Hyperoxemia during resuscitation of trauma patients and increased intensive care unit length of stay: inverse probability of treatment weighting analysis

Ryo Yamamoto1, Seitaro Fujishima2*, Junichi Sasaki1, Satoshi Gando3,4, Daizoh Saitoh5, Atsushi Shiraishi6, Shigeki Kushimoto7, Hiroshi Ogura8, Toshikazu Abe9,10, Toshihiko Mayumi11, Joji Kotsuji12, Takaaki Nakada13, Yasukazu Shiino14, Takehiko Tasai15, Kohji Okamoto16, Yuichiro Sakamoto17, Shin-Ichi Shiraishi18, Kiyotaka Takuma19, Ryosuke Tsuruta20, Tomohiko Masuno21, Naoshi Takeyama22, Norio Yamashita23, Hiroto Ikeda24, Masashi Ueyama25, Toru Hifumi26, Kazuma Yamakawa27, Akiyoshi Haginaka28, Yasuhiro Otomo29 and on behalf of the Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) Study Group

Abstract

Background: Information on hyperoxemia among patients with trauma has been limited, other than traumatic brain injuries. This study aimed to elucidate whether hyperoxemia during resuscitation of patients with trauma was associated with unfavorable outcomes.

Methods: A post hoc analysis of a prospective observational study was carried out at 39 tertiary hospitals in 2016–2018 in adult patients with trauma and injury severity score (ISS) of > 15. Hyperoxemia during resuscitation was defined as PaO2 of ≥ 300 mmHg on hospital arrival and/or 3 h after arrival. Intensive care unit (ICU)-free days were compared between patients with and without hyperoxemia. An inverse probability of treatment weighting (IPW) analysis was conducted to adjust patient characteristics including age, injury mechanism, comorbidities, vital signs on presentation, chest injury severity, and ISS. Analyses were stratified with intubation status at the emergency department (ED). The association between biomarkers and ICU length of stay were then analyzed with multivariate models.

Results: Among 295 severely injured trauma patients registered, 240 were eligible for analysis. Patients in the hyperoxemia group (n = 58) had shorter ICU-free days than those in the non-hyperoxemia group [17 (10–21) vs 23 (16–26), p < 0.001]. IPW analysis revealed the association between hyperoxemia and prolonged ICU stay among patients not intubated at the ED [ICU-free days = 16 (12–22) vs 23 (19–26), p = 0.004], but not among those intubated at the ED [18 (9–20) vs 15 (8–23), p = 0.777]. In the hyperoxemia group, high inflammatory markers such (Continued on next page)
Background
Oxygen administration has a vital role in the management of critically ill patients [1, 2]. However, supraphysiological oxygen tension in the blood and/or tissue, hyperoxemia, has been reported to affect mortality and intensive care unit (ICU) length of stay in different diseases [1, 3–5], such as traumatic brain injury [6, 7], post-cardiac arrest syndrome [8, 9], and post-cardiac surgery [10]. Moreover, various studies revealed that unnecessarily high fraction of inspired oxygen (FiO₂) was also associated with increased mortality of critically ill patients [11, 12], including sepsis [13, 14].

As several pathophysiological mechanisms behind harmful effects of hyperoxemia have been investigated, brain injury and pulmonary toxicity are emphasized as pivotal causes of unfavorable clinical outcomes in critically ill patient [15, 16]. Paradoxical reduction of oxygen delivery to the brain, due to vascular constriction and mitochondrial dysfunction, was observed in patients with traumatic/ischemic brain injury who experienced hyperoxemia [15, 17]. In addition, alveolar capillary injuries and pulmonary vasoconstriction inhibition by redundant reactive oxygen species with hyperoxemia was found in patients treated with mechanical ventilation [16, 18]. Furthermore, some basic studies suggested that hyperoxemia-induced acute lung injury (ALI) was exaggerated by inflammatory or lung-related biomarkers [19, 20].

Given that other subsets of critically ill patients, such as severely injured trauma patients, suffer from systematic inflammation, this population would be potentially affected by hyperoxemia. However, studies on clinical consequences of trauma patients who were exposed to hyperoxemia have been limited other than traumatic brain injury [21, 22]. Accordingly, this study aimed to elucidate whether hyperoxemia during resuscitation was associated with unfavorable clinical outcomes of trauma patients with severe injuries. We hypothesized that hyperoxemia exposure in the first 3 h after hospital arrival was associated with prolonged ICU stay. We also investigated the inflammatory and lung-protective biomarkers in patients with hyperoxemia to determine pathophysiological backgrounds of its potential harm.

