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Partial pressure of arterial carbon dioxide and survival to hospital discharge among patients requiring acute mechanical ventilation: a cohort study

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Abstract

Purpose—To describe the prevalence of hypocapnia and hypercapnia during the earliest period of mechanical ventilation, and determine the association between $P_a\text{CO}_2$ and mortality.

Materials and Methods—A cohort study using an emergency department registry of mechanically ventilated patients. $P_a\text{CO}_2$ was categorized: hypocapnia (< 35 mmHg), normocapnia (35 - 45 mmHg), and hypercapnia (> 45 mmHg). The primary outcome was survival to hospital discharge.

Results—A total of 1,491 patients were included. Hypocapnia occurred in 375 (25%) patients and hypercapnia in 569 (38%). Hypercapnia (85%) had higher survival rate compared to normocapnia (74%) and hypocapnia (66%), $P < 0.001$. $P_a\text{CO}_2$ was an independent predictor of survival to hospital discharge [hypocapnia (aOR 0.65 (95% confidence interval [CI] 0.48 - 0.89), normocapnia (reference category), hypercapnia (aOR 1.83 (95% CI 1.32 - 2.54)]. Over ascending ranges of $P_a\text{CO}_2$, there was a linear trend of increasing survival up to a $P_a\text{CO}_2$ range of 66 - 75 mmHg, which had the strongest survival association, aOR 3.18 (95% CI 1.35 - 7.50).

Conclusions—Hypocapnia and hypercapnia occurred frequently after initiation of mechanical ventilation. Higher $P_a\text{CO}_2$ levels were associated with increased survival. These data provide rationale for a trial examining the optimal $P_a\text{CO}_2$ in the critically ill.

Keywords

mechanical ventilation; hypercapnia; clinical outcomes

Introduction

Mechanical ventilation is a common indication for critical care services, both in the intensive care unit (ICU) and emergency department (ED)[1, 2]. As the population ages, the need is increasing[3]. Several best practices, including low tidal volume for prevention of ventilator-induced lung injury (VILI), protocols for sedation and weaning, and early detection and treatment of sepsis have improved outcomes in mechanically ventilated patients. Even with these approaches, mortality for mechanically ventilated ICU patients remains high, at over 30%[4, 5]. Therefore finding new approaches to reduce mortality is crucial.

The management of the partial pressure of arterial carbon dioxide ($P_a\text{CO}_2$) is a fundamental aspect of care in mechanically ventilated patients. In the critically ill, derangements in $P_a\text{CO}_2$ occur in up to 70% of ventilated patients[6, 7]. The prevailing paradigm is that hypercapnia has either a deleterious effect on outcome or is a simple by-product of low tidal volume ventilation (i.e. permissive hypercapnia). A recent secondary analysis found severe hypercapnia to be associated with mortality among patients with acute respiratory distress syndrome (ARDS)[8]. Hence, the normalization of $P_a\text{CO}_2$ levels can be an intuitive therapeutic goal. However, increasing data supports the notion that hypercapnia has biologically important beneficial effects through various mechanisms, including anti-inflammation, mitigation of VILI, and modulation of gene expression [9-12]. Among post-cardiac arrest patients, hypercapnia has been suggested to attenuate injury through

vasodilation and increased cerebral blood flow [13-15]. These data suggest that hypercapnia could confer additional advantages beyond low stretch ventilation and could be a therapeutic target to improve outcome. Conversely, hypercapnia also has potentially negative consequences, including increased pulmonary vascular tone, elevated intracranial pressure, and negative inotropy [16]. Despite the equipoise with respect to the optimal management of $P_a\text{CO}_2$, this has not been tested rigorously across a diverse cohort of mechanically ventilated patients, and it is currently unclear if hypercapnia has the same association with mortality among mechanically ventilated patients without ARDS. Given the fact that mechanical ventilation is delivered globally to hundreds of thousands of patients annually, and is a cornerstone of therapy in acute respiratory failure, investigating the impact of $P_a\text{CO}_2$ on outcome could have large-scale implications for many critically ill patients.

