The Clinical Implications of Carbon Dioxide Increased Level in Arterial Blood Related to Severe Exacerbations of Chronic Obstructive Pulmonary Disease

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In the evolution of patients with chronic obstructive pulmonary disease (COPD), exacerbations occur, especially, in severe stages, determining aggravated respiratory failure and decreased survival. In order to evaluate the implications of COPD exacerbations in patients with second type of chronic respiratory failure and hypercapnic encephalopathy, a prospective observational study was done among 195 COPD in patients of Targu Mures Clinical County Hospital, Romania. Inclusion criteria consisted in severe exacerbations of COPD, complicated by hypercapnia, defined by an increased level of arterial blood gas carbon dioxide ($PaCO_2$) ≥45 mmHg, suggestive for the second type of respiratory failure. The increased values of $PaCO_2$ ranged between 45 and 112 mmHg among 95 patients. The prevalence of hypercapnia in COPD patients, admitted in hospital for severe exacerbations, was high (n=91/195; 46.66%). The majority of COPD patients (93.4%) were initially hospitalized in the intensive care unit (ICU) department because of hypercapnic encephalopathy. The mortality rate was higher among patients with endotracheal tube insertion than in patients treated by noninvasive mechanical ventilation. High levels of hypercapnia, conscience disorders and respiratory acidosis may be considered factors of severity in COPD exacerbation.

Key words: $PaCO_2$, COPD, exacerbation, hypercapnia, respiratory failure, hypercapnic encephalopathy

All over the world, chronic obstructive pulmonary disease (COPD) has a high prevalence due to chronic exposure to smoking, professional particles and dust, indoor and outdoor pollution. Smoking is strongly correlated with COPD, lung cancer, cardiovascular, endocrine and metabolic diseases [1-2]. So, early and free smoking cessation among smokers can be a very good method to preventing diseases caused by smoking and even death [3]. COPD exacerbations (COPDEx) may occur in in any stage of COPD disease but most of them are related with severe and very severe stages. In COPD severe forms, exacerbations are associated with respiratory failure, hypercapnic encephalopathy and acidosis [4, 6]. Several studies proved the high benefits brought by the early treatment with noninvasive mechanical ventilation (NIMV) in conscious COPDEx patients with type II of respiratory failure, hypoxemia and hypercapnia comparing to cases treated by invasive ventilation by endotracheal tube [7-9]. The carbon dioxide level in arterial blood ($PaCO_2$) is directly linked to the impairment of the CO2 elimination by the lung (alveolar hypoventilation). Other mechanisms to increase $PaCO_2$ in COPD exacerbation are: dynamic hyperinflation caused by bronchial chronic obstruction and severe damage of the elastic tissue (emphysema) with destruction of pulmonary capillaries by emphysema, increasing the alveolar dead space, determining severe disturbances of gas exchange (by emphysema), pulmonary hypertension (by arterial hypoxemia, vessels destruction, thrombosis and polyglobulia) [10-121]. Other mechanisms of alveolar hypoventilation are the muscular dystrophy and muscular fatigue, met in advanced stages of COPD. Patient with high body mass index (BMI) may associate more severe hypercapnia that normal weight patients by decreased chest wall compliance and secondary hypoventilation [13]. Hypercapnia should be suspected in all COPD patients presenting severe exacerbations with aggravated shortness of breath, exhaustion, sweating, and most of all, changes in mental status, anxiety, headaches and diurnal hypersomnolence.

Experimental part

The aim of the study was to assess the frequency of hypercapnia and acidosis in patients with COPDEx and to define the clinical implications of hypercapnia. The design of the study consisted in an observational study on 195 patients with COPDEx and respiratory failure hospitalized during 30 consecutive months, in Pulmonology Clinical department and intensive care unit (ICU) of Targu Mures Clinical County Hospital, Romania. COPD staging was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, updated 2017, combining different parameters: severity of symptoms (COPD Assessment Test score), frequency of exacerbation, in the previous 12 months, and spirometry [4]. Respiratory failure was considered in every COPD case with low values of arterial gas oxygen level (PaO2) and oxygen saturation (SaO2). Hypoxemia was considered according to the decrease of the oxygen content in the arterial blood PaO2 below 60 mm Hg, equivalent to an oxygen saturation of 90% measured by oximetry. Hypercapnia was defined as an arterial blood gas carbon dioxide level ($PaCO_2$) increased above 45 mmHg. Respiratory acidosis was evaluated by the decreased level of ph below 7.4. Clinical and investigational outcomes, as COPD classification of risk groups [4], based upon the severity of the COPD and respiratory failure (type I and II), gender and age distribution, symptoms at the hospital admission, history of previous exacerbation, comorbidities, spirometry, analysis of blood gas (ABG), evolution under

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treatment and survival, were included in a data base and statistically evaluated by EPI Info Program version 7.

