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Physiology, Acid Base Balance

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Introduction

To maintain homeostasis, the human body employs many physiological adaptations. One of these is maintaining an acid-base balance. In the absence of pathological states, the pH of the human body ranges between 7.35 to 7.45, with the average at 7.40. Why this number? Why not a neutral number of 7.0 instead of a slightly alkaline 7.40? A pH at this level is ideal for many biological processes, one of the most important being the oxygenation of blood. Also, many of the intermediates of biochemical reactions in the body become ionized at a neutral pH, which causes the utilization of these intermediates to be more difficult.

A pH below 7.35 is an acidemia, and a pH above 7.45 is an alkalemia. Due to the importance of sustaining a pH level in the needed narrow range, the human body contains compensatory mechanisms. This discussion intends to impart a basic understanding of acid-base balance in the body while providing a systematic way to approach patients who present with conditions causing alterations in pH.

The human body experiences four main types of acid-based disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. If one of these conditions occurs, the human body should induce a counterbalance in the form of an opposite condition. For example, if a person is experiencing a metabolic acidemia, their body will attempt to induce a respiratory alkalosis to compensate. It is rare for the compensation to make the pH completely normal at 7.4. When using the term acidemia or alkalemia, one is denoting that overall the pH is acidic or alkalotic, respectively. While not necessary, it can be useful to employ this terminology to distinguish between individual processes and the overall pH status of the patient since multiple imbalances can happen at the same time.[1][2]

Cellular

A basic comprehension of respiration at the cellular level is important in understanding acid-base equilibrium in the human body. Aerobic cellular respiration is necessary for human life; humans are obligate aerobes. While individual cells can perform anaerobic respiration, in order to sustain life, oxygen must be present. One of the byproducts of aerobic cellular respiration is carbon dioxide. The simplified chemical equation denoting aerobic cellular respiration is:

- C6H12O6 (glucose) + 6O2 --> 6CO2 + 6H20 + energy (38 ATP molecules and heat)

The first stage of cellular respiration is glycolysis, which takes a six-carbon glucose and breaks it down into two pyruvate molecules which contain three carbons each. Glycolysis uses two ATP and creates four ATP, meaning it generates two net ATP. This process does not need oxygen to occur. Since patients are often deficient, it is worth noting that magnesium is a cofactor for two reactions in glycolysis.

Eventually, the pyruvate molecules are oxidized and enter into the TCA Cycle. The TCA cycle generates NADH from NAD+, FADH2 from FAD, and two ATP molecules. It is an aerobic process and does demand oxygen. Pyruvate is brought into the mitochondria and forms acetyl-CoA with the loss of carbon dioxide. This excess carbon dioxide is then exhaled during the process of expiration.

The last step in aerobic cellular respiration is the electron transport chain (ETC). The ETC produces the majority of the ATP created in cellular respiration with 34 ATP molecules being created. For the ETC reaction to occur, oxygen is needed. If there is not enough oxygen present, the products of glycolysis proceed to a reaction called fermentation to produce ATP. The byproduct of fermentation is lactic acid. During glycolysis and the TCA cycle, NAD+ is reduced to NADH and FAD is reduced to FADH2. Reduction is characterized by a gain of electrons. This is what drives the ETC. For every single molecule of glucose, ten NAD+ molecules are converted to NADH molecules, which produce three ATP molecules a piece in the ETC.

This process of aerobic cellular respiration characterizes why humans need oxygen. Anaerobic respiration allows the body to produce some ATP when there is not enough oxygen present; however, the process only generates two ATP as opposed to the 38 ATP produced with aerobic respiration. The two ATP molecules per reaction are not enough to sustain life.

As noted above, carbon dioxide is produced as a byproduct of the TCA cycle. This carbon dioxide is instrumental to acid-base balance in the body which is demonstrated with the following reaction:

- $CO2 + H20 <-> H2C03 <-> HCO3- + H+$

The carbon dioxide formed during cellular respiration combines with water to create carbonic acid. Carbonic acid then dissociates into bicarbonate and a hydrogen ion. This reaction is one of the many buffer systems in the human body; it resists dramatic changes in pH to allow a person to remain within the narrow physiological pH range. This buffer system is in equilibrium, that is, all components of the reaction exist throughout the body and are shifted to the side of the equation appropriate for the environment. This reaction can and does occur without an enzyme; however, carbonic anhydrase is an enzyme that assists with this process. It catalyzes the first reaction above to form carbonic acid which can then freely dissociate into bicarbonate and a hydrogen ion. Carbonic anhydrase is located in red blood cells, renal tubules, gastric mucosa, and pancreatic cells.