The objective of this study was to describe the prevalence of hypocapnia and hypercapnia during the earliest period of mechanical ventilation, and to determine the association between $P_a\text{CO}_2$ and mortality among mechanically ventilated non-ARDS arrest patients. We hypothesized that alterations in $P_a\text{CO}_2$ would be common, and given the pre-clinical data in this domain, hypercapnia would be associated with reduction in mortality.

Materials and Methods

Study design and participants

We conducted a cohort study, using an ED registry of patients with acute initiation of mechanical ventilation, at a tertiary academic center in St. Louis, Missouri, USA (September 2009 to March 2016)[17, 18]. Patients with initiation of mechanical ventilation in the ED were assessed for inclusion. Inclusion criteria: 1) age ≥ 18 years; and 2) mechanical ventilation via an endotracheal tube. Exclusion criteria: 1) death or discontinuation of mechanical ventilation within 24 hours; 2) chronic mechanical ventilation; 3) presence of a tracheostomy; 4) transfer to another hospital; 5) presence of acute respiratory distress syndrome (ARDS) during ED presentation[19]; and 6) cardiac arrest or drug overdose as the reason for mechanical ventilation. This study was approved by the institutional review board under waiver of informed consent, and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Additional File 1, Table S1) [20].

Procedures

Baseline demographics, comorbid conditions, indication for mechanical ventilation, illness severity, and blood pressure were collected. Pertinent treatment variables in the ED included the receipt of antibiotics and vasopressors. Arterial blood gas (ABG) analyses were performed after initiation of mechanical ventilation while subjects were in the ED. This initial blood gas was used in the analysis of $P_a\text{CO}_2$ and outcome.

All ED mechanical ventilator variables, airway pressures, pulmonary mechanics, and gas exchange variables were collected. ICU ventilator settings, airway pressures, and pulmonary mechanics were followed for up to two weeks and collected twice daily. For purposes of the

analyses, the mean values for the ICU ventilator variables over the two-week period were used.

Data was retrieved from the electronic medical record and organized and maintained in an electronic database. Data accuracy was verified with the aid of a research assistant, trained and blinded to study objectives.

Sepsis was defined as previously described[21]. Lung-protective tidal volume was defined as the use of tidal volume of 8 mL/kg predicted body weight (PBW)[22]. Static compliance (mL/ cm H₂O) of the respiratory system (C_{RS}) was calculated as: tidal volume/[plateau pressure - positive end expiratory pressure (PEEP)]. Driving pressure (cm H₂O) was calculated as: tidal volume/ C_{RS} .

The primary outcome was survival to hospital discharge.

Statistical analysis

For descriptive statistics the categorical data was displayed as counts and proportions, and continuous data as mean values and standard deviation (SD) or median values and interquartile range (IQR). Categorical variables were compared using the chi-square test. Continuous variables were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test, based on the distribution of the data. To correct for multiple comparisons we used the Bonferroni correction. Differences in P_aCO_2 categories were considered statistically significant if $P < 0.017$. Spearman's correlation coefficient (r) was used to assess the relationship between P_aCO_2 , tidal volume, respiratory rate, and pH.

To test the relationship between P_aCO_2 and survival, a multivariable logistic regression model was constructed with survival to hospital discharge as the dependent variable. P_aCO_2 in the ED was *a priori* categorized into the following groups: hypocapnia (< 35 mmHg), normocapnia (35 - 45 mmHg), and hypercapnia (> 45 mmHg), and treated as a categorical variable, with normocapnia as the reference. *A priori*, candidate variables for inclusion in the model included: 1) baseline characteristics with known prognostic significance for outcome in mechanically ventilated patients; 2) clinically relevant ED treatment variables; 3) ED ventilator variables; 4) ICU ventilator variables; and 5) pulmonary mechanic variables. Candidate variables were entered into the model if statistically different at $P < 0.20$ between P_aCO_2 groups and are displayed in Additional File 2, Table S2. Because of the high correlation between the variables related to pulmonary mechanics (plateau pressure, static compliance, driving pressure), only one of the variables was included in the model. Therefore, given the increasing evidence demonstrating the importance of driving pressure on outcome, it was decided to enter driving pressure into the model [23]. Backward elimination with a criterion of $P < 0.05$ for retention in the model was used. Statistical interactions and collinearity were assessed. Goodness of fit was evaluated with the Hosmer-Lemeshow test.

