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A Scoring System for Prediction and Risk Stratification of CO_2 Narcosis

Chang Yang[1,2,*], Jing Xi[2*], Sadaf Sheikh[2], Anoushiravan Hakim[2], Soumya Nadella[2], Suresh Dhital[2], Margaret Meier[2], Onyema Nnanna[2] and David Meyers[2]

[1]*Section of Hospital Medicine, The University of Chicago Medicine, Chicago, USA*
[2]*Department of Internal Medicine, St Luke's Hospital, Chicago,USA*

Abstract

Background: CO_2 narcosis, often induced by injudicious use of oxygen and opioids, may result in ICU admission, intubation and additional costs. The development is insidious. Currently, there is no method for early detection.

Methods: A retrospective cohort study of patients with hypercapnia admitted between June 2013 and June 2016 to a single hospital was performed. Presence of pre-defined CO_2 narcosis was determined on chart review by agreement of two reviewers. Patients were divided into derivation and validation groups, and a scoring system for prediction of CO_2 narcosis was developed and verified.

Results: 607 patients with significant hypercapnia ($PaCO_2$>50 mmHg) were identified, and 188 were determined to have CO_2 narcosis. Initial serum bicarbonate, use of supplemental oxygen, use of opioids, and BMI were found to be independent predictors. A CO_2 narcosis scoring system (0-7 points) was developed in the derivation group and then verified. The scoring system stratified patients into low risk (0-2 points, 0% likelihood), intermediate risk (3-4 points, 11-27% likelihood) and high risk (5-7 points, 52-100% likelihood). Patients with CO_2 narcosis have a higher probability of ICU admission, intubation and prolonged hospital stay. Judicious use of oxygen and opioids, and early interventions based on this risk stratification scheme, might prevent this condition.

Conclusion: This CO_2 narcosis scoring system might be useful for prediction and risk stratification of CO_2 narcosis.

Keywords: CO_2 narcosis; Blood gas; Oxygen; Patients; Bicarbonate; Obesity

Introduction

CO_2 narcosis, also known as CO_2 poisoning or intoxication, is defined as a state where patients with hypercapnia develop frank depressed mental status, including confusion, somnolence and lethargy, which may progress to coma and death [1]. While the mechanism and even the existence of this condition have been controversial for decades, recent studies have confirmed the syndrome of CO_2 narcosis, and have demonstrated that the main contributor is ventilation/perfusion (V/Q) mismatch due to a rapid reversal of hypoxic pulmonary vasoconstriction, as opposed to the long-held belief of suppression of hypoxia-driven respiratory drive [2-6].

CO_2 retention may develop rapidly with use of supplemental oxygen in susceptible patients [2,7]. CO_2 narcosis, however, often requires significant CO_2 retention, 80 mmHg for acute accumulation, and 90-100 mmHg in chronic settings [1]. Acutely confused or somnolent hospital patients frequently trigger rapid response teams, ICU admissions, invasive procedures, prolonged hospital stay and higher costs. The recognition of CO_2 narcosis is often not straightforward.

Identification and risk stratification of susceptible patients by using a scoring system might aid medical decision-making to reduce the incidence of iatrogenic CO_2 narcosis and its associated hospital costs. We therefore sought to develop a scoring system for prediction and risk stratification of CO_2 narcosis in the hospital settings.

Materials and Methods

Study population

We conducted a single-center, retrospective cohort study of patients admitted to St. Luke's Hospital, a community hospital located in St. Louis, MO, between June 2013 and June 2016. The study was approved by the institutional review board of St. Luke's Hospital (20160925.1).

Inclusion criteria were: (1) Partial arterial pressure of carbon dioxide ($PaCO_2$)>50 mmHg on arterial blood gas (ABG) testing; (2) adults ≥ 18 years old; and (3) inpatient status. Exclusion criteria were: (1) venous blood gas samples; (2) erroneous data entry; (3) index $PaCO_2$ obtained immediately after cardiac arrest; (4) actively dying patients; and (5) intubation with mechanical ventilation.

