Lidocaine increases the anti-inflammatory cytokine IL-10 following mechanical ventilation in healthy mice

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Background: Mechanical ventilation (MV) induces an inflammatory response that may result in (acute) lung injury. Lidocaine, an amide local anesthetic, has anti-inflammatory properties in vitro and in vivo, possibly due to an attenuation of pro-inflammatory cytokines, intracellular adhesion molecule-1 (ICAM-1), and reduction of neutrophils influx. We hypothesized an attenuation of MV-induced inflammatory response with intravenously administered lidocaine.
Methods: Lidocaine (Lido) (2, 4, and 8 mg/kg/h) was intravenously administered during 4 h of MV with a tidal volume of 8 ml/kg, positive end expiratory pressure 1,5 cmH₂O and FiO₂ 0.4. We used one ventilated control (CON) group receiving vehicle. After MV, mice were euthanized, and lungs and blood were immediately harvested, and cytokine levels and ICAM-1 levels were measured in plasma and lung homogenates. Pulmonary neutrophils influx was determined in LEDER-stained slices of lungs. Anesthetic need was determined by painful hind paw stimulation.
Results: Lidocaine-treated animals (Lido 2, 4 and 8 mg/kg/h) showed higher interleukin (IL)-10 plasma levels compared to control animals. Lidocaine treatment with 8 mg/kg/h (Lido 8) resulted in higher IL-10 in lung homogenates. No differences were observed in pro-inflammatory cytokines, ICAM-1, and pulmonary influx between the different ventilated groups.
Conclusions: Intravenously administered lidocaine increases levels of plasma IL-10 with infusion from 2, 4, and 8 mg/kg/h and pulmonary levels of IL-10 with 8 mg/kg/h in a murine mechanical ventilation model. Intravenously administered lidocaine appears to reduce anesthetic need in mice.

For patients with acute respiratory failure, mechanical ventilation (MV) can be life saving. However, a large body of evidence suggests that MV can result in lung injury, so-called ventilator-induced lung injury.[1,2] It is widely assumed that an inflammatory response, characterized by release of inflammatory cytokines and influx of immune cells such as neutrophils contributes to the development of lung injury.[2–4] To date, no effective therapy exists to attenuate the MV-induced inflammatory response.

Lidocaine is an amide local anesthetic and a nonspecific sodium channel blocker that is mostly used for the treatment of acute and chronic pain. It

was demonstrated that low-dose intravenous lidocaine acts as an anti-hyperalgesic and anti-inflammatory agent.[5,6] Extensive in vitro research showed that lidocaine attenuates priming of human neutrophils by inhibition of G-protein coupled receptors.[7,8] Furthermore, lidocaine attenuated activated endothelial interleukin (IL)-1, 6, and 8 concentrations and intracellular adhesion molecule-1 (ICAM-1), important for transport of immune cells to site of inflammation.[9,10] In different in vivo models, intravenous lidocaine reduced levels of tumor necrosis factor (TNF)-α, IL-1β, IL-6, and Il-8.[11–13] Also, systemic lidocaine was found to attenuate acute lung injury in rabbits.[14,15] An additional effect of lidocaine infusion is that the requirements for anesthetics are diminished.[16,17] In human research, an attenuation in inflammatory response (measured by IL-6, IL-8, and an IL-1 receptor antagonist) in plasma has been found at the end of abdominal surgery in response to lidocaine.[18–20]

Since lidocaine seems to have prominent anti-inflammatory effects, we aim to investigate the role of intravenously administered lidocaine at different dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h during 4 h of mechanical ventilation in healthy mice in an established acute phase model.[21–23]

We hypothesize that intravenously administered lidocaine attenuates the inflammatory response following MV.

Methods

All experiments were approved by the Regional Animal Ethics Committee in Nijmegen and performed under the guidelines of the Dutch Council for Animal Care and The National Institutes of Health.

Animals

All studies were performed in C57BL6 male mice in our established MV mice model.[21–23] Mice were housed in a light and temperature controlled room under specific pathogen-free conditions. Standard pelleted chow (1.00% Ca; 0.22% Mg; 0.24% Na; 0.70% P; 1.02% K; SSNIFF Spezialdiäten GmbH, Soest, Germany) and drinking water were available *ad libitum*.

