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MIP-1α and NF-κB as indicators of acute kidney injury secondary to acute lung injury in mechanically ventilated patients

Y. WU[1], L. WANG[1], L. MENG[2], G.-K. CAO[1], Y. ZHANG[3]

[1]Department of Nephrology, The First People's Hospital of Xuzhou, Xuzhou, Jiangsu, China
[2]Department of Intensive Care Unit, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China
[3]Department of Anesthesiology, Xuzhou Medical University, Xuzhou, Jiangsu, China

Abstract. – OBJECTIVE: In this study the levels of macrophage inflammatory protein-1α and NF-κB were measured in patients suffering acute kidney injury secondary to acute lung injury induced by mechanical ventilation and in controls, to determine whether they are differentially expressed.

PATIENTS AND METHODS: 160 patients were enrolled in our study: 40 had acute kidney injury secondary to acute lung injury induced by mechanical ventilation (group A), 40 had acute lung injury induced by mechanical ventilation, but no secondary acute kidney injury (group B), 40 were treated with mechanical ventilation but suffered no complications (group C), and 40 were treated with a conventional nasal catheter or oxygen mask inhalation (group D). The seric levels of MIP-1α, NF-κB and hs-CRP were compared amongst the groups at time points of 6, 12, 24, and 72 hours and at 7 days after the start of the respiratory treatment.

RESULTS: The serum levels of MIP-1α, NF-κB and hs-CRP of groups A and B were significantly higher than those of groups C and D at each time point. Also, group A had higher levels than group B at each time point, and the differences were statistically significant ($p < 0.05$). No statistically significant differences were found while comparing levels in group C with those of group D ($p > 0.05$). In groups A and B, the levels of MIP-1α increased gradually to a peak at 72 hours and then fell again on the 7th day. Levels of NF-κB in groups A and B significantly increased at 6, 12 and 24 hours, and reached a peak level at 24 h, to then fall after 72 h. The levels in group A fell back to baseline at 7 days, while group B levels fell back to baseline faster, at 72 h. Finally, the levels of hs-CRP in groups A and B kept increasing even after 7 days.

CONCLUSIONS: Based on these results, it is possible that the levels of MIP-1α and NF-κB be used as early indicators of inflammation reflecting the occurrence of acute kidney injury secondary to acute lung injury induced by mechanical ventilation.

Key Words:
Macrophage inflammatory protein, NF-κB, Mechanical ventilation, Acute lung injury, Acute kidney injury.

Introduction

Mechanical ventilation is the most effective treatment to correct severe hypoxia caused by various kinds of reasons, it also alleviates the hypoxic stress of organs, reducing the clinical emergency time, increasing the success rate of other treatments and improving long-term prognoses)[1]. The continuous improvement of respiratory machines and the changing respiratory parameters in patients allow doctors to set the most reasonable respiratory configurations to achieve an optimal state of blood oxygen supply and the best treatment effects. However, according to the statistics, the occurrence of acute lung injury caused by mechanical ventilation is about 10-50%[2], and in these cases, the mortality rate can reach 3-26%. The specific mechanisms leading to acute lung injury after mechanical ventilation are not yet clear. Some scholars have proposed, that ventilator-induced lung injury is not just a mechanical injury, but more likely results from biologically mediated inflammation[3]. In our practice, we have observed that mechanical ventilation capable of inducing acute lung injury may also be accompanied by acute kidney injury, and then multiple organ dysfunction or failure, in which cases the mortality rate gets substantially higher.

Macrophage inflammatory protein (MIP-1α) is an important cytokine of multi-cellular origin characteristic of inflammatory states and, which can activate local leukocytes[4]. NF-κB is a DNA-

Corresponding Author: Yang Zhang, MD; e-mail: zhang_yang_1212@163.com

binding protein that regulates gene expression, and is produced as a result of a variety of inflammatory reactions and immune responses; it is thought that it may play an important role in the development of the injury caused by mechanical ventilation[5]. In view of that, this study analyzed the expression levels of MIP-1α and NF-κB in acute kidney injury secondary to acute lung injury (caused by mechanical ventilation) at various time points during a clinical controlled study, to provide much needed references for clinical diagnosis and treatment, and to aid in the understanding of the pathogenesis that causes such a clinical picture.

