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Original Contribution

High total carbon dioxide predicts 1-year readmission and death in patients with acute dyspnea☆

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ABSTRACT

Rationale: Patients with acute dyspnea are a large heterogeneous patient group where initial management is important for outcome.
Objectives: The objective of the study is to investigate if venous blood gas parameters predict 1-year risk of readmission or death in patients admitted to the emergency department due to acute dyspnea.
Methods: We studied 283 patients with acute dyspnea and followed them up for 1 year regarding incidence of readmission or death.
Measurements and main results: In venous blood obtained immediately upon admission levels of total carbon dioxide (TCO_2), base excess (BE), potential hydrogen (pH), and partial pressure of carbon dioxide (pCO_2) were measured. In Cox proportional hazards models, patients belonging to top and bottom quartiles of TCO_2, BE, pH, and pCO_2 were compared to patients belonging to the 2 central quartiles and assessed for end point. After adjustment, top (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.08-2.04; $P = .016$) and bottom (HR, 1.54; 95% CI, 1.08-2.18; $P = .017$) quartiles of BE were associated with increased risk of readmission or death. The strongest predictor was top quartile of TCO_2 (HR, 1.68; 95% CI, 1.21-2.35; $P = .002$). In the combined analysis, top quartile of TCO_2 remained significantly related to the end point (HR, 1.59; 95% CI, 1.03-2.45; $P = .035$), whereas BE became nonsignificant. Comorbidities, for example, prevalent chronic obstructive pulmonary disease, did not explain the association. Neither pCO_2 nor pH predicted the end point.
Conclusions: A high value of TCO_2 appears to be an easily accessible marker for 1-year readmission or death in patients with acute dyspnea and may thus add clinically important information for risk stratification and follow-up strategies.

1. Introduction

Patients presenting with acute dyspnea at the emergency department (ED) is a large and heterogeneous patient group with high mortality and readmission rates [1-8]. Initial ED management, level of care, and follow-up strategies are important factors for the outcome of acute dyspnea patients [9-12]. However, the individual prognosis is difficult to accurately assess. The use of plasma biomarkers for improved determination of prognosis in acute dyspnea has largely focused on patients with congestive heart failure and, to a lesser degree, on patients with chronic obstructive pulmonary disease (COPD). Many biomarker studies include markers of inflammation or cardiac stress [11,13-17], whereas the value of blood gas parameters [18,19] and the role of biomarkers in unselected patients with acute dyspnea on clinical outcome have been poorly studied.

The underlying causes of dyspnea can be difficult to assess in an early setting. Risk stratification of prognosis is central for clinical decisions on the level of care, treatment intensity, and urgency of reaching a definitive underlying diagnosis. Most plasma biomarkers in acute dyspnea used at the ED have diagnostic purposes (eg, troponin T and C-reactive protein), whereas medical history and scores of vital parameters are used to assess prognosis, level of care, and treatment intensity. In Sweden, the "Medical Emergency Triage and Treatment System Adult" (METTS-A) is a standard tool for risk assessment and triage of ED patients and was used during the time of study enrollment [20].

In patients with COPD and acute dyspnea, a high pressure of carbon dioxide in arterial blood is a well-established predictor of poor prognosis and motivates a high level of care and treatment intensity [8,21]. However, in the general setting of patients with acute dyspnea at the ED, arterial blood gas analysis is usually not performed. Therefore, it cannot be evaluated or used as a routine biomarker for risk stratification. Increasing evidence points toward that arterial and venous blood gas results can be used interchangeably [18,19,22-24]. In the ED, venous

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blood can routinely be drawn and analyzed at a low cost in the same point-of-care equipment as arterial blood with immediate generation of test results [25]. To our knowledge, venous carbon dioxide and acid-base balance have never been evaluated as prognostic biomarkers in unselected ED patients admitted because of acute dyspnea.

The aim of the study was to investigate if easily accessible venous blood gas analysis of total carbon dioxide (TCO_2), base excess (BE), potential hydrogen (pH), and partial pressure of carbon dioxide (pCO_2) predicts 1-year risk of readmission or death in patients admitted to the ED due to acute dyspnea.

