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International Journal of Biochemistry & Physiology
ISSN: 2577-4360

New Trends about Biochemistry and Biophysics of Acid-Based Equilibrium and Coronavirus: A Review

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Review Article

Volume 7 Issue 1

Received Date: May 19, 2022

Published Date: June 09, 2022

DOI: 10.23880/ijbp-16000203

Abstract

The knowledge of the physiologic and biochemical principles of the acid-base equilibrium are absolutely indispensables for the arterial gasometry interpretation in the pulmonary gas interchange, and in the base preservation mechanisms in the blood. This knowledge will permit more adequacy conducts for the treatment of grave patients. This work will revise those principles, and will present the interpretation of abnormal acid-base states and there will be considerations about the treatment of those non-equilibrium in COVID-19 committed patients.

Keywords: Acid-Based Equilibrium; Biochemistry; Biophysics; Coronavirus; Covid-19; Treatment

Introduction

As a review article this work is to present information about the acid-base equilibrium, this alteration, the modifications occurred when coronavirus is introduced into the human body, the consequences to equilibrium and the treatments that are dispensable to fight against this virus pandemic disease. It presents initially the principal aspects of acid-base equilibrium, those main alterations and compensations, and some research works that were doing to show the ways of treatment of this disease.

Principal Aspects in Acid-Base Equilibrium

The Carbonic Gas

The metabolism of aliments ends into the common terminal via, known as tricarboxylic cycle or Krebs cycle [1,2]. These systems made the necessary energy to sustain organs and systems actives, permitting the normality of the vital functions. The final product of the aerobic combustion is water and carbonic gas [3]. The water resulting of this process is called endogenous water and corresponds to approximately a half litre in the 24 hours. In adult individuals and in basal conditions, the production of carbonic gas is of approximately 200 mL per minute. In exercise conditions this volume could be 10 times more [4]. It is a gas much diffusible and easily soluble in organic liquids. The carbonic gas produced in the tissues is eliminated by lungs by movements of respiratory apparatus. The major part of the carbonic gas is transported of the tissues to the lung by venous blood, in the bicarbonate form. The fraction that remains in physic solution is calling free CO_2 or molecular CO_2. The no-hydrated free CO_2 pass through rapid and easily by membranes and organic tissues, obeying always to the pressure gradients existing. In each organic liquid, the free CO_2 quantity is linearly proportional to their partial press ion.

$$[\text{free } CO_2] = \alpha \times PCO_2$$

$$[\text{free } CO_2] = 0{,}031 \times PCO^2$$

$$1{,}2 \text{ mM/L} = 0{,}03 \times 40\text{mm Hg}$$

The α constant is equal to 0.031 and it is named proportionality coefficient of the gas at 38°C. See that the CO_2 is easily soluble into organic tissues; their diffusion not is the limit factor to their passage through the venous blood to the alveoli. The only limiting factor is the alveolar ventilation, responsible by reduction of the CO_2 concentration and, obviously of the partial pression in the alveolar air ($PaCO_2$) [5].

The alveoli-capillary complex is an essentially open system, permitting exchange of heat and matter. The full equilibrium of the partial pressures of CO_2 in the alveoli and in the arterial blood only be possible on closed system [6]. However, the equilibrium of the partial pressures of CO_2 is sustained stable thanks to the great power of diffusion of the CO_2.

The concept of open system is essential for the comprehension of the acid-base equilibrium [7]. Each organism tissue is an open system. The CO_2 produced have a tendency to scape to the blood, so to alveoli and, finally, to the atmosphere. Although of the production and of the pulmonar scape of more than 20000 mM of CO_2 by day, the partial pressure of CO2 is sustained practically constant in each tissue and in blood. The pressure control is done by respiratory centre, that realize the PCO_2 and acts by a feedback negative chemiotactic mechanism. If the partial pressure of CO_2 increases, the respiratory centre is directly stimulated by the gas himself, increasing the alveoli ventilation. If, by other motive, the ventilation increases, stop the ventilatory stimuli of the central nervous system. This mechanism is very important and explains the respiratory answers, same with little variations of arterial PCO_2.

In normal conditions, the $PaCO_2$ is sustained around of 40 mmHg in sea level individuals. In right altitude the $PaCO_2$ stay below of 40 mmHg. At 2000 meters of altitude, per example, the $PaCO_2$ is approximately 35 mmHg. In these elevations, the respiratory alkaloses is considered physiologic, not been dictated by a great need of CO_2 excretion, but by other mechanisms involving the central nervous system, the bone marrow and the renal function, as answer to the hypoxic stimuli. Even so, the plasma pH normality is sustained. In pathologic conditions, the increase of the arterial PCO_2 occur almost exclusively by difficult of pulmonar elimination, as see that a ventilatory system, in normal conditions, rarely not eliminate a gas increase production [8]. In cases of carbonic gas retention in patients with ventilatory acute compromising, the increase of CO_2 it is following of a pH reduction, causing a respiratory acidosis, called not plywood. In the cases of chronic obstructive pulmonar disease, when the retention of carbonic gas is stablished insidiously, there is a renal compensation by retention of the bicarbonate, the renal activity partially fixes the acidaemia of the respiratory acidosis. In this case the respiratory acidosis is called plywood, although rarely a normal pH will be reached. In cases that the alveoli ventilation reduction occurs by obstructive process, a serious second factor is stablished. Trying win the increase of air vials resistance, the respiratory muscles develop a major resistive work, consuming more oxygen and producing more carbonic gas. Certainly, can be hit a point in that the effort of eliminate CO_2 obstructive lung ventilating will be so expensive in resistive work terms, that is more advantage to tolerate an increase of PCO_2 instead of to keep normal to the costs of an impossible effort [9].