Patients and Methods

Patients

Patients were enrolled in the study from January of 2014 until January of 2016. In total there were 160 patients and 4 groups of equal numbers: group A included patients with acute kidney injury secondary to acute lung injury caused by mechanical ventilation; group B had patients presenting acute lung injury induced by mechanical ventilation, but no secondary acute kidney injury; group C had patients on mechanical ventilation but without complications; and group D included patients treated with conventional nasal catheter or mask oxygen inhalation. Comparisons of the inter-group baseline data, showed differences among groups were not statistically significant. Group A had 26 males and 14 females, ranging from 36 to 67 years of age, the ventilator treatment span from 6 hours to 3 days with an average of 1.5 ± 0.6 days. Group B had 27 males and 13 females, ranging from 33 to 68 years of age (43.8 ± 14.5 years on average); the ventilator treatment span from 10 hours to 5 days with an average of 1.7 ± 0.8 days. Group C had 24 males and 16 females, ranging from 37 to 71 years of age (46.6 ± 17.3 years on average); the ventilator treatment span from 10 hours to 4.5 days with an average of 1.3 ± 0.8 days. Finally, group C had 25 males and 15 females, ranging from 32 to 69 years of age (45.8 ± 16.7 years on average); the respiratory treatment span from 8 hours to 3.5 days with an average of 1.2 ± 0.9 days. The most common underlying conditions causing a requirement for mechanical ventilation included chronic respiratory failure disease (CRF), acute cardiac disease (ACAD), acute cerebral disease (ACED) and trauma injuries (Table I).

All patients had clinical indications for mechanical ventilation (or otherwise respiratory treatment) and presented no contraindications. The diagnosis of acute lung injury was based on the ARDS Review Conference Standard of America and Europe, and the diagnosis of acute kidney injury based on the risk, injury, failure, loss, end stage (RIFLE) standard. The Ethics Committee of our hospital approved the research, and patients and family members signed the informed consents.

Methods

The research was completed by the same health care team of professionals, who selected possible participants based on the inclusion criteria, set respirator parameters, monitored respiratory and hemodynamic indicators, reviewed scientific and standardized nursing operations, evaluated the ventilator effects, adjusted the respirator modes in a timely manner, assessed the timing of applicable weaning, and helped prevent respiratory associated complications, etc.

Standard ELISA tests were used to measure the expression levels of serum MIP-1α, NF-κB and hs-CRP at 6, 12, 24, 72 hours and 7 days of the onset of the respiratory treatment. A kit was

Table I. Baseline data of the patients.

Group	N	Male/ female	Age (years)	Underlying condition					Duration of mechanical ventilation (days
				CRF	ACAD	ACED	Trauma	Other	
Group A	40	26/14	45.5 ± 16.9	14	8	7	9	2	1.5 ± 0.6
Group B	40	27/13	43.8 ± 14.5	13	7	8	9	3	1.7 ± 0.8
Group C	40	24/16	46.6 ± 17.3	16	10	6	7	1	1.3 ± 0.8
Group D	40	25/15	45.8 ± 16.7	12	7	5	13	3	1.2 ± 0.9
F (χ^2)		0.541	0.238			5.421			0.425
p		0.910	0.947			0.942			0.768

provided by Beijing Zhongshan Biotechnology Co, Ltd, and the manufacturer's instructions were followed to draw a concentration curve with standards and get accurate sample measurements.

Statistical Analysis

The SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was used for data entry and statistical analysis. The mean ± standard deviation was used to record the quantitative data, the comparison of inter-groups was analyzed by One-way ANOVA test followed by Post Hoc Test (LSD), and the variance of repeated measurement data to compare different time points within each group. Qualitative data was represented by cases or percentages (%), and inter-group comparison was tested by χ^2. A p-value < 0.05 denotes a difference statistical significance.

