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1. 第37回日本頭痛学会総会 (宇都宮) 2009.11.28-29. (口演) 畝川美悠紀, 冨田稔, 冨田裕, 鳥海春樹, 鈴木則宏, 麻酔下および覚醒時のK^+誘発性皮質性拡延性抑制によるDC電位の変化および片麻痺.

2. 第37回日本頭痛学会総会 (宇都宮) 2009.11.28-29. (口演) 鳥海春樹, 冨田稔, 冨田裕, 清水利彦, 畝川美悠紀, 鈴木則宏, 片頭痛発作時の血流変化に関する検討—硬膜動脈と板間静脈の血管構造とA-V シャント.

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4. 35回日本微小循環学会総会 (埼玉) 2010.2.26-27. (口演) 冨田稔, 冨田裕, 畝川美悠紀, 鳥海春樹, 鈴木則宏, Neuro-capillary coupling during cortical spreading depression.

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9. 第 22 回日本脳循環代謝学会総会 (大阪), 2010/11/26~27 (口演). 畝川美悠紀, 冨田稔, 冨田裕, 鳥海春樹, 菅野巌, 鈴木則宏. K^+による大脳皮質性拡延性抑制誘発時の毛細血管内赤血球速度および脳波に対する持続的効果.

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11. 第 22 回日本脳循環代謝学会総会 (大阪), 2010/11/26~27 (口演). 正本和人, 冨田裕, 田桑弘之, 畝川美悠紀, 鳥海春樹, 小畠隆行, 鈴木則宏, 菅野巌. マウス大脳皮質における微小血管－アストログリア構造の長期追跡イメージング法.

12. 第 22 回日本脳循環代謝学会総会 (大阪), 2010/11/26~27 (口演). 冨田裕, 安部貴人, 畝川美悠紀, 鳥海春樹, 正本和人, 菅野巌, 鈴木則宏. マウス中大脳動脈・永久閉塞モデルと虚血再灌流モデルとの *in vivo* 脳微小循環動態の比較.

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13. 9th World Congress for Microcirculation (Paris), 2010/10/25~28 (口演).Tomita Y., Abe T., Unekawa M., Toriumi H., Masamoto K., Kanno I., Suzuki N. Long-term *in vivo* investigation of mouse cerebral microcirculation after middle cerebral artery ischemia-reperfusion induced by the suture method.

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16. 7th World Stroke Congress (Seoul), 2010/11/13~16 (ポスター).Tomita Y., Abe T., Unekawa M., Toriumi H., Masamoto K., Kanno I., Suzuki N. *In vivo* visualization of mouse cerebral microcirculation during middle cerebral artery occlusion induced by the suture method.

G. 知的財産権の出願・登録状況

新規出願なし

別添 4

表　研究成果の刊行に関する一覧表

刊行書籍又は雑誌名（雑誌のときは雑誌名、巻号数、論文名）	刊行年月日	刊行書店名	執筆者名
2008 年			
Nasotracheal Intubation with a 32F Blue Line Endobroncheal Tube®. Anesth Analg 106(6): 1927, 2008.	2008 年 4 月	Springer Japan	YoshiMisonoo, Kiyoshi Moriyama,Tatsuya Yamada,Itsuo Nakatsuka,Junzo Takeda.
Neutrophil elastase and systemic inflammatory response syndrome in the initiation and development of acute lung injury among critically ill patients. Biomed Pharmacother. 2008 Jun;62(5):333-8.	2008 年 4 月	Elsevier	Fujishima S, Morisaki H, Ishizaka A, Kotake Y, Miyaki M, Yoh K, Sekine K, Sasaki J, Tasaka S, Hasegawa N, Kawai Y, Takeda J, Aikawa N
日帰り麻酔と筋弛緩薬。麻酔。57：845-852, 2008.	2008 年 4 月	Springer Japan	武田純三
麻酔とコリンエステラーゼ阻害薬. 臨床麻酔。32(7)：1149-1156, 2008.	2008 年 7 月	Lippincott Williams&Wilkins	武田純三
Mechanisms of Sevoflurane-induced Respiratory Depression in Newborn Rats. Anesthesiology. 109(2):233-242, 2008.	2008 年 4 月	真興交易医書出版部	Kuribayashi, Junya, Sakuraba, Shigeki, Kashiwagi, Masanori, Hatori, Eiki, Tsujita, Miki, Hosokawa, Yuki, Takeda, Junzo, Kuwana, Shun-ichi.
麻酔実践テキスト。南江堂、2008、東京. 第 1 章　麻酔と安全	2008 年 5 月	南江堂	武田純三、森田茂穂
Cardioprotective effects of nicorandil in patients undergoing on-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2008 22(4):548-53.	2008 年 7 月	じほう	Yamamoto S, Yamada T, Kotake Y, Takeda J.
特集　重症患者における血糖管理「高血糖と腸管壁防御機構」.ICU と CCU。32(10):815-820, 2008	2008 年 7 月	日本臨床麻酔学会	矢島 聡、森崎 浩、武田純三
合併症患者の麻酔　スタンダード.克誠堂出版、東京、2008/11/17	2008 年 7 月	誠堂出版	武田純三、高野学美、忍田純哉。
麻酔看護のポイント 360. 武田純三編、メディカ出版、大阪、2009.	2008 年 8 月	メディカ出版	武田純三
合成 Xa 阻害薬投与に伴う股関節全置	2009 年 1 月	メディカルレビ	木下智恵、小杉 志都