2. Methods

We studied patients presenting with dyspnea during 2011 at the ED of the University Hospital of Skåne in Malmö, Sweden. In 2011, the department had approximately 83 000 visits. The hospital is the only emergency hospital in the municipality of approximately 300 000 inhabitants. The study was approved by the regional board of ethics in Lund. All patients of 18 years of age or older presenting with acute dyspnea as the major complaint were eligible for the study. This yielded 5057 visits of patients with acute dyspnea of which 500 were randomly selected for review of patient records. In total, 283 fulfilled study criteria for inclusion in our analyses (Fig. 1). Data collection was performed in 2013 from the medical records of the University Hospital of Skåne. Variables recorded included sex (male/female), age (years), vital signs and symptoms according to METTS-A [20], pulse oximetry (percentages), respiratory rate (RR, rate/min), pH (pH scale), BE (millimoles per liter) [26,27], pCO_2 (kilopascal), TCO_2 (millimoles per liter), medical history, and readmission or death within 1 year. In the METTS-A ED triage system, patients with respiratory complaints are categorized into dyspnea, chest pain, or hyperventilation and ranked into 4 priority levels according to vital signs. Priority 4 comprises patients with normal vital signs; and priority 1, patients with pathologic vital signs needing immediate medical attention [20]. Additional detail on the methods for making

