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# Association between Serum Lactate Levels and Early Neurogenic Pulmonary Edema after Nontraumatic Subarachnoid Hemorrhage

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**Abstract**

**Background and Purpose:** Few studies have described the risk factors associated with the development of neurological pulmonary edema (NPE) after subarachnoid hemorrhage (SAH). We have hypothesized that acute-phase increases in serum lactate levels are associated with the early development of NPE following SAH. The aim of this study was to clarify the association between lactic acidosis and NPE in patients with nontraumatic SAH.

**Methods:** We retrospectively evaluated 140 patients with nontraumatic SAH who were directly transported to the Nippon Medical School Hospital emergency room by the emergency medical services. We compared patients in whom NPE developed (NPE group) and those in whom it did not (non-NPE group).

**Results:** The median (quartiles 1–3) arrival time at the hospital was 32 minutes (28–38 minutes) after the emergency call was received. Although the characteristics of the NPE and non-NPE groups, including mean arterial pressure (121.3 [109.0–144.5] and 124.6 [108.7–142.6] mm Hg, respectively; P=0.96), were similar, the median pH and the bicarbonate ion ($HCO_3^-$) concentrations were significantly lower in the NPE group than in the non-NPE group (pH, 7.33 [7.28–7.37] vs. 7.39 [7.35–7.43]); P=0.002; $HCO_3^-$, 20.8 [18.6–22.6] vs. 22.8 [20.9–24.7] mmol/L; P=0.01). The lactate concentration was significantly higher in the NPE group (54.0 [40.3–61.0] mg/dL) than in the non-NPE group (28.0 [17.0–37.5] mg/dL; P<0.001). Multivariable regression analysis indicated that younger age and higher glucose and lactate levels were significantly associated with the early onset of NPE in patients with SAH.

**Conclusion:** The present findings indicate that an increased serum lactate level, occurring within 1 hour of the ictus, is an independent factor associated with the early onset of NPE. Multicenter prospective studies are required to confirm our results.
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**Key words:** early neurogenic pulmonary edema, emergency room, lactic acidosis, subarachnoid hemorrhage

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## Introduction

Subarachnoid hemorrhage (SAH) is a common and frequently devastating condition associated with a high rates of morbidity and mortality[1,2]. Neurogenic pulmonary edema (NPE) is a severe complication of SAH that occurs in 10% to 40% of patients after ictus[3–7] and contributes to unfavorable outcomes[8]. NPE can produce severe hypoxemia, thus contributing to cerebral hypoxia and increasing the risk of secondary injury[9]. Two distinct clinical forms of NPE, early and late, have been described[10,11]. The early form is characterized by the development of symptoms within minutes or hours following neurologic injury; the delayed form develops approximately 72 hours after the injury[10,11]. Although both types of NPE are clinically important, prediction of early NPE may be more important because most of the time-dependent emergency procedures, such as coiling or clipping to prevent rebleeding, should be started within 3 days after the ictus[12].

Although possible pathophysiological mechanisms (e.g., an increase in the pulmonary capillary hydrostatic pressure and an increase in pulmonary capillary permeability[10,13]) have been proposed for NPE, the actual mechanism has not been established. In addition, few clinical studies have described the risk factors, or their predictive value, associated with the early form of NPE after SAH[10].

Several studies have suggested that lactate levels increase during physiologically deranging conditions, such as sepsis and post-cardiac arrest syndrome[14–16]. Recent studies have suggested that the development of metabolic acidosis within 24 hours of hospital admission is associated with poor prognosis in patients with SAH and has resulted in the creation of a new SAH physiologic derangement score[17]. A study by Mayer et al.[18] has found that transient lactic acidosis is common and seems to be a risk factor for NPE after SAH. However, that study was a case series that included only 5 patients and did not discriminate between the 2 forms of NPE, thus limiting the interpretation of the results. To our knowledge, limited evidence is available to clarify the robust relationship between lactate levels and the development of the early form of NPE following SAH.

We have hypothesized that acute-phase increases in lactate levels are associated with the early development of NPE after SAH. Therefore, the aim of the present study was to clarify the association between lactic acidosis and NPE in patients with nontraumatic SAH.

## Materials and Methods

The subjects of this retrospective study were patients treated in the emergency room (ER) and mixed intensive care unit of Nippon Medical School Hospital, a tertiary-care emergency center in Tokyo, Japan. This study was approved by the Ethics Committee of Nippon Medical School Hospital.