Data collection

Patients' electronic health records (Cerner Millennium Power Chart, Cerner Corp, Kansas City, MO) were electronically scanned for the indicator variable $PaCO_2$>50 mmHg. Identified patients were assigned to individual investigators for data extraction. Since most patients with CO_2 narcosis did not have the diagnosis code (R06.89 in ICD-10 and 786.09 in ICD-9) on file, investigators reviewed all the inpatient notes around the time of the highest PaCO2 values. Key words, such as confusion, somnolence, lethargy, hard to arouse, and altered mental status, were used to identify potential cases. CO_2 narcosis was confirmed when no other conditions might explain the altered mental status. The presence or absence of CO_2 narcosis was also reviewed by one investigator (CY). There were no classification disagreements between reviewers. For patients with multiple ABGs or multiple admissions, the one with the highest $PaCO_2$ was used. Fraction of inspired oxygen (FiO_2) was calculated according to the standard oxygen flow rate [8].

***Corresponding author:** Chang Yang, Section of Hospital Medicine-MC 5000, The University of Chicago Medicine, 5841 S Maryland Ave, Chicago, IL 60637, USA, Tel: (773) 702-5173; Fax: (773) 795-7398; E-mail: changy@uchicago.edu

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Statistical analysis and score development

SAS Statistical package v9.4 (SAS Institute, Cary, NC) was used. A two-sided $p<0.05$ was considered significant. Student's t test was applied to continuous variables and Chi-Square Test was used for categorical variables. The study population was divided into derivation and validation groups with the ratio of 1:1 using a random number generator. Univariate analysis was performed to identify variables that were associated with CO_2 narcosis. These variables included age, sex, body mass index (BMI), COPD status, home oxygen, opioids use within 24 hours prior to the highest $PaCO_2$, first serum bicarbonate on admission, and FiO_2 at the time of the highest PaCO2. Cut-off points for variable stratification were initially determined based on the univariate analysis on variables in the derivation group. Stepwise backward selection was performed until only variables with $p<0.05$ in the multivariable model remained, which were considered independent variables. All variables at different cut-off points were initially involved, by using a backward selection approach. The least significant variable was dropped in each round of comparisons, and all dropped variables (except for the most recently dropped) were re-considered for reintroduction into the model depending on the significance. The process was repeated until no more non-significant variables remained. Points were assigned to each individual variable based on the magnitude of corresponding odds ratio from the logistic regression model. Validation was performed on the validation group by evaluating the likelihood of CO_2 narcosis of each score.

Results

Patient characteristics

Eight hundred and eighty-two patients with $PaCO_2>50$ mmHg were identified, representing 1.8% of all inpatients (Figure 1). Two patients with very low PaO2 were excluded due to probable venous blood samples. Similarly, 5 patients were excluded due to inexplicable values. Four pediatric patients were also excluded. In an effort to avoid confounders to the development of hypercapnia, ABGs during cardiac arrest (25 patients), patients actively dying (40 patients) and patients already on mechanical ventilation (199 patients) were not included in the analysis. Mental status changes in these excluded patients were likely not caused by their own respiratory derangements, but extra-respiratory catastrophes from those conditions. Among the 607 patients who underwent analysis, 188 (31%) were determined to have CO_2 narcosis, representing 0.38% of all inpatients during the observation period.

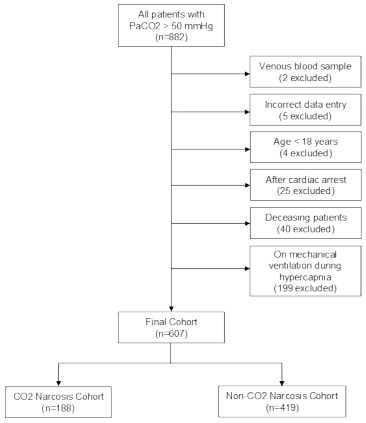

Figure 1: Flowchart of patient inclusion.