換術の術後鎮痛法 -硬膜外鎮痛とIVPCAの比較一臨床麻酔。33(1):23-29, 2009		ュー社	子、橋口さおり、津崎晃一、武田純三
睡眠時無呼吸症候群患者の麻酔管理。臨床麻酔。33(1):55-60,2009.	2008年10月	Elsevier	中塚逸央、武田純三
Hypercapnic acidosis minimizes endotoxininduced gut mucosal injury in rabbits. Intensive Care Med (2009) 35:129–135	2008年10月	Lippincott Williams&Wilkins	Hiroshi Morisaki, Satoshi Yajima, Yoko Watanabe, Takeshi Suzuki, Michiko Yamamoto, Nobuyuki Katori, Saori Hashiguchi, Junzo Takeda.
日帰り手術の麻酔。麻酔科学レビュー2009、天羽敬祐監修、総合医学社、東京、2009、153-157	2009年1月	総合医学社	武田純三
Difference in autologous blood transfusion-induced infl amatory responses between acute normovolemic hemodilution and preoperative donation. J Anesth (2009) 23:61–66	2008年5月	Mosby, Inc	Yoshifumi Kotake, Michiko Yamamoto, Midori Matsumoto, Takashige Yamada, Hiromasa Nagata, Hiroshi Morisaki and Junzo Takeda.
An individualized recruitment maneuver for mechanically ventilated patients after cardiac surgery. J Anesth (2009) 23:87–92	2009年1月	Spandidos Publications Ltd.	Ryohei Serita, Hiroshi Morisaki and Junzo Takeda.
Recurrent ST-segment elevation on ECG and ventricular tachycardia during neurosurgical anesthesia. J Anesth (2009) 23:115–118.	2008年12月	Texas Heart R Institute, Houston	Yoshifumi Kotake, Midori Matsumoto, Tomoko Yorozu and Junzo Takeda.
Exacerbation of Bleomycin-Induced Injury and Fibrosis by Pneumonectomy in the Residual Lung of Mice. J Surg Res. 2008 (in press).	印刷中	Elsevier	Kakizaki T, Kohno M, Watanabe M, Tajima A, Izumi Y, Miyasho T, Tasaka S, Fukunaga K, Maruyama I, Ishizaka A, Kobayashi K.
Occult injury in the residual lung after pneumonectomy in mice. Interact Cardiovasc Thorac Surg. 2008;7:1114-20.	2008年12月	日本心臓財団	Tajima A, Kohno M, Watanabe M, Izumi Y, Tasaka S, Maruyama I, Miyasho T, Kobayashi K.
Histopathological features and prognostic significance of the micropapillary pattern in lung	2008年7月	Springer Japan	Kamiya K, Hayashi Y, Douguchi J, Hashiguchi A, Yamada T, Izumi Y,

adenocarcinoma. Mod Pathol. 2008;21:992-1001.			Watanabe M, Kawamura M, Horinouchi H, Shimada N, Kobayashi K, Sakamoto M.
Influence of hemoglobin vesicles, cellular-type artificial oxygen carriers, on human umbilical cord blood hematopoietic progenitor cells in vitro. J Biomed Materials Res A 88:34-42, 2009 .	2009 年 2 月	中外医学社	Yamaguchi M, Fujihara M, Wakamoto S, Sakai H, Takeoka S, Tsuchida E, Azuma H, Ikeda H.
ヘモグロビン小胞体の in vitro におけるヒト血液細胞および血漿タンパクへの適合性. 人工血液 16:212-220, 2008.	2008 年 9 月	中外医学社	藤原満博, 東 寛, 池田久實.
Electrostatic interactions and complement activation on the surface of phospholipid vesicles containing acidic lipids: Effect of the structure of acidic groups. *Biochim. Biophys. Acta-Biomembranes,* 2008.	印刷中	Elsevier	Sou K, Tsuchida E
Loading of curcumin into macrophages using lipid-based nanoparticles. *Int. J. Pharm,*, **352**:287-293, 2008.	2008 年 3 月	Elsevier	Sou K, Inenaga S, Takeoka S, Tsuchida E
"Hemoglobin-vesicles as artificial oxygen carriers: Present situation and future vision" *J. Intern. Med.,* **263**:4-15, 2008.	2008 年 1 月	Blackwell Publishing	Sakai H, Sou K, Horinouchi H, Kobayashi K, Tsuchida E
"ヘモグロビン小胞体を含有する血液検体の臨床検査-デキストラン添加による干渉作用の回避-", 人工血液, 17, (2009). (in press)	印刷中		**宗 慶太郎, 小峰梨沙, 酒井宏水, 小林紘一, 土田英俊, 村田 満**
"Artificial oxygen carriers, hemoglobin vesicles and albumin-hemes based on bioconjugate chemistry" Bioconjugate Chemistry 20, (2009). (in press)	印刷中		E. Tsuchida, K. Sou, A. Nakagawa, H. Sakai, T. Komatsu, K. Kobayashi,
" Review of hemoglobin-vesicles as artificial oxygen carriers" Artificial Organs 33,139-145 (2009).	印刷中		H. Sakai, K. Sou, H. Horinouchi, K. Kobayashi, E. Tsuchida,
"トピックス:ヘモグロビン内包リポソームによる脳への酸素供給:出血性ショックラットモデルでの PET イメージングによる評価", 人工血液, 16, 169-174 (2008).	2008 年 12 月	Blackwell Publishing	**宗 慶太郎**