Results

Comparison of Serum MIP-1α Levels at Different Time Points

The serum MIP-1α levels of groups A and B were significantly higher than those of groups C and D at each time point, with group A being higher than group B each time. There were no statistically significant differences between the levels of groups C and D ($p > 0.05$). Levels in group A and B increased at 6 h, 12 h and 24 h and reached a peak level at 72 h, to fall back after 7 days (Figure 1).

Comparison of Serum NF-κB Levels at Different Time Points

The serum NF-κB levels of groups A and B was significantly higher than those of groups C and D at each time point, with group A having higher levels ($p < 0.05$). There were no significant differences while comparing the levels of group C with those of D ($p > 0.05$). Levels in groups A and B significantly increased at 6 h, 12 h and 24 h, and reached a peak level at 24 h, to then fall after 72 h. The levels in group A fell back to baseline at 7 days, while group B levels fell back to baseline at 72 h (Figure 2).

Comparison of Serum hs-CRP Levels at Different Time Points

The serum hs-CRP levels of group A and B were significantly higher than those of groups C and D at each time point, with group A having higher levels ($p < 0.05$). No statistically significant differences were found when comparing the levels between groups C and D. Groups A and B increased gradually until 7 days without showing significant peaks and not falling back (Figure 3).

Discussion

There are four types of acute lung injury caused by mechanical ventilation, namely, barotrauma, atelectrauma, volutrauma and biotrauma. The first three are categorized as mechanical traumas. They are caused by excessive expansion or rupture due to alveolar pressure gradients, re-

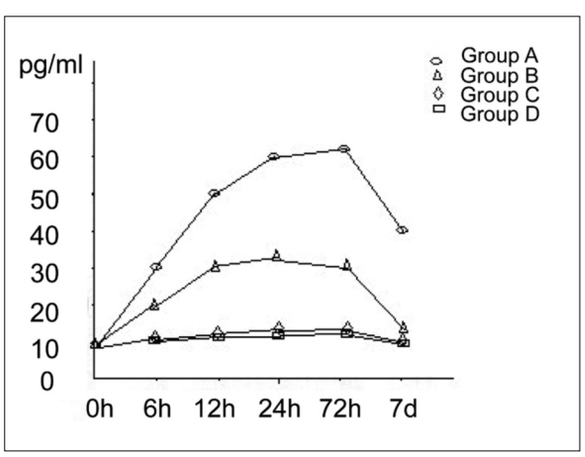

Figure 1. Comparison of MIP-1α levels in serum of subjects at different time points during and after respiratpry treatment.

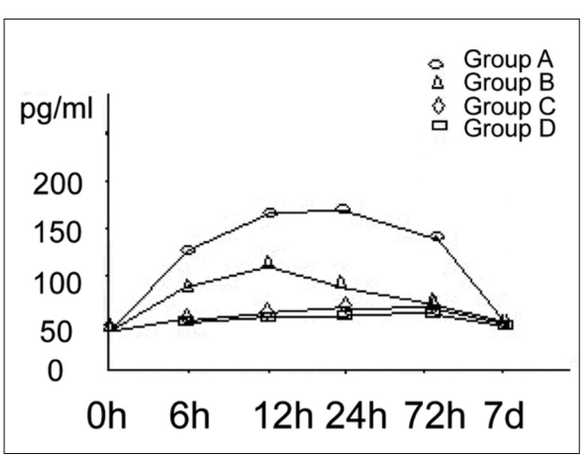

Figure 2. Comparison of NF-κß levels in serum of subjects at different time points during and after respiratpry treatment.

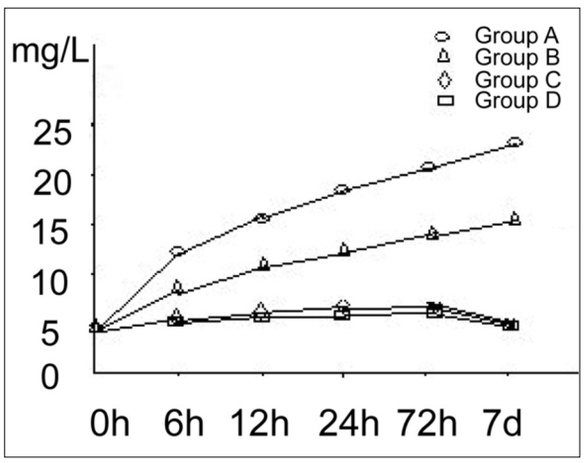

Figure 3. Comparison of hs-CRP levels in serum of subjects at different time points during and after respiratpry treatment.