Methods
Study design and settings
This study was a post hoc analysis of a nationwide multicenter prospective descriptive study conducted by the Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) study group from April 1, 2016, to January 31, 2018. Patient data including blood samples were obtained from 39 emergency departments (EDs) and ICUs in tertiary hospitals [23]. The FORECAST TRAUMA study was registered at the University Hospital Medical Information Network Clinical Trial Registry on November 15, 2015 (UMIN-CTR ID, UMIN000019588). The JAAM approved this study, and all collaborating hospitals obtained approval of their individual institutional review board (IRB) for conducting research with human participants (approval number JAAM, 2014-01; approval number 014-0307 from Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group; and approval number 20150056 from the Keio University School of Medicine Keio, institute of the corresponding author). This study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from patients or their next of kin.

Study population
The JAAM FORECAST TRAUMA study enrolled severely injured adult trauma patients (1) who were aged ≥ 16 years, (2) with injury severity score (ISS) of ≥ 16, and (3) who were directly transported from the scene. Patients without any available arterial partial pressure of oxygen (PaO₂) data within 3 h after hospital arrival were excluded. The size of the study population was dependent on the study period.

Data collection and definition
Patient data were prospectively collected and entered into an online data collection portal by treating physicians or volunteer registrars designated by each hospital. Available data included patient demographics, injury mechanism, vital signs on scene and hospital arrival, abbreviated injury scale (AIS), ISS, sequential organ failure
assessment score, laboratory data including arterial blood gas and inflammatory and lung-related biomarkers (soluble receptor for advanced glycation end-products [sRAGE], high mobility group box-1 (HMGB-1), surfactant protein D [SPD], Clara cell secretory protein [CCSP], and interleukin-8 [IL-8]), amount of transfusion, resuscitative procedure conducted at the ED, any surgical procedures or angiography, ICU and hospital length of stay, and survival status at discharge.

Arterial blood gas was obtained on arrival and at 3 h post-admission without any prespecified exception, and hyperoxemia was defined as PaO2 of ≥ 300 mmHg. Hyperoxemia during resuscitation was defined as hyperoxemia on hospital arrival and/or at 3 h after admission. Inflammatory and lung-related biomarkers were obtained at the ED. The Charlson index was scored to assess comorbidities [24]. Isolated brain injury was defined as a head AIS of ≥ 3 and other regions of ≤ 1.

Outcome measures
The primary outcome was ICU-free days until day 28, a composite of in-hospital mortality and ICU length of stay, defined as the number of days alive and out of the ICU between the day of hospital arrival and 28 days later. Secondary outcomes included survival to discharge and ventilator-free days until day 28.

Statistical analysis
Patients were divided into hyperoxemia and non-hyperoxemia groups. The hyperoxemia group consisted of patients who experienced hyperoxemia during resuscitation (hyperoxemia on hospital arrival and/or at 3 h after admission), whereas the non-hyperoxemia group consisted of patients in whom hyperoxemia was not observed both on hospital arrival and at 3 h after admission. Considering that oxygen exposure during resuscitation and its pathophysiological effect on the pulmonary tissue would significantly differ between patient on mechanical ventilation and those who were not, analyses were performed on the whole population and those who were divided based on the intubation status at the ED. Unadjusted analysis was performed on the ICU-free days using the Mann–Whitney U test, and between-group differences were presented using the Hodges–Lehmann estimator of the median of all paired differences with 95% confidence intervals (CIs).

To adjust patient characteristics between the two groups, inverse probability of treatment weighting (IPW) analyses with propensity scores were performed to compare primary and secondary outcomes [25]. The propensity score was developed using the logistic regression model to estimate the probability of being assigned to the hyperoxemia group compared with the non-hyperoxemia group [26]. Relevant covariates were carefully selected from known or possible unfavorable clinical outcome predictors in trauma patients based on previous studies (such as age, comorbidities, injury mechanism, ISS, degree of chest injury, and requirement of tube thoracotomy), intubation status at the ED, and vital signs on hospital arrival. All of this information was subsequently entered into the propensity model [27–29], in which patients with missing covariates were excluded from the propensity score calculation. The precision of propensity score discrimination was analyzed using the c-statistic [26]. IPW analyses were then performed as adjusted analyses, in which primary and secondary outcomes were compared using Mann–Whitney U tests and chi-square tests [25]. IPW was performed with restriction, in which patient data with ≤ 0.1 or ≥ 0.9 of the propensity score were not used to avoid extreme weights. Between-group differences were presented using the Hodges–Lehmann estimator with 95% CIs.

