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# Patterns and Impact of Arterial $CO_2$ Management in Patients With Acute Respiratory Distress Syndrome

## Insights From the LUNG SAFE Study

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**BACKGROUND:** Considerable variability exists regarding $CO_2$ management in early ARDS, with the impact of arterial $CO_2$ tension on management and outcomes poorly understood.

**RESEARCH QUESTION:** To determine the prevalence and impact of hypocapnia and hypercapnia on the management and outcomes of patients with early ARDS enrolled in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, an international multicenter observational study.

**STUDY DESIGN AND METHODS:** Our primary objective was to examine the prevalence of day 1 and sustained (day 1 and 2) hypocapnia ($Paco_2 < 35$ mm Hg), normocapnia ($Paco_2$ 35-45 mm Hg), and hypercapnia ($Paco_2 > 45$ mm Hg) in patients with ARDS. Secondary objectives included elucidating the effect of $CO_2$ tension on ventilatory management and examining the relationship with ARDS outcome.

**RESULTS:** Of 2,813 patients analyzed, 551 (19.6%; 95%CI, 18.1-21.1) were hypocapnic, 1,018 (36.2%; 95% CI, 34.4-38.0) were normocapnic, and 1,214 (43.2%; 95% CI, 41.3-45.0) were hypercapnic, on day 1. Sustained hypocapnia was seen in 252 (9.3%; 95% CI, 8.2-10.4), sustained normocapnia in 544 (19.3%; 95% CI, 17.9-20.8), and sustained hypercapnia in 654 (24.1%; 95% CI, 22.5-25.7) patients. Hypocapnia was more frequent and severe in patients receiving noninvasive ventilation but also was observed in patients on controlled mechanical ventilation. Sustained hypocapnia was more frequent in middle-income countries, whereas sustained hypercapnia was more frequent in Europe. ARDS severity profile was highest in sustained hypercapnia, and these patients received more protective ventilation. No independent association was seen between arterial $CO_2$ and outcome. In propensity-matched analyses, the hospital mortality rate was 36% in both sustained normocapnic and hypercapnic patients ($P = 1.0$). ICU mortality was higher in patients with mild to moderate ARDS receiving sustained hypocapnia (38.1%) compared with normocapnia (27.1%).

**INTERPRETATION:** No evidence was found for benefit or harm with hypercapnia. Of concern, ICU mortality was higher with sustained hypocapnia in mild to moderate ARDS.

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**KEY WORDS:** ARDS; epidemiology; hypercapnia; hypocapnia; mechanical ventilation

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**ABBREVIATIONS:** IQR = interquartile range; LOESS = locally estimated scatterplot smoothing; PF ratio = $Pao_2/Fio_2$; SOFA = sequential organ failure assessment

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The potential for high lung stretch to directly injure the lungs—termed ventilation-induced lung injury—is now well recognized.[1,2] Protective ventilatory strategies that reduce lung stretch improve survival in patients with ARDS.[2,3] In patients with ARDS, a key "enabler" of lung protective ventilation has been the reduction of tidal and minute ventilation, which can lead to a "permissive" hypercapnia.[4,5] However, concerns exist regarding potential deleterious effects of hypercapnia. Preclinical studies show that hypercapnia can exert both beneficial and harmful[6-10] effects. Hypocapnia is also seen in patients with ARDS, and it has the potential to exert deleterious effects[7,11,12]; indeed it is one of the criteria for the systemic inflammatory response syndrome.[13] Hypocapnia also may indicate an unnecessarily high alveolar ventilation, which may increase ventilation-induced lung injury.

There are no definitive guidelines on how to manage $Paco_2$ in patients with ARDS. We wished to examine how $Paco_2$ was managed in patients with ARDS enrolled in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study. Our primary objective was to examine the prevalence of hypocapnia ($Paco_2$ < 35 mm Hg), normocapnia ($Paco_2$ 35-45 mm Hg), and hypercapnia ($Paco_2$ > 45 mm Hg) on days 1 and 2 of ARDS. Secondary objectives included characterizing the illness severity and ventilatory management of patients with sustained hypocapnia, normocapnia, and hypercapnia, and examining the impact of $Paco_2$ on days 1 and 2 with subsequent outcomes in patients with ARDS. Our overarching hypotheses were that altered arterial $CO_2$ tensions were prevalent in ARDS, and that these alterations in $CO_2$ tension exerted effects on patient outcomes, in the LUNG SAFE patient cohort.

## Methods

### Study Design, Patients, and Data Collection

The detailed methods and protocol for data collection have published elsewhere.[14] LUNG SAFE was an international (49 countries), multicenter (459 ICUs in 435 hospitals), prospective cohort study, with a 4-week enrollment window in the winter season in both hemispheres.[14] National and site coordinators (e-Appendix 1) obtained ethics committee approval, and either patient consent or ethics committee waiver of consent as appropriate. Additional methodological details are available in e-Appendix 2.

Patients admitted to a study ICU that underwent invasive or noninvasive ventilation were enrolled in LUNG SAFE. Exclusion criteria were (1) age younger than 16 years; and (2) inability to obtain informed consent (where required). After enrollment, patients were evaluated daily for acute hypoxemic respiratory failure, and if this condition was present, patients were classified as having ARDS based on whether they fulfilled all of the Berlin criteria.[14]

Given the study focus on early $Paco_2$ management in patients with ARDS, we restricted the study population to patients that fulfilled ARDS criteria within 48 hours of onset of acute hypoxic respiratory failure. All data were recorded for each patient at the same time each day, normally as close as possible to 10:00 AM. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis.

### Data Definitions and Statistical Analyses

For the purposes of this analysis, the following definitions were applied on day 1 of ARDS: hypocapnia ($Paco_2$ < 35 mm Hg), normocapnia ($Paco_2$ 35-45 mm Hg), and hypercapnia ($Paco_2$ > 45 mm Hg). Patients were considered to have sustained hypocapnia, normocapnia, and hypercapnia if their $Paco_2$ remained in the same category on day 2 as it was on day 1 after ARDS onset. Because base excess was not collected in LUNG SAFE, we estimated this parameter applying Henderson-Hasselbalch equation, based on pH and $Paco_2$ measures.[15] Progression of ARDS severity was defined at the second day of ARDS and classified as: resolved (no fulfillment of Berlin ARDS criteria), improvement (improvement of ARDS class severity from day 1 to day 2), stable (no change in ARDS class severity), worsened (worsening of ARDS class severity from day 1 to day 2). For certain analyses, we dichotomized patients based on a $Pao_2/Fio_2$ (PF ratio) of 150 mm Hg, and termed these groups mild to moderate ARDS ($Pao_2/Fio_2$ ≥ 150 mm Hg) and moderate to severe ARDS($Pao_2/Fio_2$ < 150 mm Hg), respectively. Other data definitions are in e-Appendix 2 or have been previously reported.[14,16,17]

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Categorical data are reported as counts and percentages, and continuous data are reported as mean and SD or median and interquartile range, according to the symmetry of data distribution. To assess differences among three groups (sustained hypocapnia, normocapnia, and hypercapnia), we performed the $\chi^2$ test (or Fisher exact test) for discrete variables, and the analysis of variance (or Kruskal-Wallis test) for continuous variables. Bonferroni correction was applied to determine significance in the setting of multiple comparisons. The $\chi^2$ test (or Fisher exact test), Student *t*-test, or Wilcoxon Mann-Whitney test were used to assess differences between groups in discrete and continuous distributions of parameters, respectively. The same approach was used to assess differences among groups in a subset of patients with controlled mechanical ventilation during the first day of ARDS.

Locally estimated scatterplot smoothing (LOESS) method was used to inspect the relationship between hospital mortality and $Paco_2$, minute ventilation, and acid-base parameters (base excess, pH) measured on day 1 of ARDS in patients with sustained hypocapnia, normocapnia, or hypercapnia. We applied generalized linear mixed models (logistic-link function and binomial distribution) with random intercept for taking into account the correlation among patients within the same ICU of enrollment, to assess the relationship between hospital and ICU mortality and factors associated with $CO_2$ management, considering all possible confounders (demographic characteristics, illness severity and ventilator setting measured at the first day of ARDS, resolution of ARDS). Results were reported as OR with 95% CI. The independent predictors were identified through a stepwise regression approach. This approach combines forward and backward selection methods in an iterative procedure (with a significance level of .05 for both entry and retention) to select predictors in the final multivariable model.

