Cytokine 47 (2009) 48–55

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/issn/10434666

The effects of body temperature control on cytokine production in a rat model of ventilator-induced lung injury

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ARTICLE INFO

Article history:
Received 20 June 2008
Received in revised form 18 March 2009
Accepted 9 April 2009

Keywords:
Ventilator-induced lung injury
Cytokine
Hypothermia
Normothermia
Hyperthermia

ABSTRACT

Background and purpose: Injurious ventilation with high peak inspiratory pressure (PIP) is known to cause systemic inflammatory response through cytokine production. This study was performed to examine whether body temperature could regulate cytokine production in ventilator-induced lung injury (VILI) model. *Methods:* After performing anesthesia, tracheostomy, and catheter insertion, rats were ventilated with 17 cm H_2O of PIP in the low-pressure (LP) group or 35 cm H_2O in the high-pressure (HP) group. Then, each group was divided into three subgroups; hyperthermia (39 °C), normothermia (37 °C), and hypothermia (34 °C) group. Six groups were observed for 6 h. *Results:* Plasma levels of pro-inflammatory cytokines, TNF-a and IL–6 at 1 h after the start of observation were highest in 39 °C-HP group and were lowest in 34 °C-HP group. Furthermore, sustained high plasma levels of IL-6 were observed only in 39 °C-HP group. In contrast, plasma levels of anti-inflammatory cytokine, IL-10 at 1 h were highest in 34 °C-HP group, and lowest in 39 °C-HP group. *Conclusion:* The body temperature significantly affects cytokine production in a model of VILI. Body temperature control may be a potentially effective therapeutic modality to regulate cytokine production in VILI.

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1. Introduction

It has been noticed that mechanical ventilation can injure the lungs, depending on their settings [1,2]. Mechanical ventilation with a high peak inspiratory pressure (PIP) and/or a low positive end-expiratory pressure (PEEP) is believed to stimulate pro-inflammatory cytokine production in the lungs and to induce further lung injury and remote organ dysfunction, leading to a poor outcome [3,4]. This condition has been termed "biotrauma", a type of ventilator-induced lung injury (VILI) [2]. To avoid VILI, a lung-protective ventilation strategy, including lower tidal volume ventilation and high PEEP [5], has been proposed. Several large-scale randomized trials of this ventilation strategy have been carried out in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), and have obtained improved survivals [5–7]. Base on these results, the Surviving Sepsis Campaign guidelines also recommend the implementation of the lung-protective ventilation strategy when applying mechanical ventilation to patients with ALI/ARDS [8,9], again even in the revised version [10,11]. However, injurious ventilator settings with high PIP or low PEEP may sometimes be inevitable, for example, the former in post-pneumonectomy patients with a decreased lung capacity and the latter in patients with therapy-resistant pneumothorax. At present, there is no established method to control pro-inflammatory cytokine production in lungs due to the injurious ventilation of these patients.

On the other hand, the inflammatory cytokine production, cellular injury, and other responses to stress have recently been found to vary depending on the body temperature. Following the findings of large-scale studies in humans that neurological outcome was improved by induced hypothermia after resuscitation [12,13], induced hypothermia has become a standard therapeutic modality on patients with the risk of hypoxic encephalopathy after cardiopulmonary resuscitation [14].

Studies of body temperature control have also been conducted on conditions other than hypoxic encephalopathy. In studies using various animal models of stress, including a model of sepsis [15], hemorrhagic shock [16], and pancreatitis [17], body temperature control was shown to modify responses to stress and even to improve survival. Furthermore, the effects of body temperature control on ALI have also been investigated in animal model of LPS-induced [18–20], smoke-induced [21], or acid-induced [22] ALI, and have demonstrated the protective effects of hypothermia such as suppression of pro-inflammatory cytokine production and improvement in survival. These findings suggest that body temperature control would also affect cytokine production in the cases of biotrauma.

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1043-4666/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cyto.2009.04.004

The present study was undertaken to investigate changes in respiratory, hemodynamic parameters, and changes in plasma cytokine levels over 6 h of the mechanical ventilation under different body temperature, as well as histological changes of the lungs and cytokine levels in bronchoalveolar lavage fluid (BALF) at the end of the 6-h observation period in a rat model of VILI in which body temperature was set at 3 different levels (39, 37, and 34 °C).

2. Materials and methods

This study was carried out in accordance with The Guide for Animal Experimentation of Inohana Campus, Chiba University, and was approved by the Special Committee on Animal Welfare, Chiba University. Forty-eight healthy male 15-week-old Sprague–Dawley rats were used in this study. The body weight of these rats was 421 ± 27 g.

Anesthesia was introduced by an intraperitoneal dose of pentobarbital sodium (50 mg/kg). Polyethylene 50 cannulae were inserted into the right femoral artery and vein. The arterial line was connected to a transducer and a pressure monitor for arterial pressure measurement. Tracheostomy was performed using a 14-gauge vascular catheter, and the catheter was connected to a ventilator (SAR-830AP Small Animal Ventilation, IITC Life Science, CA).

