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Evolution of pCO_2 After Hypercapnic Failure in Patients with COPD

Evolución de la pCO_2 post fallo hipercápnico en pacientes con EPOC

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the top three leading causes of morbidity and mortality worldwide. During the disease course, a subgroup of patients develops episodes of acute hypercapnic ventilatory failure, characterized by sustained elevation of arterial partial pressure of carbon dioxide (pCO_2).
Objetive: To analyze the evolution of pCO_2 in COPD patients during the three months following hospitalization for hypercapnic ventilatory failure, exploring the clinical and functional characteristics associated with persistent versus reversible hypercapnia.
Material and Methods: A prospective, multicenter, observational study was conducted, including 27 patients hospitalized in six healthcare centers in Argentina between March 2023 and August 2024. Patients were followed up with clinical, functional, and arterial blood gas tests at 30, 60, and 90 days after hospital discharge.
Results: The mean pCO_2 was 58.4 mmHg at discharge, 48.84 mmHg at 30 days, 45.66 mmHg at 60 days, and 44.67 mmHg at 90 days. Persistent hypercapnia was observed in 43.8% of patients.
Conclusions: The persistence of hypercapnia after hospitalization identifies a clinically more complex subgroup, with a higher risk of poor outcomes. Structured pCO_2 monitoring enables targeted interventions and helps personalize the follow-up of patients with severe COPD.

Key words: COPD, Hypercapnia; Ventilatory failure

RESUMEN

Introducción: La enfermedad pulmonar obstructiva crónica (EPOC) constituye una de las tres principales causas de morbimortalidad a nivel global. En su evolución, un subgrupo de pacientes presenta episodios de fallo ventilatorio hipercápnico agudo, con elevación sostenida de la presión parcial de dióxido de carbono (pCO_2) arterial.
Objetivo: Analizar la evolución de la pCO_2 en pacientes con EPOC durante los tres meses posteriores a una internación por fallo ventilatorio hipercápnico, explorando las características clínicas y funcionales asociadas a la persistencia o reversión de la hipercapnia.

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Materiales y métodos: Se llevó a cabo un estudio observacional, multicéntrico y prospectivo, que incluyó a 27 pacientes internados en seis centros de salud de Argentina entre marzo de 2023 y agosto de 2024. Los pacientes fueron seguidos con evaluaciones clínicas, funcionales y gasométricas a los 30, 60 y 90 días del alta hospitalaria. La pCO_2 media fue de 58,4 mmHg al alta, 48,84 mmHg a 30 dias , 45,66 mmHg a 60 dias y 44,67 mmhg a 90 dias. El 43,8 % presento hipercapnia persistente.

Conclusiones: La persistencia de hipercapnia post internación identifica a un subgrupo clínicamente más complejo, con mayor riesgo de mala evolución. El monitoreo estructurado de la pCO_2 permite orientar intervenciones específicas y personalizar el seguimiento de pacientes con EPOC severa.

Palabras clave: EPOC; Hipercapnia; Fallo ventilatorio

INTRODUCTION

COPD exacerbations account for most of the healthcare system's cost burden, and there is also a direct relationship between disease severity and cost of care.[1] During hospitalization, some patients with COPD may show acute hypercapnic ventilatory failure and require non-invasive ventilation (NIV) as part of their treatment in order to reduce the work of breathing, improve gas exchange, and reverse respiratory acidosis. This intervention has been shown to reduce the need for endotracheal intubation, shorten hospital stay, and improve survival.[2-3] Once clinical stability and normalization of pH are achieved, some patients may continue to have elevated pCO_2 levels, while others return to normal.

The prevalence of hypercapnia in stable COPD is reported to be between 23–38% and is associated with an increase in hospitalizations and mortality.[4-5]

Understanding the behavior of pCO_2 after hospitalization in a COPD patient following an episode of acute hypercapnic failure could provide information to help predict which variables are associated with persistent hypercapnia, and might eventually benefit from the use of home NIV.

