Hypocapnia and Hypercapnia Are Predictors for ICU Admission and Mortality in Hospitalized Patients With Community-Acquired Pneumonia

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Objective: The purpose of our study was to examine in patients hospitalized with community-acquired pneumonia (CAP) the association between abnormal $Paco_2$ and ICU admission and 30-day mortality.

Methods: A retrospective cohort study was conducted at two tertiary teaching hospitals. Eligible subjects were admitted with a diagnosis of CAP. Arterial blood gas analyses were obtained with measurement of $Paco_2$ on admission. Multivariate analyses were performed using 30-day mortality and ICU admission as the dependent measures.

Results: Data were abstracted on 453 subjects with a documented arterial blood gas analysis. One hundred eighty-nine patients (41%) had normal $Paco_2$ (35-45 mm Hg), 194 patients (42%) had a $Paco_2 < 35$ mm Hg (hypocapnic), and 70 patients (15%) had a $Paco_2 > 45$ mm Hg (hypercapnic). In the multivariate analysis, after adjusting for severity of illness, hypocapnic patients had greater 30-day mortality (OR = 2.84; 95% CI, 1.28-6.30) and a higher need for ICU admission (OR = 2.88; 95% CI, 1.68-4.95) compared with patients with normal $Paco_2$. In addition, hypercapnic patients had a greater 30-day mortality (OR = 3.38; 95% CI, 1.38-8.30) and a higher need for ICU admission (OR = 5.35; 95% CI, 2.80-10.23). When patients with COPD were excluded from the analysis, the differences persisted between groups.

Conclusion: In hospitalized patients with CAP, both hypocapnia and hypercapnia were associated with an increased need for ICU admission and higher 30-day mortality. These findings persisted after excluding patients with CAP and with COPD. Therefore, $Paco_2$ should be considered for inclusion in future severity stratification criteria to appropriate identified patients who will require a higher level of care and are at risk for increased mortality. *CHEST 2012; 142(5):1193–1199*

Abbreviations: CAP = community-acquired pneumonia; HR = hazard ratio; LOS = length of stay; PSI = pneumonia severity index

Community-acquired pneumonia (CAP) is the leading infectious cause of death in the United States.[1] It affects 5 million people each year and leads to 1 million hospital admissions.[2] Of those admitted to the hospital with CAP, approximately 10% to 20% will require admission to the ICU,[3,4] where mortality may be as high as 50%,[5,6] especially when mechanical ventilation is needed.[7,8] The most frequent cause of mortality in hospitalized patients with CAP is respiratory failure.[9]

Respiratory failure is defined as a series of gas exchange abnormalities severe enough to deprive vital

organs of oxygen (hypoxemic respiratory failure) or cause acidosis secondary to hypercapnia (hypercapnic respiratory failure).[10] Hypoxemic respiratory failure is well recognized as a prognostic marker in different severity-of-illness scores to predict poor clinical outcomes in hospitalized patients with CAP.[11-14] By contrast, ventilatory abnormalities reflected by an alteration in $Paco_2$ have not been considered a poor prognostic marker unless arterial pH changes are observed.[13,15] $Paco_2$ is widely accepted as an indicator of ventilator adequacy. Abnormally high levels may indicate severe respiratory fatigue and impending

cardiopulmonary arrest.[16] However, limited data are available on the value of abnormal $PaCO_2$ as a predictor of severity in hospitalized patients with CAP. Therefore, our aim was to examine the association between abnormal $PaCO_2$ and the need for invasive mechanical ventilation, ICU admission, and 30-day mortality in patients hospitalized with CAP.

Materials and Methods

This is a retrospective cohort study of hospitalized patients with CAP at two academic teaching tertiary care hospitals in San Antonio, Texas. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the research protocol with exempt status.

Study Sites/Inclusion and Exclusion Criteria

We identified all patients admitted to the study hospitals between January 1, 1999, and December 1, 2002, with a primary discharge diagnosis of pneumonia (*International Classification of Diseases, Ninth Revision* codes 480.0-483.99 or 485-487.0) or a secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (518.81) or sepsis (038.xx). Inclusion criteria were (1) ≥ 18 years of age, (2) admission diagnosis of CAP, (3) a confirmed infiltrate or other finding consistent with CAP on chest radiograph or CT scan of the chest obtained within 24 h of admission, and (4) completing an arterial blood gas analysis within 24 h of admission.

