Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical characteristics, physiological features, and outcomes associated with hypercapnia in patients with acute hypoxemic respiratory failure due to COVID-19—insights from the PRoVENT–COVID study

Anissa M. Tsonas, Michela Botta, Janneke Horn, Luis Morales-Quinteros, Antonio Artigas, Marcus J. Schultz, Frederique Paulus, Ary Serpa Neto, for the PRoVENT-COVID Collaborative Group

Keywords: Coronavirus disease 2019, COVID-19, ARDS, Ventilation, Invasive ventilation, CO2 management, Hypercapnia, Sustained hypercapnia

Purpose: We determined the incidence of hypercapnia and associations with outcome in invasively ventilated COVID–19 patients.

Methods: Posthoc analysis of a national, multicenter, observational study in 22 ICUs. Patients were classified as ‘hypercapnic’ or ‘normocapnic’ in the first three days of invasive ventilation. Primary endpoint was prevalence of hypercapnia. Secondary endpoints were ventilator parameters, length of stay (LOS) in ICU and hospital, and mortality in ICU, hospital, at day 28 and 90.

Results: Of 824 patients, 485 (58.9%) were hypercapnic. Hypercapnic patients had a higher BMI and had COPD, severe ARDS and venous thromboembolic events more often. Hypercapnic patients were ventilated with lower tidal volumes, higher respiratory rates, higher driving pressures, and with more mechanical power of ventilation. Hypercapnic patients had comparable minute volumes but higher ventilatory ratios than normocapnic patients. In hypercapnic patients, ventilation and LOS in ICU and hospital was longer, but mortality was comparable to normocapnic patients. Conclusion: Hypercapnia occurs often in invasively ventilated COVID–19 patients. Main differences between hypercapnic and normocapnic patients are severity of ARDS, occurrence of venous thromboembolic events, and a higher ventilatory ratio. Hypercapnia has an association with duration of ventilation and LOS in ICU and hospital, but not with mortality.

© 2022 Published by Elsevier Inc.
1. Introduction

Understanding of the pathophysiology of so-called ‘ventilator-induced lung injury (VILI)’ has led to notable changes in ventilation management in patients with acute respiratory distress syndrome (ARDS) over recent years [1]. It is now widely accepted to use a low tidal volume (VT) and to aim for low pressures to protect the lungs against ‘volutrauma’ and ‘barotrauma’ [2], and to prefer a lower respiratory rate (RR) to prevent ‘energytrauma’ [3]. All of these measures favor the development of hypercapnia. However, several studies have shown hypercapnia to have an independent association with increased mortality in invasively ventilated patients [4,5]. This could be related to the harmful biological effects of hypercapnia as reported in experimental studies, such as reduction in wound repair [6], decreased clearance of alveolar fluid [7], and impairment of the innate immunity [8,9]. However, hypercapnia could also have beneficial effects, as similar mechanisms that impair immunity could also protect the lungs from tissue damage [10,11]. Therefore, the true net effect of hypercapnia on the body remains uncertain [12].

The incidence of hypercapnia is reportedly high in patients with ARDS [13]. The exact incidence of hypercapnia in COVID–19 patients with ARDS is much less certain. It is also unknown whether hypercapnia has an association with outcome in these patients. We studied the presence of hypercapnia in a conveniently-sized observational study that captured detailed and granular ventilation data and outcomes in COVID–19 patients that needed invasive ventilation during the first wave of the national outbreak in the Netherlands. We compared epidemiological characteristics, ventilation management and outcomes in patients with hypercapnia versus normocapnic patients. We hypothesized that hypercapnia is prevalent, and that hypercapnia has an association with worse outcome in COVID–19 patients.

2. Methods

2.1. Study design, patients, and data collection

This is a posthoc analysis of an investigator-initiated, national, multicenter, observational cohort study undertaken at 22 ICUs in the Netherlands, named the ‘Practice of VENTilation in COVID–19’ (ProVEnT-COVID) study. The study protocol of the original study [14], and the statistical analysis plan for the current analysis were prepublised [15].