Other buffer systems in the human body include the phosphate buffer system, proteins, and hemoglobin. All of these contain bases which accept hydrogen ions which keep the pH from plummeting. The phosphate buffer system, while present globally, is important for the regulation of urine pH. Proteins assist with intracellular pH regulation. Red blood cells use the reaction above to help hemoglobin buffer; carbon dioxide can diffuse across red blood cells and combine with water. This alone would cause an increase in hydrogen ions; however, hemoglobin can bind hydrogen ions. Hemoglobin also can bind carbon dioxide without this reaction. This depends on the amount of oxygen that is bound to hemoglobin. This is called the Haldane effect and the Bohr effect. When hemoglobin is saturated with oxygen, it has a lower affinity for CO2 and hydrogen ions and is able to release it.[3][4]

Organ Systems Involved

Every organ system of the human body relies on pH balance; however, the renal system and the pulmonary system are the two main modulators. The pulmonary system adjusts pH using carbon dioxide; upon expiration, carbon dioxide is projected into the environment. Due to carbon dioxide forming carbonic acid in the body when combining with water, the amount of carbon dioxide expired can cause pH to increase or decrease. When the respiratory system is utilized to compensate for metabolic pH disturbances, the effect occurs in minutes to hours.

The renal system affects pH by reabsorbing bicarbonate and excreting fixed acids. Whether due to pathology or necessary compensation, the kidney excretes or reabsorbs these substances which affect pH. The nephron is the functional unit of the kidney. Blood vessels called glomeruli transport substances found in the blood to the renal tubules so that some can be filtered out while others are reabsorbed into the blood and recycled. This is true for hydrogen ions and bicarbonate. If bicarbonate is reabsorbed and/or acid is secreted into the urine, the pH becomes more alkaline (increases). When bicarbonate is not reabsorbed or acid is not excreted into the urine, pH becomes more acidic (decreases). The metabolic compensation from the renal system takes longer to occur: days rather than minutes or hours.

Function

The physiological pH of the human body is essential for many processes necessary to life including oxygen delivery to tissues, correct protein structure, and innumerable biochemical reactions that rely on the normal pH to be in equilibrium and complete.

Oxygen Delivery to Tissues

The oxygen dissociation curve is a graph depicting the relationship of the partial pressure of oxygen to the saturation of hemoglobin. This curve relates to the ability of hemoglobin to deliver oxygen to tissues. If the curve is shifted to the left, there is a decreased p50, meaning that the amount of oxygen needed to saturate hemoglobin 50% is lessened and that there is an increased affinity of hemoglobin for oxygen. A pH in the alkalotic range induces this left shift. When there is a decrease in pH, the curve is shifted to the right, denoting a decreased affinity of hemoglobin for oxygen.

Protein Structure

It would be hard to overstate the importance of proteins in the human body. They makeup ion channels, carry necessary lipophilic substances throughout our mostly lipophobic body, and participate in innumerable biological processes. For proteins to complete necessary functions, they must be in the proper configuration. The charges on proteins are what allow their proper shape to exist. When pH is altered outside of the physiological range, these charges are altered. The proteins are denatured leading to detrimental changes in architecture that cause a loss of proper function.

Biochemical Processes

Throughout the human body, many chemical reactions are in equilibrium. One of the most important was previously mentioned with the equation:

- H20 + CO2 <-> H2CO3<-> H+ + HCO3-

The Le Chatelier Principle states that when the variables of concentration, pressure, or temperature are changed, a system in equilibrium will react accordingly to restore a new steady state. For the reaction above, this states that if more hydrogen ions are produced, the equation will shift to the left so that more reactants are formed, and the system can remain in equilibrium. This is how compensatory pH mechanisms work; if there is a metabolic acidosis present, the kidneys are not excreting enough hydrogen ions and/or not reabsorbing enough bicarbonate. The respiratory system reacts by increasing minute ventilation (often by increasing respiratory rate) and expiring more CO2 to restore equilibrium.[5]