Experimental and clinical facts show that individuals with respiratory obstruction and with resistive excessive work "choose" a minor ventilation volume as that will be necessary to keep a normal PCO_2. It explains why that obstruct patients sustain levels of the PCO_2 regulate in good levels determined more by oxygen tissue demand as by acid-basic equilibrium normality manutention. This important observation raises a question of great clinic importance: When must to interfere to normalize a $PaCO_2$ elevated abnormally?

The Plasma Bicarbonate Ion

The bicarbonate ion represents the fixed or combine form of the plasma CO_2, in opposite with the free or molecular form. The total quantity of CO_2 is the sum of bicarbonate and of the free CO_2 (α x PCO_2) and of the bicarbonate ions [10]. The bicarbonate, to the contraire of the free CO_2, is a complex ion and with two functions important and well defines:

1. It is totally part of the transport system of CO_2. To the level of the tissue capillary, the enzyme carbonic anidrase intra-erythrocyte answer by formation of the carbonic acid and of the ions H^+ and HCO_3^- inside of the red blood cells (RBC). The H^+ are tamponade by reduced haemoglobin, besides that the ion bicarbonate migrates to the plasma, being transported to the lungs. Into the pulmonar capillary occurs the inverse process. The ion HCO_3^- migrate to inside of RBC and reacts with the H^+ released by oxygen RBC, forming carbonic acid, that in its turn dehydrate, forming CO_2 and H_2O. The carbonic gas migrates to outside of RBC and, by partial pressure gradient, to outside of the capillary in the pulmonar alveoli, from it is removed by pulmonar ventilation.
2. The bicarbonate ion is integrant part, also, of the system of control of the acid-basic equilibrium. The plasma bicarbonate must be considered as a reservation of base disponible for the buffering of fixed acids that invade the extracellular space. The quantity of bicarbonate ion resulting of carbonic acid ionization is negligible when compared with the bicarbonate quantity dispensable as base reserve.

When the blood pass through by tissue capillary, the plasma bicarbonate increases of 24 to 25 mEq/L. However,

this increase of HCO_3^- generate 1 mEq of H^+ that must be buffered by haemoglobin. This demonstrate the fact of that a great quantity of hydrogen could be transferred between acid-basic systems of the blood [11].

The bicarbonate/PCO_2 system act as mechanism of defence of blood current invasion by any overhead acid or alkaline. If there is an excess of plasma acid, the bicarbonate reserve checks it out to the H^+ ions, neutralize them. The bicarbonate ions could be consumed almost fully in the neutralization process of hydrogen ions, because the bicarbonate/PCO_2 is open and the carbonic acid, a volatile acid [12].

To the contrary, the others blood buffer systems (between which the haemoglobin, the proteins, the phosphates, the sulphates etc) are grouped in one closed system, in which the sum $HBuf^+$ Buf^- remains constant. To the contrary of the buffer no-bicarbonate systems in which the sum $HBuf^+$ Buf^- remains constant, the total quantity of CO_2 of bicarbonate/PCO_2 decrease, because the open system permits the elimination of CO_2 by reaction detour to the left.

Different of that occurs with the free CO_2 molecule that spreads easily by organic liquids and whose action about the respiratory centre is extremally sensitive, the bicarbonate ion is a heavy ion with negative charge and that transit with difficult by organic tissues. By other side, passively migrates in exchange by chloride into erythrocyte membrane and moves freely between the extracellular liquid and the plasma liquid [13]. The bicarbonate is generated by CO_2 hydration and subsequent carbonic acid ionization.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H{+}{+}HCO_3{-}$$

This reaction process in practically all cells, but mainly in that rich in carbonic anidrase as the haematics, the parietals cells of stomach and the renal tissue. It supposed that the concentration of intracellular bicarbonate will be of 12 to 16 mEq/L, less more than the half of the concentration in the plasma and in the interstitial liquid. The total quantity of HCO_3^- disposable in the organism is approximately 1000 mEq and the quantity immediately disposable of bicarbonate reservation is of approximately 450 mEq in 15 litters of extracellular liquid. The plasma bicarbonate is utilized as metabolic alterations index of the acid-basic equilibrium, that is, of the accumulation or of the loss of fixed acids by organism as one all [14].

Base Difference Concept

The increase or diminished of the plasma bicarbonate express the variations that occur in the buffer system carbonic acid/bicarbonate. Occurs that this buffer system answers only for 70% of all the blood buffer systems, between the witch figure between others, the haemoglobin, the proteins, the phosphates and the sulphates. Although, the difference between the measure plasma bicarbonate and the normal plasma bicarbonate (24 mEq/L) not express the excess or deficit of blood base because limits to the result of the total base variation about on unique buffer system [8].

By this motive, it was developed the concept of base difference (BD), that express the total value of the excess or debit of blood base [15]. Of the practice point of view, the BD could be obtained by Siggard-Anderson alignment monogram, that nothing more is of that the graphic expression of the Henderson-Hasselbalch equation added of base difference grade.

In this monogram, becomes of the pH and of the blood measured PCO_2 is possible to calculate the total CO_2 (TCO2), the plasma bicarbonate (HCO_3^-) and the base difference (BD). It notes that for each conjunct of pH and PCO_2 the BD will be variable depends of the haemoglobin tax, the second more important blood buffer system. It observes that the anaemia reduces the base difference more significantly on the presence of acidosis (pH<7.2).

