

Review Article

Acid-Base Disorders in Patients with Chronic Obstructive Pulmonary Disease: A Pathophysiological Review

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The authors describe the pathophysiological mechanisms leading to development of acidosis in patients with chronic obstructive pulmonary disease and its deleterious effects on outcome and mortality rate. Renal compensatory adjustments consequent to acidosis are also described in detail with emphasis on differences between acute and chronic respiratory acidosis. Mixed acid-base disturbances due to comorbidity and side effects of some drugs in these patients are also examined, and practical considerations for a correct diagnosis are provided.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem. Its prevalence varies according to country, age, and sex. On the basis of epidemiologic data, the projection for 2020 indicates that COPD will be the third leading cause of death worldwide and the fifth leading cause of disability [1]. About 15% of COPD patients need admission to general hospital or intensive respiratory care unit for acute exacerbation, leading to greater use of medical resources and increased costs [2–5]. Even though the overall prognosis of COPD patients is lately improved, the mortality rate remains high, and, among others, acid-base disorders occurring in these subjects can affect the outcome.

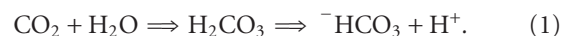
The aim of this paper is to focus on the main pathogenic mechanisms leading to acid-base disorders and their clinical consequences in COPD patients.

2. Hypercapnia and Respiratory Acidosis

A major complication in COPD patients is the development of stable hypercapnia [6, 7].

In the healthy subject, about 16,000–20,000 mmol/day of carbon dioxide (CO₂), derived from oxidation of nutrients containing carbon, are produced. Under normal conditions, the production of CO₂ is removed by pulmonary ventilation.

However, an alteration in respiratory exchanges, as occurs in advanced phase of COPD, results in retention of CO₂. Carbon dioxide is then hydrated with the formation of carbonic acid that subsequently dissociates with release of hydrogen ions (H⁺) in the body fluids according to the following equation:



Thus, the consequence of hypercapnia due to alteration of gas exchange in COPD patients mainly consists in increase of H⁺ concentration and development of respiratory acidosis, also called hypercapnic acidosis [8]. According to the traditional method to assess acid-base status, the Henderson-Hasselbach equation expresses the relationship between pH (logarithm of inverse concentration of H⁺), bicarbonate ion concentration (HCO₃⁻), and partial pressure of CO₂ (pCO₂):

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03\text{pCO}_2}. \quad (2)$$

It is evident that the pH and the concentration of hydrogen ions are strictly determined by the bicarbonate/pCO₂ ratio, rather than their individual values. A change in pH can thus be determined by a primitive alteration of numerator of this equation, that is, bicarbonate (metabolic disorders) or of

denominator, that is, $p\text{CO}_2$ (respiratory disorders). In either case, compensatory mechanisms are activated to determine a consensual variation of the other factor to keep this ratio as constant as possible and minimize changes in pH. The extent of these compensatory changes are largely dependent on that of the primary alteration and can be to some extent predicted (expected compensatory response) [9].

Consequently, the compensation to respiratory acidosis consists in a secondary increase in bicarbonate concentration, and the arterial blood gas analysis is characterized by a reduced pH, increased $p\text{CO}_2$ (initial variation), and increased bicarbonate levels (compensatory response).

3. Compensatory Mechanisms in Acute and Chronic Respiratory Acidosis

The response to respiratory acidosis occurs in a different extent either in acute or chronic phase. When hypercapnia occurs acutely, the buffering of H^+ takes place by proteins, mainly hemoglobin, and other intracellular nonbicarbonate buffers as follows:



The effectiveness of this mechanism is limited. In such condition, for every increase of 10 mmHg $p\text{CO}_2$ we expect only 1 mEq increase in bicarbonate concentration [10].

Subsequently, renal adaptive changes occur mainly in the proximal tubular cells than in distal tubules leading to increased bicarbonate reabsorption and increased excretion of titratable acid and ammonium [11, 12].

