Hypercapnia is associated with worse outcome of mechanically ventilated patients

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Andres Esteban, as principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ABSTRACT: 237 words

Rationale: Permissive hypercapnia is commonly used by intensivists around the world when managing critically ill patients. However, the effects of hypercapnia on outcome in mechanically ventilated patients have not been established.

Objective: To analyse the relationship between hypercapnia developed within the first 24 hours after the start of mechanical ventilation and outcome in mechanically ventilated patients.

Patients and methods: Secondary analysis of three prospective, cohort studies conducted in 1998, 2004 and 2010 including 18302 patients receiving mechanical ventilation for more than 12 hours in a 1-month period from 927 ICU's in 40 countries. We recorded demographic data at admission in the intensive care and variables related to management, arterial blood gases and complications in the first 24 hours after starting mechanical ventilation. To estimate the influence of hypercapnia on outcome, a logistic regression including variables associated to mortality in univariate analysis, was performed.

Results: 14612 patients were included in the analysis. The relationship between PaCO2 and mortality indicated a cut-off value at ≥ 50 mmHg. In multivariate analysis we found that severe hypercapnia (OR 1.38 IC 95%: 1.18 to 1.62) was independently associated with increased mortality, even after adjusting for a surrogate of dead space.

Conclusions: In our study, severe hypercapnia ≥ 50 mmHg is independently associated with higher mortality in mechanically ventilated patients. These data question and warrant a re-evaluation of the prevalent paradigm and the rationale for the use of "permissive hypercapnia" in mechanically ventilated patients.

INTRODUCTION

Mechanical ventilation with high tidal volumes can cause and worsen lung injury (1-3). Hickling et al (4) reported that during mechanical ventilation limiting airway pressure to less than 30 cmH_2O, was associated with lower mortality in patients with acute lung injury, which reinforced the concept of lung protective strategy. In some patients ventilated with lower tidal volumes higher $PaCO_2$ levels were observed (5, 6). In the early 1990's the concept of permissive hypercapnia began to be accepted for acute lung injury patients and there were suggestions to institute not only permissive but therapeutic hypercapnia, allowing and purposefully increasing CO_2 levels (7-9). In the ARDS-network study (10), patients in the low tidal volume group had only mild hypercapnia (35 ± 8mmH vs 40 ± 10 mmHg) and better outcome. In a secondary analysis, where different categories of hypercapnic acidosis were defined, according to different pH and PaCO2 threshold values (11), hypercapnic acidosis in the first day of mechanical ventilation was associated with a lower mortality rate only in patients receiving high tidal volume. In contrast, patients receiving low tidal volume that developed hypercapnic acidosis did not have a protective or deleterious effect. Also, in a randomized clinical trial conducted in preterm infants reported that mild permissive hypercapnia was safe, but clinical benefits were not demonstrated (12). More recently, it was reported that hypocapnia and hypercapnia were associated with higher mortality in patients with community-acquired pneumonia (13).

In patients without acute lung injury, hypercapnia is a marker of poor prognosis, and has been associated with increased mortality in hospitalized patients with community-acquired pneumonia (13-14). Severe hypercapnia has also serious hemodynamic consequences, which may impact right ventricular function (15). In experimental models, there were initial reports on the beneficial effects of hypercapnic acidosis in models of sepsis-induced acute lung injury (16-17). Recent studies have demonstrated that hypercapnia has harmful effects by impairing alveolar epithelial function, cell proliferation and importantly adverse effects on neutrophil function and innate immunity

(18-25). In view of the prevalent paradigm of to tolerate permissive hypercapnia in mechanically ventilated patients in the MICU and conflicting experimental reports on the biologic effects of hypercapnia, we set out to evaluate the impact of early hypercapnia on mortality in a large and heterogeneous cohort of critically ill patients subjected to mechanical ventilation.

METHODS

Patients

A secondary analysis of data obtained from 18 302 patients enrolled in three prospective, multicentre, and international observational studies conducted in 1998, 2004 and 2010 (26-28) was performed. The research ethics board of each participating ICU institution approved the study protocol. For the purpose of this study, we selected invasive mechanically ventilated patients longer than 24 hours. Patients were excluded if $PaCO_2$ and pH values were missing within the first 48 hours, and if it was use non-invasive ventilation as first MV support. We collected baseline characteristics, and daily ventilator, gas exchange, clinical management, and complications data while patients were ventilated or until day 28. Patients were followed in hospital for mortality and length of stay outcomes. A full description of methodology has been described previously (28).

