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Systemic Inflammation and Delirium in the Peri-extubation Period of Mechanical Ventilation: an Observational Prospective Study of Intensive Care Unit Patients

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Abstract **Background:** Delirium is a common problem in intensive care units (ICUs) and is associated with poor outcomes. The association between inflammation and delirium in the peri-extubation period of mechanical ventilation (MV) is poorly understood.
Methods: We conducted a prospective, observational study of adult patients on MV for >48 hours in an ICU. At extubation (0 h) and 24 h later, the Confusion Assessment Method for the ICU (CAM-ICU) and the following serum biomarkers were assessed: C-reactive protein (CRP), procalcitonin, white blood cell (WBC) count, interleukin (IL) -6 and -8. Patients were classified into delirious (D; at least one positive CAM-ICU) and nondelirious (N; negative CAM-ICU at both times) groups.
Results: Of the 28 enrolled patients, 12 were in group D, and 16 were in group N. Patient characteristics were not different except for the Acute Physiology and Chronic Health Evaluation Ⅱ score and Sequential Organ Failure Assessment score at 0 h. At 24 h, procalcitonin and IL-6 levels were higher in group D. During the 24-h period, CRP, IL-6, and IL-8 levels decreased in group N, and WBC count increased in group D.
Conclusions: The results indicate an association between prolonged inflammation and delirium in the peri-extubation period of MV.

Key words: delirium, mechanical ventilation, Confusion Assessment Method for the Intensive Care Unit, inflammation, C-reactive protein

Introduction

Delirium is an acute type of cerebral dysfunction associated with fluctuations in the patient's mental status and disturbed consciousness or cognition[1]. Delirium is now accepted as a common and clinically significant problem in critically ill patients being treated in intensive care units (ICUs). The introduction of the Confusion Assessment Method for the ICU (CAM-ICU)[2] and Intensive Care Delirium Screening Checklist[3] in the 2000s has revealed a high prevalence of delirium in critically ill patients. Delirium is associated with a number of complications or poor outcomes, including increased mortality[4-6],

prolonged ICU[4,7,8] or hospital stay[7-9], and long-term cognitive impairment[9,10].

Numerous studies have tried to elucidate the risk and predictors of delirium, but the results vary depending on the study location, design, patient characteristics, and the outcome assessment[11]. In both ICU and non-ICU settings, several studies have revealed that systemic inflammation is a potential risk factor for the development of delirium[12-20]. These studies focused on the serum levels of inflammatory biomarkers, including C-reactive protein (CRP)[12,13], interleukin-6 (IL-6)[14-18], IL-8[15,19], and procalcitonin[20], and revealed that these biomarkers are associated with the development of delirium.

Several studies have shown that delirium affects up to 60-80% of mechanically ventilated patients in ICUs[8,21,22]. We previously reported that the prevalence of delirium in ICU patients was 20%, and that it was 80% in mechanically ventilated patients[12]. In that observational study, the use of a mechanical ventilator, the maximum serum CRP level during the ICU stay, and the length of the ICU stay were independently associated with the development of delirium in ICU patients[12]. However, very few studies have investigated the association between inflammation and the development of delirium in mechanically ventilated patients[20,23], and the blood sampling time-points were defined without taking the patients' conditions into consideration.

Therefore, the aim of this prospective observational study was to examine the putative association between inflammation and the development of delirium in mechanically ventilated patients in an ICU. We chose a unique approach for this study by using two time points in the peri-extubation period to compare the clinical features of patients with or without delirium. The peri-extubation period was chosen because extubation is a common procedure for all mechanically ventilated patients, and it is performed at a time when relatively fewer sedatives are used in patients with stable respiratory and circulatory conditions. Additionally, the two-point assessment was used to observe the time-course of inflammation, and to avoid missing delirium, a fluctuating condition, in many patients.