Frequency distribution function of RBC velocities in single capillaries of the rat cerebral cortex using intravital confocal microscope with high-speed camera. Asian Biomed. 2: 203-218, 2008.	2008 年 6 月	Elsevier	Unekawa M, Tomita M, Osada T, Tomita Y, Toriumi H, Tatarishvili J, SuzukiN WT
2009 年			
Hypercapnic acidosis minimizes endotoxininduced gut mucosal injury in rabbits. Intensive Care Med (2009) 35:129–135	2009 年 4 月	Springer-Verlag	Hiroshi Morisaki, Satoshi Yajima, Yoko Watanabe, Takeshi Suzuki, Michiko Yamamoto, Nobuyuki Katori, Saori Hashiguchi, Junzo Takeda
Difference in autologous blood transfusion-induced inflamatory responses between acute normovolemic hemodilution and preoperative donation. J Anesth (2009) 23:61–66	2009 年 4 月	Springer	Yoshifumi Kotake, Michiko Yamamoto, Midori Matsumoto, Takashige Yamada, Hiromasa Nagata, Hiroshi Morisaki and Junzo Takeda
An individualized recruitment maneuver for mechanically ventilated patients after cardiac surgery. J Anesth (2009) 23:87–92	2009 年 4 月	Springer	Ryohei Serita, Hiroshi Morisaki and Junzo Takeda
Recurrent ST-segment elevation on ECG and ventricular tachycardia during neurosurgical anesthesia. J Anesth (2009) 23:115–118	2009 年 4 月	Springer	Yoshifumi Kotake, Midori Matsumoto, Tomoko Yorozu and Junzo Takeda
Orengedokuto and berberine improve indomethacin-induced small intestinal injury via adenosine J Gastroenterol. 2009; 44(5):380-9	2009 年 4 月	Springer	Watanabe-Fukuda Y, Yamamoto M, Miura N, Fukutake M, Ishige A, Yamaguchi R, Nagasaki M, Saito A, Imoto S, Miyano S, Takeda J, Watanabe K.
Tumor necrosis factor-α mediates hyperglycemia-augmented gut barrier dysfunction in endotoxemia. Crit Care Med 2009; 37 (3):1024 –1030	2009 年 4 月	Society of Critical Care Medicine and Lippincott Williams & Wilkins	Satoshi Yajima, Hiroshi Morisaki, Ryohei Serita, Takeshi Suzuki, Nobuyuki Katori, MD;Takashi Asahara, Koji Nomoto, Fujio

			Kobayashi, Akitoshi Ishizaka, Junzo Takeda
ステントグラフト内挿術後の腹部大動脈瘤に対し人工血管置換術を施行した1例 臨床麻酔。33(6)：1049-1050, 2009	2009年6月	臨床麻酔	鈴木康生、加藤純悟、藍 公明、森山 潔、志水秀行、武田純三
Can Mixed Venous Hemoglobin Oxygen Saturation Be Estimated Using a NICO Monitor? Anesth Analg 2009;109:119 –23	2009年6月	International Anesthesia Research Society	Yoshifumi Kotake, Takashige Yamada, Hiromasa Nagata, Takeshi Suzuki, Junzo Takeda
Epidural Cooling Minimizes Spinal Cord Injury after Aortic Cross-clamping through Induction of Nitric Oxide Synthase. Anesthesiology 2009 111(4): 818-25.	2009年10月	Lippincott Williams & Wilkins	Akiko Ishikawa, Atsuo Mori, Nobuyuki Kabei, Akihiro Yoshitake, Takeshi Suzuki, Nobuyuki Katori, Hiroshi Morisaki, Ryohei Yozu, Junzo Takeda.
ADAM28 is a serological and histochemical marker for non-small-cell lung cancers. Int. J. Cancer (2010)	2010年1月	Wilkey-Blackwell	Hiroaki Kuroda, Satsuki Mochizuki, Masayuki Shimoda, Miyuki Chijiiwa, Kazunori Kamiya, Yotari Izumi, Masazumi Watanabe, Hirohisa Horinouchi, Masahumi Kawamura, Koichi Kobayashi, Yoasunori Okada
Interactive Cardio Vascular and Thoracic Surgery. Interact Cardio Vasc Thorac Surg 10 (2010): 356-359.	2010年4月	European Association for Cardio-thoracic Surgery	Yotaro Izumi, Masafumi Kawamura, Masatoshi Gika, Hiroaki Nomori
Artificial Oxygen Carriers, Hemoglobin Vesicles and Albumin-Hemes, Based on Bioconjugate Chemistry. Bioconjugate Chemistry (2009) 20(8): 1419-1440.	2010年2月	American Chemical Society	Eishun Tsuchida, Keitaro Sou, Akito Nakagawa, Hiromi Sakai, Teruyuki Komatsu, Koichi Kobayashi
O2 Binding Properties of Human Serum Albumin Quadruple Mutant Complexed Iron Protoporphyrin IX with Axial His-186 Coordination.	2009年8月	Chemical Society of Japan	Akito Nakagawa, Teruyuki Komatsu, Stephen Curry, Eishun Tsuchida