Statistical analysis

Data are expressed as mean (SD), median (interquartile range) and proportions as appropriate. ANOVA were used to compare continuous variables and chi-square test or Fisher's exact test was used to compare proportions. We defined as statistically significant a p value less than 0.05.A recursive partitioning method (29) was first used to look for the threshold of $PaCO_2$ and pH that best discriminated for mortality in the intensive care unit. Briefly, the program selects the threshold value that produces two subsets of the greatest purity. The partitioning was started after evaluating each risk variable for its ability to separate survivors from non-survivors according with $PaCO_2$ and pH values. When raw variables were introduced, the one that achieved the most

precise discrimination between non-surviving and surviving patients was selected as the best predictor. The distinct subgroups represented by the subsets at the bottom of the classification tree were coded as dummy variables to be entered in the Cox analysis. Secondly, hypercapnia and acidosis were defined according with the relationship between $PaCO_2$ and pH and ICU mortality using the values resulting from the recursive partitioning analysis. Because the cut-off for the effects of $PaCO_2$ was much higher than normal thresholds we further compared mild hypercapnia (below this threshold) and severe hypercapnia (at or above this threshold).

To assess the independent effect of severe hypercapnia on outcome, a back step logistic regression was performed including confounding variables associated with ICU-mortality, adjusting for the variables associated with mortality with a value of $p< 0.10$ in our univariate analysis. Also, because dead space is strongly associated with mortality (30) and may in itself explain hypercapnia we calculated the corrected minute ventilation (VE_{corr}) to have a normal $PaCO_2$ (31) (calculated as minute ventilation × PaCO2/40 mmHg) as a surrogate for dead space and we introduced it in the uni and multivariate model as a co-variable.

To validate the finding that the effect of hypercapnia was consistent independently of the reason for mechanical ventilation (acute respiratory distress syndrome, COPD and sepsis), we tested these subgroups and their interaction against hypercapnia. Statistical analyses were performed using IBM SPSS software 21.0 (IBM SPSS Statistics, Chicago, USA) and Stata (Stata Software 11.0 (StataCorp LP, College Station, Texas).

RESULTS

Baseline characteristics

From the total cohort of 18 302 patients, we excluded 2500 patients because of missing values of pH, and/or PaCO2 within the first 48 hours,) and 1190 patients receiving noninvasive ventilation as primary respiratory support. Thus, 14 612 patients

were included for the analysis. Baseline characteristics of the patients are shown in Table 1.

PH and PaCO2values within first 24 hours correlated with mortality

The cut-off value for $PaCO_2$ was 50 mmHg, with a 37% of mortality in patients with a $PaCO_2$ ≥50 mmHg vs. 30% in patients with a PaCO2 < 50 mmHg, p<0.001) (Fig. 1). A cut-off point for pH related to a higher mortality was at 7.30 (59% in patients with a pH lower or equal than 7.30 vs. 25% in patients with a pH higher than 7.30 p<0.001) (Fig. 2), With these values we defined acidosis (pH lower than 7.30), severe hypercapnia ($PaCO_2$ higher than 50 mmHg) and hypercapnic acidosis (the combination of acidosis and severe hypercapnia) within first 24 hours after start the mechanical ventilation.

Characteristics of hypercapnic patients

Comparison between patients with or without severe hypercapnia is shown in Table 2. Patients with hypercapnia were older and more frequently men. Severaly hypercapnic patients had a higher percentage of COPD, chronic non-COPD pulmonary disease, asthma, ARDS, sepsis, pneumonia and less proportion of neurological disease, postoperative trauma and cardiovascular failure as the reason for mechanical ventilation. The proportion of patients receiving tidal volumes below 6 mL/kg (adjusted body weight, ABW) was significantly higher in patients with hypercapnia. Peak pressure and plateau pressure were higher and the PaO_2/FIO_2 ratio was lower in patients with severe hypercapnia (Table 2). Also VE_{corr} was higher in hypercapnic patients, suggesting that dead space was higher (Table 2).

Clinical events over the course of mechanical ventilation

Patients with hypercapnia had a larger number of complications such as: barotrauma, late-onset ARDS, sepsis, ventilator associated pneumonia and cardiovascular dysfunction (Figure 3). Also more re-intubation, mechanical ventilation days, and ICU length stay (Table 2).