H^+ excretion across apical membrane occurs by a Na^+/H^+ antiporter (NHE3) and to a lesser extent by a proton pump (Figure 1). The secreted H^+ into the tubular fluid combines with filtered bicarbonate ions leading to carbonic acid formation. The carbonic anhydrase is then split into CO_2 and H_2O . CO_2 diffuses into the cell where CO_2 is rehydrated to carbonic acid. This gives rise to bicarbonate ion that exits from the cell through the basolateral membrane into the interstitium via a $3\text{HCO}_3^-/\text{Na}^+$ (NBCe1) symporter, while H^+ is secreted again into the lumen. The basolateral membrane Na^+/K^+ ATPase antiporter, maintaining a low intracellular sodium concentration, further enhances the NHE3 activity.

In summary, reabsorption of bicarbonate requires carbonic anhydrase and is strictly associated to sodium reabsorption.

Experimental studies show that total NHE3 and NBCe1 protein abundance are upregulated by chronic respiratory acidosis [13]. However, the main mechanism responsible for the elevation in serum bicarbonate is the increased excretion of titratable acid and ammonium [12], which are stimulated by persistently elevated $p\text{CO}_2$.

Ammonia (NH_3), in the proximal cell, is formed by deamination of glutamine to glutamic acid and then to alpha-ketoglutarate. Therefore, for each molecule of glutamine, two molecules of ammonia are formed (Figure 2). Ammonia binds H^+ resulting in ammonium ion (NH_4^+) which is subsequently secreted into the renal tubular lumen by NHE3, with NH_4^+ substituting for H^+ on the transporter,

and excreted into the urine as ammonium chloride (NH_4Cl). For alternative, some NH_4^+ can be secreted into the tubular fluid as NH_3 , where it is then protonated. Thus, ammonia replaces bicarbonate ion acting as urinary buffer and binding hydrogen ion. Consequently, for each H^+ excreted as ammonium ion, a “new HCO_3^- ” is returned to the blood. Nevertheless, a significant reabsorption of NH_4^+ occurs in the ascending limb of the loop of Henle. In the distal tubule, NH_4^+ reabsorbed is subsequently excreted by a NH_4^+ -transporter belonging to Rh glycoproteins family, localized on both apical and basolateral membranes of collecting duct cells [14].

Thus, collecting duct cells plays a pivotal role in maintaining acid-base balance and net acid excretion. If ammonium reabsorbed was not excreted in the urine, it would be metabolized by the liver generating H^+ , and a “new HCO_3^- ” production would be negated.

Inorganic phosphates, particularly in the distal nephron, also play a role.

H^+ derived from the breakdown of carbonic acid are excreted into the tubular lumen where they are buffered by phosphates ($2^- \text{HPO}_4 + \text{H}^+ \Rightarrow \text{H}_2\text{PO}_4^-$), while HCO_3^- crosses the basolateral membrane via an anion exchange (AE) $\text{Cl}^-/\text{HCO}_3^-$ antiporter (Figure 3).

Phosphates then bind hydrogen ions replacing “regenerated” bicarbonate ions. Interestingly, acidemia and hypercapnia reduce the threshold for reabsorption of phosphate, thus making available a larger amount of urinary buffer in the distal tubule [15, 16].

Pendrin is a bicarbonate/chloride exchanger located in the apical domain of the type B and non-A, non-B intercalated cell of collecting ducts (Figure 4). Hypercapnia determines a reduction of pendrin expression by up to 50%, contributing to the increased plasma bicarbonate and decreased plasma chloride observed in chronic respiratory acidosis [11, 17].

The renal response is completed in its full extent after 3–5 days, resulting in a new steady state in which increase of 3.5 mEq in bicarbonate concentration is expected for every increase of 10 mmHg $p\text{CO}_2$ [18, 19]. Then, in the setting of chronic respiratory acidosis, renal compensation offers more significant pH protection in contrast to intracellular buffering in the acute situation.

For example, if we consider an acute $p\text{CO}_2$ increase to 80 mmHg, bicarbonate concentration compensatory increases by 4 mEq.