Subgroup analyses were performed to further interpretate primary results. IPW analyses on the primary outcome were repeated after excluding patients who experienced hypoxia during resuscitation, defined as PaO2 of < 60 mmHg within 3 h of hospital arrival. Another subgroup analysis was conducted after excluding patients with persistent hyperoxemia, defined as PaO2 of ≥ 300 mmHg both on hospital arrival and at 3 h after admission. Moreover, subgroup analysis was performed after excluding patients with isolated brain injury.

Furthermore, to investigate pathophysiological backgrounds of potential harm of hyperoxemia, effects of inflammatory and lung-protective biomarkers on the ICU length of stay were evaluated among patients treated with hyperoxemia. Each biomarker was analyzed along with intubation status at the ED, using ordinal logistic regression analysis after adjustment by IPW.

Descriptive statistics are presented as median (interquartile range) or number (percentage) and compared using Mann–Whitney U tests, Chi-square tests, or Fisher’s exact tests, as appropriate. Missing/ambitious values were used without manipulation. To test for all hypotheses, a two-sided α threshold of 0.05 was considered statistically significant. All statistical analyses were conducted using the SPSS, version 26.0 (IBM, Armonk, NY, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA).

Results
A total of 295 patients with severe injuries were registered in the JAAM FORECAST TRAUMA study. Among them, 244 with available PaO2 within 3 h of hospital arrival were eligible for this study. Figure 1 summarizes the patient flow diagram.

Fifty-eight patients were exposed to hyperoxemia (PaO2 of ≥ 300 mmHg) within 3 h of arrival and
295 patients were registered in the FORECAST study
- ≥16 years old
- ISS ≥16
- directly transported from the scene.

51 patients were excluded due to unavailable date on PaO₂

244 patients met all the eligibility criteria

58 patients in the hyperoxemia group
186 patients in the normoxia group

Fig. 1 Patient flow diagram. A total of 295 patients with severe injuries were registered in the JAAM FORECAST TRAUMA study, which enrolled patients (1) aged ≥16 years, (2) with injury severity score (ISS) of ≥16, and (3) directly transported from the scene. Among them, 244 with available PaO₂ within 3 h after hospital arrival were eligible for this study. Fifty-eight patients exposed to hyperoxemia (PaO₂ ≥ 300 mmHg) within 3 h after arrival were included in the hyperoxemia group, whereas 186 not exposed to hyperoxemia were included in the non-hyperoxemia group.

Yamamoto et al. World Journal of Emergency Surgery (2021) 16:19

ICU-free days were significantly fewer among patients exposed to hyperoxemia within 3 h after admission, compared with those not exposed to hyperoxemia in the unadjusted analysis [17 (10–21) vs 23 (16–26); difference in median = −4 days (95% CI = −2 to −7 days); p < 0.001; Table 3]. IPW analysis revealed that hyperoxemia during resuscitation was significantly associated with prolonged ICU stay among patients not intubated at the ED [ICU-free days = 16 (12–22) vs 23 (19–26); median difference = −5 (-3 to −10) days; p = 0.004], but not among those intubated at the ED [ICU-free days = 18 (9–20) vs 15 (8–23); median difference = 0 (-3 to 3) days; p = 0.777]. IPW analysis also identified that hyperoxemia exposure during resuscitation was associated with fewer ventilator-free days among patients not intubated [25 (15–26) vs 28 (23–28); p = 0.014], but not among those intubated at the ED. Survival to discharge were comparable between the two groups.

Subgroup analysis, excluding patients who experienced hypoxia (PaO₂ of < 60 mmHg) within 3 h after hospital arrival, also revealed the association between hyperoxemia and prolonged ICU stay among patients not intubated [25 (15–26) vs 28 (23–28); p = 0.014], but not among those intubated at the ED. Survival to discharge were comparable between the two groups.

