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Relationship between serum nitrite/nitrate (NOx) levels in the early phase of septic acute lung injury and the prognosis

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Abstract

Serum nitrite/nitrate (NOx) levels in the early phase of septic acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) were investigated. Both NOx and tumor necrosis factor α (TNF-α) levels were significantly higher in the ARDS group than in the ALI group. A negative correlation was found between the PaO_2/FIO_2 (P/F) ratio and serum NOx levels. In addition, a positive correlation was found between the TNF-α and serum NOx levels. The 30-, 60- and 90-day mortality rates were 8.7%, 15.2% and 19.6%, respectively, in the patients with ALI/ARDS. There were no differences in the P/F ratio, serum NOx levels or TNF-α levels in the early phase of ALI/ARDS between the 30-day survival and death groups. On the other hand, the P/F ratio, serum NOx levels and TNF-α levels in the early phase of ALI/ARDS were significantly higher in the 60- and 90-day death groups than in the corresponding survival groups. There were no significant differences in the 90-day mortality rates between the ALI and ARDS groups. Our findings suggested that NOx may be involved in the pathogenesis of ALI/ARDS.

Key words : sepsis, ARDS, ALI, NO, TNF-α, endotoxin, P/F ratio, mortality

I. Introduction

Septic acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) occurs in 25 to 42% of patients with sepsis syndrome, and this frequency further increases when shock persists[1]. Acute respiratory failure (ARF) associated with sepsis is often a systemic process leading to multiple organ dysfunction syndrome (MODS).

The pathogenesis of ALI/ARDS is complex, but we have reported some humoral mediators that may be involved in the development of septic ALI/ARDS[2-4].

It has been successively reported that endothelium-dependent relaxing factor (EDRF), which has a vasodilatory effect and reduces blood pressure, is very similar in characteristics to nitric oxide (NO)[5,6]. Several studies have reported strong involvement of NO in the pathogenesis of septic shock[7-10]. We have reported increases of the serum nitrite/nitrate (NOx) levels and their correlations with those of tumor necrosis factor-α (TNF-α) and interleukin 8 (IL-8) in septic shock and also increase of the serum NOx levels in septic MODS[11,12].

On the other hand, attention has recently been paid to the involvement of NO and a reactive nitrogen species, peroxynitrite ($ONOO^-$), in the pathogenesis of ARDS. We have also reported the existence of a relationship between ALI/ARDS and serum NOx levels[13,14].

In the present study, we investigated the relationship between the serum NOx levels in the early phase of ALI/ARDS and the survival prognosis.

II. Subjects and methods

Consent for participation in this study was obtained from the patients or their families. This study was approved by the Ethics Committee of Iwate Medical University.

Diagnosis of sepsis was made according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee[15].

Diagnosis of ALI/ARDS was made according to the criteria reported by Bernard et al.[16]; in this study, patients with a PaO_2/FIO_2 ratio (P/F ratio) of ≥200 but <300 were diagnosed as having ALI, and those with a P/F ratio of <200 were diagnosed as having ARDS.

The Acute Physiology and Chronic Health Evaluation score (APACHE II score)[17] and Sequential Organ Failure Assessment score (SOFA score)[18] were used as the indicators of severity. The severity was assessed by 2 or more emergency physicians certified as infection control doctors.

The study involved 46 patients with an APACHE II score of ≥15 seen over the 3-year period from April 2008 to March 2011, who had undergone endotracheal intubation and from whom blood samples could be collected within approximately 3 hours of the diagnosis of ALI/ARDS. Fourteen patients had ALI and 32 had ARDS.

The mean age of the patients was 68 ± 16 years. The mean age of the male patients was 65 ± 17 years (n=26) and that of the female patients was 71 ± 13 years (n=20), with no significant difference in age between the male and female patients. The mean age of the ALI patients was 67 ± 15 years and that of the ARDS patients was 68 ± 16 years, with no significant difference in age between the two groups.

The underlying diseases were generalized peritonitis (n=33), pneumonia (n=4), burn (n=4), multiple trauma (n=3), and drug intoxication (n=2).

