Acute Medicine & Surgery 2016; **3**: 26–31 doi: 10.1002/ams2.138

Original Article

Analysis of the clinical backgrounds of patients who developed respiratory acidosis under high-flow oxygen therapy during emergency transport

Hirokazu Ogino,[1] Naoki Nishimura,[1] Yasuhiko Yamano,[1] Genta Ishikawa,[1] Yutaka Tomishima,[1] Torahiko Jinta,[1] Osamu Takahashi,[2] and Naohiko Chohnabayashi[1]

[1]Division of Pulmonary Medicine, St. Luke's International Hospital; and [2]Center for Clinical Epidemiology, St. Luke's Life Science Institute, Tokyo, Japan

Aim: High-flow oxygen is often administered to patients during emergency transport and can sometimes cause respiratory acidosis with disturbed consciousness, thereby necessitating mechanical ventilation. Although oxygen titration in chronic obstructive pulmonary disease patients during emergency transport reduces mortality rates, the clinical risk factors for respiratory acidosis in emergency settings are not fully understood. Therefore, we analyzed the clinical backgrounds of patients who developed respiratory acidosis during pre-hospital transport.

Methods: This was a retrospective study of patients who arrived at our hospital by emergency transport in 2010 who received high-flow oxygen while in transit. Respiratory acidosis was defined by the following arterial blood gas readings: pH, ≤7.35; $PaCO_2$, ≥45 mmHg; and HCO_3^-, ≥24 mmol/L. The risk factors were identified using multivariable logistic regression analysis.

Results: In 765 study patients, 66 patients showed respiratory acidosis. The following risk factors for respiratory acidosis were identified: age, ≥65 years (odds ratio [OR] 1.4; 95% confidence interval [CI], 0.7–2.8); transportation time, ≥10 min (OR 2.0; 95% CI, 1.1–3.7); three digits on the Japan Coma Scale (OR 3.1; 95% CI, 1.7–5.8); percutaneous oxygen saturation, ≤90% (OR 1.6; 95% CI, 0.8–3.0); tuberculosis (OR 4.5; 95% CI, 1.4–15.1); asthma (OR 1.8; 95% CI, 0.6–5.3); pneumonia (OR 1.5; 95% CI, 0.7–3.1); and lung cancer (OR 3.9; 95% CI, 1.5–10.1). These underlying diseases as risk factors included both comorbid diseases and past medical conditions.

Conclusions: The factors identified may contribute to the development of respiratory acidosis. Further studies on preventing respiratory acidosis will improve the quality of emergency medical care.

Key words: Emergency transport setting, high-flow oxygen, multivariable logistic regression analysis, respiratory acidosis, CO_2 narcosis

INTRODUCTION

ALL OVER THE world and on a daily basis, patients are being sent to hospital emergency rooms by ambulances.[1] In Tokyo, a record high of 741,797 ambulances were sent out in 2012, and the number continues to increase every year.[2] Severely ill patients often show severe hypoxemia and are given high-flow oxygen (≥6 L/min via face mask) during ambulance transport. Some of these patients inadvertently develop severe respiratory acidosis, and, as a result, require mechanical ventilations such as an intratracheal intubation or a non-invasive positive-pressure ventilation.[3]

Corresponding: Naoki Nishimura, MD, PhD, Division of Pulmonary Medicine, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo City, Tokyo 104-8560, Japan. E-mail: nina@luke.ac.jp.
Received 4 Nov, 2014; accepted 23 Apr, 2015; online publication 30 June, 2015

Carbon dioxide (CO_2) narcosis is a type of hypercapnia associated with a depression of the central nervous and respiratory systems, which follows excessive administration of oxygen to patients with chronic respiratory failure caused by conditions such as chronic obstructive pulmonary disease (COPD) or the late effects of tuberculosis.[4] In the clinical setting we administered minimal oxygen, via nasal cannula, and maintained a percutaneous oxygen saturation (SpO_2) of 90–93% to avoid CO_2 narcosis in patients with COPD.[5,6] Venturi masks are often used for patients such as these because they permit tight regulation of the fraction of inspired oxygen (FiO_2).[7]