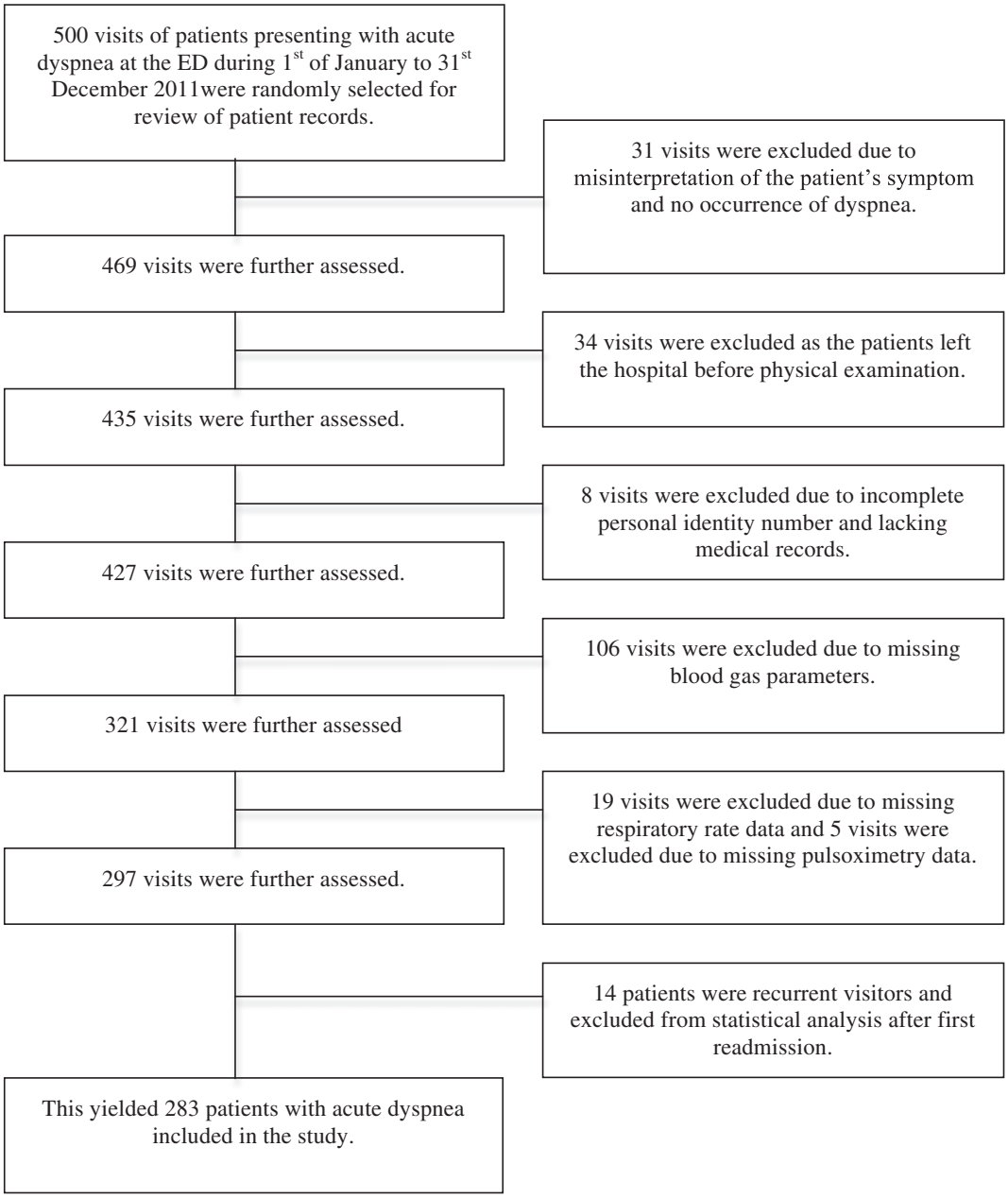

Fig. 1. Selection of patients for statistical analysis.

the measurements is provided in an online data supplement. The combined end point was either a first hospital readmission regardless of cause or death during the 1-year follow-up period. Date of death was registered from a regional or national population register. Planned revisits were not included.

Venous blood gas parameters were obtained upon arrival to the ED. The blood gas samples were immediately analyzed on a Radiometer ABL800 Flex (Copenhagen, Denmark) [25]. Among the parameters analyzed, TCO_2 represents the total dissolved carbon dioxide in the blood and is constituted to approximately 95% of bicarbonate (HCO_3-) and to 5% of carbon dioxide (CO_2), and carbonic acid (H_2CO_3) [28]. We related the venous blood gas parameters with the risk of readmission or death using Cox proportional hazard models. The following 3 adjustments were used: In model 1, we adjusted for age and sex. In model 2, we included additional adjustment for METTS-A. In model 3, we added saturation, RR, and if statistically significant acid base parameters. Finally, we also adjusted model 3 for a history of COPD. Venous blood gas parameters were divided into quartiles. The 2 central quartiles were merged and defined as the reference group and compared to the top and bottom quartiles, respectively. Statistical analysis was performed in IBM SPSS (Malmö, Sweden) Statistics version 21. $P < .05$ was considered significant. Schoenfeld's test was performed to assure validity of the proportional hazards. In the subset of the population where both venous and arterial blood gas analyses were performed, we correlated blood gas parameters using Spearman correlation analysis.

3. Results

A total of 283 patients with acute dyspnea at the ED were evaluated (Fig. 1). The mean age was 66.1 years (66.1 ± 18.5 years), and females (55.8%, 158/283) were more common than males. Most patients admitted for inpatient care was admitted to a general ward (39.9%, 113/283). A large proportion of the patients were directly discharged from the ED (36.7%, 104/283). The remaining were either admitted to an emergency ward (21.2%, 60/283) or an intensive care unit (2.1%, 6/283). During the 1-year follow-up, 74.2% (210/283) of the patients were readmitted or died, of which 67.1% (190/283) had a first readmission and 7.1% (20/283) died with no prior readmission. Detailed patient characteristics are shown in Table 1.

The bottom quartile of BE ranged from −26 to −1.0 mmol/L; and the top quartile, from 3.0 to 15 mmol/L. The bottom quartile of TCO_2 ranged from 4.0 to 24 mmol/L; and the top quartile, from 30 to 40 mmol/L. The bottom quartile of pH ranged from a value of 7.07 to 7.36; and the top quartile, from 7.44 to 7.59. The bottom quartile of pCO_2 ranged from 2.9 to 5.0 kPa, and the top quartile from 6.5 to 13.5 kPa.