Consecutive patients were eligible for participation in the original study if they were > 18 years of age, admitted to one of the participating ICUs, and had received invasive ventilation for respiratory failure related to COVID–19. COVID–19 was confirmed by RT–PCR for SARS-CoV–2. While the original study itself had no exclusion criteria, we excluded patients that were transferred from or to a non-participating ICU within the first four calendar days of invasive ventilation in the current analysis, as it was impossible to capture blood gas analyses results and ventilator settings from these patients before or after transfer. We also excluded patients without blood gas analyses results, mainly because of early death or a rapid ICU discharge.

2.2. Data collection

Demographics, chronic comorbidities, home medication, presence and severity of ARDS, and extent of infiltrates on chest imaging were collected at baseline. One hour after start of invasive ventilation and every eight hours thereafter at fixed time points (at 08.00, 16.00, and 24.00 h), the following data were collected over the first four calendar days: data regarding ventilation management, including set and measured ventilation parameters, arterial blood gas analyses and use of adjuvant therapies for refractory hypoxemia, and data regarding aspects of ICU management, including hemodynamic parameters, use of sedation, vasopressors and/or neuromuscular blocking agents (NMBA), fluid balance and kidney function. Typical ICU complications, including reintubation, venous thromboembolic events (VTE), acute kidney injury (AKI), and need for renal replacement therapy (RRT) were collected until day 28, and follow-up of extubation–, admission– and life–status was done until day 90.

2.3. Patient classification

Patients were classified as ‘hypercapnic’ or ‘normocapnic’ based on the available arterial carbon dioxide (PaCO2) measurements collected during the first four calendar days of invasive ventilation. For this, we merged the first flexible calendar day with the first full calendar day and named it ‘day 1’, and named the following days ‘day 2’ and ‘day 3’. First, per ventilation day it was determined whether a patient had a hypercapnic or normocapnic day, based on the majority of PaCO2 measurements > 45 mmHg on that day. The cutoff was chosen based on a previous analysis [13]. Herein, we ignored the first available PaCO2 measurement, i.e., the first measurement on day 1, as we considered it plausible that this value could not yet have been controlled by the ICU caregivers. Then, each patient was classified as hypercapnic or normocapnic, based on the majority of days a patient was scored as hypercapnic or normocapnic. The remaining patients were classified as ‘normocapnic’, even if some of the PaCO2 measurement were >45 mmHg or displayed hypocapnia, with a PaCO2 measurement <35 mmHg.

2.4. Outcomes

The primary endpoint was the prevalence of hypercapnia over the first three days of ventilation. Secondary endpoints included the following key ventilator settings and ventilation parameters: VT, RR, positive end–expiratory pressure (PEEP) and driving pressure (ΔP), the mechanical power of ventilation (MP) and minute ventilation (MV), and the ventilatory ratio (VR).

Other secondary endpoints were patient-centered outcomes including duration of ventilation, length of stay (LOS) in ICU and hospital, and death in ICU and hospital, and at day 28 and 90.

2.5. Calculations

We used the following equations for calculating predicted body weight (PBW), ΔP [16,17], VR [18] and MP [17,19-21]:

\[
P_{\text{predicted}} = \frac{\text{height in centimeters} - 152.4}{2} \times 0.91 + 50 \quad (\text{height in centimeters} \geq 152.4) \quad (\text{men})
\]

\[
P_{\text{predicted}} = 45.5 + 0.91 \times (\text{height in centimeters} - 152.4) \quad (\text{women})
\]

\[
\Delta P \ (\text{cm H}_2\text{O}) = \text{Peak pressure } (P_{\text{peak}}) - \text{PEEP}
\]

\[
VR = \frac{V_{\text{E measured}} + \text{PaCO}_2 \text{ measured}}{V_{\text{E predicted}} + \text{PaCO}_2 \text{ predicted}}
\]

and

\[
MP \ (\text{in J/ min}) = 0.098 \times V_T \times RR \times (P_{\text{peak}} - 0.5 \times \Delta P)
\]

2.6. Statistical analyses plan

Continuous variables are presented as medians (IQR) and categorical variables as number and proportions. Hypercapnic and normocapnic patients were compared using Wilcoxon rank–sum test and Fisher exact test for continuous and discrete variables, respectively.