Recently, several studies have shown that the use of high-flow oxygen during COPD exacerbations is associated with increased mortality rates, longer hospital stay, greater requirement for ventilation, and more frequent admissions to high dependency units.[8–12] In a randomized controlled trial that compared the effect of high-flow oxygen treatment with titrated oxygen treatment in patients with COPD exacerbation during emergency transport, titrated oxygen treatment significantly reduced mortality.[13] In contrast, a report showed that an adequate amount of oxygen administration, even high-flow oxygen, for hypercapnic patients who have hypoxemia did not induce a poor outcome, if it is carried out under tight monitoring.[14] Both of these reports indicate that it is important to give high-flow oxygen to patients with hypoxemia "under the tight saturation monitoring". Therefore, awareness of the potential harm of routine high-flow oxygen use has increased and attempts have been made to modify this practice.

Despite this clinical background, the risk factors of respiratory acidosis development in emergency settings were not fully understood, and Japanese ambulance crews have no criteria to guide them in either opting for oxygen administration or determining the proper amount of oxygen. Moreover, the oxygen administration device used in Tokyo ambulances is usually just an oxygen mask with a reservoir bag; venturi masks are generally not available. Therefore, in most cases, high-flow oxygen treatment is continued all the way from the pick-up site to the hospital.

In this study, we show the results of multivariable logistic regression analysis to detect the clinical risk factors for respiratory acidosis during emergency transport with high-flow oxygen. These results will be helpful in improving patient care when ambulance crews opt for high-flow oxygen use.

PATIENTS AND METHODS

Participants

THIS WAS A retrospective study of patients who arrived at St. Luke's International Hospital in Tokyo, Japan, by emergency transport and on high-flow oxygen (≥6 L/min via face mask) between January 1, 2010 and December 31, 2010. Patients in cardiopulmonary arrest, patients with no arterial blood gas data, and children were excluded.

Data collection

All variable data were collected using a standardized survey sheet on the day of transport and from the medical records after admission. Vital signs such as respiratory rate, percutaneous oxygen saturation, and consciousness level were documented by the ambulance crew on-site. Consciousness level was evaluated using the Japan Coma Scale (JCS). The JCS levels 0–300 indicate: 0, alert and conscious condition; 1–3, drowsy but awake without stimulation; 10–30,

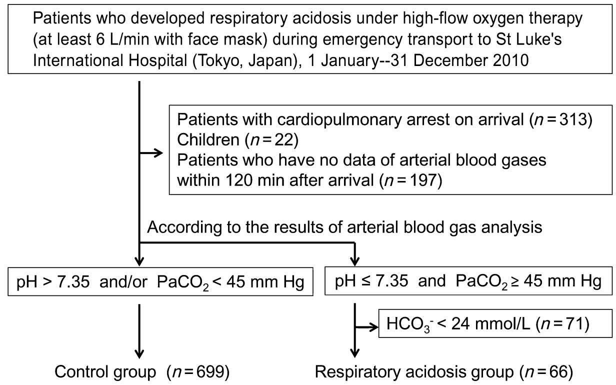

Fig. 1. Study flow of participants through this study. Patients (n = 1,368) were transported by ambulance while being administered high-flow oxygen. We excluded data on cardiopulmonary arrest patients, patients without arterial blood gas analysis data, and children. Using their arterial blood gas analysis results, 66 patients met the definition of respiratory acidosis (pH, ≤7.35; $PaCO_2$, ≥45 mmHg; and HCO_3^-, ≥24 mmol/L).

somnolence that can be aroused with some stimulation; and 100–300, coma.[15] Blood gas analysis was carried out within 120 min of patients being transferred to the hospital. Comorbid diseases and past medical histories were also obtained from the medical charts.

Definition of respiratory acidosis

We defined respiratory acidosis as: arterial pH, ≤7.35; partial pressure of arterial carbon dioxide ($PaCO_2$), ≥45 mmHg; and arterial bicarbonate ions (HCO_3^-), ≥24 mmol/L in the arterial blood gas analysis (Fig. 1). Patients with HCO_3^- <24 mmol/L were excluded in order to eliminate metabolic acidosis. The control subjects were defined as having either pH >7.35 or $PaCO_2$ <45 mmHg, or both.