Sepsis and the associated septic shock and disseminated intravascular coagulation (DIC) were treated by the usual measures. Similarly, MODS was treated with regimens that have been commonly used for various states of MODS. ALI/ARDS was controlled by mechanical ventilation at a tidal volume of 8 to 10 ml/kg and positive end-expiratory pressure (PEEP) of 5 to 12 cmH_2O. Furthermore, 0.2 mg/kg/h of sivelestat sodium hydrate was administered while the patient had an endotracheal tube in place and for 1 to 2 days after extubation. The maximum administration period was 14 days.

Samples were collected using endotoxin-free heparin syringes within approximately 3 hours of the diagnosis of ALI/ARDS. The samples were immediately centrifuged at 3000 rpm for 40 seconds to separate platelet-rich plasma (PRP), and endotoxin levels were measured immediately. The PRP samples were stored at −80°C until

Table 1. Comparison of the clinic-pathological characteristics between ALI and ARDS patients

	ALI (n=14)	ARDS (n=32)	*p* value
Age (yrs.)	66.6 ± 14.8	68.3 ± 16.3	0.7206
APACHE II score	25.0 ± 7.3	32.3 ± 8.4	0.0056
SOFA score	7.9 ± 3.3	12.8 ± 4.8	0.0004
P/F ratio	244.3 ± 32.9	136.5 ± 40.7	<0.0001
NOx (μmol/L)	62.3 ± 22.3	93.7 ± 50.8	0.0031
TNF-α (pg/mL)	141.6 ± 53.4	237.4 ± 133.8	0.0012
Endotoxin (pg/mL)	2.4 ± 3.6	6.9 ± 18.1	0.1876

measurement of the serum NOx and TNF-α levels.

NOx levels were measured by an autoanalyser (TCI-NOX 1000; Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), based on the Griess reaction [19]. The normal range of NOx is 38.3 ± 19.1 μmol/L.

TNF-α levels were measured by enzyme-linked immunosorbent assay (ELISA) (TFB, Inc., Tokyo, Japan), the detection limit of which was 3 pg/ml.

Endotoxin levels were measured by an endotoxin-specific assay using Limulus HS-T Single Test Wako (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and the Toxinometer (Wako Pure Chemical Industries, Ltd., Osaka, Japan) [20]. The cutoff value for the diagnosis of endotoxemia was 1.1 pg/ml [21].

The unpaired t-test was used to analyze the data for significant differences, and Pearson's formula was used to test for correlations. The χ^2 test was used for comparisons between the groups, and the log-rank method was used for survival curves. A p value<0.05 was used as the probability value for significant differences in all of the tests.

III. Results

On average, the APACHE II score was 30 ± 9, the SOFA score was 12 ± 5, the P/F ratio was 169 ± 63, the serum NOx level was 86 ± 47 μ mol/L, the TNF-α level was 204 ± 109 pg/mL, and the endotoxin level was 5.5 ± 15.3 pg/mL in the 46 patients at the time of diagnosis of ALI/ARDS. The endotoxin positivity rate was 60.9% (21 out of 46 cases).

The P/F ratio, APACHE II score, SOFA score, serum NOx levels and TNF-α levels were significantly higher in the ARDS group than in the ALI group, but there were no significant differences in endotoxin levels between the 2 groups (Table 1). The endotoxin positivity rate was 50% (7 out of 14 cases) in the ALI group and 65.6% (21 out of 32 cases) in the ARDS group, with no significant differences between the 2 groups (r = 0.3230).

A significant positive correlation was found between the TNF-α and serum NOx levels (r=0.7613, p<0.0001; Fig. 1). No significant correlation was found between the endotoxin and TNF-α levels (r=0.1974, p=0.1885). A significant correlation was found between the endotoxin and serum NOx levels (r=0.3266, p=0.0268).

A significant negative correlation was

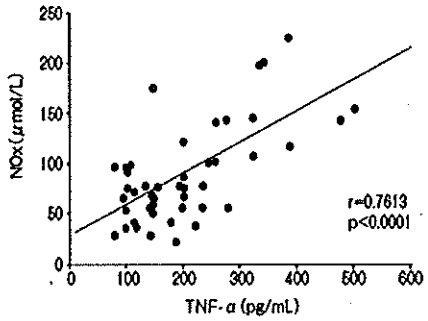

Fig.1. A significant positive correlation was observed between the TNF-α and serum NOx levels at the time of diagnosis of ALI/ARDS.