To further examine if an association between P_aCO_2 and outcome existed, survival to hospital discharge was graphed across ascending ranges of P_aCO_2 (< 35, 35-45, 46-55, 56-65, 66-75, >75 mmHg). This graph was inspected to assess if there was a threshold signal

for survival over P_aCO_2 ranges. The presence of significant linear trends in the odds of survival to hospital discharge was assessed using chi-square test for linear trend. To further test a relationship between ranges of P_aCO_2 and survival, P_aCO_2 was entered into a logistic regression model as a categorical variable using ascending ranges (i.e. < 35, 35-45, 46-55, 56-65, 66-75, >75 mmHg), with 35-45 mmHg as the reference. The model was adjusted for variables that were retained in the original model and used variables that were statistically independent of the other variables (i.e. the model was tested for collinearity).

To better control for the influence of diagnosis and etiology of respiratory failure, *a priori* subgroup analyses focused on patients with: a) sepsis; and b) trauma. As chronic obstructive pulmonary disease (COPD) is associated not only with hypercapnic respiratory failure but some data also suggests lower mortality in this cohort, a final *a priori* subgroup analysis that excluded patients with COPD was performed [4]. Since 374 patients could not be grouped into a specific indication for mechanical ventilation, a *post hoc* subgroup analysis which excluded patients mechanically ventilated for the indication of “other” was conducted. To further examine the influence of P_aCO_2 on outcomes in those patients with progressive pulmonary dysfunction, a second *post hoc* subgroup analysis was conducted on patients that developed ARDS after admission to the ICU. Finally, as there was a statistical difference in lactate levels between the groups, a subgroup analysis was conducted on those patients with lactate measured in the ED. For the subgroup analyses, we used variables that were retained in the original model. For the subgroups based on indication for mechanical ventilation (i.e. sepsis and trauma), indication for mechanical ventilation was removed as a covariable secondary to collinearity. For all models, robust standard errors to reduce the risk of type I error was used.

Assuming an approximate 1:1:1 ratio of patients in the hypocapnia, normocapnia, and hypercapnia groups, the sample size that was analyzed allowed > 80% power to detect a 10% absolute difference in survival between groups (assuming an alpha level of 0.017 when adjusted for multiple comparisons).

Results

Study population

A total of 3,525 subjects were assessed for inclusion; 1,491 were included in the final population (Figure 1).

Baseline characteristics of the study population are shown in Table 1. The median (IQR) APACHE II score for the entire cohort was 15 (11-19). The most common reason for initiation of mechanical ventilation was sepsis, followed by trauma. Post-intubation data

Table 2 displays post-intubation ventilator variables. After initial initiation of mechanical ventilation in the ED (n= 2, 854 ventilator settings), the minority of subjects had changes to tidal volume (11%), respiratory rate (18%), PEEP (7%), and F_iO_2 (32%). Tidal volume also remained fairly stable after admission to the ICU (n= 20, 364 ventilator settings) with 55% of subjects having no change to tidal volume, 23% with one to two changes, and 22% having three or more changes during the first two weeks of their ICU stay. The median (IQR)

P_aCO_2 for the entire cohort was 41 (34 - 53) mmHg. Three hundred and seventy-five (25%) subjects had exposure to hypocapnia, 547 (37%) had exposure to normocapnia, and 569 (38%) had exposure to hypercapnia. P_aCO_2 had a poor correlation with prescribed tidal volume ($r = -0.06$, $P = 0.014$) and respiratory rate ($r = 0.14$, $P = <0.001$). There was a modest correlation between P_aCO_2 and pH in the ED ($r = -0.54$, $P < 0.001$). Hypoxia in the ED ($P_aO_2 < 60$ mmHg) was more common among subjects with hypercapnia compared to normocapnia and hypocapnia, 8% vs. 2% and 1% respectively ($P < 0.001$).

Outcome analysis

The primary outcome of survival to hospital discharge occurred in 76% of subjects. Those with exposure to hypercapnia had a higher proportion of survival to hospital discharge when compared to subjects with normocapnia and hypocapnia, 85% vs. 74% and 66%, respectively ($P < 0.001$) (Figure 2). Table 3 displays the multivariable logistic regression model with P_aCO_2 treated as a categorical variable and survival to hospital discharge as the dependent variable. After adjusting for all identified significant confounders, including tidal volume, P_aCO_2 was an independent predictor of survival to hospital discharge [hypocapnia (aOR 0.65 (95% confidence interval [CI] 0.48 - 0.89), normocapnia (reference category), hypercapnia (aOR 1.83 (95% CI 1.32 - 2.54))].