In Cox proportional hazard models adjusted for age and sex, top quartile of BE (hazard ratio [HR], 1.56 [confidence interval {CI}, 1.14-2.15]; $P = .006$) and bottom quartile of BE (HR, 1.65 [CI, 1.17-2.32]; $P = .004$) were strongly associated with the end point. In the multivariate models adjusted for age, sex, METTS-A, saturation, and RR, both top quartile (HR, 1.48 [CI, 1.08-2.04]; $P = .016$) and bottom quartile (HR, 1.54 [CI 1.08-2.18]; $P = .017$) of BE were associated with increased risk of readmission or death (Table 2). However, when adjusting for TCO_2, there was no association of top quartile BE with the end point (HR, 1.13 [CI, 0.75-1.71]; $P = .570$), and the association of bottom quartile BE was no longer significant (HR, 1.63 [CI, 0.99-2.68]; $P = .056$).

When adjusting for age and sex, patients in the top quartile of TCO_2 had an increased risk of readmission or death (HR, 1.93 [CI, 1.40-2.67]; $P = .000$). This association was also seen for bottom quartile of TCO_2 (HR, 1.46 [CI, 1.02-2.07]; $P = .037$). After additional adjustment for age, sex, METTS-A, saturation, and RR, top quartile but not bottom quartile of TCO_2 remained significant (Table 2). Top quartile of TCO_2 was significant in the multivariate model including BE (HR, 1.59 [CI, 1.03-2.45]; $P = .035$). Top quartile of TCO_2 also remained significant after adjustment for a history of COPD (HR, 1.61 [CI, 1.15-2.26]; $P = .005$) with a relative risk increase greater than for prevalent COPD (HR, 1.50 [CI, 1.09-2.06]; $P = .012$). A Kaplan-Meier plot of TCO_2 in relation to the end point is shown in Fig. 2. In the patient group with top quartile levels of TCO_2, 33.8% (23/68) of the patients were discharged from the ED, 39.7% (27/68) were admitted to a general ward, 22.1% (15/68) were admitted to an emergency ward, and 4.4% (3/68) were admitted to an intensive care unit.

Older age (HR, 1. 01 [CI, 1.01-1.02]; $P = .002$) and higher priority according to METTS-A (HR, 1.31 [CI, 1.07-1.61]; $P = .008$) were other factors independently associated with the end point adjusted for BE and TCO_2. Neither pH nor pCO_2 was associated with increased risk of readmission or death (Table 2). In the subset of patients with both arterial and venous blood gas parameters obtained, there was a good correlation of blood gas parameters. In Spearman correlation analysis, venous pCO_2 and pH were strongly correlated with arterial pCO_2 ($n = 43$; $r^s = 0.763$; $P = .000$) and pH ($n = 42$; $r^s = 0.852$; $P = .000$), respectively.

Table 1
Patient base line characteristics

Age (y), mean (±SD)	66.1 (±18.5)
Sex (male), n (%)	125 (44.2%)
Medical history, n (%)	
COPD	70 (24.7%)
Congestive heart failure	58 (20.5%)
Pneumonia	27 (9.5%)
Myocardial infarction	14 (4.9%)
Pulmonary embolism	3 (1.1%)
Vital parameters, mean (±SD)	
Oxygen saturation (%)	93.6 (±5.15)
RR (min^{-1})	23.5 (±6.57)
Heart rate (min^{-1})	93.5 (±20.9)
Systolic blood pressure (mm Hg)	146 (±26.2)
Diastolic blood pressure (mm Hg)	80.9 (±14.6)
Body temperature (°C)	37.2 (±0.78)
METTS-A category, n (%)	
Priority 1	34 (12.0%)
Priority 2	72 (25.4%)
Priority 3	68 (24.0%)
Priority 4	109 (38.5%)
Venous blood gas parameters, mean (±SD)	
BE (mmol/L)	1.31 (±3.23)
pH (pH scale)	7.40 (±0.06)
TCO_2 (mmol/L)	27.3 (±3.73)
pCO_2 (kPa)	5.80 (±1.23)

4. Discussion

For patients with acute dyspnea at the ED, TCO_2 ranging from 30 to 40 mmol/L was a predictor of 1-year readmission and mortality. High and low BE was also related to poor outcome. However, this prognostic information was mediated by TCO_2, as BE became nonsignificant in the combined statistical analysis. Total carbon dioxide remained related to the end point with an effect size stronger than for prior COPD.