Exclusion criteria included (1) discharge from an acute care facility within 14 days of admission, (2) transfer from another acute care hospital, or (3) having "comfort measures only" status during the admission. If a subject was admitted more than once during the study period, only the first hospitalization was abstracted.

Study Groups

Based on the $PaCO_2$ values from the arterial blood gas measured in the first 24 h of admission with CAP, the patients were stratified into 3 groups: normal $PaCO_2$ (35-45 mm Hg), hypocapnic ($PaCO_2 < 35$ mm Hg), and hypercapnic ($PaCO_2 > 45$ mm Hg). The definition of COPD was based on clinical data obtained during chart review, as discuss previously.[17] Owing to the absence of pulmonary function test results, terms including "chronic obstructive pulmonary disease," "emphysema," and "chronic bronchitis" were used as proxy measures for COPD. Missing values or data were assumed to be normal and not show COPD. This strategy is widely used in the application of prognostic prediction rules and reflects the methods used in the original pneumonia severity index (PSI) score studies[13,18]

Data Abstraction

Chart review data included demographics, comorbid conditions, physical examination findings, laboratory data, and chest radiographic reports. Comorbid conditions were identified from either the admission note or the chart problem list. In addition, data on the CAP process of care measures were abstracted. These included timing of first dose of antibiotics, collection of blood cultures prior to antibiotic administration, and obtaining blood cultures and oxygen saturation measurement within 24 h of presentation. Antimicrobial therapy was considered guideline concordant if it agreed with the American Thoracic Society guidelines.[11]

Risk Adjustment

The PSI score was used to assess severity of illness at presentation. The PSI is a validated prediction rule for 30-day mortality in patients with CAP.[13] Patients were classified into five risk classes with 30-day mortality ranging from 0.1% for class 1 to 27% for class 5 for patients enrolled in the Patient Outcomes Research Team (PORT) cohort study.[14]

Outcomes

The primary outcome was 30-day mortality. Secondary outcomes were ICU admission, need for invasive mechanical ventilation, and hospital length of stay (LOS). Mortality was assessed using information from the Texas Department of Health and Department of Veteran Affairs clinical database. Mortality status was assessed through the end of December 2002.

Statistical Analyses

Univariate statistics were used to test the association of demographic and clinical characteristics with $PaCO_2$ levels. Categorical variables were analyzed using the χ^2 test, and continuous variables were analyzed using Student t test.

We used Cox proportional hazards model to produce survival curves after adjusting for the PSI score.[13,19] We performed a logistic regression analysis using ICU admission and 30-day mortality as the dependent variables and $PaCO_2$ as the independent variable. A subgroup analysis was repeating the univariate and multivariate analysis excluding patients with a diagnosis of COPD. A secondary analysis was performed using $PaCO_2$,

tachypnea (respiratory rate > 30/min) and arterial pH (acidosis [pH < 7.35] or alkalosis [pH > 7.45]) as independent variables using a Cox proportional hazard model to predict 30-day mortality. All analyses were performed using SPSS version 19.0 for Windows (IBM).

Results

Four hundred fifty-three patients who satisfied the inclusion criteria were identified during the study period. The distribution among groups was 189 patients (41.7%) with normal $PaCO_2$ (35-45 mm Hg), 194 patients (42.8%) with hypocapnia ($PaCO_2 < 35$ mm Hg), and 70 patients with hypercapnia (15.5%) ($PaCO_2 > 45$ mm Hg).

Patient Characteristics

Table 1 shows patient demographic characteristics by study groups. Hypocapnic patients were more likely to have been younger; to have had multilobar infiltrates, metabolic alkalosis, and chronic liver disease; and to have presented with tachycardia. They were less likely to have COPD as compared with patients with normal $PaCO_2$ levels. However, in comparison with normocapnic patients, hypercapnic patients had more preexisting comorbid conditions, such as congestive heart failure, prior stroke, and COPD. Furthermore, hypercapnic patients were more likely to have altered mental status, hypoxemia, acidosis, and a higher PSI scores.