OBJECTIVES

To describe the evolution of arterial pCO_2 values during the three months following hospitalization for hypercapnic ventilatory failure in patients with COPD.

To assess differences in demographic, clinical, and functional characteristics between groups with and without persistent hypercapnia three months after discharge.

MATERIALS AND METHODS

A multicenter observational study was conducted, prospectively and consecutively including patients with COPD who were hospitalized for acute hypercapnic respiratory failure and remained hypercapnic (pCO_2 > 45 mmHg) at the time of discharge. The study was carried out in six healthcare centers in our country. All of them have specialized Pulmonology Services and inpatient wards (Hospital Posadas, Hospital Churruca, Hospital Ramos Mejía, Sanatorio Allende in Córdoba, and Hospital Central de San Isidro). *Inclusion criteria*: patients over 18 years of age with a diagnosis of COPD defined according to GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease), or patients with a smoking history >15 pack-years, CT-confirmed emphysema, and/or use of bronchodilators prior to admission; hospitalization for acute hypercapnic respiratory failure, defined as a clinical presentation with respiratory symptoms (dyspnea and/or cough) leading to admission with arterial pCO_2 > 45 mmHg on arrival; and signing of informed consent. *Exclusion criteria:* a final arterial blood gas (ABG) prior to discharge showing pCO_2 ≤ 45 mmHg; diagnosis of asthma, neuromuscular disease, and/or chest wall disorders causing functional restriction; body mass index > 30 kg/m^2; use of home positive-pressure devices (CPAP [continuous positive airway pressure], or bilevel) prior to hospitalization; psychiatric or cognitive disorders preventing the signing of informed consent; life expectancy < 6 months due to underlying disease.

During follow-up, patients were excluded if, at 30 days after discharge, they presented: non-obstructive spirometry and/or obstructive spirometry with post-bronchodilator reversibility (greater than 12% and 200 mL); exacerbations of their respiratory disease; or, in cases where bilevel positive pressure equipment had been prescribed at discharge, if their objective use was > 4 hours and > 70% of days.

Patients with a diagnosis of COPD who were hospitalized for acute hypercapnic respiratory failure and evaluated for consultation with Pulmonology specialists were consecutively selected. At the first contact during hospitalization, patients were invited to participate in the study and sign informed consent. Three follow-up visits were performed after discharge (V1 at 30 days, V2 at 60 days, and V3 at 90 days).

At V1, demographic, clinical, and recent hospitalization data were collected. Pre- and post-bronchodilator spirometry was performed, and in cases where the patient was using NIV since discharge, objective adherence was verified

through the device software. At V2 and V3, patients were questioned regarding symptoms, new exacerbations, and NIV adherence if applicable. Arterial blood gas samples were taken at V1, V2, and V3. Patients were excluded if they presented a new exacerbation or if home NIV use was adequate (more than 4 hours/day on 70% of days).

Patients were classified according to pCO_2 behavior into four groups: ***1) Early normocapnia***: the patient showed normocapnia (< 45 mmHg) at visit 1. ***2a) Early reversible hypercapnia:*** the patient showed pCO_2 > 45 mmHg only at visit 1 (V1). ***2b) Late reversible hypercapnia***: the patient showed pCO_2 > 45 mmHg only at visits 1 and 2 (V1 + V2). ***3) Persistent hypercapnia:*** the patient showed pCO_2 > 45 mmHg at all three visits (V1 + V2 + V3).

Ethical considerations

The project was approved by the Ethics Committee of each institution, and all participants provided informed consent to take part in the study.

Statistical analysis plan

Results will be presented as mean ± standard deviation or median and range for numerical variables, and as percentages for categorical variables.

The percentage of the categories will be reported with 95% confidence intervals.

To compare demographic and clinical data across the four groups, Chi-Square or Fisher's Exact tests will be used for proportions, and analysis of variance or Kruskal–Wallis tests will be used for numerical variables. A p-value of <0.05 will be considered significant.