Baseline characteristics of the CO2 narcosis and non-narcosis cohorts are summarized in Table 1. There are no statistically significant differences in age, sex or ethnicity. Compared with the patients without CO2 narcosis, narcosis patients had higher BMI (32.9 vs 29.4, p<.001), higher rate of home oxygen use (50% vs 31%, p<0.001), a higher percentage of respiratory diseases as the principle diagnosis on admission (65% vs 49%, p<0.001), higher levels of initial serum bicarbonate on admission (36.5 vs 31.3 mmol/L, p<0.001), higher rates of supplemental oxygen (FiO2 52% vs 43%, p<0.001), higher levels of PaCO2 when altered mental status was first noticed (86.9 mmHg vs 58.6 mmHg, p<0.001), and were more likely to be transferred to ICU (63% vs 34%, p<0.001) and be intubated (28% vs 4%, p<0.001). Narcosis patients had longer stays in the ICU (4.1 vs 1.8, p<0.001) and in the hospital (10.7 vs 8.9, p<0.001).

Score derivation

In order to select appropriate variables for the development of a scoring system during the early hours of admission, the variables were first examined for statistical significance and availability on admission. Only about half the patients had pulmonary function tests, therefore forced expiratory volume in one second (FEV1) was not used even it appeared to be statistically significant between the 2 cohorts. Despite virtually all patients had chest X-ray, many were obtained later during the hospitalization. Thus, presence of pleural effusion was not included in the scoring system. For similar considerations, ABG results, ICU admission and intubation were also excluded. The following 8 variables were used for developing the scoring system: age, sex, BMI, COPD status, home oxygen, opioids use, first serum bicarbonate and FiO_2.

The study population was randomly divided into two groups, 300 patients in the derivation group and 307 patients in the validation

	CO_2 Narcosis cohort (n=188)	Non-CO_2 narcosis cohort (n=419)	p Value
Age (years)	72.7 ± 12.2	74.6 ± 13.0	.083
Male (%)	41	42	.756
Caucasian (%)	94	96	.282
BMI (kg/m²)	32.9 ± 12.9	29.4 ± 9.4	<.001
COPD (%)	64	57	.071
FEV1 (%)	0.37 ± 0.17	0.42 ± 0.18	.018
Home oxygen (%)	50	31	<.001
OSA (%)	29	20	.008
Opioids use (%)	24	16	.044
Principle diagnosis as respiratory diseases (%)	65	49	<.001
Pleural effusion on chest X-ray (%)	38	28	.01
Pneumonia on admission (%)	41	38	.447
First serum bicarbonate (mmol/L)	36.5 ± 7.2	31.3 ± 5.6	<.001
FiO_2 of ABG	0.52 ± 0.25	0.43 ± 0.24	<.001
pH of ABG	7.23 ± 0.08	7.33 ± 0.07	<.001
$PaCO_2$ of ABG (mmHg)	86.9 ± 15.6	58.6 ± 7.1	<.001
PaO_2 of ABG (mmHg)	110.9 ± 61.7	99.2 ± 60.4	.031
Bicarbonate of ABG (mmol/L)	37.5 ± 18.8	30.8 ± 7.1	<.001
ICU admission (%)	63	34	<.001
ICU stay (day)	4.1 ± 6.4	1.8 ± 3.5	<.001
Intubation and mechanical ventilation (%)	28	4	<.001
Hospital stay (day)	10.7 ± 8.1	8.9 ± 6.7	.006

Note: Data presented as mean ± SD or percentage. FEV1: Forced Expiratory Volume In One Second. OSA: Obstructive Sleep Apnea. First serum bicarbonate is obtained from the first blood work on admission.

Table 1: Characteristics of the study cohorts.

group. Univariate analysis was performed on variables to identify variables that are associated with CO_2 narcosis (Table 2). No significant differences were found between the two groups. Independent variables were derived through stepwise backward selection. Points were assigned to each individual variable based on the corresponding odds ratio and p values from the logistic regression test. FiO_2 (OR 8.91, 95% CI 2.74-28.99) and opioids use (OR 0.28, 95% CI 0.14-0.57) demonstrate the strongest association (Table 3).