Results and discussions

The study group of 195 patients with hospitalized COPD exacerbation (COPDEx) included 162 males (83%) and 33 females (17%), with an increased male/female ratio of 4.9, strongly in the favor of men and greater comparing to literature data based on a male/female ratio of 1.15 to 2, considering woman's increased sensitivity to develop COPD [11]. Our study showed a high prevalence of cigarette tobacco smoking exposure as a main risk factor for COPD and disease severity (73.8 %) compared to the Romanian national average (26%) and European prevalence of smokers in general adult population (31%) [14,15]. It was noticed a high predominance of male smokers among COPD inpatients (n=112/162; 69.1%) versus females (n=12/33; 36.3%), for odd ratio (OR) of 2.05 (0.84-4.96) and risk ratio (RR) of 1.32 (0.88-1.98), without significant differences of distribution by gender (chi^2=2.6, p= 0.106). Professional exposure to particles and dust was incriminated in 75.9% of cases (n=123/162), a high incidence consistent with other studies [16]. The clinical implications of respiratory failure among COPD inpatients varied from aggravated exertional dyspnea, increase in volume and purulence of sputum, to resting dyspnea, orthopnea, cyanosis, weakness, paradoxical breathing as a sign of muscle fatigue described in 170 patients (87.17%). In the rest of patients (n=25; 12.8%) the decision for admission was based along on the severity of comorbidities and on the lack of financial support for the ambulatory treatment.The most frequent comorbidities of COPD were cardiovascular disorders (hypertension, ischemic cardiac disease, heart failure, and dysrhythmias) (n=152; 77.9%), metabolic [diabetes mellitus (n=32; 16.4%, overweight and obesity (n=123; 63%], lung cancer (n=21; 10.7%), pulmonary fibrosis (n=25; 12.82%) like post tuberculosis or pneumoconiosis. A high severity of COPD was noticed in cases: 157 patients (80.5%) were classified in D risk group, 22 patients (11.2%) in C risk group and 16 patients (8.2%) in B risk group. The average of previous 12 months exacerbations was 3.2 exacerbations. Almost a half of COPDEx patients (n= 91/195; 46.6%) had hypercapnia associated to hypoxemia (type II respiratory insufficiency). The values of $PaCO_2$ ranged between 45 and 112 mmHg. Most of the cases with hypercapnia had a superimposed respiratory acidosis (n=86/91; 94.5%). In the most advanced COPD stage (D), the great majority of cases with increased levels of $PaCO_2$ (n=80; 87.9%) were include compare to only 11 patients (5.6%) in the C risk group [OR= 1.03 (0.4-2.5); RR= 1.01 (0.6-1.5); chi2=0.007; p=0.93] (*Table no.1*). These data are consistent with other studies results revealing the severity of COPD exacerbations, which are requiring the highest proportion of healthcare resources, prolonged hospitalization and high mortality rates [15,17]. The distribution of patients by age showed a higher frequency of exacerbations in elderly (over 70 year-old - 65.68%) (table 2), observations consistent

Table 1
DISTRIBUTION OF CASES ACCORDING TO THE SEVERITY RISK GROUP OF COPD, HYPERCAPNIA AND NUMBERS OF PREVIOUS EXACERBATIONS

COPD severity risk group	Patients with hypercapnia		Patient without hypercapnia		Nr of exacerbation in the previous year
Risk group B 16 patients	0	0	16	8.2%	•1
Risk group C 22 patients	11	5.6%	11	5.6%	•≥ 2 or ≥1 leading to admission in the hospital
Risk group D 157 patients	80	41%	77	39.48%	•≥ 2 or ≥1 leading to admission in the hospital
Total - 195	**91**		**104**		

Table 2
DISTRIBUTION OF COPD PATIENTS WITH EXACERBATIONS BY AGE

Group of age	Number of cases	%
Under 50 year - old	0	0
50 – 60 year - old	20	10.25%
60 – 70 year - old	45	23.07%
Over 70 year - old	130	65.68%%
Total	**195**	**100%**

Table 3
THE EVOLUTION OF EXACERBATED COPD CASES TREATED BY VENTILATOR SUPPORT

Patients with COPD exacerbations	Favorable evolution	Nonfavorable/ nonsurvival	Total
Invasive ventilatory support and ETT in ICU in patients with important hypercapnia and respiratory acidosis	33 47.1%	37 52.9%	70 100%
Non – invasive ventilatory support (NIMV) in conscious patients with moderate hypercapnia and acidosis	20 95.2%	1 4.8%	21 100%