Propensity score matching method was applied to evaluate the possible impact of sustained normocapnia vs sustained hypercapnia on main outcomes (mortality, ventilation-free days, and duration of mechanical ventilation) in patients with ARDS. The matching algorithm used was the greedy method, and patients were matched (1:1 match without replacement), using a caliper of 0.2 SD of the logit of the propensity score, and the similarity of the matched groups was assessed by the standardized differences of each independent variable used in the propensity score estimation. A standardized difference of less than 0.10 was considered an indicator of negligible imbalance between groups. Statistical significance of the difference in the ventilation-free days and in the duration of mechanical ventilation was evaluated with Wilcoxon signed-rank test, whereas for the difference in proportions of deaths we applied McNemar's test. Survival probability in these matched groups was estimated using the Kaplan-Meier approach and assuming that patients discharged alive from the hospital before 90 days were alive on day 90. Statistical difference between survival curves was assessed through the Klein and Moeschberger test. The same approach was also applied to evaluate the possible impact of sustained normocapnia vs sustained hypocapnia on main outcomes.

All *P* values were two-sided, with $P < .05$ considered statistically significant. Statistical analyses were performed with R, version 3.5.2. (R Project for Statistical Computing, http://www.R-project.org) and SAS software, version 9.4 (SAS Institute).

## Results

Of the 3,022 (10.4%) patients that fulfilled ARDS criteria in the LUNG SAFE cohort, the 2,813 patients that developed ARDS in the first 48 hours were managed with either invasive (n = 2,377) or noninvasive (n = 436) mechanical ventilation (e-Fig 1) constituted the study population.

### *Prevalence of Hypocapnia and Hypercapnia*

On day 1 of ARDS, 551 (19.6%; 95% CI, 18.1-21.1) patients were hypocapnic, 1,018 (36.2%; 95% CI, 34.4-38.0) were normocapnic, and 1,214 (43.2%; 95% CI, 41.3-45.0) were hypercapnic (e-Fig 1). The $Paco_2$ varied with ARDS severity; hypercapnia was more frequent in patients with moderate-severe ARDS (PF ratio < 150 mm Hg), and by type of ventilation, with hypocapnia more frequent in noninvasively ventilated patients (Fig 1, e-Table 1). More severe hypercapnia ($Paco_2 \geq 60$ mm Hg) was less common, occurring in 14.3% (95% CI, 13.0-15.6) of patients, of whom 36.3% (146/402; 95% CI, 31.6-41.0) had severe ARDS. Median $Paco_2$ on day 1 was 43 mm Hg (interquartile range [IQR], 36.0-51.9). By day 2, the frequency of normocapnia had increased, whereas the frequency of hypocapnia and hypercapnia (particularly severe hypocapnia and hypercapnia) had decreased.

### *Sustained Hypocapnia, Normocapnia, and Hypercapnia*

**Prevalence:** Sustained hypocapnia was seen in 252 (9.3%; 95% CI, 8.2-10.4), sustained normocapnia in 544 (20.0%; 95% CI, 18.5-21.5), and sustained hypercapnia in 654 (24.1%; 95% CI, 22.5-25.7) patients (e-Fig 1). Patients with sustained hypercapnia had a higher prevalence of COPD, a lower frequency of immune incompetence, liver failure, and more pneumonia and less trauma as ARDS risk factors (Table 1). Sustained hypocapnia was more frequent in middle-income countries, whereas sustained hypercapnia was more frequent in European countries. A subanalysis, confined to patients in whom mechanical ventilation was controlled, demonstrated that hypocapnia was present in 12.7% (95% CI, 10.4-15.0) of patients under controlled ventilation (e-Table 2).

**Illness Severity:** ARDS severity profile was highest in patients with sustained hypercapnia, with lower PF ratio and lung compliance compared with patients with sustained normocapnia or hypocapnia (Table 2). In

contrast, nonpulmonary sequential organ failure assessment (SOFA) scores were significantly higher in patients with sustained hypocapnia. PF ratio improved by day 2 in patients with sustained hypocapnia, normocapnia, and hypercapnia, although PF ratio remained significantly lower in patients with sustained hypercapnia (e-Table 3). In patients with PF ratio < 150 mm Hg, peak and plateau pressures were significantly higher in patients with sustained hypercapnia (Fig 2A-2C).

**Ventilatory Management:** The proportion of patients undergoing controlled mechanical ventilation was significantly lower in patients with sustained hypocapnia (Table 2). Day 1 tidal volumes were significantly lower in sustained hypercapnia, whereas respiratory rates and minute volumes were significantly higher in sustained hypocapnia patients (Table 2; Fig 2D-2F). PEEP levels were higher, whereas the proportion receiving protective mechanical ventilation was higher, in patients with sustained hypercapnia on both days 1 and 2 of ARDS (Table 2; e-Table 3). The use of neuromuscular blockade, of prone positioning, and of any adjunct were all highest in patients with sustained hypercapnia (Table 2).

**Outcomes:** No differences were seen between the groups regarding the evolution of ARDS from day 1 to day 2 (Table 3). There were no between-group differences in

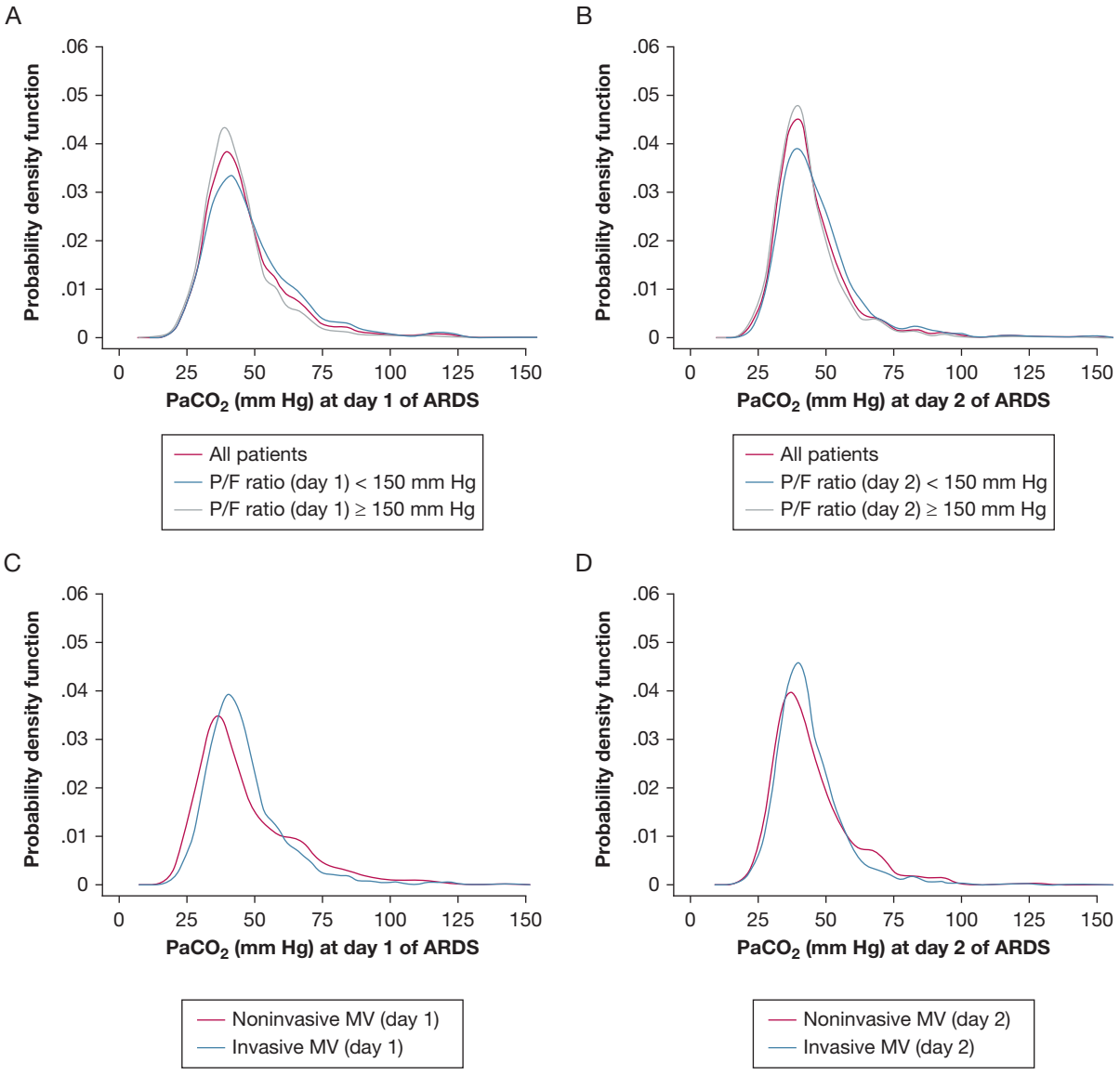


Figure 1 – *Density probability functions of $PaCO_2$ in study population (n = 2,813) stratified by P/F ratio and by mechanical ventilation, at day 1 (A, C) and at day 2 (B, D) of ARDS. P/F ratio = $Pao_2/Fio_2$.*