Conversely, the analyses on patients without persistent hyperoxemia showed comparable ICU-free days between those with or without hyperoxemia on hospital arrival (ICU-free days = 16
Among patients in the hyperoxemia group, higher inflammatory biomarkers including sRAGE and HMGB-1 were associated with prolonged ICU stay [sRAGE (pg/mL), −3.2 (−5.1 to −1.2) ICU-free days and HMGB-1 (ng/mL), −1.5 (−3.0 to −0.1) ICU-free days; Fig. 2], whereas higher lung-protective proteins including SPD and CCSP were associated shorter ICU stay [SPD (ng/mL), 4.0 (1.7 to 6.3) ICU-free days and CCSP (ng/mL), 3.8 (1.1 to 6.4) ICU-free days; Fig. 2].

**Table 1 Characteristics of patients with and without hyperoxemia**

| Case                        | Unadjusted | After IPW* |
|-----------------------------|------------|------------|
|                             | Hyperoxemia | Non-hyperoxemia | P value | Hyperoxemia | Non-hyperoxemia | P value |
| Age, years, median (IQR)    | 49 (35–67)  | 60 (46–75)  | 0.022    | 50 (31–65)  | 53 (37–69)  | 0.175   |
| Sex, male, n (%)            | 34 (58.6%)  | 126 (67.7%) | 0.202    | 83 (64.8%)  | 85 (65.9%)  | 0.860   |
| Injury mechanism, blunt, n (%) | 56 (98.2%)  | 180 (97.3%) | 1.000    | 123 (97.6%) | 125 (97.7%) | 1.000   |
| Comorbidities (Charlson index), median (IQR) | 0 (0–0) | 0 (0–0) | 0.281 | 0 (0–0) | 0 (0–0) | 0.007 |
| Vital signs on arrival, median (IQR) |                      |                           |              |                           |              |
| GCS                         | 6 (3–13)    | 14 (11–15)  | < 0.001  | 8 (5–14)    | 10 (6–14)  | 0.557   |
| RR                          | 21 (18–28)  | 21 (18–26)  | 0.687    | 20 (16–26)  | 20 (15–28) | 0.696   |
| HR                          | 96 (77–120) | 90 (73–102) | 0.083    | 96 (80–120) | 90 (73–110)| 0.153   |
| BP systolic, mmHg           | 124 (90–147)| 129 (103–154)| 0.353    | 133 (103–151)| 123 (83–158)| 0.220   |
| Injury severity, median (IQR) |                         |                           |              |                           |              |
| AIS—head                    | 4 (0–5)     | 2 (0–4)     | < 0.001  | 4 (0–5)     | 4 (0–5)    | 0.663   |
| AIS—chest                   | 3 (0–4)     | 3 (0–4)     | 0.039    | 3 (0–4)     | 3 (0–4)    | 0.136   |
| ISS                         | 29 (25–38)  | 26 (19–34)  | 0.001    | 29 (25–38)  | 29 (25–38) | 0.352   |
| SOFA score                  | 10 (8–11)   | 8 (6–10)    | 0.001    | 9 (7–11)    | 8 (7–11)   | 0.703   |
| Cardiac arrest after arrival, n (%) | 1 (1.7%) | 2 (1.1%) | 0.559 | 2 (1.6%) | 4 (3.1%) | 0.684 |
| Treatment                   |                         |                           |              |                           |              |
| Tube thoracotomy, n (%)      | 13 (22.4%)  | 44 (23.7%)  | 0.845    | 32 (25.0%)  | 40 (31.0%) | 0.284   |
| Intubation at ED, n (%)      | 47 (81.0%)  | 58 (31.2%)  | < 0.001  | 90 (70.3%)  | 96 (74.4%) | 0.462   |
| Transfusion*, U, median (IQR) |             |                           |              |                           |              |
| RBC                         | 0 (0–4)     | 0 (0–2)     | 0.017    | 0 (0–4)     | 0 (0–6)   | 0.230   |
| FFP                         | 0 (0–6)     | 0 (0–4)     | 0.024    | 0 (0–4)     | 0 (0–6)   | 0.218   |
| Platelet                    | 0 (0–0)     | 0 (0–0)     | 0.276    | 0 (0–0)     | 0 (0–0)   | 0.178   |
| Hemostatic procedure, n (%)  |             |                           |              |                           |              |
| Craniotomy                  | 19 (32.8%)  | 19 (10.5%)  | < 0.001  | 37 (28.9%)  | 29 (23.2%) | 0.301   |
| Thoracotomy                 | 2 (3.4%)    | 2 (1.1%)    | 0.248    | 4 (3.1%)    | 1 (0.8%)  | 0.181   |
| Laparotomy                  | 6 (10.3%)   | 13 (7.2%)   | 0.438    | 11 (8.7%)   | 10 (8.0%) | 0.849   |
| Angiography                 | 21 (36.2%)  | 37 (20.4%)  | 0.015    | 34 (26.6%)  | 32 (25.4%) | 0.832   |