Chemistry Letters (2009) 38(8): 776-777.			
The role of an amino acid triad at the entrance of the heme pocket in human serum albumin for O2 and CO binding to iron protoporphyrin IX. Org. Biomol. Chem. (2009)7: 3836-3841	2009 年 7 月	Royal Society of Chemistry	Teruyuki Komatsu, Akito Nakagawa, Stephen Curry, Eishun Tsuchida, Kenichi Murata
Structural and Mutagenic Approach to Create Human Serum Albumin-Based Oxygen Carrier and Photosensitizer. Drug Metab. Pharmacokinet. 24 (4): 287-299 (2009).	2009 年 6 月	日本薬物動態学会	Teruyuki Komatsu, Akito Nakagawa, Xue Qu
ヒト血清アルブミンを用いた機能分子・材料の創製. 人工血液 17(2) (2009): 82-89.	2009 年 5 月	中外医学社	小松晃之、屈　雪、土田英俊、中島晶人
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Original article

Neutrophil elastase and systemic inflammatory response syndrome in the initiation and development of acute lung injury among critically ill patients

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Abstract

Critically ill patients are commonly associated with systemic inflammatory response syndrome (SIRS) and are at a greater risk of developing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Under these conditions, large amounts of various cytokines are produced, which either directly or indirectly induce tissue injury and finally organ dysfunctions, through the activation of neutrophils and as a result of release of cytotoxic molecules, especially neutrophil elastase (NE). In the present study, we determined plasma neutrophil elastase–alpha-1 antitrypsin complex (NE–AT) and elastase digests of cross-linked fibrin (e-XDP) in critically ill patients to elucidate the significance of NE in the initiation and progression of ALI and ARDS in the presence or absence of SIRS. We found significantly increased levels of plasma NE–AT in the patients with ARDS, especially when the definition of SIRS was met. Among ALI/ARDS groups, plasma NE–AT, but not e-XDP, correlated significantly with the decrease in PaO_2/FIO_2 ratio and the duration of ALI/ARDS. Furthermore, NE–AT, but not e-XDP, significantly increased in subgroups whose PaO_2/FIO_2 ratio decreased by more than 20%. Such correlations and differences between the subgroups were not observed in the non-ALI patients. From these results, we speculate that NE–AT, but not e-XDP, may be predictive of progressive lung injury in the early stage of ALI and ARDS.

Keywords: SIRS; ALI; ARDS

1. Introduction

Patients in a critical condition, especially those suffering from severe sepsis, are commonly associated with systemic inflammatory response syndrome (SIRS) [1]. These patients are at greater risk of developing multiple organ dysfunction syndrome (MODS), including acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), which is currently the major determinant of their prognosis [2]. However, there is only a small fraction of the available evidence for the treatments [3], such as early fluid resuscitation [4], tight glucose control [5], activated protein C [6] for severe sepsis and low tidal volume ventilation for ALI/ARDS [7]. There is therefore a clear need to accumulate further clinical evidence for sepsis and septic ALI/ARDS is being awaited.

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In SIRS and sepsis, various proinflammatory and anti-inflammatory cytokines are produced in large quantities, and this either directly or indirectly induces tissue injury and finally organ dysfunction [8]. Neutrophils are intensely activated by multiple stimuli, such as bacterial toxins and endogenous proinflammatory mediators, and play key roles in inducing tissue injury and the resulting organ dysfunctions through the release of various cytotoxic molecules, including reactive oxygen intermediates and granular enzymes. Among these, neutrophil elastase (NE), a serine proteinase, is thought to be one of the major cytotoxic molecules because of its abundance and powerful degrading activity against a wide variety of substrates [9]. In addition, NE has recently become known for its proinflammatory functions [10]. Since NE is harmful even to the host, there exist multiple defensive mechanisms to neutralize free NE. In blood, alpha-1 antitrypsin (AT) and alpha-2 macroglobulin are abundant, and intravascularly released NE is immediately neutralized. In contrast, although there exist NE inhibitors in the extravascular space, such as AT, secretory leukocyte protease inhibitor (SLPI) and elafin, the concentrations of these endogenous protease inhibitors of high molecular weight may be insufficient to adequately neutralize extravascularly released NE, especially when a large amount of NE is released in patients with SIRS and sepsis [11].

Neutrophils exist mostly within the circulation and either float in or are loosely attached to the peripheral vasculature under physiological conditions, but they easily migrate out of capillaries in response to various stimuli. NE can be released either intravascularly or extravascularly, but the place where NE is released is critical in the induction of tissue injury and organ dysfunction. However, thus far, there has been no method or marker to indicate where NE is released, and a plasma marker for extravascularly released NE is eagerly awaited as it would enable prediction of the degree of NE-induced tissue injury, especially in patients with SIRS. We hypothesized that plasma levels of elastase digests of cross-linked fibrin (e-XDP) correlate with the amount of extravascularly released NE, especially in the lungs, and thus may be useful in predicting the degree of lung injury. In the present study, we determined plasma levels of NE–AT complex and e-XDP in critically ill patients, and examined their significance in ALI and ARDS.