**TABLE 1** ] Main Characteristics of Study Population Stratified by Condition (Sustained Hypocapnia, Sustained Normocapnia, and Sustained Hypercapnia)

| Parameter | Sustained Hypocapnia | Sustained Normocapnia | Sustained Hypercapnia | *P* Value |
|---|---|---|---|---|
| Patients, No. (%) | | | | |
| All | 252 (17.38) | 544 (37.52) | 654 (45.10) | … |
| Enrolled in European high-income countries | 96 (11.85) | 302 (37.28) | 412 (50.86) | … |
| Enrolled in non-European high-income countries | 64 (17.68)[a] | 150 (41.44) | 148 (40.88)[a] | … |
| Enrolled in middle-income countries | 92 (33.09)[a,b] | 92 (33.09) | 94 (33.81)[a] | … |
| Comparison among areas, *P* value | < .0001 | 0.0948 | < .0001 | |
| Age, years, mean ± SD | 62.36 ± 16.38 | 60.55 ± 16.67 | 61.61 ± 16.30 | .3724 |
| Males, No. (%) | 151 (59.92) | 340 (62.50) | 422 (64.53) | .4199 |
| BMI, median [IQR] | 24.84 [22.15-28.58] | 25.81 [22.68-30.42] | 26.93 [22.86-31.49][c,d] | .0001 |
| Clinical recognition of ARDS, No. (%) | | | | |
| At baseline | 88 (34.92) | 160 (29.41) | 208 (31.80) | .2873 |
| During ICU stay | 155 (61.51) | 322 (59.19) | 402 (61.47) | .6889 |
| ARDS less than 24 hours | 51 (20.24) | 114 (20.96) | 98 (14.98)[d] | .0180 |
| Chronic disease,[e] No. (%) | | | | |
| COPD | 21 (8.33) | 80 (14.71)[c] | 260 (39.76)[c,d] | < .0001 |
| Diabetes mellitus | 50 (19.84) | 116 (21.32) | 151 (23.09) | .5297 |
| Immune incompetence (all types) | 72 (28.57) | 113 (20.77)[c] | 111 (16.97)[c] | .0005 |
| Chronic cardiac failure | 17 (6.75) | 48 (8.82) | 80 (12.23)[c] | .0244 |
| Chronic renal failure | 30 (11.90) | 54 (9.93) | 63 (9.63) | .5847 |
| Chronic liver failure | 17 (6.75) | 24 (4.41) | 12 (1.83)[c,d] | .0010 |
| Risk factors for ARDS, No. (%) | | | | |
| None | 14 (5.56) | 46 (8.46) | 64 (9.79) | .1241 |
| Only nonpulmonary | 46 (18.25) | 133 (24.45) | 80 (12.23)[d] | < .0001 |
| Only pulmonary | 157 (62.30) | 289 (53.13)[c] | 424 (64.83)[d] | .0001 |
| Both | 35 (13.89) | 76 (13.97) | 86 (13.15) | .9075 |
| Risk factors for ARDS,[e] No. (%) | | | | |
| Pneumonia | 162 (64.29) | 282 (51.84)[c] | 447 (68.35)[d] | < .0001 |
| Extrapulmonary sepsis | 47 (18.65) | 94 (17.28) | 92 (14.07) | .1511 |
| Aspiration of gastric contents | 36 (14.29) | 78 (14.34) | 73 (11.16) | .2028 |
| Pancreatitis | 11 (4.37) | 10 (1.84) | 8 (1.22)[c] | .0097 |
| Pulmonary vasculitis | 2 (0.79) | 4 (0.74) | 4 (0.61) | .9186 |
| Trauma | 7 (2.78) | 44 (8.09)[c] | 11 (1.68)[d] | < .0001 |
| Inhalation | 6 (2.38) | 10 (1.84) | 14 (2.14) | .8691 |
| Pulmonary contusion | 6 (2.38) | 30 (5.51) | 17 (2.60)[d] | .0137 |
| Burn | 0 (0.00) | 1 (0.18) | 2 (0.31) | 1.0000 |
| Noncardiogenic shock | 15 (5.95) | 35 (6.43) | 38 (5.81) | .9004 |
| Drowning | 0 (0.00) | 0 (0.00) | 1 (0.15) | 1.0000 |
| Drug overdose | 5 (1.98) | 9 (1.65) | 12 (1.83) | .9427 |
| Blood transfusion | 6 (2.38) | 30 (5.51) | 19 (2.91)[d] | .0272 |
| Other risk factors | 5 (1.98) | 18 (3.31) | 11 (1.68) | .1648 |

*(Continued)*

**TABLE 1** ] *(Continued)*

| Parameter | Sustained Hypocapnia | Sustained Normocapnia | Sustained Hypercapnia | *P* Value |
|---|---|---|---|---|
| ICU characteristics | | | | |
| Academic hospital, No. (%) | 181 (76.37) | 412 (77.74) | 467 (73.43) | .2222 |
| % of ICU on hospital beds, median [IQR] | 2.47 [1.54-4.00] | 2.61 [1.54-4.17] | 2.60 [1.58-4.33] | .6942 |
| Beds per physician, median [IQR] | 4.50 [3.00-9.40] | 4.50 [2.67-9.00] | 4.50 [2.67-9.00] | .4817 |
| Beds per nurse, median [IQR] | 1.50 [0.94-2.00] | 1.50 [1.00-2.00] | 1.33 [1.00-2.00] | .3995 |

Sustained hypocapnia was defined as $Paco_2$ < 35 mm Hg during the first 48 hours after ARDS onset; sustained normocapnia was defined as 35 ≤ $Paco_2$ < 45 mm Hg during the first 48 hours after ARDS onset; sustained hypercapnia was defined as $Paco_2$ ≥ 45 mm Hg during the first 48 hours after ARDS onset. For categorical data, statistical difference among groups was tested with $\chi^2$ or Fisher exact test, according to number of expected cases. For continuous data, statistical differences among groups were tested with analysis of variance or Kruskal-Wallis test based on normal data distribution. IQR = interquartile range [first and third quartile].
[a]*P* < .05, comparison with "European high-income countries" (Bonferroni correction).
[b]*P* < .05, comparison with "non-European high-income countries" (Bonferroni correction).
[c]*P* < .05, comparison with "sustained hypocapnia" (Bonferroni correction).
[d]*P* < .05, comparison with "sustained normocapnia" (Bonferroni correction).
[e]Sum of percentages is greater than 100%, because patient could have more than one chronic disease/risk factor.

the length of ICU or hospital stay, in ICU or hospital mortality, or in the limitation of life-sustaining measures in the ICU (Table 3).

LOESS analyses of the relationship between unadjusted mortality risk and day 1 $Paco_2$ showed increased mortality risk with more severe degrees of hypocapnia (Fig 3A). An increase in mortality risk was seen with increasing base deficit (Fig 3B), with decreasing pH (Fig 3C), and with increasing minute ventilation (Fig 3D).

Multivariable analyses of the factors associated with hospital mortality in these patients identified age, pH, respiratory rate, immunocompromised status, lack of adjunct use, and nonpulmonary SOFA score, mechanical ventilation, PEEP, and total respiratory rate as independently associated with outcome. The same predictors were found for ICU mortality, with the addition of PF ratio (<150 mm Hg; ≥150 mm Hg). $Paco_2$, both as a continuous variable and dichotomized by category (sustained hypocapnia, normocapnia, or hypercapnia) was not associated with ICU or hospital mortality in these analyses, either in the whole population or when dichotomized by PF ratio of 150 (Table 4; e-Table 4).

In a propensity-matched analysis, there were no differences between the sustained normocapnia and hypercapnia groups regarding the duration of invasive mechanical ventilation, the length of ICU or hospital stay, ICU (32% vs 32%, respectively) or hospital mortality (36% vs 36%, respectively), or in the limitation of life-sustaining measures in the ICU (Table 5; e-Table 5). A Kaplan-Meier analysis of hospital survival showed no significant between-group differences (Fig 4A).