### Patients

We performed a records review to determine the eligibility of 244 consecutive patients with SAH admitted from January 1, 2008, through August 31, 2013. Patients transported directly to the ER by the emergency medical service (EMS) were included, regardless of disease severity. The exclusion criteria were age <15 years; prehospital cardiopulmonary arrest or cardiopulmonary arrest or both upon arrival; history of heart disease, pulmonary disease, or previously identified chest radiograph abnormality[3]; presence of chronic, organic brain disease; and transfer from other hospitals.

### Diagnosis and Definition

Upon admission, diagnoses of SAH were confirmed by board-certified neurosurgeons on the basis of computed tomography scans. The responsible lesions were confirmed with either computed tomographic angiography or digital subtraction angiography. The present study focused on the early form of NPE, in which symptoms develop within minutes to hours following the ictus[10,11]. We evaluated initial chest radiographs and arterial blood gas levels, obtained in the ER before surgery. To objectively and quantitatively define NPE in the present study, we used the definition of

acute respiratory disease syndrome used in previous studies[19–21]. Therefore, NPE was defined as having an acute onset, with a confirmed diagnosis of SAH (known clinical insult)[20]; bilateral, diffuse, alveolar infiltrates in the chest radiograph (not fully explained by lobar/lung collapse, aspiration pneumonia, or nodules) on arrival[20]; and respiratory failure not fully explained by cardiac failure or fluid overload, with an oxygen partial pressure/fraction of inspired oxygen ratio ($PaO_2/FiO_2$)<300 mm Hg, regardless of the positive end-expiratory pressure level[7,19,20]. The $FiO_2$ for patients not receiving mechanical ventilation was estimated with reference to the Japanese Respiratory Society guidelines for oxygen therapy (i.e., 6 L/min with an oxygen reservoir mask, estimated $FiO_2$=0.6; 8 L/min, $FiO_2$=0.8; 10 L/min, $FiO_2$>0.9)[22,23]. All chest radiographic findings were reviewed by a pulmonologist. All patient outcomes were evaluated with the Glasgow Outcome Scale on the day of discharge and were classified as good recovery, moderate disability, severe disability, persistent vegetative state, or death[24].

**Measurements and Treatment**

The times of emergency calls received by the EMS and of the patients' arrival at the hospital were provided by the EMS personnel. We regarded the time of the emergency call as the time symptoms began. In Tokyo, EMS personnel directly transport patients with acute-onset, severe distress to the nearest tertiary care ER. Japanese EMS personnel are allowed to provide oxygen according to the patient's oxygenation status (i.e., oxygen saturation measured with a pulse oximeter) but are not allowed to administer any drip infusions, except to patients in cardiopulmonary arrest[25]. As soon as a patient arrived at the ER, arterial blood gas measurements and chest radiographs were obtained, and additional blood samples were collected. Therefore, these variables were not affected by the administration of any fluids. Immediately after SAH was diagnosed, intensive care was performed according to our department's standardized protocol, which is based on the current guidelines[1,12,26]. Initial management included prompt cardiopulmonary support, early management of SAH, maintenance of the normal circulating blood volume, and treatment of acute hydrocephalus with external ventricular drainage[26]. Surgical aneurysmal clipping or intravascular coil embolization was performed within 3 days.

**Statistical Analysis**

Because the data were not expected to be normally distributed owing to the small number of patients, nonparametric analyses were used. Data are presented as medians (quartiles 1–3). Patients were divided into 2 groups: those with NPE (NPE group) and those without (non-NPE group). The groups were compared by means of the Mann-Whitney *U*-test, and categorical comparisons were made by means of Fisher's exact test or a $\chi^2$ test. Multivariable logistic regression analysis was performed to control for potentially confounding variables associated with NPE, including age; sex; SAH severity (i.e., World Federation of Neurological Surgeons grade); body temperature; mean arterial pressure; and levels of glucose, aspartate aminotransferase (AST), and lactate[10,12,17,18]. Statistical analyses were performed with the software package IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY, USA); a P-value<0.05 was considered statistically significant.

## Results

The records of 244 consecutive patients with SAH were reviewed (**Fig. 1**); patients were excluded because they had been transferred from other hospitals (55 patients) or from our emergency outpatient clinic (7 patients), had SAH that developed in-hospital (18 patients), or were missing chest radiographs (3 patients) or medical records (1 patient). Also excluded were 17 patients with a history of heart disease, 2 patients with cardiopulmonary arrest, and 1 patient with meningioma. The records of the remaining 140 patients were analyzed.