RESULTS

A total of 27 patients were enrolled between March 2023 and August 2024 (11 from Hospital Churruca, 6 from Hospital Posadas, 3 from Hospital Central de San Isidro, 2 from Hospital Castex, 2 from Sanatorio Allende, and 3 from Hospital Ramos Mejía). 55.6% were male, with a mean age of 67.69 years (±8.17). A total of 7.4% required invasive ventilation, and 29.6% had to be admitted to the Intensive Care Unit. The mean total length of hospital stay was 11.85 days (±7.63), and 29.6% of patients were discharged with home non-invasive ventilation (NIV) equipment. The pCO_2 at discharge was 58.54 mmHg (±10.5). At the 30-day follow-up (V1), 25 patients (92.6%) were included; 66.7% were included at V2 (n=18), and 59.3% at V3 (n=16). Eleven patients were excluded from the study during follow-up (4 due to adequate adherence to home NIV, 4 lost to follow-up, 1 death, 1 exacerbation, and 1 due to two consecutive samples with pCO_2 < 45). Table 1 shows the characteristics of enrolled patients. The mean pCO_2 values were 58.54 mmHg (±10.5) at discharge, 48.84 mmHg (±8.5) at V1, 45.66 mmHg (±6.1) at V2, and 44.67 mmHg (±6.0) at V3. (Fig. 1).

At 30 days, 64% of patients (n=16) remained hypercapnic; at 60 days, this decreased to 38.9% (n=7); and at 90 days, 43.8% of patients (n=7) were still hypercapnic. (Fig. 2). 36% of patients showed early normocapnia (9/25), and 43.8% had persistent hypercapnia (7/16). 5 patients were classified as having early reversible hypercapnia, and 1 patient as having late reversible hypercapnia.

The persistent hypercapnia group presented mean pCO_2 values of 52.8, 51.7, and 51.7 mmHg during follow-up visits. The Student's T-test was used for numerical variables and the Fisher's Exact test for categorical variables. Characteristics were compared between the early normocapnia group and the persistent hypercapnia group. The reversible hypercapnia groups were not included due to their small sample size. The following variables were analyzed: age, sex, ABG at V0, total days of hospitalization, need for invasive ventilation, non-invasive ventilation, body mass index, spirometry values, smoking status and pack-years, frequent exacerbator phenotype, pharmacological treatment used, and comorbidities. No significant differences were found between the variables analyzed in both groups. (Table 2).

DISCUSSION

To the authors' knowledge, this is the first study in our country aiming to describe the evolution of

	Day 0	Visit 1 (30 days)	Visit 2 (60 days)	Visit 3 (90 days)	Máxima
pCO_2 > 45	YES	NO			Early normocapnia
pCO_2 > 45	YES	YES	NO		Early reversible hypercapnia
pCO_2 > 45	YES	YES	YES	NO	Late reversible hypercapnia
pCO_2 > 45	YES	YES	YES	YES	Persistent hypercapnia

TABLE 1. Baseline characteristics of the studied population

N=25 in V1	N	%	M	SD
Age (years)			67.69	8.17
Masc.	15	55		
Weight (kg)			59.38	23.6
Height (m)			1.61	0.09
BMI (kg/m^2)			24.7	4.6
FVC (L)			1.93	0.7
FVC %			64.38	17.37
FEV1 (L)			0.81	0.26
FEV1%			35.83	15.6
FEV1/FVC			45.5	11.89
Active smoker	16	64		
Former smoker	9	36		
Pack/years			54.8	28.6
Frequent exacerb.	9	36		
ICS+LABA+LAMA	10	40		
LTOT	6	24		
IV during hospitalization	2	7.4		
NIV during hospitalization	14	51.9		
ICU during hospitalization	8	29.6		
ICU (days)			1.67	3.15
Ward (days)			9.83	6.77
Length of hospital stay			11.85	7.63
Discharge with NIV	8	29.6		
Discharge with O_2	11	40.7		