*IPW inverse probability weighting, GCS Glasgow Coma Scale, RR respiratory rate, HR heart rate, BP blood pressure, AIS Abbreviated Injury Scale, ISS Injury Severity Score, SOFA sequential organ failure assessment, ED emergency department, RBC red blood cell, FFP flesh frozen plasma

**Discussion**

In these post hoc analyses of a nationwide multicenter prospective observational study, hyperoxemia during the initial resuscitation was found to be associated with prolonged ICU stay. This relationship was validated among patients not treated with mechanical ventilation at the ED, using IPW analyses that adjusted several prognostic factors. Notably, the observed association was consistent across several subgroup analyses.

Several reasons could be considered for the relationship between hyperoxemia exposure and prolonged ICU stay among severely injured trauma patients. First,
hyperoxemia might have affected study participants who had moderate-to-severe traumatic brain injury. Although results on clinical consequences have been conflicting [30, 31], previous studies on traumatic brain injury reported that improvement of mitochondrial function in the injured cerebral tissue was not obtained by increasing FiO₂ to 1.0 from 0.5. In addition, supranormal oxygen levels in the cerebral blood have been reported to suppress cell metabolism, resulting in paradoxical neuronal death [30, 32]. Second, supraphysiologic FiO₂, hyperoxia, could induce ALI among considerable number of patients exposed to hyperoxemia. Several studies suggested that hyperoxia-induced ALI should be considered when FiO₂ exceeds 0.6–0.7 and may become problematic when FiO₂ exceeds 0.8 [33, 34]. In this study, the significantly higher FiO₂ on hospital arrival was observed in the hyperoxemia group [1.0 (0.8–1.0)], and the higher FiO₂ remained even at 3 h after admission. It should be also emphasized that the association between higher amount of lung-protective biomarkers and shorter ICU length of stay was observed in the hyperoxemia group, including CCSP, an important protein against oxidative stress in the respiratory system [35], and SPD, a pulmonary collectin against oxidative injury [36, 37].

Furthermore, systemic and/or lung tissue inflammation following severe injuries would have affected the baseline condition before hyperoxemia exposure. Given that animal studies found pre-administration of anti-inflammatory medication attenuated hyperoxia-induced ALI [38], systemic inflammation caused by trauma and/or chest injury itself would magnify the adverse effects of hyperoxia and hyperoxemia. Indeed, this study found that higher inflammatory biomarkers such as sRAGE and HMGB-1 were associated with unfavorable outcomes among patients exposed to hyperoxemia: sRAGE is a central cell surface receptor for HMGB-1, and both sRAGE and HMGB-1 are involved in the host response to injury, infection, and inflammation [39, 40].

Although a recent retrospective study on trauma patients reported that PaO₂ of ≥ 150 mmHg on hospital admission was related to decreased in-hospital mortality, several differences should be noted in this study. First,
the definition of hyperoxemia is different; patients with hyperoxemia (PaO\(_2\) of \(\geq 150\) mmHg) in the abovementioned study included only small number of patients exposed to PaO\(_2\) of \(\geq 300\) mmHg [median PaO\(_2\) was 230 (186–308) mmHg], although the harmful effect of hyperoxemia has been identified at PaO\(_2\) of \(\geq 300\) mmHg among critically ill patients [41, 42]. Second, hyperoxemia during resuscitation (on hospital arrival and at 3 h after admission) was examined in the current study because investigating only PaO\(_2\) on arrival would reflect prehospital treatment, rather than in-hospital critical care of trauma patients. Third, FiO\(_2\)- and lung-related biomarkers were not measured in the abovementioned study, although hyperoxia-induced ALI has been suggested as a potential cause of unfavorable clinical outcomes in patients who experienced hyperoxemia [16, 18]. The harm of hyperoxemia during resuscitation was not confirmed in patients intubated at the ED in this study, probably because precise control over FiO\(_2\) during the lung-protective ventilation: Minimizing the length of exposure time to hyperoxia (supraphysiologic FiO\(_2\)) would have diminished the relatively small degree of deleterious effects of hyperoxemia. The comparable mortality between the hyperoxemia and non-hyperoxemia groups obtained in this study is similar to that of a retrospective study on wartime pediatric trauma patients, which revealed no survival benefits of normoxia over hyperoxemia [21]. Considering that differences in the median ICU-free days between the two groups were only a few days in this study, prospective study involving sufficient number of patients should be conducted to confirm the possible harm of hyperoxemia in trauma patients.