The median time from the receipt of the emergency call to the patient's arrival at the hospital was 32 minutes (28–38 minutes). Significant differences were not observed between the NPE and

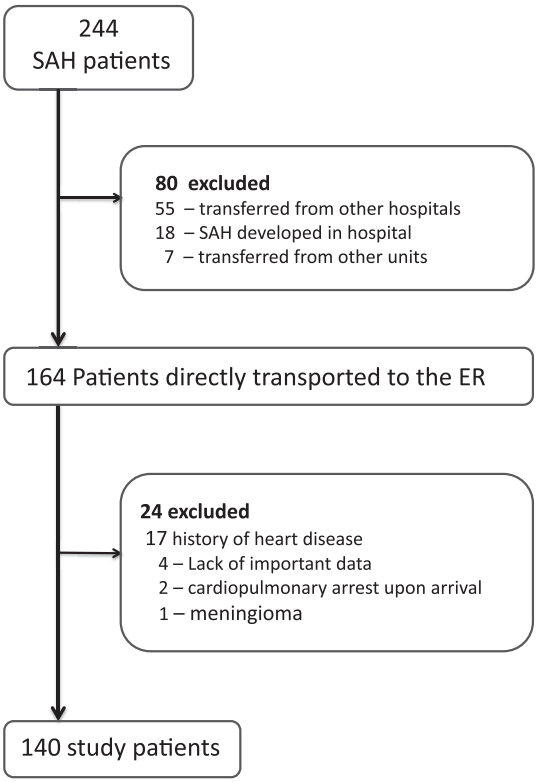


Fig. 1 Flow diagram depicting patient enrollment. SAH: subarachnoid hemorrhage, ER: emergency room

non-NPE groups with regard to the severity of SAH (P=0.68; **Table 1**), the hospital mortality rate (P=0.24), or the hospital Glasgow Outcome Score (P=0.16; **Table 2**).

Additionally, the mean arterial pressure did not differ significantly between the groups (P=0.96; **Table 3**). However, both the median pH (P=0.002) and bicarbonate ion ($HCO_3^-$) concentration (P=0.01) were significantly lower in the NPE group than in the non-NPE group. In contrast, the median lactate concentration was significantly higher in the NPE group than in the non-NPE group (P<0.001).

Multivariable regression analysis indicated that younger age and increased levels of glucose and lactate were significantly associated with the development of NPE (**Table 4**).

## Discussion

The present results suggest that lactic acidosis, occurring immediately after SAH, was more frequent in patients with NPE than in patients without. The increased lactate level was an

Table 1 Patient characteristics

| | NPE group (n=15) | Non-NPE group (n=125) | *P* value |
|---|---|---|---|
| Sex (male/female) | 5/10 | 43/82 | 0.93 |
| Age, years | 48.0 (47.3–65.5) | 66.0 (57.0–76.5) | <0.001 |
| World Federation of Neurological Surgeons grade | | | 0.68 |
| 1 | 0 ( 0.0%) | 4 ( 3.2%) | |
| 2 | 1 ( 6.7%) | 13 (10.4%) | |
| 3 | 0 ( 0.0%) | 2 ( 1.6%) | |
| 4 | 5 (33.3%) | 34 (27.2%) | |
| 5 | 9 (60.0%) | 72 (57.6%) | |
| Cause of subarachnoid hemorrhage | | | |
| Ruptured cerebral aneurysm | 9 (60.0%) | 108 (86.4%) | 0.41 |
| ACA | 2 | 27 | |
| ICA | 1 | 33 | |
| MCA | 3 | 32 | |
| VBA | 3 | 16 | |
| Dissection | 5 (33.3%) | 9 ( 7.2%) | 0.001 |
| Internal carotid artery | 0 | 2 | |
| Basilar artery | 0 | 2 | |
| Vertebral artery | 5 | 5 | |
| Others | 1 ( 6.7%) | 8 ( 6.4%) | 0.97 |

Data are presented as medians (quartiles 1–3) or n (%).