Methods

Setting and patients

We conducted a prospective, observational study in the 20-bed ICU at the Advanced Medical Emergency and Critical Care Center, an academic and tertiary emergency center at Yamaguchi University Hospital, from July 2010 to December 2011. The protocol of this study was approved by the Institutional Review Board of Yamaguchi University Hospital (approval number H16-137). Patients were eligible if they were ≥20 years old and had received invasive mechanical ventilation for >48 h. The exclusion criteria, defined *a priori*, were: (a) expected persistent disturbed consciousness (i.e., anoxic encephalopathy, brain stem hemorrhage, or head trauma); (b) neurological or neurosurgical disease; (c) mechanical ventilation required for >28 days; (d) a "do not resuscitate" order; (e) history of chronic dementia, psychosis, mental retardation, or neuromuscular disease; (f) visual or hearing disturbances; and (g) difficulty in understanding the Japanese language. Before the extubation, consent documents were obtained from the patients or from their surrogates if the patients were unable to give their consent.

Study design and data collection

Figure 1 shows the design of the study. We set two time points for delirium assessment and blood sampling: at extubation (defined as 0 h), and at 24 h after extubation (defined as 24 h). We selected 24 h after extubation as a time-point because, in our routine clinical practice, blood sampling and laboratory tests are performed on a daily basis.

Upon enrollment, the demographic data, clinical diagnosis, and Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ score were recorded for each patient. The APACHE Ⅱ score provides a classification of the severity of disease. It is calculated from the scores for 12 routine physiologic measurements made during the first 24 h after ICU admission, the patient's age, and the scores for chronic diseases[24]. Patients were followed throughout their ICU stay, and their physiological variables, all administered medications, the results of routine daily

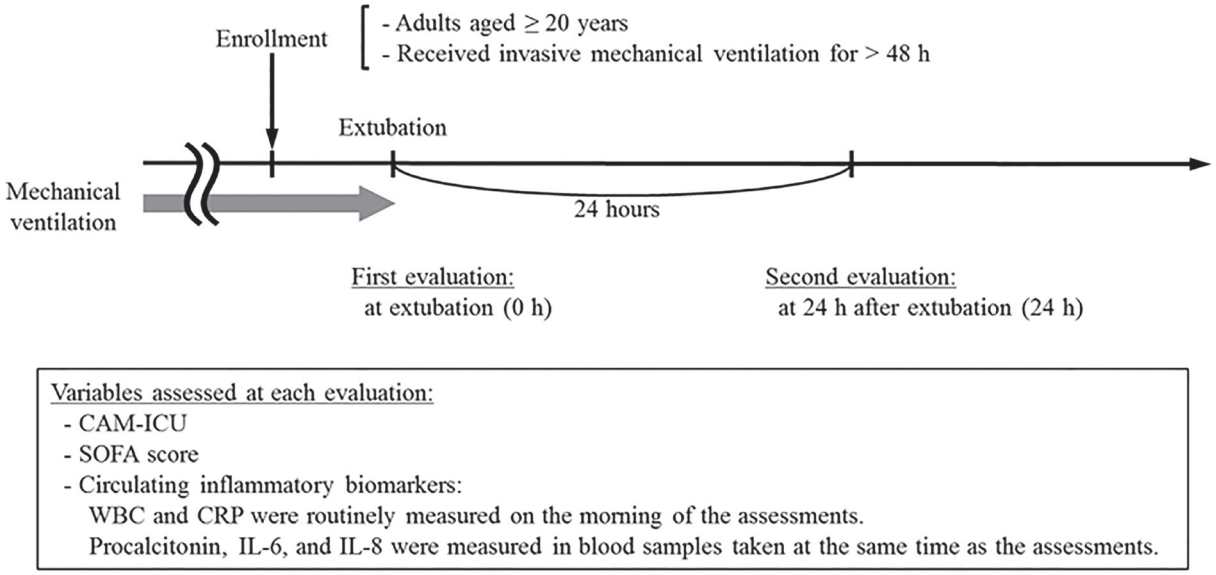

Figure 1 Patient eligibility and summary of the study protocol.
CAM-ICU Confusion Assessment Method for the Intensive Care Unit, *SOFA* Sequential Organ Failure Assessment, WBC white blood cell, *CRP* C-reactive protein, *IL* interleukin.

laboratory tests, the period of mechanical ventilation, and the length of ICU stay were recorded.