Legend: ETT - endotracheal tube; ICU - Intensive Care Unit

Table 4
EVOLUTION OF COPD EXACERBATIONS BY THE TYPE OF RESPIRATORY FAILURE

	Favorable evolution	Unfavorable evolution	Total
Type II of Respiratory Failure	53 58.25%	38 41.75%	91 100.00%
Type I of Respiratory Failure	102 98.07%	2 1.93%	104 100.00%
Total patients	155	40	195

Legend: COPDEx – COPD exacerbation

with the literature data [18]. Most patients with COPDEx have advanced age (with neglected old COPD) and multiple exacerbations in the previous year.

93.4% (n=85/91) patients with documented hypercapnia, revealed by blood gas analysis, associated hypercapnic encephalopathy, with obnubilation, headache, drowsiness or inability to focus, or decompensated core pulmonale, with peripheral edema, and cardiac failure (table 2). These clinical implications are induced by the severe evolution of COPD and the number of previous exacerbation. Studies reported the increased frequency of severe COPD exacerbations determined a high mortality [19]. Cardiovascular comorbidities are frequent and contributed as a major cause of mortality, along with hypercapnic encephalopathy [20-24]. At the admission in hospital, all the patients received systemic corticoids, oxygen, antibiotics, anticoagulants and cardiovascular support as well as long and short acting bronchodilators and cortisone inhalers. Patients received maximization of bronchodilation: repeated inhalations of rapid short-acting beta-agonists (Salbutamol) and anticholinergic (Ipratropium), in addition to the combination of long acting bronchodilation and inhaled corticoids, long term oxygen therapy, in low fraction of inspired oxygen (FiO2) of 2-3 litters/minute, with the goal to reach a target oxygen saturation (SaO2) of 90 to 93% [4,25]. The development of the COPD worsening by increased levels of $PaCO_2$, suggestive for hypercapnia, with hypercapnic encephalopathy, exhaustion, respiratory acidosis and/or depression in the level of consciousness was an indication for mechanical ventilation in 93.4% of cases (n=85/91) in the ICU department. The type of ventilatory support was chosen according to the severity of the symptoms, level of consciousness, comorbidities and level of hypercapnia and acidosis. So, 70 patients underwent invasive mechanical ventilation with endotracheal intubation (ETT) and 15 patients required only noninvasive mechanical ventilation (NIMV). Other 6 conscious patients received NIMV in Pulmonology Department, through a noninvasive interface (oronasal mask) and close monitoring, with spontaneously triggered mode (ST), and a backup respiratory rate of 15 respiration/minute, with positive inspiratory pressure (between 12 - 16 cmH2O) and positive expiratory pressure (between 4-6 cmH2O). The inspiratory pressure was gradually increased as needed to achieve alleviation of dyspnea. A favorable evolution was reported among patients under NIMV in ICU (95.2%) and mortality rate was significantly higher in the group of severe hypercapnic patients, requiring ETT (52.9%) [chi^2=15.195, p=0.00009] (table 3).

The highlight of hypercapnia together with the hypercapnic encephalopathy led to an early transfer of patients to the ICU. Only 58.25% of the patients with type II of respiratory failure (hypercapnia and acidosis) had a favorable evolution compared to 98% of the patients without hypercapnia [chi^2=46.991, p=0.000] (table 4). These observations sustained hypercapnia could be considered a predictor of worse evolution in COPDEx and blood gas analysis had to be always considered and repeated, if needed. NIMV is a well-tolerated method of therapy that allowed the clinical improvement of patients, with mild to moderate hypercapnia in 95% of cases. A meta-analysis, made on a large number of studies and patients, showed NIMV, associated with standard therapy, in patients with COPDex and hypercapnia, decreased mortality, intubation rate, treatment failure and hospitalization duration related to treatment [26].

Conclusions

Patients with COPD exacerbations with increased $PaCO_2$ have a high risk of developing type II of respiratory failure, with a high rate of mortality. Respiratory failure and hypercapnic encephalopathy are considered major causes of death in COPD patients. High levels of hypercapnia, conscience disorders and respiratory acidosis may be considered factors of severity in COPD exacerbation. NIMV is a well-tolerated method of therapy that allows, in the great majority of cases, a significant improvement of conscious patients with COPD severe exacerbations and hypercapnia. Hypercapnia can be considered a predictor of worse evolution during exacerbations of COPD and it should always be considered by repeated analysis of blood gas.

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