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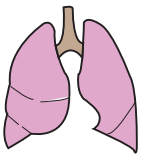
ACID BASE PHYSIOLOGY

Terminology Acids have been defined in a number of ways (initially from the latin sour). Arrhenius theory describes an acid as a substance which dissociates in water to produce hydrogen ions. Bronsted-Lowry defined an acid as a substance which donates a proton and the substance which accepts the proton is the conjugate base. This is the most commonly used definition in biological sciences. Note that CO2 is not a B-L acid but represents the potential to be an acid via combination with H2O to form carbonic acid, and is often therefore called an acid regardless. There are two main approaches to interpreting acid base physiology. The conventional approach and the physico-chemical approach first described by Stewart.

Conventional approach Analysis based on the interactions of hydrogen ions, bicarbonate and carbon dioxide. Underpinned by the Henderson-Hasselbach equation which is based on the law of mass action. Overall the daily production and consumption of hydrogen ions is very large due to processes such as ATP turnover and mitochondrial activity (>500 moles). The net production requiring either excretion from the lungs (volatile - 12 moles) or from the kidney (fixed - 0.1 mole) is much smaller but of significant physiological importance. In the conventional approach it is the interaction of the hydrogen ions which determine the pH, the bicarbonate which is the most important buffer in the system and is regulated by the kidney and the pCO_2 which is regulated by the respiratory system which determine the physiological acid-base state. The benefits of this system is that it can be applied clinically to assess patient acid base status based on their history, the severity of the disorder and identify mixed disorders.

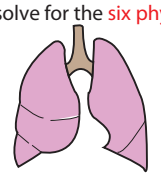


RESPIRATORY SYSTEM
Excretion of volatile acid (CO_2)

LIVER
Net producer of H^+ or
Net consumer of H^+

RENAL SYSTEM
Reabsorption of HCO_3^-
Excretion of fixed acids (H^+)

Stewart Approach Developed using the physicochemical laws including the law of mass action, law of electroneutrality, and the conservation of mass. Stewart characterised 3 independent variables. The total weak acids (A_{TOT}), which is the sum of all weak acids (by definition are incompletely dissociated). It is often simplified when considering the IV compartment to albumin which predominates. The amount of albumin is determined by the liver (therefore independent). The second independent variable is the pCO_2, which is controlled by the resp system. The final variable is the strong ion difference (SID) which is the difference between the completely dissociated cations (Na^+, K^+, Ca^{++}, Mg^{++}) and anions (Cl^- and other anions). It is often simplified to $Na^+ - Cl^-$ and is usually around 40-45. It is determined by the kidneys and to a lesser extent GIT system. Using the three independent variables it is possible to determine the dependent variables which include [H^+], [HA], [A^-], [OH^-], [HCO_3^-], using a 4th order polynominal equation to solve for the six physicochemical laws (which include the henderson-hasselbach).

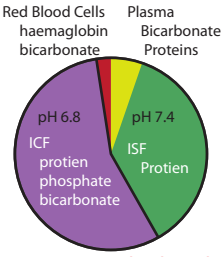


RESPIRATORY SYSTEM
Excretion of CO_2
Determines pCO_2

LIVER
Producer of weak acids
Main determinant A_{TOT}

RENAL SYSTEM
Excretion of Cl^- and other strong ions
Main determinant SID

Importance of pH. There are two main reasons why pH is so important. The first is the Davis hypothesis and relates primarily to small molecules. This states that many biologically significant compound are completely ionised near neutral pH and therefore are trapped within the cell and its organelles. The second reason relates to larger protiens which maintain optimal performance at a specific pH intra cellularly and extracellularly. We usually required to infer the ICF pH from ECF measurements when attempting to maintain this optimal pH level. This becomes somewhat fraught in the setting of changing temperatures because as the temperature drops the CO2 becomes less soluble (and therefore the pH increases). Some teaching supports correcting the plasma pH back to its value at 37 degrees (7.4) by adjusting the system (adding more CO2) this is the pH stat approach. What has been found experimentally however is that imidazole groups intracellularly remains ionised (alpha) at a constant amount regardless of temperature, therefore ICF pH remains near neutrality (6.8) despite temp changes. This approach advocates accepting that plasma pH will vary with temp (usually by 0.015 pH units per degree) but this will not affect the ICF pH. Alpha stat is more accepted.



Buffering a buffer is a substance with the capacity to bind or release H^+ and thus minimise changes in pH. Buffers consist of a mixture of a weak acid and its conjugate base. A buffer is most effective at its pKa, at which it is 50% ionised. Most of the buffering capacity in the body occurs in a narrow range of pH. The effectiveness of a buffer in a physiological system is also dependent on if it is open like the bicarbonate system where CO2 may be removed via the lungs or closed (chemical). Buffering may occur for a target pH of 7.4 which is the pH of the ECF or 6.8 which is the pH of the ICF. RBCs are usually considered in the ECF category due to its importance as a buffer in this compartment. The major buffer system in the ECF is the CO2-bicarbonate buffer system. This is responsible for about 80% of extracellular buffering. It is the most important ECF buffer for metabolic acids but it cannot buffer respiratory acid-base disorders. The components are easily measured and are related to each other by the Henderson-Hasselbalch equation. $pH = pK'a + \log10 ([HCO3] / 0.03 \times pCO2)$ The pK'a value is dependent on the temperature, [H+] and the ionic concentration of the solution. It has a value of 6.099 at a temperature of 37C and a plasma pH of 7.4. On chemical grounds, a substance with a pKa of 6.1 should not be a good buffer at a pH of 7.4 if it were a simple buffer. The system is more complex as it is 'open at both ends' (meaning both [HCO3] and pCO2 can be adjusted) and this greatly increases the buffering effectiveness of this system. The excretion of CO2 via the lungs is particularly important because of the rapidity of the response. The adjustment of pCO2 by change in alveolar ventilation has been referred to as physiological buffering. Protein buffers in blood include haemoglobin (150g/l) and plasma proteins (70g/l). Buffering is by the imidazole group of the histidine residues which has a pKa of about 6.8. This is suitable for effective buffering at physiological pH. Haemoglobin is quantitatively about 6 times more important then the plasma proteins as it is present in about twice the concentration and contains about three times the number of histidine residues per molecule. The phosphate system HPO_4^{-2} and $H_2PO_4^-$ has a pKa of 6.8 and so has a theoretic advantage over bicarbonate. It only exists in very small concentration in the ECF however and is a closed system so makes minimal contribution. It is however a significant buffer in the ICF.