In agreement to Henderson-Hasselbach equation,

$$\text{pH} = 6.1 + \log(28/0.03 \times 80) = 7.17. \quad (4)$$

Conversely, if we consider a chronic increase of $p\text{CO}_2$ to 80 mmHg, we could observe a compensatory increase of about 14 mEq in bicarbonate concentration. Thus,

$$\text{pH} = 6.1 + \log(38/0.03 \times 80) = 7.29. \quad (5)$$

In the last example, the variation in pH value is significantly smaller than in the previous one (0.11 versus 0.23 units). This explains why chronic respiratory acidosis is generally less severe and better tolerated than acute with similar

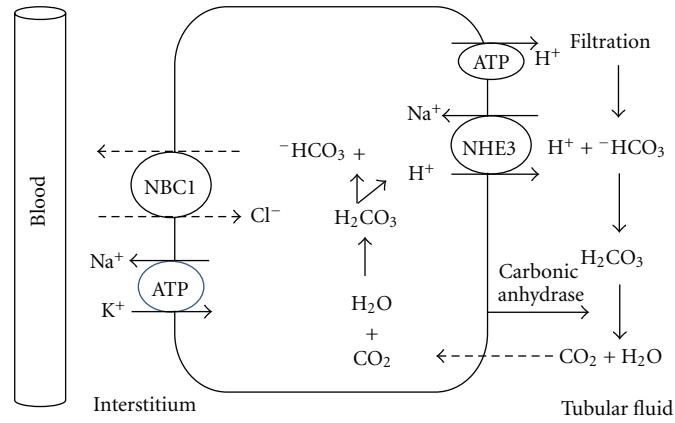


FIGURE 1: H⁺ secretion and ⁻HCO₃ reabsorption in the tubular cells.

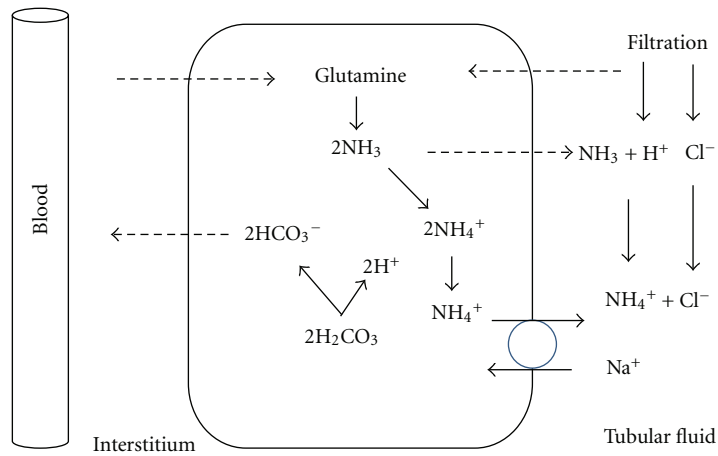


FIGURE 2: Cellular mechanism for ammoniogenesis and NH₄⁺ secretion. NH₃ can be secreted into the tubular fluid, where it is then protonated, or it can bind H⁺ within the cell, and be secreted as ammonium ion.

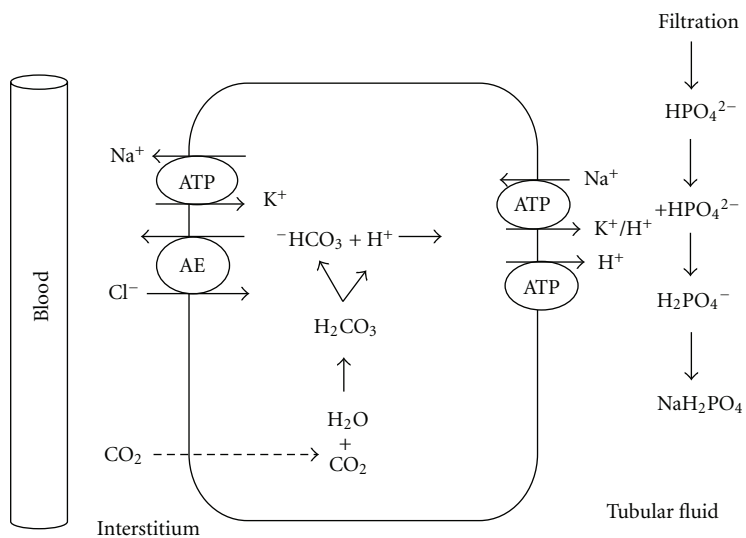


FIGURE 3: Titration of nonvolatile acids. H⁺ secreted into the tubular fluid combines with phosphate (urinary buffer), and a new ⁻HCO₃ is generated within the cell.