The presence of delirium was assessed using the CAM-ICU (officially translated Japanese version[25]) each time by the same intensivist, who is well trained in performing assessments with this tool. The CAM-ICU, Sequential Organ Failure Assessment (SOFA) score[26], and vital signs were assessed at 0 h and at 24 h. The CAM-ICU is a well-validated and reliable tool for monitoring delirium in ICU patients[1], and is designed to detect the presence of clinical features of delirium using nonverbal, objective tests[2]. The SOFA score is a well-validated and reliable scoring system for assessing organ dysfunction. It is composed of scores for six organ systems determined by physiological variables, results of laboratory tests, or the doses of inotropic agents[26].

The target sedation depth and the doses of sedatives or analgesic agents during mechanical ventilation were managed by intensivists at our ICU. The target sedation depth is stated in terms of the Richmond Agitation-Sedation Scale (RASS)[27] at the start of sedation. The sedative agents were selected after considering their pharmacological characteristics to avoid physiological stress responses and prolonged sedation. The bolus administration of sedatives was allowed at the discretion of the intensivists on duty.

Definition of the patient groups

The patients were divided into two groups according to the results of the CAM-ICU assessments at the two time points. Patients whose CAM-ICU was positive at least once at 0 h and/or at 24 h were classified as group D, and those whose CAM-ICU was negative at both times were classified as group N.

Measurement of inflammatory biomarkers

Serum samples were obtained at 0 and 24 h, and were stored at −80 °C until later assay. The serum IL-6, IL-8, and procalcitonin levels were measured using a chemiluminescent enzyme immunoassay (Human IL-6 CLEIA Fujirebio; Fujirebio Inc., Tokyo, Japan), an enzyme-amplified sensitivity immunoassay (IL-8 EASIA; Life Technologies, Carlsbad, CA, USA), and an electrochemiluminescence immunoassay (ECLusys BRAHMS PCT; Roche Diagnostics, Basel, Switzerland), respectively. The white blood cell (WBC) counts and CRP levels were also measured at our hospital laboratory as a part of routine clini-

cal practice using samples obtained in the mornings of the days on which CAM-ICU were assessed at 0 and 24 h.

Data analysis and statistics

All data were analyzed using the SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA). Results are presented as medians (interquartile ranges) for continuous variables, and as the number of cases (percentage) for categorical variables. Mann-Whitney *U* test, Fisher's exact test, or Pearson's χ^2 test were performed, as appropriate, to detect differences between the two groups. The changes in variables from 0 to 24 h were assessed using Wilcoxon's signed-rank test. Values of $P<0.05$ were considered statistically significant.

Results

Patient characteristics and medications (Table 1)

Twenty-eight patients were enrolled in the study. Group D and group N comprised 12 (42.9%) and 16 patients, respectively. In group D, 11 patients were positive for CAM-ICU at 0 h and 6 patients were positive at 24 h. Five patients in group D were positive for CAM-ICU at both times. There were no statistically significant differences in background characteristics in terms of age, gender, or body weight. The diagnoses at admission were similar between the two groups. The APACHE Ⅱ score and the SOFA score at 0 h were significantly higher in group D than in group N. The length of mechanical ventilation was not significantly different. The lengths of ICU or hospital stay and the in-hospital mortality rates were also similar in both groups. The use of midazolam, dexmedetomidine, and fentanyl was significantly greater in group D than in group N. Similar proportions of patients received propofol in both groups.

Table 1 Patient characteristics and medications used in each group

Variable	Group N (n = 16)	Group D (n = 12)	P value
Age (years)	63 (45-73)	69 (60-75)	0.22
Male, *n* (%)	9 (56)	7 (58)	0.91
Body weight (kg)	59.5 (53.0-68.0)	58.5 (51.3-68.5)	0.98
Diagnosis at admission, *n* (%)			1.00
Upper respiratory tract infection	10 (63)	3 (25)	
Cardiovascular disease	3 (19)	3 (25)	
Burn	2 (13)	2 (17)	
Sepsis	0 (0)	2 (17)	
Other	1 (6)	2 (17)	
APACHE Ⅱ score	10 (7-15)	19 (12-24)	0.02
SOFA score at extubation	2 (0-3)	5 (2-8)	0.02
Length of mechanical ventilation (days)	7 (5-9)	9 (6－12)	0.14
Length of ICU stay (days)	9 (7-26)	20 (9-30)	0.20
Length of hospital stay (days)	21.50 (10.75-55.50)	42.50 (14.75-94.25)	0.25
Hospital mortality, *n* (%)	0 (0)	1 (8)	1.00
Medication			
Sedatives, *n* (%)			
Midazolam	6 (38)	10 (83)	0.02
Propofol	14 (88)	9 (75)	0.62
Dexmedetomidine	1 (6)	7 (58)	0.04
Fentanyl, *n* (%)	6 (38)	10 (83)	0.02

