lung protective ventilation according to the baby lung concept of the inhomogeneous ARDS lung [22,23]. To further enhance clinical relevance, we prevented hemodynamic instability by fluid support and metabolic acidosis by adequate infusion of sodium bicarbonate. In summary, a mouse model was established for the current study, which evoked moderate lung injury by ventilation for a six-hour period.

Microvascular leakage, a hallmark of VILI evokes lung edema, reduction of lung compliance, surfactant dysfunction, and finally deterioration of pulmonary gas exchange [4]. Statins prevented pulmonary hyperpermeability in ALI evoked by different stimuli, including endotoxin and ischemia/reperfusion [8-10]. Of note, simvastatin treatment also reduced VILI-associated pulmonary hyperpermeability and improved pulmonary gas exchange in the current study.

Different mechanisms of endothelial barrier protection by HMG-CoA reductase inhibitors have been reported, including inhibition of the RhoA/Rho kinase pathway with consecutive reduction of endothelial myosin light chain phosphorylation [24-26], stabilization of endothelial junctions by polymerization of cortical actin [25], as well as downregulation of endothelial caldesmon and upregulation of integrin β4 expression in endothelial cells [25]. Although these mechanisms were not evaluated in detail in the current study, they may have been contributing to the observed improvement of barrier function in murine VILI. Notably, an additional way of endothelial cell protection by simvastatin has now been observed by electron microscopy. Simvastatin attenuated VILI-evoked cell swelling and loss of intracellular vesicle...
structures in lung endothelium, which are indicators of energy depletion and impaired cell metabolism. Previous in vitro and in vivo studies linked cyclic stretch with apoptosis and necrosis of pulmonary epithelial cells [27,28]. In line with the works of Vaneker et al. this study provides ultrastructural in vivo evidence for lung endothelial cell injury following ventilation with moderate tidal volumes [29]. The observed morphologic findings resemble alterations observed in capillary stress failure previously described by West et al. To the best of our knowledge this is the first study showing that a pharmacologic treatment attenuated endothelial injury VILI. This previously undescribed effect of simvastatin treatment suggests a so far unknown beneficial effect of
HMG-CoA reductase inhibitors, which may be further examined in future studies.

In VILI, PMN and Gr-1\textsuperscript{high} monocytes infiltrate the lungs and have been identified as major effector cells for the development of tissue damage [30-32]. Reportedly, simvastatin inhibited tissue leukocyte infiltration in ALI both in animal experiments and in humans [8,9,12]. Leukocyte rolling, adhesion and transmigration were attenuated by simvastatin, at least partly by reduction of adhesion molecules including CEACAM-1, VCAM-1.

**Figure 4** Simvastatin treatment limited VILI-associated pulmonary leukocyte infiltration. After 6 h mechanical ventilation (MV) of simvastatin (6 h Vent + Simva) or sham treated mice (6 h Vent.) and in non-ventilated sham (NV) or simvastatin (NV + Simva) treated mice, leukocytes isolated from whole left lung tissue and from blood were differentiated by flow cytometry. MV increased pulmonary PMN (a) and Gr-1\textsuperscript{high} monocytes (b). Simvastatin reduced PMN and monocyte counts in the lungs of ventilated mice. MV also increased circulating blood neutrophils (c) and Gr-1\textsuperscript{high} monocytes (d), whereas leukocyte (e) and lymphocyte (f) counts were not significantly altered by MV (F). PMN and Gr-1\textsuperscript{high} monocyte counts were higher in Simvastatin treated, ventilated mice (6 h Vent. + Simva), as compared to sham treated, ventilated mice (6 h Vent.). (a-b: NV n = 6; NV + Simva n = 7; 6 h Vent. N = 7; 6 h Vent. + Simva n = 6. c-d: NV n = 9; NV + Simva n = 9; 6 h Vent. N = 8; 6 h Vent. + Simva n = 8; *P < 0.05; **P < 0.01, ***P < 0.001).
and PCAM-1 [33-36]. In line, the significant recruitment of PMN and Gr-1\textsuperscript{high} monocytes in murine VILI was diminished by simvastatin in the current study. Moreover, an MV-induced increase of circulating PMN and Gr-1\textsuperscript{high} monocytes in the blood was even more pronounced in simvastatin-treated mice. This observation may suggest that simvastatin-evoked inhibition of endothelial leukocyte recruitment contributed to reduced pulmonary and concomitantly increased blood counts of PMN and Gr-1\textsuperscript{high} monocytes.