Regulation of the Acid-Base There are two major systems which regulate acid base physiology and several lesser contributors. The first is the respiratory system. Important characteristics are; CO2 is the only acid excreted by the lungs, this excretion is very rapid and the system is high capacity compared to the kidneys (15 moles vrs 0.1 moles). The control of the system is based on central chemoreceptors which rely on CO2 crossing the BBB and increasing local [H^+] which is relayed to the respiratory centre in the medulla to alter ventilation and therefore the pCO2. This is augmented by the peripheral chemoreceptors in the aortic arch and carotid bodies. These sense changes in pO2, pCO2 and pH, and therefore are very important in a metabolic acidosis providing the stimulus for respiratory compensation (H^+ does not cross the BBB therefore the central chemoreceptors do not play a role). The other main system is the renal system which is involved in the excretion of fixed acids is the distal tubule and the reabsorption of bicarbonate in the proximal tubule. It is the balance of these two processes which determines the kidneys response to changes in pH (in alkalosis less HCO3 is reabsorbed and H excreteted, in acidosis the oppostie). The renal response is influenced by the pCO2, the pH, the bicarbonate level, ECF volume, angiotensin, aldosterone and hypokalaemia. Minor regulation takes place by the bones (in persistent metabolic acidosis as a source of CaCO3 for buffering) and the liver as a net producer or consumer of hydrogen ions through metabolic processes.

Analysis of blood gas .A deranged pH is responded to by the body in three ways, buffering, compensation and correction. The most important aspect to assessment is a clinical history, especially regarding the chronicity (and therefore opportunity for appropriate compensation).

Respiratory Acidosis

Definition: is a primary acid base disorder in which arterial pCO_2 rises to a higher level than expected
Causes: Most due to decreased alveolar ventilation, others are increased inspired CO_2 or CO_2 production
Effects: (increased CO_2) increased ventilation, cerebral vasodilation, SNS activation, tachycardia, decreased intracellular metabolism and central depression at high levels
Acute buffering: intracellular buffering with Hb leads to increase in HCO_3 Expected $HCO_3 = 24+1(\triangle pCO_2/10)$
Chronic compensation: is renal retention of HCO3 which is slower >6hrs and leads to a more pronounced correction, pCO_2 Expected $HCO_3 = 24+4(\triangle pCO_2/10)$ (outside expected = mixed disorder).
Correction: Increase ventilation

Respiratory Alkalosis

Definition: is a primary acid base disorder in which arterial pCO_2 decreases to a level less than expected
Causes: Always due to increased alveolar ventilation
Effects: (decreased CO_2) cerebral vasoconstriction adn associated short term ICP drop, arrhythmias, decreased myocardial contractility, increased neuromuscular irritability, decreased respiratory drive, Hb-O2 curve left.
Acute buffering: Intracellular and plasma protiens, leads to decreased HCO_3 Expected $HCO_3 = 24-2(\triangle pCO_2/10)$
Chronic compensation: is renal loss of HCO3 which is slower >6hrs and leads to a more pronounced correction, pCO_2 Expected $HCO_3 = 24-5(\triangle pCO_2/10)$
Correction: treat precipitant (lung pathology causing sensation of dyspnoea (PE, asthma, pneumonia), anxiety.

Metabolic Acidosis

Definition: is a primary acid base disorder leading to an increase in fixed acids in the blood.
Causes: Classified by the anion gap = [Na] - [Cl] - [HCO3] normally 8-16. Normal AG include renal tubular acidosis, diarrhoea, addition of Cl ions. Increased AG causes include ketoacidosis, lactic acidosis, renal failure, toxins (incl. ethylene glycol, methanol, salicylates).
Effects: Hb-O2 curve right, decreased 2,3DPG (Hb-O2 curve left), incr resp rate (Kussmaul), decreased myocardial contractility, SNS activation, decreased catecholamine sensitivity, K shift out of ICF (inc K lvls) .
Acute buffering: via HCO_3 causing sharp drop according to formula Expected $pCO_2 = 1.5(\text{actual } [HCO_3] +8)$
Acute compensation: increased respiratory rate
Correction: correct cause, renal and liver HCO_3 production

Metabolic Alkalosis

Definition: is a primary acid base disorder leading to an overall increase in bicarbonate in the blood.
Causes: loss of H^+ (Cl^- in Stewart) from the kidney (diuretics) or gut (vomiting, NG tube - 90% total) or increased HCO3, citrate in blood, sodium bicarb IV, adrenocortical excess syndromes.
Effects: Decreased myocardial contractility, decreased cerebral blood flow, confusion/obtundation, neuromuscular excitability, Hb-O2 shift left.
Hypokalaemia can be life threatening
Acute compensation: decreased respiratory rate
Expected $pCO_2 = 0.7(\text{actual } [HCO_3] +20)$ (+/- 5)
Correction: Treat precipitant and the maintaining process (without which the kidney usually corrects the system quickly by excreting bicarb). Give oxygen! Replace chloride and potassium.