Values presented are medians (interquartile ranges), unless otherwise stated.
Group N nondelirious patient group, *Group D* delirious patient group, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit

Inflammatory biomarkers (Table 2, Figure 2)

The serum levels of procalcitonin and IL-6 were significantly higher in group D than in group N at 24 h, but not at 0 h. For group N vs group D, procalcitonin values at 0 h and at 24 h were 0.04 (0.02-0.38) vs 0.16 (0.06-1.42), respectively (P = 0.06), and 0.04 (0.02-0.27) vs 0.19 (0.07-0.88), respectively (P = 0.04). The

Table 2 Comparison of inflammatory biomarkers in the nondelirium and delirium groups

	Time (h)	Group N (n = 16)	Group D (n = 12)	P value
CRP (mg/dl)	0	1.96 (0.91-10.34)	3.61 (2.01-8.55)	0.38
	24	1.40 (0.40-10.10)	3.96 (1.84-7.96)	0.15
Procalcitonin (ng/ml)	0	0.04 (0.02-0.38)	0.16 (0.06-1.42)	0.06
	24	0.04 (0.02-0.27)	0.19 (0.07-0.88)	0.04
WBC count (/μl)	0	9,350 (7,095-10,453)	8,020 (7,208-10,995)	0.38
	24	8,880 (7,250-11,680)	10,915 (8,190-14,580)	0.31
IL-6 (pg/ml)	0	8.25 (4.80-69.30)	17.35 (9.43-68.23)	0.50
	24	5.75 (3.43-24.63)	31.45 (7.98-69.23)	0.03
IL-8 (pg/ml)	0	5.15 (2.00-41.83)	3.90 (2.00-43.15)	0.88
	24	2.00 (2.00-18.35)	12.00 (2.00-43.83)	0.06

Values are presented as medians (interquartile ranges)
Group N nondelirious patient group, *Group D* delirious patient group, *CRP* C-reactive protein, *WBC* white blood cell, *IL* interleukin