Table 3 depicts the comparison of the clinical outcomes between patients with or without hypercapnia. A multivariate analysis was performed to determine the

relationship between hypercapnia with ICU mortality. In a multivariate analysis, we found that only severe hypercapnia (OR 1.4 IC 95%: 1.1 to 1.6) and hypercapnic acidosis (OR 1.8 IC95%: 1.5 to 2.3) were independently associated with ICU mortality adjusted for age, period of time, SAPS II, PaO_2/FiO_2 ratio, VE_{corr}, airway pressure, reason for MV (ARDS, sepsis, cardiac arrest, neurological disease), and complications over the course of MV (late-onset ARDS, sepsis, cardiovascular failure, renal failure, barotrauma, hepatic failure, ventilator-associated pneumonia and coagulopathy) (Table 3). The same results were found with the median of $PaCO_2$ in the 28 days evolution (data not shown)

When we analysed for subgroups of patients, hypercapnia was independently associated with mortality in sepsis, ARDS and pneumonia as a reason to initiate MV but not in COPD (Fig 4).

DISCUSSION

We provide evidence that severely hypercapnic patients undergoing mechanical ventilation have increased ICU-mortality, more mechanical ventilation days and ICU length stay as well as more complications. These findings are consistent in all subgroups analysed including sepsis, ARDS and pneumonia.

The basis for the use of “permissive hypercapnia” strategy stems from two previous observational reports in the 1990’s that suggested that reducing the aggressiveness of mechanical ventilation at the price of hypercapnia was associated with improved survival (4, 5). In a subsequent study in 49 preterm infants, there was no difference in mortality or medical complications comparing patients with hypercapnia and normocapnia and the conclusion was that that permissive hypercapnia was safe but not protective (12). Also, in a secondary analysis of data from the ARDS network study (11), the authors reported that the presence of hypercapnic acidosis (defined as pH <7.35 and $PaCO_2$ of >45 mm Hg) at the time of randomization, using a multivariate logistic regression analysis, and controlling for other comorbidities and severity of lung injury, was associated with reduced 28 days mortality only in patients randomized to 12

ml of tidal volume. There was no difference in mortality among patients randomized to 6 ml/kg of tidal volume. The study had some limitations, such as the small number of patients included in each subgroup, the arbitrary definition of hypercapnic acidosis but there was no difference in the patients with “protective ventilation” where hypercapnia was expected to occur.

A relationship between a high dead space and mortality was already shown in patients with ARDS (30). In our study, we took the “corrected minute ventilation” as a surrogate for dead space (31). Indeed, the association of severe hypercapnia and mortality could be a simple marker of lung severity. It is interesting to see that even after adjusting for corrected minute ventilation, severe hypercapnia remains strongly associated with mortality. More over, Brown et al (32) showed that minute ventilation (>13.9 L/min) was important predictor of hospital mortality at 90 days in acute lung injury, similar data to our study (>13 L/min).

In patients with chronic lung diseases hypercapnia is an indicator of poor prognosis. In COPD patients, hypercapnia was an independent predictor of death (14, 33) and in hospitalized patients with community-acquired pneumonia, in-hospital mortality was greater in patients with hypercapnia (34). Furthermore, abnormally high or low CO_2 levels were associated with increased mortality in patients with community-acquired pneumonia (13). In our study, there was no effect of hypercapnia in this subgroup possibly because we adjusted on corrected minute ventilation, a surrogate for dead space.

Initial studies utilizing in vitro models of VILI and sepsis reported on the beneficial effects of hypercapnia, which supported the notion of “permissive and even therapeutic hypercapnia” for patients with lung injury (7-9). However, more recent studies reported that high levels of $PaCO_2$ activate specific signalling pathways independently of pH, or reactive oxygen species, leading to impaired lung function (17, 22, 36). Also, in a model of ventilator-induced lung injury the probability of wound repair was significantly reduced in hypercapnic lungs compared to normocapnia (18). This concept was further