Simvastatin reduced production and liberation of various cytokines in animal models of ALI, sepsis and asthma as well as in humans following LPS-inhalation [9,11,12,37-40]. In the current study, VILI-associated pulmonary production of IL-1\textbeta, MIP-1\alpha and IL-12p40 was reduced by simvastatin treatment. Thus, alteration

![Figure 5 Simvastatin attenuated VILI-associated pulmonary cytokine production](image)

**Table 1 Simvastatin treatment reduced IL-12p40 levels in plasma**

|        | NV         | NV + Simva | 6 h Vent. | 6 h Vent. + Simva |
|--------|------------|------------|-----------|------------------|
| IL-1\textbeta | 445.30     | 100.70     | 505.30    | 52.19            |
| IL-6    | 57.58      | 62.99      | 133.40    | 90.38            |
| IL-12p40| 642.10     | 99.32      | 593.10    | 128.60           |
| MIP-1\alpha | 307.20    | 149.10     | 386.50    | 78.94            |
| MIP-2   | 15.28      | 35.02      | 10.03     | 9.42             |
| MCP-1   | 99.84      | 173.30     | 153.50    | 29.41            |

Cytokine levels were assessed in blood plasma after 6 h mechanical ventilation (MV) of simvastatin (6 h Vent. + Simva) or sham treated mice (6 h Vent.) and in plasma of non-ventilated simvastatin (NV + Simva) or sham (NV) treated mice. MV induced a systemic inflammatory response indicated by elevated cytokine levels in blood. Simvastatin treatment reduced IL-12p40 levels in plasma significantly. The levels of IL-1\textbeta, MIP-1\alpha, IL-6, MIP-2 and MCP-1 in VILI did not show statistically significant alterations due to simvastatin treatment. (n = 8 each group; * P < 0.05, ** P < 0.01, *** P < 0.001 vs. NV; # P < 0.05, ### P < 0.001 vs. NV + Simva; a P < 0.05 vs. 6 h Vent.).
of chemotaxis may have been contributing to the limitation of PMN and Gr-1<sup>high</sup> monocyte influx into the lungs in this study. Particularly IL-1β may be a key mediator in VILI, as IL-1β blockade as well as IL-1β deficiency resulted in reduced pulmonary PMN recruitment and hyperpermeability in animal models of VILI [41]. Therefore, dampening of pulmonary IL-1β production by simvastatin may have been adding to the observed attenuation of microvascular leakage, pulmonary leukocyte recruitment and endothelial cell injury.

Although increasing evidence derived from experimental and observational studies suggests beneficial effects of simvastatin in ALI as well as in pneumonia [8-11,14,16,42], a retrospective study analyzing an ALI patient cohort did not find an outcome improvement by conventional statin treatment [43]. Of note, statin doses of 5 mg/kg/d did not improve experimental ALI [8], whereas higher doses of 10 to 20 mg/kg/d evoked protective effects. Further, previous studies suggested a delay of at least 6 h for the development of barrier-protective effects by simvastatin [24,25]. Thus, mice were pretreated with 20 mg/kg/d simvastatin commencing 24 h before the onset of ventilation in the current study. Although mandatory for this experimental approach, simvastatin pre-treatment does not match the clinical scenario. However, animal studies are limited to hours while ARDS patients often are ventilated for days or even weeks. Taking this long time course in account we believe that simvastatin may deliver its beneficial effects over time when it is given with the initiation of MV. Notably, an upcoming randomized controlled NHLBI sponsored trial is going to investigate statin therapy in ALI (NCT00979121). As patients included in this trial will presumably receive respirator therapy, the effects of statins on VILI observed in the current experimental study may possibly contribute to the outcome of the treatment arm.