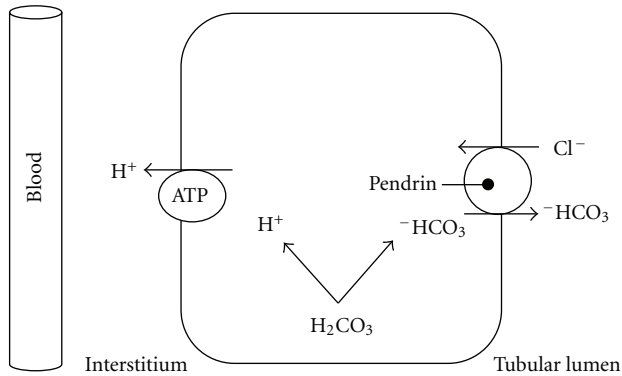


FIGURE 4: Pendrin, localized in the cellular apical membrane of cortical collecting ducts and connecting tubules, acts as a $\text{Cl}^-/\text{HCO}_3^-$ exchanger regulating the acid-base status and chloride homeostasis.

hypercapnia. Figure 5 shows the different slope of the relationship between pCO_2 and bicarbonate in acute and chronic respiratory acidosis.

4. Clinical Consequences of Acidosis

Acidosis is an adverse prognostic indicator and is responsible for several deleterious effects on hemodynamics and metabolism [20–22]. Acidosis causes myocardial depression, arrhythmias, decrease of peripheral vascular resistances, and hypotension. In addition, hypercapnic acidosis is responsible for weakness of respiratory muscles, increase of proinflammatory cytokines and apoptosis, and cachexia. Moreover, in hypercapnic COPD patients a decrease of renal blood flow, an activation of the renin-angiotensin system, and increase of circulating values of antidiuretic hormone, atrial natriuretic peptide, and endothelin-1 have been reported [23]. It has been supposed that these hormonal abnormalities can play a role in retention of salt and water and development of pulmonary hypertension, independently from the presence of myocardial dysfunction.

Clinical and epidemiological data clearly demonstrate that severity of acidosis is associate with poor prognosis.

In the study of 139 patients with COPD and respiratory failure, Jeffrey et al. [24] concluded that arterial H^+ concentration is an important prognostic factor for survival.

In a retrospective study on 295 episodes of COPD exacerbation, Guy et al. [25] reported that intubation and mortality rate was highest at the lowest pH group. Similarly, Kettel et al. [26] and Warren et al. [27] reported an higher mortality rate in patients with a pH value at admission below 7.23 and 7.26, respectively. Plant et al. [28] reported that the more acidemic patients had an higher mortality rate both in group with conventional therapy and in group undergone to noninvasive ventilation. Similar findings were reported by more recent papers [29–31] confirming that a more severe acidosis worsens the outcome of COPD patients.

Prognosis of COPD patients is also adversely affected by comorbidity. Chronic renal failure was found associated with COPD in 22–44% of cases, depending on the study series

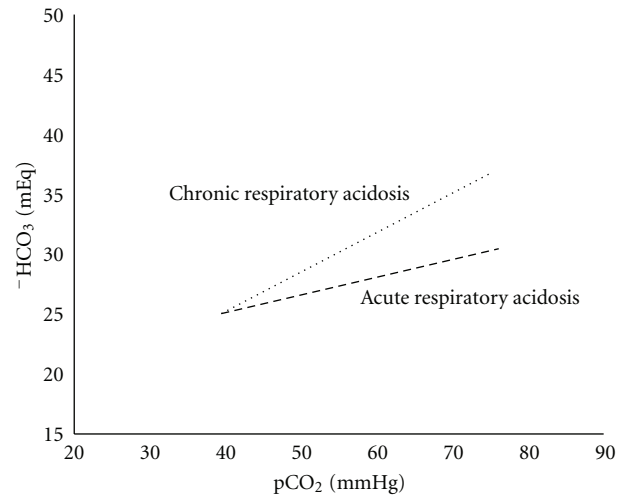


FIGURE 5: Relationship between pCO_2 and bicarbonate in acute and chronic respiratory acidosis.

and diagnostic criteria [32–34]. Renal failure can contribute to development of hypertension, peripheral arterial vascular disease, and onset of ischemic heart disease.

In addition, when renal failure occurs in COPD patients, the compensatory role of kidney in respiratory acidosis may be less effective, resulting in a reduced ammoniogenesis and titratable acidity production with consequent smaller increase of serum bicarbonate and more severe acidosis. Clinical reports demonstrated that bicarbonate levels in these patients are inversely related to survival and that concomitant renal failure is predictive of death and risk of exacerbation [31, 35, 36].