The daily means of the following ventilation variables and parameters were presented in cumulative distribution plots: VT, RR, PEEP, MV, ΔP, MP and VR. Linear mixed–effect models were used to assess the
trends of \( V_t \), RR, PEEP, MV, \( \Delta P \), MP and VR, which all served as outcomes in the model, over time. Centers and patients were treated as random effects to account for clustering and repeated measurements. The PaCO\(_2\) groups, time as a continuous variable, and an interaction between PaCO\(_2\) groups and time were treated as fixed effect exposures. The overall difference among groups over time is represented by group \( P \)-values, while interaction \( P \)-values represent a statistical assessment of whether the trend over time differed among the groups.

Time until extubation and length of ICU– and hospital stay are shown in cumulative distribution plots with death as a competing risk until day 28 and day 90, respectively. Twenty-eight and 90-day mortality are depicted in Kaplan–Meier curves.

To further assess independent association of hypercapnia with 28–day mortality, a Cox proportional hazard model with center as frailty was used. The following variables with a known or suspected association with 28–day mortality were included in the model: 1) demographic characteristics, including age, body mass index (BMI), chronic kidney disease, chronic obstructive pulmonary disease (COPD) and diabetes; 2) laboratory tests and vital signs, including arterial pH, plasma lactate and heart rate, in the first day aggregated as the median from a maximum of four assessments; 3) ventilation variables and parameters, including respiratory system compliance (Crs), PEEP, PaO\(_2\)/FiO\(_2\), \( V_t \), RR, VR and MP, in the first day aggregated as the median from a maximum of four assessment; 4) organ support, including use of vasopressor and use of NMBA, on the first day; and 5) use of prone positioning on day 1.

All analyses were conducted in R v.3.6.1 (R Foundation, Vienna, Austria) and significance level was set at 0.05.

3. Results

3.1. Patients

Between March 1, 2020 and June 1, 2020, we screened 1340 patients in 22 ICUs (eFig. 1). Main reasons for exclusion were not having received invasive ventilation, and presence of an alternative diagnosis. The main reason for exclusion from the current analysis was early transfer from or to a non-participating ICU.

3.2. Incidence of dyscapnia

Hypercapnia occurred often, with 4717 out of 8218 (57.4%) blood gas analyses showing a PaCO\(_2\) > 45 mmHg. Hypercapnia occurred much less often, with 499 out of 8218 (6.1%) blood gas analyses showing a PaCO\(_2\) < 35 mmHg. Of 824 patients analyzed, 485 (58.9%) were classified as hypercapnic (eFig. 1). Hypercapnic patients had a median of 8 [7 to 10] blood gas analyses showing a PaCO\(_2\) > 45 mmHg, and a median of 0 [0 to 0] blood gas analyses showing a PaCO\(_2\) < 35 mmHg; normocapnic patients had a median of 2 [1 to 4] blood gas analyses showing a PaCO\(_2\) > 45 mmHg, and a median of 1 [0 to 2] blood gas analyses showing a PaCO\(_2\) < 35 mmHg. Median daily PaCO\(_2\) differed between hypercapnic and normocapnic patients, and this difference increased slightly over the first days of ventilation: 48.8 [45.0 to 53.8] vs. 40.5 [37.4 to 43.3] mmHg, 51.5 [47.9 to 57.5] vs. 41.3 [38.5 to 43.8] mmHg, and 52.5 [48.8 to 59.3] vs. 42.5 [39.4 to 45.5] mmHg on day 1, 2 and 3, respectively (all \( P < 0.001 \)) (Figure 1 and eTable 1). Consequently, the proportion of patients classified as being hypercapnic increased over day 1 – day 3 (Figure 1).

3.3. Baseline characteristics

Compared to normocapnic patients, hypercapnic patients had a higher BMI and were more likely to have a history of COPD (Table 1). ARDS was more often classified as severe, based on the cutoff for PaCO\(_2\)/FiO\(_2\) of 100 mmHg, and VTE was more frequently diagnosed in hypercapnic patients than in normocapnic patients. Heart rate was slightly higher in hypercapnic patients, while arterial pH was slightly lower compared to normocapnic patients.