In a propensity matched analysis, there were no overall differences between the sustained normocapnia and hypocapnia groups regarding the duration of invasive mechanical ventilation, the length of ICU or hospital stay, ICU (33% vs 39%, respectively) or hospital mortality (39% vs 44%, respectively), or the limitation of life-sustaining measures in the ICU (Table 6; e-Table 6). Of concern, ICU mortality was significantly higher in patients with mild to moderate ARDS receiving sustained hypocapnia (38%) vs sustained normocapnia (27%; Table 6). In a subsequent multivariate analysis restricted to patients with sustained normocapnia and sustained hypocapnia and with PF ratio ≥ 150 mm Hg, lower $Pco_2$ was associated with increased ICU and hospital mortality (e-Table 7). A Kaplan-Meier analysis of hospital survival showed no significant between-group differences (Fig 4B).

## Discussion

Both hypocapnia and hypercapnia were prevalent on days 1 and 2 of ARDS, with sustained hypocapnia and hypercapnia present in a significant minority of patients. Patients with sustained hypercapnia had more severe ARDS than patients with sustained normocapnia or hypocapnia. Of concern, patients with ARDS managed with hypocapnia and normocapnia received less protective mechanical ventilation, with higher tidal and minute volumes and higher respiratory rates being the "cost" of maintaining normocapnia/hypocapnia in these patients. We did not find any evidence in the patient

**TABLE 2** ] Illness Severity (on Day 1 of ARDS) and Ventilatory Management in Patients With Sustained Hypocapnia, Sustained Normocapnia, and Sustained Hypercapnia

| Parameter | Sustained Hypocapnia (n = 252) | Sustained Normocapnia (n = 544) | Sustained Hypercapnia (n = 654) | *P* Value |
|---|---|---|---|---|
| Illness Severity | | | | |
| Gas exchange | | | | |
| $Pao_2/Fio_2$, mm Hg, mean ± SD | 172.05 ± 64.51 | 177.29 ± 66.17 | 151.08 ± 63.97[a,b] | < .0001 |
| $Pao_2/Fio_2$ < 150 mm Hg, No. (%) | 103 (40.87) | 218 (40.07) | 347 (53.06)[a,b] | < .0001 |
| $Pao_2/Fio_2$ < 100 mm Hg, No. (%) | 39 (15.48) | 82 (15.07) | 171 (26.15)[a,b] | < .0001 |
| $Spo_2$, %, median [IQR] | 96.0 [94.0-98.0] | 96.0 [94.0-99.0] | 96.0 [93.0-98.0][a,b] | < .0001 |
| $Paco_2$, mm Hg, mean ± SD | 29.54 ± 3.62 | 39.56 ± 2.65 | 60.72 ± 15.33 | N/A |
| pH, mean ± SD | 7.40 ± 0.10 | 7.37 ± 0.09[a] | 7.29 ± 0.12[a,b] | < .0001 |
| SOFA scores, mean ± SD | | | | |
| SOFA score | 9.45 ± 3.74 | 8.47 ± 3.74[a] | 8.86 ± 3.88 | .0217 |
| Adjusted SOFA score | 9.46 ± 4.02 | 8.76 ± 3.88 | 9.02 ± 4.04 | .0511 |
| Nonpulmonary SOFA score | 6.62 ± 3.62 | 5.76 ± 3.7[a] | 5.81 ± 3.74[a] | .0242 |
| Adjusted nonpulmonary SOFA score | 6.49 ± 4.06 | 5.79 ± 3.88[a] | 5.74 ± 3.96[a] | .0192 |
| Component—respiration | 2.79 ± 0.69 | 2.76 ± 0.70 | 3.04 ± 0.7[a,b] | < .0001 |
| Component—coagulation | 1.26 ± 1.41 | 0.92 ± 1.23[a] | 0.90 ± 1.34[a] | .0002 |
| Component—liver | 0.79 ± 1.12 | 0.57 ± 0.97 | 0.41 ± 0.84[a,b] | <.0001 |
| Component—cardiovascular | 1.77 ± 1.72 | 1.82 ± 1.74 | 1.90 ± 1.76 | .4396 |
| Component—CNS | 1.81 ± 1.67 | 1.68 ± 1.60 | 1.73 ± 1.72 | .7327 |
| Component—renal | 0.82 ± 1.12 | 0.71 ± 1.11 | 0.73 ± 1.08 | .2912 |
| Ventilatory management | | | | |
| Invasive mechanical ventilation, No. (%) | 190 (75.40) | 474 (87.13)[a] | 538 (82.26) | .0002 |
| Controlled ventilation, No. (%) | 102 (41.98) | 308 (57.46)[a] | 391 (61.29)[a] | < .0001 |
| $Fio_2$, median [IQR] | 0.50 [0.40-0.70] | 0.50 [0.40-0.75] | 0.60 [0.45-0.90][a,b] | < .0001 |
| Noninvasive ventilation | 64 (25.40) | 80 (14.71)[a] | 125 (19.11) | .0013 |
| Set respiratory rate, breaths/min, mean ± SD | 17.51 ± 6.06 | 17.77 ± 6.22 | 18.22 ± 6.76 | .3805 |
| Total respiratory rate, breaths/min, mean ± SD | 23.59 ± 6.34 | 20.83 ± 6.59[a] | 21.29 ± 6.81[a] | < .0001 |
| Tidal volume, mL/kg PBW, mean ± SD | 8.04 ± 2.11 | 7.80 ± 1.89 | 7.37 ± 1.98[a,b] | < .0001 |
| High tidal volume, >8 mL/kg PBW), No. (%) | 102 (45.74) | 186 (37.96) | 176 (29.83)[a,b] | < .0001 |
| Dynamic compliance, mL/cm $H_2O$, mean ± SD | 44.90 ± 54.98 | 39.47 ± 41.48 | 29.92 ± 21.03[a,b] | < .0001 |
| PEEP, cm $H_2O$, mean ± SD | 7.54 ± 2.60 | 7.89 ± 2.84 | 8.70 ± 3.41[a,b] | < .0001 |
| PIP, cm $H_2O$, mean ± SD | 23.31 ± 8.98 | 24.77 ± 9.11 | 27.51 ± 8.64[a,b] | < .0001 |
| Plateau pressure measured, No. (%) | 65 (25.79) | 155 (28.49) | 152 (23.24) | .1167 |
| Plateau pressure, cm $H_2O$, mean ± SD | 21.29 ± 5.19 | 22.21 ± 5.92 | 25.07 ± 6.41[a,b] | < .0001 |
| Driving pressure, cm $H_2O$, mean ± SD | 13.77 ± 4.19 | 13.88 ± 5.13 | 15.64 ± 6.30[b] | .0234 |
| Minute ventilation, L/min, mean ± SD | 11.19 ± 4.01 | 9.74 ± 3.19[a] | 9.46 ± 3.61[a] | < .0001 |
| Standardized minute ventilation, L/min, median [IQR] | 7.78 [6.16-9.74] | 9.23 [7.53-11.21][a] | 13.10 [10.08-16.87][a,b] | < .0001 |
| Use of adjunctive measures days 1-2, No. (%) | | | | |
| Neuromuscular blockade | 12 (4.76) | 59 (10.85)[a] | 149 (22.78)[a,b] | < .0001 |
| Recruitment maneuvers | 30 (11.90) | 76 (13.97) | 118 (18.04)[a] | .0350 |
| Prone position | 3 (1.19) | 13 (2.39) | 49 (7.49)[a,b] | < .0001 |

*(Continued)*

**TABLE 2** ] *(Continued)*

| Parameter | Sustained Hypocapnia (n = 252) | Sustained Normocapnia (n = 544) | Sustained Hypercapnia (n = 654) | *P* Value |
|---|---|---|---|---|
| ECMO | 5 (1.98) | 8 (1.47) | 18 (2.75) | .3063 |
| Inhaled vasodilators | 13 (5.16) | 21 (3.86) | 41 (6.27) | .1726 |
| HFOV | 4 (1.59) | 3 (0.55) | 1 (0.15)[a] | .0376 |
| None of the above | 200 (79.37) | 404 (74.26) | 411 (62.84)[a,b] | < .0001 |

Sustained hypocapnia was defined as $Paco_2$ < 35 mm Hg during the first 48 hours from ARDS onset; sustained normocapnia was defined as 35 ≤ $Paco_2$ < 45 mm Hg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as $Paco_2$ ≥ 45 mm Hg during the first 48 hours from ARDS onset. For categorical data, statistical difference among groups was tested with $\chi^2$ or Fisher exact test, according to number of expected cases. For continuous data, statistical difference among groups was tested with analysis of variance or Kruskal-Wallis test based on normal data distribution. ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; SOFA = sequential organ failure assessment. See Table 1 legend for expansion of other abbreviation.