Surprisingly, little is known about TCO_2 in patients with dyspnea at the ED, its prognostic value, and its impact on patient outcome. The mechanisms causing dyspnea are still incompletely understood [1], and the knowledge of which factors contribute to the blood concentration of TCO_2 is largely based on experimental animal studies and theoretical conclusions [29-33].

In the steady state at the dissociation equilibrium, TCO_2 is used as a surrogate marker of bicarbonate. Both BE and TCO_2 increase as a result of metabolic alkalosis. The underlying causes to these shifts are many. Possible explanations to metabolic alkalosis in the acutely dyspneic patient may be diuretic treatment, hypokalemia, or posthypercapnia [28]. Total carbon dioxide additionally increases in compensation to respiratory acidosis [28]. In this study, elevated BE did not associate with the end point when adjusting for TCO_2, although it may have correlated to the end point with a larger study size. This suggests that elevated TCO_2 in the dyspneic patient is not caused by metabolic alkalosis. It also suggests that the raised levels of TCO_2 are not only a consequence of increased bicarbonate levels.

Table 2
Cox proportional hazard models adjusted for age, sex, METTS-A, respiratory rate, and oxygen saturation

Model 3	Quartile 1			Quartiles 2 and 3		Quartile 4		
	No. events/N	HR (95% CI)	*P*	No. of events/N	HR (95% CI) *P*	No. of events/N	HR (95% CI)	*P*
BE	56/71	1.535 (1.080-2.181)	.016860	82/126	Reference	72/86	1.482 (1.075-2.043)	.016418
TCO_2	45/59	1.348 (0.942-1.930)	NS	106/156	Reference	59/68	1.682 (1.205-2.349)	.002270
pH	58/73	0.918 (0.507-1.663)	NS	105/144	Reference	47/66	1.139 (0.633-2.051)	NS
pCO_2	47/71	0.903 (0.638-1.277)	NS	109/147	Reference	54/65	1.196 (0.850-1.683)	NS

Regardless of the causal mechanism, patients with acute dyspnea and poorer outcome in terms of readmissions and mortality tended to have both elevated TCO_2 and negative BE values. In the multivariate analysis, elevated TCO_2 remained significant, but base deficit became borderline significant. This finding can partly be explained by the presence of hypoventilated and metabolically compensated patients with COPD. As BE is reduced by respiratory acidosis, this can also explain the trend of base deficit with increased rates of readmission and mortality. In comparison to BE that only quantifies metabolic acid base disorders, TCO_2 is a marker of both respiratory and metabolic acid base balance disorders [34,35] that, in this study, correlated to poorer outcome. Therefore, we speculate that TCO_2 in patients with acute dyspnea is an indicator of uncompensated respiratory acidosis. Given this, TCO_2 may be more suitable than BE for assessing acute dyspnea in the chronically ill patients, as it involves both metabolic and respiratory components. Total carbon dioxide may also be more suitable than venous pCO_2 in predicting outcome in the critically ill with history of COPD. It is less transient in nature than the gas parameters and seems to be a better marker for long-term outcome than venous pCO_2 and venous pH that showed no correlation to the end point.

In common conditions causing acute dyspnea such as COPD, pneumonia, ischemic heart disease, congestive heart failure, and pulmonary embolism, deranged TCO_2 levels can represent a transient or permanent systemic impairment. As high TCO_2 predicted poor outcome during as much as 1 year after the acute episode of illness, it can stand for an unmasked underlying cardiopulmonary fragility, which, in the long term, associates with increased readmissions and mortality rates. In the heterogeneous patient group with dyspnea, the diagnostics is challenging, and a correct early management is important for prognosis. There are some biomarkers used for diagnostic and prognostic purposes in dyspnea patients. These have been included in scores often together with vital signs to predict poorer outcome [9-11], but at present, there is no separate blood biomarker for evaluation of prognosis and risk stratification of dyspnea patients. Traditionally, arterial blood gas analysis has predominantly been used to evaluate blood gas and acid-base disorders. In fact, in this and recent studies, there is a good correlation of venous to arterial blood gas parameters (with the exception of pO_2) [19,22-24,36]. Easily accessible venous blood gas may thus be used in the ED to add clinically important information in a broad patient group with acute dyspnea without restricting the use of arterial blood gas when indicated.

