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Impact of early hyperoxia on 28-day in-hospital mortality in patients with myocardial injury

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Abstract

Introduction

Despite relevant evidence that supplemental oxygen therapy can be harmful to patients with myocardial injury, the association between hyperoxia and the clinical outcome of such patients has not been evaluated. We assessed whether early hyperoxia negatively affects outcomes in hospitalized patients with myocardial injury.

Methods

This was a retrospective study conducted at a tertiary referral teaching hospital. Between January 2010 and December 2016, 2,376 consecutive emergency department patients with myocardial injury, defined as a peak troponin-I level ≥ 0.2 ng/mL, within the first 24 hours of presentation were included. The metrics used to define hyperoxia were the maximum average partial pressure of oxygen ($\text{PaO}_{2\text{MAX}}$), average partial pressure of oxygen ($\text{PaO}_{2\text{AVG}}$), and area under the curve during the first 24 hours (AUC_{24}). The association between early hyperoxia within 24 hours after presentation and clinical outcomes was evaluated using multiple imputation and logistic regression analysis. The primary outcome was 28-day in-hospital mortality. The secondary outcomes were new-onset cardiovascular, coagulation, hepatic, renal, and respiratory dysfunctions (sequential organ failure sub-score ≥ 2).

Results

Compared with normoxic patients, the adjusted odds ratios (ORs) for $\text{PaO}_{2\text{MAX}}$, $\text{PaO}_{2\text{AVG}}$, and AUC_{24} were 1.55 (95% confidence interval (CI) 1.05–2.27; $p = 0.026$), 2.13 (95% CI 1.45–3.12; $p = 0.001$), and 1.73 (95% CI 1.15–2.61; $p = 0.008$), respectively, in patients with mild hyperoxia and 6.01 (95% CI 3.98–9.07; $p < 0.001$), 8.92 (95% CI 3.33–23.88; $p < 0.001$), and 7.32 (95% CI 2.72–19.70; $p = 0.001$), respectively, in patients with severe hyperoxia. The incidence of coagulation and hepatic dysfunction (sequential organ failure sub-score ≥ 2) was significantly higher in the mild and severe hyperoxia group.

Conclusions

Hyperoxia during the first 24 hours of presentation is associated with an increased 28-day in-hospital mortality rate and risks of coagulation and hepatic dysfunction in patients with myocardial injury.

- 1 **Study design and setting** This was a single-center retrospective observational cohort study conducted between January 2010 and April 2017 at Gyeongsang National University Hospital, a tertiary referral hospital located in the south-central region of the Republic of Korea. The Gyeongsang National University hospital institutional review board approved this study with the exemption of informed consent because of the retrospective nature of the analysis. The patients who presented to our ED were all enrolled in the National Emergency Department Information System (NEDIS), which is a national database prepared by 146 emergency medical centers and managed by a government-funded national ED control agency [16, 17]. In our ED, triage nurses and attending physicians entered the patients' data including physiologic parameters at ED arrival, symptoms, and diagnosis. Basic demographic and temporal information, treatment details including drugs and procedures, and outcomes were obtained from the hospital information system of our hospital. The input data were organized using the standard NEDIS registry format in the electronic medical record (EMR) system. The validity of all data was ensured by the use of function modules within the system before the data were saved.
- 2 **Participants** Among the consecutive ED patients ≥ 16 years of age, medically ill, and hospitalized after ED treatment, patients included in this study were those with peak TnI levels ≥ 0.2 ng/mL during the first 24 hours of presentation (assumed myocardial injury) with available partial pressure of oxygen (PaO₂) results. We excluded patients who were transferred to other facilities after admission, who were discharged with no prospect of recovery, who left the hospital against medical advice, or who died within 24 hours of ED arrival. The purpose of this study was to compare hyperoxic patients with normoxic patients; since a single event of hypoxia within 24 hours after ED arrival might have worsened the outcomes of patients who were no longer hypoxic after ED treatment (such as supplemental oxygen), we did not include patients with a minimum PaO₂ < 60 mmHg within 24 hours of presentation in the final analysis. Patients who were ≥ 16 years of age, medically ill, or hospitalized after ED treatment with peak TnI levels ≥ 0.2 ng/mL within the first 24 hours of presentation, but who did not have PaO₂ results, were used for propensity analysis after exclusion according to criteria described previously. The inclusion and exclusion processes are illustrated in Fig. 1. Fig. 1. Flowchart of the inclusion and exclusion processes.
- 3 **Data collection** Data were collected from the NEDIS registry and the EMR system of our hospital. Demographic data including age, sex, and category (diseased or injured) and physiological data including mental status described using the alert, verbal, pain, unresponsive (AVPU) scale; systolic blood pressure; heart rate; respiratory rate; body temperature; and arterial oxyhemoglobin saturation were extracted. We also extracted data from the 'prehospital record' and 'list of therapeutic management' sections of the EMR to determine whether a given patient received any supplemental oxygen therapy. The National Early Warning Score (NEWS) was calculated for each patient.