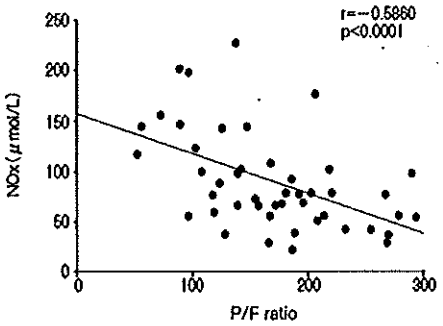

Fig.2. A significant negative correlation was observed between the P/F ratio and serum NOx levels at the time of diagnosis of ALI/ARDS.

Table 2. The 30-, 60- and 90-day mortality rates in the ALI and ARDS groups

	Mortality		
	30days	60days	90days
ALI	0% (0/14)	7.1% (1/14)	7.1% (1/14)
ARDS	12.5% (4/32)	14.3% (6/32)	25.0% (8/32)
ALI/ARDS	8.7% (4/46)	15.2% (7/46)	19.6% (9/46)

found between the P/F ratio and serum NOx levels ($r = -0.5544$, $p<0.0001$; Fig. 2). A negative correlation was also found between the P/F ratio and TNF-α levels ($r = -0.5800$, $p<0.0001$). No significant correlation was found between the P/F ratio and endotoxin levels ($r = -0.1726$, $p = 0.2512$).

A significant positive correlation was found between the serum NOx levels and APACHE II score, and between the serum NOx levels and SOFA score ($r = 0.6698$, $p<0.0001$ and $r=0.6753$, $p<0.0001$, respectively).

A significant positive correlation was found between the TNF-α levels and APACHE II score, and between the TNF-α levels and SOFA score ($r=0.6233$, $p<0.0001$ and $r=0.6662$, $p<0.0001$, respectively).

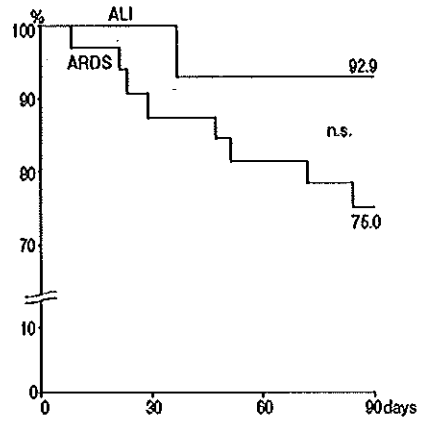

Fig. 3. The Kaplan-Meier survival curve from the time of diagnosis to day 90 in the ALI and ARDS groups. There were no significant differences in the survival between the 2 groups.

No significant correlation was found between the endotoxin levels and APACHE II score ($r=0.1716$, $p=0.2542$) or between the endotoxin levels and SOFA score ($r=0.1281$, $p=0.3962$).

Table 3. Comparison of the P/F ratio, APACHE II score, SOFA score, serum NOx levels and TNF- α levels in patients with ALI/ARDS between the 30-day death group and the corresponding survival group

	Survivors (n=42)	Nonsurvivors (n=4)	p value
Age (yrs.)	66.4 ± 15.8	82.3 ± 3.8	<0.0001
APACHE II score	28.9 ± 7.7	42.5 ± 10.6	0.0878
SOFA score	10.7 ± 4.6	17.3 ± 5.0	0.0869
P/F ratio	173.5 ± 63.1	125.8 ± 43.4	0.1417
NOx (μmol/L)	80.7 ± 42.2	145.0 ± 57.1	0.1156
TNF- α (pg/mL)	186.6 ± 91.8	360.3 ± 95.0	0.0826
Endotoxin (pg/mL)	5.4 ± 15.9	6.5 ± 5.9	0.7830

Table 4. Comparison of the P/F ratio, APACHE II score, SOFA score, serum NOx levels and TNF- α levels in patients with ALI/ARDS between the 60-day death group and the corresponding survival group

	Survivors (n=39)	Nonsurvivors (n=7)	p value
Age (yrs.)	66.2 ± 16.3	77.0 ± 7.5	0.0118
APACHE II score	28.1 ± 7.3	41.4 ± 7.7	0.0027
SOFA score	10.4 ± 4.5	16.6 ± 4.0	0.0062
P/F ratio	177.2 ± 61.8	125.3 ± 53.6	0.0469
NOx (μmol/L)	75.9 ± 37.3	144.1 ± 53.9	0.0148
TNF- α (pg/mL)	175.8 ± 75.7	389.1 ± 179.5	0.0212
Endotoxin (pg/mL)	3.0 ± 4.4	19.3 ± 37.0	0.2898