The causes of dyspnea, death, and readmission were not systematically registered, and the underlying conditions leading to the events remain unclear. However, the intention of the study was to evaluate long-term prognostic factors for all-cause readmission or death in unselected patients with acute dyspnea. The knowledge of the actual underlying conditions seems to be less important for this purpose. The diseases causing dyspnea often coexist and share the same risk factors. A distinction between them is difficult to accurately assess in the clinical setting. Identification of the prognostic factors for specific diagnoses in patients with dyspnea was, therefore, not in the scope of this study. Apart from having dyspnea as the main complaint, we intentionally applied no selection criteria for the study population to maintain the heterogeneity and aiming at making results applicable on a random dyspneic patient seeking medical care. We do acknowledge that many patients were excluded due to missing blood gas parameters. A selection bias would despite this probably have lead to enrichment of even more severely ill patients. Most of the patients excluded were either relatively young patients not hospitalized or terminally ill patients where the ED physician judged that prognostic and diagnostic efforts were unnecessary.

Given the easy accessibility, fast response time, low costs, and negligible risks of a venous blood gas analysis, we find our results encouraging and potentially clinically applicable. Total carbon dioxide may help deciding the level of care upon admission and determining the follow-

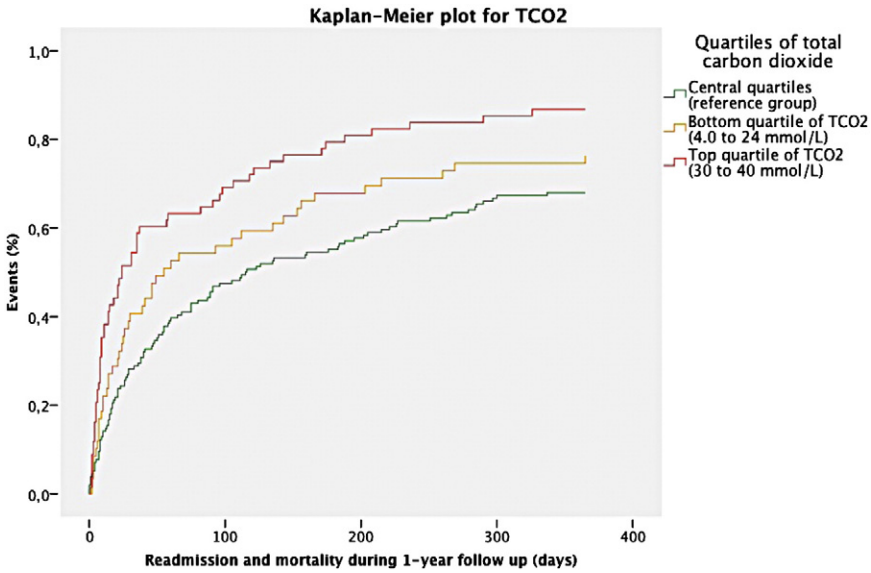

Fig. 2. Cumulative end point curves for quartiles of total carbon dioxide during the 1-year follow-up period.

up strategies for out-of-hospital care in patients with acute dyspnea to prevent readmissions and death. It should, however, be emphasized that the sample size is moderate and replications of our results in similar patient cohorts are essential for clinical implementation.

In conclusion, a high level of TCO_2 in patients with acute dyspnea is a marker for worse outcome. This easily accessible blood gas parameter may prove useful in the ED for risk stratification of dyspnea patients.

Author contributions

Conception and design: NL, AR, KG, OM
Analysis and interpretation: NL, AR, PS, KG, OM
Drafting the manuscript for important intellectual content: NL, AR, PS, SE, TW, KG, OM

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