2. Methods

2.1. Study population

We conducted a single-center retrospective observational study at the university hospital of the School of Medicine, Keio University. The study population included 136 patients, who were admitted to our intensive care unit, followed up for more than 7 days, and whose blood was drawn on the day of admission. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. There were 94 men and 42 women (mean ± SEM age, 60.9 ± 1.4 years). Sixty-four had cardiovascular diseases, 32 had gastrointestinal diseases, 10 had respiratory diseases, seven had neurological diseases, and 23 had other diseases. Patients receiving postoperative care were included in each category. Based on the definition by the American–European consensus conference, all the patients were divided into the following three groups: (1) non-ALI: the PaO_2/FIO_2 ratio on the day of inclusion in the study was >300 or an apparent cause for hypoxia was identified; (2) mild ALI: $200 < PaO_2/FIO_2 \leq 300$ with bilateral infiltration on chest X-ray; and (3) ARDS: $PaO_2/FIO_2 \leq 200$ and bilateral infiltration on chest X-ray. One hundred twelve patients were categorized as non-ALI, 16 as mild ALI, and eight as ARDS. To analyze the outcome, the mild ALI and ARDS groups were combined because of the small patient numbers in these two groups. Plasma was used for the analysis of NE–AT and e-XDP. However, NE–AT and e-XDP in four and three patients were not determined because of insufficient sample volume, respectively.

The diagnosis of SIRS and sepsis was made based on the diagnostic criteria adopted by the combined committee of American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) [2]. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score and multiple organ dysfunction score (MODS) were determined on the day of inclusion in the study [12,13].

2.2. Determination of neutrophil elastase-related molecules

The NE–AT complex and elastase digests of e-XDP in plasma were determined with a latex agglutination method specific for each molecule [14,15]. The detection limits were 14.3 ng/ml for NE–AT and 0.1 U/ml for e-XDP.

2.3. Statistical analysis

We used the Mann–Whitney U test to compare two or three independent groups and the Kruskal–Wallis test to compare more than three groups. To examine the correlations between two parameters, Spearman's rank correlation was used. Statistical significance was accepted at $p < 0.05$.

3. Results

3.1. Patient characteristics

Of the 136 patients, 112 were placed in the non-ALI category, 16 in the ALI category, and eight in the ARDS category. Ninety-seven patients (71.3%) fulfilled the criteria of SIRS and 80 patients (58.8%) fulfilled the criteria of sepsis on the day of inclusion in the study. On the day of inclusion, the mean APACHE II score of the patients was 9.6 ± 0.5 (range 0–31), the mean SOFA score was 5.1 ± 0.3 (range 0–16), and the mean MODS score was 3.0 ± 0.3 (range 0–14). Mortality at discharge was 8.1%.

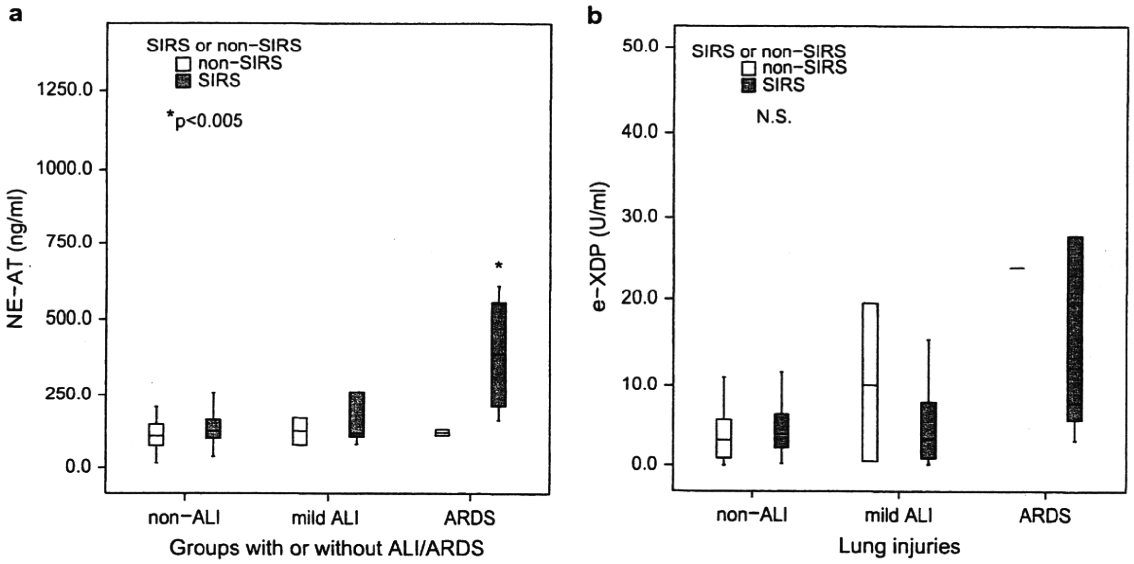

Fig. 1. Box plots showing median plasma levels of (a) NE–AT and (b) e-XDP in patients with or without SIRS in the non-ALI, mild ALI, and ARDS groups. Boxes show interquartile ranges and I bars represent highest and lowest values. *$p < 0.005$. NE–AT, neutrophil elastase–alpha-1 antitrypsin complex; e-XDP, elastase digests of cross-linked fibrin; and SIRS, systemic inflammatory response syndrome.