Figure 3 displays survival to hospital discharge rates across ascending ranges of P_aCO_2 . There was a significant linear trend of increasing survival (chi-square for linear trend, $P < 0.0001$) across the range. There was an increasing odds of survival to hospital discharge with incremental increases in P_aCO_2 up to a range of 66 - 75 mmHg, which had the strongest association with survival to hospital discharge, [aOR 3.18 (95% CI 1.35 - 7.50)] (Table 4). There was a decrease in the strength of the relationship between P_aCO_2 and survival when P_aCO_2 was greater than 75 mmHg, [aOR 1.72 (95% CI 0.95 - 3.09)].

Subgroup analyses

When the analysis was restricted to patients mechanically ventilated for sepsis [aOR 2.47 (95% CI 1.40 - 4.33)], and trauma [aOR 2.94 (95% CI 1.46 - 5.90)], elevated P_aCO_2 remained an independent predictor of survival (Additional File 3, Table S3). After exclusion of patients with COPD (Additional File 4, Table S4), elevated P_aCO_2 was an independent predictor of survival [aOR 1.84 (95% CI 1.24 - 2.73)]. In the subgroup analysis that excluded patients mechanically ventilated for the indication of "Other" (Additional File 5, Table S5) elevated P_aCO_2 was an independent predictor of survival [aOR 2.74 (95% CI 1.90 - 3.96)]. In the subgroup analysis of patients that developed ARDS after admission (Additional File 6, Table S6), elevated P_aCO_2 was again an independent predictor of survival [aOR 2.49 (95% CI 1.04 - 5.94)]. Finally, in patients with lactate measured in the ED (Additional File 7, Table S7) elevated P_aCO_2 remained an independent predictor of survival [aOR 1.96 (95% CI 1.33 - 2.89)].

Discussion

The original goal of mechanical ventilation was the normalization of arterial oxygen and carbon dioxide tension[24]. With increasing knowledge of VILI, the dangers of hyperoxia,

and the tolerance of hypercapnia, this therapeutic goal has appropriately shifted to protecting the patient from the mechanical power and oxygen delivered by the ventilator[22, 25-27]. While significant clinical data exists regarding VILI and hyperoxia, comparatively little has been devoted to the influence that $P_a\text{CO}_2$ management may have on outcome, and these analyses have focused primarily on the cardiac arrest population[6, 7, 14]. A previous secondary analysis found an association between hypercapnia (i.e. $P_a\text{CO}_2 > 50$ mmHg) and mortality among patients with ARDS [8]. It is possible this association between severe hypercapnia and mortality was driven by increased dead-space, which is common in patients with ARDS, and associated with increased mortality [28]. The focus of this investigation was to test the association between $P_a\text{CO}_2$ and survival among mechanically ventilated patients without ARDS, and the results have several implications.

First, hypocapnia and hypercapnia were common, occurring in 25% and 38% of patients respectively. This is consistent with previous data, demonstrating that deviations in $P_a\text{CO}_2$ away from normocapnia occur frequently during the earliest time period of mechanical ventilation[6, 7, 14]. There was also a poor correlation between $P_a\text{CO}_2$ and prescribed minute ventilation (tidal volume, respiratory rate). We are unable to explain factors potentially associated with this poor correlation, which could be related to factors such as increased dead space, hyperinflation, spontaneous respiratory efforts, or different sedation depth between groups. But given our observed association between $P_a\text{CO}_2$ and survival, this finding suggests that: 1) early, frequent arterial blood gas analysis should be used to titrate ventilator settings quickly; and/or 2) non-ventilator parameters that affect arterial CO_2 should be addressed (i.e. temperature, neuromuscular blockade, and shock resuscitation).