explored in a recent study showing that hypercapnia causes significant mitochondrial stress via the activation of miR-183, which resulted in mitochondrial dysfunction by downregulating isocytrate dehydrogenase 2 (IDH2) and leading to impaired cell proliferation which could explain the impaired wound repair (18, 21). Also, it has been reported that hypercapnia impairs innate immune immunity in Drosophila melanogaster (19) by decreasing the expression of antimicrobial peptides and in a mouse model of pseudomonas pneumonia, where hypercapnia impaired neutrophil function and increased animal mortality (23). Also, it is known that elevated CO_2 levels contribute to increased bacterial and fungal virulence and survival that may render hypercapnic tissues more susceptible to infection. (34-36). These and other recent data suggest that hypercapnia impairs innate immunity via evolutionarily conserved mechanisms (22) and provides the rationale of why patients exposed to hypercapnia have impaired ability to fight off infection due to the inability to mount and effective defence against pathogens. In patients, hypercapnia has a number of clinical consequences and severe hypercapnia can induce or increase pulmonary hypertension and markedly worsen right ventricular function (37). Elevated pulmonary vascular resistance is a strong marker of poor outcome in acute lung injury (38-40). Why did the earlier studies suggested beneficial effects of hypercapnia? A first reason is that they primarily showed a reduction in ventilator-induced lung injury. Second, our analyses do not suggest a significant effect of mild hypercapnia. Third, the initial impairment in the innate immunity response by impairing the release of IL-6 and TNFα (41) could be beneficial in the early stages of sepsis by limiting the cytokine storm and thus have a transient beneficial effect. However, prolonged hypercapnia by impairing innate immunity limits the ability to fight off infection, hinder the host response to infection and result in worse outcomes (24, 42-44).

Our study provides new information suggesting that severe hypercapnia is deleterious in mechanically ventilated patients. These data should lead to considerations for a paradigm shift for the treatment of critically ill patients as the results do not support the

previously proposed paradigm that hypercapnia has a protective effect or at the best is perfectly safe. This is important in an area where new techniques of CO2 removal are proposed (45). Although not a prospective study our results are the largest evidence in the literature published in a population of patients from 927 ICU's.

Our study has limitations. The data represents a secondary analysis of a database that was not designed for the purpose of this study. However, the prospective design of this observational study shows the real-life clinical approaches to mechanically ventilated patients from ICU's in 40 countries. We have validated the results of our analysis in different subgroup of patients and have found consistent results (ARDS, pneumonia and sepis patients). The measures of arterial blood gases and patient/ventilator interaction parameters were reported only once daily and it is possible that a single measure each day was insufficient to reflect patients' respiratory progression along the day. Data collection was, however, performed always at the same time of the day.

As such, our study represents a large multinational survey that reflects the mechanical ventilation practice around the globe and is the largest cohort of mechanically ventilated patients with hypercapnia analysis published to date.

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Figure Legends

Figure 1 Effects of PCO_2 in ICU Mortality.

Figure 2 Effects of pH in ICU Mortality.

Figure 3 Clinical events over the course of mechanical ventilation between non-hypercapnic and hypercapnic patients.

Figure 4 Adjusted Odds Ratios for ICU mortality in multivariate analysis.

Table 1 - Demographic characteristics of patients included in the analysis

	N = 14612
Age, years, mean (SD)	59.2 (17.5)
Female, n (%)	5561(38.2)
SAPS II, points, mean (SD)	45.1 (17.6)
Reason to start mechanical ventilation, n (%)	
Chronic obstructive pulmonary disease	805 (5.5)
Asthma	180 (1.2)
Chronic pulmonary disease non-COPD	147 (1.0)
Neurological disease	3031 (20.7)
Neuromuscular disease	189 (1.3)
Postoperative	3148 (21.5)
Acute respiratory syndrome distress	531 (3.6)
Pneumonia	1577 (10.8)
Sepsis	1459 (10)
Congestive Heart Failure	960 (6.6)
Aspiration	393 (2.7)
Cardiac arrest	724 (5.0)
Trauma	941 (6.4)
Other	957 (6.5)
Arterial blood gases on day 1	
pH, mean (SD)	7.38 (0.09)
PaCO2, mmHg, mean (SD)	38.9 (10.1)
Ratio PaO2 to FiO2, mean (SD)	250.1 (111.7)

Table 2 - Comparison between patients with early hypercapnia and patients without early hypercapnia

	Severe hypercapnia (≥50 mmHg) N = 1560	No or Mild Hypercapnia (<50 mmHg) N = 13052	P Value
Age, years, mean (SD)	61.4 (15.6)	59.0 (17.7)	< 0.001
Female, n (%)	505 (32.1)	5056 (38.7)	< 0.001
SAPS II, points, mean (SD)	44.9 (17.5)	45.1 (17.7)	0.7
Reason to start mechanical ventilation, n (%)			
Chronic obstructive pulmonary disease	396 (25.4)	396 (3.1)	< 0.001
Asthma	59 (3.8)	121 (1.0)	< 0.001
Chronic pulmonary disease non-COPD	43 (2.8)	104 (0.8)	< 0.001
Neurological disease	105 (6.7)	2926 (22.4)	< 0.001
Neuromuscular disease	14 (1.0)	175 (1.3)	0.52
Postoperative	200 (12.8)	2948 (22.6)	< 0.001
Acute respiratory distress syndrome	73 (6.8)	425 (3.3)	< 0.001
Pneumonia	243 (15.6)	1334 (10.2)	< 0.001
Sepsis	121 (7.8)	1338 (10.3)	0.001
Congestive Heart Failure	81 (5.2)	879 (6.7)	0.02
Aspiration	39 (2.5)	354 (2.7)	0.62
Cardiac arrest	56 (3.6)	668 (5.1)	0.01
Trauma	57 (3.7)	884 (6.8)	0.001
Other	76 (4.9)	881 (6.7)	0.01
Arterial Blood Gases on Day 1			