Experimental design

Four groups of mice (*n* = 8/group, randomly allocated) were studied after MV: control mice with vehicle (CON) and three groups of mice treated with different doses of lidocaine 2% (Lido) (Fresenius Kabi, Zeist, the Netherlands), 2 mg/kg/h (Lido 2), 4 mg/kg/h (Lido 4), and 8 mg/kg/h (Lido 8). Lidocaine was administered intravenously via an indwelling intravenous tail catheter just before MV and continued during 4 h. The control group (CON) received an equal volume of NaCl 0.9% intravenously. Intra-arterial carotid blood pressure and heart rhythm was measured throughout the experiment. Arterial blood gas analysis (iSTAT, Abbott, Birmingham, United Kingdom) was performed after 4 h of MV (data not shown).

Lipopolysaccharide (LPS) was measured in the ventilation circuit by Limulus Amebocyte Lysate testing (Cambrex Bio Science, Walkersville, MD; detection limit: 0.06 IU/ml) to rule out contamination with LPS in our experimental setting. No LPS could be detected in air, tubing, or ventilator.

Mechanical ventilation and anesthetic need

Mice were anesthetized with an intraperitoneal injection of a combination of ketamine, medetomidine, and atropine (KMA): 7.5 μl per gram of body weight of induction KMA mix (consisting of 1.26 ml ketamine, 100 mg/ml; 0.2 ml medetomidine, 1 mg/ml; 1 ml atropine, 0.5 mg/ml; and 5 ml NaCl, 0.9%). Animals were orally intubated and mechanically ventilated (*MiniVent*, Hugo Sachs Elektronik-Harvard apparatus, March-Hugstetten, Germany) for 4 h. The following MV settings were used: tidal volume 8 ml/kg and frequency 170 / min, 1,5 cm H_2O positive end-expiratory pressure and fraction of inspired oxygen was set to 0.4. These settings are within the normal range of tidal volume, and respiratory rate measured during spontaneous ventilation in C57BL6 mice.[24]

To maintain anesthesia, 5.0 μl per gram of body weight boluses of maintenance KMA mix (consisting of 0.72 ml ketamine, 100 mg/ml; 0.08 ml medetomidine, 1 mg/ml; 0.3 ml atropine, 0.5 mg/ml; and 18.9 ml NaCl, 0.9%) was administered when showed a positive reaction after manually

administered painful hind paw stimulation via an intraperitoneally placed catheter. Painful hind paw stimulation was performed every 30 min and represented anesthetic need. Rectal temperature was monitored continuously and maintained between 36.0°C and 37.5°C using a heating pad.

Tissue harvesting

Blood was collected by exsanguination, centrifuged (5 min, 14,000 rpm), and plasma was stored at −80°C for cytokine analysis. Immediately after exsanguination, heart and lungs were carefully removed en block via midline sternotomy. The right upper and lower lobes were snap frozen in liquid nitrogen and stored at −80°C. The left lobes were snap frozen and placed in 500 μl lysis buffer containing phosphate buffered saline, 0.5% triton X-100, and protease inhibitor (complete EDTA-free tablets, Roche, Woerden, the Netherlands). Subsequently, the left lobes were homogenized using a polytron and subjected to two rapid freeze-thaw cycles using liquid nitrogen. Finally, homogenates were centrifuged (10 min, 14,000 r.p.m., 4°C), and the supernatant was stored at −80°C until cytokine analysis.

Cytokine analysis

A simultaneous Luminex assay was used to determine plasma cytokine levels of TNF-α, IL-6, IL-10, keratinocyte-derived chemokine (KC), and IL-1β (Milliplex, Millipore, Billerica, MA, USA).

TNF-α, IL-6, and KC (murine equivalent of human IL-8) in lung homogenate were determined by enzyme-linked-immunosorbent assay (ELISA) (for IL-6 and IL10; CytoSet, BioSource, CA, USA; for TNF-α and KC; ELISA-Kit, R&D Systems, Minneapolis, MN, USA). Lower detection limits: IL-1α and IL-1β 40 pg/ml; TNF-α: 32 pg/ml; IL-6: 160 pg/ml; IL-10: 16 pg/ml and KC: 160 pg/ml.