Clinical Outcomes

Overall 30-day mortality was higher in patients with hypocapia and hypercapnia compared with the reference group with normal $PaCO_2$ levels (13.4% and 20.0% vs 5.3%, respectively; $P = .01$). Both groups (hypocapnic and hypercapnic) also had significantly higher ICU admissions. However, there were no statistically significant differences among groups for invasive mechanical ventilation and mean hospital LOS (Table 2).

Table 3 shows univariate and multivariable analysis of specific variables according to 30-day mortality, ICU admission, and invasive mechanical ventilation. In the univariate analysis, both hypocapnia and hypercapnia were associated with 30-day mortality and need for ICU admission. However, these conditions were not associated with mechanical ventilation and LOS. The same results were found in the multivariable analysis after adjusting for severity of illness (PSI).

Figure 1 shows the survival curves based on the Cox proportional hazard model. It demonstrates that both hypocapnia and hypercapnia had significantly increased mortality compared with the reference group with normal $PaCO_2$.

Table 1—Comparison of Demographic and Clinical Characteristics Among Patients With CAP According to Levels of $PaCO_2$

Variables	$PaCO_2 < 35$ mm Hg (n = 194)	$PaCO_2$ 35-45 mm Hg (n = 189)	$PaCO_2 > 45$ mm Hg (n = 70)
Age (SD), y	56 (15.0)[a]	60 (15.3)	60 (17.1)
Men	150 (77.7)	136 (72.0)	61 (87.1)[a]
Comorbid conditions			
COPD	33 (17.0)[a]	57 (30.2)	36 (51.4)[a]
Congestive heart failure	21 (10.8)	26 (13.8)	18 (25.7)[a]
History of stroke	19 (9.8)	19 (10.1)	15 (21.4)[a]
History of malignancy	15 (7.7)	15 (7.9)	6 (8.6)
Chronic liver disease	31 (16.0)[a]	16 (8.5)	10 (14.3)
Renal insufficiency	21 (10.8)	23 (12.2)	4 (5.7)
Physiologic parameters			
Respiratory rate > 30/min	28 (14.4)	21 (11.1)	14 (20.0)
Heart rate > 125/min	43 (22.2)[a]	23 (12.2)	14 (20.0)
Systolic BP < 90 mm Hg	7 (3.6)	4 (2.1)	2 (2.9)
Temperature < 95°F (< 30°C) or > 104°F (> 40°C)	8 (4.1)	2 (1.1)	2 (2.9)
Altered mental status	29 (14.9)	19 (10.1)	18 (25.7)[a]
Arterial pH < 7.35	13 (6.7)	11 (5.8)	25 (35.7)[a]
BUN > 30 mg/dL	49 (25.3)	44 (23.3)	9 (12.9)
$PaO_2 < 60$ mm Hg	56 (28.9)	44 (23.3)	39 (55.7)[a]
Hematocrit < 30%	21 (10.8)	14 (7.4)	5 (7.1)
Multilobar infiltrates	97 (50.0)[a]	72 (38.5)	29 (42.6)
Pleural effusion	58 (29.9)	52 (27.5)	17 (24.3)
PSI score, mean (SD)	92 (37.7)	90 (34.7)	109 (39.2)[a]

Values are given as No. (%) unless otherwise indicated. CAP = community-acquired pneumonia; PSI = pneumonia severity index.
[a]$P < .05$ compared with reference group ($PaCO_2$ 35-45 mm Hg).

Table 2—Comparison of Outcomes Among All Patients With CAP According to Levels of $PaCO_2$

Outcome	$PaCO_2 < 35$ mm Hg (n = 194)	$PaCO_2$ 35-45 mm Hg (n = 189)	$PaCO_2 > 45$ mm Hg (n = 70)
30-d mortality	26 (13.4)[a]	10 (5.3)	14 (20.0)[a]
ICU admission	62 (32.0)[a]	29 (15.3)	38 (54.3)[a]
Invasive mechanical ventilation	24 (12.4)	16 (8.5)	11 (15.7)
Length of stay, mean (SD)	10 (27.4)	7 (9.6)	9.6 (9.5)

Values are given as No. (%) unless otherwise indicated. See Table 1 legend for expansion of abbreviation.
[a]$P < .05$ compared with reference group ($PaCO_2$ 35-45 mm Hg).