Statistical analysis

For univariate analysis, Student's t-test was used to test the differences between continuous variables, and χ^2-tests were used for assessing differences in proportions between patients who had respiratory acidosis and those who did not. All factors related to patient characteristics and underlying disease for which the P-value was <0.05 in the univariate analysis, as well as the other aforementioned clinically important factors (e.g., emergency transportation time), were included in the multivariable logistic regression analyses. All analyses were carried out using IBM SPSS software (Chicago, IL, USA). Prior ethical approval was obtained from the Research Ethics Committee of St. Luke's

International Hospital (approval code 11-R128, approval date 19 October, 2011).

RESULTS

Study population

DURING THE STUDY period, 1,368 patients were given high-flow oxygen (≥6 L/min via face mask) while being transported by ambulances. We excluded data on cardiopulmonary arrest patients (313 cases), patients with no arterial blood gas analysis data (197 cases), and children (22 cases). A total of 765 patients (mean age, 65 years; male, 64%) were analyzed. Of these, 699 (mean age, 64 years; male, 63%) were enrolled in the control group while 66 (mean age, 70 years; male, 71%) were enrolled in the respiratory acidosis group (Fig. 1).

Patient characteristics

Table 1 shows patient characteristics and the results of the univariate analysis. The mean ages of patients in the respiratory acidosis group and the control group were 70 and 64 years, respectively; the difference was clearly significant. Consciousness level and SpO_2 at the time when the ambulance crew arrived were significantly worse in the respiratory acidosis group than in the control group. In addition, the percentage of patients who received mechanical ventilation after admission was significantly higher in the respiratory acidosis group. The causes of mechanical ventilation, such as respiratory acidosis or other reasons, were not evaluated in this study.

Underlying diseases of patients

Table 2 shows the patients' underlying diseases and the results of the univariate analysis. Underlying diseases indicate both comorbid disease and conditions identified in the patients' medical histories. However, they are not necessarily major causes for ambulance transport. The prevalence of several respiratory-related diseases, such as tuberculosis, asthma, pneumonia, and lung cancer (primary or metastatic), was significantly higher in the respiratory acidosis group.

Results of multivariable logistic regression analyses

The multivariable logistic regression analyses were constructed by using candidate predictors with P-values <0.05 in the univariate analyses, along with clinically important factors for the development of respiratory acidosis. We set the cut-off age at 65 years, according to the World Health Organization's definition of geriatrics; we also set a three-digit JCS level code and a 10-min transportation time as risk factors (Table 3). In total, eight risk factors were identified in this analysis: age, ≥65 years (odds ratio [OR] 1.4; 95% confidence interval [CI], 0.7–2.8); transportation time, ≥10 min (OR 2.0; 95% CI, 1.1–3.7); three digits on the JCS (OR 3.1; 95% CI 1.7–5.8); SpO_2, ≤90% (OR 1.6; 95% CI, 0.8–3.0); tuberculosis (OR 4.5; 95% CI, 1.4–15.1); asthma (OR 1.8; 95% CI, 0.6–5.3); pneumonia (OR 1.5; 95% CI, 0.7–3.1); and underlying lung cancer (OR 3.9; 95% CI, 1.5–10.1). These underlying diseases included both comorbid diseases and conditions identified in the patients' medical histories.

Table 1. Characteristics of patients who developed respiratory acidosis under high-flow oxygen therapy during emergency transport to St Luke's International Hospital (Tokyo, Japan), 1 January–31 December 2010

Characteristic	Respiratory acidosis (n = 66)	Control (n = 699)	P-value†
Age, years	70 (16)‡	64 (20)	<0.01
Male	47 (71)	446 (63)	<0.01
Transportation time, min	15 (24)	11 (11)	<0.01
Respiration rate, /min	23 (7)	23 (10)	>0.99
Japan Coma Scale§			<0.05
JCS 0	17 (27.0)	237 (35.3)	
JCS 1-digit codes	14 (22.2)	204 (30.4)	
JCS 2-digit codes	9 (14.3)	89 (13.3)	
JCS 3-digit codes	23 (36.5)	141 (21.0)	
SpO_2§			<0.01
$SpO_2 \geq 95\%$	24 (43.6)	338 (54.7)	
$90\% \leq SpO_2 < 95\%$	8 (14.6)	123 (19.9)	
$85\% \leq SpO_2 < 90\%$	5 (9.1)	68 (11.0)	
$SpO_2 < 85\%$	18 (32.7)	89 (14.4)	
pH	7.25 (0.09)	7.41 (0.07)	<0.01
$PaCO_2$, mmHg	72 (26)	37 (7)	<0.01
PaO_2, mmHg	191 (143)	194 (112)	>0.99
HCO_3^-, mmol/L	30 (7)	23 (5)	<0.01
Lactate, mmol/L	1.9 (1.4)	2.6 (2.4)	<0.01
Mechanical ventilation	37 (56)	157 (23)	<0.01
Death within 30 days	9 (14)	63 (9)	<0.01