The results of this study must be interpreted within the context of the study design. Post hoc analyses of the FORECAST TRAUMA study were conducted, which did not record indications of oxygen administration. Thus, our results could have been different if the respiratory condition during resuscitation had contained unrecorded strong prognostic factors. Another limitation is that variables relating to neurologic and pulmonary function were not available in the database. Although hyperoxemia-induced brain injury and ALI could be considered main causes of prolonged ICU stay following hyperoxemia exposure, objective data did not directly validate such physiological mechanism. Moreover, only hyperoxemia on hospital arrival and at 3 h after admission were investigated. Previous studies on hyperoxemia in various critically ill patients reported that clinical outcomes were different depending on timing (arrival, within a few hours, or within a day), definition (PaO\(_2\) \(\geq 300\) mmHg, \(\geq 400\) mmHg, or highest quartile of observed data), and obtained data (highest, lowest, or defined time point) for hyperoxemia [1, 9, 42]. Therefore, our results would vary if PaO\(_2\) was measured at different time points or if hyperoxemia was differently defined. Furthermore, this study was not designed to examine whether hyperoxemia would be more harmful than hypoxia. Considering that various studies reported the harmfulness of hypoxia during trauma resuscitation, hypoxia should be avoided more reliably. Finally, some biases could not be adjusted with IPW: some variables for propensity score calculation such as vital signs on arrival could be intermediate variables between prehospital hyperoxemia and outcomes, and survival bias would exist because hyperoxemia was defined based on PaO\(_2\) within 3 h after admission.

**Conclusions**

This study identified that hyperoxemia within 3 h after hospital arrival was associated with prolonged ICU stay among severely injured trauma patients not intubated at the ED. Further research is necessary to elucidate the harmful effect of different degrees and durations of hyperoxemia exposure.

**Abbreviations**

ICU: Intensive care unit; FiO\(_2\): Fraction of inspired oxygen; ALI: Acute lung injury; JAAM: Japanese Association for Acute Medicine; FORECAST: Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma; ED: Emergency department; UMIN-
CTR: University Hospital Medical Information Network Clinical Trial Registry; IRB: Institutional review board; ISS: Injury severity score; PaO2: Partial pressure of oxygen; AIS: Abbreviated injury scale; sRAGE: Soluble receptor for advanced glycation end-products; HMGB-1: High mobility group box-1; SPD: Surfactant protein D; CCSP: Clara cell secretory protein; IL-8: Interleukin-8; IPW: Inverse probability of treatment weighting.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13017-021-00363-2.

Additional file 1. Table S1. Hyperoxemia and ICU-free days in subgroups.

Acknowledgements

This study was supported by the Japanese Association for Acute Medicine (JAAM, 2014-01). The JAAM FORECAST Study Group thanks Shuta Fukuda for his special assistance in completing the study.

Authors’ contributions

RY, SF, and JS contributed to the acquisition of data, conceived and designed the study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. All authors contributed to the acquisition of the data and reviewed and discussed the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the Japanese Association for Acute Medicine (grant number 2014-01).

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All collaborating hospitals obtained approval of their individual Institutional Review Board (IRB) for conducting research with human participants (approval number JAAM, 2014-01 from Japanese Association for Acute Medicine; approval number 014-0307 from Hokkaido University Graduate School of Medicine, head institute of the FORECAST group; and approval number 20150056 from the Keio University School of Medicine Keio, institute of the corresponding author).

Consent for publication

Not applicable.

Competing interests

Dr. Fujishima reports grants and personal fees from Asahi Kasei Japan Co.; grants from Shionogi Co., Ltd.; grants from Chugai Pharmaceuticals Co., Ltd.; grants from Otsuka Pharmaceutical Co., Ltd.; grants from Teijin Pharma, Ltd.; grants from Pfizer Inc.; grants from Tsumura & Co.; grants from Astellas Pharma Inc.; and personal fees from Takeda Pharmaceutical Co., Ltd., outside the submitted work. Dr. Gando reports personal fees from ASAIHKASEI PHARMA JAPAN, and personal fees from GRIFOLS, outside the submitted work.