pH, mean (SD)	7.30 (0.10)	7.39 (0.08)	<0.001
$PaCO_2$, mmHg, mean (SD)	59.1 (11.2)	35.6 (6.7)	<0.001
PaO_2 /FiO_2 ratio, mean (SD)	199.4 (98.9)	255.1 (111.8)	<0.001
Ventilatory settings on day 1			
Tidal volume, ml/kg ABW			
Lower than 6 ml/kg	454(31.0)	2162 (17.5)	< 0.001
6 to 10 ml/kg	738(50.4)	6917 (56.0)	< 0.001
Higher than 10 ml/kg	272 (18.2)	3275 (26.0)	< 0.001
Peak pressure, cmH_2O, mean (SD)	29.9 (9.1)	26.1 (7.6)	<0.001
Plateau pressure, cmH2O, mean (SD)	22.8 (6.5)	20.5 (5.6)	<0.001
VE_{corr}, liters/minute, mean (SD)	13.3 (8.3)	8.3 (2.8)	<0.001
Complications over the course of mechanical ventilation, n (%)			
Barotrauma	75 (4.8)	404 (3.1)	<0.001
Acute respiratory distress syndrome	278 (17.8)	1295 (10.0)	<0.001
Sepsis	436 (27.9)	3133 (23.9)	0.001
Ventilator associated pneumonia	268 (17.2)	1772 (13.6)	<0.001
Cardiovascular failure	660 (42.3)	5014 (38.4)	<0.001
Renal failure	262 (16.8)	2031 (15.6)	0.2
Hepatic failure	88 (5.6)	893 (6.8)	0.07
Hematological failure	185 (11.9)	1611 (12.3)	0.5
Duration of mechanical ventilation, days, median (IQR)	5 (2, 9)	4 (2, 8)	<0.001
Scheduled extubation, n (%)	787 (89.6)	7478 (90.8)	0.2
Failed extubation n (%)	130 (14.8)	1077 (13.1)	0.15

Tracheostomy, n (%)	237 (15.9)	1755 (14.0)	0.02
Length of intensive care unit stay, days, median (IQR)	9 (5, 16)	8 (4, 15)	<0.001
Length of hospital stay, days, median (IQR)	18 (10, 32)	18 (9, 31)	0.1
ICU mortality	571 (36.6)	3942 (30.2)	<0.001
Hospital mortality	647 (43.6)	4645 (37.9)	<0.001

Table 3 – Multivariable analysis of variables associated with ICU mortality

	Multivariate analysis	
	Odds ratio (CI 95%)	P value
Age	1.01 (1.00 to 1.01)	<0.001
SAPS II score	1.02 (1.01 to 1.02)	<0.001
Reason for MV		
ARDS	1.52 (1.16 to 1.99)	0.02
Sepsis	1.24 (1.02 to 1.52)	0.02
Cardiac arrest	1.78 (1.35 to 2.3)	<0.001
Neurological disease	1.94 (1.61 to 2.33)	<0.001
Hypercapnic acidosis	1.74 (1.36 to 2.24)	<0.001
Severe Hypercapnia	1.38 (1.18 to 1.62)	<0.001
No Hypercapnia (PaCO2 < 42)	0.92 (0.81 to 0.95)	0.04
Mild Hypercapnia (PaCO2 43 to 50)	0.86 (0.79 to 0.95)	0.01
VE_{corr}	1.03 (1.02 to 1.04)	<0.001
Complication of MV		
Cardiovascular dysfunction	2.20 (1.97 to 2.46)	<0.001
Haematological failure	1.59 (1.39 to 1.86)	<0.001
Hepatic failure	1.69 (1.39 to 2.06)	<0.001
Renal failure	1.88 (1.64 to 2.16)	<0.001
Late-onset ARDS	1.52 (1.33 to 1.87)	0.001
Sepsis	1.15 (1.01 to 1.31)	0.02