These previous clinical studies indirectly confirm the role and the importance of kidney function as compensatory organ in acid-base disorders.

5. Mixed Acid-Base Disorders

Respiratory acidosis is not the only acid-base disturbance observed in patients with COPD. The presence of comorbidity and side effects of some drugs used to treat COPD patients cause different disorders. These conditions are defined as mixed acid-base disorders.

The main clinical conditions leading to a mixed acid-base disorder are summarized in Table 1. Heart failure, acute pulmonary edema, renal failure, and the onset of sepsis or severe hypoxia are, for example, the most common causes of metabolic acidosis associated with hypercapnia. An abuse of diuretics with volume depletion, hypokalaemia, and use of steroids are the most commonly associated factors with simultaneous presence of metabolic alkalosis.

Metabolic alkalosis may also be the consequence of a too rapid removal of CO_2 in patients undergoing mechanical ventilation. In these subjects, the kidney is not able to quickly remove the bicarbonate excess after the normalization of CO_2 tension, even though some authors hypothesized that cellular transport processes might have a “memory” of pre-existing conditions, and increased bicarbonate reabsorption might persist for some time [13, 37].

TABLE 1: Mixed acid-base disturbances in COPD.

Acute on chronic respiratory acidosis	Respiratory acidosis and metabolic alkalosis
	Volume depletion
	Diuretics
Reexacerbation of COPD	Vomiting
	Severe hypokalemia
	Steroids
	Posthypercapnic alkalosis
Respiratory acidosis and metabolic acidosis	Resp. acidosis, met. acidosis, and met. alkalosis
Severe hypoxemia	
Acute pulmonary edema	
Renal failure	Renal failure and vomiting
Sepsis	Severe hypoxemia and volume depletion
Shock	Sepsis and hypokalemia
Diabetes mellitus	
Acute alcoholism	
Exogenous poisoning	

Both metabolic acidosis and metabolic alkalosis can coexist with respiratory acidosis. This clinical setting may occur, for example, in patients with COPD who develop heart failure and are treated with high doses of diuretics or who have renal failure and vomiting or severe hypoxia and extracellular volume depletion.

In these cases, even if the final shift of the pH depends on the prevalence of acidogenic or alkalogenic factors, the production and/or removal of both metabolic bases and inorganic acids are altered.

Systematically investigated studies on acid-base disorders in patients with COPD are few, but there are evidences that about one-third of these patients have multiple disorders in which the associated respiratory acidosis-metabolic alkalosis is the most frequently found disorder [38, 39].

The presence of a mixed acid-base disturbance complicates the clinical pathophysiology and poses difficulties in diagnosis and treatment.

A limitation of the Henderson-Hasselbach method in this clinical setting is the dependence of serum bicarbonate on $p\text{CO}_2$. A variation in the bicarbonate level can be due to a metabolic disorder or can be the consequence of an initial variation in $p\text{CO}_2$. In the mixed disorders, the bicarbonate level can result in a confounding factor because the altered bicarbonate value, alone, suggests an acid-base imbalance, but it does not distinguish the metabolic component from respiratory component.

Therefore, alternative methods have been proposed to better quantify the metabolic component in mixed disorders.

Among these, standard base excess (SBE), corrected anion gap (cAG), and the Stewart approach are the most frequently utilized [40–43].

SBE can be defined as the amount of strong acid or strong base that must be added to each liter of fully oxygenated blood to restore the pH to 7.40 at a temperature of 37°C and $p\text{CO}_2$ kept at 40 mmHg and hemoglobin concentration standardized to 5 g/dL. The cAG is the difference between the sum of the main cations and the main anions, corrected for

albumin concentration and serum phosphate. Nevertheless, SBE and cAG do not entirely solve the problem and are been criticized.

SBE is an approach that extrapolates results “in vitro” to the more complex multicompartimental real-life situation of body fluids because, in vivo, acid or base loads are not only titrated in the blood compartment, and total buffering capacity can be different from in vitro.

Furthermore, SBE does not resolve the interdependence of $p\text{CO}_2$ and bicarbonate because, in respiratory disorders, the renal compensatory adjustments result in changes in SBE.