Normal acid-base equilibrium and the Henderson-Hasselbach equation

$$pH = pK + \log \frac{Base}{Acid}$$

$$pH = 6.1 + \log \frac{24}{1.2}$$

$$pH = 6.1 + \log 20$$

$$pH = 6.1 + 1.3$$

$$pH = 7.4$$

Acid-Base Equilibrium Alterations

Denominates acidaemia to the state in that the blood pH is inferior to 7.35 and basaemia or alkalemia to the state in that the blood pH is higher than 7.45 [7]. You can observe that by the Henderson-Halsselbalch equation that the acidaemia could occur by one reduction of the [HCO_3^-], that characterize a metabolic alteration, or by an increase of the pH could be associated or an increase of [HCO_3^-] or a reduction of blood PCO_2.

Metabolic Acidosis

Independently of fix acid type cumulated in blood (lactic acid, aceto-acetic acid, β-hydroxybutyric, sulphuric etc), that

matters are the cumulation of protons (hydrogen ions). So, the lactate ions, acetate, β-hydroxybutyrate etc, could be grouped by the general denomination of Anion (A^-). In the metabolic acidosis, the is an increase of H^+ and A^-. The addiction of a strong acid into blood determines their buffering by the bicarbonate/carbonic acid system. The reaction of strong acid with sodium bicarbonate generates a sodium inert salt that will depend of the anion type. Generates, still, carbonic acid, that produce carbonic gas and water quickly eliminate by lungs and by kidney. It is possible "delete" the excess of strong acids abnormally produced in the organism by the bicarbonate uptake. These mechanisms bring, intrinsically, any cost, decreasing the base (bicarbonate) reservations. In the Henderson-Hasselbalch equation, there is so a reduction of the numerator of the normal of 24 mEq/L to something, per example, almost of 12 mEq/L.

$$pH = pK + \log \frac{Base}{Acid}$$

$$pH = 6.1 + \log \frac{12}{1.2}$$

$$pH = 6.1 + \log 10$$

$$pH = 6.1 + 1.0$$

$$pH = 7.1$$

In the metabolic acidosis the pH there is decreased, but much less intensively of that if the fix acid would be been addicted to a hypothetic blood, released of any buffer system. The addiction of 12 mEq of a strong acid to a litter of one solution without buffer system could produce a pH of 1.92, acidity incompatible with the life [7].

The metabolic acidosis is the more frequent detour of the acid-basic equilibrium founded in the clinic practice. The frames more frequent are:

1. Diabetic ketoacidosis
2. Lactic acidosis
3. Renal acidosis

Frames less intensive and clinically less expressive could occur in situations of fever or prolonged fast.

Diabetic Ketoacidosis: Frequently, surgery interventions are realized in diabetic patients. The surgery stress, the prolonged fast, the medicine interaction and, sometimes, the inadequate control of the patient in the post-surgery period could induce to the ketoacidosis or to hyperglycaemic crises [16]. In the diabetic patient, because of the inefficient actuation or of insulin absence in the carbohydrate metabolism, the glucose not is metabolized adequacy by Krebs cycle. With that, not there is sufficient production of oxalacetate and occur accumulation of Acetyl-coenzyme A, product intermediate of the fatty acid metabolism. The accumulation of acetyl-coenzyme A causes the production, in the liver, of right quantities of acetone, of aceto-acetate and of β-hydroxybutyrate. Those substances are known collectively as ketonic bodies or ketones. The total concentration of ketonic bodies in the human blood of well-fed individuals does not pass normally of 1 mg/100mL. The urinary lost is inferior of 1 mg in 24 hours. The presence of ketonic bodies more quantities in the blood or in the urine is known, respectively, by ketonemia (or hyperketonaemia) and ketonuria. The general condition is called ketosis. The predominant ketonic body in the ketosis is the β-hydroxybutyrate. The aceto-acetic and β-hydroxybutyric acids are strong acids that, when present in the blood and in the tissues, let to a state known as keto-acidosis. In the not controlled diabetes could be fatal.

The control of diabetic patient in post-surgery period is done by the measurement of the glycaemia to the border of bed of four-to-four hours [17]. The insulin simple administrated will depend of the results of glucose measurement and/or of glycaemia. It is good to avoid the use of insulin NPH because there is a minor control of the glycaemia levels in the 24 hours. It was also avoided not administrate the insulin in the serum in the same way with the glucose serum, but the possibility of interruption of the venoclisis when the glucose will be metabolized before that the insulin action stops, what could induce a hypoglycaemic crisis. In the diabetic ketoacidosis, the patient hydration and the insulin administration are, generally, sufficient to correct the base problem; having an adequacy renal function, the normalization of acid-basic equilibrium is the rule, will be the administration of bicarbonate rarely necessary.

Lactic acidosis: In the carbon hydrate aerobic metabolism (aerobic glycolysis) the pyruvate is oxidate to CO_2 and water in the process known as oxidative phosphorylation by tricarboxylic cycle more known as Krebs cycle. The pyruvate oxidation in this cycle determines the production of 38 high energy phosphate bounds (ATP=triphosphate adenosine) responsible by approximately 290 Kcal per mol of oxidate glucose in the tissues. In the absence of oxygen, the pyruvate not has conditions of go in the tricarboxylic cycle and goes by alternative vial, the Embden-Meyerhof cycle, also known as anaerobic glycolysis [18].