The main finding of this study was an association between higher $P_a\text{CO}_2$ levels and survival. These findings were stable across models and subgroup analyses. Furthermore, $P_a\text{CO}_2$ was adjusted for lung-protective tidal volume, driving pressure, and arterial pH, which suggests that hypercapnia may have exerted a beneficial effect independent of pulmonary mechanics or acidosis. When placed in context of the frequency of abnormalities in arterial CO_2 tensions during early mechanical ventilation, our findings suggest that early hypercapnia (or avoiding hypocapnia) could be a therapeutic target going forward, and provide scientific rationale for future studies to determine the optimal $P_a\text{CO}_2$ range for patients undergoing acute mechanical ventilation.

There are several strengths to the study. The sample size is large and the population of ventilated patients is diverse, enhancing external validity. Our results also remained consistent across several analyses, suggesting internal consistency. These data also have biological plausibility in that pre-clinical data shows hypercapnia can modulate inflammation, VILI, and immunity [9, 11, 12, 29, 30]. Hypercapnia can decrease some key components of inflammatory pathways, such as tumor necrosis factor- α and interleukin (IL)-1, which contribute to tissue injury [9, 31]. Hypercapnia has also been found to attenuate neutrophil activity through lowered intracellular pH [12, 32]. In pulmonary endothelial cells, hypercapnia decreases the DNA-binding activity of nuclear factor (NF)- κB , a regulator of pro-inflammatory pathways. This decreased binding attenuates IL-8 production, with a commensurate decrease in cell injury[33].

There are also several limitations to the study. First, as an observational cohort study, we can only describe associations and not causal inference. The dose-response association between increasing P_aCO_2 levels (up to a point) and survival seen in this study is consistent with previous pre-clinical data, and could suggest causality [34]. While we hypothesize that the association between hypercapnia and survival is secondary to hypercapnia-induced gene modification and anti-inflammation, without a biomarker assessment, we are unable to determine the direct effects of hypercapnia on end-organ damage or survival. Second, although we used multivariable logistic regression analyses to adjust for multiple potential confounders, there still exists the possibility that a CO_2 -associated confounder (i.e. low tidal volume, pH) drove the observed association between hypercapnia and survival. There was no observed difference in ICU tidal volume between the groups, and our statistical models adjusted for these confounders and were consistent in their results. It is also possible that unmeasured confounders which may affect both P_aCO_2 levels as well as outcome (e.g. pulmonary embolism, cardiac output, treatment/resuscitation variables) were responsible for the observed associations. We also did not formally study the time from intubation until the blood gas analyses were obtained; it is possible that the incidence of P_aCO_2 derangements, as well as the strength of the association with outcome, could have been different had this been standardized. Going forward, this level of granular data will be critical to examine in a prospective fashion in order to draw stronger conclusion regarding P_aCO_2 and outcome. Third, hypercapnia may also reflect a patient population that is less ill and therefore has a higher likelihood to survive. A higher APACHE II score and higher incidence of hypotension in the hypercapnic group suggests this was not the case. Finally, this is a very heterogeneous sample of mechanically ventilated patients. This, along with the study design, make it impossible to draw any conclusive results, and this study should be viewed as exploratory in nature and hypothesis-generating for future clinical studies. Although we adjusted the multivariable logistic regression model for the indication for mechanical ventilation, and performed multiple subgroup analyses, further studies are needed to test the association between P_aCO_2 and outcomes among specific, more homogeneous, patient populations. Other patient-centered clinical outcomes, such as lengths of stay and ventilator duration, should also be examined with these future studies.

Conclusions

In this observational study, derangements in arterial CO_2 tension were common during the earliest phases of mechanical ventilation, and higher P_aCO_2 levels are associated with increased survival to hospital discharge. Given the continued high mortality seen in mechanically ventilated patients, and the heterogeneity seen within this cohort, future research should focus on interventions which are relatively simple and scalable to real world conditions. Our current findings, placed in context of previous data, suggest that future investigation into early manipulation of arterial CO_2 tension is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Not applicable.