Conclusions

This study shows, for the first time, that high-dose simvastatin markedly reduced VILI-associated microvascular leakage and improved pulmonary gas exchange in mechanically ventilated mice. Simvastatin prevented recruitment of PMN and Gr-1<sup>high</sup> monocytes to the lung, limited pulmonary cytokine production and attenuated endothelial injury in VILI. The data suggest that high-dose simvastatin offers a promising perspective to prevent VILI in addition to lung protective ventilation.

Key messages

- Simvastatin improved microvascular leakage and improved oxygenation in VILI.
- Simvastatin limited pulmonary hyperinflammation in VILI.
- Simvastatin protected against VILI induced pulmonary endothelial injury.
- Simvastatin offers a promising perspective to limit VILI in addition to lung protective ventilation.

Abbreviations

ALI: acute lung injury; ALT: Alanine transaminase; BAL: bronchoalveolar lavage; ELISA: enzyme-linked immuno sorbent assay; HMG COA: 3-hydroxy-3-methylglutaryl coenzyme A; HAS: human serum albumin; HMG: human serum albumin; LPS: lipopolysaccharide; MV: mechanical ventilation; PEEP: positive end-expiratory pressure; VILI: ventilator-induced lung injury; Vt: tidal volume pressure.

Acknowledgements

We thank A. Santel for thoughtful discussion and useful advice and Andrea Schoenknecht for technical support. This study was supported in part by grants from the German Research Foundation to MW (OP 86/7-1) and SH (HI-789/6-1), and the German Federal Ministry of Education and Research to HCM, NS and SR (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis PROGRESS).

Author details

1Department of Infectious Diseases and Pulmonary Medicine, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. 2Institute for Anatomy and Cell Biology, Saarland University Faculty of Medicine, Kirberger Straße, Building 61, 66421 Homburg Saar, Germany. 3Institute for Functional and Applied Anatomy, Medical School of Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. 4BMBF-Forsys Junior Research Group "Systems Biology of Lung Inflammation (FORSYS Lung)".
Competing interests
The authors declare that they have no competing interests.

Received: 25 March 2010 Revised: 13 May 2010 Accepted: 30 July 2010 Published: 30 July 2010