3.2. Plasma levels of NE–AT and e-XDP in non-ALI, mild ALI, and ARDS

Fig. 1a,b shows plasma NE–AT and e-XDP levels in the non-ALI, mild ALI, and ARDS groups with or without SIRS. NE–AT was detectable in all the patients, but e-XDP was undetectable in four patients. Among the three groups, plasma NE–AT and e-XDP levels were significantly higher in the ARDS group than in the non-ALI group ($p < 0.005$, $p < 0.05$, data not shown). When the presence of SIRS was considered, NE–AT levels were still significantly higher in the patients with SIRS and ARDS than in the SIRS and non-ALI groups (Fig. 1a). In contrast, there was no statistically significant difference in e-XDP levels among the groups (Fig. 1b). NE–AT levels were significantly higher in the patients with SIRS than in those without SIRS (115.0 ± 10.1 vs. 176.2 ± 17.7, $p < 0.05$), but there was no difference in e-XDP levels between the groups (5.3 ± 1.0 vs. 12.4 ± 3.3, $p = 0.15$). NE–AT levels were also significantly higher in septic patients than those in nonseptic patients (122.1 ± 8.2 *vs.* 210.7 ± 28.3, $p < 0.01$). Although there was a trend for higher e-XDP levels in sepsis, there was no statistically significant difference (5.4 ± 0.8 vs. 17.4 ± 5.6, $p = 0.06$). There was a weak correlation between NE–AT and e-XDP levels ($r = 0.178$, $p < 0.05$).

3.3. Correlations of NE–AT and e-XDP with clinical indices

We then divided patients into two subgroups with or without ALI/ARDS, namely non-ALI and ALI/ARDS groups, and examined the relationships of NE–AT and e-XDP with various clinical indices. In the ALI/ARDS group, plasma NE–AT levels significantly correlated with the decrease between the initial and lowest PaO_2/FIO_2 (P/F) ratio, and the duration of ALI/ARDS during hospital stay (Fig. 2a,b). When only patients with mild ALI were analyzed, the correlations with the decrease in P/F ratio and the duration of ALI/ARDS were still significant ($r = 0.40$, $p = 0.034$; $r = 0.43$, $p = 0.019$). In contrast, plasma e-XDP did not correlate with these parameters (Fig. 2c,d). NE–AT also correlated well with APACHE II, SOFA, and MODS scores on the first day in the ALI/ARDS group (Fig. 3a,b), but e-XDP did not (Fig. 3c,d). In the non-ALI group, neither NE–AT nor e-XDP correlated with any of the above parameters, except that a weak correlation was observed between NE–AT and the decrease in P/F ratio and SOFA score.

3.4. NE–AT and e-XDP for subsequent development of lung injury and fatal outcome at the 28th day

We next examined whether plasma NE–AT and e-XDP levels were predictive of patients' subsequent development of lung injury and fatal outcome at the 28th day in the patients with or without ALI and ARDS. In the ALI/ARDS group, plasma NE–AT levels were significantly higher in the subgroup with a decrease of more than 20% between the initial and lowest P/F ratios than in those with a decrease of equal to or less than 20% (Fig. 4a). In contrast, there was no difference in e-XDP level between the two subgroups (Fig. 4b). Similar results were observed when patients were divided into two subgroups with and without a decrease of more than 10% in the P/F ratio (data not shown).

We then examined plasma NE–AT and e-XDP levels and fatal outcome at the 28th day. There was a trend for a higher median NE–AT level in deceased patients than in alive patients, although the difference was not statistically significant