Score validation

Validation was performed on the validation group by evaluating the likelihood of CO_2 narcosis of each score (Table 4). As the score increased, the likelihood also increased. There are 0% and 100% likelihood of developing CO2 narcosis with a score of 0 and 7, respectively. Among patients stratified as high risk, the likelihood of developing CO2 narcosis during the hospitalization is more than 50%. The area under the curve of receiver-operating characteristics in the derivation group (0.7865, 95%CI 0.7293-0.8436) is similar to the one in the validation group (0.7762, 95% CI 0.7168-0.8356), respectively (Figure 2).

Discussion

CO2 narcosis is a condition of decompensated hypercapnia that can lead to depressed mental status, coma and death if not recognized and expeditiously treated. Unfortunately, confusion and lethargy are relatively common conditions among hospitalized patients. Diagnosis is often delayed until overt mental status changes occur, which can result in ICU transfer and increased hospital costs. This study analyzed 607 inpatients with hypercapnia to develop a scoring system using readily available clinical data in the early hours of admission to predict development of CO_2 narcosis. PaO_2 and pH have previously been proposed as predictors,9 but have not been widely adopted due to low availability of ABG results. Based on the likelihood in our scoring system, patients can be stratified into low, intermediate and high-risk categories on admission, therefore appropriate interventions can be initiated early for prevention.

Worsening hypercapnia and ensuing CO_2 narcosis can develop insidiously often as a result of injudicious use of supplemental oxygen, i.e., oxygen-induced hypercapnia [9]. The previously accepted hypothesis of diminished hypoxic ventilatory drive has been proved to play only a minor role. Instead, the major contributors during the acute phase are increased dead space (48%), Haldane effect (30%) and decreased minute ventilation (22%) [1,10]. V/Q mismatch as a result of lung parenchymal damage other than alveolar hypoventilation is a chronic contributor [11,12]. Development of hypercapnia due to oxygen use may occur rapidly. $PaCO_2$ increases by 6-23 mmHg within 15 minutes of exposure to 100% oxygen in COPD patients [2,3]. 42 mmHg after 30 minutes of an FiO_2>28% among COPD exacerbation patients [13] and 52 mmHg over 20 min among patients with neuromuscular disorders [14] likely due to rapid V/Q mismatch from a loss of hypoxic pulmonary vasoconstriction. Many patients in our cohort developed narcosis with nasal oxygen at 2-3 liters/minute. Low flow continuous oxygen has been associated with significant hypercapnia among patients with severe COPD, neuromuscular disorder and obesity [7,15-17].

Variable	Overall	Derivation group	Validation group	p Value
Male	251 (41.4%)	128 (42.7%)	123 (40.1%)	0.26
Opioids use	105 (17.3%)	53 (17.7%)	52 (16.9%)	0.50
COPD	358 (59.0%)	175 (58.3%)	183 (59.6%)	0.34
Home oxygen use	223 (36.7%)	109 (36.3%)	114 (37.1%)	0.25
Age	73.97	74.49	73.46	0.32
BMI	30.61	30.90	30.33	0.54
First serum bicarbonate	32.92	32.86	32.98	0.81
FiO_2	0.46	0.46	0.46	0.81

Note: Data presented as mean and percentage.

Table 2: Comparison of derivation and validation groups.

Variable	Odds ratio	95% CI	p Value	Points	
First serum bicarbonate	1.184	1.121-1.250	<0.0001	0	If <= 22
				1	If>22 and <= 28
				2	If>28 and <= 40
				3	If>40
FiO_2	8.911	2.739-28.994	0.0003	0	If <= 0.3
				1	If>0.3 and <= 0.5
				2	If>0.5
BMI	1.027	1.003-1.052	0.0261	0	If<43
				1	If >= 43
Opioids use	0.28	0.138-0.568	0.0004	0	If No
				1	If Yes
Note: CI indicates confidence interval					

Table 3: Multivariate logistic regression in the derivation group.