GLUCOSE $2LAC^-$
+ +
2ADP 2ATP
+ +
$2PO_4$ $2H_2O$

All the enzyme of the Embden-Meyerhof vial are founded in the extramitochondrial fraction soluble in cells, au contrary of the oxidative phosphorylation, in which the

pyruvate must be transferred to inside of the mitochondria, when process the aerobic combustion of Krebs cycle. The anaerobic glycolysis produce only two phosphate bounds of high energy (ATP) for each molecule-gram of metabolized glucose. This indicate that the loss of oxygen in tissues blocks the adequate utilization of the energetic potential of glucose combustion, it will be this metabolic vial an emergency and peccary alternative. The anaerobic glycolysis occurs when the partial pression of oxygen in tissues is inferior to 20 mmHg. This hypoxia can occur by three fundamental mechanisms [19]:

1. Oxygenation hypoxia of the blood, but insufficient tissue flux. This situation can be founded in conditions of low cardiac debit, determine by circulant volume (great haemorrhages, extreme dehydrations), or by cardiac bomb failure (cardiogenic chock).
2. Adequacy tissue flux hypoxia, but insufficient blood oxygen. This situation occurs in patients with reduced potential of oxygen transport, by loss of haemoglobin (extreme anaemia) or still in patients with normal haemoglobin concentration, but with accentuate desaturation resulting in hypoxemia grave, frequently found in cases in that the pulmonar gas exchange is compromised by pneumopathies grave.
3. Adequacy tissue flux hypoxia, oxygen normal of the arterial blood, but incapable of oxygen liberation by haemoglobin. This situation, much rarer, can occur in cases of extreme deviation of the haemoglobin dissociation curve to the left, as in the deep hypothermia, in the extreme alkalosis or, still, in the reduction of organic intra-erythrocyte phosphate, the 2,3-diphosphoglycerate (2,3-DPG).

The final aerobic glycolysis consequence, undependably of the cause, is the lactic acid cumulus.

$$PIRUVATE \rightarrow H^+ + Lac$$

Renal acidosis: Diary, by ingestion and by metabolism, the organism generates an excess of hydrogen ions. The majority part of this H^+ comes from amino acids with sulphur radicals (methionine, cysteine), that are metabolized to sulphur acid (H_2OSO_4). This production of acids, that varies of 50 to 100 mEq by day, is fully buffered, reducing the bicarbonate concentration in equal quantity. To replace the bicarbonate, the kidney needs to excrete diary of 50 to 100 mEq of H^+. An equal number of HCO_3^- is generate for each H^+ secreted by the distal nephron. Other way of proton's excretion is the mechanism of ammonia formation, by which the acid bound to the NH_3 to form NH_4A. Beyond of the diary hydrogen ion production excretion, the kidney must recovery all the bicarbonate that pass by the renal tubule. So, admitting a glomerular filtration of 180 L/day and know that the plasma bicarbonate is 24 mEq/L, filter diary about 4300 mEq of bicarbonate. The loss of this bicarbonate in the urine takes a reduction of the blood pH to levels incompatible with the life. Even small loses of bicarbonate would redound in reduction of blood pH, and urine alkalinization. It is imperative, therefore, that stablish, in the renal tubule, a mechanism of recover the bicarbonate, and urine acidification [20].

In general, the metabolic acidosis occurs when there is comprising of glomerular filtration low of 25 mL/100 mL [21]. In these conditions, the plasma creatinine elevates up to 3 to 4 mg%. Beyond of creatine, there is elevation of other substances, particularly phosphates, sulphates and organic acids (the residual anions), that increase in the blood. It is possible calculate the residual anions (gap anion). They represent the difference between the measured cations (sodium) and the measured anions (bicarbonate and chloride).

$$RESIDUAL\ ANIONS = Na^+ - (HCO_3^- + Cl^-)$$

In normal individual:

$$RESIDUAL\ ANIONS = 140 - (24 + 100) = 16\ mEq/L$$

The increase up of 16 mEq/L of the residual anions in the metabolic acidosis means that there was addition of organic acids. Beyond of renal insufficiency, other situations can take to the increase of residual anions with the diabetic acidosis, lactic acidosis or intoxications.

Hyperchloremic Metabolic Acidosis: The hyperchloremia cold occur by administration of chloride, as HCl, or ammonium chloride. Also, the administration of great quantities of physiologic serum (Na^+=154mEq/L e Cl^- = 154mEq/L) could introduce hyperchloremic acidosis. Patients that have uretosigmoidostomy frequently develop hyperchloremic metabolic acidosis and hypokalaemia. The basic mechanism is the follow: the urea of the urine unfolds in the intestinal tube, forming ammonium chloride, that is absorbed in the blood, producing an acidosis similar to that produced by parenteral administration of NH_4Cl, the patient lost great quantity of potassium, because, to the contraire of the sodium chloride and of the urea, that ion not is reabsorbed by intestinal mucous. Furthermore, the patient frequently shows diarrhea, that also propitiates great loss of potassium [22].

Hyperchloremia by Excessive Loss of Bicarbonate: The gastrointestinal loss of alkalis occurs by loss of fluid below of the pylorus. As result of diarrhoea or loss of biliary secretion, pancreatic or intestinal (by fistula, drainage or vomits in the presence of intestinal obstruction) could to emerge a hyperchloremic metabolic acidosis. The loss of bicarbonate by gastrointestinal system is plywood by a major chorine renal retention, that determine a normal value of residuals anions [22].