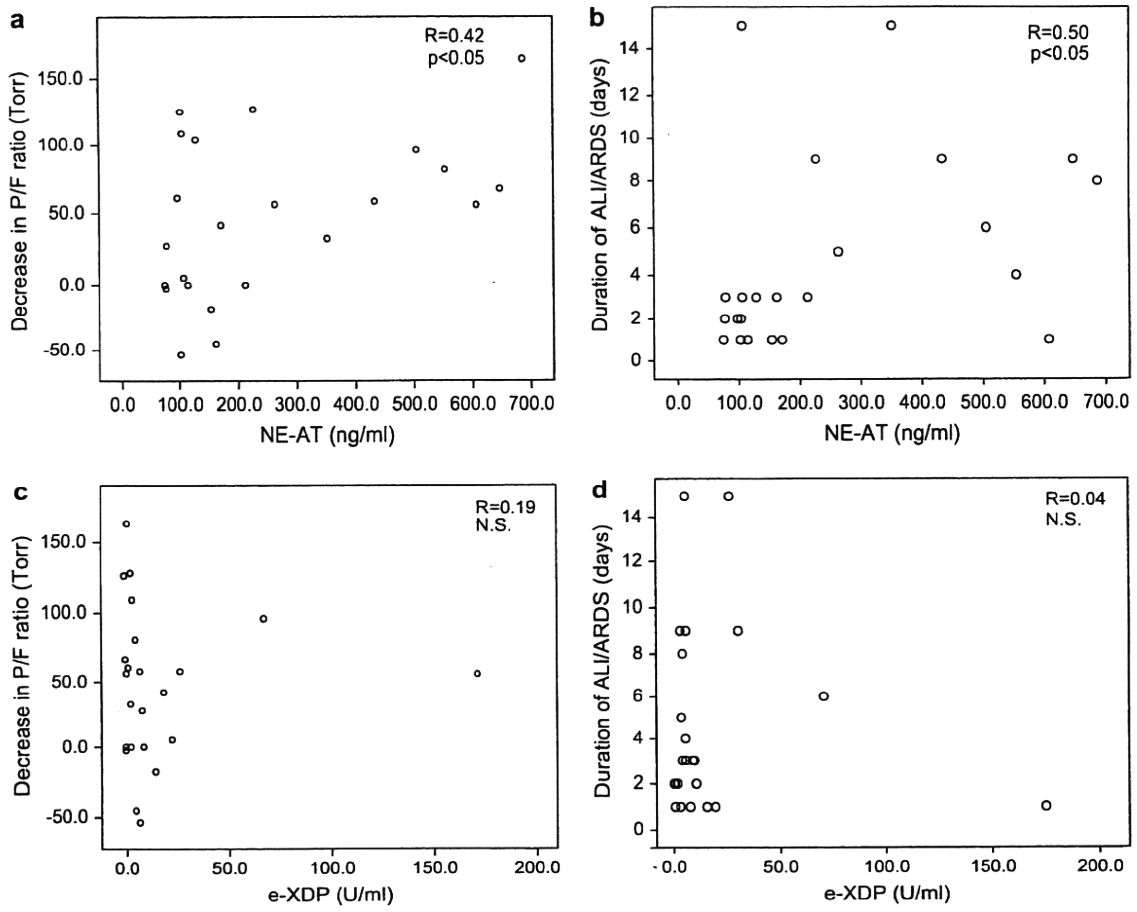

Fig. 2. Comparison of plasma NE–AT and e-XDP with the decrease in P/F ratio and duration of ALI/ARDS. (a) NE–AT *vs.* decrease in P/F ratio. (b) NE–AT *vs.* duration of ALI/ARDS. (c) e-XDP *vs.* decrease in P/F ratio. (d) e-XDP *vs.* duration of ALI/ARDS. NE–AT, neutrophil elastase–alpha-1 antitrypsin complex; e-XDP, elastase digests of cross-linked fibrin; and P/F ratio, PaO_2/FIO_2.

($p = 0.20$, data not shown). There was no difference in e-XDP between the two subgroups ($p = 0.44$, data not shown).

4. Discussion

In the present study, we examined plasma NE–AT and e-XDP levels in critically ill patients to elucidate the significance of NE in the initiation and progression of ALI and ARDS in the presence or absence of SIRS. We found significantly increased levels of plasma NE–AT in the patients with ARDS, especially when the definition of SIRS was met. Among the ALI/ARDS groups, the plasma NE–AT levels, but not the e-XDP levels, correlated significantly with the decrease between the initial and lowest P/F ratios and the duration of ALI/ARDS during the hospital stay. Furthermore, the levels of NE–AT, but not e-XDP, significantly increased in the subgroup with a decrease of more than 20% between the initial and lowest P/F ratios than in those with a decrease of equal to or less than 20%. In contrast, the above correlations and differences between the subgroups were not observed in the non-ALI patients. From these results, we speculated that NE–AT, but not e-XDP, may be predictive of progressive respiratory failure in the early stage of ALI and ARDS. In addition, the combined criteria of ALI/ARDS and SIRS may be useful for predicting neutrophil activation *in vivo*, and thus applicable for selecting the target for an anti-neutrophil strategy in critically ill patients.

High levels of plasma NE–AT have been reported previously. Rocker et al. examined plasma NE–AT in 50 patients with respiratory failure and showed that higher levels of NE–AT occurred in pre-ARDS and ARDS, as diagnosed by Petty's definition [15]. Moreover, they found that NE–AT was significantly correlated with the P/F ratio, BAL protein, and differential neutrophil counts. Donnelly et al. prospectively examined plasma NE–AT levels in patients with multiple trauma and found that NE–AT increased in patients who developed ARDS as defined by Murray's expanded definition [16]. In the present study, we examined critically ill patients with various etiologies and classified them into non-ALI, mild ALI, and ARDS with or without SIRS, following the definition by the American–European consensus conference. We found that plasma NE–AT increased in patients who fulfilled the criteria of SIRS and ARDS. Furthermore, NE–AT was predictive of progressive lung injury among patients with ALI and ARDS. Our results support the idea that NE makes a significant contribution to the initiation and development of ALI and ARDS during the early phase of critical illness, especially when SIRS is complicated.

