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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

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ABSTRACT

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 ventilation ratio. Hypercapnia has an association with duration of ventilation and LOS in ICU and hospital, but not with mortality.

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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 (V_T) 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 prepublished [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 adjunctive 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 ($PaCO_2$) 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 $PaCO_2$ measurements > or < 45 mmHg on that day. The cutoff was chosen based on a previous analysis [13]. Herein, we ignored the first available $PaCO_2$ 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 $PaCO_2$ measurement were >45 mmHg or displayed hypocapnia, with a $PaCO_2$ 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: V_T, 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]:

$$\text{PBW (kg)} = 50 + 0.91*(\text{height in centimeters} - 152.4)\ \text{(in men)} \quad \text{[Eq.1]}$$

$$\text{PBW (kg)} = 45.5 + 0.91*(\text{height in centimeters} - 152.4)\ \text{(in women)} \quad \text{[Eq.2]}$$

$$\Delta P\ (\text{cm } H_2O) = \text{Peak pressure } (P_{peak}) - \text{PEEP} \quad \text{[Eq.3]}$$

$$VR = V_{E\ measured} * PaCO_{2\ measured} / V_{E\ predicted} * PaCO_{2\ predicted} \quad \text{[Eq.4]}$$

and

$$MP\ (\text{in J/min}) = 0.098 * V_T * RR * (Ppeak - 0.5 * \Delta P)$$

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: V_T, RR, PEEP, MV, ΔP, MP and VR. Linear mixed–effect models were used to assess the

trends of V_T, RR, PEEP, MV, ΔP, 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%) Figure 3 blood gas analyses showing a $PaCO_2 > 45$ mmHg. Hypocapnia 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 PaO_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.

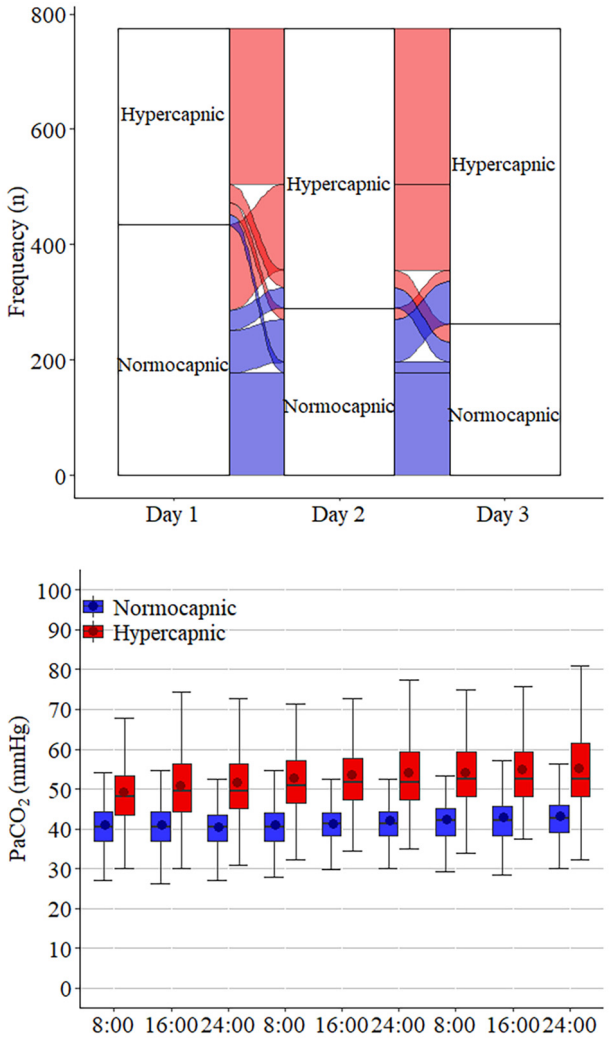

Fig. 1. Group assignment $PaCO_2$ (upper panel) and $PaCO_2$ values (lower panel) in hypercapnic (red) and normocapnic patients (blue). White boxes represent number of blood gas analyses that are classified as hypercapnic and normocapnic; flows between boxes represent categorized patients. $PaCO_2$ values at successive time points are presented as medians (horizontal bar), means (closed circle), interquartile ranges (box tops and bottoms). Whiskers extend to 1.5 times the interquartile range beyond the first and third quartiles per the conventional Tukey method.