IL-1β and IL-1α in lung homogenate were determined using a radioimmunoassay as described previously.[23] Total protein concentrations in the lung homogenates were determined using a bicinchoninic acid assay (Thermo Fisher Scientific, Etten-Leur, the Netherlands). Cytokine concentrations in the homogenates were normalized for protein concentration.

ICAM-1 analysis

Concentration of mouse sICAM-1 was determined in plasma and lung tissue using the quantikine mouse sICAM (CD54) ELISA (MIC100) kit (R & D systems, Abingdon, United Kingdom). Lower detection limits: 24,8 ng/ml.

Pulmonary neutrophil influx

After overnight incubation in 4% buffered formalin solution, the right middle lung lobe was dehydrated and embedded in paraplast (Amstelstad, Amsterdam, the Netherlands). Sections of 4-μm thickness were used. Enzyme histochemistry using chloracetatesterase (LEDER staining) was used to visualize the enzyme activity in the neutrophils. Neutrophils were counted manually (10 fields per mouse, blinded), and after automated correction for air/tissue ratio, the average number of neutrophils/μm² per mouse was calculated.[23]

Statistical analysis

We performed a sample size calculation based on previous investigations considering a difference of 40% in cytokine levels between ventilated and control mice with a type 1 error of 5% ($\alpha = 0.05$) and a power of 80% ($\beta = 0.2$).[21–23] This resulted in a group size of eight animals per group.

Shapiro–Wilk tests showed that data were not normally or log normally distributed.

Data are therefore expressed as median with interquartile range and depicted as column bar graphs. Differences between controls vs. lidocaine groups were studied using Mann–Whitney tests. Statistical analysis was performed using Graphpad Prism 5 software (Graphpad Software, La Jolla, CA, USA). P-values < 0.05 were considered significant.

Results

Cardiopulmonary physiology

All mice in this experiment exhibited stable hemodynamic variables during MV ($P > 0.05$).

Mean arterial pressure was within normal limits and remained above 65 mmHg (except in one mouse measured in the Lido 8 group), which was in line with previous data from our lab in this

model.[21–23] We did not observe arrhythmic changes in the different MV groups (except one mouse measured in the Lido 8 group). Blood gas values remained within normal range after 4 h of MV, and no differences were observed within the ventilated groups (data not shown). Four mice, one in each group, died during the experiment (n = 7 in each group remaining). Two mice died during instrumentation (CON, Lido 2, no measurement on hemodynamics obtained yet), one mouse died in its cage before the experiment started without apparent reason (Lido 4). One mouse died before the end of the experiment (Lido 8) from severe hypotension and bradycardia resulting in death.

Cytokine analysis in plasma

Cytokine analysis in plasma revealed no significant differences between the ventilated groups in IL-1β, IL-6, TNF-α, and KC. However, IL-10 analysis showed a significant increase in all the lidocaine groups, 2, 4, and 8 mg/kg/h (Lido 2, Lido 4, and Lido 8) in comparison with the control group (CON) (Fig. 1).

Cytokine analysis in lungs

IL-10 analysis showed a significant increase between the control group (CON) in comparison with the lidocaine 8 mg/kg/h group (Lido 8) but not in comparison with the lidocaine 2 mg/kg/h and 4 mg/kg/h group (Fig. 2).

Cytokine analysis in lung homogenates revealed no significant differences between the different ventilated groups in IL-1β, IL-6, TNF-α, KC, and IL-1α.

ICAM-1 analysis

ICAM-1 analysis in plasma and lung homogenates showed no significant differences between the different ventilated groups (Fig. 3).

Pulmonary neutrophil influx

No significant differences between pulmonary neutrophil influx measured per μm^2 were observed between the different ventilated groups (Fig. 4).

Anesthetic need

Mice showed a decrease in anesthetic need in lidocaine 2 mg/kg/h and lidocaine 8 mg/kg/h (lido 2 and 8) group, compared with control mice (CON) (Fig. 5).

Discussion

This study is the first to show that intravenously administered lidocaine caused an increase in pulmonary and systemic IL-10 levels following MV in healthy mice compared to control animals.