[a]*P* < .05, comparison with "sustained hypocapnia" (Bonferroni correction).

[b]*P* < .05, comparison with "sustained normocapnia" (Bonferroni correction).

cohort for a direct effect—beneficial or harmful—of hypercapnia. In contrast, we did find evidence for potential harm with hypocapnia in patients with mild to moderate ARDS receiving sustained hypocapnia.

Protective ventilation using lower tidal volumes reduces mortality in ARDS patients.[2,3] In the absence of clinical trials examining the effects of hypercapnia independent of changes in ventilatory strategy, the potential for

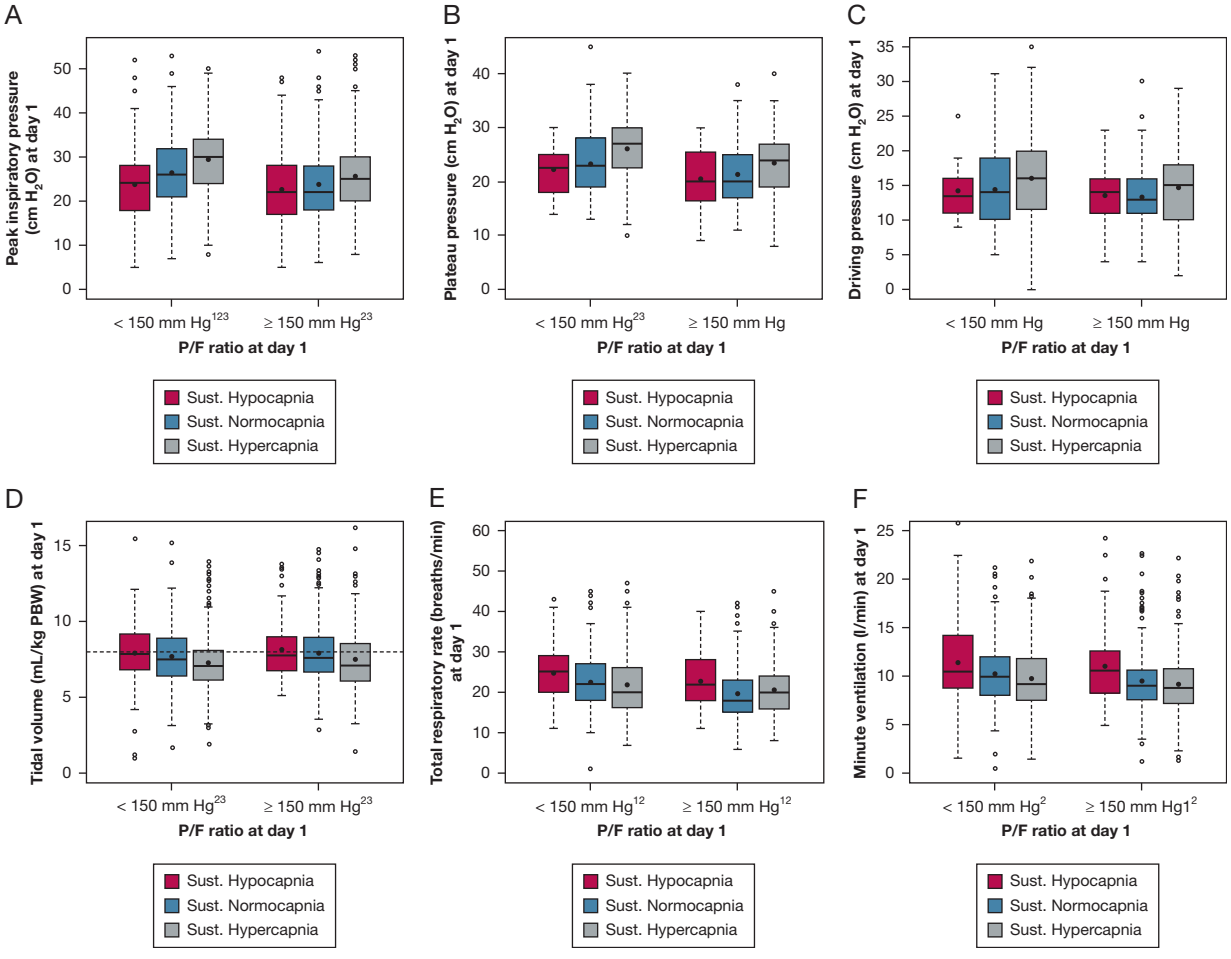


Figure 2 – *Relationship between ARDS severity and ventilator variables at day 1 of ARDS in patients with sustained hypocapnia, sustained normocapnia, and sustained hypercapnia. A, Boxplot of peak inspiratory pressure. B, Boxplot of plateau pressure. C, Boxplot of driving pressure. D, Boxplot of tidal volume per PBW. E, Boxplot of total respiratory rate. F, Boxplot of minute ventilation.* P < *.05 for sustained hypocapnia vs sustained normocapnia (Bonferroni correction).* P < *.05 for sustained hypocapnia vs sustained hypercapnia (Bonferroni correction).* P < *.05 for sustained normocapnia vs sustained hypercapnia (Bonferroni correction). PBW = predicted body weight.*

**TABLE 3** ] Outcomes of Patients With Sustained Hypocapnia, Sustained Normocapnia, and Sustained Hypercapnia

| Parameter | Sustained Hypocapnia (n = 252) | Sustained Normocapnia (n = 544) | Sustained Hypercapnia (n = 654) | *P* Value |
|---|---|---|---|---|
| Progression of ARDS (from day 1 to day 2)[a] | | | | |
| Resolved ARDS | 68 (27.31) | 141 (26.16) | 127 (19.48)[b,c] | .0067 |
| Improvement ARDS severity | 54 (21.69) | 100 (18.55) | 144 (22.09) | .2975 |
| No change ARDS severity | 91 (36.55) | 244 (45.27) | 312 (47.85)[b] | .0093 |
| Worsened ARDS severity | 36 (14.46) | 54 (10.02) | 69 (10.58) | .1594 |
| Duration of invasive mechanical ventilation, days, median [IQR] | | | | |
| All patients | 10.0 [6.0-18.0] | 8.0 [4.0-15.0][b] | 9.0 [5.0-16.0] | .0236 |
| Survivors at ICU discharge | 9.0 [5.0-18.0] | 7.0 [4.0-14.0] | 10.0 [5.0-16.0][c] | .0213 |
| Length of stay in ICU, days, median [IQR] | | | | |
| All patients | 11.5 [7.0-20.0] | 10.0 [6.0-19.0] | 11.0 [6.0-20.0] | .3576 |
| Survivors at ICU discharge | 11.5 [7.0-20.0] | 10.0 [6.0-19.0] | 11.0 [7.0-21.0] | .3600 |
| Length of stay in hospital, days, median [IQR] | | | | |
| All patients | 18.0 [10.0-34.0] | 18.0 [10.0-33.5] | 17.0 [9.0-31.0] | .4023 |
| Survivors at hospital discharge | 26.0 [14.0-38.0] | 23.0 [14.0-40.0] | 22.0 [13.0-40.0] | .7819 |
| ICU mortality, No. (%) | | | | |
| All patients | 94 (37.30) | 160 (29.41) | 220 (33.64) | .0686 |
| $Pao_2/FIo_2 < 150$ mm Hg at day 1 (n = 668) | 41 (39.81) | 78 (35.78) | 128 (36.89) | .7831 |
| $Pao_2/FIo_2 \geq 150$ mm Hg at day 1 (n = 782) | 53 (35.57) | 82 (25.15) | 92 (29.97) | .0607 |
| Hospital mortality, No. (%) | | | | |
| All patients | 106 (42.74) | 187 (34.38) | 245 (37.52) | .0764 |
| $Pao_2/FIo_2 < 150$ mm Hg at day 1 (n = 668) | 47 (46.08) | 83 (38.07) | 137 (39.48) | .3780 |
| $Pao_2/FIo_2 \geq 150$ mm Hg at day 1 (n = 782) | 59 (40.41) | 104 (31.90) | 108 (35.29) | .1956 |
| Limitation of life-sustaining measures in ICU, No. (%) | 72 (28.57) | 135 (24.82) | 160 (24.46) | .4200 |
| By 48 hours from ARDS onset | 13 (5.16) | 22 (4.04) | 28 (4.28) | .7686 |

Sustained hypocapnia was defined as $Paco_2 < 35$ mm Hg during the first 48 hours from ARDS onset; sustained normocapnia was defined as $35 \leq Paco_2 < 45$ mm Hg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as $Paco_2 \geq 45$ mm Hg during the first 48 hours from ARDS onset. For categorical data, statistical difference among groups was tested with $\chi^2$. For continuous data, statistical difference among groups was tested with the Kruskal-Wallis test. See Table 1 legend for expansion of abbreviation.