The cAG should reveal the presence of unmeasured anions in the blood, and it is useful to determine the cause of metabolic acidosis (hyperchloremic rather than normochloremic) once it has been diagnosed.

The Stewart approach [43] is based on the principals of conservation of mass, electrical neutrality, and dissociation constant of electrolytes and identified three independent variables determining hydrogen ion concentration in solution: strong ion difference (SID), $p\text{CO}_2$, and total weak acid (A_{tot}). Although Stewart method proposes a different approach, its reliability compared to the traditional method is still a debated question. Some authors [39, 44, 45] consider the diagnostic performance of the Stewart method better than the conventional approach to assess acid-base status, especially to quantify the metabolic component, but others [46–49] concluded that it does not improve the diagnostic accuracy and does not provide any tool to better manage these disorders because the traditional approach, with only minor adjustments, can provide the same practical information.

So when and how to suspect a mixed disorder according to the traditional method?

For this purpose, a stepwise approach has been proposed by several authors [50–53], and some simple concepts could help in supposing the presence of a mixed disorder.

(1) *Discordant Variation of Bicarbonates and $p\text{CO}_2$* . Compensatory mechanisms are aimed to keep constant

bicarbonate/pCO₂ ratio, and a primitive variation of one of the terms is followed by a consensual variation of the other. Therefore, increase of bicarbonates and decrease of pCO₂ or decrease of bicarbonates and increase of pCO₂ suggest a mixed disorder.

(2) *The Presence of Normal pH Value and Significant Alteration in Bicarbonates and pCO₂ Levels Also Suggest a Mixed Disorder.* The adaptive mechanisms do not restore the pH to a normal value. Normal pH, in this case, argues for the coexistence of two opposing problems rather than a perfectly compensated simple disorder.

(3) *Compensatory Response Is Significantly Different than Expected Response.* Observed bicarbonate levels or pCO₂ significantly different than “expected” proves the existence of a mixed disorder. In fact, the amount of compensatory variation depends on the extension of primitive change, and it can be reasonably provided. When expected response does not occur, there is an additive disorder responsible for variation of bicarbonate or pCO₂.

(4) *Delta Ratio, That Is, $\Delta\text{anion gap}/\Delta\text{HCO}_3^- > 2$.* When a metabolic acid (HA) is added to extracellular fluid, it dissociates in H⁺ and organic anion (A⁻). H⁺ react with a molecule of bicarbonate while unmeasured organic anion (A⁻) will increase anion gap (positive less negative charges). Theoretically, the variation in the anion gap should be equal to the decrease in bicarbonate so that the ratio between these two changes should be equal to one. Nevertheless, a significant amount of organic acid is buffered by intracellular proteins, not by HCO₃⁻, while most of excess anions remain in the extracellular fluids because they do not freely cross the cellular membrane. Consequently, in a pure metabolic acidosis, the change in bicarbonate concentration is lesser than anion gap, and delta ratio is between 1 and 2. A delta ratio value above 2 indicates a lesser fall in bicarbonate than expected on basis of the change in anion gap. This finding suggests a concurrent metabolic alkalosis or preexisting high HCO₃⁻ levels due to chronic respiratory acidosis.

In any case, the interpretation of arterial blood gas analysis cannot ignore the findings of clinical history and physical examination that can support a correct diagnosis.

Clinicians should also consider the preexisting conditions, drugs usually taken, symptoms presented in the last days and hours as well as hydration status of patients, the presence of heart and renal failure, diabetes, hypokalemia, or signs of sepsis.

Therapy of mixed disorders is often difficult. The attempt to correct the pH at all costs with the use of alkaline or acidifying drugs could be harmful, and the clinician’s attention should be paid to identify underlying pathophysiological changes.

6. Conclusions

Respiratory acidosis due to hypercapnia is a common and severe complication observed in patients with chronic obstructive pulmonary disease in advanced phase. Development of acidosis worsens the prognosis and is associated with higher mortality rate. Mechanisms of compensation consist of an increased renal reabsorption of bicarbonate and

increased excretion of H⁺. These adjustments of renal function are more effective in chronic form and explain why the latter is less severe and better tolerated than acute. Mixed acid-base disorders are also frequently observed in COPD patients. Clinical history, physical examination, and a careful evaluation of arterial blood gas analysis may help in proper diagnosis and targeted therapy.

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