References
1. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SR, Apezteguia C, Nightingale P, Amaglia AC, Tobin MJ. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002, 287:345-355.
2. Dhanireddy S, Altemeier WA, Matute-Bello G, O'Mahony DS, Glenny RW, Martin TR, Liles WC. Mechanical ventilation induces inflammation, lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. Lab Invest 2006, 86:790-799.
3. O'Mahony DS, Liles WC, Altemeier WA, Dhanireddy S, Frevert CW, Liggitt D, Martin TR, Matute-Bello G. Mechanical ventilation interacts with endotoxemia to induce extra-pulmonary organ dysfunction. Crit Care Med 2006, 10:R136.
4. Verbrugge SJ, Lachmann B, Kesiogirou L. Lung protective ventilatory strategies in acute lung injury and acute respiratory distress syndrome: from experimental findings to clinical application. Clin Physiol Funct Imaging 2007, 27:67-90.
5. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000, 342:1301-1308.
6. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Pesenti A, Rezende VL, Fradkin L, Meira AF, Zazpe J, Bauer SB, Seeger W, Lopez-Sendon JL, Viale P, Belen BM, Mietto H, Moreira-Neto L, Musso F, Delcroix M, Chatte M, Mendonca R, Radford S, Almeida C, Roca I, Cattaneo L, Maggiore SM, Cattaneo S. Mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. Am J Respir Crit Care Med 2006, 174:1277-1283.
7. Hammerschmidt S, Kuhn H, Grasenack T, Gessner C, Wirtz H. HMG CoA reductase inhibition modulates VEGF-induced endothelial cell cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Physiol Lung Cell Mol Physiol 2004, 287:L575-L583.
8. Jackson JB, Rollins SM, Bultman SJ, Dube S, Bedi R, Mitchell G, Backer M, Shanker V, Griffo AM, Willard RE, Green RE, Garcia GJN. Cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Cell Biol 2004, 30:662-670.
9. Zeng L, Xu H, Chew TL, Eng E, Sadeghi MM, Adler S, Kanwar YS, Danesh FR. HMGCoxA reductase inhibition modulates VEGF-induced endothelial cell hyperpermeability by preventing RhoA activation and myosin regulatory light chain phosphorylation. J Surg Res 2005, 129:1845-1847.
10. Hammerschmidt S, Kuhn H, Grasenack T, Gessner C, Wirtz H. HMG CoA reductase inhibition modulates VEGF-induced endothelial cell cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Crit Care Med 2006, 174:1277-1283.
11. Zeng L, Xu H, Chew TL, Eng E, Sadeghi MM, Adler S, Kanwar YS, Danesh FR. HMGCoxA reductase inhibition modulates VEGF-induced endothelial cell hyperpermeability by preventing RhoA activation and myosin regulatory light chain phosphorylation. J Surg Res 2005, 129:1845-1847.
12. Hammerschmidt S, Kuhn H, Grasenack T, Gessner C, Wirtz H. HMG CoA reductase inhibition modulates VEGF-induced endothelial cell cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Crit Care Med 2006, 174:1277-1283.
13. Zeng L, Xu H, Chew TL, Eng E, Sadeghi MM, Adler S, Kanwar YS, Danesh FR. HMGCoxA reductase inhibition modulates VEGF-induced endothelial cell hyperpermeability by preventing RhoA activation and myosin regulatory light chain phosphorylation. J Surg Res 2005, 129:1845-1847.
14. Mortensen EM, Pugh MI, Copeland LA, Restrepo MI, Comelli JE, Anzueto A, Pugh JA. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. Eur Respir J 2008, 31:611-617.
15. Schmidt H, Hennen R, Keller A, Russ M, Muller-Werdan U, Werdan K, Buerke M. Association of statin therapy and increased survival in patients with multiple organ dysfunction syndrome. Intensive Care Med 2006, 32:1248-1251.
16. Thomsen RW, Riis A, Konumb JR, Christensen S, Johnsen SP, Sorensen HT. Preadmission use of statins and outcomes after hospitalization with pneumonia: population-based cohort study of 29,900 patients. Arch Intern Med 2008, 168:2081-2087.
17. Ranieri VM, Suter PM, Tortorolla C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999, 282:54-61.
18. Hoetzel A, Dolinay T, Vallbracht S, Zhang Y, Kim HP, Redigio E, Alber S, Kaynar AM, Schmidt R, Rywer SW, Choi AM. Carbonic anhydrase IX protects against ventilator-induced lung injury via PPAR-gamma and inhibition of Egr-1. Am J Respir Crit Care Med 2008, 177:1223-1232.
19. Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2008, 295:L375-L385.
20. Papastavrou S, Yerapundar A, Reddy SR, Reddy MM, Qayoum MD, Burdick E, Cozzi P, Cressoni M, Colombo A, Marin J,Gattinoni L. Lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. Lab Invest 2006, 86:790-799.
21. Vaporidi K, Voloudakis D, Cadrinio E, Caoioni P, Valenza F, Polli F, TALLARINI F, Cozzi P, Cressoni M, Colombo A, Marin J, Gattinoni L. Lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. Lab Invest 2006, 86:790-799.
22. Chiumello T, Lattuca E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marin J, Gattinoni L. Lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. Lab Invest 2006, 86:790-799.
23. Gattinoni L, Pesenti A. The concept of “baby lung”. Intensive Care Med 2005, 31:776-784.
24. Chen W, Pandyala S, Natarajan V, Garcia GJN, Jacobson JR. Endothelial cell barrier protection by simvastatin: GTPase regulation and NADPH oxidase inhibition. Am J Physiol Lung Cell Mol Physiol 2008, 295:L375-L385.
25. Jacobson JB, Dukde SM, Brikov KS, Ye SQ, Grigoryev DN, Gengis RE, Garcia GJN. Cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Crit Care Med 2004, 170:346-355.
26. Zeng L, Xu H, Chew TL, Eng E, Sadeghi MM, Adler S, Kanwar YS, Danesh FR. HMGCoxA reductase inhibition modulates VEGF-induced endothelial cell hyperpermeability by preventing RhoA activation and myosin regulatory light chain phosphorylation. J Surg Res 2005, 129:1845-1847.
27. Hammerschmidt S, Kuhn H, Grasenack T, Gessner C, Wirtz H. HMG CoA reductase inhibition modulates VEGF-induced endothelial cell hyperpermeability by preventing RhoA activation and myosin regulatory light chain phosphorylation. J Surg Res 2005, 129:1845-1847.
32. Kawano T, Mori S, Cybulsky M, Burger R, Ballin A, Cutz E, Bryan AC. Effect of granulocyte depletion in a ventilated surfactant-depleted lung. J Appl Physiol 1987, 62:27-33.