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, ΔP, 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 ΔP did not change over the first 4 calendar days of ventilation, while V_T slightly increased and ΔP 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.

Table 1
Baseline characteristics, medical history, organ support and ventilation variables of patients categorized according to $PaCO_2$ measurements.

	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/m^2	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
Lung parenchyma affected – no (%)			0.164
0%	3 (1.8)	8 (5.9)	
25%	52 (30.8)	45 (33.3)	
50%	50 (29.6)	42 (31.1)	
75%	52 (30.8)	36 (26.7)	
100%	12 (7.1)	4 (3.0)	
Chest X–ray performed – no (%)	290 (90.9)	190 (89.6)	0.653
Quadrants affected – no (%)			0.575
1	21 (7.2)	13 (7.0)	
2	72 (24.7)	41 (21.9)	
3	83 (28.5)	47 (25.1)	
4	115 (39.5)	86 (46.0)	
Severity of ARDS – no (%)			0.002
Mild	71 (14.9)	79 (23.7)	
Moderate	337 (70.6)	224 (67.1)	
Severe	69 (14.5)	31 (9.3)	
Thromboembolic complications – no (%)	163 (33.6)	87 (25.7)	0.017
Pulmonary embolism	126 (26.0)	66 (19.5)	0.030
Deep vein thrombosis	33 (6.8)	11 (3.2)	0.027
Ischemic stroke	16 (3.3)	10 (2.9)	0.842
Myocardial infarction	5 (1.0)	10 (2.9)	0.061
Systemic arterial embolism	2 (0.4)	2 (0.6)	0.999
Co–existing disorders – no (%)			
Hypertension	159 (32.8)	112 (33.0)	0.940
Heart failure	20 (4.1)	16 (4.7)	0.730
Diabetes	102 (21.0)	87 (25.7)	0.130
Chronic kidney disease	15 (3.1)	20 (5.9)	0.055
Baseline creatinine, μmol/L[a]	77.0 [61.0–93.0]	77.0 [64.0–102.2]	0.058
Liver cirrhosis	1 (0.2)	2 (0.6)	0.572
Chronic obstructive pulmonary disease	48 (9.9)	19 (5.6)	0.028
Active hematological neoplasia	5 (1.0)	9 (2.7)	0.100
Active solid neoplasia	16 (3.3)	5 (1.5)	0.119
Neuromuscular disease	3 (0.6)	3 (0.9)	0.694