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Abbreviations

ABG	arterial blood gas
ANOVA	one-way analysis of variance
aOR	adjusted odds ratio
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	acute respiratory distress syndrome
CI	confidence interval
COPD	chronic obstructive pulmonary disease
C_{RS}	static compliance of the respiratory system
ED	emergency department
F_iO₂	fraction of inspired oxygen
ICU	intensive care unit
IL	interleukin
IQR	interquartile range
NF	nuclear factor
P_aCO₂	partial pressure of arterial carbon dioxide
PBW	predicted body weight
PEEP	positive end-expiratory pressure
SD	standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VILI	ventilator-induced lung injury

Highlights

- Hypocapnia and hypercapnia occur frequently after initiation of mechanical ventilation.
- Higher $P_a\text{CO}_2$ levels are associated with increased survival.
- Over ascending ranges of $P_a\text{CO}_2$, there is a linear trend of increasing survival up to a $P_a\text{CO}_2$ range of 66 - 75 mmHg, which has the strongest survival association

Objective

Figure 1. Study flow diagram

Figure 2. Partial pressure of arterial carbon dioxide ($P_a\text{CO}_2$) and survival to hospital discharge among patients with hypocapnia, normocapnia, and hypercapnia

Hypercapnia was associated with a higher proportion of survival to hospital discharge when compared to subjects with normocapnia and hypocapnia, 85% vs. 74% and 66%, respectively ($P < 0.001$).

Figure 3. Partial pressure of arterial carbon dioxide (PaCO₂) and survival to hospital discharge
There was a significant linear trend of increasing survival (chi-square for linear trend, $P < 0.0001$) across the range.

Table 1

Baseline characteristics at the time of intubation.

	All Subjects n = 1491	Hypocapnia ^a n = 375	Normocapnia ^b n = 547	Hypercapnia ^c n = 569	P - value
Age (years)	59 (17)	58 (17)	60 (18)	59 (16)	0.305
Female gender, n (%)	688 (46)	178 (47)	240 (44)	270 (47)	0.409
Race, n (%)					0.003
Black	859 (58)	211 (56)	308 (56)	340 (60)	
White	615 (41)	153 (41)	235 (43)	227 (39)	
Other	17 (1)	11(3)	4 (1)	2 (1)	
Comorbidities, n (%)					
Chronic obstructive pulmonary disease	375 (25)	41 (11)	83 (15)	251 (44)	<0.001
Malignancy	262 (18)	83 (22)	83 (15)	96 (17)	<0.001
Congestive heart failure	350 (23)	60 (16)	109 (20)	181 (32)	<0.001
Diabetes mellitus	526 (35)	118 (31)	190 (35)	218 (38)	0.132
End stage renal disease	116 (8)	24 (6)	46 (8)	46 (8)	0.885
Cirrhosis	117 (8)	53 (14)	36 (7)	28 (5)	0.148
Indication for mechanical ventilation, n (%)					
Asthma	39 (3)	0	11 (2)	28 (5)	<0.001
Chronic obstructive pulmonary disease	122 (8)	4 (1)	9 (2)	109 (19)	<0.001
CHF/pulmonary edema	100 (7)	12 (3)	29 (5)	59 (10)	<0.001
Sepsis	471 (31)	142 (38)	159 (29)	170 (30)	0.010
Trauma	385 (26)	91 (24)	198 (36)	96 (17)	<0.001
Other	374 (25)	126 (34)	141 (26)	107 (19)	<0.001
APACHE II score *	15 (11 - 19)	14 (10 - 19)	13 (9 - 18)	16 (12 - 21)	<0.001
Mean arterial pressure (mmHg)	87 (69 - 107)	85 (69 - 101)	89 (71 - 112)	86 (68 - 107)	0.045
Hypotension (MAP < 70 mmHg), n (%)	380 (25)	96 (26)	126 (23)	158 (28)	0.193
Vasopressor infusion, n (%)	320 (21)	100 (27)	102 (19)	118 (21)	0.012

	All Subjects n = 1491	Hypocapnia ^a n = 375	Normocapnia ^b n = 547	Hypercapnia ^c n = 569	P - value
Antibiotic administration, n (%)	697 (47)	205 (55)	222 (41)	270 (47)	<0.001
Lactate, mmol/L (n= 1,070)	2.3 (1.4 - 4.0)	2.8 (1.7 - 4.9)	2.4 (1.5 - 4.2)	2.0 (1.2 - 3.4)	<0.001

^aPaCO₂ < 35 mmHg;
^bPaCO₂ 35–45 mmHg;
^cPaCO₂ > 45 mmHg.

Continuous variables are reported as mean (standard deviation) and median (interquartile range).