Related Testing

Arterial blood gas (ABG) sampling, is a test often performed in an inpatient setting to assess the acid-base status of a patient. A needle is used to draw blood from an artery, often the radial, and the blood is analyzed to determine parameters such as the pH, pC02, pO2, HCO3, oxygen saturation, and more. This allows the physician to understand the status of the patient better. ABGs are especially important in the critically ill. They are the main tool utilized in adjusting to the needs of a patient on a ventilator. The following are the most important normal values on an ABG:

- pH = 7.35 to 7.45
- pCO2 = 35 to 45 mmHg
- pO2 = 75 to 100 mmHg
- HCO3- = 22 to 26 mEq/L
- O2 Sat = greater than 95%

The ability to quickly and efficiently read an ABG, especially in reference to inpatient medicine, is paramount to quality patient care.

1. Look at the pH

2. Decide whether it is acidotic, alkalotic, or within the physiological range
3. PaCO2 level determines respiratory contribution; a high level means the respiratory system is lowering the pH and vice versa.
4. HCO3- level denotes metabolic/kidney effect. An elevated HCO3- is raising the pH and vice versa.
5. If the pH is acidotic, look for the number that corresponds with a lower pH. If it is a respiratory acidosis, the CO2 should be high. If the patient is compensating metabolically, the HCO3- should be high as well. A metabolic acidosis will be depicted with an HCO3- that is low.
6. If the pH is alkalotic, again, determine which value is causing this. A respiratory alkalosis will mean the CO2 is low; a metabolic alkalosis should lend an HCO3- that is high. Compensation with either system will be reflected oppositely; for a respiratory alkalosis the metabolic response should be a low HCO3- and for metabolic alkalosis, the respiratory response should be a high CO2.
7. If the pH level is in the physiological range but the PaCO2 and/or bicarb are not within normal limits, there is likely a mixed disorder. Also, compensation does not always occur; this is when clinical information becomes paramount.
8. Sometimes it is difficult to ascertain whether a patient has a mixed disorder. This is discussed later.

Other tests that are important to perform when analyzing the acid-base status of a patient include those that measure electrolyte levels and renal function. This helps the clinician gather information that can be used to determine the exact mechanism of the acid-base imbalance as well as the factors contributing to the disorders.[6][3]

Pathophysiology

Increased Anion Gap Metabolic Acidosis

A primary metabolic acidosis, that is, one which is the primary acid-base disorder, has many causes. These are separated into those which cause a high anion gap and those that do not. The plasma anion gap is a way to help clinicians determine the cause of a metabolic acidosis. When there is a metabolic acidosis present, certain ions in the blood are measured that help determine the etiology of an acidemia. The anion gap increases whenever bicarbonate is lost due to it combining with a hydrogen ion that was previously attached to a conjugate base. When bicarbonate combines with a hydrogen ion, the result is carbonic acid (H2CO3). The conjugate base can be any negatively charged ion that isn't a bicarbonate or a chloride.

The formula for anion gap is:

- [Na]-([Cl]+[HCO3])

Humans are electrically neutral, but all cations and anions are not being measured. The normal anion gap is equal to 8 +/- 4. Most of this number is due to albumin; this anion is not accounted for in the formula which is a large reason why the gap is not closer to zero. Albumin is normally 4 mg/dL. Because of the large effect of albumin on anion gap, if a patient's albumin level is abnormal, their expected anion gap will not be accurate. This can be corrected using simple math. The normal anion gap and albumin level differ by a factor of three (normal anion gap of 12, normal albumin of 4 mg/dL). If a patient has an anion gap of 24, that means there are 12 units of the conjugate base present that normally would not be due to the combination of hydrogen ions with bicarbonate. If this same patient has an albumin level of 3mg/dL, their expected anion gap should actually be about 9. This means that, rather than 12 units of the conjugate base present, there are really 15 units.

A more complex method of analyzing ion contribution to pH alterations is the strong ion difference/strong ion gap. This method emphasizes the effect of other ions on acid-base balance and is useful for learning about acid-base balance. However, this approach is more burdensome than the standard anion gap and involves more calculations. Many therefore believe that its use in clinical practice is limited.