Author details

1Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Tokyo, Japan. 2Center for General Medicine Education, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo, 160-8582, Japan. 3Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan. 4Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan. 5Division of Traumatology, Research Institute, National Defense Medical College, Tokorozawa, Japan. 6Emergency and Trauma Center, Kameda Medical Center, Kameda, Japan. 7Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan. 8Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Osaka, Japan. 9Department of General Medicine, Juntendo University, Tokyo, Japan. 10Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan. 11Department of Emergency Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan. 12Division of Disaster and Emergency Medicine, Department of Surgery Related, Kobe University Graduate School of Medicine, Kobe, Japan. 13Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine, Chiba, Japan. 14Department of Acute Medicine, Kawasaki Medical School, Kurashiki, Japan. 15Department of Trauma and Critical Care Medicine, Kyorin University School of Medicine, Tokyo, Japan. 16Department of Surgery, Center for Gastroenterology and Liver Disease, Kitakyushu City Yahata Hospital, Kitakyushu, Japan. 17Emergency and Critical Care Medicine, Saga University Hospital, Saga, Japan. 18Department of Emergency and Critical Care Medicine, Aizu Chuo Hospital, Aizuwakamatsu, Japan. 19Emergency & Critical Care Center, Kawasaki Municipal Kawasaki Hospital, Kawasaki, Japan. 20Advanced Medical Emergency & Critical Care Center, Yamaguchi University Hospital, Ube, Japan. 21Department of Emergency and Critical Care Medicine, Nippon Medical School, Tokyo, Japan. 22Advanced Critical Care Center, Aichi Medical University Hospital, Nagakute, Japan. 23Advanced Emergency Medical Service Center, Kurume University Hospital, Kurume, Japan. 24Department of Emergency Medicine, Teikyo University School of Medicine, Tokyo, Japan. 25Department of Trauma, Critical Care, and Burn Center, Japan Community Healthcare Organization, Chukyo Hospital, Nagoya, Japan. 26Department of Emergency and Critical Care Medicine, St. Luke’s International Hospital, Tokyo, Japan. 27Division of Trauma and Surgical Critical Care, Osaka General Medical Center, Osaka, Japan. 28Department of the National Center for Global Health and Medicine, Tokyo, Japan. 29Trauma and Acute Critical Care Center, Medical Hospital, Tokyo Medical and Dental University, Tokyo, Japan.

Received: 24 February 2021 Accepted: 16 April 2021
Published online: 29 April 2021

References

1. Helmerhorst HJF, Roos-Blom MJ, van Weeren J, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies. Crit Care Med. 2015;43(7):1508–19. https://doi.org/10.1097/CCM.0000000000000998.
2. Angus DC. Oxygen therapy for the critically ill. N Engl J Med. 2020;382(11): 1054–6. https://doi.org/10.1056/NEJMe2000800.
3. Damiani E, Adario E, Girard M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18(6):711. https://doi.org/10.1186/s13054-014-0711-x.
4. Barbateskovic M, Schjerring OL, Krauss SR, Jakobsen JC, Meyhoff CS, Dahl RM, et al. Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. Cochrane Database Syst Rev. 2019;2019(11):CD012631. https://doi.org/10.1002/14651858.CD012631.pub2.
5. Palmer E, Post B, Klaukauh R, Marga G, MacCallum NS, Brealey D, et al. The association between supraphysiologic arterial oxygen levels and mortality in critically ill patients: a multicenter observational cohort study. Am J Respir Crit Care Med. 2019;200(11):1373–80. https://doi.org/10.1164/rccm.201904-0849OC.
6. Dringer MN. Hyperoxia: good or bad for the injured brain? Curr Opin Crit Care. 2008;14(2):167–71. https://doi.org/10.1097/MCC.0b013e3282f75522.
7. Tollaas CM, Reinert M, Seiler G, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurol Surg. 2004;101:435–44.
8. Roberts BW, Kilgannon JH, Hunter BR, Puskirich MA, Pierce L, Donnino M, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. Circulation. 2018;137(20):2114–24. https://doi.org/10.1161/CIRCULATIONAHA.117.032054.