CHF: congestive heart failure; APACHE: acute physiology and chronic health evaluation; MAP: mean arterial pressure

* modified score, which excludes Glasgow Coma Scale

P-values are from the chi-square test for categorical variables, the one-way analysis of variance (ANOVA) for continuous variables, and the Kruskal-Wallis test (lactate).

Table 2
Ventilator variables in the emergency department and intensive care unit

Emergency Department	All Subjects n = 1491	Hypocapnia ^d n = 375	Normocapnia ^b n = 547	Hypercapnia ^c n = 569	p - values
Tidal volume (mL/kg PBW)	7.5 (6.4 - 8.8)	7.7 (6.8 - 8.8)	7.3 (6.4 - 8.5)	7.3 (6.4 - 8.7)	0.002
Tidal volume 8 mL/kg PBW	937 (63)	212 (57)	364 (67)	361 (63)	0.008
Respiratory rate	16 (14 - 20)	14 (14 - 20)	16 (14 - 20)	16 (14 - 20)	<0.001
Minute Ventilation (mL/kg PBW * min)	123 (105 - 146)	122 (103 - 144)	121 (103 - 138)	128 (108 - 153)	<0.001
FiO ₂	67 (40 - 100)	70 (40 - 100)	60 (40 - 100)	70 (50 - 100)	0.012
PEEP	5 (5 - 5)	5 (5 - 5)	5 (5 - 5)	5 (5 - 7)	<0.001
pH	7.33 (7.23-7.41)	7.41 (7.33-7.47)	7.37 (7.31-7.41)	7.24 (7.17-7.30)	<0.001
PaCO ₂ (mmHg)	41 (34 - 53)	30 (26 - 33)	39 (37 - 42)	58 (50 - 75)	<0.001
PaO ₂ (mmHg)	142 (93 - 216)	169 (113 - 239)	146 (103 - 212)	117 (80 - 201)	<0.001
Hypoxia (PaO ₂ < 60 mmHg), n (%)	66 (4)	5 (1)	12 (2)	49 (8)	<0.001
PaO ₂ /FiO ₂	233 (142 - 345)	278 (166 - 390)	250 (166 - 355)	195 (117 - 294)	<0.001
Intensive care unit					
Tidal volume (mL/kg PBW)	8.0 (7.0 - 9.0)	8.0 (7.0 - 9.0)	8.0 (7.0 - 9.0)	8.0 (7.0 - 9.0)	0.312
FiO ₂	43 (40 - 51)	43 (40 - 51)	43 (40 - 50)	45 (40 - 53)	<0.001
PEEP	5 (5 - 5)	5 (5 - 5)	5 (5 - 5)	5 (5 - 6)	<0.001
pH	7.40 (7.35-7.43)	7.41 (7.37-7.45)	7.40 (7.36-7.43)	7.38 (7.36-7.42)	<0.001
Hypoxia (PaO ₂ < 60 mmHg), n (%)	217 (15)	51 (14)	75 (14)	91 (16)	0.383
Pulmonary Mechanics					
Plateau pressure (mmHg)	20 (17 - 23)	19 (17 - 22)	19 (17 - 22)	22 (19 - 25)	<0.001
Plateau pressure > 30 mmHg, n (%)	64 (4)	8 (2)	11 (2)	45 (8)	<0.001
Static compliance (mL / cm H ₂ O)	36 (28 - 46)	39 (31 - 50)	39 (29 - 50)	32 (25 - 42)	<0.001
Driving pressure (cm H ₂ O)	14 (11 - 18)	12 (10 - 16)	13 (10 - 17)	15 (12 - 20)	<0.001
Duration of mechanical ventilation (hours)	77 (41 - 171)	71 (42 - 177)	83 (39 - 173)	74 (42 - 166)	0.937

Continuous variables are reported as median (interquartile range).

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$P_{aCO_2} > 35$ mmHg;
 P_{aCO_2} 35-45 mmHg;
 $P_{aCO_2} < 45$ mmHg.

* Pulmonary mechanics are the mean values during the first two weeks of mechanical ventilation, combining values from emergency department and intensive care unit.