Immunosuppression	11 (2.3)	11 (3.2)	0.391
Asthma	29 (6.0)	19 (5.6)	0.881
Obstructive sleep apnea syndrome	27 (5.6)	17 (5.0)	0.756
Previous medication – no (%)			
Systemic steroids	17 (3.5)	18 (5.3)	0.222
Inhalation steroids	63 (13.0)	32 (9.4)	0.122
Angiotensin converting enzyme inhibitor	84 (17.3)	65 (19.2)	0.520
Angiotensin II receptor blocker	54 (11.1)	36 (10.6)	0.910
Beta–blockers	96 (19.8)	67 (19.8)	0.999
Insulin	28 (5.8)	29 (8.6)	0.127
Metformin	72 (14.8)	62 (18.3)	0.212
Statins	160 (33.0)	98 (28.9)	0.223
Calcium channel blockers	89 (18.4)	60 (17.7)	0.854
Organ support at start of ventilation – no (%)			
Continuous sedation	470 (96.9)	325 (96.4)	0.697
Inotropic or vasopressor	390 (80.4)	257 (76.3)	0.166
Fluid balance, mL	634.0 [65.5–1491.5]	708.5 [52.6–1365.6]	0.795
Urine output, mL	771.0 [415.0–1178.8]	702.5 [382.5–1165.0]	0.206
Ventilation support at start of ventilation			
Tidal volume, mL/kg PBW	6.4 [5.9–7.0]	6.5 [5.9–7.2]	0.100
Minute ventilation, L/min	9.6 [8.3–11.1]	9.5 [8.2–10.9]	0.530
PEEP, cmH_2O	13.0 [11.0–14.8]	12.0 [10.3–14.0]	0.027
Peak pressure, cmH_2O	27.0 [24.2–30.0]	26.0 [23.0–29.4]	0.014
Driving pressure, cmH_2O	14.0 [12.0–16.3]	13.5 [12.0–16.0]	0.243
Mechanical power, J/min	18.6 [15.5–22.3]	17.3 [14.5–21.7]	0.012
Ventilatory Ratio	1.7 [1.5–2.1]	1.4 [1.3–1.7]	<0.001
Compliance, mL/cmH_2O	32.2 [25.8–39.8]	33.5 [27.4–40.6]	0.098
Total respiratory rate, mpm	21.8 [19.5–24.0]	21.0 [19.2–23.3]	0.009
FiO_2	0.60 [0.52–0.70]	0.56 [0.48–0.66]	<0.001
$etCO_2$, mmHg	38.3 [33.5–43.5]	34.3 [31.1–39.0]	<0.001
Vital signs at start of ventilation			
Heart rate, bpm	85.3 [76.2–99.1]	83.0 [72.2–95.8]	0.013
Mean arterial pressure, mmHg	81.2 [73.8–89.5]	81.0 [75.0–87.2]	0.305
Laboratory tests at start of ventilation			
pH	7.35 [7.29–7.39]	7.38 [7.34–7.42]	<0.001