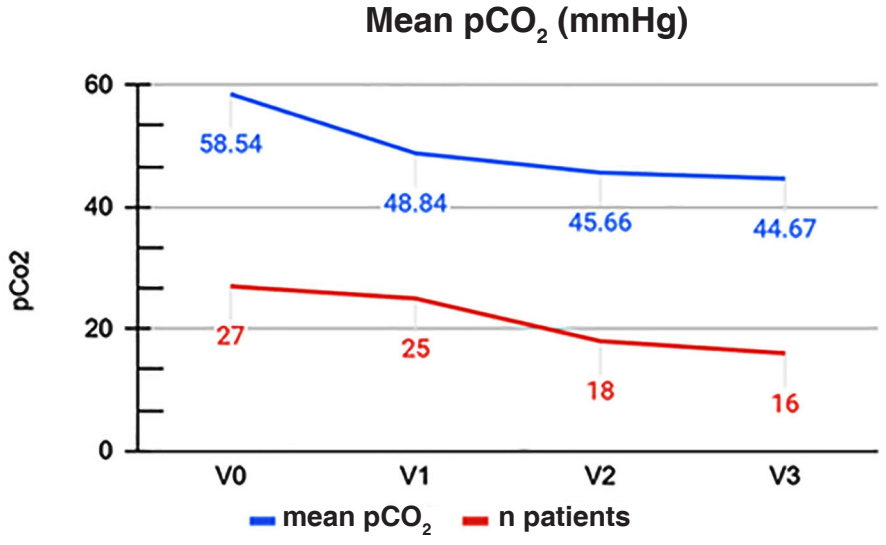

Figure 1. Evolution of mean PCO2 and number of patients according to follow-up visit

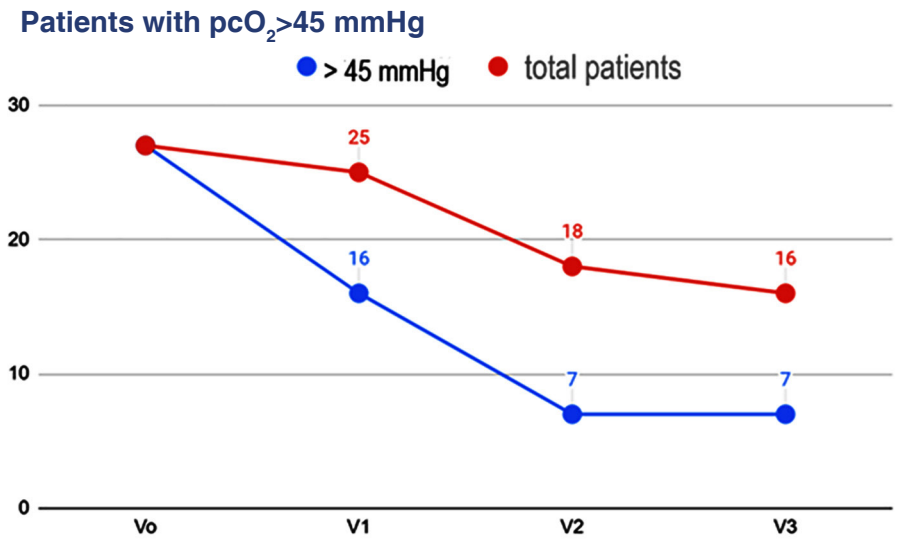

Figure 2. Patients with hypercapnia (pcO_2 >45 mmHg) according to follow-up visit.