[a]Progression of ARDS was not available for 10 patients (0.69%).

[b]$P < .05$, comparison with "Sustained hypocapnia" (Bonferroni correction).

[c]$P < .05$, comparison with "Sustained normocapnia" (Bonferroni correction).

hypercapnia to impact on outcome—for either benefit or harm—remains a source of controversy. Substantial data from preclinical models demonstrate potentially beneficial effects, including suppressive effects of hypercapnia on the pro-inflammatory response to injury,[11-13,18-25] potent antioxidant effects,[26] and also potentially harmful effects including reduced wound healing,[10] reduced neutrophil and macrophage phagocytosis, and reduced bacterial killing.[9]

In the clinical context, a secondary analysis of the ARDS network low tidal volume trial[2] found an association between the presence and severity of hypercapnic acidosis on day 1 and lower mortality in patients that received traditional—but not protective—tidal volume ventilation.[27] In contrast, Nin et al[28] found that a $Paco_2$ of over 50 mm Hg in patients with moderate-severe ARDS during the first 48 hours was associated with a higher ICU mortality in a secondary analysis of three noninterventional cohort studies, and suggested that this "severe" hypercapnia could no longer be considered "safe."[28] A number of small clinical studies of "induced" or "permitted" hypercapnia in other settings, such as patients undergoing pancreaticoduodenal surgery[29] or pulmonary lobectomy,[30] suggest that hypercapnia

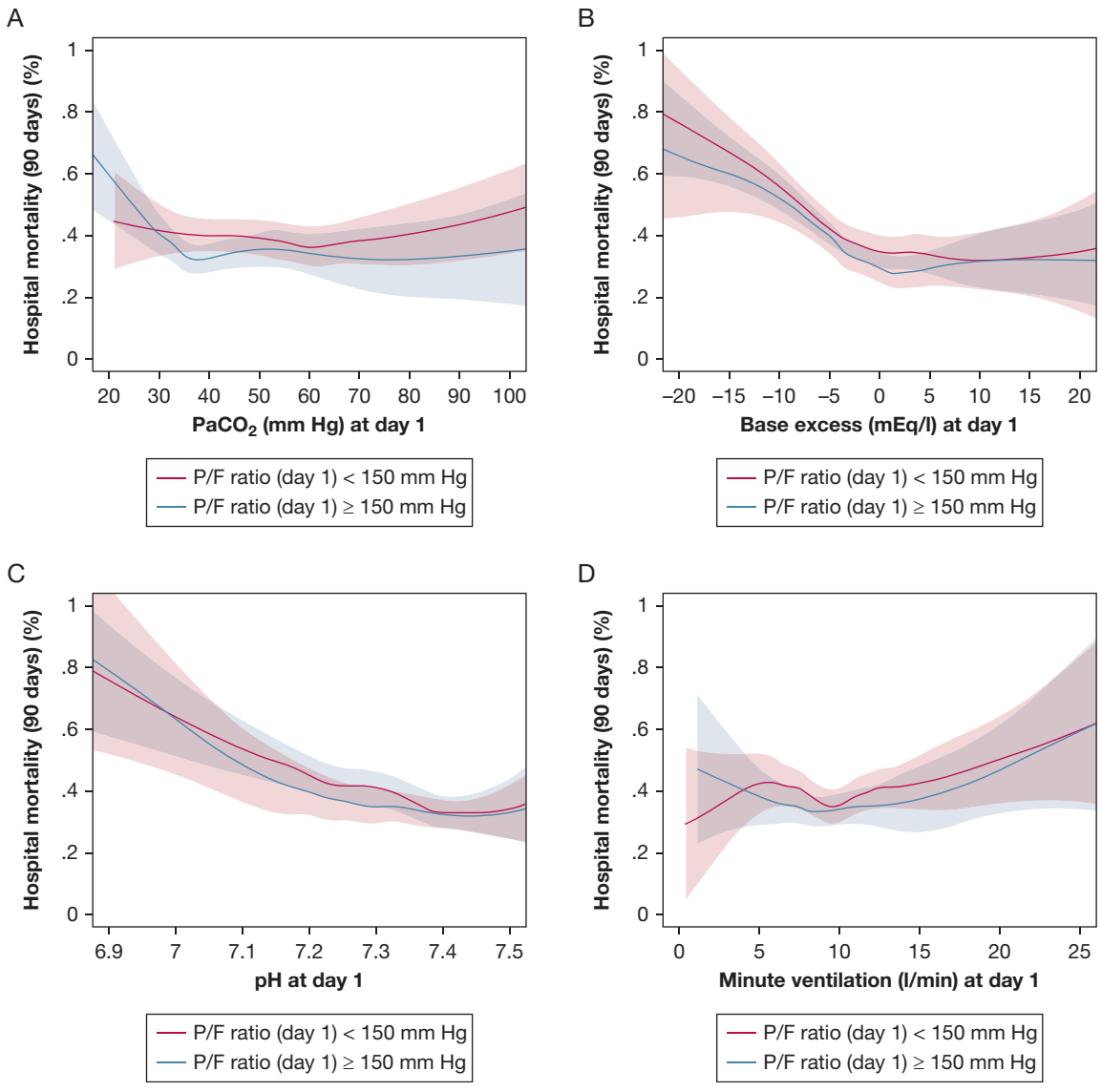


Figure 3 – *LOESS curves of the relationship between hospital mortality and $PaCO_2$ and acid-base parameters in patients with sustained hypocapnia, sustained normocapnia, and sustained hypercapnia, stratified by ARDS severity. A, Relationship between hospital mortality and $PaCO_2$ at day 1 of ARDS. B, Relationship between hospital mortality and base excess at day 1 of ARDS. C, Relationship between hospital mortality and pH at day 1 of ARDS. D, Relationship between hospital mortality and minute ventilation at day 1 of ARDS. LOESS = locally estimated scatterplot smoothing.*

is well tolerated and may have some beneficial effects.

In the LUNG SAFE cohort, although milder degrees of hypercapnia were prevalent in early ARDS, and the proportion of patients with permissive hypercapnia increased with greater ARDS severity, median arterial $CO_2$ tension remained in the normal range at all three levels of ARDS severity. We specifically wished to examine patients with sustained conditions to determine any potential impact on management or outcome. Patients with sustained hypercapnia had more severe ARDS, with worse oxygenation and higher airway pressures. Pulmonary causes of ARDS, particularly pneumonia, were highest in this group. The ventilatory management of patients with sustained hypercapnia did differ from that of the other groups, with more patients receiving controlled ventilation, muscle paralysis, and protective lung ventilation strategies that resulted in lower tidal and minute ventilation. Despite these patients having more severe ARDS, crude mortality rates were comparable to that seen in the sustained normocapnia and hypocapnia groups.

These data suggest that many physicians are reluctant to allow hypercapnia to facilitate lower tidal volumes in

**TABLE 4** ] Factors at Day 1 of ARDS Associated With Hospital and ICU Mortality (90 Days) in Patients With Sustained Hypocapnia, Sustained Normocapnia, and Sustained Hypercapnia (n = 1,450)

| Parameters | OR (95% CI) | *P* Value |
|---|---|---|
| Outcome: hospital mortality—Model on 93.4% of study population (1,355 patients) | | |
| Age, y | 1.028 (1.019-1.035) | < .0001 |
| BMI | 0.980 (0.963-0.997) | .0211 |
| Immune incompetence, ref. No. | 2.627 (1.938-3.561) | < .0001 |
| Chronic liver failure, ref. No. | 3.815 (1.886-7.717) | .0002 |
| ARDS risk factors, ref. No. | 1.652 (1.020-2.677) | .0413 |
| pH, 0.01 unit | 0.976 (0.965-0.987) | < .0001 |
| Adjusted nonpulmonary SOFA score | 1.085 (1.047-1.124) | < .0001 |
| Total respiratory rate, breaths/min | 1.043 (1.023-1.063) | < .0001 |
| PEEP, cm $H_2O$ | 0.948 (0.908-0.990) | .0179 |
| Adjunctive measures[a] during day 1 or day 2, ref. No. | 1.432 (1.079-1.900) | .0128 |
| Invasive mechanical ventilation, ref. No. | 1.504 (1.033-2.192) | .0333 |
| Outcome: ICU mortality—Model on 93.8% of study population (1,360 patients) | | |
| Age, y | 1.022 (1.013-1.031) | < .0001 |
| BMI | 0.981 (0.963-0.999) | .0367 |
| Immune incompetence, ref. No. | 2.229 (1.633-3.043) | < .0001 |
| Chronic liver failure, ref. No. | 3.558 (1.768-7.160) | .0004 |
| pH, 0.01 unit | 0.976 (0.964-0.987) | < .0001 |
| Adjusted nonpulmonary SOFA score | 1.088 (1.048-1.129) | < .0001 |
| Total respiratory rate, breaths/min | 1.043 (1.022-1.065) | < .0001 |
| PEEP, cm $H_2O$ | 0.946 (0.903-0.991) | .0191 |
| Adjunctive measures[a] during day 1 or day 2, ref. No. | 1.585 (1.176-2.137) | .0025 |
| Noninvasive mechanical ventilation, ref. No. | 0.634 (0.428-0.940) | .0233 |
| $Pao_2/Fio_2 \geq 150$ mm Hg, ref. < 150 mm Hg | 0.755 (0.575-0.991) | .0432 |