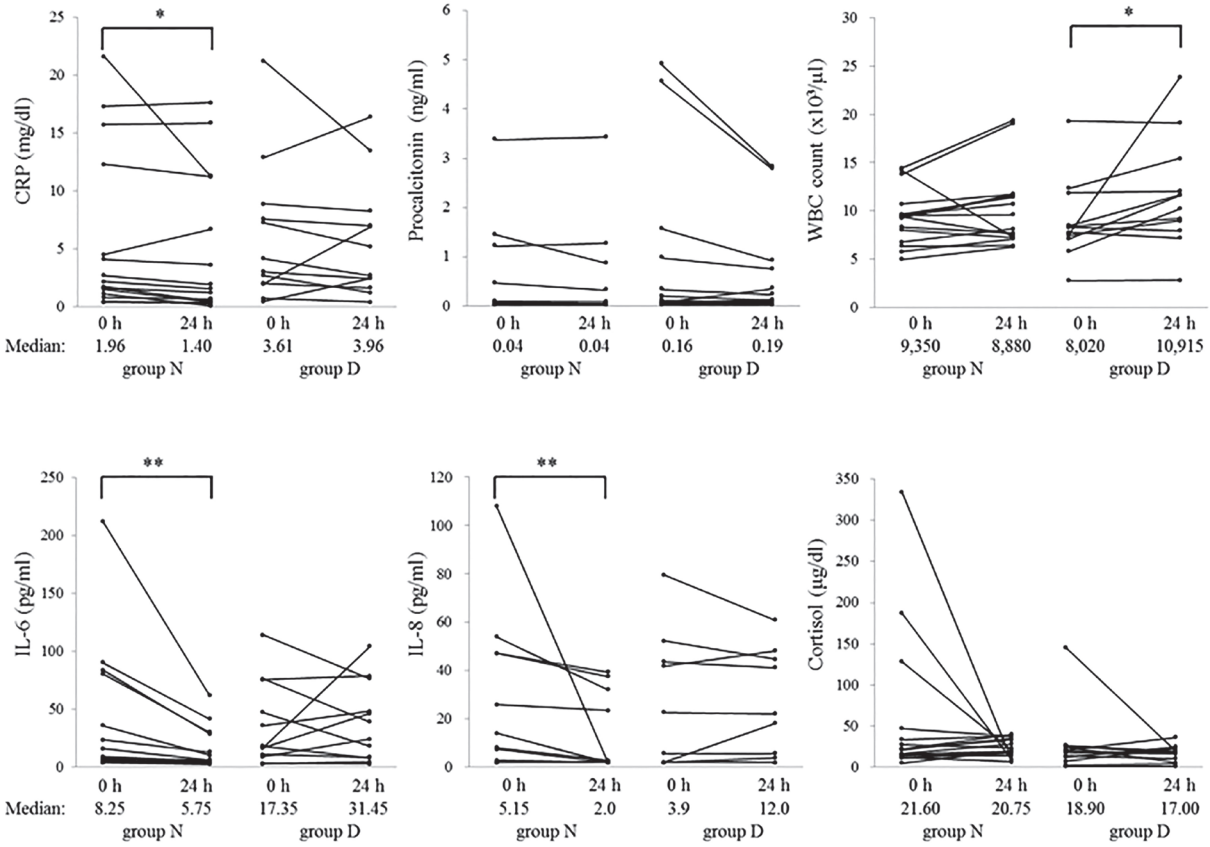

Figure 2 Changes in inflammatory biomarkers from 0 h to 24 h after extubation in each group.
Group N nondelirious patient group, *Group D* delirious patient group
* P<0.05, ** P<0.01, *CRP* C-reactive protein, *WBC* white blood cell, *IL* interleukin.

IL-6 values at 0 h and at 24 h were 8.25 (4.80-69.30) vs 17.35 (9.43-68.23), respectively (P = 0.50), and 5.75 (3.43-24.63) vs 31.45 (7.98-69.23), respectively (P = 0.03). CRP, WBC counts, and IL-8 levels were not significantly different between the two groups at either time.

The changes in inflammatory biomarkers from 0 to 24 h are shown in Figure 2. CRP, IL-6, and IL-8 levels decreased significantly from 0 to 24 h in group N (CRP, P = 0.03; IL-6, P<0.01; IL-8, P<0.01). By contrast, only the WBC counts increased significantly in group D (P = 0.03). None of the other biomarkers changed significantly between 0 and 24 h in either group.

Discussion

This prospective observational study explored the putative association between inflammatory biomarkers and the development of delirium during 24 h after extubation in mechanically ventilated patients treated in an ICU. The two-point assessment enabled us to evaluate the changes in inflammatory biomarkers and to improve the detection rate of delirium. Delirium was observed in 42.9% of the patients. Although the APACHE Ⅱ score and the SOFA score at 0 h were significantly higher in group D than in group N, the lengths of mechanical ventilation and ICU stay, and the in-hospital mortality rates were similar in both groups. At 24 h after extubation, the procalcitonin and IL-6 levels were significantly higher in group D than in group N. There were significant decreases in the CRP, IL-6, and IL-8 levels from 0 to 24 h after extubation in group N, but none of these three biomarkers changed significantly in group D. By contrast, of all the variables assessed, only the WBC counts in group D increased significantly from 0 to 24 h. Overall, these findings suggested an association between inflammatory biomarkers and development of delirium in mechanically ventilated patients treated in an ICU.