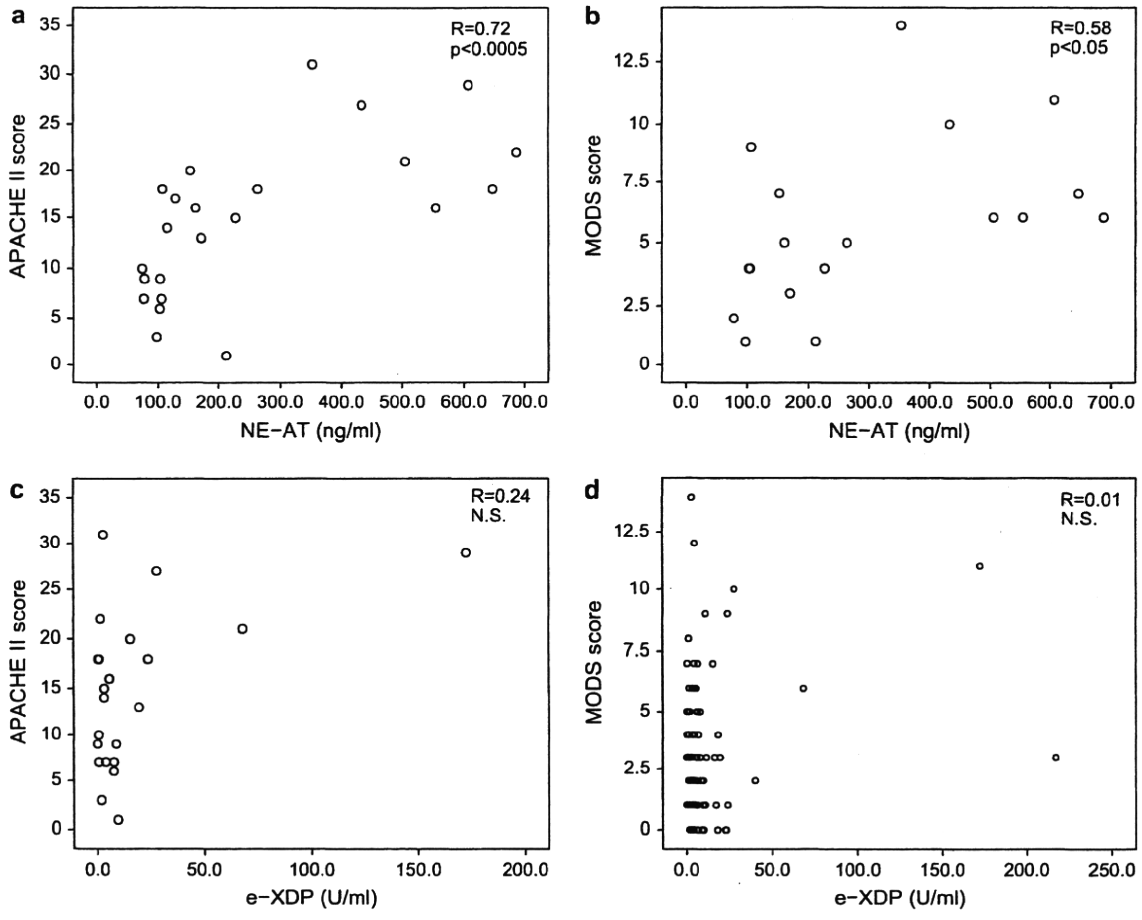

Fig. 3. Comparison of plasma NE–AT and e-XDP with the decrease in P/F ratio and duration of ALI/ARDS. (a) NE–AT *vs.* APACHE II score. (b) NE–AT *vs.* MODS score. (c) e-XDP *vs.* APACHE II score. (d) e-XDP *vs.* MODS score. NE–AT, neutrophil elastase–alpha-1 antitrypsin complex; e-XDP, elastase digests of cross-linked fibrin; APACHE II, acute physiology and chronic health evaluation; and MODS, multiple organ dysfunction score.

NE is a potent serine proteinase and could harm vital organs and tissues in addition to killing of invading microorganisms. Acting as protection against the harmful effects of NE, there are several endogenous NE inhibitors, including AT, in the circulation and they can neutralize NE soon after NE is released. In contrast, in SIRS and sepsis, neutrophils are activated, migrate out from the vasculature, firmly attach to lung endothelial and epithelial cells, and can directly injure them by releasing NE to the neutrophil–stromal cell interface, where no or only a very low concentration of natural NE inhibitors exist. In the present study, we expected that the amount of e-XDP produced would correlate with that of NE released

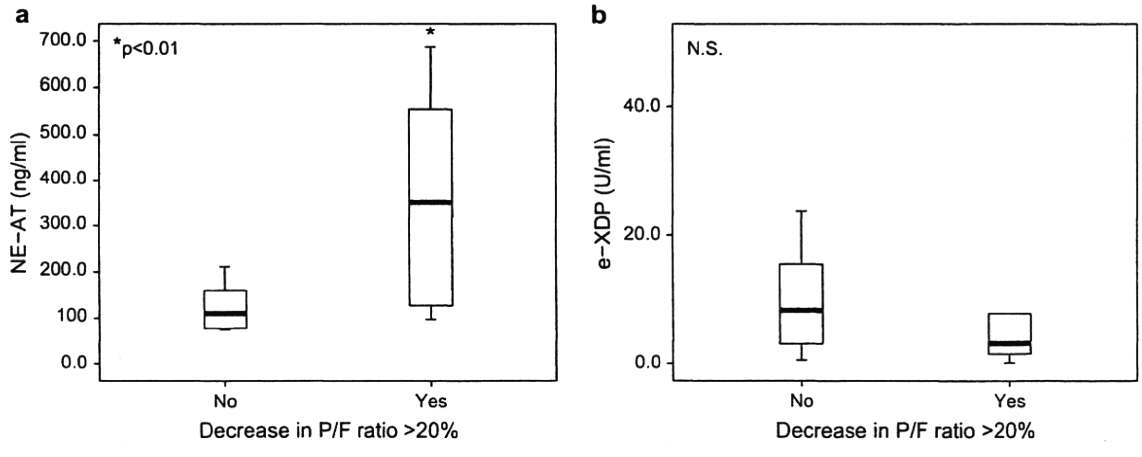

Fig. 4. Box plots showing median plasma levels of (a) NE–AT and (b) e-XDP in two groups of patients, one with a decrease of more than 20% in P/F ratio and another group with a decrease of equal to or less than 20%. Boxes show interquartile ranges and I bars represent highest and lowest values. $*p < 0.01$. NE–AT, neutrophil elastase–alpha-1 antitrypsin complex; e-XDP, elastase digests of cross-linked fibrin; and P/F ratio, PaO_2/FIO_2.