IL-10 is a well-known anti-inflammatory cytokine which limits the immune response during infections and is produced by nearly every type of cell in the immune system.[25,26] IL-10 is known to decrease the synthesis of pro-inflammatory cytokines in acute phase response as IL-1α, IL-1β, IL-6, and TNF-α by neutrophils.[27] In mouse lung fibroblast exposed to mechanical stretch, IL-10 inhibited inflammatory cytokines.[25] Low lung concentrations of IL-10 in patients with acute lung injury is an indication for development of adult respiratory distress syndrome.[28] Administration of IL-10 has shown protective effects in LPS-induced lung injury.[29] Interestingly, inhaled IL-10 attenuates biotrauma and mortality in a ventilator-induced lung injury model in rats.[30]

We did not observe an attenuation of pro-inflammatory cytokine levels, pulmonary ICAM-1 levels, or pulmonary neutrophil influx. A possible explanation for this could be that although IL-10 is known to attenuate inflammation, the acute phase response in our MV model is only a mild inflammatory response.

We did not include an unventilated group, whereas the placement of an indwelling tail catheter in an awake mouse provides extreme stress which could lead to false high cytokine levels. Furthermore, previous investigations have shown that cytokine levels of unventilated mice are below or extremely close to detection limits.[21–23] Dosage of lidocaine, especially 8 mg/kg/h, is relatively high. In comparison, dosages of 2 mg/kg/h can be considered safe in humans, 4 mg/kg/h is relatively high, and 8 mg/kg/h is considered too high in humans.[31] Previous research has shown an ED50 for central nervous system and cardiac toxicity in mice of approximately 19.5 mg/kg and
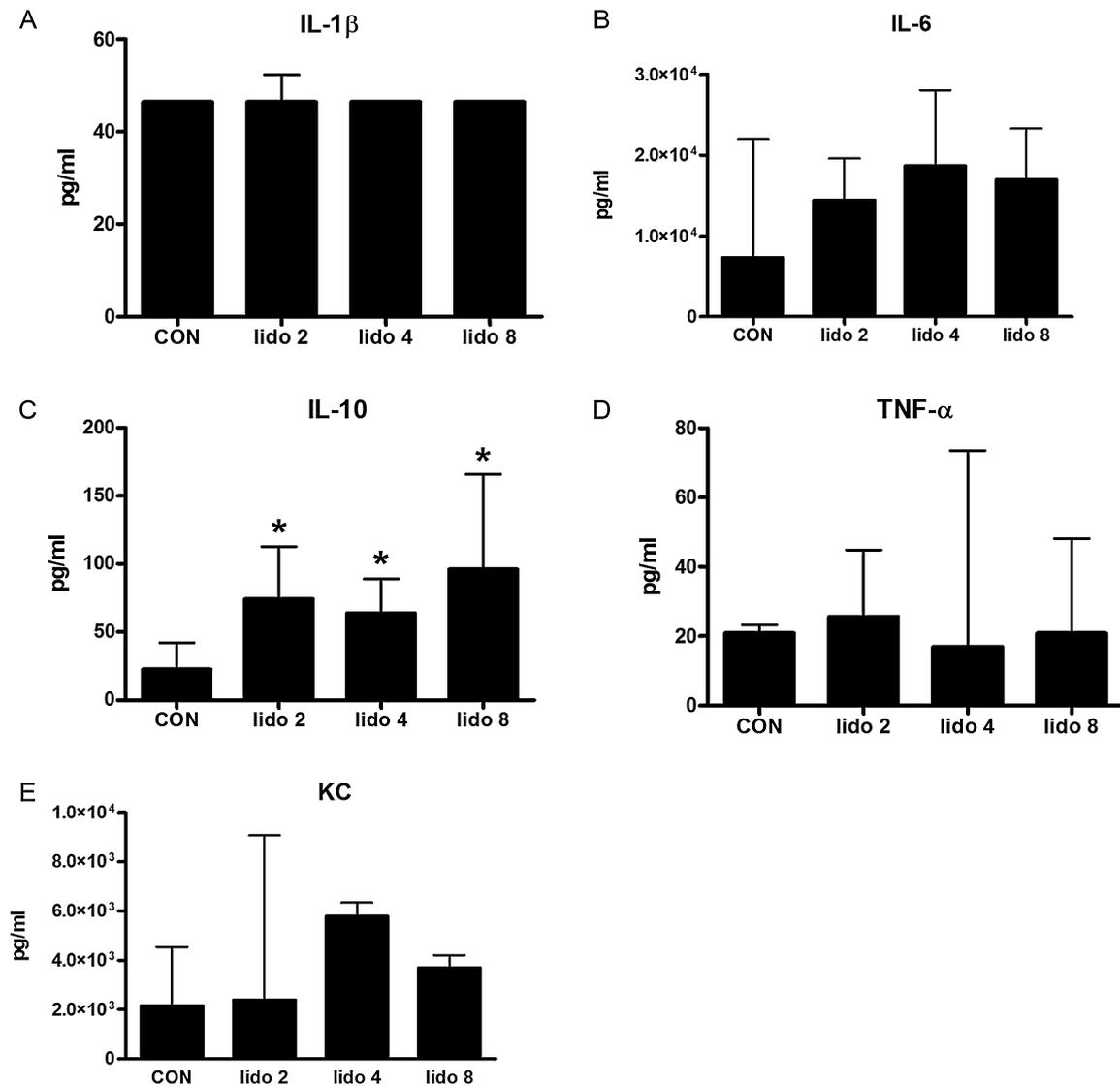
Fig. 1. Cytokine levels in plasma. Levels of interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor (TNF)-α, and keratinocyte derived chemokine (KC) in ventilated control (CON) compared with ventilated lidocaine mice (Lido) receiving lidocaine in different dosages. Lidocaine was given in dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h. (Panels A–E). Lido 2,4, and 8 showed increased IL-10 compared with CON. No differences were observed within the different ventilated groups of IL-1β, IL-6, IL-10, TNF-α, and KC. Data are expressed as median with interquartile range (IQR). (*$P < 0.05$)