It has been suggested that systemic inflammation is associated with the development of delirium[28]. IL-6 and IL-8 are major proinflammatory cytokines, of which levels increase in the early phase of systemic inflammation, reaching peak levels at 4-6 h after the initial insult[29]. CRP and procalcitonin are also biomarkers of inflammation or infection. Procalcitonin can be detected at only 4 h after the initial insult and its levels peak at 8-24 h[30]. CRP secretion also begins within 4-6 h of the insult, and peaks at 36-50 h[31]. Although procalcitonin is primarily regarded as a biomarker of bacterial infection[32], the procalcitonin level has also been reported to rise in inflammatory conditions in the absence of infection[33-36]. Our results suggest that the inflammatory condition was resolving in nondelirious patients, but was prolonged in delirious patients. The higher APACHE Ⅱ score on admission and SOFA score at extubation in group D represent more severe disease on admission and more severe organ dysfunction at extubation, and these factors probably contributed to the prolonged inflammatory state. Although the cause and effect relationship between disease severity or organ dysfunction, inflammation and the development of delirium is unclear in this study, future studies should evaluate whether extubation after improvements in inflammation or organ dysfunction decreases the incidence of the delirium.

The peri-extubation period was selected as a reference point in this study, and we evaluated patient delirium and measured biomarkers twice in this period. This design was used for the following four reasons. First, for necessity, the respiratory and circulatory conditions of all of the patients were sufficiently stable during this period to enable successful extubation (in fact, only one patient in group N required re-intubation), and the depth of sedation was likely to be minimal. We considered that this design would reduce the influence of factors other than inflammation, such as sedatives and the severity of the primary disease, that might be linked to the development of delirium. Second, this approach addresses the important issue of the timing of blood sampling from nondelirious patients, which was not resolved in previous studies[14,19,20]. Those studies also investigated the association between delirium and inflammatory biomarkers in ICU patients. However, the timing of blood sampling from nondelirious patients differed in these earlier studies because it was impossible to define

a specific time point in their clinical course in relation to the presence of delirium. It is unclear which of these studies used the most appropriate design to allow fair comparisons between delirious and nondelirious patients. Compared with these earlier studies, the timing of blood sampling of our study is well-defined and considered the patients' pathological and clinical conditions. Third, the design of our study and the measurement of biomarkers at the time of extubation and 24 h later enabled us to assess whether inflammation improved or worsened after extubation. Because the biomarkers were only assessed once in the earlier studies, there was no record of their changes over time; this factor was acknowledged as a limitation in these earlier studies[14,19,20]. The fourth reason for our design was that the sensitivity of detecting delirium might be improved by repetitive assessment of the CAM-ICU. Delirium can fluctuate quickly, and it may be missed if it is only assessed once. Therefore, the design of this study allowed us to assess the relationships between delirium and the changes in inflammatory biomarkers over time in the two groups of patients under stable clinical conditions.

There were some limitations to this study. First, it was a single-institution observational study involving a small number of patients. Second, there was substantial heterogeneity in the underlying diseases. Nevertheless, inflammation is a nonspecific process associated with most illnesses. The aim of the study was to investigate the association between this nonspecific process and the development of delirium. Therefore, the heterogeneity of the underlying diseases might be an advantage in terms of fulfilling the aim of this study. A multicenter study of a larger number of patients, with heterogeneity in the underlying diseases, may provide more generalized, reliable evidence. Third, the prevalence of delirium during the entire ICU stay was not evaluated in this study. We only assessed the prevalence of delirium for 24 h after extubation. Therefore, we cannot compare the prevalence of delirium in this population with the prevalence reported in earlier studies.

Finally, as the fourth limitations, we cannot exclude the possibility that the use of sedatives and opioids might influence our results. Earlier studies have investigated sedatives and opioids as potential risk factors for delirium. Although a definitive con clusion has not been reached, propofol and dexmedetomidine are generally thought to have more favorable effects than benzodiazepines in terms of reducing the prevalence of delirium 1. In the present study, the proportions of patients who were administered midazolam, dexmedetomidine, and fentanyl were significantly different between the two study groups. However, this study was not designed to evaluate the effects of these agents on the development of delirium, and we cannot exclude the possibility of such effects. Additionally, it remains unclear whether these agents could modulate inflammation.

Conclusions

The results of our study suggest that prolonged systemic inflammation is associated with the delirium observed in the peri-extubation period of mechanical ventilation in ICU patients. Future studies should examine whether extubation after the improvement of inflammation or organ dysfunction decreases the incidence of delirium.

Acknowledgments

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Conflict of interest

The authors state no conflict of interest.

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