Table 1 (*continued*)

	Hypercapnic ($n = 485$)	Normocapnic ($n = 339$)	*p* value
PaO_2, mmHg	80.8 [72.5–93.7]	82.7 [73.5–98.8]	0.035
PaO_2 / FiO_2, mmHg	118.8 [93.0–157.5]	138.0 [103.5–187.5]	<0.001
$PaCO_2$, 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; FiO_2: fraction of inspired oxygen; $etCO_2$: end tidal carbon dioxide, PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; ECMO: extracorporeal membrane oxygenation; NMBA: neuromuscular blocking agents.
[a] Most recent measurement in 24 h before intubation – or at ICU admission under invasive ventilation.

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

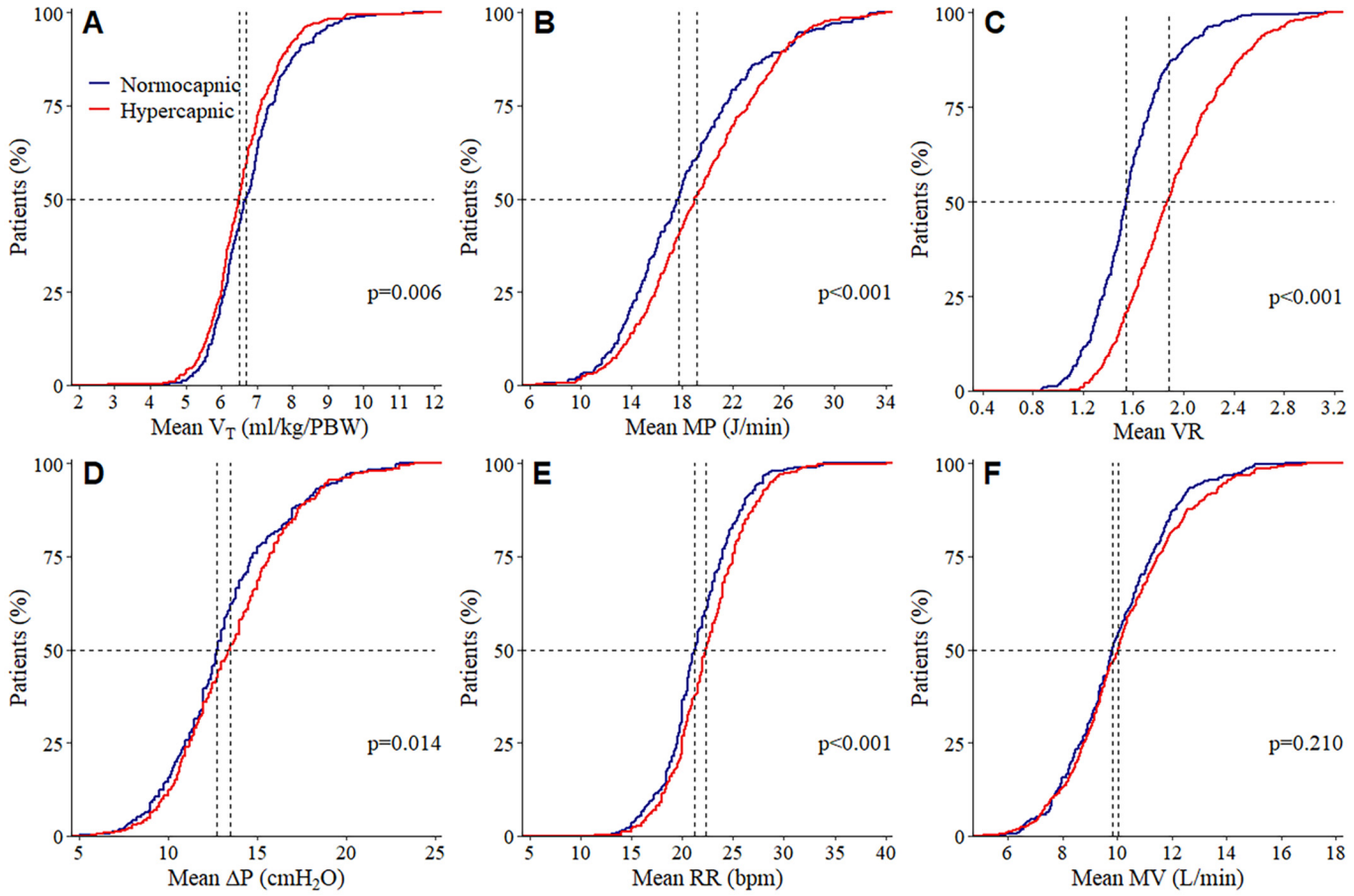

Fig. 2. Cumulative frequency distributions of the means of ventilation variables on Day 1 stratified by group defined by $PaCO_2$ measurements. Horizontal dotted lines represent 50% of the patients and vertical dotted lines represent the median of the means of the variable on Day 1. All measurements are mean over a maximum of six measurements. P–values from Wilcoxon rank–sum test.
ΔP = driving pressure; MP = mechanical power; MV = minute ventilation; PBW = predicted body weight; RR = respiratory rate; VR = ventilatory ratio; V_T = tidal volume.

Table 2
Clinical outcomes of patients categorized according to $PaCO_2$ measurements.

	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 (%)[a]	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.