We evaluated the $PaCO_2$ interaction with pH level and respiratory rate to determine an association with 30-day mortality. We found that hypocapnia was independently associated with higher 30-day mortality (hazard ratio [HR] = 2.99; 95% CI, 1.23-7.25; $P = .015$), but there was not an association with alkalosis (HR = 1.18; 95% CI, 0.55-2.55; $P = .7$) or tachypnea (HR = 1.77; 95% CI, 0.71-4.40; $P = .2$). In addition, hypocapnia and acidosis were independently associated with higher 30-day mortality (HR = 2.63; 95% CI, 1.27-5.46; $P = .009$ and HR = 3.81; 95% CI, 1.66-8.78; $P = .002$, respectively) but not with tachypnea (OR = 1.71; 95% CI, 0.77-3.77; $P = .2$). Hypercapnia was independently associated with higher 30-day mortality (OR = 3.36; 95% CI, 1.35-8.40; $P = .009$) but not with acidosis (OR = 2.11; 95% CI, 0.81-5.50; $P = .1$) or tachypnea (OR = 0.19; 95% CI, 0.02-1.41; $P = .1$).

Subgroup Analysis

To assess the influence of COPD on outcomes, we performed an additional analysis excluding patients with a history of COPD (n = 126 [27.8%]). In this subgroup (n = 327), 30-day mortality and ICU admission were also greater among patients with hypocapnia and hypercapnia as compared with the reference group. Furthermore, higher need for invasive mechanical ventilation was observed among hypercapnic patients without COPD (Table 4).

Table 5 shows the univariate and multivariable analyses after adjusting for severity of illness (PSI) in subjects without COPD. Both hypocapnia and hypercapnia were associated with higher 30-day mortality and ICU admission in the univariate and multivariate analyses. Patients without COPD and hypercapnia also have an increased risk for invasive mechanical ventilation in the univariate analysis.

DISCUSSION

The main findings of our study are that patients hospitalized with CAP with abnormal $PaCO_2$ levels (hypercapnia or hypocapnia) at the clinical presentation to the hospital were more likely to die within 30 days of admission and require ICU care when compared with those with normal $PaCO_2$. These findings remain after adjusting for severity of illness and excluding patients with COPD from the cohort. This suggests that $PaCO_2$ may play an important role in the clinical outcomes in hospitalized patients with CAP.

ICU admission is an important decision that affects outcomes, treatment, and costs.[20-22] For several decades, a number of predictor severity tools, such as PSI,[13] CURB-65,[23] and Infectious Diseases Society of America/American Thoracic Society guidelines,[11,12] have been developed to predict 30-day mortality, but they also have been recommended to identify patients for consideration of the need for ICU admission. A recent meta-analysis suggests that these severity score systems are not accurate to predict ICU admission.[24] These scores include several demographic, comorbid condition, physiologic, laboratory

Table 3—Comparison of 30-d Mortality, ICU Admission, and Mechanical Ventilation Among Hypocapnic ($PaCO_2 < 35$ mm Hg) and Hypercapnic ($PaCO_2 > 45$ mm Hg) Patients With CAP vs Normal Group

Outcome	Univariable			Multivariable		
	OR	95% CI	P Value	HR	95% CI	P Value
Hypocapnic group						
30-d mortality	2.77	1.30-5.92	.009	2.84	1.28-6.30	.01
ICU admission	2.59	1.58-4.26	< .001	2.88	1.68-4.95	< .001
Invasive mechanical ventilation	1.53	0.78-2.97	.2	1.49	0.75-2.95	.2
Hypercapnic group						
30-d mortality	4.47	1.88-10.63	.001	3.38	1.38-8.30	.008
ICU admission	6.55	3.54-12.11	< .001	5.35	2.80-10.23	< .001
Invasive mechanical ventilation	2.02	0.89-4.59	.09	1.82	0.78-4.25	.17