Electrocardiograms obtained during the ED stay were reviewed. Temporal parameters between ED arrival and hospital discharge (date of ED arrival, admission, death, and discharge) and final outcomes of the patient (discharge, transfer, death, or other) were collected. Initial laboratory results within 2 hours of ED arrival including PaO₂, initial complete blood count (white blood cell, hemoglobin, and platelet levels), and serum glucose, creatinine, albumin, bilirubin, and c-reactive protein (CRP) levels, were collected. The estimated glomerular filtration rate was calculated using the formula proposed by Levey et al. [18]. All PaO₂ and TnI results within 24 hours were also collected. We collected the following additional data to evaluate new occurrences of organ dysfunction in each patient using the Sequential Organ Failure Assessment score [19]: the maximum serum bilirubin and creatinine levels and the minimum platelet count from 24 hours to 28 days; whether a given patient received vasopressors within 24 hours or after the first 24 hours of ED arrival; and whether endotracheal intubation was performed after the first 24 hours of ED arrival. We also determined whether patients underwent coronary angiography (CAG). An alternative diagnosis other than myocardial infarction (MI) was sought in each patient. The final diagnosis other than MI was extracted from the "final diagnosis" section of the EMRs. We collected clinically relevant diseases potentially related to elevated TnI levels, including pulmonary embolism, kidney disease (acute kidney injury and chronic kidney disease), aortic disease (aortic dissection, aortic aneurysm, and arterial thromboembolism), cardiac arrhythmia, active cancer, and cerebrovascular accident (ischemic and hemorrhagic stroke).

- 4 **Study outcomes**The primary outcome was the in-hospital mortality rate within 28 days of presentation. Secondary outcomes were new-onset cardiovascular, coagulation, hepatic, and renal dysfunctions (Sequential Organ Failure Assessment sub-score ≥ 2), and respiratory dysfunction after the first 24 hours of ED arrival. Since the PaO₂/FiO₂ ratio was not available in the majority of our patients who were not admitted to the intensive care unit, respiratory dysfunction was defined as a need for endotracheal intubation.
- 5 **Statistical analysis**Due to its retrospective nature, this study was potentially confounded by selection bias. We therefore performed a propensity analysis to investigate the extent to which execution of a blood gas test (PaO₂ in our study; "treatment" variable) influenced the 28-day in-hospital mortality rate (dependent variable), considering the independent variables in patients who had PaO₂ results (study group) versus those who did not (control group). An available PaO₂ result within the first 24 hours after ED arrival was used as the treatment variable, and the 28-day in-hospital mortality rate was used as the dependent variable. In a multivariate logistic regression analysis, demographic (age and sex), physiological (NEWS), biochemical (highest levels of TnI within 24 hours, white blood cells, hemoglobin, platelets, serum glucose, creatinine, albumin, bilirubin, and CRP), and electrocardiographic (STEMI or not) data, and whether patients underwent CAG, were used as independent variables, and execution of a blood gas test (whether the patient had PaO₂ results) was used as the dependent variable. We selected significant variables that affected the propensity of execution of a blood gas test, and the average treatment effect was calculated using propensity score matching. We calculated

the hyperoxia metrics used in a previous study [19], including the maximum PaO₂ (PaO₂MAX), average PaO₂ (PaO₂AVG), and area under the curve within the first 24 hours of admission (AUC24). To estimate the cumulative exposure to hyperoxia in each patient, we used the PaO₂AVG at the start (0 hour) and endpoint (24 hour) of the curve to calculate AUC24 using the trapezoid integration method. Since hyperoxia has not been defined formally, we used cutoffs based on those determined by previous studies [14,20] (normoxia, 60–120 mmHg; mild hyperoxia, 120–180 mmHg; and severe hyperoxia, > 180 mmHg) and distribution-based cutoffs in our population using the 9th and 10th deciles (cutoff at the 80th and 90th percentiles, respectively) of the PaO₂MAX, PaO₂AVG, and AUC24. The variables with the most missing values in our dataset were the initial PaO₂ (11.4%), initial CRP (3.1%), AUC24 (2.4%), and arterial oxyhemoglobin saturation (SpO₂) (1.1%). We performed multiple imputations using chained equations (imputation number = 20) to impute missing values [21]. Predictive mean matching values from the five nearest neighbors were chosen for imputation. We assumed that the majority of the data were missing at random, because the missing laboratory results were due to the physicians' decision to order tests depending on the patient's condition. The AUC24 could be calculated only when all time-related information included in the PaO₂ report was available. Missing time variables were caused by mechanical failure during a certain study period. As we hypothesized that the mechanism underlying these missing values was completely random, the AUC24 was not used for imputation and was inserted as a passive variable. We conducted a logistic regression analysis using the imputed data, including all demographic, physiologic, laboratory, and clinical variables, and a multivariate analysis was performed using the variables that yielded a p-value < 0.001 in the univariate analysis. The adjusted odds ratios (ORs) for PaO₂MAX, PaO₂AVG, and AUC24 of the mild hyperoxia and severe hyperoxia groups compared with the normoxia group were calculated. The same analysis was performed on each secondary outcome (cardiovascular, coagulation, hepatic, renal, and respiratory dysfunctions). The Kaplan–Meier method and log rank test were used to compare the survival probabilities of the normoxia, mild hyperoxia, and severe hyperoxia groups. The χ^2 test was used to determine differences in categorical data and the Mann–Whitney U test for differences in continuous data, as all continuous variables showed a skewed distribution. All p-values were two-sided, and a value of $p < 0.05$ was considered to indicate statistical significance. Analyses were conducted using Stata, version 13 (StataCorp, LP, College Station, TX, USA).