3.4. Associations with ventilation parameters

At start of invasive ventilation, hypercapnic patients received ventilation with comparable \( V_t \) as normocapnic patients, but with higher RR, higher PEEP and more MP. MV was not different, but VR was higher in hypercapnic patients (Table 1). The trajectories of \( V_t \), \( \Delta P \), MV and VR were different between hypercapnic and normocapnic patients (eTable 1, Fig. 2 and eFigure 2 to 4). In hypercapnic patients, \( V_t \) and \( \Delta P \) did not change over the first 4 calendar days of ventilation, while \( V_t \) slightly increased and \( \Delta P \) slightly decreased in normocapnic patients (eFigure 4). MV and VR increased in both groups, but MV increased more in normocapnic patients, while VR increased more in hypercapnic patients.
| Hypercapnic (n = 485) | Normocapnic (n = 339) | p value |
|----------------------|-----------------------|---------|
| Age, years | 65.0 [59.0–72.0] | 66.0 [57.0–73.0] | 0.368 |
| Male gender – no (%) | 354 (73.0) | 245 (72.3) | 0.874 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
| Body mass index, kg/m² | 28.1 [25.7–30.9] | 27.5 [25.2–30.1] | 0.032 |
| Use of non–invasive ventilation – no (%) | 37 (7.8) | 34 (10.4) | 0.208 |
| Duration of non–invasive ventilation – hours | 8.0 [2.0–15.0] | 8.0 [3.0–24.0] | 0.635 |
| Chest CT scan performed – no (%) | 168 (34.6) | 133 (39.2) | 0.186 |
3.5. Outcomes

Duration of ventilation and ICU– and hospital stay was longer in hypercapnic patients (eFigures 5 to 6). No significant differences were found in ICU–, hospital– and 90–day mortality between the hypercapnic and normocapnic patients (Table 2 and Fig. 3). Hypercapnia had no association with 28–day mortality (uncorrected HR, 1.10 [95% confidence interval 0.86 to 1.42]; \( P = 0.45 \) and corrected HR, 0.99 [95%–confidence interval 0.74 to 1.31]; \( P = 0.93 \)).

4. Discussion

The findings of this posthoc analysis of a large cohort of patients that received invasive ventilation for acute hypoxemic respiratory failure due to COVID–19 can be summarized as follows: (1) hypercapnia was common; (2) hypercapnic patients had a higher BMI and more often a history of COPD; (3) in hypercapnic patients, ARDS was more often classified as severe and VTE was diagnosed more often. In addition, (4) hypercapnic patients received ventilation with a slightly lower \( V_T \), a higher

---

### Table 1 (continued)

|                | Hypercapnic \((n = 485)\) | Normocapnic \((n = 330)\) | \( p \) value |
|----------------|----------------------------|---------------------------|--------------|
| PaO₂, mmHg     | 80.8 [72.5–93.7]           | 82.7 [73.5–98.8]          | 0.035        |
| PaO₂ / FiO₂, mmHg | 118.8 [93.0–157.5]       | 138.0 [103.5–187.5]      | <0.001       |
| PaCO₂, mmHg    | 47.1 [42.4–52.5]           | 39.7 [36.0–44.6]          | <0.001       |
| Lactate, mmol/L| 1.1 [0.9–1.5]              | 1.2 [1.0–1.5]             | 0.272        |
| Adjunctive therapies at start of ventilation |                       |                           |              |
| Prone positioning – no. (%) | 182 (38.4)        | 77 (23.1)                  | <0.001       |
| Duration of prone positioning – hours | 9.0 [4.4–14.0]       | 7.0 [3.5–14.0]             | 0.164        |
| Recruitment maneuvers – no. (%) | 11 (2.8)            | 7 (2.5)                    | 0.999        |
| ECMO – no. (%) | 0 (0.0)                   | 0 (0.0)                    | NA           |
| Use of NMBA – no. (%) | 151 (31.2)       | 74 (21.8)                  | 0.003        |

Data are median [quartile 25% – quartile 75%] or No (%). Percentages may not total 100 because of rounding.