Score	Likelihood of CO_2 narcosis	Risk of CO_2 narcosis
0	0.0%	Low risk (0-2 points)
1	0.0%	
2	0.0%	
3	11.4%	Intermediate risk (3-4 points)
4	26.9%	
5	51.8%	High risk (5-7 points)
6	63.6%	
7	100.0%	

Table 4: The CO_2 narcosis score.

Importantly, CO_2 narcosis did not develop with the acute CO_2 retention observed in the abovementioned studies [3,7,11,13-17], suggesting a sustained elevation of $PaCO_2$ is required for narcosis to occur. In our cohort, most cases of CO_2 narcosis develop 1-2 days after admission. The mechanism of increased blood CO_2 and depressed level of consciousness remains largely elusive [1].

With the scoring system developed here, patients can be stratified into low, intermediate and high-risk categories during the early hours of hospitalization (Table 4). For patients at low risk (0-2 points), no intervention is required; for patients with intermediate risk (3-4 points), transcutaneous $PaCO_2$ sensor [18], closed-loop oxygen delivery system [19], and more frequent mental status check may reduce the incidence; and for patients in the high-risk category (5-7 points), early use of noninvasive ventilation such as BiPAP maybe indicated. Since the majority of hospitals have adopted electronic health record systems, this algorithm could be readily embedded in the system to alert clinicians automatically.

A common misconception is that supplemental oxygen or high oxygen saturation is beneficial for patients with cardiac or respiratory diseases. Despite recommendations that maintaining oxygen saturation at 88-92% balances the risks of oxygen induced hypercapnia and tissue hypoxia [10,20,21] many hospitals still have policies to keep it

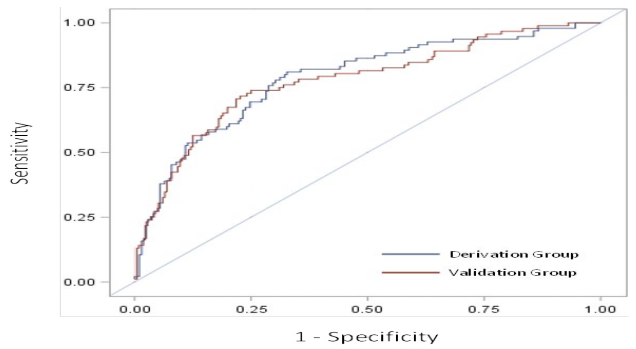

Figure 2: Comparison of the CO_2 narcosis score in the derivation and validation groups.

Note: The areas under the curves for the derivation and validation groups are 0.7865 (95% CI 0.7293-0.8436) and 0.7762 (95% CI 0.7168-0.8356), respectively.

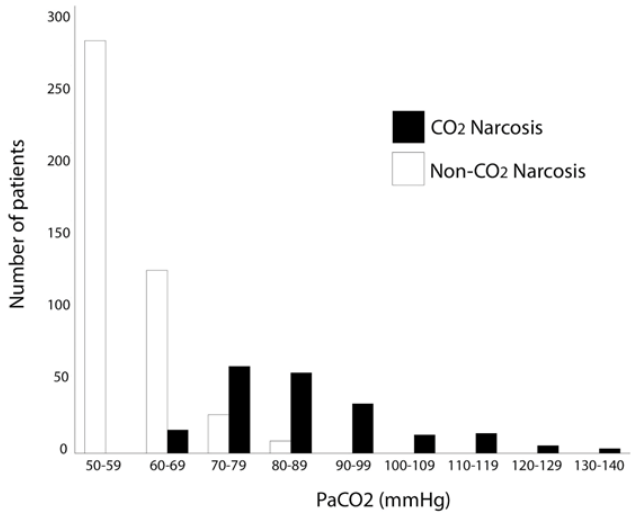

Figure 3: Distribution of $PaCO_2$ values between CO_2 narcosis and non-CO_2 narcosis cohorts.