Table 5. Comparison of the P/F ratio, APACHE II score, SOFA score, serum NOx levels and TNF- α levels in patients with ALI/ARDS between the 90-day death group and the corresponding survival group

	Survivors (n=37)	Nonsurvivors (n=9)	p value
Age (yrs.)	66.3 ± 16.5	74.1 ± 10.9	0.0002
APACHE II score	27.5 ± 7.0	40.9 ± 6.8	0.0031
SOFA score	10.0 ± 4.2	16.8 ± 3.7	0.0004
P/F ratio	181.6 ± 60.4	118.7 ± 48.4	0.0050
NOx (μmol/L)	72.8 ± 35.5	141.9 ± 47.3	0.0021
TNF- α (pg/mL)	171.1 ± 73.6	327.4 ± 117.7	0.0107
Endotoxin (pg/mL)	3.1 ± 4.5	15.4 ± 32.9	0.2965

The 30-, 60- and 90-day mortality rates were 8.7%, 15.2% and 19.6%, respectively, in the 46 patients with ALI/ARDS (Table 2) . The 30-, 60- and 90-day mortality rates tended to be higher in the ARDS group than in the ALI group, but there were no significant differences.

The Kaplan-Meier survival curve from the onset of ALI/ARDS to day 90 is shown in Fig. 3. There were no significant differences in mortality rates between the ALI and ARDS groups.

There were no significant differences in the P/F ratio, APACHE II score, SOFA score, serum NOx levels, TNF- α levels, or endotoxin levels between the 30-day death and survival groups (Table 3) .

The APACHE II score, SOFA score,

serum NOx levels and TNF-α levels were significantly higher in the 60- and 90-day death groups than in the corresponding survival groups (Tables 4, 5). There were no significant differences in the endotoxin levels between the 60-day death and survival groups or between the 90-day death and survival groups.

IV. Discussion

Inducible nitric oxide synthase (iNOS) is induced by the stimulation of inflammatory cytokines and endotoxin in macrophages, neutrophils, vascular endothelial cells, airway epithelial cells and alveolar epithelial cells, and produces a large amount of NO. NO reacts with superoxide (O_2^-) to produce peroxynitrite ($ONOO^-$). Peroxynitrite itself is toxic, and hydroxyl radicals (·OH) generated form peroxynitrite have even higher toxicity and are known to damage not only bacteria and tumor cells, but also normal pneumocytes, thereby acting against living bodies[20].

Administration of steroids has also been reported to inhibit the induction of iNOS, thereby suppressing lung damage[23]. Also, administration of the iNOS antagonists, aminoguanidine (AG) and S-methylisothiourea sulfate, has also been reported to inhibit ARDS expression as well as iNOS activity, in a canine model of ARDS [24]. Because NOS inhibitors suppress the formation of edema induced by various stimuli in lung tissue, NO is speculated to be involved in the formation of inflammatory edema.

The relationship between iNOS and other NOS isoforms, i.e., endothelial NOS (eNOS) and neuronal NOS (nNOS), has not been well understood, but Jeremy et al.[22] have reported that AG administration inhibited iNOS and induced recovery of reduced eNOS and nNOS in a rat model of sepsis. The regulatory mechanisms of the 3 NOS isoforms, mainly by NO, is expected to be elucidated in the future.

To date, many clinical reports have shown the involvement of iNOS and NO in the pathogenesis of ALI and ARDS, and their relationship with various humoral mediators has also been suggested[13,14,25-27]. Cells circulating in blood vessels, such as neutrophils, platelets and monocytes, and cells in the lung tissue, such as macrophages, vascular endothelial cells and alveolar endothelial cells, are known to be involved in the development of lung injury seen in ALI/ARDS. In sepsis, endotoxin and other mediators are released into the blood, which activate complement and macrophages, producing TNF, interleukin-1 (IL-1), IL-8, etc, which, in turn, activate neutrophils. Activated neutrophils produce reactive oxygen species and macrophages also produce NO[14]. A strong negative correlation was found between the P/F ratio and serum NOx levels in the present study. Namely, if the P/F ratio is low, serum NOx levels are high, suggesting the involvement of NO in the development of lung injury. In addition, a positive correlation was found between the TNF-α and serum NOx levels, as in a previous study[11], suggesting that TNF-α may be involved in NO production. A significant negative correlation was found between the serum NOx levels and the P/F ratio, consistent with previously reported results from animal experiments[23,24]. However, it is unclear whether NO is directly involved