CT: computed tomography; ARDS: acute respiratory distress syndrome; PEEP: positive end expiratory pressure; FiO₂: fraction of inspired oxygen; etCO₂: end tidal carbon dioxide, PaO₂: partial pressure of oxygen; PaCO₂: partial pressure of carbon dioxide; ECMO: extracorporeal membrane oxygenation; NMBA: neuromuscular blocking agents.

\( ^* \) Most recent measurement in 24 h before intubation – or at ICU admission under invasive ventilation.
RR, a higher PEEP and ΔP, and more MP over the first days of invasive ventilation; (5) MV was not different, but VR was higher in hypercapnic patients. Lastly, (6) hypercapnia had an association with a longer duration of ventilation and a longer LOS in ICU- and hospital, but not with higher mortality rates.

This study is the first to detail the prevalence of dyscapnia and the association of hypercapnia with major outcomes in invasively ventilated COVID-19 patients. Strengths of this analysis are the collection of an extensive ventilation picture in the first days of invasive ventilation and a long and complete follow-up, allowing us to understand the associations of sustained hypercapnia with ventilation management and outcomes. Other strengths are the size of the cohort, and the fact that patients of both academic and non-academic hospitals were included, increasing the generalizability of the findings. Also, patients were included in a relatively short period of time, meaning that ventilation practices and other therapeutic approaches did not or had hardly changed over the course of the study.

Findings of previous studies indicate a strong increase in prevalence of hypercapnia in ARDS patients over recent decades [4,22-25]. Prevalence of hypercapnia in this cohort of invasively ventilated COVID-19 patients was remarkably higher and remained present much longer compared to what was reported in ventilated ARDS patients in the LUNG SAFE study [13]. In that study, 43.2% of patients had hypercapnia on the first day of ventilation, but only 24.1% still had hypercapnia on day 2. Also, in our cohort the prevalence of sustained hypocapnia was lower than in the LUNG SAFE study that reported a prevalence of hypocapnia of 9.3%. Next to the possibility

### Table 2
Clinical outcomes of patients categorized according to PaCO₂ measurements.

| Outcome                         | Hypercapnic (n = 485) | Normocapnic (n = 339) | p value |
|---------------------------------|-----------------------|-----------------------|---------|
| Duration of ventilation – days  | 15.0 [9.0–24.0]       | 12.0 [6.0–21.0]       | 0.001   |
| In survivors at day 28 – days  | 17.0 [10.0–31.0]      | 13.0 [8.0–22.8]       | <0.001  |
| Reintubation – no (%)           | 61 (12.7)             | 43 (12.8)             | 0.999   |
| Acute kidney injury – no (%)    | 242 (50.2)            | 151 (44.7)            | 0.136   |
| Need for RRT – no (%)           | 104 (21.4)            | 52 (15.3)             | 0.030   |
| Need of rescue therapy – no (%)| 408 (84.6)            | 236 (70.2)            | <0.001  |
| Prone positioning              | 336 (69.7)            | 169 (50.1)            | <0.001  |
| Recruitment maneuver            | 27 (6.9)              | 25 (9.0)              | 0.310   |
| Use of NMBA                     | 265 (54.6)            | 141 (41.6)            | <0.001  |
| ECMO                            | 4 (0.8)               | 4 (1.2)               | 0.722   |
| Use of vasopressor              | 461 (95.1)            | 324 (95.6)            | 0.868   |
| Use of inotropic                | 46 (9.5)              | 40 (11.8)             | 0.299   |
| ICU length of stay – days       | 17.0 [10.0–28.0]      | 14.0 [8.0–23.0]       | 0.001   |
| In survivors – days             | 20.5 [12.8–33.3]      | 15.0 [10.0–27.3]      | <0.001  |
| Hospital length of stay – days  | 26.0 [16.0–41.0]      | 21.0 [13.0–33.8]      | 0.001   |
| In survivors – days             | 33.0 [24.0–49.0]      | 27.0 [18.0–40.8]      | <0.001  |
| ICU mortality – no (%)          | 179 (37.1)            | 113 (33.3)            | 0.300   |
| Hospital mortality – no (%)     | 181 (38.2)            | 117 (35.3)            | 0.416   |
| 28-day mortality – no (%)       | 157 (32.4)            | 108 (32.0)            | 0.940   |
| 90-day mortality – no (%)       | 187 (40.4)            | 123 (38.2)            | 0.553   |

Data are median [quartile 25% - quartile 75%] or No (%). Percentages may not total 100 because of rounding.