Multivariable analysis adjusted for pneumonia severity of index score. HR = hazard ratio. See Table 1 legend for expansion of other abbreviation.
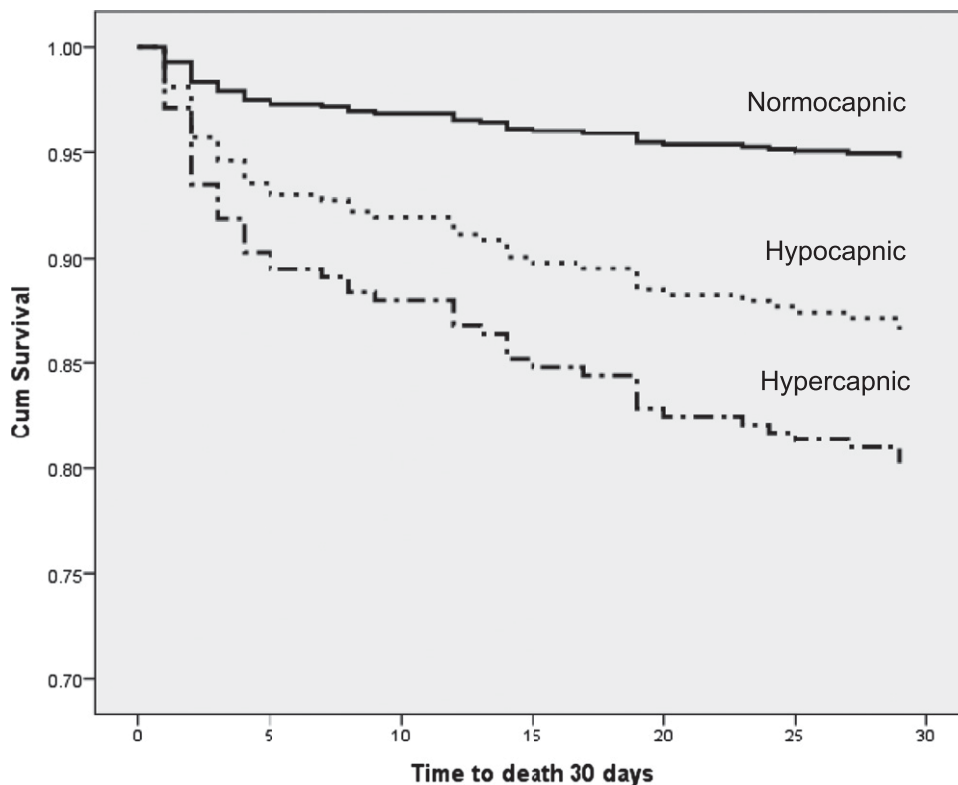
FIGURE 1. Cox survival curves of patients with hypocapnia ($PaCO_2 < 35$ mm Hg) and hypercapnia ($PaCO_2 > 45$ mm Hg) vs those with normocapnia ($PaCO_2$ 35-45 mm Hg) at admission. Cum = cumulative.

or radiologic variables, but none consider $PaCO_2$ levels as criteria of severity. In addition, recent new severity scores, such as SCAP[25] or SMART-COP,[15] have included low arterial pH as criteria, but $PaCO_2$ has not been used as a predictive variable. It is well known that the levels of $PaCO_2$ determine arterial pH value, but often pH values can be compensated by bicarbonate levels, especially in patients with chronic disease, and may not reflect an abnormal $PaCO_2$ value. Our results suggest that abnormal $PaCO_2$ levels should be considered in severity of illness scores and require further validation.

Additionally, our study shows that patients admitted for CAP with hypocapnia and hypercapnia have a higher risk of mortality within 30 days of admission when compared with normal $PaCO_2$ levels. Compared with normocapnia, hypocapnia was associated with increase in mortality of more than threefold in general and nearly fivefold in an analysis that excluded

patients with COPD. Similarly, hypercapnia was associated with increased mortality of nearly threefold in general and nearly ninefold if patients with COPD were excluded. These results are consistent with data previously published by Sin et al,[26] which showed that hospitalized patients with CAP had higher in-hospital mortality when they had abnormal $PaCO_2$ levels at admission.