Treatment of Metabolic Acidosis: In the metabolic acidosis, the buffering process by bicarbonate/carbonic acid

system and by buffer no-bicarbonate systems, mainly the haemoglobin. By this motive, the total acidosis correction could be based in the total blood base difference (BD) and not simply in the deficit of bicarbonate express by numerator of the Henderson-Hasselbach equation. Mellemgaard and Astrup proposed an equation to correct the deficit of base of the metabolic acidosis, based in the premise that 30% of body weight is extracellular water compromised by acidosis and that could suffer correction based in the deficit of base in blood.

$$N° \text{ mEq } NaHCO_3 = \text{Peso (kg)} \times 0{,}3 \times [BD]$$

The practice has showed that the use of the determinate values by this equation tend to super correct the metabolic deviation, leading to a metabolic alkalosis; tend also to cause hypernatremia with hyperosmolarity, because of sodium that follow the bicarbonate, effect not always desirable in patients just compromised (hyperosmolarity of decompensated patient, neurological pictures with cerebral edema, renal insufficiency and congestive cardiac insufficiency).

In reality, insofar as process the acid-basic equilibrium correction, also acts about the subjacent cause of the metabolic detour, so that there is a concomitant physiologic correction. By this way, in clinic practice, there has been corrected the metabolic acidosis with the half of the calculate dose by Mellemgaard and Astrup equation, followed of arterial gasometry, that points need or not of new correction. In general, metabolic acidosis with inferior base difference to -5 mEq/L not are corrected with sodium bicarbonate, holps that the physiologic equilibrium stablishes with the base problem treat.

Recently, the adverse effects of the bicarbonate associate to the undesirable haemoglobin dissociation curve detour to the left have limited the use of sodium bicarbonate in the metabolic acidosis treatment. The current orientation is that the use will be indicated when the present acidaemia grade blocks the actuation of vasoactive drugs in patients hemodynamically stables (pH low than 7.1). In other circumstance and with renal function preserved, the base pathology correction will be sufficient to normalize the acid-basic detour [23].

Respiratory Compensation of Metabolic Acidosis: Normally, the blood pH reduction directly stimulates the respiratory centre, determine a lung hyperventilation. The alveoli carbonic gas remotion reflects in the reduction of blood carbonic gas partial pressure, that, by this way, reduce the carbonic acid concentration, the denominator of Henderson-Hasselbalch equation [23,24].

The relation between the blood carbonic gas partial pressure, express in mmHg, and the carbonic acid concentration, in mEq/L, remains a linear correlation express by a proportionality constant α, that result of two factors: carbonic gas solubility coefficient in liquids and conversion coefficient of unit of mmHg to mEq/L. The proportionality coefficient is equal to 0.03.
So, in normal conditions has:

$$HHCO_3 \text{ (mEq/L)} = \alpha \times PCO_2 \text{ (mm Hg)}$$
$$HHCO_3 = 0{,}03 \times PCO_2$$
$$HHCO_3 = 0{,}03 \times 40$$
$$HHCO_3 = 1{,}2 \text{mEq/L}$$

When the patient hyperventilation, the partial pressure of the carbonic gas in the arterial blood pass, by example, to 200 mmHg. In these conditions, the carbonic acid pass to 0.6 mEq/L.

$$HHCO_3 = 0{,}03 \times 20$$
$$HHCO_3 = 0{,}62 \text{mEq/L}$$

The Henderson-Halsselbalch equation to a patient with metabolic acidosis and ideal respiratory compensation, is the following:

$$PH = pK + \log \frac{Base}{Acid}$$

$$pH = 6.1 + \log \frac{12}{0.62}$$

$$pH = 6.1 + \log 20$$

$$pH = 6.1 + 1.3$$

$$pH = 7.4$$

As see, in metabolic acidosis, the blood could be it pH totally compensate by a respiratory alkalosis. Normally, this compensation is partial, in the sense of reduce the grade of acidaemia determine by fixed acids. In cases of extreme reduction of bicarbonate, the hyperventilation is notable, been known as Kussmaul respiration [25].

Metabolic Alkalosis

The metabolic alkalosis is a clinic situation very low frequent and occur essentially in two situations [26]:

1. Excessive administration of sodium bicarbonate.
2. Loss of chloride by height gastrointestinal obstruction.

Metabolic Alkalosis by Excessive Administration of Bicarbonate: This iatrogenic occurs by indiscriminate administration of sodium bicarbonate, mainly without gasometry control. The literature shows disastrous cases, in

that, in reanimation maneuvers, the excessive administration of bicarbonate takes to acute hyperosmolarity (350 mOsm/L), with plasma bicarbonate up to 50 mEq/L and pH reaches levels of 7.54. The recovery of patients with cardiorespiratory blocks and that received excessive quantities of sodium bicarbonate is minor than patients whose normalization of the acidaemia does by mechanical hyperventilation (in it more recent normalization in the attendance to cardiorespiratory block, the American Heart Association no recommend the use of bicarbonate) [27].

Metabolic Alkalosis by High Gastrointestinal Obstruction: The loss of chloride acid by vomits, as in high gastrointestinal obstruction, takes to metabolic alkalosis. The physiologic mechanism of this alkalosis has home in the stomach parietal cells. There, by the action of carbonic anidrase (c.a.) enzyme, makes carbonic acid through water and carbonic gas.

$$CO_2 + H_2O \xrightarrow{c.a.} H_2CO_3$$

This dissociates in hydrogen and bicarbonate ions. The hydrogen ion, add with the chloride ion, migrates to the stomach light. For each molecule of HCl formed and lost in stomach, there is production of one molecule of bicarbonate that pass of parietal cell to the blood.