RRT: renal replacement therapy; NMBA: neuromuscular blocking agents; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; PEEP positive end expiratory pressure.

*a Assessed in the first four days of ventilation.

**Fig. 3.** Mortality in the hypercapnic (red) and normocapnic (blue) patients.
that permissive hypercapnia is increasingly accepted in ARDS patients in general, it could also be the consequence of the high use of a low VT in COVID–19 patients. Indeed, in our cohort VT was lower than in all previous studies in patients with ARDS, but in line with other cohorts of COVID–19 patients [26–31]. Another explanation is that COVID–19 patients can have more wasted ventilation, possibly related to the high incidence of VTE. This is in line with the finding that VR was higher, while MV was comparable in hypercapnic patients compared to normocapnic patients in our cohort.

The number of studies that report on PaCO2 over more than one day of invasive ventilation in COVID–19 patients is scarce. In a study from the UK, median PaCO2 slightly increased from 43 [38 to 49] mmHg at the first day to 46 [41 to 52] mmHg at the third day of ventilation [32]. In a study from Argentina, median PaCO2 at the first and third day were not different, 46 [40 to 55] mmHg and 45 [40 to 52] mmHg [30]. While these PaCO2 values are comparable to PaCO2 values in patients in our cohort, unfortunately these studies did not classify and compare patients according to whether they had sustained hypercapnia or normocapnia.

Hypercapnia was associated with a longer duration of ventilation and longer LOS in ICU and hospital. However, despite the finding that hypercapnic patients were sicker, as is reflected by the higher incidence of severe ARDS and presence of VTE, mortality was not different between hypercapnic and normocapnic patients. It is noticeable that while AP and MP were higher in hypercapnic patients than in normocapnic patients, reflecting more severe lung disease, differences were small. This may be because of a proper adjustment of ventilator settings by the caregivers—use of a lower VT and preventing the use of a higher RR, by that preventing a rise in AP and MP, and thus ventilator–induced lung injury [33].

It remains a debate whether hypercapnia itself should be accepted or prevented, as it is known to have opposite biological effects, making it difficult to determine the net consequence [34]. Though the prevalence of hypercapnia has increased over the years, mortality in ARDS patients has decreased substantially [35], and mortality in patients with ARDS due to COVID–19 seems to be not different from that in patients with ARDS due to another cause. Anyway, in this study, hypercapnia had no association with mortality, possibly suggesting at the very least that hypercapnia is not harmful.

This study has limitations. Due to its observational nature, we can only speak of associations and not of causality. Local protocols regarding management of hypercapnia, and more specifically the use of permissive hypercapnia, were unknown. As we were blinded for spontaneous efforts of patients, driving pressure could have been underestimated. Patients in the normocapnic cohort were less sick, and therefore could have had spontaneous breathing earlier and more often, making it possible that differences in driving pressure were overestimated between the two cohorts. Dead space ventilation was estimated with VR, and not quantified directly by volumetric capnography. The type of humidification was not collected per patient and therefore the individual effects of instrumental dead space could not be considered in our analysis. However, type of humidifier used per center was identified, and only small differences were seen in MV and PaCO2 between centers that used heated humidification and those that used heat and moisture exchangers [36]. Although we tried to correct for confounding as much as possible, there is always the possibility that we may have not taken all potential confounders into account, or missed some due to the fact that the data were incomplete. Lastly, new strains of COVID–19 have afflicted the world since this study, and it is unclear what the impact of these strains are on the progress of the disease, i.e., whether patients can become so severely ill that they need intensive care. Also, after the first waves a large proportion of the population was vaccinated, and although this protects against development of severe illness well, some of those patients may still need intensive care. Therefore, our findings need confirmation in later cohorts in the pandemic.