Note: Number of patients in CO_2 narcosis and non-CO_2 narcosis cohorts are plotted with $PaCO_2$ values. Total number of patients is 607.

greater than 92%. Another common error is accepting the face value of peripheral pulse oximetry while not appreciating that it has a wide range of variations depending on severity of vasculopathy, hypotension, vasospasm, sensor positioning or manicure.

Predicting and avoiding CO_2 narcosis would likely reduce hospital costs. Patients developing CO_2 narcosis are more likely to be transferred to ICU, be intubated and mechanically ventilated, and have longer ICU and hospital stays, compared with the patients without CO_2 narcosis [13,22].

Serum bicarbonate levels represent renal compensation for respiratory acidosis and reflect the severity of chronic CO_2 retention. We observed higher levels of bicarbonate in the CO_2 narcosis cohort (36.5 vs 31.3 mmol/L, p<0.0001). We further demonstrated a stepwise association of higher baseline serum bicarbonate with higher likelihood of developing CO_2 narcosis. The lack of a significant difference between baseline bicarbonate and ABG bicarbonate during CO_2 narcosis (36.5 vs 37.5 mmol/L, p=0.516), indicates that acute renal compensation was not sufficient to prevent narcosis. When arterial blood CO2 values were compared, much higher levels of CO_2 were found in the CO_2 narcosis cohort (86.9 vs 58.6 mmHg, p<.001), consistent with previous findings that $PaCO_2$ often exceed 80 mmHg for narcosis to develop.1 The distribution of $PaCO_2$ values between the two cohorts substantially differed (Figure 3). The highest level of $PaCO_2$ in our study was 138 mmHg. The highest value reported in the literature is 233 mmHg [23].

Surprisingly, age appears not to be a risk factor, as CO_2 narcosis rarely occurs in young patients. Oxygen therapy has previously been associated with development of hypercapnia in elderly patients but not young adults or children [24]. Development of CO_2 narcosis might require additional insults, which likely accumulate with aging.

The levels of FiO_2 in both cohorts may not represent baseline or pre-treatment conditions. The ABGs were often obtained after patients' clinical conditions had undergone rapid changes, and supplemental oxygen had been increased by the initial responders, before arterial blood was drawn. Therefore, the true levels of FiO_2 causing CO_2 narcosis are likely to be lower than observed, as suggested by previous studies [7,15,16]. Prospective randomized controlled trials are required to determine the true narcosis-inducing levels of FiO_2.

There are additional limitations of this study. It is a single center study with a slightly older patient population than other areas. Retrospective studies and chart review are subject to limited information and insufficient controls. Smoking history and FEV1 might be independent risk factors, but they were not well documented or only available in portions of our patients. Similarly, if morphine milligram equivalents could have been accurately calculated, low dose opioids might have been shown to be safe. Prospective randomized controlled studies will be needed to refine and validate the CO_2 narcosis scoring system.

Conclusion

This is the first study to investigate risk factors of CO_2 narcosis among hospitalized patients. Four independent risk factors were identified, baseline serum bicarbonate, supplemental oxygen use, BMI and opioids use. The CO_2 narcosis scoring system developed here stratifies patients into low, intermediate, and high risk groups during early hours of hospitalization using readily available clinical data. When this scoring system is applied, appropriate interventions might be employed for the prevention of CO_2 narcosis, improving patient safety and reducing costs.

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Author contributions: C. Y. is the guarantor, and contributed to study conception, design, and manuscript drafting. J. X. contributed to data analysis and manuscript drafting. S. S., A. H., S. N., S. D., M. M., and O. N. contributed to data collection. D. M. contributed to study design and manuscript revision. All authors have reviewed the manuscript, warrant accuracy, and consent to publication.

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None.

Conflict of Interest Statements

No conflicts exist for all authors.

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