in the development of acute lung injury. It has been reported that synergistic or additive effects of endotoxin and cytokines are important for the development of septic shock[28], and it is possible that endotoxin, together with cytokines, whose production it induces, may be involved in NO production. Also in the present study, there were no significant differences in the endotoxin positivity rate, i.e., the rate of endotoxemia, or in the endotoxin levels between the ALI and ARDS groups.

The mortality rate of ALI/ARDS was previously said to be 30 to 40%[29, 30]. However, a recent study has reported that the mortality has declined to the range of 20-29%[31]. Recently, we reported that the 30-day mortality rates of patients with ARDS and ALI were 19.5% and 23.0%, respectively, in 158 patients with ALI/ARDS in the Tohoku district, Japan[32]. In addition, Oda et al. have reported, based on a study of 79 patients with ALI/ARDS, that the 28-day mortality rate of ALI/ARDS was 31.6%[33].

In the present study, the 30-, 60- and 90-day mortality rates in the 46 patients with ALI/ARDS were 8.7%, 15.2% and 19.6%, respectively, which were almost the same as the mortality rates reported in our recent study on the relationship between ALI/ARDS and high mobility group box 1 (HMGB1) and between ALI/ARDS and interleukin-18[31,35]. Considering the APACHE II score of 30 ± 9 and SOFA score of 11 ± 5, the mortality rates of the patients seemed to be very low in the present study. We aimed at collecting blood samples within approximately 3 hours of the diagnosis of ALI/ARDS, that is to say, the treatment was initiated at an early stage, and good results were considered to be obtained as a result. In addition, there were no significant differences in the 90-day mortality rates between the ALI and ARDS groups. Namely, the findings suggest that the P/F ratio alone at the time of diagnosis of ALI/ARDS does not allow precise prediction of the prognosis.

There were no significant differences in the P/F ratio, APACHE II score, SOFA score, serum NOx levels or TNF-α levels between the 30-day survival and death groups. The P/F ratio, APACHE II score, SOFA score, serum NOx levels and TNF-α levels were significantly higher in the 60- and 90-day death groups than in the corresponding survival groups. It appears that if the early NOx values are high, the tissue and cell damage caused by NOx is severe. The NOx values gradually declined even in the group that died, but they declined more slowly than in the group that survived. That is why death can be prevented by multidisciplinary treatment in the first 30 days, if the early NOx values are high. However, as one might expect, there is a limit, and when 30 days have passed, there appears to be a higher likelihood that organ dysfunction attributable to the tissue and cell damage caused by NOx will develop, and death will ensue.

Thus, our findings suggest that the P/F ratio, serum NOx levels and TNF-α levels in the early phase of septic ALI may be only weakly related to death up to day 30, but more strongly related to death after day 60. However, the endotoxin levels in the early phase of ALI were not related to the mortality up to day 90.

In the present study, 9 out of 46 patients

with septic ALI/ARDS (19.6%) died, and the causes of death were MODS in 7 cases and heart failure in 2. As reported previously [32, 34, 35], it was confirmed that very few patients died of ARF alone. Therefore, it would be important to prevent the development of MODS associated with ALI/ARDS for reducing mortality rates, as pointed out by Suchyta et al.[36] For this purpose, it is considered necessary to initiate multidisciplinary treatments from as early a stage as possible, considering that ALI/ARDS occurs acutely and progresses rapidly.

Serum NOx levels at the onset of septic ALI were strongly correlated with the APACHE II and SOFA scores, suggesting that NO may be strongly involved in the pathogenesis of sepsis.

NO appears to be involved in the pulmonary oxygenation capacity in ALI/ARDS. There were no significant differences in the mortality rates between the ALI and ARDS groups. The 30-, 60- and 90-day mortality rates were 8.7%, 15.2% and 19.6%, respectively, in the 46 patients with ALI/ARDS.