5. Conclusion

In this cohort of invasively ventilated COVID–19 patients, hypercapnia was prevalent and associated with a different ventilation strategy, possibly due to a higher dead space. Also, hypercapnia was associated with a longer duration of ventilation and higher LOS in ICU and hospital, but not with mortality. The findings of this study may be useful in generating new hypotheses that need to be tested in future studies, preferably randomized clinical trials.

Declaration of Competing Interest
Any Serpa Neto reports personal fees from Dräger, outside the submitted work. All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154022.

References

[1] Penuelas O, Muriel A, Abraira V, Frutos-Vivar F, Manco JB, Raymondos K, et al. Inter-country variability over time in the mortality of mechanically ventilated patients. Intensive Care Med. 2020;46(3):444–53. https://doi.org/10.1007/s00134-019-05887-9.

[2] Rackley CR, MacIntyre NR. Low tidal volumes for everyone? Chest. 2019;156(4):783–91. https://doi.org/10.1016/j.chest.2019.06.007.

[3] Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med. 2018;44(11):1914–22. https://doi.org/10.1007/s00134-018-5375-6.

[4] Nin N, Muriel A, Penuelas O, Brochard L, Lorente JA, Ferguson ND, et al. Severity hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Med. 2017;43(2):200–8. https://doi.org/10.1007/s00134-016-4611-1.

[5] Tiruvoipati R, Pilcher D, Buscher H, Botha J, Bailey M. Effects of hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients. Crit Care Med. 2017;45(7). https://doi.org/10.1097/CCM.0000000000002332. e569–e56.

[6] O’Toole D, Hassett P, Contreras M, Higgins BD, McKeown ST, McAuley DF, et al. Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. Thorax. 2009;64(11):976–82. https://doi.org/10.1136/thx. 2008.103094.

[7] Briva A, Vadazs I, Lencau E, Welch LC, Chen J, Dada LA, et al. High CO2 levels impair alveolar epithelial function independently of pH. PLoS One. 2007;2(11):e12318. https://doi.org/10.1371/journal.pone.0001238.

[8] O’connor DF, Nichol AD, Hopkins N, Boylan J, O’Brien S, O’Connor C, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. Crit Care Med. 2008;36(7):2128–35. https://doi.org/10.1097/CCM.0b013e31817d0189.

[9] Gattinoni L, Howell HA, Nordal A, Vohwinkel CJ, Welch LC, Beitel GJ, et al. Hypercapnic impair lung neutrophil function and increases mortality in murine pseudomonas pneumonia. Am J Respir Cell Mol Biol. 2013;49(5):821–8. https://doi.org/10.1165/rccm.2012-0487ox.

[10] Contreras M, Ansari B, Carley G, Higgins BD, Hassett P, O’Toole D, et al. Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-kappaB-dependent mechanism. Crit Care Med. 2012;40(9):2622–30. https://doi.org/10.1097/CCM.0b013e318258b8b4.

[11] Chonghaile MN, Higgins BD, Costello J, Laffey JG. Hypercapnic acidosis attenuates lung injury induced by established bacterial pneumonia. Anesthesiology. 2008;109(5):837–48. https://doi.org/10.1097/ALN.0b013e3181895b67.

[12] Masterson C, Orlulakowski G, Kavanagh BP. Hypercapnic: clinical relevance and mechanisms of action. Curr Opin Crit Care. 2015;21(1):7–12. https://doi.org/10.1097/MCC.0000000000000164.

[13] Madotto F, Rezaoghi E, McNicholas BA, Pham T, Slutsky AS, Bellani G, et al. Patterns and impact of arterial CO2 management in patients with acute respiratory distress syndrome: insights from the LUNG SAFE study. Chest. 2020;158(5):1967–82. https://doi.org/10.1016/j.chest.2020.05.005.

[14] Botta M, Tsonas A, Pillay J, Boers LS, Algera AG, Bos LDJ, et al. Ventilation management and clinical outcome in invasively ventilated COVID–19 patients [ProVENT–COVID] – a national, multicentre, observational cohort study. Lancet Respir Med. 2021;9(2):139–48. https://doi.org/10.1016/S2213-2600(20)30459-8.