See Table 2 legend for expansion of abbreviations.
[a]We considered as adjunctive measures performed during day 1 or day 2, the following procedures or treatment: neuromuscular blockade, recruitment maneuvers, prone position, extracorporeal membrane oxygenation (ECMO), inhaled vasodilators, high-frequency oscillatory ventilation (HFOV). Effects estimates evaluated by mixed-effects logistic regression model.

patients with ARDS. Indeed, ongoing concerns regarding hypercapnia may constitute a barrier to the institution of protective lung ventilation strategies by clinicians. The "cost" of this is illustrated by the fact that patients managed with normocapnia received less protective lung ventilation.

The potential for hypocapnia to exert deleterious effects in the critically ill is long recognized,[13,24] with potentially harmful effects in ARDS first suggested in 1971.[31] Hypocapnia per se may directly injure the lung via several mechanisms, including increased lung permeability and edema,[12] decreased compliance,[32] potentially mediated via surfactant inhibition,[33] and potentiation of acute inflammation.[11,34,35] In experimental models, many of these adverse effects can be ameliorated by normalizing alveolar $CO_2$.[12,33,34,36] Hypocapnia can attenuate hypoxic pulmonary vasoconstriction, thereby increasing intrapulmonary shunt.[37] The potential for hypocapnia to worsen brain injury[7,38] and other acute systemic organ injury[24] is also increasingly recognized. Hypocapnia also may be associated with higher mortality in patients with ARDS because high tidal volume ventilation (usually used to achieve hypocapnia) directly causes lung injury.

In the LUNG SAFE cohort, we found that hypocapnia was prevalent, with approximately one in five patients being hypocapnic on day 1 of ARDS and one in 10 having sustained hypocapnia. These patients had less severe ARDS, with better oxygenation and lower peak and plateau pressures. In contrast, nonpulmonary SOFA scores were

**TABLE 5** ] Management Factors and Main Outcomes in Matched Sample With Sustained Normocapnia and Sustained Hypercapnia

| Parameter | Sustained Normocapnia | Sustained Hypercapnia | *P* Value |
|---|---|---|---|
| No. | 275 | 275 | … |
| Tidal volume, mL/kg PBW; mean ± SD | 7.68 ± 1.88 | 7.39 ± 2.02 | .0297 |
| Plateau pressure, cm $H_2O$; mean ± SD | 23.01 ± 6.11 | 24.55 ± 6.46 | .9429 |
| Driving pressure, cm $H_2O$; mean ± SD | 14.70 ± 5.31 | 15.51 ± 6.15 | .6787 |
| PEEP, cm $H_2O$; mean ± SD | 8.18 ± 2.89 | 8.71 ± 3.35 | .0460 |
| Minute ventilation, L/min; mean ± SD | 9.71 ± 3.11 | 9.31 ± 3.38 | .1011 |
| PIP, cm $H_2O$; mean ± SD | 27.40 ± 9.56 | 27.12 ± 8.56 | .9113 |
| Total respiratory rate, breaths/min; mean ± SD | 20.84 ± 6.27 | 20.52 ± 6.34 | .5182 |
| Base excess, mEq/L; mean ± SD | −3.55 ± 5.07 | 3.72 ± 6.59 | < .0001 |
| $F_{IO_2}$, median [IQR] | 0.60 [0.45-0.80] | 0.60 [0.40-0.80] | .3913 |
| $Pa_{O_2}/F_{IO_2}$ < 150 mm Hg, No. (%) | 133 (48.36) | 124 (45.09) | .4437 |
| Outcomes | | | |
| Duration of invasive mechanical ventilation, days; median [IQR] | | | |
| All patients | 8.0 [4.0-17.0] | 10.0 [5.0-20.0] | .4364 |
| Survivors at ICU discharge | 8.0 [4.0-15.0] | 9.0 [4.0-19.0] | .7836 |
| Length of stay in ICU (days), median [IQR] | | | |
| All patients | 11.0 [6.0-21.0] | 12.0 [7.0-24.0] | .2516 |
| Survivors at ICU discharge | 11.0 [7.0-21.0] | 12.0 [7.0-25.0] | .9710 |
| Length of stay in hospital, days; median [IQR] | | | |
| All patients | 18.0 [10.0-35.0] | 20.0 [11.0-39.0] | .6996 |
| Survivors at hospital discharge | 27.0 [15.0-43.0] | 25.0 [14.0-45.0] | .7376 |
| ICU mortality, No. (%) | | | |
| All patients | 87 (31.64) | 88 (32.00) | 1.0000 |
| $Pa_{O_2}/F_{IO_2}$ < 150 mm Hg at day 1 | 51 (38.35) | 45 (36.29) | .5235 |
| Hospital mortality,[a] No. (%) | | | |
| All patients | 98 (35.64) | 99 (36.13) | 1.0000 |
| $Pa_{O_2}/F_{IO_2}$ < 150 mm Hg at day 1 | 54 (40.60) | 48 (38.71) | .5572 |
| Limitation of life sustained measures in ICU, No. (%) | 60 (21.82) | 68 (24.73) | .4705 |

Sustained normocapnia was defined as 35 ≤ $Pa_{CO_2}$ < 45 mm Hg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as $Pa_{CO_2}$ ≥ 45 mm Hg during the first 48 hours from ARDS onset. Statistical tests accounted for the matched nature of the sample (paired *t* test or Wilcoxon signed rank test for continuous variables, McNemar's test for dichotomous variables). See Table 1 and 2 legends for expansion of abbreviations.
[a]For one patient with sustained hypercapnia, vital status was missing.

significantly higher in patients with sustained hypocapnia, whereas pneumonia was less common, suggesting a different pattern of ARDS, with perhaps greater systemic involvement.

Of concern, fewer patients with sustained hypocapnia received protective ventilation, and these patients received higher tidal and minute volumes and higher respiratory rates, which constitutes the "ventilatory cost" of hypocapnia. The rationale for these patients receiving hypocapnia was not clear, with pH being highest in this group, suggesting that compensation for metabolic acidosis was not a factor. Hypocapnia was more prevalent and more severe in patients receiving noninvasive ventilation, and in patients from middle-income countries, both factors that have been associated with higher mortality risk in the LUNG SAFE cohort.[16,39] Although respiratory drive may have played a role in driving hypocapnia in some of these patients, 12.7% of patients under controlled ventilation had sustained hypocapnia, suggesting that their clinicians may have been providing unnecessarily high stress and strain to the lungs of these patients. This potentially could have led to the increased mortality in patients with hypocapnia.