TABLE 2. Clinical, gasometric and functional characteristics according to the evolution of

	PH (>45 at V3)	SD	EN (< =45 at V1)	SD	p
Age (years)	69	11.5	66.22	5.14	NS
pH at V0	7.42	0.12	7.41	0.42	NS
PCO_2 at V0	53.97	5.08	54.55	5.12	NS
PO_2 at V0	64.7	5.77	62.88	14.9	NS
Bic at V0	31.07	4.83	33.37	3.84	NS
Total days	13	8.6	12	7.95	NS
Weight (kg)	59.2	16.69	67	19.76	NS
Height (m)	1.59	0.11	1.59	0.82	NS
BMI (kg/m^2)	23	4.12	26.07	5.39	NS
FVC (L)	2.29	0.91	1.7	0.57	NS
FVC %	73.29	26.03	64.44	9.11	NS
FEV1	0.82	0.33	0.77	0.24	NS
FEV1%	36.57	23.1	37.56	10.72	NS
FEV1/FVC	40	12.9	50.4	11.98	NS
Pack/years	58	14.9	56	14.8	NS

pCO_2 levels in COPD patients after a hypercapnic exacerbation.

Although the mechanisms that explain the development of hypercapnia are not fully understood, there is evidence of a worse prognosis in patients who remain hypercapnic during the stable phase (6). A study by Dreher et al found that among stable COPD patients, 16% of those in GOLD stage 3 and 38% of those in GOLD stage 4 developed hypercapnia (7).

In our study, nearly 40% of the patients who completed follow-up at 60 and 90 days continued to have pCO_2 > 45 mmHg.

Costello et al[8], in a cohort followed over 5 years, classified 85 COPD patients after an exacerbation into three types: patients with normocapnic

respiratory failure (type 1), patients who were hypercapnic at hospital admission and subsequently return to normocapnia (type 2.1), and patients who remain hypercapnic after the acute event (type 2.2). Survival was significantly worse in type 2 patients, whereas type 1 and type 2.1 patients had a similar survival. Only 24% of type 2.1 patients progressed over time to type 2.2.

According to current evidence, COPD patients who present hypercapnia during the stable phase (most studies consider 1 month of clinical stability) benefit from the use of home non-invasive positive pressure ventilation, in terms of survival[9-10]. In 2014, Struik et al[11] included 201 COPD patients who had experienced an exacerbation with pCO_2 > 45 mmHg (they were enrolled 48 hours after discontinuation of ventilatory support) to be randomized to receive either home NIV or standard treatment. At 12 months, the NIV arm showed a significant reduction in pCO_2 but no benefit in terms of survival and/or hospital readmissions. In the same year, Köhnlein et al[12] published the first study demonstrating a reduction in mortality after 12 months in COPD patients who received home NIV in addition to standard treatment (12% vs. 33%). Patients included in the NIV + O_2 arm had severe COPD, received outpatient treatment, and had no respiratory symptoms in the previous 4 weeks. Also, their pCO_2 values were greater than 52 mmHg.

Subsequently, Murphy et al[13] showed longer time to readmission or death at 12 months in the group of patients assigned to NIV + O_2 (vs. those with O_2 alone). The study included COPD patients with hypercapnic exacerbations requiring acute NIV at least 2 weeks after resolution of acidosis (pH > 7.30), and who continued to have pCO_2 > 53 mmHg within 4 weeks of clinical stability. It is important to note that in all three studies mentioned above, morbid obesity and sleep apnea were considered as exclusion criteria.

Likewise, in a post hoc analysis of the HOT-HMV trial, the same authors[14] showed that 35% of patients randomized to the O_2 arm experienced an improvement in hypercapnia at 6 weeks (pCO_2 < 53 mmHg) and showed a trend toward better outcomes compared to those who remained hypercapnic. Being able to identify the subgroup of patients who will evolve with hypercapnia is useful for planning follow-up, defining ventilatory treatment more precisely, and modifying medium- and long-term prognosis.