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References

1) **Bernard GR, Artigas A, Brigham KL, et al.:** TheAmerican-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med **149**, 818-824, 1994.
2) **Endo S, Inada K, Ceska M, et al.:** Plasmainterleukin 8 and polymorphonuclear leukocyte elastase concentrations in patients with septic shock. J Inflamm **45**, 136-142, 1995.
3) **Endo S, Sato N, Nakae H, et al.:** Surfactant A and D (SP-A, SP-D) levels in patients with ARDS. Res Commun Molecul Pathol Pharmacol **111**, 245-251, 2002.
4) **Miyata M, Sato N, Kojika M, et al.:** Blood levels of type II phospholipase A2 and platelete-activating factor acetylkydrolase elevated in acute lung injury/acute respiratory distress syndrome. Med Postgr **44**, 188-194, 2006.
5) **Palmer RMJ, Ferrige AG and Moncada S:** Nitric oxide release accounts for the biological activity of endothelium derived relaxing factor. Nature **327**, 524-526, 1987.
6) **Ignarro LJ, Ferrige AG, Buga GM, et al.:** Endothelium-derived xingfactor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ Res **60**, 82-92, 1987.
7) **Moncada S, Palmer RMJ and Higgs EA:** Nitric oxide: Physiology,pathophysiology, and pharmacology. Pharmacol Rev **43**, 109-142, 1991.
8) **Hibbs J, Westenfelder C, Taintor R, et al.:** Evidence for cytokine-inducible nitric oxide synthesis from L-arginine in patients receiving interleukin 2 therapy. J Clin Invest **89**, 867-877, 1992.
9) **Ochoa J, Curti B, Peitzman AB, et al.:** Increased circulating nitrogen oxides after human tumor immunotherapy with toxic hemodynamic changes. J Natl Cancer Inst **84**, 964-967, 1992.
10) **Kilbourn R, Logothetis C and Stiriegel A:** Interleukin-2 (IL-2) mediated hypotension in human is reversed by NG-monomethyl-L-arginine (NMA), an inhibitior of nitric oxide (NO) production. Proc Am Soc Clin Oncol **12**, 243, 1993.
11) **Endo E, Inada K, Nakae H, et al.:** Nitrite/nitrate oxide (NOX) and cytokine levels in patients with septic shock. Res Commun Molecul Pathol Pharmacol **91**, 347-356, 1996.
12) **Endo S, Inada K, Takakuwa T, et al.:** Nitrite / nitrate (NOx) and sFas antigen levels in patients with multiple organ failure. Res Commun Molecul Pathol Pharmacol **92**, 253-256, 1996.
13) **Takahashi G, Sato N, Kojika M, et al.:** A study

of the relationship between the blood levels of nitrite/nitrate (NOx) and the development of ALI/ARDS in sepsis. Med Postgr 44, 61-66, 2006.

14) **Akitomi S, Sato N, Kojika M, et al.**: A case report on consecutive measurements of nitrite/nitrate (NOx) and cytokines from the early stage of septic acute respiratory distress syndrome (ARDS). Med Postgr 47, 180-184, 2009.

15) Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101, 1644-1655, 1992. /Crit Care Med 20, 864-874, 1992.

16) **Bernard GR, Artigas A, Brigham KL, et al.**: The American-European Consensus Conference on ARDS. Difinition, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149, 818-924, 1994.

17) **Knaus WA, Draper EA, Wagner DP, et al.**: A severity of disease classification system. Crit Care Med 13, 818-829, 1985.

18) **Vincent JL, de Mendonça A, Cantraine F, et al.**: Use of the SOFA score to asses the incidence of organ dysfunction/failure in intensive care units: Results of a multicentre, prospectivestudy. Crit Care Med 26, 1793-1800, 1998.

19) **Green LG, Wagner DA, Glogowski J, et al.**: Analysis of nitrate, nitrite, and [15N] nitrate in biological fluids. Anal Biol 126, 131-138, 1982.

20) **Oishi H, Takaoka A, Hatayama Y, et al.**: Automated Limulus amebocyte lysate (LAL) test for endotoxin analysis using a new Toxinometer ET-201. J Parenter Sci Technol 39, 194-200, 1985.