The mnemonic MUDPILES has classically been used to teach students about the causes of high anion gap metabolic acidosis. MUDPILES stands for methanol, uremia, diabetic ketoacidosis, paraldehyde, infection, lactic acidosis, ethylene glycol, and salicylates. A new mnemonic, GOLDMARK, has been suggested to be an

improvement. GOLDMARK is an anagram for glycols (ethylene and propylene), oxoproline, lactate, methanol, aspirin, renal failure, and ketones. If a patient has an anion gap over 12, these mnemonics are helpful to remember the possible causes of the disorder.[7][8]

Narrow Anion Gap Metabolic Acidosis

If the acidosis involves a normal anion gap, there is a loss of bicarbonate rather than an increased amount of hydrogen ions, with a concomitant increase in chloride ions. To keep a physiological neutral state, chloride ions migrate out of the cells and into the extracellular space. This causes the patient's serum chloride to increase and keeps the anion gap at a normal level. This means that a metabolic acidosis without an abnormal anion gap is also a hyperchloremic metabolic acidosis. A metabolic acidosis without an increased anion gap results from many processes including severe diarrhea, type I renal tubular acidosis (RTA), long-term use of carbonic anhydrase inhibitors, and suctioning of gastric contents. When a patient has a narrow ion gap hyperchloremic acidosis, the provider can calculate the urine anion gap (UAG) to help determine etiology.

The following is the equation for urine anion gap where Na is sodium, K is potassium, and Cl is chloride:

- (Na + K) – Cl

The renal system attempts to ameliorate the effects of pathological metabolic acidosis by excreting ammonium (NH_4^+) into the urine. A UAG between 20 to 90 mEq/L denotes low or normal NH_4^+ secretion. One between -20 mEq/L and -50 mEq/L suggests the main cause of the metabolic acidosis is prolonged severe diarrhea.

Another important formula to use with metabolic acidosis is the Winter formula. This equation provides the clinician with the expected PCO_2 value. This is important because there could be another acid-base disorder present.

The Winter formula is:

- Expected $PCO_2 = (1.5 \times HCO_3) + 8 +/- 2$

If the PCO_2 value is within range of the expected PCO_2, there is no mixed disorder, just respiratory compensation. When the value is lower or higher than expected, there is a mixed disorder; lower would mean a respiratory alkalosis and higher a respiratory acidosis. A shortcut for the Winter formula is that the last two digits of the pH +/- 2 is about equal to the expected PCO_2.[9][10]

Respiratory Acidosis

During exhalation, carbon dioxide produced by cellular respiration is projected into the environment. In the human body, carbon dioxide combines with water via carbonic anhydrase and forms carbonic acid which dissociates into a hydrogen ion and bicarbonate. This is why a reduced respiratory rate will lead to a decreased pH; the more carbon dioxide is exhaled, the less carbon dioxide present for this reaction.

Respiratory acidosis as a primary disorder is often caused by hypoventilation. This can be due to multiple causes including chronic obstructive pulmonary disease, opiate abuse/overdose, severe obesity, and brain injury. When respiratory acidosis occurs, the metabolic response should be to increase the amount of bicarbonate via the renal system. This does not always occur, and renal pathology can easily hinder the appropriate physiological response, leading to increased danger for the patient.

Metabolic Alkalosis

Metabolic alkalosis also can be divided into two main categories that help ascertain the cause: chloride responsive vs. non-chloride responsive. In non-chloride-responsive metabolic alkalosis, the urine chloride is < 20 mEq/L. Some causes include vomiting, hypovolemia, and diuretic use.

Respiratory Alkalosis

Any pathology that leads to the increased expiration of carbon dioxide can result in respiratory alkalosis. When excess CO_2 is expired, the pH of the human body is increased due to less carbonic acid being created. Physiologically, the appropriate compensation is a decreased amount of bicarbonate being created by the

renal system. Some causes of respiratory alkalosis include panic attacks with hyperventilation, pulmonary embolism, pneumonia, and salicylate intoxication.[11]

Clinical Significance

Acid-base balance in the human body is one of the most paramount physiological processes. The clinical significance of acid-base balance is one which is hard to deny. Some of the most common admissions to hospitals are due to diseases that can dangerously affect the acid-base balance. This is why it is important for clinicians to understand basic principles which govern this portion of human homeostasis.

Continuing Education / Review Questions

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