Site categorization: ACA, anterior communicating artery, anterior cerebral artery, and pericallosal artery combined; ICA, internal carotid artery, posterior communicating artery, ophthalmic artery, and anterior choroidal artery combined; MCA, middle cerebral artery; VBA, vertebrobasilar arteries

Table 2 Comparison of Glasgow Outcome Scores at the time of hospital discharge between the groups[a)]

| | NPE group (n=15) | non-NPE group (n=125) |
|---|---|---|
| Good recovery | 4 (26.7%) | 20 (16.0%) |
| Moderate disability | 6 ( 40%) | 22 (17.6%) |
| Severe disability | 1 ( 6.7%) | 23 (18.4%) |
| Persistent vegetative state | 1 ( 6.7%) | 16 (12.8%) |
| Dead | 3 (20.0%) | 44 (35.2%) |

[a)] $\chi^2$=6.66, p=0.16

Table 3 Comparison of variables between patients with and without neurogenic pulmonary edema

| | NPE group (n=15) | Non-NPE group (n=125) | P Value |
|---|---|---|---|
| MAP (mmHg) | 121.3 (109.0–144.5) | 124.6 (108.7–142.6) | 0.96 |
| Body temperature (°C) | 35.9 (35.0–36.4) | 35.8 (35.0–36.6) | 0.89 |
| $PaO_2/FiO_2$ | 118.0 (69.3–148.8) | 313.5 (152.5–461.0) | <0.001 |
| pH | 7.33 (7.28–7.37) | 7.39 (7.35–7.43) | 0.002 |
| $PCO_2$ (mmol/L) | 40.0 (33.8–47.3) | 38.0 (33.0–42.7) | 0.38 |
| $PO_2$ (mmol/L) | 104.0 (69.3–147.8) | 291.0 (146.2–459.0) | <0.001 |
| Lactate (mg/dL) | 54.0 (40.3–61.0) | 28.0 (17.0–37.5) | <0.001 |
| $HCO_3^-$ (mmol/L) | 20.8 (18.6–22.6) | 22.8 (20.9–24.7) | 0.01 |
| brain natriuretic peptide (pg/mL) | 336.2 (175.0–563.4) | 123.1 (56.1–304.0) | 0.02 |
| Glucose (mg/dL) | 282.0 (212.0–319.3) | 196.0 (167.0–235.8) | 0.001 |
| AST (IU/L) | 40.0 (23.3–77.0) | 27.0 (22.0–40.0) | 0.05 |
| ALT (IU/L) | 32.0 (19.5–51.5) | 17.0 (13.0–25.0) | 0.01 |
| Hypertension | 6 (40.0%) | 58 (46.4%) | 0.64 |
| Diabetes mellitus | 1 ( 6.7%) | 6 ( 4.8%) | 0.75 |

Data were presented as medians (quartiles 1–3) or n (%).

MAP, mean arterial pressure; $PaO_2$, oxygen partial pressure in arterial blood; $FiO_2$, fraction of inspired oxygen; $PO_2$, oxygen partial pressure; $PCO_2$, carbon dioxide partial pressure; $HCO_3^-$, bicarbonate ion; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 4 Logistic regression analysis for predicting early neurogenic pulmonary edema[a)]

| | β | SE | OR | *P*-value |
|---|---|---|---|---|
| Lactate | 0.04 | 0.02 | 1.04 (1.00–1.09)* | 0.04 |
| Age | −0.11 | 0.04 | 0.90 (0.83–0.97)* | 0.004 |
| Glucose | 0.03 | 0.009 | 1.03 (1.01–1.05)* | 0.001 |
| Mean arterial pressure | −0.01 | 0.01 | 0.99 (0.96–1.02)* | 0.49 |
| Body temperature | 0.35 | 0.42 | 1.42 (0.62–3.26) | 0.41 |
| Sex (female) | 1.69 | 0.96 | 5.4 (0.82–35.9) | 0.08 |
| World Federation of Neurological Surgeons grade | −0.41 | 0.42 | 0.66 (0.29–1.50) | 0.32 |
| Aspartate aminotransferase | 0.00008 | 0.008 | 1.00 (0.98–1.02) | 0.99 |

[a)] Area under the curve=0.92

β, partial regression coefficient; SE, standard error; OR, odds ratio (95% confidence interval)

*Risk increase for every 10 in scale

independent factor associated with the early onset of NPE.

The present study has shown that acute-phase increases in lactate levels are associated with early NPE after SAH; this finding is consistent with our hypothesis. That most of our patients arrived in the ER within 1 hour after the ictus suggests that the physiological derangements start immediately after the ictus; the onset of the derangements was represented by the development of lactic acidosis at

the time when most of the ER physicians are focused on the neurological disturbances. Although the present study could not confirm a cause-and-effect relationship, several possible reasons for the association can be considered. The increased lactate levels observed in patients with NPE may have been caused by increased production of lactic acid (via either anaerobic or aerobic glycolysis) or decreased clearance of lactic acid or both[27–33].