†For univariate analysis, Student's t-test was used to test differences in continuous variables and the χ^2-test was used for differences in proportions between two groups. $P < 0.05$ was considered significant. ‡n (%) or mean (SD). §Because of missing values, total numbers of each category do not equal 66 in the respiratory acidosis group or 699 in the control group. HCO_3^-, bicarbonate ions; JCS, Japan Coma Scale; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SpO_2, percutaneous oxygen saturation.

Table 2. Underlying diseases and results of univariate analysis of patients who developed respiratory acidosis under high-flow oxygen therapy during emergency transport to St Luke's International Hospital (Tokyo, Japan), 1 January–31 December 2010

	Respiratory acidosis (n = 66)	Control (n = 699)	P-value†
COPD	4 (6)‡	18 (3)	0.11
(Old) tuberculosis	7 (11)	14 (2)	<0.01
Thoracic deformity	1 (2)	0 (0)	<0.01
Sleep apnea	2 (3)	0 (0)	<0.01
Asthma	7 (11)	38 (5)	<0.01
Pneumonia	20 (30)	118 (17)	<0.01
Lung cancer (metastatic or primary)	9 (14)	22 (3)	<0.01
Interstitial lung disease	0 (0)	8 (1)	0.38
Home oxygen therapy	0 (0)	3 (0)	0.59
Heart failure (acute or chronic)	16 (24)	173 (25)	0.93
Chronic kidney disease	6 (9)	56 (8)	0.76
Neuromuscular disease	3 (5)	14 (2)	0.18
Cerebrovascular accident	22 (33)	194 (28)	0.34
Seizure	4 (6)	53 (7)	0.65
Drug overdose	5 (7)	69 (10)	0.55
Trauma	5 (8)	80 (11)	0.34

Underlying diseases indicate both comorbid disease and conditions identified in the patients' medical histories, as they were documented in patients' medical records. They are not necessarily the major causes of ambulance transport. †χ^2-test was used for differences in proportions between two groups. P < 0.05 was considered significant. ‡n (%); percentage means the prevalence rate in each group. COPD, chronic obstructive pulmonary disease.

These results suggested that the development of respiratory acidosis was heavily influenced by a worsened consciousness at the time of ambulance arrival and the presence of tuberculosis and lung cancer as underlying diseases.

DISCUSSION

IN THE PRESENT study, we reported eight risk factors for respiratory acidosis in the setting of pre-hospital transport. Carbon dioxide narcosis, which is often caused by high-flow oxygen administration, is a severe problem in the emergency department because of the need for mechanical ventilation. These factors identified in this study might be able to pick up the "CO_2 narcosis high-risk patients" and regulate tight oxygen administration more easily.

Table 3. Risk factors of CO_2 narcosis in patients who developed respiratory acidosis under high-flow oxygen therapy during emergency transport to St Luke's International Hospital (Tokyo, Japan), 1 January–31 December 2010, identified by multivariable logistic regression analysis

	Odds ratio	95% CI	P-value
(Old) tuberculosis†	4.5	1.4–15.1	0.01
Lung cancer†	3.9	1.5–10.1	<0.01
JCS ≥ 3-digit codes	3.1	1.7–5.8	<0.01
Transportation time ≥10 min	2.0	1.1–3.7	0.02
Asthma†	1.8	0.6–5.3	0.29
SpO_2 ≤90%	1.6	0.8–3.0	0.16
Pneumonia†	1.5	0.7–3.1	0.28
Age ≥65 years	1.4	0.7–2.8	0.29

†Underlying diseases indicate both comorbid diseases and conditions identified in the patients' medical histories, as they were documented in patients' medical record. They are not necessarily the major causes of ambulance transport. JCS, Japan Coma Scale; SpO_2, percutaneous oxygen saturation.