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

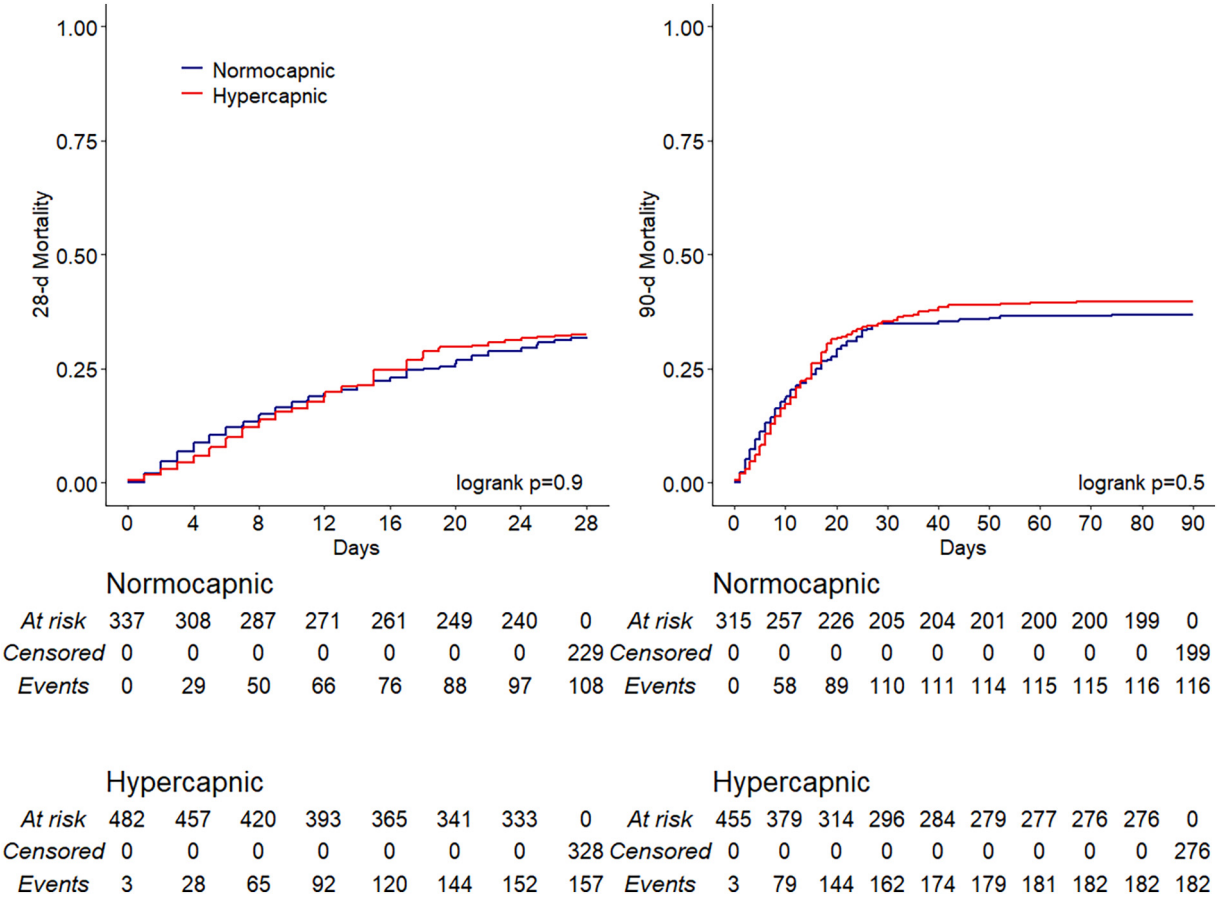

Fig. 3. Mortality in the hypercapnic (red) and normocapnic (blue) patients.

that permissive hypercapnia is increasingly accepted in ARDS patients in general, it could also be the consequence of the high use of a low V_T in COVID–19 patients. Indeed, in our cohort V_T 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 $PaCO_2$ over more than one day of invasive ventilation in COVID–19 patients is scarce. In a study from the UK, median $PaCO_2$ 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 $PaCO_2$ at the first and third day were not different, 46 [40 to 55] mmHg and 45 [40 to 52] mm [30]. While these $PaCO_2$ values are comparable to $PaCO_2$ 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 ΔP 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 V_T and preventing the use of a higher RR, by that preventing a rise in ΔP 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 $PaCO_2$ 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

Ary 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.

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