21.2 mg/kg.[32] The cardiac side effects of lidocaine, contributed by the blockage of voltage-gated sodium channels, appear at plasma levels higher than 10 μg/ml in humans.[33] Considering the high ED50 for lidocaine in mice and extensive animal research in lidocaine toxicity with similar dosage, we did not measure plasma levels of lidocaine, and we have strong indications we stayed under critical plasma levels of lidocaine. One mouse however died in the 8 mg/kg/h group, because of uncontrollable hypotension, which could possi-

bly indicate an overdose of lidocaine. In lung homogenates, a significant increase of IL-10 was observed only at 8 mg/kg/h lidocaine (Lido 8), suggesting a possible dose-related effect. Mice in our experiment showed a decrease in anesthetic need with lidocaine administration which is consistent with previous experiments.[16,17] Although a decreased anesthetic need did not lead to an attenuation of other cytokine levels in our experiment, an influence on the level of IL-10 cannot completely be ruled out.
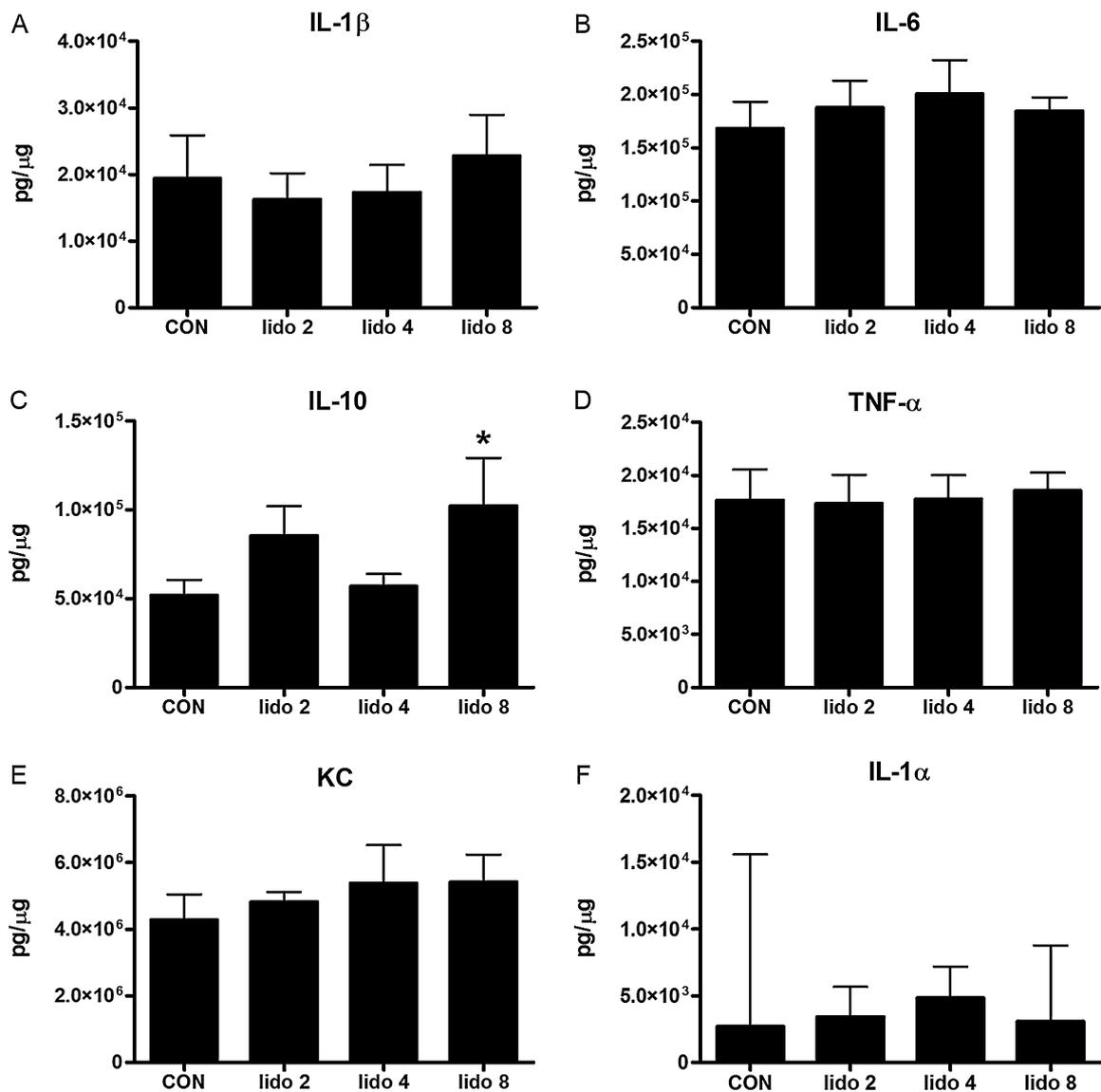
Fig. 2. Cytokine levels in lung homogenates. Levels of interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor (TNF)-α, keratinocyte derived chemokine (KC), and IL-1α in ventilated control (CON) compared with ventilated lidocaine mice (Lido) receiving lidocaine in different dosages. Lidocaine was given in dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h. (Panels A–F). Lido 8 showed increased IL-10 compared with CON. No differences were observed within the different ventilated groups of IL-1β, IL-6, IL-10, TNF-α, KC, and IL-1α. Data are expressed as median with interquartile range (IQR). (*$P < 0.05$)

In conclusion, low-dose intravenously administered lidocaine in MV increases levels of plasma IL-10 with infusion from 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h and pulmonary levels of IL-10 with 8 mg/kg/h, in a murine mechanical ventilation model indicating a modulatory role of lidocaine in inflammatory response. After 4 h of MV, no effects were found on pro-inflammatory cytokines, neutrophil influx, or ICAM-1 levels.

More research has to be performed to elucidate the exact role of lidocaine in ventilator-induced pulmonary inflammation and cytokine levels during time, and since we only ventilated mice for 4 h, the full impact of lidocaine on the MV-induced inflammatory response, cannot be fully described.