21) **Yaegashi Y, Inada K, Sato N,et al.**: Highly sensitive assay for the diagnosis of sepsis. Jpn J Crit Care Endotoxemia 7, 25-28,2003. (in Japanese)

22) **Toga H, Tobe T, Ueda Y, et al.**: Inducible nitric oxide synthase expression and nuclear factor-kappa B activation in alveolar type II cells in lung injury. Exp Lung Res 27, 485-504, 2001.

23) **Numata M, Suzuki S, Miyazawa N, et al.**: Inhibition of inducible nitric oxide synthase prevents LPS-induced acute lung injury in dogs. J Immunol 160, 3031-3037, 1998.

24) **Scott JA, Mehta S, Duggan M, et al.**: Functional inhibition of constitutive nitric oxide synthase in a rat model of sepsis. Am J Respir Crit Care Med 165, 1426-1432, 2002.

25) **Kobzik L, Bredt DS, Lowenstein CJ, et al.**: Nitric oxide synthase in human and rat lung: immunocytochemical and histochemical location. Am J Respir Cell Mol Biol 9, 371-377, 1993.

26) **Kooy NW, Royall JA, Ye YZ, et al.**: Evidence for in vivo peroxynitrite production in human acute lung injury. Am J Respir Crit Care Med 151, 1250-1254, 1995.

27) **Sittipunt C, Steinberg KP, Ruzinski JT, et al.**: Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163, 503-510, 2001.

28) **Endo S, Inada K, Inoue Y, et al.**: Two types of septic shock classified by the plasma levels of cytokines and endotoxin. Circ Shock 38, 264-274, 1992.

29) **Luhr OR, Antonsen K, Karlsson M, et al.**: The ARF Study Group. Incidence and mortality after acute reapiratory failure and acute repiratory distress syndrome I Sweden, Denmark, and Iceland. Am J Resir Crit Care Med 159, 1849-1861, 1999.

30) **Bersten AD, Edibam C, Hunt T, et al.**: The Australian and New ZealandIntensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 165, 443-448, 2002.

31) **Zambon M** and **Vincent JL**: Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest 133, 1120-1127, 2008.

32) **Endo S, Miyate Y, Hirota K, et al.**: A survey on acute respiratory failure in intensive care unit patients. JJSEM 10, 415-421, 2007. (in Japanese)

33) **Oda S, Hirasawa H, Kitamura N, et al.**: Epidemiology of acute lung injury (ALI) / acute respiratory distress synsrome (ARDS) in Chiba prefecture - prospective multicenter cohort study of population-based morbidity and outcome. JJAAM 18, 219-228, 2007. (in Japanese)

34) **Kikuchi S, Kojika M, Takahashi G, et al.**: Assessment of HMGB1 values in the early stage after the onset of ALI/ARDS and the outcome. J Iwate Med Assoc 61, 283-293, 2009.

35) **Makabe H, Kojika M, Takahashi G, et al.**: Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndorome. J Anesth 5, 658-663, 2012.

36) **Suchyta MR, Orme JF Jr** and **Morris AH**: The changing face of organfallure in ARDS: Chest 124, 1871-1879, 2003.

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敗血症性急性呼吸不全発症早期の nitrite/nitrate（NOx）値と予後の検討

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要旨

septic acute lung injury（ALI）/acute respiratory distress syndrome（ARDS）発症早期の nitrite/nitrate（NOx）値について検討した．ALI 群に対して ARDS 群では NOx 値，tumor necrosis factor α（TNF-α）値いずれも有意に高値を示した．PaO2/FIO2（P/F ratio）と NOx 値間には負の相関関係がみられた．また，TNF-α値と NOx 値間には正の相関関係がみられた．ALI/ARDS の 30 日死亡率は 8.7%，60 日死亡率は 15.2%，90 日死亡率は 19.6% であった．30 日目まででは，ALI /ARDS 発症早期の P/F ratio，NOx 値，および TNF-α値はいずれも生存群と死亡群間で差はみられなかった．ALI/ARDS 発症早期の P/F ratio，NOx 値，および TNF-α値は 60 日目，90 日目で，生存群に対して死亡群間で高値であった．ALI 群と ARDS 群間に 90 日までの死亡率に有意差はみられなかった．ALI/ARDS 発症に NOx が関与している可能性が示唆された．