We first hypothesized that COPD should be selected as a risk factor for respiratory acidosis. However, this factor was shown to be of low significance in the univariate analysis. We found a description of COPD in the medical records of only 22 out of the 765 patients; this was lower than expected,[16] meaning that it would be difficult to diagnose COPD in an emergency setting. We also failed to diagnose COPD retrospectively with medical charts after admission, because respiratory function tests were carried out in only a few patients. Moreover, there is a possibility that analyzing only patients who were administered high-flow oxygen would lead to a low incidence of COPD patients, because the ambulance crew would avoid giving high-flow oxygen to patients with COPD. These factors would prevent it from being considered an actual risk factor.

Acute respiratory acidosis can be caused by both pulmonary and extrapulmonary diseases, such as depression of the central respiratory center by cerebral diseases, drugs, or oxygen.[17,18] It sometimes leads to CO_2 narcosis, which is defined as respiratory acidosis with a disturbed consciousness and shortness of breath,[5] especially in severe conditions. However, it does not have detailed diagnostic criteria and is usually diagnosed empirically.[19–22] On a narcotic level, Westlake reported mental disturbances with pH ≤7.2 and $PaCO_2$ ≥100 mmHg, and most patients were conscious if pH ≥7.3 and $PaCO_2$ ≤ 80 mmHg in the arterial blood gas analysis.[23] However, in cases of acute respiratory acidosis or renal failure, a lower $PaCO_2$ could be able to induce severe acidemia, resulting in mental disturbance, because renal compensation does not work immediately and completely.[17,18]

In this paper, we first tried to analyze the risk factors of CO_2 narcosis induced by high-flow oxygen. However, we could compare neither severe symptoms of CO_2 narcosis, such as consciousness levels, between pre- and post-emergency transportation, nor the rate of climb of the SpO_2 during emergency transportation. We also could not evaluate the respiratory acidosis induced by other reasons due to the limited information obtained from the retrospective analysis. We also just evaluated the clinical backgrounds of respiratory acidosis which was seen after emergency transportation with high-flow oxygen administration, therefore, there is a possibility that these factors might not reflect the risk factors of CO_2 narcosis induced by high-flow oxygen, and the severe symptoms were not caused by respiratory acidosis.

However, despite of these concerns, these clinical background of respiratory acidosis might be the risk factors for CO_2 narcosis induced by high-flow oxygen partially because of the following reason. That is, as the rate of respiratory acidosis progression was an important aspect, the arterial pH was significantly lower in the respiratory acidosis group, and, subsequently, transportation time >10 min was determined to be a risk factor for respiratory acidosis in this study. This was why we surmised that the acute respiratory acidosis in the respiratory acidosis group of patients was the result of the administration of high-flow oxygen.

In this study, all patients transported under high-flow oxygen treatment were analyzed. The patients had a wide variety of causes that accounted for the emergency transport. There is room for discussion as to whether we should analyze the risk factors of each patient simultaneously, however, the purpose of this study was to assist ambulance crews in developing better prediction methods for respiratory acidosis. Therefore, we just analyzed the clinical data of all patients who needed high-flow oxygen. In the future, we should analyze the relationships between development of respiratory acidosis and the causes of emergency transportation with high-flow oxygen administration.

This study had several limitations. First, it was performed retrospectively. As mentioned above, the medical records data on the day of transport or after admission were inadequate in some cases. Second, this study was carried out at only one institution. Finally, there is a possibility that it is difficult to gather information of risk factors of respiratory acidosis in the emergency setting. To resolve this problem, we should increase the number of patients for analysis and try to identify the risk factors that are easy to gather. They are, for example, physical findings such as respiratory muscle fatigue, the Hoover sign, and paradoxical breathing. In the future, it could be possible to integrate each patient's data adequately by prospective analysis, and to establish external validation by analyzing the data in multiple hospitals. As a result, constructing a significant scoring system for predicting respiratory acidosis or CO_2 narcosis in the emergency setting is anticipated.