Both hypocapnia and hypercapnia are independently associated with a greater tendency toward respiratory failure. Hypocapnia can cause or aggravate cellular ischemia by inducing a leftward shift in the oxyhemoglobin dissociation curve and reducing oxygen delivery to tissues.[27] It is common in several diseases (eg, high-altitude pulmonary edema, lung injury, or hepatic failure) and a criterion for systemic inflammatory response syndrome.[28] In respiratory disorders such as pneumonia, hypocapnia can worsen ventilation-perfusion matching and gas exchange in

Table 4—*Comparison of Outcomes Among Patients With CAP Without COPD According to Levels of $PaCO_2$*

Outcome	$PaCO_2 < 35$ mm Hg (n = 161)	$PaCO_2$ 35-45 mm Hg (n = 132)	$PaCO_2 > 45$ mm Hg (n = 34)
30-d mortality	22 (13.7)[a]	4 (3.0)	9 (26.5)[a]
ICU admission	48 (29.8)[a]	19 (14.4)	17 (50.0)[a]
Invasive mechanical ventilation	16 (9.9)	8 (6.1)	7 (20.6)[a]

Values are given as No. (%), unless otherwise indicated. See Table 1 legend for expansion of abbreviation.
[a]$P < .05$ compared with reference group ($PaCO_2$ 35-45 mm Hg).

Table 5—Subgroup Analysis of Patients With CAP After Excluding Those With COPD: Comparison of 30-d Mortality, ICU Admission, and Mechanical Ventilation Among Hypocapnic and Hypercapnic Patients With CAP vs Normal Group

	Univariable			Multivariable		
Outcome	OR	95% CI	P Value	HR	95% CI	P Value
Hypocapnic (non-COPD)						
30-d mortality	5.06	1.70-15.1	.004	4.91	1.61-14.99	.005
ICU admission	2.53	1.40-4.57	.002	2.55	1.34-4.84	.004
Invasive mechanical ventilation	1.71	0.71-4.13	.2	1.56	0.63-3.88	.3
Hypercapnic (non-COPD)						
30-d mortality	11.52	3.29-40.34	< .001	8.98	2.45-32.92	.001
ICU admission	5.95	2.59-16.63	< .001	4.25	1.72-10.52	.002
Invasive mechanical ventilation	4.02	1.34-12.03	.01	3.08	0.97-9.80	.056

Multivariable analysis adjusted for PSI score. See Tables 1 and 3 legends for expansion of abbreviations.

the lung via a number of mechanisms, including bronchoconstriction, reduction in collateral ventilation, reduction in parenchymal compliance, and attenuation of hypoxic pulmonary vasoconstriction and increased intrapulmonary shunting.[29] Additionally, hypercapnia can increase sympathetic neural drive, cardiac output, heart rate, and systemic and pulmonary BP.[30] In patients with respiratory disorders, mainly associated with hypoxemia, hypercapnia can increase pulmonary vascular resistance, enhance hypoxic vasoconstriction, mediate large airway constriction, impair contractility of vascular smooth muscles, and limit gas exchange.[31-33] In our study, hypocapnia and hypercapnia were independently associated with 30-day mortality with no relationship to respiratory rate or pH level, suggesting that they are likely to be intrinsically involved in the poor prognosis of these patients.

Our study has several limitations. First, this is a retrospective study involving only two centers with a relatively small sample size. Second, our sample was predominately male because of the higher population of veterans enrolled in this cohort. It is unknown if abnormal $PaCO_2$ levels in women would have similar results. Third, our cohort did not have information regarding certain variables that may influence the association of hypocapnia or hypercapnia, such as obtaining an arterial blood gas analysis, the presence of chronic hypercapnia prior to hospitalization, lactate levels, cause(s) of death, and the use of noninvasive ventilation. Finally, we used the decision of ICU admission as the gold standard, because this reflected the actual clinical practice. However, the variability of clinical judgment and bed availability may play a role and influenced the site-of-care decisions.

In conclusion, our study demonstrates significantly higher ICU admissions and increased 30-day mortality among patients with hypocapnia and hypercapnia hospitalized with CAP. Further prospective studies are needed to confirm this important finding and establish a role for $PaCO_2$ levels in predictive schemes to asses risk stratification and need for ICU care in patients with CAP.

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