During the experiment, lactated Ringer's solution containing pentobarbital sodium (3.3 mg/mL), pancuronium bromide (0.13 mg/mL), and heparin (4 μ/mL) were continuously infused into the right femoral vein at a rate of 3 mL/kg/h.

2.1. Experimental protocol

Rats were divided into 6 groups with 2 different ventilator settings and 3 different levels of body temperatures (shown below). After the surgical procedure and the following 30-min stabilization period under each body temperature control, the ventilator setting (shown below) was applied to each group consisting of 8 rats.

(1) Hyperthermia 39 °C-high-pressure (HP) group
(2) Hyperthermia 39 °C-low-pressure (LP) group
(3) Normothermia 37 °C-HP group
(4) Normothermia 37 °C-LP group
(5) Hypothermia 34 °C-HP group
(6) Hypothermia 34 °C-LP group

The ventilator settings of the HP group: F_IO_2 1.0, PIP 35 cm H_2O, PEEP 2 cm H_2O, respiratory rate (RR) 16/min, inspiration/expiration (I/E) ratio of 1:2.

The ventilator settings of the LP group: F_IO_2 1.0, PIP 17 cm H_2O, PEEP 2 cm H_2O, RR 50/min, I/E ratio of 1:2.

Body temperature was kept constant with a heating pad (BWT-100, Bio Research Center, Nagoya, Japan) and cool air, while body temperature was monitored with a rectal probe inserted 2 cm from the anal sphincter. In each group, body temperature was attempted to be kept within target level ± 0.5 °C. Time to reach target temperature was approximately within 10 min. The respiratory dynamics and hemodynamics were evaluated before and 1, 2, 4, and 6 h after the start of the mechanical ventilation under different body temperature.

2.2. Sample collection

Arterial blood gas analysis was performed with 0.1 mL of the whole blood, using a blood gas analyzer (i-STAT®, i-STAT Corporation, NJ). These data were corrected based on the body temperature at the time of blood sampling. The plasma cytokine levels were measured before and 1, 2, and 6 h after the start of the mechanical ventilation under different body temperature. A 0.5 mL of the whole blood sample was immediately centrifuged at 3000 rpm for 10 min and the plasma obtained was stored at −80 °C. The same amount of normal saline was infused intra-arterially following these blood samplings. After 6 h of the mechanical ventilation under different body temperature, each rat was sacrificed with an overdose of pentobarbital sodium. In each sacrificed rat, the lower lobe of the right lung was removed after ligating the corresponding bronchi, and was fixed in 15% formalin. BALF was also obtained from a sacrificed rat by the infusion of physiological saline (5 mL) via the tracheostomy cannula and following 2 sessions of lavage. The BALF obtained was immediately stored at −80 °C.

2.3. Cytokine measurement

The cytokines measured were tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-10, high mobility group box-1 protein (HMGB-1), and macrophage inflammatory protein-2 (MIP-2). For measurement of TNF-α, IL-1β, IL-6, IL-10, and MIP-2, the Biosource ELISA kits (Invitrogen Corporation, CA) for the corresponding cytokines were employed. HMGB-1 was measured with an HMGB-1ELISA kit (Shino-Test Corporation, Tokyo, Japan). Immediately before the measurement, frozen plasma samples were thawed for 30 min at room temperature. The procedure and time indicated for each ELISA kit were carefully followed. Dual measurements were performed and the average value was used as the measured value. Absorbance was measured with an Ultrospec visible plate reader (Amersham Pharmacia Biotech, Buckinghamshire, England) at a wavelength of 450 nm.

2.4. Histological examination

Histological examination of the lungs was assigned to the pathologists of the Animal Pathology Division of a commercial laboratory (SRL, Inc., Tokyo, Japan). The histological changes were scored by the pathologists using five grades from 0 to 4 for 10 items: microscopic atelectasis, microscopic emphysema, perivascular edema, alveolar edema, congestion, alveolar hemorrhage, perivascular hemorrhage, alveolar mononuclear cell infiltration, interstitial polymorphonuclear leukocytes (PMNs) infiltration, and hyaline membrane formation. When providing each sample to the pathologist, only the date of collection and sample number were disclosed.

2.5. Statistical analysis

The data are shown as the mean ± standard deviation (SD). For multigroup comparisons of repeating data (variations over time) in the parametric data, a repeated measure analysis of variance (ANOVA) was used. If there were any significant differences in the repeated measure ANOVA, a one-way ANOVA with Fisher's PLSD as a post-hoc analysis was used for multigroup comparisons of each single factor. In the non-parametric data, Kruskal–Wallis analysis with Dunn's multiple comparison test was used. A statistical analysis was conducted using the Statview 4.5 software package (SAS Institute Inc.) and the Prism 5 software package (GraphPad Software Inc.). A P value less than 0.05 is considered to be statistically significant.

3. Results

3.1. Background factors, and changes in hemodynamic and respiratory parameters

Background factors are shown in Table 1. Also shown in Table 1 are the hemodynamic parameters and blood gas analysis values in

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