The post-prandial plasma bicarbonate excess is called "alkaline wave" [8,28] and tend to regret when the pancreatic and biliary juices, know alkaline, are formed and secreted in the subsequent step of the digestion. In the high gastrointestinal obstruction, the chloride acid is loss by persistent vomits and not neutralize the alkaline juices and, consequently, the blood alkalosis. Per example, the increase of plasma bicarbonate of 24 to 48 mEq/L determine the following alterations in the Henderson-Hasselbalch equation:

$$PH = pK + \log \frac{Base}{Acid}$$

$$pH = 6.1 + \log \frac{48}{1.2}$$

$$pH = 6.1 + \log 40$$

$$pH = 6.1 + 1.6$$

$$pH = 7.7$$

In the metabolic alkalosis, the alkalemia is associated to an excess of bicarbonate ions [8]. In the same way that in metabolic acidosis, in the states more advantage could there is a respiratory compensation, now with alveolar hypoventilation, express by retention of carbonic gas by a more slow and superficial respiration [29]. Although, the respiratory compensation in the metabolic alkalosis not is so intense and dramatic how in the metabolic acidosis.

Hypokalaemia Alkalosis: A relevant aspect that follows the metabolic alkalosis is the hypopotassaemia, that can be determinate by two processes, one in the cellular membrane and the other in the renal tubule distal circumvolution [30].

a) Cellular membrane alterations

Although the cellular membrane will be permeably to the water and to the electrolytes, the ions sodium and potassium in and out of the cell are sustained in different concentrations, respecting the electric equilibrium of the both sides of the membrane. This mechanism, that take constant the cationic concentrations of the both sides of membrane, depend of the active transport of these ions by a process energetically dependent known as "sodium pump".

The cellular membrane is permeable to the hydrogen ion and when being reduced in the extracellular space by metabolic alkalosis, there is a migration of hydrogen of in to out of the cell. To sustain the electric equilibrium of the both sides of the membrane, the potassium ion migrates of out to into of the cell, determining a fall of the extracellular potassium and consequent hypokalaemia.

a) Renal tubule distal circumvolution alterations

By aldosterone effect, there is reabsorption of sodium to the level of renal tubule distal circumvolution. The ultrafiltered glomerular reabsorption of sodium is almost complete, particularly in hyponatremia cases. To each reabsorbed sodium ions, eliminate one potassium ion or one hydrogen ion. The hydrogen or potassium preferential elimination depend of acid-basic equilibrium and of the disponible of these ions in the extracellular liquid. So, in the alkalosis cases, in which the bicarbonate cumulus generates lack of hydrogen ion in the extracellular space, the potassium ion is preferentially permuted by sodium and, of this form, lost to the renal tubule light. This loss of potassium also takes to hypokalaemia. By other side, the minor elimination of hydrogen ions determines a minor urine acidification that, in advantage cases, can turn on alkaline (alkaluria). In phases still more advantages of metabolic alkalosis, the potassium became so low that, technologically, the kidney would be of excrete it in favour of the hydrogen ions that again acidification the urine, an extreme phenomenon known as paradox aciduria. In the acidosis states, occur inverse mechanisms in the equilibrium between the potassium and the hydrogen, as to the level of cellular membrane, as of distal nephron.

As the hypo and hyperpotassaemia states follows of important clinic manifestations in the central nervous system, and mainly in the cardiac rhythm (hypokalaemia

ventricular arrhythmia and asystole in the hyperkalaemia), is imperative not negligent the potassium metabolism in the treatment of the detours of acid-basic equilibrium. It is important remember that, independently of the type or of the ethiology, all acidosis state follows of hyperkalaemia and all alkalosis state follows of hypokalaemia.

Metabolic Alkalosis Treatment: In this treatment, takes the same Mellemgaard and Astrup equation using the absolute number of the calculate base difference [27].
Administers ammonium chloride, that is transformed in ammonia and chloride acid.

$$N° \text{ mEq/L } NH_4CI - \text{Weight (kg)} \times 0{,}3 \times [BD]$$

The ammonia form urea metabolized in the urea cycle. The hydrochloric acid reacts with the bicarbonate excess, producing carbonic acid that transforms in water and carbonic gas, that by it turn are easy eliminate by lungs. Also, to this case the dose administrated must be the half of the predicable in the Mellemgaard and Astrup equation, followed of new arterial gasometry. Patients with high gastrointestinal obstruction, mainly by neoplasia or pylorus cicatricial stenosis, frequently arise to the hospital in conditions of dehydration and hypokalaemia. Before of any surgery intervention eying correct the high obstruction, the patients must be hydro electrolytically equilibrated and have corrected their metabolic alkalosis, au contraire can occur serious problems in the anaesthesia induction and in the trans surgery period.

Respiratory Acidosis

The respiratory acidosis occurs by retention of carbonic gas due of respiratory insufficiency by alveolar hypoventilation. There is a significative difference between the acute respiratory insufficiency and the chronic respiratory insufficiency, so that each case will be analysed separated [31].