Lidocaine could prove to be an interesting therapeutic in multiple hit models. Furthermore,

A

B
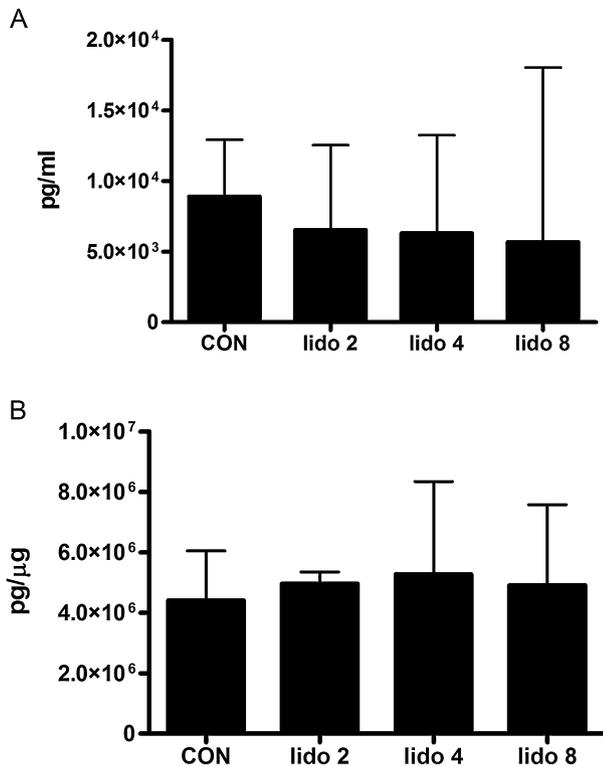
Fig. 3. Intracellular adhesion molecule (ICAM)-1 levels in plasma (Panel A) and lung homogenates (Panel B). Levels of in ventilated control (CON) compared with ventilated lidocaine mice (Lido) receiving lidocaine in different dosages. Lidocaine was given in dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h. No differences of ICAM-1 were observed between the different ventilated groups. Data are expressed as median with interquartile range (IQR).
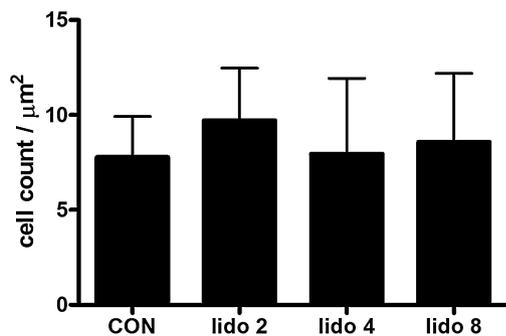
Fig. 4. Pulmonary neutrophils influx in lung. Neutrophil influx was measured by cell count in ventilated control (CON) compared with ventilated lidocaine mice (Lido) receiving lidocaine in different dosages. Lidocaine was given in dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h. No differences were observed between the different ventilated groups. Data are expressed as median with interquartile range (IQR).
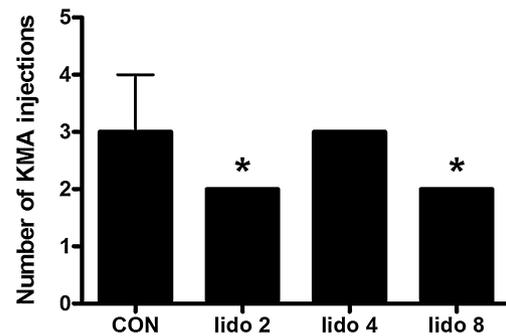
Fig. 5. Anesthetic need in mice. Anesthetic need was determined by painful hind paw stimulation every 30 min. If the mouse retracted his hind paw, 5.0 µl per gram of body weight boluses of maintenance ketamine, medetomidine, and atropine (KMA) mix (consisting of 0.72 ml ketamine, 100 mg/ml; 0.08 ml medetomidine, 1 mg/ml; 0.3 ml atropine, 0.5 mg/ml; and 18.9 ml NaCl, 0.9%) was administered. The number of KMA injections was measured in the different ventilated groups receiving lidocaine in dosages of 2 mg/kg/h, 4 mg/kg/h, and 8 mg/kg/h. (Lido 2, 4, and 8) compared with ventilated control (CON). Differences were observed between CON compared with Lido 2 and Lido 8. Data are expressed as median with interquartile range (IQR). (*$P < 0.05$)

intravenously administered lidocaine decreases anesthetic need.

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