CONCLUSION

TO OUR KNOWLEDGE, this is the first report to indicate the risk factors for respiratory acidosis by analyzing the clinical backgrounds of patients administered high-flow oxygen while being transported by ambulance. It should be possible to improve the quality of the data by collecting prospectively in a future multicenter trial and to construct a relevant scoring system for predicting respiratory acidosis or CO_2 narcosis. It should also be possible to reduce the incidence of respiratory acidosis when ambulance crews titrate oxygen to patients in the respiratory acidosis risk group; this should, in turn, improve the quality of emergency medical care.

CONFLICT OF INTEREST

NONE.

REFERENCES

1 Ray P, Birolleau S, Lefort Y *et al*. Acute respiratory failure in the elderly: Etiology, emergency diagnosis and prognosis. Crit. Care 2006; 10: R82.

2 Morimura N, Aruga T, Sakamoto T *et al*. The impact of an emergency telephone consultation service on the use of ambulances in Tokyo. Emerg. Med. J. 2011; 28: 64–70.

3 Westlake EK, Simpson T, Kaye M. Carbon dioxide narcosis in emphysema. Q. J. Med. 1955; 24: 155–74.

4 Bradley JM, Lasserson T, Elborn S *et al*. A systematic review of randomized controlled trials examining the short-term benefit of ambulatory oxygen in COPD. Chest 2007; 131: 278–85.

5 Rudolf M, Banks RA, Semple SJ. Hypercapnia during oxygen therapy in acute exacerbations of chronic respiratory failure. Hypothesis revisited. Lancet 1977; 2: 483–6.

6 Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur. Respir. J. 2004; 23: 932–46.

7 Campbell EJ, The J. Burns Amberson lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. Am. Rev. Respir. Dis. 1967; 96: 626–39.

8 Denniston AK, O'Brien C, Stableforth D. The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: A prospective audit of pre-hospital and hospital emergency management. Clin. Med. 2002; 2: 449–51.

9 Joosten EA. The effects of oxygen therapy in patients presenting to an emergency department with exacerbation of chronic obstructive pulmonary disease. Med. J. Aust. 2007; 5: 235–8.
10 Robinson T, Young I. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2001; 163: 1524–9.
11 Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: Implications for the provision of non-invasive ventilation and oxygen administration. Thorax 2000; 55: 550–4.
12 Wijesinghe M, Perrin K, Healy B *et al*. Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. Intern. Med. J. 2011; 41: 618–22.
13 Austin MA, Wills KE, Blizzard L *et al*. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomised controlled trial. BMJ 2010; 341: c5462.
14 Gomersall CD, Joynt GM, Freebairn RC, Lai CK, Oh TE. Oxygen therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: A randomized, controlled pilot study. Crit. Care Med. 2002; 30: 113–16.
15 Ono K, Wada K, Takahara T *et al*. Indications for computed tomography in patients with mild head injury. Neurol. Med. Chir. (Tokyo) 2007; 47: 291–7.
16 Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults—United States, 2011. MMWR Morb. Mortal. Wkly Rep. 2012; 61: 938–43.
17 Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. N. Engl. J. Med. 2014; 371: 1434–45.
18 Seifter JL. Integration of acid-base and electrolyte disorders. N. Engl. J. Med. 2014; 371: 1821–31.
19 Spindelboeck W, Moser A. Spontaneous tension pneumothorax and CO_2 narcosis in a near fatal episode of chronic obstructive pulmonary disease exacerbation. Am. J. Emerg. Med. 2012; 30: 1664.e3–4.
20 Miyamoto M, Miyamoto T, Hirata K. [Hypercapnic coma (CO_2 narcosis)]. Ryoikibetsu Shokogun Shirizu 2000; 29: 164–6. (In Japanese.)
21 Ichinose Y, Yonemaru M. CO_2 narcosis. Ryoikibetsu Shokogun Shirizu 1994; 4: 455–8. (In Japanese.)
22 Campbell EJ. Treatment of respiratory acidosis in chronic obstructive lung disease. JAMA 1972; 219: 1477.
23 Westlake EK. Respiratory failure and carbon dioxide narcosis. Postgrad. Med. J. 1958; 34: 2–6.