PBW: predicted body weight; F_iO_2 : fraction of inspired oxygen; PEEP: positive end-expiratory pressure; P_aCO_2 : partial pressure of arterial carbon dioxide; P_aO_2 : partial pressure of arterial oxygen; F_iO_2 : fraction of inspired oxygen

P values are from the one-way analysis of variance (ANOVA) or Kruskal-Wallis test, based on data distribution.

Table 3

Multivariable logistic regression model with partial pressure of arterial carbon dioxide (P_aCO_2) entered as a categorical variable and survival to hospital discharge as the dependent variable.

Variables	aOR	95% LCI	95% UCI	Standard Error	p-value
Hypocapnia ^a	0.64	0.46	0.88	0.10	0.006
Normocapnia ^b			Reference		
Hypercapnia ^c	2.00	1.43	2.79	0.34	<0.001
Age	0.76	0.70	0.83	0.03	<0.001
ED Apache II	0.98	0.96	1.00	0.01	0.034
Malignancy	0.51	0.37	0.71	0.09	<0.001
Reason for Mechanical Ventilation					
Respiratory failure	2.45	1.52	3.95	0.60	<0.001
Trauma	0.52	0.37	0.74	0.09	<0.001
ICU FiO_2	0.97	0.96	0.98	0.01	<0.001
ICU pH	1.41	1.19	1.67	0.12	<0.001
Vasopressor infusion	0.68	0.48	0.95	0.12	0.025
Antibiotics	1.53	1.14	2.05	0.23	0.005
Driving pressure	0.97	0.95	1.00	0.01	0.022

^a $P_aCO_2 < 35$ mmHg;

^b P_aCO_2 35-45 mmHg;

^c $P_aCO_2 > 45$ mmHg.

Removed from model for non-significance: emergency department (ED) respiratory rate ($p = 0.98$), race ($p = 0.66$), ED tidal volume ($p = 0.58$), congestive heart failure ($p = 0.87$), partial pressure of arterial oxygen/fraction of inspired oxygen ratio ($p = 0.62$), ED pH ($p = 0.54$), ED hypotension ($p = 0.55$), ED positive end expiratory pressure ($p = 0.33$), ICU positive end expiratory pressure ($p = 0.36$), diabetes mellitus ($p = 0.39$), liver cirrhosis ($p = 0.18$), reason for mechanical ventilation: sepsis ($p = 0.16$), chronic obstructive pulmonary disease ($p = 0.13$), obesity ($p = 0.07$).

APACHE: acute physiology and chronic health evaluation; ED: emergency department; FiO_2 : fraction of inspired oxygen; aOR: adjusted odds ratio; LCI: lower confidence interval; UCI: upper confidence interval; ICU: intensive care unit

Table 4

Multivariable logistic regression model with partial pressure of arterial carbon dioxide (P_aCO_2), entered as a categorical variable using ascending ranges of P_aCO_2 , and survival to hospital discharge as the dependent variable.

Variables	aOR	95% LCI	95% UCI	Standard Error	p-value
$PaCO_2$ (mmHg)					
< 35	0.64	0.46	0.88	0.10	0.006
35-45			Reference		
46-55	1.68	1.13	2.52	0.34	0.011
56-65	2.69	1.36	5.33	0.94	0.004
66-75	3.53	1.47	8.48	1.58	0.005
>75	1.74	0.98	3.10	0.51	0.058
Age	0.76	0.70	0.83	0.03	0.000
ED Apache II	0.98	0.96	1.00	0.01	0.031
Malignancy	0.51	0.36	0.71	0.09	0.000
Reason for Mechanical Ventilation					
Respiratory failure	2.46	1.51	4.01	0.61	0.000
Trauma	0.52	0.37	0.73	0.09	0.000
ICU FIO_2	0.97	0.96	0.98	0.01	0.000
ICU pH	1.42	1.20	1.68	0.12	0.000
Vasopressor infusion	0.68	0.49	0.95	0.12	0.024
Antibiotics	1.52	1.13	2.04	0.23	0.005
Driving pressure	0.97	0.95	0.99	0.01	0.016

APACHE: acute physiology and chronic health evaluation; ED: emergency department; FIO_2 : fraction of inspired oxygen; aOR: adjusted odds ratio; LCI: lower confidence interval; UCI: upper confidence interval; ICU: intensive care unit