Acute Respiratory Insufficiency: The acute respiratory insufficiency occurs in normal individuals that, for some reason, suffer alveolar hypoventilation [32]. Between than stand out:

1. Extrapulmonary factors by disfunction of central nervous system, as produced by cranioencephalic trauma, cerebral vascular accident and cardiorespiratory stroke and, still, in respiratory centre disfunction by drugs, as in the suicide trials or iatrogenic administrations to elder and sensitive patients;
2. Peripheric nervous system diseases, as the polyradiculoneuritis and a Guillain-Barré syndrome;
3. Myoneural plaque compromise as the myasthenia;
4. Skeletal muscles compromise as the myopathies;
5. Breathing bellows integrity compromise as occurs in the thoracic trauma, haemothorax, pneumothorax, or in the hydrothorax of expressive extension;
6. Resistive or capacitive mechanical alterations of pulmonar structure, mainly in the aerial vias obstruction by bronchospasm, strange body, tongue fall or glottis edema.

It is extensa the list of causes that determine the respiratory insufficiency. In all the cases the result is predicable: carbonic gas retention by alveolar hypoventilation. Per example, supposes that the partial pressure of carbonic gas hights of 40 to 80 mmHg, the behaviour of the Henderson-Hasselbalch equation would be the following:

$$PH = pK + \log \frac{Base}{Acid}$$

$$pH = pK + \log \frac{Base}{\alpha x PCO2}$$

$$pH = 6.1 + \log \frac{24}{0.03x80}$$

$$pH = 6.1 + \log \frac{24}{2.4}$$

$$pH = 6.1 + 1.0$$

$$pH = 7.1$$

The alveolar hypoventilation increases the carbonic acid concentration, having with this significative pH reduction.

Acute Respiratory Insufficiency Treatment: The treatment consists of prompt clearance of the aerial vias and in the begin of the mechanical ventilation [33]. With this, the partial pressure of carbonic gas in the arterial blood returns to the normal of 40 mmHg and the pH is restored into their normality level. Not is too much to emphasize that the mechanical ventilation must be instituted immediately, because on the contrary the patient can go into histotoxic hypoxia with possible irreversible alterations of central nervous system.

Chronic Respiratory Insufficiency: This is founded in the chronic obstructive pulmonar disease (COPD) when, by rupture of alveolar partitions, forms emphysematous cysts that diminish the alveolar surface, determining the carbonic gas retention. In the same way that in the acute respiratory insufficiency, increase the denominator of the Henderson-Hasselbach equation. However, as the picture develops insidiously and progressively, it is triggered a renal compensation mechanism with bicarbonate retention and it increase in the plasma. Thus, the carbonic gas retention

into the levels of pH is attenuated by bicarbonate action. Admitting that the carbonic gas partial pressure of 40 to 80 mmHg during a period of much years, there is increase of bicarbonate, let's say of 24 to 36 mmEq/L. In these conditions, the final pH will be of 7.28 instead of 7.1, therefore closer of the normal of the inside internal environment. In the end, what control catalytically the intermediary reactions of the metabolism are the internal environment acidosis and not isolated parameters, as the carbonic gas partial pressure or the plasma bicarbonate levels.

$$\mathrm{PH} = \mathrm{pK} + \log \frac{Base}{Acid}$$

$$\mathrm{pH} = \mathrm{pK} + \log \frac{Base}{\alpha x PCO2}$$

$$\mathrm{pH} = 6.1 + \log \frac{36}{0.03x80}$$

$$\mathrm{pH} = 6.1 + \log \frac{36}{2.4}$$

$$\mathrm{pH} = 7.28$$

In the chronic respiratory insufficiency, there is also a biochemical (increase of haemoglobin) and haemodynamic adaptation in the sense of acclimatize the patient to significative levels of hypoxemia [34].

Chronic Respiratory Insufficiency Treatment: Always that possible must avoid submit patients with chronic respiratory insufficiency to the mechanical ventilation, once that is difficult withdraw of respirator [35]. Palliative measures, such as low concentrations oxygen administration (FIO_2 26% to 28%), fluidizers, bronchodilators, respiratory physiotherapy and inhalations must be aggressively employed, in the sense of meliorate the alveolar ventilation. The metabolic alkalosis that normally follows the picture is a compensation mechanism and the positive base difference not must be corrected, given the risk of taking the patient to intense acidaemia with clinic worse. Patients with chronic respiratory insufficiency are of difficult treatment, but the conservatory conduct, although aggressive, must be the therapeutic base.

Respiratory Alkalosis

The respiratory alkalosis occurs in two circumstances:

1. Mechanical hyperventilation;
2. Hysterical hyperventilation;

In both the circumstances, there is reduction of the carbonic gas partial pressure in the alveoli and, consequently, in the arterial blood. Per example, if the pulmonar hyperventilation determine arterial PCO_2 of 20 mmHg (Hypocapnia or Hypocarbia), the Henderson-Hasselbach equation determine an alkaline pH [36].

One of the aspects that have been empathized with the respiratory alkalosis by mechanical hyperventilation is the possibility of occur of hypokalaemia and ventricular arrythmias potentially fatal. Although this eventuality be real, in clinic practice not it has observed this occurrence. Of a general manner, the patient, when under control ventilation, is deliberately sustain in hypocapnia with the objective of avoid spontaneous inspiratory movements that can interfere with the ventilatory pattern controlled by respirator. Carbonic gas partial pressures in arterial blood between 30 mmHg are acceptable in patients under mechanical ventilation. In neurological patients, in the sense of reduce the cerebral edema, has worked with PCO_2 between 25 and 28 mmHg without, to observe arrythmia potentially grave. Anyway, is easy adjust the respirator reducing the respiratory minute volume. The case of hysterical hyperventilation generally occurs in young patients, objectively anxious and with facial blush. Complain of tingling in finger tips and in perioral region. In general, a tranquilized attitude is sufficient to correct the respiratory alkalosis of psychosomatic nature.