Patients in our study had a mean pCO_2 of nearly 60 mmHg upon discharge, which almost normalized by 60 days (45.66 mmHg at V2). Also, the group of patients with persistent hypercapnia showed no changes between V2 and V3. In other words, 60 days after discharge appeared to be the most appropriate time point to differentiate persistent from reversible hypercapnia. It was also the time when the highest number of dropouts occurred. According to our results, at 30 days, 16 patients still had hypercapnia; at 60 days, only 7 did. This suggests that 56% would have been candidates for home NIV despite spontaneously progressing to normocapnia.

Why does a COPD patient develop hypercapnia? The mechanisms explaining the development of hypercapnia are not fully understood. It has been associated with increased inspiratory loads and reduced strength/endurance of the inspiratory muscles. Inspiratory loads are largely determined by increased airway resistance, air trapping, and increased ventilatory demands (the latter due to greater muscular energy requirements imposed by ventilation with increased dead space). Regarding muscle strength/endurance, reduced performance may be linked to nutritional factors, neuropathic effects, systemic inflammation, diaphragmatic flattening (due to air trapping), and chronic muscle overload.[15-17] As a response to the imbalance between inspiratory load and the respiratory pump capacity, there may be a "down-regulation" of the central respiratory drive and hypoventilation, aimed at reducing energy demand and preventing muscle fatigue (18-20).

De Vito E. describes three physiological characteristics of COPD associated with chronic hypercapnia: 1) inadequate gas exchange (due to ventilation–perfusion mismatch), 2) airflow obstruction with consequent increased resistive work, hyperinflation, and auto-PEEP (intrinsic positive end-expiratory pressure), 3) mechanical disadvantage of the diaphragm, with reduced ability to shorten, reduced tidal volume generation, possibly reduced pressure-generation capacity, and ultimately reduced inspiratory muscle reserve. All of the above indicates that the occurrence of hypercapnia is related to the balance between the magnitude of the inspiratory load and the strength of the inspi-

ratory muscles. Since esophageal pressure (Pes) and P0.1 are elevated, the respiratory centers are already stimulated. That is, these patients "opt" for hypoventilation rather than respiratory muscle fatigue, and its manifestation as chronic hypercapnia may serve a homeostatic purpose: avoiding fatigue and maintaining more comfortable breathing.[21] The variables described in the literature as being associated with persistent hypercapnia after an exacerbation are diverse: low FEV_1, prior acute hypercapnic respiratory failure[22], high pCO_2 at discharge, GOLD D COPD[23], low resting pO_2, low minute ventilation (Ve), high residual volume (RV), low percentage of emphysema on chest CT, chronic oxygen use, and low ventilatory reserve (Ve/MVV [minute ventilation/maximal voluntary ventilation]).[6] In our study, no significant differences were found between the analyzed variables and the persistence of hypercapnia at 90 days.

This is the first study in our country to explore the evolution of these patients, who are at increased risk of readmission and death. Some strict exclusion criteria were selected to reduce potential confounders, such as the absence of obesity, which lowers the likelihood of sleep-related breathing disorders (although these were not ruled out with polysomnography or night polygraphy), or the presence of new respiratory symptoms during follow-up (common in severe COPD), which could alter the natural evolution of pCO_2 levels.

The first and main limitation of the study is the small sample size. Despite designing a multicenter study in facilities with pulmonology services and inpatient bed availability, it was difficult to increase the number of patients included within the planned time frame.

Another limitation of our study was the absence of a systematic record of pre-hospitalization pCO_2 values, which prevented us from reliably determining the presence of baseline hypercapnia in all patients. Nevertheless, the main objective was to evaluate the evolution of pCO_2 following the episode of acute hypercapnic respiratory failure.

CONCLUSION

In our study, a gradual decrease in pCO_2 levels was observed since hospital discharge. 43% of all patients remained with elevated values at 90 days. Assessment at 60 days after discharge proved to be the most appropriate time point to define the management of persistent hypercapnia. The small number of recruited patients, together with those excluded during follow-up, makes it necessary to confirm these findings in larger studies.

Conflict of interest

None of the authors has any conflicts of interest to declare.

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