peated alveolar collapse and expansion, or overdistension of alveoli, which can lead to alveolar or visceral pleural rupture, increased alveolar capillary endothelial cell gap, and edema[6]. Biotrauma, instead, is caused by the involvement of inflammatory cells, cytokines and inflammatory mediators, whose manifestations are similar to those of the endotoxin (LPS)[7] induced acute lung injury (ALI)[8]: The main pathological features are high permeability pulmonary edema, neutrophil activation and aggregation, alveolar hemorrhage and alveolar septal thickening.

MIP-1α belongs to the chemokine C-C subfamily; it is produced by various kinds of cells, including monocytes-macrophages, neutrophils, fibroblasts, epithelial cells, lymphocytes and endothelial cells. Research has shown that the expression of MIP-1α is regulated by many cytokines and chemicals: TNF-α, IFN-γ, IL-1β, thymosin α1, LPS ICAM and others can up-regulate its expression; while NO, IL-4, IL-10, IL-13, G-CSF and glucocorticoid hormone can inhibit it[9]. The chemokine receptors belong to the G protein-coupled receptors. At present, the widely accepted MIP-1α receptors include CCR5 and CCR9[10]. In a mouse study using high-pressure mechanical ventilation, on isolated perfused mice lungs it was found that MIP-1α, MIP-2, TNF-α and IL-6 were overexpressed in bronchoalveolar lavage fluid (BALF)[11]. And, in another study, in rats, it was shown that from a repertoire of cytokines and inflammatory mediators present in bronchoalveolar lavage, only MIP-1α was overexpressed significantly in isolated rat lungs subjected to high tidal volume ventilation, in the absence of LPS pre-treatment[12]; suggesting that MIP-1α may play a more important role in the development of ventilation-induced lung injury than other inflammatory mediators. Additionally, pre-treating rats with anti-MIP-1α antibody before experimental mechanical ventilation lowered the degree of pulmonary edema and decreased the number of neutrophils in the lung tissues by 51-65%, compared to the results in the mock pre-treated group[13]; and this again seems to point to MIP-1 playing a leading role in the aggregation and activation of neutrophils, and arguing for the benefit of controlling the activity of MIP-1α as a useful strategy against ventilation-induced lung injury.

On the other hand, research[14] has proven that the NF-κB signal transduction pathway can mediate the release of cytokines and inflammatory mediators in VILI. The specific inhibitor of NF-κB, caffeic acid phenethyl ester, can effectively inhibit nerve cells to produce MIP-1α and MIP-1β[15]. Furthermore, in the study[11] mentioned earlier about the high pressure mechanical ventilation in mice, the activation of NF-κB in lung tissue was related to the release of MIP-1α and MIP-2.

The kidney is highly sensitive to ischemia and reperfusion injury. It has been shown[16] that even though the intrinsic expression of MIP-1α in normal rat kidneys is low, the levels of the cytokine increase significantly after ischemia-reperfusion and that renal tubular injury was significantly reduced (with survival rates increased) in MIP-1α knockout mice and normal mice treated with antineutrophil serum or MIP-1α monoclonal antibody. Another study[17] in rats found that the activity of NF-κB was significantly increased in a model of acute kidney injury; and that if such activity was inhibited by transfected oligonucleotides, the kidney mononuclear cell infiltration was reduced by 60%, and the levels of MIP-1α and indicators of acute renal injury were reduced, suggesting a role for NF-κB in the development of the disease.

Conclusions

Based on the literature and the results of our study that showed the highest plasma levels of MIP-1α, NF-κB and hs-CRP in patients suffering acute kidney injury secondary to acute lung injury induced by mechanical ventilation, we con-

clude that the levels of MIP-1α and NF-κB can be used as early indicators of inflammation that reflect the occurrence of both these complications in mechanically ventilated patients. Larger studies are warranted to establish actual specific indicator levels.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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