[15] ProVENT-COVID collaborators. Prevalence of hypercapnia and associations with outcome in patients with COVID–19 ARDS - insights from the ProVENT-COVID study. https://sites.google.com/view/provent-covid/effects-of-dyscapnia-sap; https://doi.org/10.1016/j.jcrc.2022.154022.

[16] Ramírez AM, Meade MO, Slutsky AS, Brochard L, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747–55. https://doi.org/10.1056/NEJMoa1410639.
Urner M, Juni P, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of mechanical power. Intensive Care Med. 2016;42(10):1567–75. https://doi.org/10.1007/s00134-016-4505-2.

Cattaneo L, Marini JJ, Collino F, Maiolo G, Rapetti F, Tonetti T, et al. The future of mechanical ventilation: lessons from the present and the past. Crit Care. 2017;21(1):183. https://doi.org/10.1186/s13054-017-1750-x.

Vasques F, Dusci E, Pasticci J, Romitti F, Vassalli F, Quintel M, et al. Is the mechanical power the final word on ventilator-induced lung injury?–we are not sure. Ann Transl Med. 2018;6(19):395. https://doi.org/10.21037/atm.2018.08.17.

Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Penuelas O, Abraira V, et al. Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med. 2013;188(2):220–30. https://doi.org/10.1164/rcrcc.201212-2169OC.

Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788–800. https://doi. org/10.1001/jama.2016.0291.

Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, et al. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med. 2008;177(2):170–7. https://doi.org/10.1164/rccm.200706-893OC.

Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernández M, Gea A, Arruti E, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46(12):2200–11. https://doi.org/10.1007/s00134-020-06192-2.

Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–70. https://doi.org/10.1016/S0140-6736(20)31189-2.

Fusina F, Albani F, Bertelli M, Cavallo E, Crisci S, Caserta R, et al. Corrected minute ventilation is associated with mortality in ARDS caused by COVID-19. Respir Care. 2021;66(4):619–25. https://doi.org/10.4187/respcare.08314.

Schenck EJ, Hoffman K, Goyal P, Choi J, Torres I, Rajwani K, et al. Respiratory mechanics and gas exchange in COVID-19-associated respiratory failure. Ann Thorac Soc. 2020;17(9):1158–61. https://doi.org/10.15113/AnnalsATS.202005-427RL.

Estenssoro E, Loundet C, Rios FG, Kanore Edul VS, Plotnikow G, Andrian M, et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): a prospective, multicentre cohort study. Lancet Respir Med. 2021;9(9):989–98. https://doi.org/10.1016/S2213-2600(21)00229-0.

COVID-ICU group on behalf of the REVA network and the COVID-ICU investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60–73. https://doi.org/10.1007/s00134-020-06294-x.

Thomson RJ, Hunter J, Dutton J, Schneider J, Khouzami M, Casement A, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 admitted to an intensive care unit in London: a prospective observational cohort study. PLoS One. 2020;15(12):e0243710. https://doi.org/10.1371/journal.pone.0243710.

Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, et al. Mechanical power and development of ventilator-induced lung injury. Anesthesiology. 2016;124(5):1100–8. https://doi.org/10.1097/ALN.0000000000001056.

Morales-Quinteros L, Camprubi-Rimbals M, Brigue J, Bos LD, Schultz MJ, Artigas A. The role of hypercapnia in acute respiratory failure. Intensive Care Med Exp. 2019;7(Suppl. 1):39. https://doi.org/10.1186/s40635-019-0229-z.

Macia J, Jor O, Holub M, Sklenka P, Bursa F, Burda M, et al. Past and present ARDS mortality rates: a systematic review. Respir Care. 2017;62(1):113–22. https://doi.org/10.4187/respcare.04716.

Schultz MJ, Bos LD, Paulus F, Neto AS. Instrumental dead space in ventilator management - Authors' reply. Lancet Respir Med. 2021;9(3):e23. https://doi.org/10.1016/S2213-2600(21)00015-1.