33. Lin Y, Ye S, Chen Y, Li X, Yang Gw, Fan A, Wang Y. The effect of simvastatin on the serum monocyte chemoattractant protein-1 and intracellular adhesion molecule-1 levels in diabetic rats. Journal of Diabetes and its Complications 2009, 23:214-218.

34. Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, Sibelius U, Grandel U, Grimminger F, Seeger W, Meyer J, Darius H, Buerke M. Simvastatin inhibits inflammatory properties of Staphylococcus aureus alpha-toxin. Circulation 2002, 106:2104-2110.

35. Wei H, Fang L, Song J, Chatterjee S. Statin-inhibited endothelial permeability could be associated with its effect on PECAM-1 in endothelial cells. FEBS Lett 2005, 579:1272-1278.

36. Zapolska-Downar D, Siennicka A, Kaczmarczyk M, Kolodziej B, Naruszewicz M. Simvastatin modulates TNF[alpha]-induced adhesion molecules expression in human endothelial cells. Life Sciences 2004, 75:1287-1302.

37. Kim DY, Ryu SY, Lim JE, Lee YS, Ro JY. Anti-inflammatory mechanism of simvastatin in mouse allergic asthma model. European Journal of Pharmacology 2007, 557:76-86.

38. McKay A, Leung BP, Mcmens IB, Thomson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma1. J Immunol 2004, 172:2903-2908.

39. Souza Neto JL, Araujo FI, Dominici VA, Azevedo IM, Egito ES, Brandao-Neto J, Medeiros AC. Effects of simvastatin in abdominal sepsis in rats. Acta Cir Bras 2006, 21:8-12.

40. Yasuda H, Yuen PST, Hu X, Zhou H, Star RA. Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. Kidney Int 2006, 69:1535-1542.

41. Frank JA, Pittet JF, Wray C, Matthay MA. Protection from experimental ventilator-induced acute lung injury by IL-1 receptor blockade. Thorax 2008, 63:147-153.

42. Nakagawa H, Tsunooka N, Yamamoto Y, Yoshida M, Nakata T, Kawachi K. Pitavastatin prevents intestinal ischemia/reperfusion-induced bacterial translocation and lung injury in atherosclerotic rats with hypoadiponectinemia. Surgery 2009, 145:542-549.

43. Kor DJ, Iscimen R, Yilmaz M, Brown MJ, Brown DR, Gajic O. Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. Intensive Care Med 2009, 35:1039-1046.

doi:10.1186/cc9209
Cite this article as: Müller et al. Simvastatin attenuates ventilator-induced lung injury in mice. Critical Care 2010, 14:R143.