Hypoxemia and Acidosis: The hypoxemia is of risk, because can lead to tissue hypoxia, acidosis, organs and systems deterioration and eventually the death [37]. The dispensable energy to the vital functions of the organism is stored in the triglycerides form, glucose, glycogen, phosphocreatine and ATP. Under strength stress and in prolonged fast the energetic substrate is obtained by catabolism of the cell components. The oxygen is essential to the triglycerides and the glucose metabolism. In anaerobic conditions the glucose generates lactic acid that reduce the pH and bocks the major part of the intracellular enzymatic reactions. Molecules of phosphocreatine and ATP kept principally in skeletal muscles become the primary sources of energy. The reduction of ATO synthesis by hypoxia inhibit the sodium pump and the active transport by cell membranes, that compromise the cell integrity. The potassium migrates to out and the sodium to into the cells, that create an osmotic gradient and cell swelling.

The lactic acid cumulus that results of anaerobic glucose break the lysosome membranes and the extravasation of it contents compromise further the protein synthesis. A prolonged energetic deficiency leads a one irreversible cellular lesion and eventually the tissue necrosis and organs and systems dysfunction [38].

Acidosis and Alkalosis and COVID-19

Alfano, et al. [39] determines baseline arterial blood gas analyses that revealed a low arterial partial pressure

of oxygen between 70.2 ± 25.1 mmHg, oxygen saturation of about 92% and a mild reduction of PO_2/FiO_2 ratio of 231±129, an acid-basic alterations founded in 79.7% of the patient. The metabolic alkalosis was the main alteration (33.6%) followed by respiratory alkalosis (30.3%). All patients with metabolic acidosis died at the end of the follow-up. They conclude that variations of pH occurred in the majority of patients admitted with COVID-19 that experienced all the type of acid-base disorders, notably metabolic and respiratory alkalosis were the most common alterations in this group of patients. Wu, et al. [40] compared patients with respiratory alkalosis with those without respiratory alkalosis and determines that the patients with the disease were significantly older, had a higher proportion of female, and showed higher righter ratios of underlying diseases including hypertension and cardiovascular disease. They demonstrated higher possibility of developing severe events compared with those without respiratory alkalosis. Bezuidenhout, et al. [41] related that an alkalaemia was observed in 36 of the 56 intensive care unit patients and that a higher arterial pH and partial pressure of oxygen in arterial blood were associated with survival. Also, Nechipurenko, et al. [42] described that at the early stages of the disease, inflammation, difficult in gas exchange in the lungs and thrombosis collectively contribute to the onset of acidosis. They show that a decrease in blood pH leads to a decrease in oxygen saturation, which contributes to the exacerbation of acidosis and results in a deterioration of the patient's condition. This decrease also causes conformation changes in the S-protein of the virus and thus lead to a decrease in the affinity and avidity of protective antibodies than, hypoxia and acidosis lead to dysregulation of the immune system and multidirectional pr0- and anti-inflammatory reactions, a "cytokine storm".

Models of Treatment of Patients with COVID-19

Busana, et al. [43] settled 498 ventilation-perfusion compartments and, after calculating blood composition, they randomly chose 10 combinations of five parameters controlling a bimodal distribution of blood flow. This model showed that a large fraction of the blood flow was likely distributed in regions with very low ventilation-perfusion and a smaller fraction in regions with moderately high ventilation-perfusion. Their data suggest that shunt alone cannot completely account for the observed hypoxemia and a significant ventilation-perfusion inequality must be present in COVID-19. The high cardiac output and the extensive microthrombosis later found in the autopsy further support the hypothesis of a pathological perfusion of non/poorly ventilated lung tissue.

The particular clinical presentation in COVID-19 patients according Dhont and collaborators contrasts with the experience of physicians usually treating critically ill patients in respiratory failure and ensuring timely referral to the intensive care unit can be challenging. Preserved a oxygen saturation despite low partial pressure of oxygen in arterial blood samples occur, due to leftward shift of oxyhaemoglobin dissociation curve induced by hypoxemia-driven hyperventilation as well as possible direct viral interactions with haemoglobin. Ventilation-perfusion mismatch, ranging from shunts to alveolar dead space ventilation, is the central hallmark and offers various therapeutic targets. The initial management of hypoxemia includes conventional oxygen therapy, high-flow nasal canula oxygen, and non-invasive ventilation. For patients requiring invasive mechanical ventilation, lung-protective ventilation with low tidal volumes and plateau pressure is recommended [44]. These authors also presented promising therapies for COVID-19 as the use of remdesivir and corticosteroids although further studies may be need to confirm their effectiveness. Other therapies are being tested in clinical trials. Physicians are living a scenario that none of us have ever seen about the demand for hospital, made us the certain that we should try to decrease the number of infected patients and that an optimized critical care support is the best strategy to improve patient's survival. Because of these studies certain drugs were tested to be used as a tool against the coronavirus but until now those tentative failed and new ones will be tried in the future.

Conclusion

The COVID-19 is the disease of 21th century. The implications in alterations of the acid-basic equilibrium as the respiratory alkalosis are the more important indicators that this disease affects one of the principal's systems of the body, the respiratory system, whose depends the heart, the kidneys, the brain, and the whole body to survive. To take care of this system is vital to the entire body functions.

Acknowledgments

The author thanks to the Biosciences Department by support this work.

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