Hemodynamic disturbances and physiological derangements can also result in increased lactate production due to anaerobic glycolysis[30]. The mechanism of NPE has been hypothesized to involve comorbid hemodynamic and inflammatory mechanisms[34]. Mayer et al.[18] have demonstrated that transient lactic acidosis is maximal at onset of ictus and precedes the onset of postictal hypotension. In a case series, they showed depressed cardiac output and left ventricular systolic function, characterized by reduced stroke volume[18]. Another study, also comparing patients with and without NPE, has shown that patients with NPE have a significantly lower left ventricular ejection fraction and a significantly higher frequency of echographic wall motion abnormalities[35]. Thus, cardiac dysfunction may play an important role in NPE, and the reduced systemic blood flow results in less oxygen being delivered to the tissue, which in turn leads to increased anaerobic metabolism and overproduction of lactate.

In addition to the anaerobic glycolysis of lactic acid, aerobic glycolysis must also be considered in the relationship between NPE and high lactate levels. A recent study has shown that catecholamine levels are significantly higher within 48 hours of SAH onset in patients with NPE than in patients without NPE[35]. Increased catecholamine levels is a factor in the overproduction of lactate under aerobic conditions[30]. A landmark study by James et al.[27] has suggested that increased blood lactate levels often reflect increased aerobic glycolysis in skeletal muscle, because of epinephrine-stimulated $Na^+$, $K^+$-ATPase activity. In the present study, although mean arterial pressures were similar in patients with and without NPE, lactate levels were significantly higher in patients with NPE and remained associated with NPE after confounding variables were controlled for. Furthermore, the present study has found that serum glucose levels in patients with NPE were significantly higher than those in patients without NPE and were independently associated with NPE; this finding is consistent with the catecholamine surge hypothesis. Therefore, we speculate that a catecholamine surge after SAH induces elevation of the lactate level, which is caused by aerobic glycolysis coupled to $Na^+$, $K^+$-ATPase activity.

A decline in lactate clearance may also contribute to increased lactate levels[30–33]. Most lactate is converted back to pyruvate and eventually to glucose through gluconeogenesis in the liver; therefore, liver dysfunction causes an elevation of lactate levels[30–33]. In the present study, AST levels in patients with NPE were significantly higher than those in patients without NPE but were not independently associated with NPE, according to multivariable analysis. Additional, larger studies are required to confirm our results.

This study has several limitations. First, we did not evaluate each patient according to echocardiographic findings. Therefore, we cannot describe the possible effect of cardiac dysfunction (e.g., cardiac stunning, Takotsubo cardiomyopathy, or ischemic heart disease) that may be directly or indirectly related to the development of NPE[21,36]. A second limitation is that an epileptic insult may be associated with both elevated lactate levels and NPE development[37,38]. Although we attempted to exclude all cases of SAH involving seizures, the exclusion might not have been complete because the study involved a retrospective review of records. A third limitation is that we might have included patients with SAH who delayed calling the EMS system (e.g., those for whom bystanders had taken a wait-and-see approach; those who were unconscious and unobserved for some time; or those who had experienced more than a single SAH ictus, that is, a second ictus); the EMS could not bring such patients to the hospital immediately after the primary ictus. A fourth limitation of this study is that despite oxygen having been administered to the patients by the EMS on the basis of oxygen saturation

measured with a pulse oximeter and despite chest radiographs and arterial blood gases having been evaluated upon arrival to minimize the effect of any fluid, prehospitalization hypoxia might also have greatly affected the lactate elevation. Moreover, some of our patients might have had negative pressure pulmonary edema (e.g. airway obstruction or endotracheal tube obstruction)[39], or NPE after admission. However, these are unmeasured variables that we could not evaluate in the current study[39]. A fifth and final limitation of the present study is that this was a single-center, retrospective study, with a limited number of patients, performed at a university tertiary care center; thus, the condition of these patients was more severe than that of the general population of patients with SAH. As a result, we could not demonstrate a cause-and-effect relationship, and the results might not be applicable to all patients with SAH.

In conclusion, acute physiologic derangements, following SAH, start within 1 hour of the ictus. Lactic acidosis appears to be associated with NPE developing soon after SAH. Further multicenter prospective studies are required to confirm our results.

**Conflict of Interest:** The authors declare no conflict of interest.

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