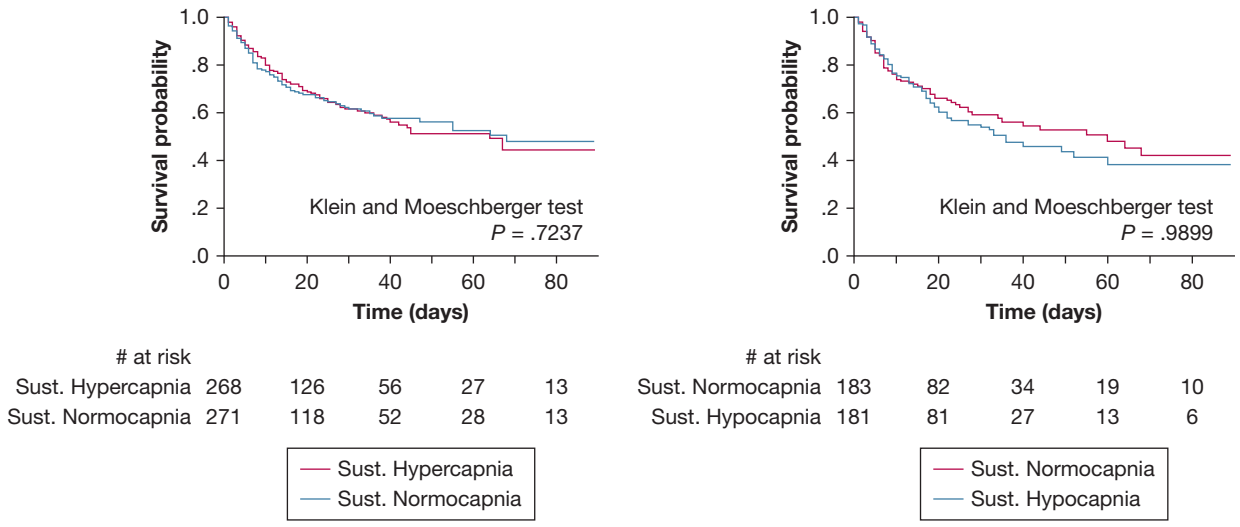


Figure 4 – *Propensity-matched analyses of mortality rates. A, Survival probability during hospital stay in matched sample (n = 550) between sustained normocapnia and sustained hypercapnia. B, Survival probability during hospital stay in matched sample (n = 374) between sustained normocapnia and sustained hypocapnia. 1. Kaplan Meier's approach assumed as censored those patients discharged alive before day 90. 2. The number of patients at risk reported at the bottom of the figure is referred to as the end of the corresponding day.*

We conducted a number of different analyses to examine the potential for a role for $CO_2$ tension on patient outcome from ARDS, including LOESS modeling, multivariate analyses, and propensity-matched analyses. The findings across these analyses regarding hypercapnia were quite consistent, in that no link between elevated $CO_2$ tension and outcome was found. Our findings of a lack of a direct effect of hypercapnia on outcomes in this cohort should provide some reassurance regarding the safety of hypercapnia in patients with ARDS.

In contrast, we did find evidence for potential harm with hypocapnia in patients with mild to moderate ARDS receiving sustained hypocapnia compared with normocapnia. ICU mortality was significantly higher in patients with a PF ratio $\geq$ 150 mm Hg at day 1 of ARDS in patients with sustained hypocapnia. A multivariate analysis restricted to patients with sustained normocapnia and sustained hypocapnia and with PF $\geq$ 150 mm Hg found that lower $P_{CO_2}$ was associated with increased ICU and hospital mortality. This supports the findings in the propensity-matched analysis, suggesting that this finding is robust. The higher frequency of mild to moderate ARDS in patients with hypocapnia may explain why this effect was not detected in patients with PF $<$ 150 mm Hg. Hypocapnia was more frequent in patients receiving noninvasive ventilation, which has been associated with worse outcomes in the LUNG SAFE cohort,[16] suggesting the need for caution regarding hypocapnia in patients with ARDS.

This study has several limitations. Although we instituted a robust data quality control program in which all centers were requested to verify data that appeared inconsistent or erroneous, we did not have access to the source data for the patients in the enrolling ICUs, and possibly not all patients with ARDS in participating centers were enrolled. We cannot make causal inferences for any associations seen, given the observational nature of our study. Our dataset comprises daily arterial blood gas and $F_{IO_2}$ data, taken at a standardized time each morning. Possibly these data do not properly reflect the spectrum of $F_{IO_2}$ use and $Pa_{O_2}$ data over the course of that day. Possibly clinicians could have reduced $F_{IO_2}$ on the basis of the arterial blood gas analyses, thereby reducing exposure time. Given this, in these analyses, we focused on patients that had hypocapnia, normocapnia, and hypercapnia on both days 1 and 2 of ARDS. Finally, our assumption that inpatients at day 90 survived to hospital discharge is a further limitation.

In conclusion, both hypocapnia and hypercapnia were prevalent in early ARDS in the LUNG SAFE cohort. Patients with ARDS receiving sustained hypercapnia had more severe ARDS and received more protective

**TABLE 6** ] Management Factors and Main Outcomes in Matched Sample With Sustained Normocapnia and Sustained Hypocapnia

| Parameter | Sustained Normocapnia | Sustained Hypocapnia | *P* Value |
|---|---|---|---|
| No. | 187 | 187 | … |
| Tidal volume, mL/kg PBW; mean ± SD | 7.69 ± 1.93 | 8.11 ± 2.15 | .0511 |
| Plateau pressure, cm $H_2O$; mean ± SD | 22.38 ± 5.33 | 21.23 ± 5.19 | .8746 |
| Driving pressure, cm $H_2O$; mean ± SD | 14.55 ± 4.50 | 13.63 ± 4.10 | .7822 |
| PEEP, cm $H_2O$; mean ± SD | 7.57 ± 2.55 | 7.61 ± 2.65 | .9153 |
| Minute ventilation, L/min; mean ± SD | 9.72 ± 3.50 | 11.05 ± 3.93 | .0009 |
| PIP, cm $H_2O$; mean ± SD | 24.31 ± 10.06 | 24.44 ± 8.57 | .9003 |
| Total respiratory rate, breaths/min; mean ± SD | 20.49 ± 6.41 | 22.85 ± 6.21 | .0002 |
| Base excess, mEq/L; mean ± SD | −1.22 ± 4.60 | −6.05 ± 5.18 | < .0001 |
| $F_{IO_2}$, median [IQR] | 0.50 [0.40-0.80] | 0.50 [0.40-0.70] | .4830 |
| $Pa_{O_2}/Fi_{O_2}$ < 150 mm Hg, No. (%) | 69 (36.90) | 72 (38.50) | .8358 |
| Outcomes | | | |
| Duration of invasive mechanical ventilation (days), median [IQR] | | | |
| All patients | 8.00 [4.00-16.00] | 10.00 [6.00-18.00] | .1248 |
| Survivors at ICU discharge | 7.00 [4.00-16.00] | 10.00 [5.00-18.00] | .4289 |
| Length of stay in ICU (days), median [IQR] | | | |
| All patients | 10.00 [6.00-18.00] | 12.00 [7.00-21.00] | .4339 |
| Survivors at ICU discharge | 10.00 [6.00-18.00] | 13.00 [7.00-22.00] | .5953 |
| Length of stay in hospital, days; median [IQR] | | | |
| All patients | 19.00 [10.00-34.00] | 19.00 [10.00-34.00] | .9749 |
| Survivors at hospital discharge | 26.00 [16.00-43.00] | 27.00 [15.50-39.50] | .7547 |
| ICU mortality, No. (%) | | | |
| All patients | 61 (32.62) | 72 (38.50) | .2780 |
| $Pa_{O_2}/Fi_{O_2}$ < 150 mm Hg at day 1 | 29 (42.03) | 28 (38.89) | .7744 |
| $Pa_{O_2}/Fi_{O_2}$ ≥ 150 mm Hg at day 1 | 32 (27.12) | 44 (38.26) | .0410 |
| Hospital mortality,[a] No. (%) | | | |
| All patients | 72 (38.50) | 81 (44.26) | .2660 |
| $Pa_{O_2}/Fi_{O_2}$ < 150 mm Hg at day 1 | 30 (43.48) | 33 (46.48) | .5488 |
| $Pa_{O_2}/Fi_{O_2}$ ≥ 150 mm Hg at day 1 | 42 (35.59) | 48 (42.86) | .1102 |
| Limitation of life-sustaining measures in ICU, No. (%) | 51 (27.27) | 50 (26.74) | 1.0000 |

Sustained normocapnia was defined as 35 ≤ $Pa_{CO_2}$ < 45 mm Hg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as $Pa_{CO_2}$ ≥ 45 mm Hg during the first 48 hours from ARDS onset. Statistical tests accounted for the matched nature of the sample (paired *t* test or Wilcoxon signed-rank test for continuous variables, McNemar's test for dichotomous variables). See Table 1 and 2 legends for expansion of abbreviations.
[a]For one patient with sustained hypercapnia, vital status was missing.

mechanical ventilation, whereas hypocapnia was more frequent and severe in patients receiving noninvasive ventilation. No evidence was seen of benefit or harm with hypercapnia in our cohort. In contrast, ICU mortality was higher in patients with mild to moderate ARDS receiving sustained hypocapnia, suggesting the need for caution regarding ARDS patients with sustained hypocapnia.

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